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Review

Oxidative Stress, Inflammaging, and Environmental Exposures in Ocular Surface Diseases

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Highlights

What are the main findings?

- Environmental exposures may contribute to ocular surface damage by disrupting redox homeostasis, epithelial barrier function, and tear film stability.
- Oxidative stress, chronic inflammation, and inflammaging may interact to promote the development and persistence of ocular surface diseases.

What are the implications of the main findings?

- Tear oxidative stress biomarkers may help characterize disease-related pathophysiology and support future approaches to disease stratification and monitoring.
- Integrating environmental exposure reduction, antioxidant strategies, and inflammatory control may provide a framework for developing preventive and therapeutic approaches to ocular surface diseases.

Abstract

The ocular surface is continuously exposed to environmental factors, including air pollutants, ultraviolet (UV) radiation, artificial light, and tobacco smoke. These exposures may induce oxidative stress by increasing reactive oxygen species (ROS) production and impairing antioxidant defenses, potentially contributing to inflammation, epithelial barrier dysfunction, and disrupted tear film homeostasis. This review aims to integrate current evidence on environmental exposures, oxidative stress, and inflammaging to clarify their potential interactions in ocular surface diseases and identify implications for research and clinical practice. It examines the effects of particulate matter ($PM_{2.5}$), ozone, Asian dust, volatile organic compounds (VOCs), tobacco smoke, blue light, and UV radiation, focusing on redox homeostasis, inflammatory signaling, and antioxidant defenses. It also discusses the interplay of environmental exposures, oxidative stress, immune responses, and inflammaging, defined as chronic low-grade inflammation associated with aging, in dry eye disease and allergic conjunctivitis. Furthermore, the potential of tear oxidative stress biomarkers for characterizing disease-related pathophysiology and preventive and therapeutic strategies involving exposure reduction, antioxidant approaches, and inflammatory control are considered. Overall, these processes may interact to compromise ocular surface homeostasis. Further research is needed to clarify their relationships and establish the clinical utility of tear biomarkers and targeted interventions.

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1. Introduction

1.1. The Ocular Surface and Environmental Exposures: Characteristics of a Tissue Directly Exposed to the External Environment

As illustrated in Figure 1, the ocular surface comprises the cornea, conjunctiva, tear film, eyelids, and meibomian glands, which collectively play essential roles in maintaining visual function and protecting the eye from environmental insults. The tear film covers the corneal and conjunctival surfaces and is conventionally described as comprising three layers, from outermost to innermost: the lipid, aqueous, and mucin layers (Figure 2). Because these tissues are directly exposed to the external environment, they are routinely subjected to various environmental factors, including air pollutants, temperature fluctuations, humidity, wind, ultraviolet (UV) radiation, and allergens. Although the ocular surface is protected by multiple defense mechanisms, including the tear film, mucins, intercellular junctions, innate immune responses, and antioxidant defenses, changes in environmental conditions and repeated exposure to harmful substances may compromise ocular surface homeostasis [1].

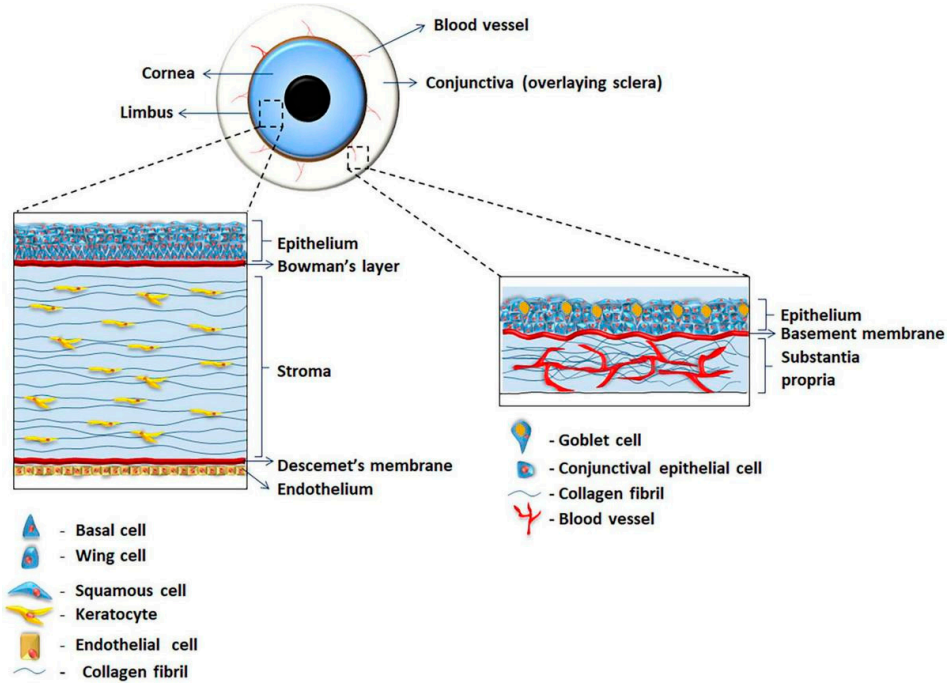


Figure 1. Histological Structure of the Cornea and Conjunctiva. Schematic illustration of the anatomical and histological structures of the cornea and conjunctiva, which constitute the ocular surface. From the superficial to the deeper layers, the cornea consists of the epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium. The corneal epithelium comprises basal cells, wing cells, and superficial squamous cells and functions as a physical barrier at the ocular surface. The conjunctiva consists of the epithelium and substantia propria, with goblet cells embedded in the epithelium that contribute to the production of mucins in the tear film. Blood vessels are distributed throughout the conjunctival substantia propria, which also plays a role in immune surveillance and inflammatory responses. The corneal limbus lies at the boundary between the cornea and conjunctiva and is essential for maintaining corneal epithelial homeostasis. This figure illustrates the fundamental tissue architecture of the ocular surface relevant to understanding environmental exposure-induced damage.

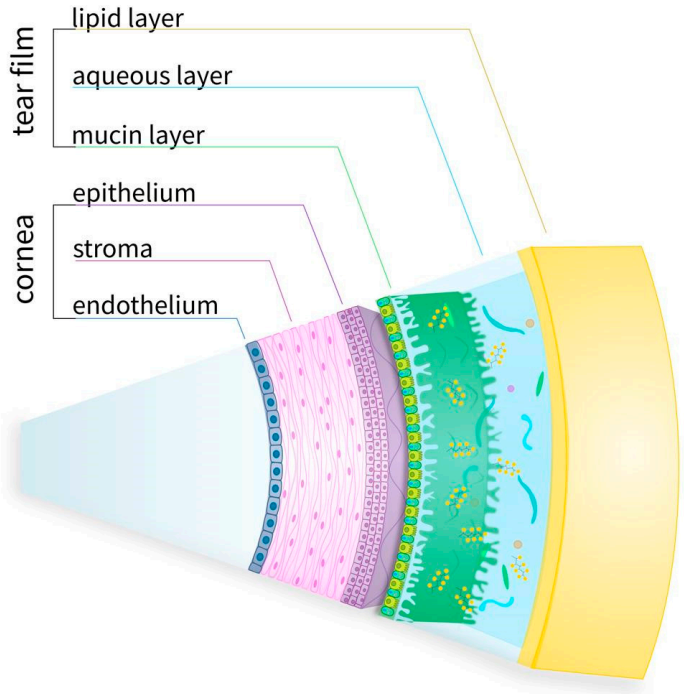


Figure 2. Structure of the Tear Film and Corneal Layers. Schematic illustration of the tear film and the major structural layers of the cornea. Traditionally, the tear film has been described as comprising lipid, aqueous, and mucin layers, which contribute to reducing tear evaporation, maintaining ocular surface hydration, and promoting tear film spreading and stability over the corneal epithelium, respectively. The cornea consists primarily of the epithelium, stroma, and endothelium. The epithelium serves as the first line of defense against external physical and chemical insults. Tear film instability and corneal epithelial damage compromise ocular surface homeostasis, potentially leading to dryness, increased sensitivity to irritants, and inflammatory responses. This figure illustrates how the tear film and corneal tissues interact to maintain the protective functions of the ocular surface.

Environmental exposures encompass a wide range of factors, including fine particulate matter such as particulate matter of 2.5 μm or less in diameter ($PM_{2.5}$), reactive gases such as ozone, Asian dust, volatile organic compounds (VOCs), tobacco smoke, UV radiation, and blue light, which constitutes part of the visible light spectrum. Although these exposures differ in their sources, physicochemical properties, routes of contact with the ocular surface, and biological effects, they affect tear film stability, epithelial cell function, inflammatory responses, and redox homeostasis. In particular, air pollutants commonly occur as mixtures of particulate and gaseous components. Therefore, in addition to the effects of individual pollutants, the combined effects of multiple environmental exposures need to be considered [2,3].

Understanding how the ocular surface responds to environmental exposures requires consideration not only of its immediate protective responses to external stimuli but also of the intracellular signaling pathways and tissue repair processes activated following exposure. Environmental factors may increase the production of reactive oxygen species (ROS), and when these exceed the capacity of antioxidant defense mechanisms to maintain redox balance, oxidative stress may develop. This can potentially damage cellular components, including lipids, proteins, and nucleic acids. These changes further activate inflammatory signaling pathways, contributing to epithelial barrier dysfunction and disruption of tear film homeostasis [4].

Thus, the ocular surface is not only a tissue directly affected by environmental exposures but also an important biological system in which to investigate the interplay among redox responses, inflammation, and tissue repair following environmental stress.

1.2. Clinical Significance of Environmental Factors in Ocular Surface Diseases

Ocular surface diseases, including dry eye disease (DED), allergic conjunctivitis, blepharitis, and corneoconjunctival epithelial disorders, can cause ocular discomfort, foreign body sensation, burning, itching, tearing, and fluctuations in visual function, thereby affecting patients' quality of life. The symptoms and clinical manifestations of these conditions may be influenced not only by individual predisposition and immunological background but also by environmental conditions and patterns of everyday exposure. The TFOS Lifestyle Report summarizes the associations between ocular surface health and a range of environmental factors, including temperature, humidity, wind, UV radiation, allergens, and indoor and outdoor air pollution [1].

Recent systematic reviews have reported associations between exposure to air pollution, including particulate matter (PM), and clinical manifestations related to dry eye symptoms, conjunctivitis, and allergic eye diseases. Cell-based experiments and animal models have also demonstrated that exposure to particulate matter can induce inflammatory responses, oxidative stress, cellular injury, and changes in tear secretion. These findings provide biological plausibility for the associations between environmental pollution and ocular surface symptoms observed in clinical studies [2,3]. In addition, a review of indoor air pollution discussed the potential effects of particulate matter, semivolatile organic compounds, heavy metals, combustion products, and tobacco smoke on the ocular surface, identifying inflammatory responses, oxidative damage, and disruption of intercellular junctions as potential underlying mechanisms [5].

However, epidemiological associations vary by exposure level, duration, climate, and host susceptibility, and observational data cannot isolate individual causal pollutants from co-existing meteorological factors [6,7]. Therefore, elucidating how these exposures disrupt cellular redox balance and immune regulation across diverse age and susceptibility profiles is essential.

1.3. Oxidative Stress and Inflammation in Ocular Surface Injury

Oxidative stress is generally understood as a state in which the balance between the production of oxidizing molecules, including ROS, and the antioxidant defense mechanisms that regulate them is disrupted. ROS also play essential roles in intracellular signaling and host defense; therefore, their presence alone is not necessarily harmful. Rather, their effects depend on the amount produced, their intracellular localization, the duration of their activity, and the capacity of antioxidant mechanisms to regulate them. Excessive or sustained oxidative stress may induce lipid peroxidation, oxidative protein modifications, deoxyribonucleic acid (DNA) damage, and mitochondrial dysfunction, potentially compromising cellular homeostasis [4].

At the ocular surface, the tear film and epithelial cells constitute the first line of defense against the external environment. When environmental pollutants or light exposure induce oxidative stress, they may cause epithelial injury, activate inflammatory signaling pathways, and alter intercellular junctions. These responses may impair epithelial barrier function and destabilize the tear film, potentially increasing susceptibility to subsequent environmental insults. Thus, oxidative damage and inflammatory responses induced by environmental exposures should not be regarded as independent phenomena; rather, they may interact and jointly alter ocular surface homeostasis [2,3].

Navel et al. provided important evidence regarding oxidative stress in DED through a systematic review and meta-analysis [8]. Their findings indicated that patients with DED tended to have higher levels of lipid peroxidation products and other oxidative stress-related markers than healthy controls, suggesting a role for oxidative stress in tear fluid, conjunctival cells, and conjunctival tissues. However, the number of studies included was

limited, and heterogeneity existed in the biomarkers measured, specimen types, and patient characteristics. Further investigation is therefore needed to establish the diagnostic utility of individual biomarkers and their relationships with disease activity.

The interaction between oxidative stress and inflammation is an important concept for understanding ocular surface pathophysiology. Oxidative stress may activate inflammation-related pathways, whereas ROS and inflammatory mediators produced by inflammatory cells may further amplify tissue injury. Furthermore, when mitochondrial dysfunction or cellular damage persists, cellular responses such as cell death and senescence affect tissue repair capacity [4,9].

Accordingly, oxidative stress in ocular surface diseases should be investigated not merely as an indicator of cellular injury but as a component of disease pathogenesis that links environmental exposures, inflammation, epithelial barrier function, and tissue repair.

1.4. Inflammaging and Age-Related Changes at the Ocular Surface

Inflammaging refers to the chronic, low-grade inflammatory state associated with aging and is conceptually linked to changes in immune function, cellular senescence, mitochondrial function, and tissue repair capacity. Age-related inflammation persist in the absence of overt infection or acute tissue injury and is considered to contribute to the pathogenesis of various age-related diseases. At the ocular surface, age-related changes in cellular function and tear film homeostasis may likewise increase susceptibility to chronic inflammation and tissue injury.

A systematic review and meta-analysis by Kitazawa et al. indicated that age-related changes in the ocular surface microenvironment contribute to the pathophysiology of DED. Specifically, the authors reported changes associated with cellular senescence in the ocular surface epithelium, lacrimal glands, and meibomian glands; accumulation of 8-hydroxy-2′-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage; and alterations in markers associated with cell proliferation [10]. These findings suggest that age-related changes at the ocular surface affect not only tear secretion and tear film stability but also epithelial maintenance and repair.

Furthermore, Kitazawa et al. analyzed gene expression profiles associated with cellular senescence in human corneal and conjunctival epithelial cells and reported molecular changes in senescent cells involving inflammatory mediators and the regulation of the extracellular microenvironment [9]. The senescence-associated secretory phenotype (SASP), which refers to the secretory profile associated with cellular senescence, may also affect neighboring cells and the surrounding tissue microenvironment through inflammatory cytokines and other bioactive factors [11,12]. If sustained, these changes contribute to impaired epithelial barrier function and the persistence of chronic inflammation. However, the causal relationships between cellular senescence and ocular surface diseases, as well as the specific roles of SASP in individual conditions, require further investigation using both experimental models and human clinical studies.

The relationship between environmental exposures and inflammaging is another important area for investigation. Repeated oxidative stress induced by $PM_{2.5}$, ozone, UV radiation, tobacco smoke, and other environmental factors may alter intracellular redox balance and induce DNA damage, mitochondrial dysfunction, and inflammatory signaling. If these responses are not adequately resolved, they may affect age-related ocular surface vulnerability through cellular senescence and changes in tissue repair. Conversely, age-related changes in antioxidant defenses and tissue repair capacity may amplify responses to the same environmental exposures.

Therefore, environmental exposures and inflammaging should be viewed not as a simple unidirectional causal relationship but as interconnected processes potentially mediated

by oxidative stress, cellular senescence, inflammation, and tissue repair. Nevertheless, the extent to which these interactions occur at the human ocular surface remains insufficiently understood. Future studies should integrate environmental exposure levels, age, markers of cellular senescence, and oxidative stress- and inflammation-related tear biomarkers.

1.5. Objectives and Scope of This Review

The aim of this review is to characterize the relationships among environmental exposures, oxidative stress, inflammation, and inflammaging and to provide an integrated discussion of the cellular and molecular mechanisms involved in the onset and progression of ocular surface diseases. Previous studies in environmental ophthalmology have examined associations between individual air pollutants or meteorological conditions and ocular surface symptoms. However, further investigation is warranted into approaches that integrate oxidative stress, inflammatory responses, cellular senescence, and alterations in tear film homeostasis induced by environmental exposures and relate these processes to age-associated pathophysiology [1,3].

First, this review examines major environmental exposures, including $PM_{2.5}$, ozone, Asian dust, VOCs, tobacco smoke, blue light, and UV radiation, with an emphasis on their characteristics and potential effects on the ocular surface. Second, it considers the pathophysiological mechanisms potentially linking environmental exposures to ocular surface injury, focusing on ROS production, antioxidant defense mechanisms, mitochondrial dysfunction, inflammatory signaling, and alterations in epithelial barrier function. Third, it discusses age-related ocular surface vulnerability and responses to environmental exposures from the perspectives of inflammaging, cellular senescence, and SASP.

Furthermore, this review examines oxidative stress-related markers and inflammatory biomarkers in tear fluid, considering their potential utility and limitations in the assessment of ocular surface pathophysiology. Building on this evidence, it compares mechanisms shared across ocular surface diseases, including DED and allergic conjunctivitis, with disease-specific features, and discusses potential preventive and therapeutic strategies combining environmental exposure reduction, preservation of antioxidant defenses, and inflammatory control.

Throughout this review, findings from epidemiological studies, clinical investigations, animal experiments, and cell-based studies are considered separately to distinguish observed associations from experimentally supported mechanisms. Particular emphasis is placed on differentiating established evidence from hypotheses that require further validation regarding the interactions between environmental exposures, cellular senescence, and inflammaging. In this context, epidemiological and clinical studies are considered primarily as evidence of associations between environmental exposures and ocular surface findings, whereas cell-based and animal studies are used to explore potential underlying biological mechanisms. Findings from experimental models are therefore interpreted as supporting biological plausibility rather than establishing causality or clinical relevance in humans. Ultimately, this review aims to provide a framework for understanding ocular surface diseases not solely in terms of localized inflammation or tear abnormalities but as conditions shaped by the interplay among environmental exposures, redox homeostasis, immune responses, and age-related changes.

Despite previous reviews, including those that have comprehensively discussed the role of oxidative stress in various ocular diseases involving both the anterior and posterior segments [4], the present review focuses specifically on the ocular surface and adopts an integrated perspective on environmental exposures and age-related inflammatory changes. In particular, it considers how repeated environmental insults may interact with oxidative stress, mitochondrial dysfunction, cellular senescence, and chronic low-grade inflammation

(inflammaging), potentially contributing to impaired epithelial barrier function, tear film instability, and persistent ocular surface inflammation. By bringing these interconnected processes together, this review aims to provide a framework for understanding the potential contribution of environmental factors to age-related ocular surface vulnerability, while also discussing the implications for tear biomarkers and preventive and therapeutic strategies.

1.6. Literature Search Strategy

A literature search was conducted to identify studies relevant to environmental exposures, oxidative stress, cellular senescence, inflammaging, and ocular surface diseases. The databases searched included [PubMed/MEDLINE and Google Scholar]. Search terms were selected to cover the main topics of this review and included combinations of the following keywords: "ocular surface disease," "dry eye disease," "allergic conjunctivitis," "environmental exposure," "air pollution," "particulate matter," "ultraviolet radiation," "oxidative stress," "reactive oxygen species," "mitochondrial dysfunction," "cellular senescence," "senescence-associated secretory phenotype," and "inflammaging."

Studies were selected based on their relevance to the scope of this review, with particular attention to evidence linking environmental exposures to oxidative stress, inflammatory responses, cellular senescence, and the pathophysiology of ocular surface diseases. Epidemiological and clinical studies were considered to assess associations between environmental factors and ocular surface findings, whereas animal and cell-based studies were included to examine potential underlying molecular and cellular mechanisms. Relevant original research articles and review articles were considered. Reference lists of relevant publications were also examined to identify additional studies. The selection of literature was based on its scientific relevance and contribution to the topics discussed in this review; this search was not intended to constitute a systematic review.

To focus on recent advances and emerging concepts, this review primarily synthesizes literature published over the past decade rather than compiling an exhaustive historical bibliography. Readers seeking a more comprehensive list of foundational studies on ocular oxidative stress and environmental factors are referred to previously published extensive reviews [1,3,4,13].

2. Oxidative Stress and Inflammatory Mechanisms in the Ocular Surface

Understanding the pathophysiology of ocular surface diseases requires an integrated perspective on oxidative stress induced by environmental exposures and tear film abnormalities, together with the subsequent inflammatory responses, cellular injury, and alterations in tissue repair. Oxidative stress not only directly damages cellular components but also contributes to the initiation and persistence of inflammation by modulating intracellular signaling pathways and innate immune responses. Conversely, ROS produced by activated immune and epithelial cells during inflammation may cause further oxidative damage. These reciprocal interactions are considered important mechanisms underlying the development and progression of chronic inflammatory ocular surface diseases, including DED [4,13].

This section reviews the interactions among ROS and reactive nitrogen species (RNS) production, antioxidant defense mechanisms, mitochondrial dysfunction, inflammatory signaling, epithelial barrier function, and immune responses. Understanding these mechanisms provides a foundation for interpreting the ocular surface effects of individual environmental exposures, which are discussed in subsequent sections.

2.1. Production of ROS and Reactive Nitrogen Species (RNS)

ROS and RNS comprise reactive molecules generated through intracellular metabolic and enzymatic reactions. They participate in both physiological intracellular signaling and pathological oxidative and nitrosative stress. Representative ROS include the superoxide anion ($O_2\bullet^-$), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($\bullet OH$), whereas RNS include nitric oxide ($NO\bullet$) and peroxynitrite ($ONOO^-$). These molecules differ in their reactivity, lifetimes, intracellular localization, and molecular targets; therefore, their biological effects should not be regarded as uniform [4,14].

At the ocular surface, the mitochondrial electron transport chain, the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) family, xanthine oxidoreductase, and nitric oxide synthases contribute to ROS and RNS production. In mitochondria, electron leakage from the electron transport chain generates superoxide, which is subsequently converted into hydrogen peroxide by enzymes such as superoxide dismutase (SOD). At appropriate concentrations and in specific intracellular locations, hydrogen peroxide participates in cellular signaling. However, when its production exceeds the capacity of antioxidant systems to eliminate it, oxidative stress may be amplified [4,13,14].

Environmental exposures can alter these endogenous redox processes. For example, reactive gases such as ozone react with lipids and proteins in the tear film, potentially promoting the formation of oxidation products. Transition metals and organic compounds contained in particulate matter may also influence redox reactions and intracellular ROS-generating pathways. Ultraviolet radiation and photochemical stimuli can likewise contribute to ROS generation, depending on the exposure conditions. However, these effects vary according to the composition and concentration of the agents, exposure duration, and experimental conditions. Therefore, environmental factors should not be assumed to induce ocular surface damage through identical mechanisms [2,13].

Excessive ROS and RNS production can cause lipid peroxidation of cellular membranes, oxidative modification of proteins, and nucleic acid damage. Malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE), both generated during lipid peroxidation, are commonly used indicators of oxidative damage. Similarly, 8-hydroxy-2′-deoxyguanosine (8-OHdG) is used to assess oxidative DNA damage. These biomarkers are useful for investigating oxidative stress at the ocular surface; however, an increase in any single marker is insufficient to establish the source of ROS or a causal relationship with disease pathogenesis [4,13,14].

A systematic review and meta-analysis by Navel et al. found that several oxidative stress-related markers were elevated in patients with DED compared with healthy controls, suggesting that a localized oxidative environment may develop in tear fluid, conjunctival cells, and conjunctival tissue [8]. These findings support the potential involvement of oxidative stress in ocular surface disease. Nevertheless, differences in sample types and measurement methods across studies warrant cautious interpretation of the clinical significance of individual biomarkers [8]. Overall, ROS and RNS should be viewed not merely as cytotoxic agents but also as important regulators linking environmental exposures, intracellular metabolism, and inflammatory responses. In ocular surface diseases, it is therefore important to assess not only the amount of oxidant production but also its localization and duration, as well as the balance between oxidant generation and antioxidant defense.

2.2. Antioxidant Defense Mechanisms and Redox Homeostasis at the Ocular Surface

Because the ocular surface is continuously exposed to environmental oxidants, it possesses multiple antioxidant defense mechanisms that regulate the effects of ROS and RNS. These mechanisms include enzymatic antioxidant systems, nonenzymatic antioxidants, and regulatory pathways that modulate gene expression in response to oxidative stress. Coordinated activity among the tear film, corneal and conjunctival epithelia, and lacrimal

glands helps maintain redox homeostasis, thereby preserving cellular function and tissue integrity at the ocular surface [13,14].

Enzymatic antioxidant systems include SOD, catalase (CAT), and glutathione peroxidase (GPx). SOD converts superoxide into hydrogen peroxide, whereas CAT and GPx contribute to the removal of hydrogen peroxide and other peroxides. Glutathione (GSH) is one of the major intracellular reducing agents and works in conjunction with enzymes such as glutathione reductase to maintain the intracellular reducing environment. The tear film also contains components with antioxidant activity, which contribute to the chemical defenses operating at the interface between the external environment and the ocular surface epithelium [4,13,14].

The nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway is an important regulator of antioxidant responses. In response to oxidative stress or electrophilic stimuli, Nrf2 activity is modulated, leading to changes in the expression of multiple genes involved in antioxidant defense and cellular protection. These genes include heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1) [4,13,14]. Although the Nrf2 pathway plays an important role in maintaining cellular redox homeostasis, its effects depend on cell type, stimulus intensity, and exposure duration. Consequently, increased Nrf2 activity should not invariably be interpreted as protective [13,14].

In DED, tear film instability and hyperosmolarity impose stress on ocular surface cells, potentially amplifying oxidative stress and inflammatory responses through reciprocal interactions. The meta-analysis by Navel et al. reported increases in several oxidative stress-related markers, together with reduced CAT activity in some studies [8]. However, changes in antioxidant factors are not uniform and may vary according to disease severity, the presence or absence of Sjögren syndrome, and the type of specimen analyzed. These findings suggest that redox homeostasis at the ocular surface is not determined by a single antioxidant molecule [8].

When antioxidant defenses are insufficient to counterbalance the oxidative burden imposed by environmental exposures, cellular damage may accumulate, potentially activating inflammatory signaling pathways and cell death mechanisms. Conversely, an adequate adaptive defense response may mitigate cellular injury and help maintain tissue homeostasis. Accordingly, understanding the pathophysiology of ocular surface diseases requires assessment not only of increased oxidant levels but also of antioxidant capacity and the adaptive responses that regulate redox balance.

2.3. Mitochondrial Dysfunction and Oxidative Stress

Mitochondria are essential organelles that generate cellular energy and participate in ROS production, intracellular calcium regulation, metabolic signaling, and the regulation of cell death. In ocular surface cells, including corneal epithelial cells, the appropriate regulation of energy metabolism and intracellular signaling is essential for epithelial maintenance, post-injury repair, and responses to external stimuli. Mitochondrial dysfunction may impair electron transport chain efficiency, increase ROS production, alter mitochondrial membrane potential, and disrupt mitochondrial dynamics, thereby compromising cellular redox homeostasis [4,15].

Under physiological conditions, mitochondria-derived ROS are regulated and participate in intracellular signaling. However, persistent mitochondrial dysfunction may lead to excessive ROS production, which can further damage mitochondrial components and establish a self-amplifying cycle of oxidative stress. In addition, molecules released from damaged mitochondria, including mitochondrial DNA, may act as damage-associated molecular patterns (DAMPs) recognized by the innate immune system, potentially trigger-

ing inflammatory responses. Thus, mitochondria are not only a source of oxidative stress but may also play an important role in linking cellular injury to inflammation [4,13,15].

In DED, tear film instability and hyperosmolar stress have been investigated as potential triggers of intracellular stress responses, mitochondrial dysfunction, and inflammation. Hu et al. reviewed the interplay among mitochondrial injury, the accumulation of oxidants, and inflammatory responses in DED and discussed the potential of therapeutic strategies targeting antioxidant defenses [13]. Yang et al. also comprehensively examined the roles of mitochondria in corneal physiology and pathophysiology, highlighting the interactions among mitochondrial redox signaling, cell death, and inflammatory pathways [13,15].

Endoplasmic reticulum stress is another intracellular stress response associated with mitochondrial dysfunction and oxidative stress. Zha et al. reported that PERK–CHOP signaling, which is associated with endoplasmic reticulum stress, contributes to ROS production and nucleotide-binding oligomerization domain-like (NOD-like) receptor pyrin domain-containing 3 (NLRP3) inflammasome activation in an experimental model of DED [16]. These findings suggest that endoplasmic reticulum stress may link oxidative stress to inflammatory signaling. However, further validation using clinical specimens is needed to determine whether the pathways observed in specific experimental models operate similarly across different forms of human DED [16].

Taken together, mitochondrial dysfunction may be positioned as a pathophysiological mechanism linking the amplification of oxidative stress, DAMP-mediated activation of innate immunity, and cell death. Clarifying how environmental exposures affect mitochondrial function and dynamics remains an important research priority for understanding the onset and progression of ocular surface damage.

2.4. Inflammatory Signaling Pathways: NF-κB, MAPK, and the NLRP3 Inflammasome

Inflammatory responses at the ocular surface involve the transmission of signals from receptors that recognize external stimuli or cellular damage to intracellular signaling pathways, resulting in the production of inflammatory mediators and activation of immune cells. Several interconnected pathways participate in this process, including nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and the NLRP3 inflammasome. Although these pathways are essential for physiological defense responses at the ocular surface, their excessive or sustained activation may promote chronic inflammation and tissue damage [17,18].

The NF-κB signaling pathway is a major transcriptional regulatory mechanism that responds to oxidative stress and inflammatory stimuli. Upon activation by inflammatory cytokines, pattern-recognition receptor signaling, or signals associated with cellular injury, NF-κB translocates to the nucleus and regulates the expression of inflammatory cytokines, chemokines, and adhesion molecules. At the ocular surface, changes in the expression of inflammatory mediators, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α), as well as matrix metalloproteinases (MMPs) involved in extracellular matrix degradation, may influence inflammatory responses and epithelial injury [13,17].

ROS contribute to NF-κB pathway activation, although their effects vary depending on the type of stimulus, intracellular localization, and cellular redox state. NF-κB also regulates the expression of molecules involved in innate immune responses, in addition to controlling inflammatory gene expression. Thus, oxidative stress and NF-κB-mediated inflammation should not be considered independent processes; rather, their interactions jointly influence the pathophysiology of ocular surface diseases.

The MAPK signaling pathway comprises three major groups: extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinases (JNK), and p38 MAPK. These kinases respond to external stimuli, oxidative stress, cytokines, and cellular injury, thereby regu-

lating transcription factor activity, inflammatory mediator production, cell proliferation, differentiation, and cell death. At the ocular surface, MAPK activation may contribute to inflammatory responses and epithelial stress responses, while crosstalk with the NF-κB pathway may further modulate inflammation [17].

Nevertheless, NF-κB and MAPK regulate a broad range of cellular functions, and their activation does not necessarily indicate a pathological response. Because these pathways also participate in tissue repair and physiological defense, their roles in ocular surface diseases should be evaluated in consideration of activation intensity, duration, cell type, and disease stage.

The NLRP3 inflammasome is a multiprotein complex that recognizes intracellular danger signals and regulates the maturation and release of inflammatory cytokines. Its principal components are the sensor protein NLRP3, the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD: caspase recruitment domain), and caspase-1. In general, NLRP3 inflammasome activation involves an initial priming process, often mediated by pathways such as NF-κB, that induces the expression of inflammasome components and cytokine precursors, followed by stimuli that promote inflammasome assembly. Activated caspase-1 facilitates the maturation of IL-1β and IL-18, thereby amplifying inflammatory responses. It also contributes to gasdermin D (GSDMD)-mediated changes in plasma membrane permeability and pyroptosis [18,19].

The role of inflammasomes at the ocular surface has been investigated in studies of DED, keratitis, and allergic diseases. Ge et al. reviewed the role of the NLRP3 inflammasome in corneal diseases and discussed the possibility that excessive ROS production, mitochondrial dysfunction, and Toll-like receptor-mediated NF-κB signaling contribute to inflammasome activation in DED [19]. Zha et al. also reported an association among endoplasmic reticulum stress-related PERK–CHOP signaling, ROS production, and NLRP3 inflammasome activation in experimental DED [16,19].

Collectively, NF-κB, MAPK, and the NLRP3 inflammasome link oxidative stress to ocular surface inflammation, though their relative contributions depend on stimulus intensity, cell type, and disease stage [16,17].

2.5. Epithelial Barrier Dysfunction and Cell Death at the Ocular Surface

The corneal and conjunctival epithelia form physical and biological barriers that protect the ocular surface from the external environment. Tight junctions between corneal epithelial cells, cell adhesion structures, plasma membranes, the cytoskeleton, and surface glycoproteins are important for restricting the entry of external agents and maintaining tissue homeostasis. The tear film also contributes to ocular surface lubrication, removal of foreign particles, antimicrobial defense, and maintenance of the epithelial microenvironment. Preservation of these barrier functions and tear film homeostasis is fundamental to ocular surface resistance to environmental exposures [13,20].

When environmental exposures or oxidative stress damage epithelial cell membranes, the cytoskeleton, and intercellular junctions, barrier function may deteriorate. In addition, inflammatory cytokines and MMPs alter intercellular junctions and the extracellular matrix, potentially affecting epithelial permeability and tissue integrity. Such damage may increase susceptibility to external stimuli and promote further irritation and inflammation through tear film instability and irregularities in the epithelial surface.

In DED, tear film instability and hyperosmolar stress place additional stress on the ocular surface epithelium and amplify oxidative stress and inflammation. Hu et al. described how oxidative stress may not only damage cellular membranes and organelles but also contribute to changes in inflammatory signaling and tear film homeostasis [13]. Epithelial barrier dysfunction should therefore be regarded not merely as a consequence of oxidative

stress but also as a potential contributor to disease persistence by increasing susceptibility to external stimuli [13].

When oxidative stress is severe or persistent, cellular adaptive and repair mechanisms may be insufficient to compensate for the damage, potentially leading to cell death. Several forms of cell death have been described, including caspase-mediated apoptosis, necrosis involving plasma membrane disruption and inflammation, and pyroptosis associated with inflammasomes and GSDMD. These forms of cell death differ in their morphological and molecular characteristics and do not have uniform effects on inflammation.

Pyroptosis is particularly relevant because it is an inflammatory form of cell death associated with inflammasome activation and may amplify local inflammation through the release of IL-1β and IL-18. Ge et al. reviewed the association between NLRP3 inflammasome activation, pyroptosis, and inflammatory responses in experimental models of corneal disease. However, findings obtained from corneal injury models should not be directly generalized to chronic DED or ocular surface damage caused by environmental exposures without further supporting evidence [19].

Unlike cell death, cellular senescence is a state in which cells remain viable but undergo changes in proliferative capacity and other cellular functions. Senescent cells secrete inflammatory mediators through the SASP, thereby influencing neighboring cells and the tissue microenvironment and potentially contributing to persistent inflammation and altered tissue repair. Accordingly, ocular surface injury should be evaluated with due consideration of the distinctions among reversible cellular stress, cell death, and cellular senescence.

Overall, epithelial barrier dysfunction and cell death represent processes at the intersection of environmental exposure-induced oxidative stress, inflammatory signaling, and altered tissue repair. Understanding these mechanisms is important for developing therapeutic strategies that combine epithelial protection with inflammatory control.

2.6. Interactions Between Oxidative Stress and Immune Responses

The ocular surface possesses innate immune mechanisms that protect tissues against environmental particles and pathogens and promote repair following injury. Epithelial cells, resident immune cells, and protective factors in the tear film recognize external stimuli and produce inflammatory mediators when necessary. When appropriately regulated in intensity and duration, these responses contribute to the maintenance of tissue homeostasis. However, excessively strong stimuli or inadequate resolution of inflammation may lead to persistent tissue damage and potentially contribute to the development of chronic inflammatory diseases [21].

The interactions between oxidative stress and immune responses can be understood from three main perspectives. First, ROS generated by environmental exposures or cellular injury may influence redox-sensitive signaling pathways and responses mediated by pattern-recognition receptors, potentially promoting the production of inflammatory mediators. Second, activated immune cells, including neutrophils and macrophages, produce ROS and RNS during host defense and inflammatory responses; thus, immune activation itself may increase the oxidative burden. Third, DAMPs released from cells or organelles damaged by oxidative stress may stimulate the innate immune system and further amplify inflammation [4,19].

In DED, epithelial injury, tear film instability, and inflammation are thought to interact and contribute to disease persistence. Rolando et al. emphasized the importance of distinguishing physiological para-inflammation at the ocular surface from pathological responses that may progress to chronic inflammatory disease [21]. Adaptive immune responses to low-level stress may contribute to tissue repair and the maintenance of homeostasis,

whereas stronger or persistent stimuli may lead to cellular injury and amplification of inflammation [21].

In addition to innate immunity, adaptive immunity, particularly T-cell-mediated responses, also contributes to immune activity at the ocular surface. In DED, immune cell activation mediated by inflammatory cytokines and antigen presentation is thought to be associated with epithelial injury and persistent inflammation. Chu et al. reviewed the interplay among signaling pathways, including NF-κB and MAPK, inflammatory cytokines, and immune cell activation in the inflammatory mechanisms of DED [17]. However, the contributions of individual immune cell populations vary according to disease subtype, severity, and stage; ocular surface diseases cannot be fully explained by a single immune pathway [17].

These interactions between oxidative stress and immune responses provide an important conceptual link between environmental exposures and ocular surface diseases. For example, repeated exposure to air pollutants may induce oxidative stress in epithelial cells, potentially activating inflammatory signaling and innate immune responses and thereby amplifying ocular surface inflammation. Conversely, pre-existing inflammation or changes in antioxidant defense capacity may alter susceptibility to the same environmental exposure. Nevertheless, the magnitude and clinical significance of these interactions have not been adequately established for every environmental factor. Experimental findings should therefore be evaluated separately from epidemiological associations.

The interactions between oxidative stress and inflammatory signaling at the ocular surface are illustrated in Figure 3. Overall, oxidative stress and immune responses are physiological defense mechanisms that help maintain ocular surface homeostasis; however, when their regulation is disrupted, they may also amplify tissue damage. An integrated understanding of environmental exposures, redox homeostasis, inflammatory signaling, epithelial barrier function, and immune responses is essential for elucidating the pathophysiology of ocular surface diseases and developing more effective preventive and therapeutic strategies.

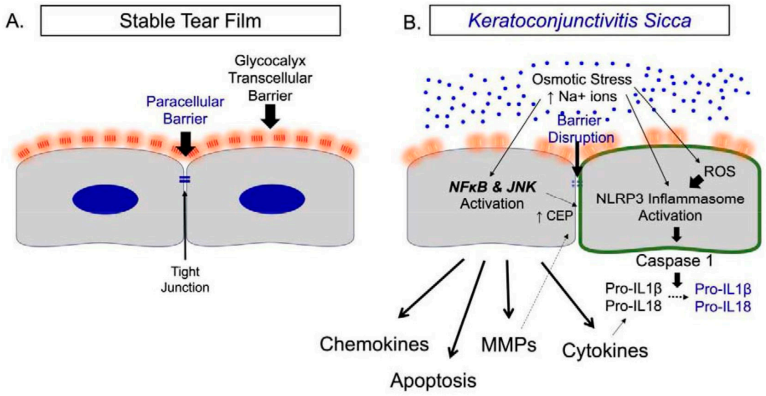


Figure 3. Interactions Between Oxidative Stress and Inflammatory Signaling in the Ocular Surface. Schematic illustration of the interactions between oxidative stress and inflammatory signaling in the ocular surface. Mitochondrial dysfunction and other cellular sources contribute to the generation of reactive oxygen and nitrogen species (ROS/RNS), whereas the Nrf2/antioxidant response element (ARE) pathway regulates cellular antioxidant defenses. Excessive oxidative stress may activate NF-κB, mitogen-activated protein kinase (MAPK), and NLRP3 inflammasome signaling, promoting inflammatory mediator production, epithelial barrier dysfunction, and cell injury. Reciprocal interactions between oxidative stress and inflammation may sustain tissue damage and impair ocular surface homeostasis. Although these interactions are supported by experimental and biological evidence, the relative contribution of individual pathways may vary among ocular surface diseases and has not been fully established in all clinical conditions.

3. Environmental Exposures and Ocular Surface Oxidative Stress

The ocular surface is directly exposed to the external environment and is therefore susceptible to a wide range of environmental factors, including airborne particulate matter, reactive gases, chemical compounds, tobacco smoke, and optical radiation. Although these exposures differ in their physicochemical properties and biological effects, they may affect tear film stability, epithelial barrier function, redox homeostasis, and inflammatory responses. A recent systematic review identified associations between particulate matter exposure and dry eye symptoms, conjunctivitis, and allergic eye diseases across epidemiological studies, animal experiments, and cellular models [3].

However, the strength of evidence linking environmental exposures to ocular surface damage varies among exposure types. For particulate matter, evidence has accumulated from both clinical and experimental studies, whereas some molecular mechanisms associated with ozone and blue light have been investigated primarily in animal models and cultured cells. In addition, for particles such as Asian dust, which contain a complex mixture of mineral and biological components, it is difficult to isolate the effects of individual constituents. Accordingly, clinical associations observed in humans should be distinguished from molecular mechanisms demonstrated experimentally when evaluating the effects of each environmental exposure.

This section reviews major environmental exposures and examines their potential associations with oxidative stress, inflammation, epithelial barrier dysfunction, and cellular responses at the ocular surface.

3.1. Particulate Matter ($PM_{2.5}$) and Ocular Surface Inflammation

$PM_{2.5}$ refers to fine particulate matter with an aerodynamic diameter of 2.5 μm or less. It originates from various sources, including traffic emissions, industrial activities, and fossil fuel combustion. Its chemical composition varies according to the source and geographical location and may include metals, organic compounds, and combustion-derived constituents. Because the ocular surface is directly exposed to these particles, $PM_{2.5}$ is an important environmental factor in the investigation of air pollution-associated ocular surface disorders.

In a systematic review of studies published between 2009 and 2024, Iqbal et al. synthesized findings from 102 studies and characterized the associations between particulate matter exposure and ocular surface dysfunction [3]. In vitro studies have reported oxidative stress, inflammatory responses, and apoptosis following particulate matter exposure, whereas animal studies have demonstrated reduced tear production and ocular surface damage, with findings resembling dry eye disease. Clinical studies have also reported subjective symptoms, including itching, burning, and irritation, as well as findings associated with dry eye disease, conjunctivitis, and allergic eye diseases [3].

One of the major proposed mechanisms underlying $PM_{2.5}$-induced ocular surface damage is oxidative stress. Redox-active metals and organic constituents in particulate matter may influence intracellular ROS production. Excessive ROS generation can induce lipid peroxidation, oxidative protein modification, DNA damage, and mitochondrial dysfunction, potentially compromising epithelial cell viability and repair capacity. Furthermore, activation of inflammatory signaling pathways in response to oxidative stress may promote cytokine production and cell death, thereby amplifying ocular surface inflammation [2,3].

$PM_{2.5}$ may also affect the physical barrier function of the corneal epithelium. Sun et al. investigated the effects of $PM_{2.5}$ collected from the ambient environment on the corneal epithelial barrier [22]. Their findings indicated that particulate matter exposure was associated with corneal epithelial barrier disruption and implicated Wnt/β-catenin signaling in this process. These findings suggest that environmental particulate matter may

affect not only oxidative stress and inflammatory responses but also the structural integrity and maintenance mechanisms of the epithelium [22].

Furthermore, particulate matter exposure may influence tear homeostasis and immune responses at the ocular surface. Reduced tear production, tear film instability, epithelial damage, and inflammation may interact to increase sensitivity to external stimuli and contribute to persistent ocular surface symptoms. However, the effects of $PM_{2.5}$ depend on its chemical composition, concentration, exposure duration, and coexistence with other environmental factors. Therefore, it would be inappropriate to assume that all particulate matter acts through a single, universally applicable mechanism.

3.2. Ozone Exposure and Oxidative Injury

Ozone (O_3) is a highly oxidizing gas generated in the troposphere primarily through photochemical reactions involving nitrogen oxides and VOCs. Unlike particulate matter, ozone is a reactive gas that can interact directly with tear film and ocular surface constituents, potentially initiating oxidative reactions. Accordingly, ozone-associated ocular surface injury may involve chemical reactions with tear film components, oxidative stress in epithelial cells, and subsequent inflammatory responses.

Ozone may react with biological membrane lipids and proteins to generate oxidation products. These reactions alter the lipid environment of the ocular surface and epithelial cell function, potentially contributing to oxidative stress and inflammation. However, the concentrations, exposure durations, and amounts reaching ocular tissues under experimental conditions differ substantially from those encountered in the ambient environment. Caution is therefore required when extrapolating experimental findings to everyday ozone exposure.

Tian et al. investigated the effects of repeated ozone exposure on the cornea using mouse corneas and human corneal epithelial cells [23]. In the ozone-exposed group, corneal stromal thinning and increased epithelial thickness were observed, accompanied by impaired epithelial barrier function. Corneal tissues also exhibited inflammatory cell infiltration and increased levels of 3-nitrotyrosine, suggesting enhanced nitrative stress. Furthermore, activation of pathways involving NLRP3, caspase-1, and GSDMD was reported, suggesting that pyroptosis, an inflammatory form of programmed cell death, may contribute to ozone-induced corneal injury [23].

These experimental findings suggest that ozone may induce structural and inflammatory changes in the cornea. However, the extent to which these effects occur under real-world ambient exposure conditions remains unclear. 3-Nitrotyrosine may therefore serve as a candidate marker for further investigation of ozone-associated nitrative stress.

3.3. Asian Dust and Desert Dust: Particles, Metals, and Bioaerosols

Asian dust consists predominantly of mineral particles originating from arid and semiarid regions of East Asia and transported over long distances by wind. During transport, these particles acquire or mix with air pollutants, metals, organic compounds, and microorganisms or their derived components, depending on regional and meteorological conditions. Consequently, the health effects of Asian dust may depend not only on the physical irritation caused by the particles themselves but also on their chemical composition and associated pollutants.

Because the ocular surface is directly exposed to Asian dust, exposure may cause conjunctival irritation, foreign body sensation, tearing, and redness. Asian dust events also coincide with exposure to other environmental factors, including airborne pollen, making it important to investigate the effects of combined exposures. Ko et al. examined the association between Asian dust events and acute conjunctivitis and reported an association

between Asian dust exposure and inflammatory ocular surface symptoms. This study provides clinical evidence that Asian dust may adversely affect ocular surface health [24].

Potential mechanisms underlying the effects of Asian dust include not only mechanical irritation but also oxidative stress and inflammation induced by particle-associated constituents. Transition metals in the particles influence redox reactions and potentially promote ROS production. In addition, biological components adhering to particle surfaces and coexisting air pollutants affect innate immune responses and allergic inflammation. However, the chemical composition of Asian dust varies according to its source and transport pathway, making it difficult to identify any single constituent as the principal cause of ocular surface damage in all settings.

Regarding the relationship between Asian dust and allergic conjunctivitis, Mimura et al. investigated the effects of Asian dust exposure in mice sensitized to Japanese cedar pollen [25]. Compared with exposure to Japanese cedar pollen alone, combined exposure to Japanese cedar pollen and Asian dust exacerbated clinical findings, including conjunctival redness and edema, and was associated with increased serum IgE levels and inflammatory cell infiltration. These findings suggest that Asian dust may not only act as a direct ocular surface irritant but also exacerbate pre-existing allergic inflammation [25].

Potential mechanisms underlying this exacerbation include effects on the epithelial barrier, activation of innate immune responses, and modulation of immune responses to allergens. However, because this study was conducted using an animal model, further research is needed to determine the magnitude of the exacerbating effects of Asian dust on allergic conjunctivitis in humans and to clarify the underlying molecular mechanisms. Detailed characterization of the chemical and biological properties of the particles is also required to determine the contributions of biological and metal-containing components.

3.4. VOCs and Indoor Air Pollution

VOCs comprise a broad group of organic chemicals that readily evaporate at room temperature. They include substances with diverse chemical structures and toxicological properties, such as formaldehyde, benzene, and toluene. Potential indoor sources include building materials, furniture, paints, adhesives, cleaning agents, disinfectants, and combustion products. Indoor VOC concentrations vary according to emission sources and ventilation conditions; consequently, exposure depends on the characteristics of individual environments, including workplaces, healthcare facilities, and homes.

Yang et al. reviewed the relationship between indoor air pollution and ocular diseases, summarizing evidence concerning particulate matter, volatile and semivolatile organic compounds, heavy metals, combustion products, tobacco smoke, and their associations with ocular surface disorders [5]. The review identified chronic inflammation, oxidative injury, and disruption of tight junctions as potential mechanisms underlying ocular surface damage associated with indoor air pollution [5].

The effects of VOCs on the ocular surface depend on the specific compound, its concentration, exposure duration, and coexistence with other pollutants. Irritant substances such as formaldehyde may act on sensory nerves and epithelial tissues of the ocular surface, potentially causing irritation, burning, and tearing. At sufficiently high concentrations or with prolonged exposure, these substances also affect epithelial cell function and inflammatory responses. However, acute ocular irritation should be distinguished from the development of chronic ocular surface disease mediated by oxidative stress.

A systematic review and meta-analysis investigating the ocular irritant effects of formaldehyde reported an association between exposure and ocular irritation symptoms. However, substantial heterogeneity existed among the included studies, and exposure concentrations and assessment methods were not uniform [26]. Accordingly, the reported

irritant effects of a specific VOC cannot automatically be generalized to the oxidative toxicity of all VOCs or to the risk of developing ocular surface disease.

Indoor environments contain not only VOCs but also $PM_{2.5}$, tobacco smoke, combustion products from cooking, low humidity, and inadequate ventilation. These environmental factors affect tear evaporation, tear film stability, epithelial barrier function, and inflammatory responses through different pathways. Therefore, investigations of indoor environmental conditions and ocular surface disease should consider not only individual chemical compounds but also ventilation conditions and coexisting pollutants.

3.5. Tobacco Smoke and Oxidative Damage to the Ocular Surface

Tobacco smoke is a complex environmental exposure containing numerous chemicals, reactive oxygen and nitrogen species, particulate components, and combustion products. The ocular surface may be exposed to tobacco smoke through both active smoking and secondhand smoke. Tobacco smoke may disrupt ocular surface homeostasis through both the direct effects of irritants and indirect effects mediated by oxidative stress and inflammation.

Li et al. investigated the mechanisms by which tobacco smoke pollution induces dry eye-like changes using mice and cultured human corneal epithelial cells [27]. Ocular surface damage following tobacco smoke exposure was observed, and experiments using lipid-soluble tobacco smoke constituents also examined responses associated with oxidative stress and inflammation. These findings provide experimental evidence that tobacco smoke can act directly on the ocular surface and induce pathological changes associated with dry eye disease [27].

Tobacco smoke-induced oxidative stress may result from both the direct effects of oxidizing substances in the smoke and alterations in intracellular ROS production. Excessive ROS may induce lipid peroxidation, oxidative protein modification, and mitochondrial dysfunction, potentially impairing the maintenance and repair of corneal and conjunctival epithelia. In addition, activation of inflammatory signaling pathways and induction of cell death may compromise epithelial barrier function, potentially increasing susceptibility to further environmental insults.

Tobacco smoke may also affect tear film integrity and conjunctival function. Maintaining ocular surface health requires not only the aqueous and lipid layers of the tear film but also mucins produced by conjunctival goblet cells. If tobacco smoke exposure alters tear film stability or the epithelial microenvironment, increased tear evaporation and frictional stress may exacerbate dry eye symptoms. However, these effects vary according to exposure levels, smoking status, pre-existing ocular surface disease, and other environmental conditions. Further clinical studies are therefore needed to clarify the contribution of individual mechanisms.

Tobacco smoke is also a component of indoor air pollution and may coexist with other pollutants, including particulate matter and VOCs. In a review of indoor environments and dry eye disease, Li et al. summarized associations between tobacco smoke, particulate matter, volatile compounds, low humidity, ventilation conditions, and changes in ocular surface oxidative injury, inflammation, and tear film characteristics [28]. However, the strength of evidence varies among environmental factors, and more standardized exposure measurements are needed to accurately assess the contribution of individual exposures [28].

3.6. Blue Light and Visible-Light-Induced Oxidative Stress

Blue light generally refers to the short-wavelength region of visible light. It is emitted by sunlight, light-emitting diode (LED) lighting, and digital device screens. The biological effects of light depend not only on wavelength but also on irradiance, exposure duration, spectral distribution, and the amount of light reaching ocular tissues. Accordingly, exposure

associated with everyday screen use should be distinguished from the high-intensity light irradiation employed in experimental studies.

Recent studies have investigated the effects of blue light on the ocular surface, focusing on oxidative stress, inflammatory signaling, and corneal epithelial repair. Jin et al. investigated corneal epithelial dysfunction following exposure to LED-derived blue light and reported the involvement of ROS-mediated Protein kinase B:PKB (AKT) and ribosomal protein S6 kinase (AKT/S6K) signaling [29]. This study suggests that blue light may influence corneal epithelial cellular responses under specific irradiation conditions [29].

Furthermore, Ge et al. investigated the role of the NLRP3 inflammasome in blue light-induced corneal epithelial injury. Experiments using mice and cultured human corneal epithelial cells demonstrated delayed corneal epithelial repair, shortened tear film breakup time, and exacerbated epithelial damage following blue light exposure [30]. Increased responses involving NLRP3, ASC, caspase-1, IL-1β, and IL-18 were also reported. Inhibition of NLRP3 was associated with reductions in oxidative stress and cellular injury [30].

These studies suggest that blue light may affect the corneal epithelium through oxidative stress and inflammatory signaling under specific experimental conditions. However, the irradiation conditions used in experiments are not equivalent to the light exposure typically received from digital device screens during everyday use. Therefore, experimentally demonstrated corneal epithelial injury should not be interpreted as evidence that ordinary screen use causes ocular surface damage of a comparable magnitude.

Furthermore, the association between digital device use and ocular discomfort may involve multiple factors beyond light exposure, including reduced blink frequency, incomplete blinking, sustained exposure near work, and environmental conditions such as humidity and airflow. Thus, investigations of ocular surface symptoms associated with screen use should distinguish the direct phototoxic effects of blue light from changes in tear evaporation and blinking behavior associated with digital device use.

3.7. Ultraviolet Radiation and Ocular Surface Phototoxicity

UV is classified into UVA, UVB, and UVC according to wavelength. Most UV radiation reaching the Earth's surface is UVA, although some UVB also reaches the surface. In contrast, UVC is almost entirely absorbed by the atmosphere under normal environmental conditions. The amount of UV radiation reaching the ocular surface varies according to solar elevation, season, latitude, cloud cover, surrounding reflective surfaces, outdoor activity, and the use of eye protection.

UV radiation can alter intracellular redox status through photochemical reactions. UVA contributes to ROS generation primarily through photosensitized reactions, whereas UVB may induce oxidative stress and inflammatory responses in addition to directly damaging nucleic acids and proteins [1,4]. Depending on the wavelength and exposure level, these effects affect ocular surface tissues, including the corneal epithelium and conjunctiva, potentially leading to cellular injury and altered tissue repair [1].

Potential mechanisms of UV-induced ocular surface injury include excessive ROS production, lipid peroxidation, DNA damage, and activation of inflammatory signaling pathways. Intense UV exposure can cause acute corneal epithelial injury, whereas long-term exposure may be associated with structural changes in the conjunctiva and cornea. However, the extent and nature of UV-induced damage depend on wavelength and exposure conditions; therefore, the effects of UVA and UVB should not be treated as identical [1].

UV exposure assessment may incorporate estimates of individual exposure based on outdoor activity as well as biomarkers such as conjunctival ultraviolet autofluorescence (CUVAF). CUVAF has been investigated as an indicator of UV-associated changes in conjunctival tissue. However, it may reflect cumulative exposure and individual variability

rather than only recent UV exposure. Consequently, CUVAF alone has limitations as a direct measure of UV exposure over a specific period or of the magnitude of oxidative stress.

Although both UV radiation and blue light are associated with optical exposure, they differ in wavelength, photochemical reactions, tissue penetration characteristics, and the strength of available evidence regarding ocular injury. Clinical evidence concerning UV-associated ocular surface phototoxicity and long-term tissue changes has accumulated, whereas recent findings on the molecular mechanisms of blue light are more dependent on specific experimental conditions. Distinguishing these forms of optical exposure is therefore important for appropriate risk assessment.

3.8. Combined and Cumulative Environmental Exposures

In real-world settings, the ocular surface is rarely exposed to a single environmental factor in isolation. Instead, multiple factors, including particulate matter, ozone, VOCs, tobacco smoke, UV radiation, low humidity, and airflow, may act simultaneously or sequentially. Under these conditions, the effects of individual exposures are not necessarily additive; interactions among them may modify their overall impact on the ocular surface.

For example, in environments with high levels of air pollution, $PM_{2.5}$ may coexist with gaseous pollutants such as ozone. Indoors, VOCs, tobacco smoke, combustion products from cooking, low humidity, and inadequate ventilation may occur concurrently. These factors affect tear film stability, epithelial barrier function, redox homeostasis, and inflammatory responses through different pathways. The combined effects of multiple environmental stimuli may therefore make it more difficult to maintain ocular surface homeostasis [3,5,28].

The interaction between oxidative stress and inflammation is important for understanding the pathophysiology of combined environmental exposures. When multiple environmental factors increase ROS production beyond the capacity of antioxidant defense systems, lipid peroxidation, protein oxidation, and mitochondrial dysfunction may be exacerbated. Subsequent activation of inflammatory signaling pathways, together with impairment of epithelial barrier function and cellular repair, may increase ocular surface vulnerability to further environmental insults. However, whether multiple exposures exert genuinely synergistic effects depends on the combination of substances, their concentrations, the sequence of exposure, and exposure duration. These interactions therefore require specific experimental and clinical evaluation.

The effects of environmental exposures also vary according to individual biological characteristics. Aging, pre-existing dry eye disease, allergic inflammation, reduced tear secretion, and differences in antioxidant defense capacity may influence ocular surface responses to environmental stimuli. In particular, alterations in cellular repair capacity and the presence of chronic inflammation associated with aging may prolong the effects of repeated environmental exposures. Nevertheless, longitudinal studies specifically investigating interactions between environmental exposures and inflammaging at the ocular surface remain insufficient. Mechanistic hypotheses should therefore be distinguished from findings that have been clinically established.

A comprehensive assessment of combined exposures requires more than measuring the concentration of a single pollutant. It should also consider individual living environments, time spent indoors and outdoors, season, meteorological conditions, and exposure duration. Integrating tear biomarkers of oxidative stress, inflammatory cytokines, tear film stability, and ocular surface epithelial findings provide a more detailed understanding of the relationship between environmental exposures and biological responses.

Future research should combine epidemiological studies measuring multiple environmental factors simultaneously, experimental studies using standardized exposure conditions, and intervention studies evaluating environmental improvements. Such an approach

may help distinguish the independent effects of individual exposures from their interactions and provide a more accurate assessment of environmental factors contributing to the onset and progression of ocular surface diseases. Table 1 summarizes the major environmental exposures, their potential mechanisms, and their effects on the ocular surface.

Table 1. Environmental Exposures, Potential Mechanisms, and Effects on the Ocular Surface.

Environmental Exposure	Potential Mechanisms	Potential effects on the Ocular Surface	Evidence and Limitations
Particulate matter ($PM_{2.5}$ and PM_{10}) [3,22,31]	Oxidative stress, inflammatory signaling, epithelial barrier disruption	Tear film dysfunction, corneal epithelial injury, ocular irritation and inflammation	Supported by clinical observational and experimental studies; causal relationships and exposure–response patterns require further investigation
Ozone (O_3) [23]	Oxidative and nitrative stress, NLRP3 inflammasome-related signaling	Corneal epithelial injury, impaired barrier integrity and inflammation	Mechanistic evidence includes animal and human corneal epithelial cell experiments; direct translation to real-world human exposure requires caution
Asian dust and desert dust [3]	Particle-induced irritation, oxidative stress and inflammatory responses; effects may depend on particle composition	Conjunctival irritation and potentially exacerbated ocular surface inflammation	Clinical associations have been reported, but effects may vary with particle composition, co-exposures and meteorological conditions
Volatile organic compounds (VOCs) and indoor air pollution [28,32]	Chemical irritation, oxidative stress and inflammatory responses	Dry eye symptoms, tear film instability and epithelial dysfunction	Evidence varies by compound and exposure level; individual VOC-specific causal effects remain incompletely characterized
Tobacco smoke [28,32]	Oxidative stress, ocular surface irritation and inflammatory responses	Dry eye symptoms and possible impairment of ocular surface homeostasis	Clinical and review evidence supports an association, although exposure intensity, smoking type and confounding factors affect interpretation
Blue light and visible light [32]	Potential photochemical oxidative stress, depending on wavelength, intensity and exposure duration	Potential ocular surface effects under specific exposure conditions	Evidence for clinically meaningful direct injury to the human ocular surface from ordinary screen exposure remains limited
Ultraviolet radiation (UV) [32]	Photochemical reactions, ROS generation and cellular damage	Ocular surface phototoxicity, depending on wavelength and dose	Biological plausibility is well established for UV-related ocular injury, but effects depend on the ocular structure, wavelength and exposure dose
Combined and cumulative environmental exposures [3,28,32]	Interactions among oxidative stress, inflammation, tear film instability and epithelial barrier dysfunction	Potential exacerbation or persistence of ocular surface symptoms and disease	Evidence is emerging; pollutant mixtures, personal exposure levels and long-term cumulative effects remain insufficiently characterized

4. Inflammaging and Age-Related Vulnerability of the Ocular Surface

The ocular surface is a functionally integrated system comprising the cornea, conjunctiva, lacrimal glands, meibomian glands, and tear film. It provides protection against external insults while maintaining the transparency, lubrication, and homeostasis required for normal ocular function. However, aging induces structural and functional changes

in these tissues, potentially compromising tear film stability, epithelial barrier integrity, immune responses, and tissue repair capacity. Consequently, older individuals become more susceptible to ocular surface diseases, particularly dry eye disease, and may exhibit delayed recovery from environmental insults [10,33].

A key concept for understanding these age-related changes is *inflammaging*, which refers to the persistent, low-grade chronic inflammation associated with aging. This process is closely linked to cellular senescence, oxidative stress, mitochondrial dysfunction, and age-related changes in the immune system. At the ocular surface, cellular senescence and the development of a proinflammatory microenvironment have also been implicated in epithelial barrier disruption and impaired tear homeostasis [10,12].

This section outlines the molecular basis of inflammaging and examines age-related changes in antioxidant defense mechanisms, cellular senescence and the SASP, mitochondrial function, interactions with environmental exposures, and the mechanisms responsible for ocular surface repair and homeostasis.

4.1. The Concept and Molecular Basis of Inflammaging

Inflammaging is generally understood as a state of persistent, low-level inflammatory signaling that develops with aging, even in the absence of overt acute infection or tissue injury. Unlike the transient inflammatory response to infection, inflammaging is characterized by inadequate regulation of inflammatory initiation and resolution, resulting in a sustained proinflammatory tissue environment. Contributing factors include cellular senescence, the accumulation of DAMPs, alterations in immune cell function, oxidative stress, and declining intracellular quality control mechanisms [9–11,33].

At the ocular surface, aging affects multiple components, including the corneal and conjunctival epithelia, lacrimal glands, and meibomian glands. A systematic review and meta-analysis examining the relationship between aging and dry eye disease reported not only impaired ocular surface integrity and reduced tear film stability but also inflammatory cell infiltration, changes associated with cellular senescence, and the accumulation of 8-OHdG, a marker of oxidative DNA damage [10]. These findings suggest that age-related ocular surface vulnerability involves changes in the overall tissue microenvironment rather than merely a reduction in tear volume.

At the molecular level, NF-κB-mediated inflammatory gene expression, inflammatory mediators such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF), and NLRP3 inflammasome-associated responses contribute to the development of an age-related inflammatory environment. Mitochondria-derived ROS and extracellularly released DAMPs further amplify inflammatory signaling [9–11,33].

However, these molecular pathways are unlikely to be activated to the same extent in every ocular surface tissue or patient. Inflammaging at the ocular surface should therefore be considered a multifactorial process involving interactions among changes in tear secretion, the tear film lipid layer, epithelial barrier integrity, sensory innervation, and local immune regulation.

4.2. Age-Related Changes in Antioxidant Defense Mechanisms

The ocular surface is routinely exposed to environmental stimuli, including ultraviolet radiation, oxygen, airborne particulate matter, ozone, smoke, and microbial components. Antioxidant defense mechanisms that limit ROS generation and eliminate reactive oxidants are therefore essential for maintaining epithelial homeostasis. Major antioxidant systems include enzymatic defenses, such as SOD, catalase, and glutathione peroxidase, as well as intracellular reducing systems centered on glutathione.

In the aging ocular surface, changes in the ability to process damaged proteins, DNA, and organelles are also important, in addition to increased oxidative stress. When oxidative damage occurs continuously and antioxidant defenses, DNA repair, and cellular quality control mechanisms such as autophagy are insufficient, intracellular damage may accumulate, potentially contributing to epithelial dysfunction and cellular senescence.

Recent studies using corneal epithelial cells have demonstrated that sustained hyperosmolar stress, which is relevant to dry eye pathophysiology, can induce cellular senescence accompanied by increased ROS production, mitochondrial dysfunction, DNA damage, metabolic abnormalities, and impaired mitophagy [34]. Although this study did not directly investigate aging itself, it provides important mechanistic insights into the relationship between stress responses and cellular senescence at the ocular surface.

Oxidative stress acts not only as an indicator of inadequate antioxidant defense but also as a signaling mechanism that can induce inflammation. ROS-mediated changes in intracellular signaling may promote inflammatory gene expression, while the oxidative environment generated during inflammation may further exacerbate cellular injury. This reciprocal amplification can establish a vicious cycle. In the aging ocular surface, such interactions increase susceptibility to epithelial dysfunction, even in response to relatively mild environmental stimuli.

Nevertheless, it cannot be assumed that antioxidant enzyme activity or antioxidant concentrations decline uniformly across all ocular surface compartments with age. The cornea, conjunctiva, tear film, lacrimal glands, and meibomian glands differ in their patterns of oxidative exposure and protective mechanisms. Accordingly, age-related changes should be evaluated separately for each tissue and compartment.

4.3. Cellular Senescence, SASP, and Chronic Inflammation

Cellular senescence is a state of persistent cell cycle arrest that can be induced by DNA damage, oxidative stress, telomere shortening, and mitochondrial dysfunction. Although senescence serves a physiological role by limiting the uncontrolled proliferation of damaged cells, the accumulation of senescent cells within tissues may adversely affect neighboring cells and the surrounding tissue environment.

One of the defining features of senescent cells is the SASP. SASP components include inflammatory cytokines such as IL-6 and IL-8, chemokines, and MMPs. The composition of the SASP varies according to cell type and the stimulus that induces senescence. Although the SASP can facilitate the clearance of senescent cells by immune cells, its prolonged activity may contribute to chronic inflammation, extracellular matrix remodeling, and dysfunction of neighboring cells.

Cellular senescence at the ocular surface has also been demonstrated in studies using human tissue. Tomioka et al. compared conjunctival epithelia from middle-aged and older individuals and reported increased expression of the senescence marker p16^INK4a in the older group, accompanied by reduced positivity for the proliferation-associated marker Ki67 and the stem cell-associated marker p63. In addition, p16 inhibitor of nuclear kinase 4a ($p16^{INK4a}$)-positive cells exhibited reduced expression of zonula occludens-1 (ZO-1), a protein involved in epithelial tight junctions [12]. These findings suggest that age-related cellular senescence is associated with changes in conjunctival epithelial regenerative capacity and barrier function.

Further studies have investigated the functional significance of cellular senescence and the SASP at the ocular surface using human cornea-derived cells and mouse models. Kitazawa et al. demonstrated that radiation-induced senescent cells acquired a SASP capable of impairing epithelial barrier function, in addition to exhibiting reduced proliferative capacity and increased p16 expression. In aged mice, senescent cells accumulated at

the ocular surface, accompanied by chronic inflammation and impaired epithelial barrier function. In a dry eye model induced by lacrimal gland excision, aged mice developed more pronounced pathological changes, including corneal opacity, than young mice. The findings also suggested that senolytic treatment targeting senescent cells may alleviate these lesions [11].

Despite these findings, the evidence supporting a direct contribution of cellular senescence to human ocular surface diseases remains limited. Human tissue studies have demonstrated age-related changes in senescence-associated markers and epithelial barrier-related proteins, whereas evidence linking SASP-mediated inflammation to functional impairment has been derived mainly from cell-based and animal models. SASP-related mediators, including IL-6, IL-8, and matrix metalloproteinases (MMPs), may contribute to the local inflammatory environment, extracellular matrix remodeling, and impaired epithelial homeostasis. In addition, oxidative stress may promote cellular senescence through DNA damage and mitochondrial dysfunction, while ROS and inflammatory mediators released by senescent cells may further amplify oxidative and inflammatory signaling. This reciprocal interaction provides a plausible mechanism linking oxidative stress, cellular senescence, and chronic inflammation at the ocular surface. However, the extent to which these SASP-mediated pathways contribute to the onset or progression of specific ocular surface diseases in humans has not yet been fully established.

These studies indicate that cellular senescence is not merely a marker of aging but may also functionally contribute to changes in the inflammatory microenvironment of the ocular surface. However, the beneficial effects of senescent cell clearance have been demonstrated primarily in experimental models. Further clinical studies are required to establish the efficacy and safety of senolytic approaches for age-related ocular surface diseases in humans.

4.4. Interactions Among Mitochondrial Dysfunction, DNA Damage, and Cellular Senescence

Mitochondria are involved not only in cellular energy production but also in the regulation of redox balance, intracellular signaling, cell death, and inflammatory responses. When mitochondrial function is impaired by aging or chronic environmental stress, adenosine triphosphate (ATP) production may decline and ROS generation may increase, compromising cellular function. Furthermore, inadequate clearance of damaged mitochondria may contribute to the persistence of oxidative stress and inflammatory signaling.

In the ocular surface epithelium, mitochondrial dysfunction, oxidative DNA damage, and cellular senescence may interact in a mutually reinforcing manner. For example, increased ROS can damage both nuclear and mitochondrial DNA and activate cell cycle arrest pathways, including p53–p21 and p16– retinoblastoma protein (Rb), through the DNA damage response. Persistent activation of these pathways may reduce cellular proliferation and renewal capacity. Conversely, mitochondrial dysfunction and impaired quality control in senescent cells further increase ROS production and the release of inflammatory mediators.

This interaction is also supported by experimental models of hyperosmolar stress relevant to dry eye disease. Zhang and Fan reported that sustained hyperosmolar stress in human corneal epithelial cells induced cellular senescence accompanied by mitochondrial dysfunction, DNA damage, metabolic abnormalities, and impaired mitophagy [34]. Mitophagy is a selective form of autophagy that removes damaged mitochondria; its impairment may therefore lead to the accumulation of dysfunctional mitochondria.

Taken together, these mechanisms suggest that, in the aging ocular surface, environmental insults or tear film hyperosmolarity may cause prolonged cellular injury when mitochondrial quality control is compromised. This may delay recovery and favor the persistence of cellular senescence and chronic inflammation. Nevertheless, further studies are needed to determine the extent to which mitochondrial dysfunction directly drives

age-related ocular surface changes and to clarify the temporal sequence of these pathways in human disease.

4.5. Synergistic and Interactive Effects of Environmental Exposures and Inflammaging

Age-related ocular surface vulnerability is likely to arise not only from intrinsic aging processes but also from their interactions with long-term environmental exposures. Particulate matter such as $PM_{2.5}$, ozone, tobacco smoke, VOCs, and ultraviolet radiation may induce oxidative stress and inflammation at the ocular surface. A systematic review of particulate matter exposure reported associations between environmental pollution and ocular surface inflammation, epithelial injury, and dry eye symptoms based on both experimental and clinical studies [3].

In younger individuals, cellular damage induced by environmental stimuli may be repaired relatively rapidly through antioxidant defenses, epithelial renewal, and tear-mediated clearance. In contrast, the aging ocular surface, in which cellular senescence has progressed and antioxidant defenses and repair mechanisms have changed, may exhibit prolonged injury following exposures of comparable intensity. Repeated activation of inflammatory signaling by recurrent exposures may promote the development of a proinflammatory microenvironment mediated by the SASP, potentially increasing susceptibility to subsequent environmental insults and establishing a vicious cycle.

Conceptually, this interaction can be summarized as a sequence of (1) increased ROS production induced by environmental exposures, (2) DNA and mitochondrial damage, (3) induction of cellular senescence and the SASP, (4) chronic inflammation and impaired epithelial barrier function, and (5) increased susceptibility to external stimuli. However, this sequence represents a pathophysiological model integrating multiple experimental and clinical findings; not every step has been directly demonstrated in the human ocular surface.

The effects of environmental exposures are also likely to depend on factors beyond exposure intensity and duration, including age, underlying diseases, contact lens wear, medication use, tear secretion, and meibomian gland function. When multiple exposures occur simultaneously, their effects may not simply be additive and could potentially interact synergistically. Nevertheless, studies quantitatively evaluating these interactions in clinical settings remain limited.

Future research should therefore integrate environmental exposure measurements with clinical ocular surface assessments and simultaneously evaluate markers of oxidative stress, cellular senescence, inflammatory cytokines, and epithelial barrier function. Such an approach may help distinguish the contributions of age-related vulnerability from those of environmental exposures and identify the exposure conditions that are particularly important for patients with specific underlying characteristics.

4.6. Age-Related Changes in Ocular Surface Repair and Homeostasis

Figure 4 illustrates the proposed mechanisms underlying ocular surface vulnerability associated with environmental exposures and inflammaging. Ocular surface homeostasis is maintained by multiple mechanisms, including epithelial cell renewal, regeneration mediated by limbal stem cells, tear secretion, suppression of tear evaporation by meibomian gland-derived lipids, maintenance of surface wettability by mucins, neural reflexes, and local immune regulation. Aging may affect these mechanisms to varying degrees and reduce the overall functional reserve of the ocular surface [33,35].

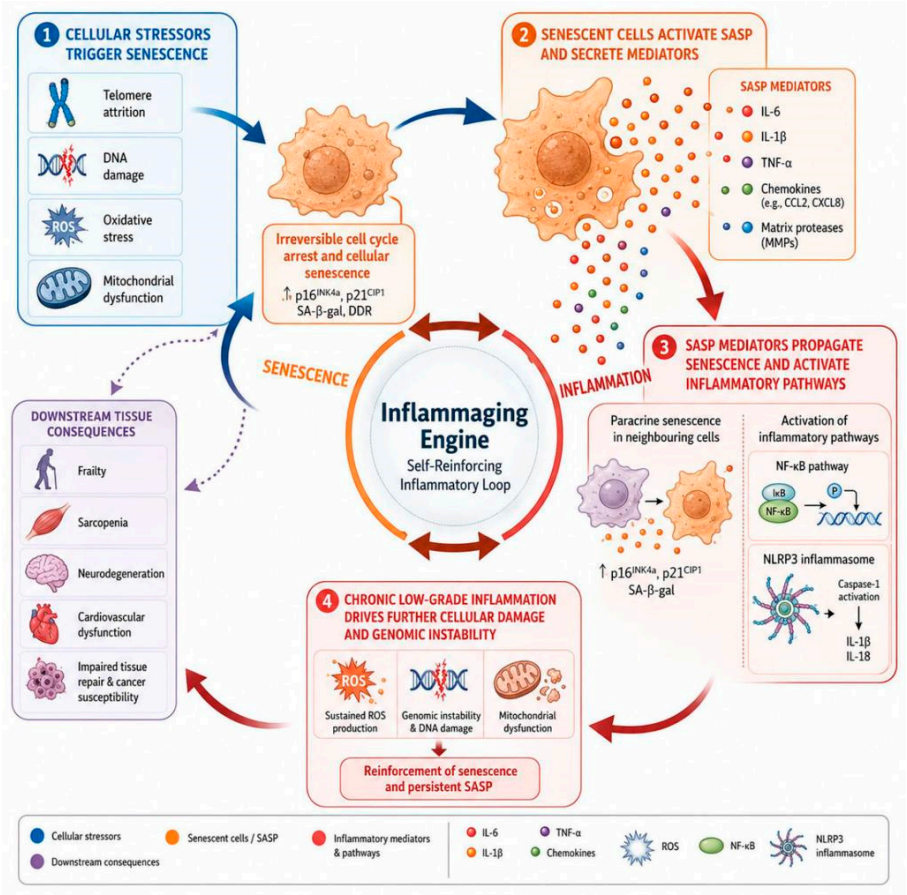


Figure 4. Environmental Exposures and Inflammaging in Age-Related Ocular Surface Vulnerability. Conceptual model illustrating the interactions between environmental exposures, cellular senescence, and inflammaging in the ocular surface. Age-related impairment of antioxidant defenses, mitochondrial dysfunction, and DNA damage may promote cellular senescence and the senescence-associated secretory phenotype (SASP). The resulting chronic inflammatory environment, together with repeated environmental insults, may compromise epithelial repair and tissue homeostasis, increasing ocular surface vulnerability. The relative contributions of these processes may vary according to age, exposure history, and individual susceptibility. This figure represents an integrative conceptual model based on available experimental and clinical observations. Although individual components of these pathways have been reported, their interactions and overall contribution to age-related ocular surface diseases remain to be fully validated in humans.

In the aging conjunctival epithelium, increased expression of cellular senescence markers has been reported alongside reduced expression of proliferation-associated and stem cell-associated markers [12]. These changes may impair the cellular proliferation and tissue remodeling required after epithelial injury. Altered expression of proteins involved in intercellular adhesion may also compromise barrier integrity, potentially allowing environmental insults and inflammatory mediators to exert greater effects within the tissue.

Tear film and secretory gland function are also important in understanding age-related ocular surface disorders. Changes in lacrimal gland function may affect tear volume and the availability of protective tear components, whereas structural and secretory changes in the meibomian glands compromise maintenance of the tear film lipid layer. Furthermore, age-related changes in corneal sensation and blink reflexes alter tear distribution and responses to ocular surface irritation. In combination, these changes destabilize the tear film and increase its osmolarity, further promoting epithelial injury and inflammation [10,35].

Importantly, age-related alterations in ocular surface homeostasis cannot necessarily be explained by abnormalities in a single structure or function. Tear secretion may remain

relatively preserved despite abnormalities in the lipid layer or epithelial barrier. Conversely, ocular surface symptoms occur even without a marked reduction in tear volume, owing to inflammation, altered sensory function, or cellular senescence. Comprehensive assessment of age-related ocular surface disorders should therefore incorporate tear volume, tear film stability, epithelial damage, meibomian gland function, ocular surface inflammation, and patient-reported symptoms.

Potential future therapeutic strategies include approaches targeting cellular senescence or the SASP, preserving mitochondrial function and antioxidant defenses, improving tear homeostasis, and reducing environmental exposures. However, senescent cell-targeting therapies, including senolytic treatments, require further evaluation to establish their long-term safety at the ocular surface, their effects on normal tissue repair, and their clinical efficacy in humans.

In summary, age-related ocular surface vulnerability likely reflects the interplay of altered tear function, changes in antioxidant defenses, cellular senescence, chronic inflammation, and reduced repair capacity. Inflammaging provides an important conceptual framework for understanding these interconnected changes. Elucidating the interactions between aging and environmental exposures may contribute to the development of preventive strategies and personalized treatments for ocular surface diseases.

5. Tear Oxidative Stress and Biomarkers of Ocular Surface Disease

Tears are not merely responsible for maintaining ocular surface hydration; they are also important biological fluids that protect the cornea and conjunctiva from environmental insults through antioxidants, antimicrobial proteins, and immunomodulatory factors. Tear composition is influenced by lacrimal and meibomian gland function, the condition of the ocular surface epithelium, local inflammation, aging, and environmental factors such as air pollution and UV radiation. Accordingly, the measurement of tear molecules has attracted considerable attention as a noninvasive approach to assessing oxidative stress and inflammation at the ocular surface [13,36].

DED is a multifactorial disorder characterized by interrelated tear film instability, increased tear osmolarity, ocular surface inflammation, and epithelial damage. Oxidative stress may not only damage cellular components, including lipids, proteins, and nucleic acids, but also amplify inflammatory signaling, further compromising ocular surface homeostasis. Consistent with this possibility, alterations in lipid peroxidation products and oxidative stress-related molecules have been reported in tears and ocular surface tissues from patients with DED [8,13].

However, several challenges must be addressed before tear biomarkers can be routinely applied in clinical practice. These include establishing the relationship between biomarker levels and disease activity, standardizing specimen collection, storage, and analytical procedures and defining clinically meaningful diagnostic thresholds [37]. This section outlines the antioxidant functions of tears and the mechanisms underlying redox homeostasis, reviews oxidative stress-related biomarkers and inflammatory cytokines, and examines their associations with DED and allergic conjunctivitis. It also discusses methodological standardization and the potential applications of tear biomarkers in environmental exposure assessment and personalized medicine.

5.1. Antioxidant Functions of Tears and Redox Homeostasis

Tears consist of water, electrolytes, lipids, mucins, proteins, and other constituents. They provide lubrication, facilitate the removal of foreign particles, protect against microorganisms, and maintain the integrity of the ocular surface epithelium. Tear proteins such as lactoferrin, lysozyme, and lipocalin primarily contribute to antimicrobial defense and tissue

protection, whereas antioxidant-related molecules, including SOD, glutathione-associated enzymes, and peroxiredoxins, contribute to the maintenance of redox balance. Because the protein composition of tears reflects aspects of ocular surface homeostasis, changes in this composition may provide useful information about disease-associated alterations [38].

Redox homeostasis is maintained by a balance between the generation of ROS and the antioxidant defense mechanisms that eliminate or regulate them. ROS also participate in physiological intracellular signaling; therefore, their presence is not necessarily harmful. However, when ROS production exceeds the capacity of antioxidant defenses, oxidative damage can occur to cellular components, including lipid membranes, proteins, and DNA. At the ocular surface, tear film instability, increased tear osmolarity, UV radiation, and particulate matter may contribute to oxidative stress [13].

In DED, tear hyperosmolarity and inflammation may promote ROS production, potentially leading to epithelial cell injury and increased production of inflammatory mediators. Conversely, oxidative damage may compromise the epithelial barrier and further aggravate tear film instability. Thus, oxidative stress and inflammation may interact bidirectionally, sustaining and amplifying the pathological processes underlying ocular surface disease.

Nevertheless, an increase in antioxidant-related molecules in tears does not necessarily indicate enhanced protective capacity. Such an increase may also represent a compensatory response to oxidative stress, with upregulated expression or secretion of antioxidant enzymes. Accordingly, antioxidant status should not be interpreted on the basis of the concentration of an individual molecule alone. Rather, oxidative damage products, multiple antioxidant indicators, tear volume, and clinical findings should be evaluated together [8,13].

5.2. Oxidative Stress-Related Biomarkers in Tears

Oxidative stress-related biomarkers in tears can be broadly classified into two categories: molecules generated as a consequence of oxidative damage and indicators of the defense systems that maintain redox balance. The former include lipid peroxidation products, oxidized proteins, and molecules associated with oxidative DNA damage, whereas the latter include antioxidant enzyme activities and total antioxidant capacity. A systematic review and meta-analysis of DED reported a tendency toward elevated levels of lipid peroxidation products and certain other oxidative stress-related indicators in patients with DED. However, findings are not necessarily consistent across all biomarkers because specimen characteristics, analytical methods, and patient populations differ among studies [8].

5.2.1. Lipid Peroxidation Products

Lipid peroxidation is a process in which cellular membrane lipids and lipids present in tears undergo oxidation mediated by ROS and other reactive species. Representative biomarkers include MDA and 4-HNE. These compounds are generated in association with the oxidation of polyunsaturated fatty acids and are used to assess the extent of oxidative damage.

Elevated levels of lipid peroxidation-related biomarkers have been reported in tears and ocular surface tissues from patients with DED. Increases in MDA and 4-HNE may indicate that oxidative stress affects the lipid environment and epithelial function of the ocular surface [8,13]. However, tear lipids also include components derived from the meibomian glands. Consequently, measured levels may be influenced not only by oxidative reactions but also by lipid secretion, tear volume, and tear film stability. Lipid peroxidation products should therefore not be regarded as standalone diagnostic markers; they are better interpreted in conjunction with clinical findings and other oxidative stress-related indicators.

5.2.2. Protein Oxidation Products

Proteins can be affected by ROS and reactive nitrogen species, resulting in the oxidation of amino acid residues, alterations in protein structure, and cross-link formation. Protein oxidation can be assessed using markers such as protein carbonyls, nitrated proteins, and 3-nitrotyrosine (3-NT). These molecules serve as indicators of oxidative and nitrative stress [13].

Tear proteins contribute to antimicrobial defense, immunomodulation, epithelial protection, and tear film stabilization. Therefore, not only changes in protein abundance but also oxidative modifications and functional alterations may influence the protective capacity of the ocular surface. Tear proteomic analyses have also revealed changes in inflammatory proteins and proteins associated with oxidative stress responses in DED [38].

However, changes in the concentration of a specific protein must be distinguished from evidence that the protein has undergone oxidative modification. Proteomic measurements of protein abundance and analytical methods that directly detect oxidative modifications assess different biological phenomena and should not be interpreted interchangeably.

5.2.3. Biomarkers of Oxidative DNA Damage

8-OHdG is a representative biomarker associated with oxidative DNA damage and is used to assess nucleic acid damage caused by oxidative stress. At the ocular surface, ROS-induced DNA damage may contribute to impaired cellular function and cellular senescence. Assessing the extent of oxidative damage may therefore help elucidate the underlying disease mechanisms [13].

However, when 8-OHdG is measured in tears, the result does not necessarily reflect damage occurring exclusively at the local ocular surface. Its concentration may be influenced by release into tears, contamination with cell-derived material, and specimen processing. Consequently, caution is required when directly attributing tear 8-OHdG levels to DNA damage in ocular surface tissues. The diagnostic utility of tear 8-OHdG also requires further validation for specific diseases and analytical methods.

5.2.4. Antioxidant Capacity and Redox Balance

In addition to measuring oxidative damage products, evaluating antioxidant defense mechanisms is important. Representative indicators include the activities of antioxidant enzymes, such as SOD, GPx, and catalase, as well as total antioxidant capacity (TAC). These measures can help characterize the capacity of tears to defend against oxidative challenges.

A meta-analysis of DED studies reported not only increases in certain oxidative stress-related indicators but also decreases in the activities of some antioxidant enzymes. However, changes in antioxidant markers are not necessarily unidirectional and may vary according to disease phenotype, severity, and specimen collection methods [8]. Simultaneous assessment of increased oxidative damage products and impaired antioxidant defenses may therefore provide a more comprehensive evaluation of redox status than any single biomarker.

Future studies should investigate panels combining lipid peroxidation products, antioxidant enzyme activities, TAC, and other relevant indicators and evaluate their associations with clinical findings and tear film function. Such integrated assessments help stratify DED phenotypes from the perspective of oxidative stress.

5.3. Inflammatory Cytokines and Chemokines in Tears

Inflammatory cytokines and chemokines in tears are promising candidate biomarkers for evaluating local immune responses at the ocular surface. These molecules are produced by epithelial cells, immune cells, and other cell types and regulate inflammatory responses, immune cell recruitment, and tissue repair. In DED, alterations in the composition of tear

cytokines and chemokines have been reported, and some of these changes are associated with clinical findings and disease pathophysiology [39].

Representative proinflammatory cytokines include interleukin (IL)-1β, IL-6, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and IL-17. IL-1β and TNF-α contribute to the amplification of inflammatory responses, whereas IL-6 participates in the regulation of inflammation and immune responses. IFN-γ and IL-17 are associated with inflammatory responses involving adaptive immunity. Among chemokines, C-C motif chemokine ligand 2 (CCL2), CCL3, CCL4, and CXCL8: C-X-C motif chemokine ligand 8 (CXCL8: IL-8) have attracted attention because they may contribute to immune cell recruitment and the persistence of local inflammation [39].

Nevertheless, changes in these mediators vary according to disease characteristics and patient background. Although increases in multiple tear cytokines have been reported in patients with DED, some factors decrease or show no statistically significant changes. Tear cytokine profiles also differ between Sjögren syndrome-associated DED and non-Sjögren DED [40]. Accordingly, changes in a single cytokine should not be used as a universal indicator of ocular surface inflammation or disease severity.

MMP-9 in tears has also gained clinical relevance as an indicator associated with inflammation-related extracellular matrix degradation and epithelial barrier disruption. MMP-9 detection may assist in the assessment of ocular surface inflammation. However, a positive result is not specific to any single disease and should be interpreted in conjunction with clinical findings [36].

In allergic conjunctivitis, IL-4, IL-5, and IL-13 are important mediators associated with T helper 2 (Th2)-type immune responses and represent potential biomarkers of allergic inflammation. Although DED and ocular allergy share some symptoms and inflammatory molecular changes, they differ in their underlying immune pathways and clinical characteristics. Analyzing combinations of cytokines and chemokines therefore help characterize the pathophysiological features of these two conditions in greater detail [36].

Future studies should measure not only proinflammatory cytokines but also anti-inflammatory factors, molecules involved in epithelial protection, and oxidative stress-related indicators. Such an integrated approach may help characterize not only the intensity of inflammation but also its regulatory status and relationship with epithelial damage.

5.4. Associations Between Oxidative Stress Biomarkers and Dry Eye Disease and Allergic Conjunctivitis

In DED, tear film instability and hyperosmolarity impose stress on the ocular surface epithelium, potentially leading to reciprocal amplification of inflammation and oxidative stress. A systematic review and meta-analysis of oxidative stress-related biomarkers reported a tendency toward elevated levels of lipid peroxidation products, including MDA and 4-HNE, in patients with DED. In contrast, changes in antioxidant enzymes varied according to the biomarker and study population, indicating that a uniform redox profile is not observed in all patients [8].

These findings support a role for oxidative stress in the pathophysiology of DED. However, elevated oxidative stress-related biomarkers in tears do not necessarily establish oxidative stress as the direct cause of the disease. Oxidative damage products also increase as a consequence of inflammation or epithelial injury. Longitudinal and interventional studies are therefore needed to clarify causal relationships. Furthermore, DED encompasses diverse pathophysiological phenotypes, including aqueous-deficient disease, evaporative disease, and forms associated with systemic disorders. The utility of oxidative stress-related biomarkers should consequently be investigated separately across relevant disease phenotypes [13].

In allergic conjunctivitis, activation of inflammatory cells and the production of inflammatory mediators also affect redox status. Tear IL-4, IL-5, and IL-13 are associated with allergic inflammation, whereas IL-1β, TNF-α, IFN-γ, and IL-17 may also change in other ocular surface disorders, including DED [36]. Combining oxidative stress-related biomarkers with inflammatory cytokines therefore helps us investigate the relationship between allergic inflammation and oxidative damage at the ocular surface.

Nevertheless, further clinical validation is needed to determine how accurately tear MDA, 4-HNE, 8-OHdG, and related biomarkers reflect disease activity or treatment response in allergic conjunctivitis. At present, these molecules are more appropriately regarded as candidate indicators for investigating disease mechanisms than as established diagnostic biomarkers.

Furthermore, correlations between tear biomarkers and clinical parameters, including subjective symptoms, tear film breakup time, corneal and conjunctival staining, and tear secretion, are not necessarily strong. In DED, subjective symptoms diverge from objective clinical findings, and molecular biomarkers similarly reflect different aspects of the disease [39]. Tear biomarkers should therefore complement rather than replace conventional clinical assessments, particularly in the stratification of disease phenotypes and the evaluation of treatment responses.

5.5. Analytical Methods, Standardization, and Clinical Validity of Tear Biomarkers

Because tears can be collected using relatively noninvasive procedures, they are suitable specimens for studies requiring repeated measurements and for monitoring treatment over time. However, differences in collection methods and sample preparation can alter specimen volume and composition, compromising the comparability of measurements. A scoping review examining the methodology of tear biomarker research found that capillary collection and Schirmer strips were widely used, but substantial variability existed among studies in collection, processing, and analytical procedures [37].

Capillary collection allows tears to be collected directly and may minimize stimulation during sampling. However, the volume obtained is often small, and collection can be time-consuming. Schirmer strips are convenient in clinical practice, but their use may induce reflex tearing during tear absorption. In addition, cellular components and proteins adsorbed onto the strips affect analytical results. Thus, the choice of collection method is not merely a technical consideration; it may also influence the biological components ultimately measured. The method should therefore be selected according to the objectives of the study [37].

After collection, storage temperature, storage duration, the number of freeze–thaw cycles, centrifugation, extraction solvents, and dilution before analysis may also influence measured values. When tear volume is limited, evaporation during collection and sample dilution may have particularly substantial effects on concentration estimates. It is therefore important to document and, where possible, standardize the time of collection, collection method, sample volume, processing procedures, storage conditions, and analytical methods.

Available analytical techniques include enzyme-linked immunosorbent assays (ELISAs), multiplex immunoassays, mass spectrometry-based proteomic analyses, and metabolomic analyses. ELISA is suitable for the quantitative assessment of specific molecules, although the range of analytes that can be measured is limited. Multiplex assays enable simultaneous measurement of multiple cytokines; however, detection limits and inter-assay differences require careful consideration, particularly when analyte concentrations are low. Proteomic analyses enable the comprehensive exploration of numerous proteins, but candidate biomarkers must subsequently be validated in independent populations to establish their reproducibility and clinical utility [37].

International reporting guidelines published in 2025 emphasized the importance of appropriately reporting specimen collection, storage, sample preparation, analytical procedures, and data normalization to improve the reproducibility and transparency of tear research [41]. Such standardization is essential not only for comparing findings across studies but also for translating biomarkers into clinical practice.

When evaluating clinical validity, at least three distinct concepts should be considered:

Analytical validity: Whether the analytical method can quantify the target molecule accurately and reproducibly.

Clinical validity: Whether the measured value is associated with disease presence, phenotype, severity, prognosis, or other clinically relevant outcomes.

Clinical utility: Whether using the measurement improves diagnosis, treatment selection, patient monitoring, or other aspects of clinical management.

The discovery of a candidate biomarker does not establish all three of these properties. Future research should include prospective studies using standardized analytical procedures, validation of reproducibility in independent populations, establishment of diagnostic thresholds, and assessment of the added value of biomarkers beyond existing clinical tests [42].

Moreover, because many tear biomarkers lack strict disease specificity and vary across assay platforms, establishing standardized protocols and reference ranges in independent cohorts is essential prior to clinical implementation [37,41,42].

Tear biomarkers associated with oxidative stress, inflammation, and ocular surface dysfunction are summarized in Table 2. These biomarkers provide insights into the underlying pathophysiological mechanisms of ocular surface diseases, although their clinical utility and diagnostic value vary among biomarkers.

Table 2. Tear Biomarkers of Oxidative Stress, Inflammation, and Ocular Surface Dysfunction.

Biomarker Category	Representative Biomarkers	Potential Biological Significance	Evidence and Limitations
Lipid peroxidation [8,39]	Malondialdehyde (MDA), 4-hydroxy-2-nonenal (4-HNE), hexanoyl-lysine (HEL)	Reflect lipid oxidative damage and may be associated with tear-film instability and ocular surface epithelial injury	Increased levels of MDA and 4-HNE have been reported in dry eye disease (DED); HEL findings are less consistent
Reactive oxygen species and oxidative damage [8,39]	Reactive oxygen species (ROS), hydrogen peroxide (H_2O_2), oxidative DNA damage markers	Indicate redox imbalance and potential oxidative injury to ocular surface cells	Assays and sample types vary; some markers are better established in experimental models than in routine clinical practice
Antioxidant defense [8,39]	Superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), total antioxidant capacity	Reflect antioxidant defense and the balance between oxidant production and antioxidant capacity	Results may differ according to disease subtype, sampling methods, and assay conditions; directions of change are not uniformly consistent
Pro-inflammatory cytokines [27,36,39]	IL-1α, IL-1β, IL-6, TNF-α, IFN-γ, IL-17	Reflect inflammatory activation and immune responses associated with ocular surface disease	Reported in DED and ocular allergy; levels may overlap between diseases and are not independently diagnostic
Allergy-associated cytokines [36]	IL-4, IL-5, IL-13	Reflect type 2 immune responses relevant to allergic conjunctivitis	Potentially informative in allergic inflammation, but clinical interpretation depends on disease phenotype and concurrent treatment
Chemokines and inflammatory mediators [36,39]	IL-8/CXCL8, CCL2 and other chemokines	May reflect inflammatory-cell recruitment and local immune activation	Findings vary across studies, and no single chemokine is a universally validated marker of disease severity

Table 2. *Cont.*

Biomarker Category	Representative Biomarkers	Potential Biological Significance	Evidence and Limitations
Matrix remodeling and epithelial injury [36,39]	Matrix metalloproteinase-9 (MMP-9)	Reflects inflammatory activity and tissue-remodeling processes at the ocular surface	MMP-9 is used in some clinical settings, but its performance depends on the clinical context and testing method
Tear-film and epithelial homeostasis [36,40]	Mucins (MUC1, MUC2, MUC4, MUC5AC, MUC16), epidermal growth factor (EGF)	Reflect tear-film mucin-layer integrity, epithelial protection, and tissue maintenance	Changes have been reported in ocular surface disorders, but expression and clinical relevance vary by disease
Tear metabolomic profile [39]	Selected lipid and non-lipid metabolites	May help characterize metabolic alterations and distinguish specific DED subtypes	Promising for disease stratification, but further validation is required before routine clinical use
Methodological considerations [37]	Collection method, sample volume, storage, assay platform, normalization	Influence the reliability and comparability of measured tear biomarkers	Standardized collection, processing, reporting, and clinical validation remain important unmet needs

5.6. Environmental Exposure Assessment Using Tears and the Potential for Personalized Medicine

Because tears are located at the interface between the ocular surface and the external environment, they represent a promising biological specimen for evaluating the biological effects of environmental exposures. Exposure to $PM_{2.5}$, ozone, tobacco smoke, and ultraviolet radiation may induce oxidative stress and inflammatory responses. By combining measurements of oxidative damage products, antioxidant-related molecules, and inflammatory cytokines in tears, it may be possible to characterize ocular surface responses to environmental stimuli from multiple perspectives [13].

However, identifying specific environmental exposures based solely on tear biomarkers is challenging. Oxidative stress-related indicators, such as MDA and 4-HNE, may be altered not only by environmental pollution but also by aging, systemic diseases, medications, local inflammation, and tear film instability. Therefore, tear analysis should not be used in isolation to identify exposure sources. Instead, biomarker measurements should be interpreted in conjunction with information on individual living environments, exposure timing, outdoor activities, occupations, and meteorological and air pollution data.

In the future, longitudinal integration of tear biomarkers with environmental monitoring data may enable the assessment of individual ocular surface responses to specific exposures and differences in individual susceptibility. For example, repeated measurements of oxidative stress-related indicators and inflammatory cytokines in tears before and after exposure, together with clinical assessments such as tear film breakup time and corneal and conjunctival staining, may help characterize the temporal changes associated with environmental stimuli.

From the perspective of personalized medicine, tear biomarkers eventually support patient stratification into phenotypes such as oxidative stress-dominant, inflammation-dominant, and aqueous tear-deficient subtypes, allowing treatment strategies to be tailored to individual profiles. However, these classifications currently represent research frameworks rather than established diagnostic categories. Clinical trials are needed to determine whether biomarker-guided treatment selection leads to better outcomes than conventional approaches based on symptoms and ocular surface findings.

Although tear collection is relatively noninvasive, the volume available for analysis is limited, and differences in collection procedures and analytical methods affect the results. For implementation in personalized medicine, standardization of analytical methods will be essential, alongside careful consideration of turnaround time, cost, reproducibility, and the added value of biomarker measurements for clinical decision-making [37,42].

Overall, oxidative stress-related indicators and inflammatory biomarkers in tears offer promising tools for understanding the molecular mechanisms underlying ocular surface diseases and evaluating responses to environmental exposures and changes during treatment. Future research should integrate oxidative damage products, antioxidant defense factors, cytokines and chemokines, and the tear proteome with standardized clinical data and environmental exposure information. Developing such integrated approaches will be an important step toward more precise pathophysiological classification of ocular surface diseases and the implementation of personalized medicine.

6. Ocular Surface Diseases Associated with Oxidative Stress and Environmental Exposures

Ocular surface diseases arise from abnormalities in interconnected tissues and functions, including those of the tear film, cornea, conjunctiva, eyelids, and meibomian glands. These tissues are particularly susceptible to environmental influences because they are directly exposed to air pollutants, UV radiation, allergens, tobacco smoke, and dry air. Recent systematic reviews have reported associations between PM, air pollution, and ocular conditions such as dry eye disease, conjunctivitis, and allergic eye diseases [3,43]. Environmental exposures also exacerbate pre-existing disease by altering ocular surface barrier function and local immune responses, rather than acting as independent triggers alone [32].

Oxidative stress is an important pathophysiological mechanism that may link these diverse conditions. Excessive generation of ROS and alterations in antioxidant defenses can damage cellular components, including membrane lipids, proteins, and DNA, while activating inflammatory signaling pathways. These processes compromise the epithelial barrier and delay tissue repair [13]. Nevertheless, each ocular surface disease has distinct pathophysiological characteristics, and oxidative stress alone cannot explain the full spectrum of clinical manifestations.

This section reviews the effects of oxidative stress and environmental exposures on ocular surface diseases, focusing on dry eye disease, allergic conjunctivitis, corneal epithelial injury, and chronic inflammatory ocular surface disorders. Common mechanisms across these conditions and disease-specific features are also discussed.

6.1. Dry Eye Disease

DED is a multifactorial ocular surface disorder characterized by the loss of tear film homeostasis. Tear film instability, increased osmolarity, ocular surface inflammation, epithelial damage, and alterations in neurosensory function interact in its pathogenesis. Oxidative stress has attracted attention as a potential mechanism linking these pathological changes [13].

Tear film instability can produce localized desiccation and hyperosmolarity at the ocular surface, placing stress on epithelial cells. This may increase ROS production and inflammatory signaling, potentially resulting in lipid peroxidation, oxidative protein modifications, and mitochondrial dysfunction. Oxidative damage may, in turn, compromise epithelial barrier integrity and tear film stability, thereby sustaining inflammation. This self-amplifying interaction provides an important model for understanding the chronicity of DED [13].

Environmental exposures act as external factors that promote this vicious cycle. A systematic review integrating preclinical and clinical studies reported associations between exposure to particulate matter, including $PM_{2.5}$ and PM_{10}, and changes in ocular surface oxidative stress, inflammation, cell death, and tear secretion [3]. In addition, recent reviews of indoor environmental conditions have identified tobacco smoke, combustion products generated during cooking, volatile organic compounds, low humidity, and inadequate

ventilation as factors associated with tear film instability, alterations in meibomian gland function, and impairment of goblet cells and the mucin layer [28].

However, the strength of the association between environmental exposures and DED may vary according to the type, intensity, and duration of exposure, as well as individual characteristics such as age and underlying disease. Furthermore, associations observed in observational studies do not, by themselves, establish that a specific exposure directly causes DED. Prospective studies combining environmental measurements with standardized ocular surface assessments are therefore needed [32].

In addition to conventional management, including artificial tears and anti-inflammatory treatment, approaches aimed at reducing environmental exposures and targeting antioxidant defenses are under investigation. Although experimental studies have reported promising findings for antioxidants and mitochondria-targeted therapies, adequately powered comparative clinical trials are needed to establish their clinical efficacy and appropriate indications [13]. At present, oxidative stress should therefore be regarded as an important component of DED pathophysiology, while clinical assessment and management should continue to be guided by established clinical findings.

6.2. Allergic Conjunctivitis

Allergic conjunctivitis is an inflammatory ocular surface disease caused by immune responses to allergens such as pollen, house dust mites, and animal-derived antigens. Typically, IgE-mediated mast cell activation and the release of inflammatory mediators, including histamine, produce itching, conjunctival hyperemia, tearing, and conjunctival edema. With repeated allergen exposure, eosinophils, T cells, and other immune cells also contribute to persistent inflammation. Increasing attention has been given to the concept that allergic conjunctivitis comprises a group of conditions with distinct immunological endotypes, rather than representing a single uniform immune response [44].

Although environmental pollutants are distinct from the allergens that directly trigger allergic conjunctivitis, they may alter ocular surface defense mechanisms and amplify responses to allergens. Exposure to PM, ozone, and nitrogen oxides induce oxidative stress and inflammatory signaling in epithelial cells and alter epithelial barrier permeability. These changes could facilitate allergen penetration into the epithelium and intensify local immune responses [43,44].

A systematic review published in 2026 examined associations between allergic conjunctivitis and particulate matter, multiple air pollutants, pollen, and indoor and occupational exposures [44]. However, exposure assessment, disease diagnosis, and study populations differed among the included studies. The findings should therefore not be interpreted as indicating that a specific pollutant has the same effect in all patients.

Oxidative stress is a potential mechanism linking allergic inflammation with epithelial injury. ROS may alter epithelial stress responses and influence inflammatory pathways, such as NF-κB, as well as the production of epithelial-derived immunomodulatory factors. Conversely, cellular activation and the release of inflammatory mediators during allergic inflammation may also alter redox status. Environmental exposure-related oxidative stress and allergen-induced immune responses may therefore interact and amplify one another.

Disruption of the ocular surface epithelial barrier also plays an important role in allergic conjunctivitis pathogenesis. Alterations in epithelial tight junctions and in the glycocalyx and membrane-associated mucins covering the cell surface may weaken protection against external antigens [45]. Such barrier dysfunction may arise as a consequence of inflammation but may also promote further allergen penetration, thereby contributing to persistent inflammation.

Clinically, in addition to controlling immune responses with antiallergic eye drops, supportive measures include reducing exposure during periods of high pollen counts, removing particles deposited on the ocular surface, and improving indoor environmental conditions. However, therapies directly targeting oxidative stress have not been established as standard treatments for allergic conjunctivitis. Future studies should integrate oxidative stress biomarkers, epithelial barrier indicators, and allergy-associated cytokines to clarify how environmental exposures influence disease pathophysiology and treatment responses.

6.3. Ocular Surface Epithelial Injury and Disruption of Corneal Epithelial Homeostasis

The corneal epithelium serves as the first line of defense against the external environment while maintaining corneal transparency. Its physical and chemical defense mechanisms include epithelial tight junctions, adherens junctions, cell-surface mucins, and continuous renewal of corneal epithelial cells. Disruption of these mechanisms facilitate the entry of foreign particles and irritants, increasing susceptibility to inflammation and corneal epithelial injury.

Experimental studies using $PM_{2.5}$ and PM_{10} have provided important insights into environmentally induced corneal epithelial injury. Niu et al. reported that $PM_{2.5}$ exposure impaired corneal epithelial defense mechanisms and altered the expression of tight junction-associated proteins and thrombospondin 1 (THBS1) [31]. In a study using $PM_{2.5}$ collected from the ambient environment, exposure altered corneal epithelial cell organization and microvillar structure and reduced the levels of cell adhesion-associated proteins, including E-cadherin and ZO-1 [22].

Studies of PM_{10} exposure have also demonstrated reductions in tight junction-associated proteins and mucins, together with impaired barrier function, in human corneal epithelial cells and mouse corneas. Furthermore, the mitochondria-targeted antioxidant Plastonequinonyl-decyl-triphenylphosphonium (SKQ1) was reported to ameliorate some of these changes under experimental conditions [46]. These findings support the possibility that oxidative stress contributes to particulate matter-induced epithelial injury. However, beneficial effects observed in experimental models cannot automatically be extrapolated to preventive or therapeutic efficacy in humans.

Ozone is another environmental factor that affects the corneal epithelium. Studies using mice and cultured corneal epithelial cells have shown that ozone exposure compromises corneal barrier integrity and may involve inflammatory mechanisms, including nitrative stress and pathways associated with the NLRP3 inflammasome [23]. These findings suggest that environmental oxidants may not only directly damage cells but also amplify tissue injury through signaling pathways involved in inflammation and cell death.

Corneal epithelial homeostasis depends not only on cell survival but also on proliferation, migration, differentiation, and re-epithelialization of injured areas. Persistent oxidative stress may alter intracellular metabolism and mitochondrial function, potentially impairing cellular responses required for tissue repair. In addition, increased production of inflammatory mediators and matrix-degrading enzymes may alter the extracellular environment and further impede epithelial regeneration.

Collectively, these findings suggest that oxidative stress, inflammation, disruption of intercellular adhesion, and impaired repair mechanisms are interconnected in corneal epithelial injury. Future studies examining the type and concentration of environmental exposures, recovery time after exposure, effects of repeated exposure, and individual differences in antioxidant defenses help establish risk assessment approaches and preventive strategies for environmentally induced corneal injury.

6.4. The Role of Oxidative Stress in Chronic Inflammatory Ocular Surface Diseases

Chronic inflammatory ocular surface diseases are characterized not only by persistent inflammation but also by epithelial barrier disruption, extracellular matrix remodeling, and altered secretory function. Representative conditions include vernal keratoconjunctivitis, atopic keratoconjunctivitis, chronic blepharitis, and meibomian gland dysfunction (MGD). Although these disorders differ in their clinical manifestations and immunological backgrounds, oxidative stress and inflammation may interact to sustain tissue injury [13,45].

6.4.1. Chronic Allergic Keratoconjunctivitis

In vernal keratoconjunctivitis and atopic keratoconjunctivitis, recurrent immune responses can cause chronic inflammation of the conjunctiva and cornea. Severe cases involve corneal epithelial damage, erosions, and tissue remodeling. Epithelial cells serve not only as a physical barrier but also produce cytokines and chemokines that regulate local immune responses. When the epithelial barrier is compromised, antigens and irritants may penetrate tissues more readily, potentially intensifying inflammation [45].

Oxidative stress induced by environmental pollutants may contribute to this self-amplifying process. PM and diesel exhaust particles induce oxidative stress in ocular surface epithelial cells and promote the production of inflammatory mediators. In environments where pollen and particulate matter coexist, pollutants also amplify responses to allergens [3,44].

However, the severity of chronic allergic keratoconjunctivitis cannot be explained by oxidative stress alone. Th2-type immune responses, mast cell and eosinophil activation, epithelial-derived cytokines, and tissue remodeling all contribute to disease progression. Oxidative stress should therefore be understood as one component of a multifactorial pathophysiological process.

6.4.2. Chronic Blepharitis and Meibomian Gland Dysfunction

Chronic inflammation of the eyelid margin and MGD can compromise ocular surface homeostasis through abnormalities in the tear film lipid layer and increased tear evaporation. Lipids secreted by the meibomian glands reduce tear evaporation and contribute to tear film stability. Changes in the quantity or composition of these lipids destabilize the tear film and increase stress on the ocular surface epithelium.

MGD is a heterogeneous condition characterized by varying features, including obstruction of gland orifices, alterations in the properties of secreted lipids, and loss of glandular structure. Kim et al. reported that ocular surface symptoms, tear-related parameters, and inflammatory protein profiles differ according to MGD phenotype [47]. This heterogeneity should be considered when investigating the role of oxidative stress in MGD; patients should not be assumed to share a single underlying pathophysiological process.

Oxidative stress may affect lipid metabolism and secretory function in the meibomian glands. However, it remains unclear whether oxidative damage contributes to the initiation of MGD or represents a secondary change following inflammation and secretory dysfunction. Further studies combining structural and functional assessments of the meibomian glands, tear lipid analysis, and oxidative stress biomarkers are needed.

6.4.3. Chronic Inflammation and Tissue Remodeling

Persistent chronic inflammation can alter interactions between epithelial and stromal cells, leading to extracellular matrix degradation and remodeling and, in some cases, fibrosis. In severe allergic ocular surface diseases and cicatrizing conjunctival disorders, such remodeling may influence the clinical course and visual function [45].

Oxidative stress may affect tissue remodeling by modulating intracellular signaling and the regulation of matrix-degrading enzymes. Conversely, enzymes and mediators released during inflammation can also alter the tissue microenvironment and prolong epithelial damage. Therefore, in chronic inflammatory ocular surface diseases, control of inflammation should be considered together with the maintenance and restoration of tissue barrier integrity.

At present, disease-specific evidence remains limited regarding whether interventions targeting oxidative stress can clinically attenuate tissue remodeling in chronic inflammatory ocular surface diseases. Future prospective studies should evaluate the relationships among oxidative stress biomarkers, disease severity, tissue damage, and treatment response.

6.5. Shared Pathophysiological Mechanisms and Disease-Specific Features

DED, allergic conjunctivitis, environmentally induced corneal epithelial injury, and chronic inflammatory ocular surface diseases have distinct clinical presentations but share several potential pathophysiological mechanisms. Oxidative stress, epithelial barrier dysfunction, activation of inflammatory signaling, and alterations in tissue repair are particularly important processes to consider across these conditions [3,13].

6.5.1. A Conceptual Model of Shared Pathophysiological Mechanisms in Ocular Surface Diseases

Ocular surface diseases, including dry eye disease (DED), allergic conjunctivitis, environmentally induced corneal epithelial injury, and chronic inflammatory ocular surface diseases, have distinct clinical and immunological characteristics but may share several pathophysiological components, including redox imbalance, epithelial barrier disruption, inflammatory responses, and altered tissue repair [3,13]. Figure 5 presents a conceptual model of these shared mechanisms. The relative contribution of these processes varies according to the underlying disease and the nature of environmental or endogenous stimuli. For example, particulate matter and ozone may primarily induce oxidative or nitrative injury, whereas allergens trigger immune-mediated inflammation. In DED, tear film instability and hyperosmolarity may further aggravate epithelial stress and inflammatory responses. These processes may interact and contribute to persistent inflammation and tissue injury, although their relative importance differs among individual diseases [3,43].

Ocular surface diseases are therefore usefully conceptualized not as the result of a single linear pathway but as dynamic systems in which environmental exposures, oxidative stress, epithelial barrier function, inflammation, and tissue repair interact. However, these relationships vary according to the disease and exposure conditions, and not every pathway has been demonstrated in every condition. This shared model is not intended to replace disease-specific mechanisms; rather, it provides a conceptual framework for integrating environmental factors and biological responses of the ocular surface.

6.5.2. Shared Pathophysiological Mechanisms

First, oxidative stress and inflammation interact bidirectionally. ROS not only damage cellular components but may also contribute to the activation of inflammatory pathways. Conversely, mediators released by inflammatory and epithelial cells alter redox status and promote further cellular injury. This interaction has received particular attention in DED and ocular surface damage associated with environmental pollutants [3,13].

Second, epithelial barrier disruption is a shared mechanism. Tight junctions in the corneal and conjunctival epithelia, together with cell-surface mucins, regulate the entry of external stimuli and antigens. Experimental studies have demonstrated that exposure to $PM_{2.5}$ and PM_{10} can alter tight junction-associated proteins and mucins, thereby impairing

corneal epithelial barrier function [31,46]. In allergic ocular surface diseases, epithelial barrier dysfunction may also facilitate antigen penetration and local immune responses [45].

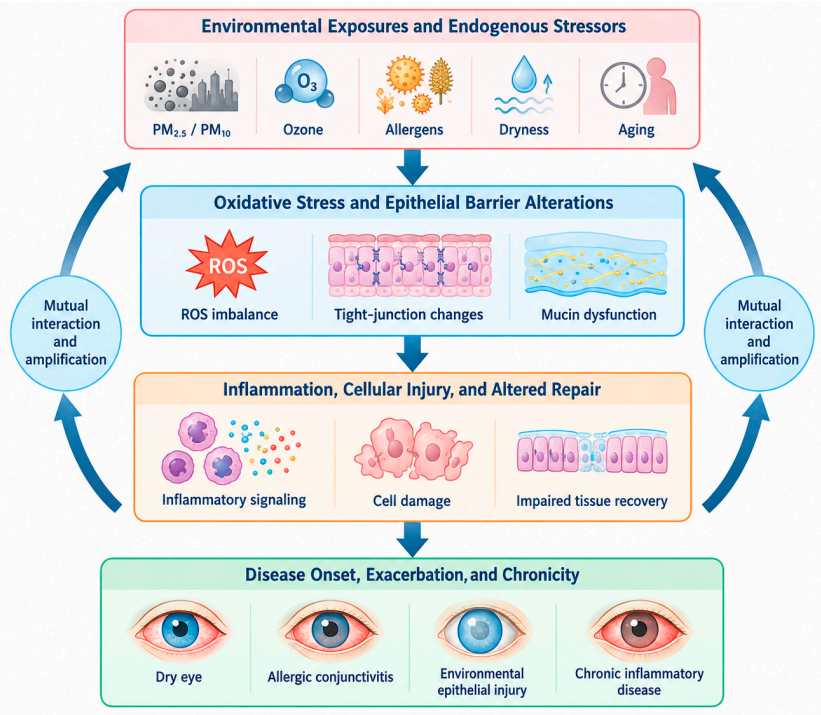


Figure 5. Conceptual Model of Shared Pathophysiological Mechanisms in Ocular Surface Diseases. Conceptual illustration of shared pathways through which environmental exposures and endogenous stressors may contribute to ocular surface disease. Particulate matter, ozone, allergens, dryness, and aging may affect redox homeostasis and epithelial barrier integrity, potentially promoting inflammation, cellular injury, and alterations in tissue repair. These processes may contribute to disease onset, exacerbation, or chronicity in dry eye disease, allergic conjunctivitis, environmental epithelial injury, and chronic inflammatory ocular surface disorders. Reciprocal interactions among inflammation, barrier dysfunction, and impaired repair may further compromise ocular surface homeostasis. The relative contributions of these pathways vary across diseases and exposure conditions, and not all proposed mechanisms have been established in every disease. Accordingly, this figure should be interpreted as a proposed integrative framework for understanding shared and disease-specific mechanisms, rather than as a representation of fully established causal pathways.

Third, alterations in repair mechanisms and the capacity to maintain homeostasis may contribute to disease persistence. Repeated environmental stimuli and chronic inflammation may impair epithelial cell function, delay the repair of damaged areas, and increase susceptibility to further external insults. When combined with aging and cellular senescence, these vulnerabilities may be further amplified. However, the extent to which impaired repair contributes to disease onset and progression requires investigation for each individual condition.

6.5.3. Ocular Surface Microbiome as an Emerging Modifier of Ocular Surface Pathology

The ocular surface microbiome has recently attracted attention as a potential modifier of ocular surface homeostasis and disease. Alterations in microbial composition have been reported in patients with dry eye disease and allergic eye diseases, suggesting possible interactions between resident microorganisms, epithelial barrier function, and local immune responses [48,49]. Environmental conditions, aging, and local inflammation may also influence the composition of the ocular surface microbiome. These findings raise the possibility that microbial communities contribute to the interactions among environmental

exposures, epithelial integrity, and inflammatory responses. However, current evidence is largely based on observational studies, and interpretation is complicated by the low microbial biomass of the ocular surface, differences in sampling and analytical methods, and the potential effects of contamination. Therefore, the ocular surface microbiome should currently be regarded as an emerging area of investigation rather than an established causal mechanism or a clinically validated therapeutic target [50].

6.5.4. Disease-Specific Features

Despite these shared mechanisms, the predominant pathophysiological processes differ among ocular surface diseases. The disease-specific characteristics and the potential roles of oxidative stress and environmental exposures are summarized in Table 3.

Table 3. Shared and Distinct Pathophysiological Mechanisms in Ocular Surface Diseases.

Ocular Surface Disease	Main Pathophysiological Features	Role of Oxidative Stress	Inflammation and Immune Responses	Relationship with Environmental Exposures
Dry eye disease (DED) [3,28,43]	Tear-film instability, tear hyperosmolarity, epithelial damage, and disruption of ocular surface homeostasis	ROS generation and impaired antioxidant defense may contribute to epithelial injury and tear-film dysfunction	Inflammatory cytokines and immune activation can perpetuate epithelial damage and a self-reinforcing cycle of disease	Air pollution, particulate matter, low humidity, and other environmental conditions may exacerbate symptoms and ocular surface dysfunction; evidence for causality varies by exposure
Allergic conjunctivitis [3,36,43]	Allergen-triggered conjunctival inflammation, mast-cell activation, and type 2 immune responses	Oxidative stress may contribute to epithelial irritation and tissue injury, although its contribution varies with disease severity and phenotype	IgE-mediated mast-cell activation and type 2 cytokines, including IL-4, IL-5, and IL-13, are important features; other inflammatory pathways may also be involved	Airborne allergens and particulate matter may trigger or aggravate symptoms; pollutant–allergen interactions may modify inflammatory responses
Environmental corneal epithelial injury [23,31,43,46]	Direct epithelial stress, altered barrier integrity, and, depending on exposure, cell injury or death	Oxidative damage is implicated in experimental models of particulate matter- and ozone-associated corneal injury	Inflammatory signaling may accompany epithelial damage and contribute to impaired barrier function	$PM_{2.5}$, PM_{10}, and ozone have been investigated in experimental models; findings support biological plausibility, but experimental exposure conditions may not fully represent real-world human exposure
Chronic inflammatory ocular surface diseases [3,36,43]	Persistent inflammation, epithelial dysfunction, and, in some conditions, impaired tissue repair	Oxidative stress may interact with chronic inflammation and cellular injury, but its relative contribution differs among diseases	Sustained immune activation and inflammatory mediator release may contribute to ongoing tissue damage; mechanisms depend on the specific disease	Environmental exposures may act as aggravating factors in susceptible individuals, but evidence should be interpreted in the context of the underlying disease and individual susceptibility
Shared mechanisms across ocular surface diseases [3,28,32,43]	Interactions among epithelial barrier dysfunction, tear-film disturbance, inflammation, cellular injury, and altered repair	Redox imbalance may act as a connecting mechanism linking environmental stress with epithelial dysfunction	Inflammatory signaling can amplify tissue injury, while barrier disruption may increase vulnerability to further environmental insults	Exposure intensity, duration, pollutant mixtures, age, and individual susceptibility may influence disease onset, exacerbation, or persistence

Note: This table provides a qualitative synthesis of reported pathophysiological features and potential mechanisms based on the available literature. The proposed relationships should not be interpreted as equally established across all diseases, and the strength of evidence varies among conditions.

This comparison indicates that, although oxidative stress may be a shared component of several ocular surface diseases, its relative importance and principal sites of action differ among conditions. In DED, its relationship with tear film instability and hyperosmolarity is particularly relevant, whereas allergic conjunctivitis is primarily characterized by interactions between antigen-specific immune responses and epithelial barrier function. In environmentally induced corneal epithelial injury, direct cellular damage from exposure is important, while in chronic inflammatory diseases, persistent inflammation and tissue remodeling may substantially influence the clinical course.

Accordingly, oxidative stress-targeted treatments should not be applied uniformly to all ocular surface diseases. Their potential role should instead be evaluated in relation to the predominant disease mechanisms, extent of oxidative damage, characteristics of inflammation, and tear and epithelial function. Future studies integrating oxidative stress-related indicators, inflammatory biomarkers, epithelial barrier assessments, and environmental exposure data may clarify both the shared and disease-specific mechanisms, thereby informing preventive and therapeutic strategies tailored to individual pathophysiological profiles.

7. Therapeutic and Preventive Strategies

Strategies addressing oxidative stress and environmental exposures in ocular surface diseases should extend beyond suppressing inflammation with a single medication. Instead, they should integrate exposure reduction, preservation of antioxidant defenses against ROS, modulation of inflammatory signaling, and protection of tear film homeostasis and epithelial barrier function. In dry eye disease and allergic conjunctivitis, environmental factors may contribute to disease onset and exacerbation; however, exposure patterns, underlying conditions, the degree of inflammation, tear secretion capacity, and the severity of epithelial damage vary among individuals. Accordingly, therapeutic and preventive strategies should be based on environmental management and standard pharmacological treatment, supplemented by interventions tailored to the underlying pathophysiology [3,13].

Importantly, antioxidant effects or protective effects against environmental exposure demonstrated in experimental systems do not necessarily translate into clinical efficacy in humans. Accordingly, antioxidant-based interventions discussed in this review should be regarded as potential therapeutic approaches unless their clinical efficacy has been demonstrated in appropriately designed human studies. Established clinical management strategies should be distinguished from experimental or investigational antioxidant interventions. This section focuses on relatively recent clinical studies and reviews, distinguishing established management strategies from therapeutic candidates that require further investigation.

7.1. Reduction and Management of Environmental Exposures

Reducing environmental exposures is a fundamental preventive strategy aimed at minimizing factors that contribute to the onset and exacerbation of ocular surface diseases. Particulate matter ($PM_{2.5}$ and PM_{10}), ozone, VOCs, tobacco smoke, low humidity, and wind may compromise ocular surface homeostasis through tear film evaporation, irritation of the ocular surface epithelium, oxidative stress, and inflammatory responses. Therefore, clinical assessments should address not only ocular symptoms but also residential and occupational environments, outdoor activities, air-conditioning use, exposure to tobacco smoke, seasonal factors, and screen time to identify individual exposure patterns [28,32].

Practical measures include reducing outdoor exposure when air pollution levels are high, when appropriate; ensuring adequate indoor ventilation and air purification; avoiding tobacco smoke; preventing direct airflow toward the eyes; and improving low-humidity conditions. For individuals who use digital devices for prolonged periods, conscious

blinking, regular breaks, and adjustments to screen positioning and the work environment may also help reduce tear film evaporation. Although these interventions are generally feasible, the preventive efficacy of all such measures has not been established to the same extent. Patient counseling should therefore consider both the strength of the scientific evidence and practical feasibility, prioritizing measures that patients can sustain over time.

A prospective study evaluating home environmental conditions and recommending modifications for patients with DED provides some evidence of the potential clinical benefits of environmental improvement. Among patients who implemented measures such as improving ventilation and replacing air-conditioner filters, improvements were reported in selected parameters, including tear osmolarity and meibomian gland findings. However, implementation depended on patients' own choices, and the control conditions were limited. Consequently, it cannot be concluded that specific environmental modifications directly caused the observed improvements in symptoms or clinical findings [51].

In allergic conjunctivitis, reducing exposure to allergens such as pollen should be accompanied by attention to combined exposure to air pollutants. Practical measures include modifying outdoor activities according to pollen forecasts, washing the face and maintaining periocular hygiene after returning indoors, and adjusting ventilation practices. Nevertheless, environmental management alone may not adequately control inflammation, and pharmacological treatment may be necessary when symptoms persist [44].

7.2. Therapeutic Strategies Targeting Antioxidant Defense Mechanisms

Therapeutic strategies targeting oxidative stress are based on reducing excessive ROS production, maintaining antioxidant defense systems, and limiting oxidative damage to cell membranes, proteins, and nucleic acids. At the ocular surface, antioxidants in the tear film, intracellular antioxidant enzymes in epithelial cells, and mitochondrial function contribute to the maintenance of redox homeostasis. When these defense mechanisms are disrupted by environmental exposures or chronic inflammation, epithelial damage and activation of inflammatory signaling may be promoted [13].

Potential therapeutic agents include molecules with antioxidant properties, mitochondria-targeted antioxidants, and compounds that support antioxidant enzyme systems. For example, SKQ1, a mitochondria-targeted antioxidant, has been reported to potentially mitigate changes in epithelial barrier function induced by particulate matter exposure in experimental models of ocular surface injury. These findings support a role for oxidative stress in environmentally induced ocular surface damage. However, effects observed in experimental models cannot be directly extrapolated to therapeutic efficacy in humans [46].

In clinical practice, unestablished antioxidant formulations or supplements should not replace standard treatment solely because they are intended to target oxidative stress. The effects of antioxidants vary according to their route of administration, ability to reach the ocular surface, stability, concentration, and toxicity. Moreover, ROS are involved in intracellular signaling and host defense; therefore, nonselective suppression of ROS is not necessarily beneficial in all circumstances. Future studies should evaluate not only changes in oxidative stress-related biomarkers but also clinical outcomes, including symptoms, corneal and conjunctival epithelial damage, tear film stability, and quality of life.

7.3. Modulation of Inflammatory Signaling and Immune Responses

Oxidative stress and inflammation can reinforce one another. ROS affect inflammation-related signaling pathways, including NF-κB, and the expression of inflammatory mediators, while factors released by inflammatory cells further promote ROS production. When this cycle persists, epithelial damage, disruption of tear film homeostasis, and alterations in sensory nerve function may occur concurrently, potentially contributing to chronic disease [13].

Treatment should focus on controlling inflammatory responses according to the underlying disease pathophysiology. In DED, tear supplementation with artificial tears provides a foundation for management, while topical anti-inflammatory or immunomodulatory agents may be considered in patients with an inflammatory component. When MGD is present, warm compresses, eyelid hygiene, and, when indicated, specialized treatments can be combined to improve the function of the tear film lipid layer. Treatment selection should be based not only on symptom severity but also on epithelial damage, tear secretion, tear film stability, eyelid findings, and comorbid conditions [52].

In allergic conjunctivitis, topical antihistamines, mast cell stabilizers, or eye drops with both activities are commonly used as first-line treatments. More intensive anti-inflammatory treatment may be required in severe cases or in patients with corneal involvement, following careful assessment of disease severity and treatment-related risks. However, topical corticosteroids carry risks, including elevated intraocular pressure and exacerbation of infection. Their use should therefore be restricted to appropriate indications and accompanied by ophthalmological monitoring. The effects of preservatives and other excipients in ophthalmic formulations on the ocular surface should also be considered. In patients with concomitant DED or epithelial damage, the choice of formulation should be individualized [53].

Environmental exposure reduction and anti-inflammatory treatment can be regarded as complementary interventions acting at different stages of the disease process. Exposure management reduces external factors that may trigger or exacerbate inflammation, whereas pharmacological treatment controls inflammatory responses that have already developed. Combining these approaches is mechanistically reasonable; however, whether particular environmental interventions combined with specific anti-inflammatory medications produce additive or synergistic benefits requires confirmation in disease-specific clinical trials.

7.4. Preservation of Tear Film Homeostasis and Ocular Surface Barrier Function

Maintaining tear film homeostasis and the integrity of the ocular surface epithelial barrier is essential for protection against environmental exposures and for interrupting the cycle of inflammation and oxidative stress. In addition to lubricating the ocular surface, tears contain antimicrobial and antioxidant factors that protect the corneal and conjunctival epithelia from external insults. Tear film instability or impaired mucin-layer function may increase epithelial susceptibility to environmental stress and aggravate inflammation and cellular injury [13,52].

The fundamental management of DED involves combining tear supplementation with artificial tears, measures to reduce tear evaporation, and interventions to improve eyelid and meibomian gland function according to the underlying pathophysiology. Artificial tears form the basis of symptomatic relief; however, their effects on the ocular surface may vary depending on their composition, viscosity, and preservative content. Their selection should therefore take into account the frequency of use and the presence of concomitant epithelial damage. In patients with impaired tear film stability or mucin-related function, treatments aimed at protecting and repairing the ocular surface epithelium may be considered in addition to tear supplementation [52].

Rebamipide is one example of a treatment targeting mucin-related function and epithelial protection. Clinical studies and meta-analyses in patients with DED have reported improvements in tear film stability and ocular surface findings following rebamipide eye drop treatment, although the magnitude of these effects varies according to the outcome measures, observation periods, and study designs. Accordingly, drugs intended to protect the ocular surface, such as rebamipide, should not be classified collectively as antioxidants; rather, they should be evaluated according to their principal mechanisms of action and clinical indications [54].

Environmental management may also contribute to the maintenance of tear film homeostasis. A small randomized controlled trial conducted under low-humidity conditions associated with digital device use investigated the use of a desktop humidifier and evaluated its effects on symptoms and tear-related parameters [55]. However, findings from a study involving a single device used for a short period cannot establish the long-term efficacy of humidifiers in general or their ability to prevent the onset of DED. A practical approach is to combine indoor humidity control, avoidance of direct airflow toward the eyes, appropriate blinking, and breaks during screen-based activities according to the patient's living and working environment.

Protecting the ocular surface barrier also requires attention to irritation caused by ophthalmic medications themselves. In patients who use multiple eye drops over extended periods or who already have epithelial damage, the effects of preservatives and other excipients should be considered. Changes in formulation or administration practices may be appropriate when indicated. In allergic conjunctivitis, protecting the tear film and ocular surface epithelium while controlling inflammation may also help address concomitant dry eye symptoms and ocular surface damage [53].

7.5. An Integrated Approach Combining Environmental Measures and Pharmacological Treatment

Given the multifactorial nature of ocular surface diseases, clinical management should pair targeted environmental modifications with pathophysiology-based pharmacotherapy (e.g., tear supplementation, lid hygiene, or anti-inflammatory agents), introduced in manageable steps to support patient adherence [52,53].

An advantage of an integrated approach is that it addresses persistent environmental stimuli that may not be adequately managed by pharmacological treatment alone. Reducing environmental triggers while controlling symptoms and inflammation with medication may help reduce treatment burden and support long-term symptom management. However, introducing multiple interventions complicate self-management and reduce adherence. It is therefore preferable to establish priorities in collaboration with patients and introduce interventions in stages, assessing both their effectiveness and feasibility.

7.6. Clinical Evidence and Limitations of Preventive and Therapeutic Interventions

A schematic overview of how environmental exposure assessment may inform the prevention of ocular surface diseases and personalized management is presented in Figure 6. Evidence concerning environmental interventions and ocular surface treatments continues to accumulate, although its strength varies across interventions. For DED, clinical studies and international management guidelines are available for artificial tears, anti-inflammatory medications, and treatments targeting tear film or eyelid function [52]. By contrast, studies of environmental exposure reduction differ in their methods of exposure measurement, diagnostic criteria, intervention protocols, and assessment periods, making direct comparisons between findings difficult [32].

One important clinical challenge is that, although associations between environmental exposures and ocular surface diseases have been reported, the extent to which exposure-reduction interventions prevent disease onset or progression remains insufficiently established. Observational studies may be affected by interactions among meteorological conditions, air pollution, seasonality, lifestyle factors, and underlying diseases, limiting the ability to estimate the independent effects of specific exposures. In studies of indoor environmental improvements, multiple measures are often implemented simultaneously, making it difficult to determine which interventions contribute to observed clinical changes [51].

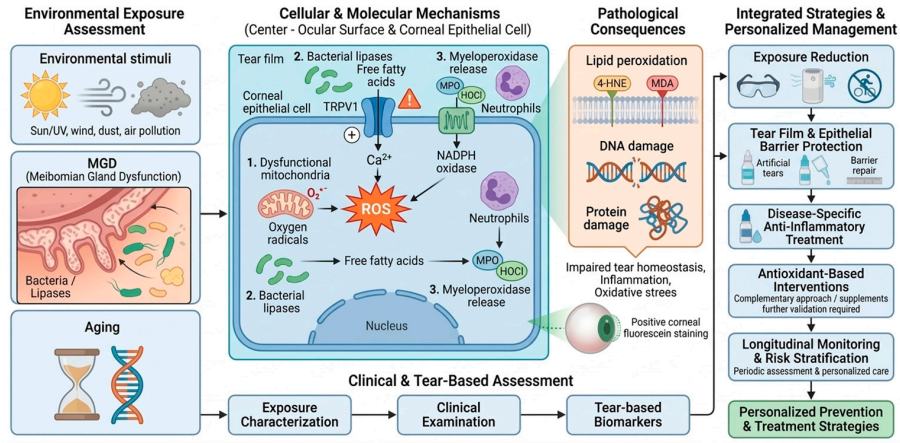


Figure 6. From Environmental Exposure Assessment to Prevention and Personalized Management of Ocular Surface Disease. Conceptual framework linking environmental exposure assessment to the prevention and management of ocular surface disease. Exposure characterization, clinical examination, and tear-based biomarkers help identify oxidative stress, inflammation, and impaired tear homeostasis. These findings inform integrated strategies, including exposure reduction, tear film and epithelial barrier protection, and disease-specific anti-inflammatory treatment. Antioxidant-based interventions represent a potential complementary approach, although their clinical efficacy requires further validation. Longitudinal monitoring may support risk stratification and the development of personalized prevention and treatment strategies.

Antioxidant therapy also requires a clear distinction between reductions in ROS or epithelial protection demonstrated in experimental studies and improvements in symptoms or clinical findings in humans. Future studies should incorporate not only antioxidant-related biomarkers but also patient-reported outcomes, tear film stability, corneal and conjunctival staining, epithelial barrier function, and recurrence frequency. The safety of interventions, long-term effectiveness, cost-effectiveness, and patient adherence should also be considered.

Future research should prioritize prospective studies integrating individual exposure histories with ocular surface findings, interventional trials using standardized environmental measures, and comparative trials combining environmental modifications with pharmacological treatment. Assessment of oxidative stress-related indicators and inflammatory biomarkers in tears also help identify patient subgroups more likely to benefit from specific interventions. However, measurement methods and clinical interpretation of these biomarkers require standardization. At present, treatment decisions based solely on individual biomarkers should therefore be approached with caution.

Overall, combining environmental exposure reduction, preservation of antioxidant defenses, inflammatory control, and protection of tear film homeostasis and epithelial barrier function represents a rational strategy that reflects the multifactorial nature of ocular surface diseases. Nevertheless, mechanistic plausibility is not equivalent to demonstrated clinical efficacy. At present, management should be based on established standard treatments, supplemented by individualized environmental measures, while novel antioxidant interventions should be evaluated in light of evidence from high-quality clinical studies.

Environmental prevention and therapeutic strategies for ocular surface diseases are summarized in Table 4. These strategies include reducing environmental exposures, maintaining ocular surface homeostasis, controlling inflammation, and tailoring management to individual patient needs.

Table 4. Environmental Prevention and Therapeutic Strategies for Ocular Surface Diseases.

Strategy	Rationale and Potential Approaches	Potential Clinical Applications	Evidence and Limitations
Reduce particulate matter exposure [3,28,32]	Monitor air quality; reduce exposure during periods of high pollution; improve indoor filtration and ventilation where appropriate	Prevention or mitigation of pollution-associated ocular irritation and exacerbation of dry eye symptoms	Clinical and experimental evidence supports an association between particulate matter and ocular surface effects; the benefit of specific exposure-reduction interventions requires further evaluation
Improve indoor air quality [28,32]	Reduce indoor pollutants and irritants; avoid tobacco smoke; maintain appropriate ventilation and humidity	Management of dry eye symptoms associated with indoor environmental exposures	Evidence varies among pollutants. Indoor exposure assessments and intervention studies remain limited for several individual chemicals and pollutant mixtures
Reduce exposure to irritants and allergens [3,36,43]	Identify relevant triggers; minimize avoidable exposure to airborne allergens and irritants; consider seasonal and occupational exposure patterns	Allergic conjunctivitis and exposure-related ocular irritation	Allergen avoidance is biologically and clinically relevant, but pollutant–allergen interactions and the effectiveness of individual environmental measures vary
Support tear-film homeostasis [28,32]	Use appropriate lubricating eye drops; address contributing factors such as tear-film instability and meibomian gland dysfunction	Dry eye disease and ocular surface discomfort	Lubricants are established components of DED management; the optimal formulation and treatment plan depend on disease subtype and severity. The benefit of any particular formulation should not be inferred from environmental-exposure studies alone
Control ocular surface inflammation [32,36]	Select disease-appropriate anti-inflammatory treatment after clinical assessment; manage underlying allergic or inflammatory disease	Allergic conjunctivitis and inflammatory forms of dry eye disease	Treatment should follow disease-specific evidence and clinical guidelines. Environmental exposure studies do not independently establish the efficacy of a particular anti-inflammatory medication
Protect the corneal epithelial barrier [23,31,46,56]	Reduce exposure to damaging environmental agents and maintain ocular surface lubrication and homeostasis	Suspected or established environmental corneal epithelial injury	Experimental studies demonstrate particulate matter-associated barrier disruption and potential protective effects of antioxidants in cell models; direct evidence for specific protective treatments in humans remains limited
Investigate antioxidant-based approaches [3,43,46]	Study interventions that reduce oxidative damage or support endogenous antioxidant defenses	Potential adjunctive approaches for oxidative stress-associated ocular surface injury	Mechanistic and experimental evidence supports further investigation, but antioxidant effects observed in experimental systems should not be interpreted as proof of clinical efficacy in patients
Use individualized exposure assessment [3,28,32]	Record occupational, outdoor, and indoor exposures; assess symptom timing, clinical findings, and relevant comorbidities	Patients with recurrent symptoms or suspected exposure-related exacerbations	Exposure histories can help guide evaluation, but self-reported exposure does not establish causality. Objective exposure measurements and prospective studies are needed
Integrate prevention with disease-specific management [3,28,32]	Combine feasible environmental modifications with appropriate clinical evaluation, diagnosis, and treatment	Long-term management of recurrent or persistent ocular surface symptoms	A combined approach is clinically reasonable, but the incremental benefit of individual environmental interventions and their combinations requires stronger intervention evidence

8. Research Gaps and Future Perspectives

Understanding of the relationships among environmental exposures, oxidative stress, inflammation, and aging in ocular surface diseases has advanced through epidemiological studies, experimental investigations, and tear biomarker analyses. Nevertheless, many aspects of the processes through which these factors interact to initiate and drive disease progression remain unclear. Key priorities include developing methods to accurately assess individual environmental exposures, establishing integrated pathophysiological models that incorporate oxidative stress, chronic inflammation, and aging, standardizing tear biomarkers, and translating molecular findings into clinically relevant preventive and therapeutic strategies [37,42].

Future research should move beyond examining associations between a single environmental factor and an individual clinical parameter. Instead, it should integrate assessments of individual exposure histories, genetic background, lifestyle, aging, immune responses, tear film characteristics, and ocular surface epithelial status. In addition, longitudinal studies are needed to determine whether changes in environmental exposures precede changes in biomarkers or clinical findings, rather than relying solely on cross-sectional associations. Such research may facilitate the prediction of disease onset, early identification of high-risk individuals, and development of personalized preventive and therapeutic strategies.

8.1. Measurement of Environmental Exposures and Assessment of Individual Exposure Levels

One of the major challenges in elucidating the relationship between environmental exposures and ocular surface diseases is the accurate assessment of the actual exposure experienced by each individual. Studies of air pollution frequently use $PM_{2.5}$ or ozone concentrations measured at fixed monitoring stations as exposure indicators. However, these regional measurements do not adequately reflect individual mobility patterns, time spent indoors and outdoors, occupation, transportation methods, air-conditioning systems, or ventilation conditions. Consequently, even when an association is observed between regional pollution levels and ocular surface findings, the actual exposure experienced by an individual patient may not have been accurately estimated [3].

Future studies benefit from combining environmental data from fixed monitoring stations with portable sensors, location-based mobility records, individual activity logs, and indoor environmental measurements. For example, the BIKE-EYE pilot study, which investigated urban bicycle commuters, combined portable particulate matter measurements with ophthalmological assessments to examine associations between commuting-related pollution exposure and conjunctival hyperemia or corneal epithelial damage. Furthermore, substances considered to be derived from particulate matter were detected in tear samples collected after exposure, suggesting that tears have potential as a biological matrix for monitoring environmental exposures [57]. However, because this was a small pilot study, the causal relationship between the measured exposures and ocular surface damage, as well as the generalizability of the findings to other populations, requires confirmation in larger studies.

Environmental exposures also rarely occur as isolated factors. Particulate matter, ozone, pollen, temperature, humidity, ultraviolet radiation, and indoor pollutants overlap spatially and temporally and may interact with one another. Therefore, in addition to conventional approaches that analyze individual pollutants independently, statistical models that simultaneously account for multiple exposures and the exposome concept, which considers the cumulative spectrum of environmental exposures, are becoming increasingly important [56]. Future studies should distinguish short-term symptom fluctuations associated with transient exposures from chronic damage related to cumulative long-term exposures, incorporating exposure intensity, duration, and frequency into the assessment.

Furthermore, it is important to distinguish the amount of an exogenous substance that reaches the ocular surface from the biological responses it induces. Environmental sensors can help estimate exposure concentrations, but the combined assessment of particles or chemicals in tears, oxidative stress-related molecules, and inflammatory cytokines provide additional information linking the external environment to ocular surface responses. However, appropriate control samples and validated analytical methods are essential to establish whether substances detected in tears are derived from environmental sources and whether specific substances contribute causally to ocular surface damage.

8.2. Integrated Pathophysiological Models of Oxidative Stress, Inflammation, and Aging

Although oxidative stress, inflammation, and aging have each been investigated in ocular surface disease research, the temporal sequence through which these factors interact and contribute to disease onset and chronicity remains insufficiently understood. Age-related declines in mitochondrial function and changes in antioxidant defenses promote the accumulation of ROS. In turn, oxidative stress may activate inflammation-related signaling pathways, while chronic inflammation may further impair cellular function and tissue repair. In DED, tear film instability, hyperosmolarity, epithelial damage, and inflammation are interrelated. These processes should therefore be investigated as a dynamic pathophysiological network rather than as independent phenomena [13,58].

Future studies should simultaneously assess oxidative stress-related molecules, inflammatory mediators, markers of cellular senescence, mitochondrial function, and indicators of tear film homeostasis. For example, oxidative damage markers such as 4-HNE, MDA, and 8-OHdG could be analyzed alongside inflammatory cytokines and indicators of epithelial damage to quantify aspects of the biological response to environmental exposures. However, individual markers are not completely specific to particular pathophysiological processes and may be influenced by sample collection conditions and analytical methods. Therefore, no single marker should be regarded as a surrogate for the entire disease process [13].

To investigate the effects of aging, longitudinal studies following the same individuals over extended periods are essential, in addition to cross-sectional comparisons between age groups. It is difficult to distinguish age-specific changes from the effects of coexisting factors without considering not only chronological age but also menopause, systemic diseases, medication use, lacrimal and meibomian gland function, smoking, and occupational exposures. Furthermore, the extent to which cellular senescence and reduced tissue repair capacity alter susceptibility to environmental exposures should be investigated using both cellular and animal models and clinical data.

The value of such integrated models lies in their potential to identify the pathways that sustain disease, rather than simply classifying patients as having a state of increased oxidative stress. In the future, these models will help determine whether exposure reduction, anti-inflammatory treatment, support of antioxidant defenses, or improvement of tear film homeostasis should be prioritized according to individual pathophysiological characteristics. However, achieving this goal requires more than demonstrating associations between molecular pathways and clinical outcomes; it is also necessary to determine whether modifying these pathways through targeted interventions produces clinically meaningful improvements.

8.3. Standardization and Longitudinal Assessment of Tear Biomarkers

Tears are biological samples collected in close proximity to the ocular surface and contain proteins, lipids, metabolites, cytokines, and other molecules. They therefore represent a promising source of information for assessing ocular surface inflammation, oxidative stress, and changes in epithelial function. However, tear composition is influenced by col-

lection methods, sample volume, stimulation during collection, time of day, environmental conditions, storage duration, and analytical platforms. These variations complicate comparisons between studies and hinder the reproducibility and clinical translation of candidate biomarkers [37].

A Delphi consensus study aimed at developing international reporting guidelines for tear research examined the standardization of reporting items related to terminology, sample collection, storage, preprocessing, analysis, and data normalization [41]. Future studies should clearly report tear collection methods and timing, whether collection involved stimulation, storage conditions, analytical platforms, detection limits, and methods for handling missing data. Such reporting would facilitate the accumulation of comparable data across institutions. This is particularly important in patients with low tear volume, in whom collection methods may affect sample dilution and analyte recovery. The compatibility of collection and analytical methods should therefore be carefully evaluated.

Another challenge is that cross-sectional comparisons of biomarker levels alone may be insufficient to assess disease progression or treatment response. For example, longitudinal studies involving repeated assessments of the same patients are needed to determine whether individuals with elevated inflammatory cytokines or oxidative stress-related molecules are more likely to develop progressive epithelial damage or recurrent disease. It is also important to establish whether changes in tear biomarkers precede changes in clinical symptoms, corneal and conjunctival staining, or tear film stability, or whether they instead fluctuate secondarily in response to changes in disease activity.

A recent review of the tear proteome in DED summarized changes in proteins associated with inflammation, oxidative stress, and epithelial remodeling, as well as changes in components involved in ocular surface defense and tear film homeostasis, including lactoferrin, lysozyme, and lipocalin-1 [38]. These findings suggest that assessment should encompass multiple functional categories, including inflammation, epithelial protection, lipid metabolism, and immune defense, rather than relying on a single inflammatory marker. Nevertheless, even molecules reported to change consistently across multiple studies may not have sufficiently validated diagnostic accuracy or prognostic value.

The clinical application of tear biomarkers requires more than the discovery of candidate molecules. It also requires analytical validation, reproducibility testing in independent populations, establishment of diagnostic thresholds, and assessment of clinical utility. Furthermore, it must be demonstrated that test results can inform treatment selection or improve patient outcomes. A recent expert review similarly identified standardized collection and analytical procedures, appropriate reference values, and improved diagnostic accuracy, together with applications in prognostic assessment, treatment selection, and longitudinal monitoring, as important priorities for future research [42].

8.4. Omics Analyses and Integrated Cellular and Molecular Investigations

Omics approaches, including proteomics, lipidomics, metabolomics, and transcriptomics, provide powerful tools for understanding ocular surface diseases as networks of interacting biological processes rather than as disorders driven by a single molecule or pathway. Because tears contain molecules derived from the ocular surface epithelium, lacrimal glands, meibomian glands, immune cells, and other sources, comprehensive analysis of tear composition may enable multidimensional assessment of ocular surface responses to environmental exposures and chronic inflammation [38].

A review summarizing metabolic alterations in DED reported changes in glucose, lipid, and amino acid metabolism and their associations with immune and inflammatory responses [59]. These findings highlight the need to conceptualize oxidative stress at the ocular surface not merely as an increase in ROS but as part of broader changes in metabolic

networks involving cellular energy metabolism, lipid homeostasis, antioxidant defenses, and immune responses. However, whether changes in individual metabolites contribute to disease pathogenesis or arise as consequences of inflammation and tissue damage requires careful investigation.

Future studies should integrate tear omics with gene expression analyses of ocular surface epithelial cells and immune cells, functional assessments of cellular activity, and histological findings. For example, relating changes in tear lipid composition to meibomian gland function and tear evaporation, while jointly assessing inflammatory cytokines and oxidative damage markers in relation to epithelial barrier function, may clarify the relationships between molecular changes and clinical phenotypes. Incorporating records of environmental exposures further help identify molecular responses associated with specific exposures.

A framework combining tear multi-omics analyses with biosensors and machine learning has also been proposed as a potential approach to diagnosis and personalized treatment [60]. However, as the number of analyzed molecules increases, the risks of false-positive findings due to multiple testing, overfitting, and confounding become more prominent. Exploratory and validation studies should therefore be clearly distinguished, reproducibility should be confirmed in independent cohorts, and evaluation should address not only model discrimination but also clinical utility. In addition, comparability of measurements across analytical platforms, data sharing between institutions, and quality control remain important challenges.

8.5. Effects of Individual Differences, Genetic Background, Lifestyle, and Combined Exposures

Even among individuals living in similar environments, the onset and severity of ocular surface diseases vary considerably. This heterogeneity is likely influenced by multiple factors, including age, sex, genetic background, systemic diseases, medication use, tear secretion, meibomian gland function, immune responses, and lifestyle. Recent reviews and meta-analyses of DED risk factors have examined associations with a broad range of factors, including systemic diseases and lifestyle, in addition to local ocular factors [61,62]. However, statistical associations with these factors do not necessarily establish causal relationships.

Regarding genetic background, genetic variants involved in inflammatory responses, antioxidant defenses, epithelial barrier maintenance, and tear secretion may contribute to differences in susceptibility to environmental exposures. Future studies should jointly assess genetic information and environmental exposures to determine whether populations particularly susceptible to ocular surface damage under specific environmental conditions can be identified. However, evaluating gene–environment interactions with sufficient statistical power requires large study populations, and replication in independent populations is essential.

Lifestyle factors also require consideration in combination rather than solely in isolation. Assessing smoking, screen time, sleep, occupational exposures, and outdoor activities independently may be insufficient in some circumstances. For example, prolonged screen use in a low-humidity environment may simultaneously reduce blinking and increase tear evaporation. Similarly, in populations exposed to both tobacco smoke and air pollution, it may be difficult to estimate the independent effects of each exposure. Future studies should evaluate the additive and synergistic effects of multiple exposures and determine whether disease risk varies according to specific exposure combinations.

To better understand individual differences, it may be useful to analyze patients not only according to diagnostic labels but also according to pathophysiological characteristics, such as aqueous-deficient, evaporative, inflammation-predominant, or epithelial damage-predominant phenotypes, together with their exposure histories and systemic backgrounds.

However, whether these classifications can predict differential treatment responses must be established in clinical studies. The objective should not be to subdivide disease phenotypes indefinitely but rather to improve the accuracy of predictions regarding patient prognosis and treatment selection.

8.6. Applications in Preventive Medicine and Personalized Healthcare

An integrated understanding of the relationships among environmental exposures, oxidative stress, inflammation, and aging may contribute not only to the treatment of ocular surface diseases but also to disease prevention and early intervention. Conventional clinical practice has primarily focused on diagnosing disease based on symptoms and ocular surface findings and selecting treatment according to disease severity. In the future, integrating individual exposure histories, lifestyle factors, tear biomarkers, and ocular surface findings enable earlier assessment of the risk of disease onset or exacerbation [56].

At least three stages are required to advance personalized healthcare. First, predictive models should be developed to estimate the risk of disease onset or exacerbation based on environmental exposures and individual characteristics. Second, the accuracy and reproducibility of these models should be validated using tear biomarkers and clinical findings. Third, studies should determine whether interventions guided by risk assessment improve symptoms, epithelial damage, recurrence frequency, quality of life, or other relevant outcomes compared with usual care. Even a highly accurate predictive model does not necessarily lead to patient benefit when used to guide interventions; therefore, clinical utility must be evaluated directly.

Research integrating digital phenotyping with genomic information has also begun in this field. A prospective cohort study protocol integrating digital data and genomic information in DED has been reported, representing progress toward a research framework that captures individual characteristics from multiple perspectives [63]. However, publication of a study protocol does not demonstrate the effectiveness of a predictive model. Its validity must be established through adequate sample sizes, appropriate control of confounding, independent external validation, and long-term follow-up.

From a preventive medicine perspective, population-level measures are also important, in addition to environmental management for individual patients. These measures include improving indoor environments in workplaces and schools, using air pollution information to guide preventive actions, and reducing exposure to tobacco smoke. Reducing environmental exposures may represent a relatively feasible intervention for many patients, although the magnitude of benefit and the measures required are likely to vary according to exposure patterns and disease characteristics. Individual lifestyle counseling and broader environmental improvements should therefore be regarded as complementary rather than competing preventive strategies.

Ultimately, the goal is to establish a framework that integrates environmental exposure assessment, tear biomarkers, omics analyses, and clinical phenotypes to support pathophysiology-guided prevention and treatment selection. Achieving this goal will require the progressive implementation of standardized measurement methods, prospective longitudinal studies, validation in independent cohorts, interventional trials, and cost-effectiveness analyses. Personalized healthcare for ocular surface diseases represents a promising direction, but at present, it should be regarded as a research-driven approach intended to complement established diagnostic and therapeutic practices rather than replace standard care.

9. Conclusions

9.1. An Integrated Understanding of Environmental Exposures, Oxidative Stress, and Inflammaging

The ocular surface is continuously exposed to a variety of environmental factors, including air pollutants, pollen, UV radiation, tobacco smoke, and fluctuations in temperature and humidity. These exposures contribute to the development and exacerbation of ocular surface diseases, including DED and allergic conjunctivitis, through disruption of tear film homeostasis, impairment of epithelial barrier function, increased oxidative stress, and alterations in immune and inflammatory responses [3,32].

A central concept discussed in this review is that environmental exposures, oxidative stress, chronic inflammation, and age-related changes in immune and tissue function should be understood as interconnected pathophysiological processes. Age-related alterations in antioxidant defenses and tissue repair mechanisms increase the vulnerability of the ocular surface to environmental insults. Conversely, oxidative stress and chronic inflammation may perpetuate epithelial damage and further compromise ocular surface homeostasis. Understanding these interactions is important for elucidating the mechanisms underlying the development and chronic progression of ocular surface diseases [13].

However, epidemiological evidence linking environmental exposures to ocular surface diseases, experimental evidence implicating oxidative stress and inflammation, and clinical evidence demonstrating the efficacy of treatments targeting specific mechanisms must be evaluated separately. At present, causal relationships and underlying mechanisms have not been established for all environmental factors. Further investigation is also needed to determine the extent to which inflammaging contributes to individual ocular surface diseases.

9.2. Future Perspectives on the Prevention, Diagnosis, and Treatment of Ocular Surface Diseases

Future research should improve the accuracy of environmental exposure assessment and link individual exposure histories to clinical findings, while integrating assessments of oxidative stress, inflammation, cellular senescence, and tear film homeostasis. In addition, tear biomarkers and omics analyses help establish indicators for the early detection of disease, pathophysiological stratification, and prediction of treatment responses. However, their clinical implementation will require standardized measurement methods, reproducibility in independent populations, and rigorous validation of diagnostic accuracy and clinical utility [37,42].

From a clinical perspective, reducing environmental exposures, maintaining tear film homeostasis, protecting the ocular surface barrier, and providing anti-inflammatory treatment tailored to the underlying pathophysiology constitute practical approaches that can be implemented at present. Novel therapeutic strategies, including antioxidant interventions, should not be assumed to be clinically effective solely on the basis of promising experimental findings. Their safety and efficacy must instead be established through appropriately designed clinical trials.

The ultimate goal is to deepen our understanding of interactions between the environment and the host, thereby advancing beyond the treatment of established ocular surface diseases toward the early identification of high-risk individuals and the development of preventive, diagnostic, and therapeutic strategies tailored to individual pathophysiological profiles and living environments. Interdisciplinary research spanning environmental medicine, ocular surface science, immunology, aging research, and biomarker science will provide an important foundation for achieving this goal.

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Abbreviations

The following abbreviations are used in this manuscript:

UV	Ultraviolet
$PM_{2.5}$	Particulate matter of 2.5 μm or less in diameter
VOCs	Volatile organic compounds
ROS	Reactive oxygen species
DED	Dry eye disease
PM	Particulate matter
DNA	Deoxyribonucleic acid
8-OHdG	8-hydroxy-2′-deoxyguanosine
SASP	Senescence-associated secretory phenotype
RNS	Reactive nitrogen species
$O_2\bullet^-$	Superoxide anion
H_2O_2	Hydrogen peroxide
•OH	Hydroxyl radical
NO•	Nitric oxide
$ONOO^-$	Peroxynitrite
NADPH	Nicotinamide adenine dinucleotide phosphate
NOX	Nicotinamide adenine dinucleotide phosphate oxidase
SOD	Superoxide dismutase
MDA	Malondialdehyde
4-HNE	4-hydroxy-2-nonenal
CAT	Catalase
GPx	Glutathione peroxidase
GSH	Glutathione
Nrf2	Nuclear factor erythroid 2-related factor 2
HO-1	Heme oxygenase-1
NQO1	NAD(P)H quinone dehydrogenase 1
DAMPs	Damage-associated molecular patterns
NLRP3	Nucleotide-binding oligomerization domain-like (NOD-like) receptor pyrin domain-containing 3
NF-κB	Nuclear factor kappa B
MAPK	Mitogen-activated protein kinase

IL	Interleukin
TNF-α	Tumor necrosis factor-α
MMP	Matrix metalloproteinase
ERK	Extracellular signal-regulated kinases
JNK	c-Jun N-terminal kinases
CARD	Caspase recruitment domain
ASC	Apoptosis-associated speck-like protein containing a CARD
GSDMD	Gasdermin D
O_3	Ozone
LED	Light-emitting diode
AKT	Protein Kinase B:PKB
S6K	Ribosomal protein S6 kinase
CUVAF	Conjunctival ultraviolet autofluorescence
ZO-1	Zonula occludens-1
$p16^{INK4a}$	p16 inhibitor of nuclear kinase 4a
ATP	Adenosine triphosphate
Rb	Retinoblastoma protein
3-NT	3-nitrotyrosine
TAC	Total antioxidant capacity
IFN-γ	Interferon-gamma
CCL2	C-C motif chemokine ligand 2
CXCL8	Chemokine ligand 8
Th2	T helper 2
ELISA	Enzyme-linked immunosorbent assay
THBS1	Tight junction-associated proteins and thrombospondin 1
SkQ1	Plastonequinonyl-decyl-triphenylphosphonium

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