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Review

Lipid Peroxidation and Ferroptotic Vulnerability of the Nasal Epithelial Barrier in Allergic Rhinitis: From the ALOX15/ACSL4–GPX4 Axis to Oxidative Biomarkers and Antioxidant Targets

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Abstract

Allergic rhinitis (AR) is usually framed through the IgE–mast cell–type 2 cytokine axis, yet oxidative injury concentrates in the nasal epithelium that first meets allergens, pollen oxidases and pollutants. Lipid peroxidation has been reported in AR for almost twenty years; only since 2023 has it been tied to ferroptosis, an iron-dependent cell death driven by phospholipid peroxidation. This review joins them, focused on the nasal epithelial barrier. We summarise the machinery that sets ferroptotic vulnerability in a mucosal epithelium—phospholipid supply, initiation, labile iron, and the glutathione peroxidase 4 (GPX4) and Nrf2 defences—then review the clinical biomarkers by compartment. Nasal and exhaled 8-isoprostane and serum thiol oxidation are the most reproducible signals, serum malondialdehyde and total antioxidant status are not, and 4-hydroxynonenal adducts and transferrin receptor 1 have never been measured in nasal tissue. Three regulatory axes—GAS1–METTL3–GPX4, METTL3–PTBP1–TXNIP and FOXP1–SDHAF2–ALOX15—link allergen or IL-4/IL-13 exposure to lipid peroxidation in nasal epithelial cells; the one study that assessed the barrier found it compromised. Every claim is graded by the system it came from, epithelial protection is weighed against the ferroptosis

Academic Editor: Morana Jaganjac

Received: 21 October 2026
Revised: 11 November 2026
Accepted: 16 November 2026
Published: 24 November 2026

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tolerance of type 2 lymphocytes, and antioxidant strategies and a research agenda are mapped onto the AR evidence.

Keywords: allergic rhinitis; ferroptosis; lipid peroxidation; nasal epithelial barrier; GPX4; ALOX15; 4-hydroxy-2-nonenal; malondialdehyde; Nrf2; antioxidants

1. Introduction

Allergic rhinitis (AR) is one of the most common chronic conditions worldwide. Estimates in the ARIA documents place the global number of affected individuals at roughly 400 million, with the four major allergic diseases together affecting about one fifth of the world's population and AR alone affecting an estimated 15% of the United States population, approximately 50 million people [1–4]. In a European survey of almost 1500 patients, two thirds had moderate-to-severe disease and more than 40% had persistent symptoms, and the paediatric burden on sleep, school performance and quality of life is well documented [5,6]. Prevalence has risen steeply in rapidly urbanising regions, a trend that is hard to explain through the IgE–mast cell–type 2 cytokine framework alone and that has fuelled the epithelial barrier hypothesis, according to which damage to mucosal barriers by modern environmental agents is an upstream cause of allergic sensitisation and chronic inflammation rather than merely its consequence [7–11].

The nasal epithelium occupies a peculiar position in this hypothesis. It is the first mucosal surface to meet inhaled allergens, pollen grains and sub-pollen particles that carry their own NAD(P)H oxidases, fine particulate matter rich in redox-active transition metals, ozone and tobacco smoke [12–15]. The same tissue is exposed to the oxidant burst of recruited eosinophils, neutrophils and macrophages, to type 2 cytokines that reprogram its lipid metabolism, and to histamine, which disrupts its tight junctions directly [16,17]. Oxidative stress in AR has therefore been studied for decades, and reviews in this journal and elsewhere have catalogued elevated oxidant markers and depleted antioxidants in the blood and airway fluids of patients with AR, together with the NOX/DUOX and Nrf2 pathways that govern them [18–20]. What these reviews could not do, because the data did not exist, was to connect lipid peroxidation in the nasal mucosa to a defined cellular outcome.

That outcome now has a name. Ferroptosis is an iron-dependent form of regulated cell death executed by the uncontrolled peroxidation of polyunsaturated phospholipids, first described in 2012 and now understood as a metabolic nexus at which iron handling, lipid composition and thiol redox control converge [21–23]. Its central brake is glutathione peroxidase 4 (GPX4), a selenoprotein that reduces phospholipid hydroperoxides in situ; its principal substrates are arachidonoyl- and adrenoyl-phosphatidylethanolamines generated by ACSL4 and LPCAT3; and its enzymatic initiators include the 15-lipoxygenase (ALOX15) scaffolded by PEBP1, an axis that was demonstrated in asthmatic airway epithelium in the very paper that defined it [24–27]. Between 2023 and 2026 a handful of experimental studies extended this biology to AR, reporting that house dust mite (HDM) or IL-4/IL-13 exposure induces ferroptosis-type lipid peroxidation in human nasal epithelial cells and in murine nasal mucosa, and that at least one of these pathways compromises the epithelial barrier [28–30]. Figure 1 places these studies against the wider chronology of ferroptosis research and shows how recent the nasal work is.

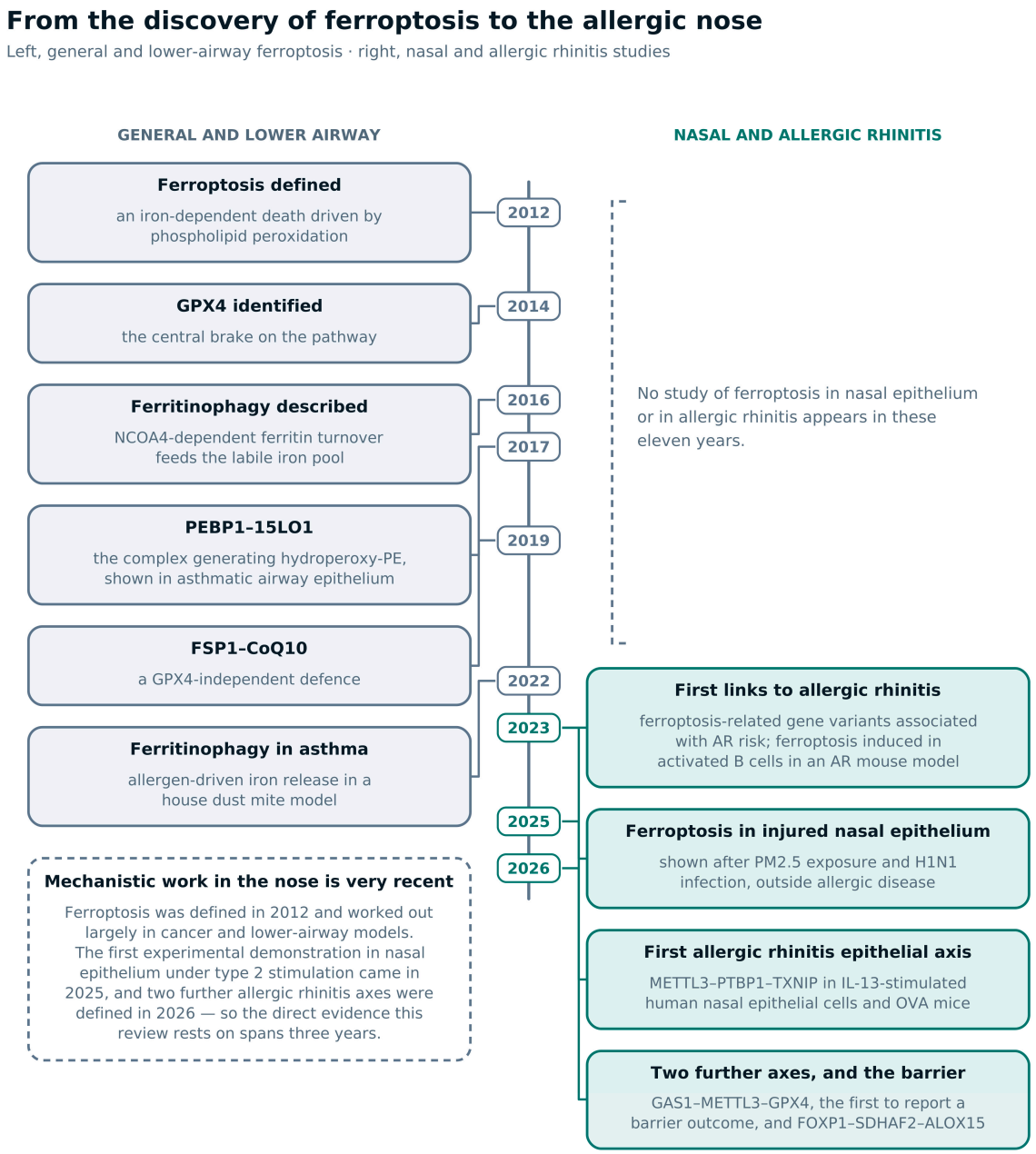

Figure 1. Chronology of ferroptosis research from its definition in 2012 to the first allergic rhinitis studies. The lower track shows the landmark studies that established the pathway in general and lower-airway systems: the definition of ferroptosis as an iron-dependent, peroxidation-driven death modality (2012), the identification of GPX4 as its central brake (2014), the demonstration of the PEBP1–15LO1 complex in asthmatic airway epithelium (2017), the description of the FSP1–CoQ10 defence (2019) and the ferritinophagy-dependent mechanism in house dust mite asthma (2022). The upper track shows the nasal and allergic rhinitis literature: a candidate-gene association between ferroptosis-related variants and AR risk (2023), the first demonstration of ferroptosis in nasal epithelium under type 2 stimulation (2024) and the two defined AR signalling axes reported in 2026. The figure makes explicit that mechanistic work in the nose spans only three years, which is the central limitation of the evidence base reviewed here.

Several reviews have already addressed ferroptosis across allergic diseases, including a 2026 synthesis with a dedicated AR section, a review spanning upper and lower airway inflammation, and shorter overviews [31–35]. We do not duplicate them. Their scope is the disease family; ours is a single tissue compartment, the nasal epithelial barrier,

and a single biochemical process, lipid peroxidation, viewed from both ends: from the clinical biomarker studies that have measured its products in patients, and from the molecular studies that have begun to explain how it is generated and what it does to the barrier. Three features distinguish this review. First, we integrate the two-decade clinical literature on lipid peroxidation markers in AR—including nasal lavage and exhaled breath condensate data, thiol/disulphide homeostasis and iron status—which the ferroptosis reviews have largely ignored. Second, we grade every mechanistic claim by the system in which it was obtained (AR patients or AR models; adjacent nasal disease such as chronic rhinosinusitis or pollutant-injured nasal epithelium; or asthma and lower-airway models), so that readers can see exactly which parts of the ferroptosis narrative in AR are demonstrated and which are borrowed. Third, we approach the problem from the perspective of tissue pathology, asking which readouts could realistically be obtained from nasal biopsies and lavage fluid to test the model in patients.

Scope and Literature Search

This is a narrative review with a structured search. We searched PubMed/MEDLINE, Scopus and Web of Science from inception to 20 October 2026, without language restriction, using combinations of the terms "allergic rhinitis", "nasal epithelium", "nasal mucosa", "rhinosinusitis", "ferroptosis", "lipid peroxidation", "malondialdehyde", "4-hydroxynonenal", "isoprostane", "oxidative stress", "GPX4", "ALOX15", "ACSL4", "iron", "ferritinophagy", "Nrf2", "tight junction", "epithelial barrier" and "antioxidant". Reference lists of retrieved reviews were searched by hand. We included primary studies and reviews in humans, animal models and nasal epithelial cell systems; studies in asthma and other lower-airway diseases were included only where they supply mechanisms that have not yet been tested in the nose, and are labelled as such throughout. Where a claim rests on a study whose full text we could not verify, we say so. Figure 2 sets out the search and selection process and the exclusion rules applied. The review is organised from mechanism (Section 2) through the nasal barrier (Section 3) and the clinical biomarker evidence (Section 4) to the direct and extrapolated evidence for ferroptosis in AR (Sections 5 and 6), an integrative model (Section 7), therapeutic implications (Section 8) and a research agenda (Section 9).

Eligibility criteria. Records were eligible if they reported original data or a systematic synthesis on lipid peroxidation, ferroptosis, oxidative stress or antioxidant status in one of three settings: patients with allergic rhinitis; animal models of allergic rhinitis; or nasal epithelial cells or nasal tissue exposed to allergen, type 2 cytokines or pollutants. Studies of other nasal disease (chronic rhinosinusitis, viral, smoke or particulate injury) and of asthma or other lower-airway and non-airway systems were eligible only where they supplied a mechanism that has not yet been tested in the nose, and are labelled as such wherever they are used. Records were excluded if they did not address lipid peroxidation or ferroptosis in a nasal or airway context, if no abstract could be retrieved, if they were conference abstracts, editorials or commentaries without primary data, or if the article carried a retraction, correction or erratum. The 98 references added by manual searching were not part of the database yield: they were taken from the reference lists of retrieved articles and admitted only where they supplied a foundational definition, a methodological standard or a specific mechanistic result cited in support of a stated claim. These are concentrated in Section 2 and in the assay descriptions rather than in the allergic rhinitis evidence base, which rests on the studies retrieved by the search.

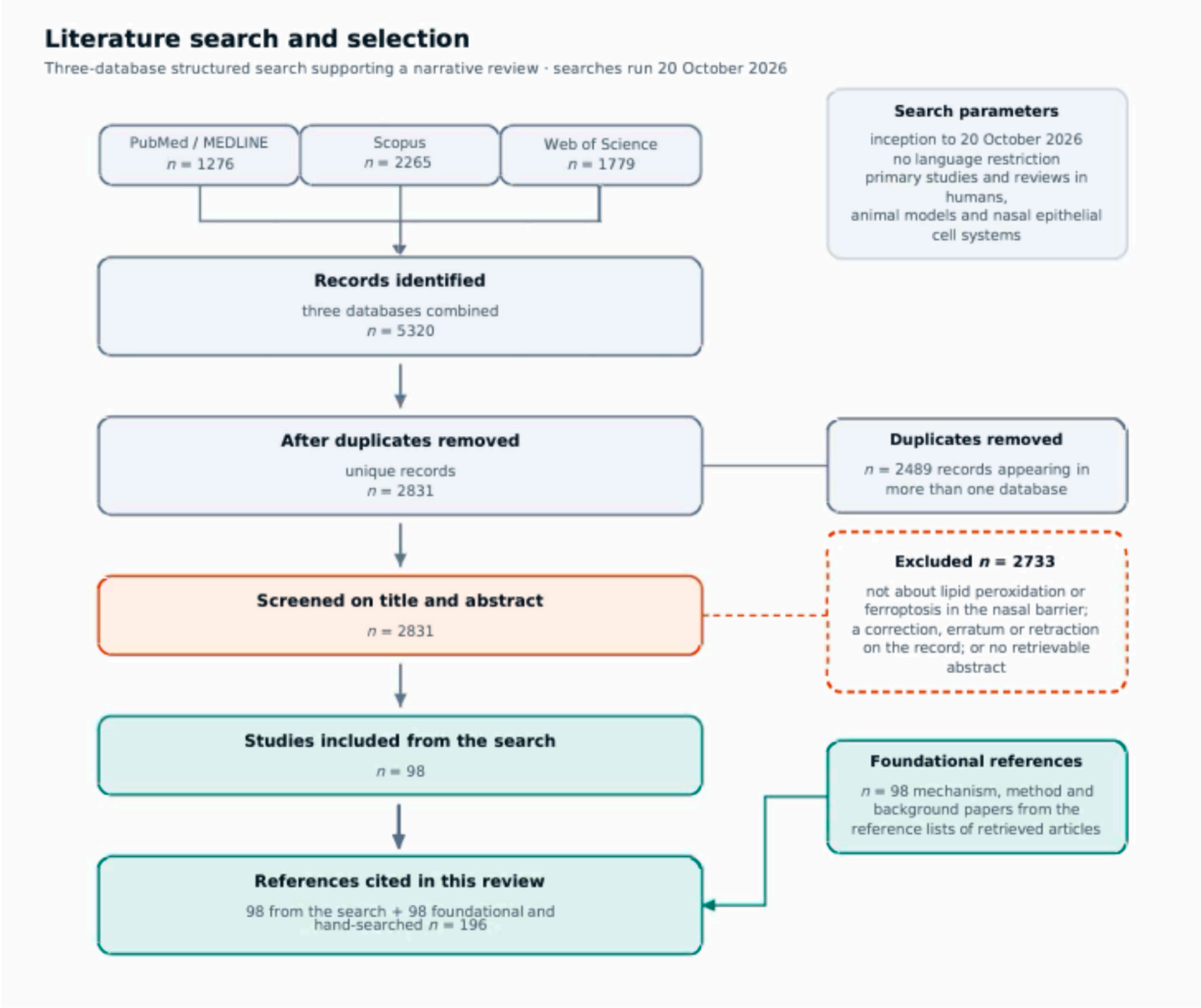

Figure 2. Literature search and selection. Records were identified in PubMed/MEDLINE (n = 1276), Scopus (n = 2265) and the Web of Science Core Collection (n = 1779) from inception to 20 October 2026 without language restriction, giving 5320 records; removing the 2489 that appeared in more than one database left 2831 unique records. These were screened on title and abstract, and 2733 were excluded as not concerning lipid peroxidation or ferroptosis in the nasal epithelial barrier, as carrying a retraction, correction or erratum, or as having no retrievable abstract. Ninety-eight studies were included from the search; a further 98 foundational, mechanistic and methodological references were identified from the reference lists of retrieved articles, giving the 196 references cited in this review.

Evidence grading. Three tiers are used throughout the text. AR-direct denotes a finding obtained in patients with allergic rhinitis, in an animal model of allergic rhinitis, or in nasal epithelial cells stimulated with allergen or with IL-4/IL-13. Nasal-adjacent denotes a finding in human nasal tissue or nasal epithelial cells outside allergic rhinitis, principally chronic rhinosinusitis with nasal polyps and pollutant-, virus- or smoke-injured nasal epithelium. Asthma/non-airway denotes a finding from lower-airway or wholly non-airway systems, which we treat as hypothesis-generating for the nose and never as established there. Antioxidant and anti-ferroptotic strategies in allergic rhinitis grades on a deliberately different axis, because the question it answers is the strength of therapeutic evidence rather than the provenance of a mechanism; its tiers combine study design with provenance (randomised trial in AR, non-randomised clinical study in AR, preclinical AR model, preclinical asthma model, or mechanistic proposal), and they nest within the three tiers above, its AR tiers falling inside AR-direct and its asthma tier inside asthma/non-airway.

2. Lipid Peroxidation and Ferroptosis: The Machinery That Sets Vulnerability in a Mucosal Epithelium

2.1. Chemistry of Lipid Peroxidation and Its Products

Lipid peroxidation is a radical chain reaction [36]. Hydroperoxides decompose, particularly in the presence of ferrous iron, to alkoxyl radicals and to a family of reactive electrophilic aldehydes of which malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE) are the most studied. Both adduct proteins and DNA bases and act as signalling electrophiles at sub-lethal concentrations [37]; MDA is most often measured by the thiobarbituric acid reactive substances (TBARS) assay, which is sensitive but not specific. The F_2-isoprostanes, including 8-iso-prostaglandin $F_{2\alpha}$ (8-isoprostane), are products of free-radical-catalysed arachidonate peroxidation and the most chemically specific available index of lipid peroxidation in vivo. Two caveats matter for airway fluids: 8-iso-$PGF_{2\alpha}$ can also be generated enzymatically by cyclooxygenase, which is induced in inflamed type 2 airways, and the specificity of the analyte is not inherited by the immunoassays most often used on nasal lavage and exhaled breath condensate [16,38,39].

The distinction between generic "lipid ROS" and the ferroptotic death signal matters for this review. Redox lipidomics has shown that the lethal species in ferroptosis are not random peroxidation products but specific oxygenated phosphatidylethanolamines—15-hydroperoxy-arachidonoyl-PE and the corresponding adrenoyl species—generated from PUFA-PE [25]. Imaging identifies the endoplasmic reticulum as the initial site of the peroxidation front, although ferroptosis can also begin at mitochondrial and lysosomal membranes [40]. Measuring MDA or 8-isoprostane in nasal lavage therefore tells us that peroxidation is occurring in the nasal compartment; it does not by itself tell us that epithelial cells are dying by ferroptosis. We return to this point when we assess the clinical biomarker literature (Section 4) and the research agenda (Section 9).

Figure 3 sets out the chain reaction and the products by which it is measured.

2.2. Substrate Supply: ACSL4, LPCAT3 and Fatty Acid Transporters

Cells become ferroptosis-prone when their membranes are rich in PUFA-containing phospholipids. Acyl-CoA synthetase long-chain family member 4 (ACSL4) activates arachidonic and adrenic acid for esterification, and lysophosphatidylcholine acyltransferase 3 (LPCAT3) incorporates them into PE; ACSL4 deletion renders cells markedly resistant to GPX4 inhibition, which is why its expression is used as a marker of ferroptotic sensitivity [26,41]. Upstream, fatty acid import shapes the substrate pool, and the transporter SLC27A2 (FATP2) has surfaced specifically in type 2 nasal inflammation: in nasal polyp epithelium it routes arachidonic and adrenic acid into phospholipids and marks lipid peroxidation, alongside up-regulated ALOX15 and DUOX1, with ACSL4 and LPCAT3 enriched in SLC27A2-positive cells [42]. This observation is important because it shows, in human nasal tissue, that type 2 inflammation reconfigures epithelial lipid metabolism towards the very substrates that ferroptosis requires.

2.3. Initiation: Lipoxygenases, NADPH Oxidases, Mitochondria and Labile Iron

Peroxidation can be initiated enzymatically or non-enzymatically. The enzymatic route most closely tied to ferroptosis is ALOX15 (15-lipoxygenase-1), which oxygenates free arachidonate but, when complexed with phosphatidylethanolamine-binding protein 1 (PEBP1), is redirected to membrane-esterified PE, generating the hydroperoxy-PE death signal; the complex was demonstrated in airway epithelial cells from patients with asthma, in which IL-13 drives both 15LO1 expression and glutathione depletion [27,43]. Non-enzymatic initiation requires reactive oxygen species and iron. In the nasal mucosa the principal ROS sources are the epithelial NADPH oxidases NOX1 and NOX4, which are overexpressed

in allergic nasal mucosa [44], and the dual oxidases DUOX1/DUOX2, constitutively abundant at airway mucosal surfaces [45], with NOX4-derived ROS driving MUC5AC hypersecretion in human nasal epithelial cells [46]; mitochondrial complex III, whose oxidative damage amplifies allergic airway inflammation in vivo [47]; inducible nitric oxide synthase, elevated in nasal air in AR [48,49]; and, uniquely for allergic disease, the NAD(P)H oxidases carried by pollen grains and sub-pollen particles themselves [12,13].

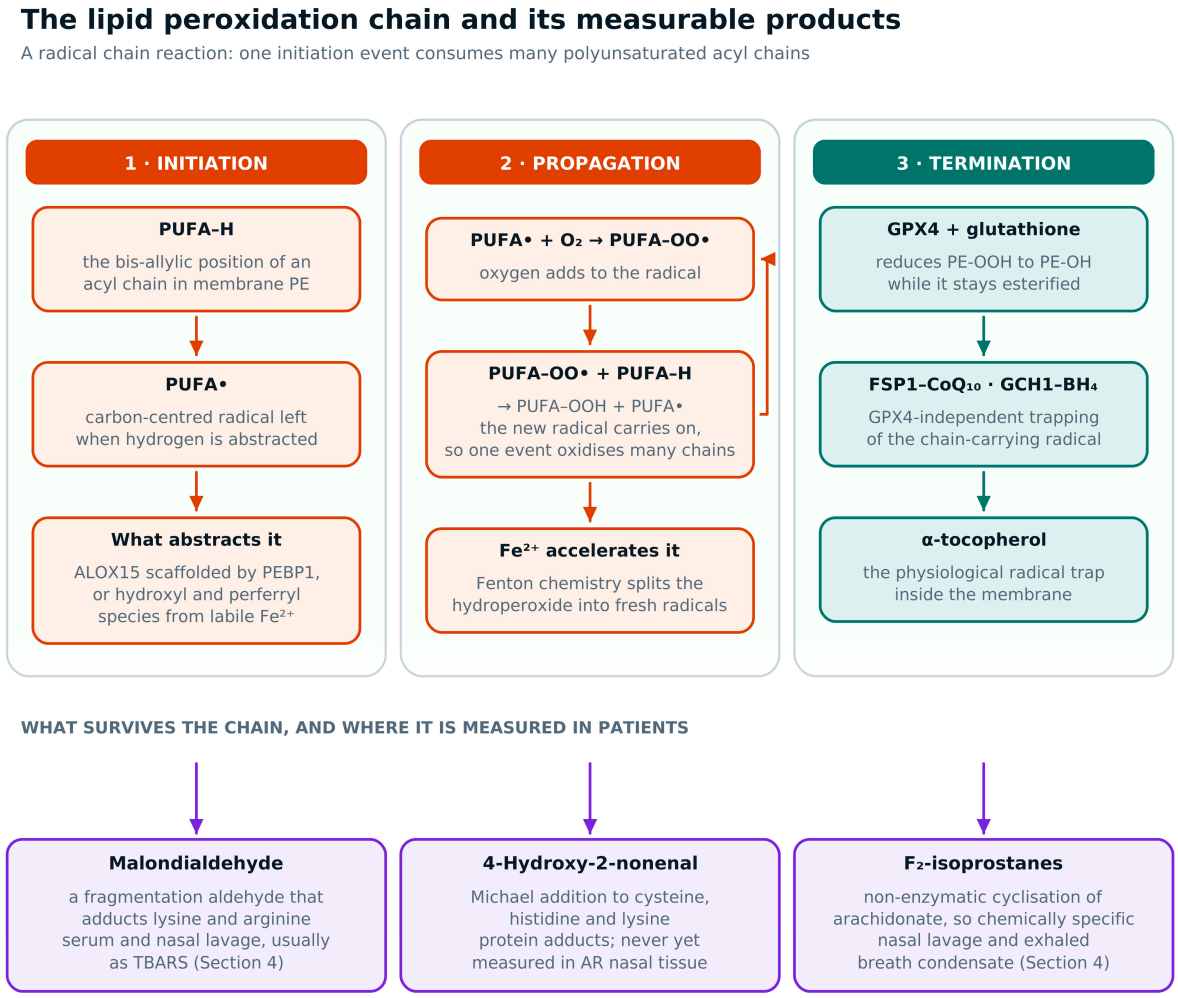

Figure 3. The chemistry of lipid peroxidation: initiation, propagation, termination and the products measured in patients. Initiation abstracts a hydrogen atom from the bis-allylic position of a polyunsaturated acyl chain, either enzymatically through a lipoxygenase or non-enzymatically through hydroxyl and perferryl species generated by Fenton chemistry on labile Fe^{2+}. The resulting carbon-centred radical adds molecular oxygen to give a peroxyl radical, which abstracts a further hydrogen atom and so propagates the chain; a single initiation event therefore oxidises many acyl chains. Termination occurs when the chain-carrying radical is reduced—by α-tocopherol within the membrane, by GPX4 acting on the esterified hydroperoxide, or by the GPX4-independent FSP1–CoQ10 and GCH1–BH4 systems. Fragmentation of the hydroperoxides yields the electrophilic aldehydes malondialdehyde and 4-hydroxy-2-nonenal, which adduct proteins and are detected as thiobarbituric acid reactive substances or by specific immunoassay, while non-enzymatic cyclisation of arachidonic acid yields the F_2-isoprostanes, the most chemically specific of the markers used in nasal lavage and exhaled breath condensate (Section 4).

Iron enters the equation twice: as the catalytic metal of the lipoxygenases described above, and through Fenton-type chemistry, in which ferrous iron homolytically reduces lipid hydroperoxides to alkoxyl radicals and so accelerates chain propagation. The labile

iron pool is fed by transferrin receptor-mediated uptake and by ferritinophagy, the NCOA4-dependent autophagic degradation of ferritin shown to be necessary for erastin-induced ferroptosis [50,51]. HDM exposure activates ferritinophagy and raises unbound iron in airway epithelial cells, and both the iron chelator deferoxamine and the radical-trapping antioxidant ferrostatin-1 protect them [52]. Transferrin receptor 1 itself accumulates on the surface of ferroptotic cells and has been validated as a tissue marker of ferroptosis suitable for immunohistochemistry, together with anti-MDA-adduct staining [53]. Iron overload also activates gasdermin D and amplifies allergic airway inflammation through pyroptosis, a reminder that excess iron in allergic airways has more than one lethal outlet [54].

2.4. Defence: GPX4–Glutathione–Selenium, FSP1–CoQ10, DHODH, GCH1–BH4 and Nrf2

GPX4 is the principal enzyme able to reduce phospholipid hydroperoxides while they remain esterified within membranes, and its inactivation—pharmacologically by RSL3 or genetically—is sufficient to trigger ferroptosis in cultured cells and acute tissue injury in mice [24,55]. It is not, however, the sole such activity: peroxiredoxin 6 contributes a smaller one, apparently indirectly, by directing selenium utilisation for GPX4 synthesis [56,57]. GPX4 depends on two supplies: reduced glutathione, synthesised from cysteine imported as cystine by system xc^-, the Na^+-independent cystine/glutamate antiporter (SLC7A11/xCT with SLC3A2), whose inhibition by erastin was the original route to ferroptosis [21,58]; and selenium, because only the selenocysteine form of the enzyme survives the overoxidation that peroxide stress imposes [59]. Three GPX4-independent systems act in parallel, and are reviewed in detail elsewhere: FSP1 regenerates reduced coenzyme Q10 at the plasma membrane, which traps lipid radicals [60,61]; a proposed equivalent role for mitochondrial dihydroorotate dehydrogenase (DHODH) is contested, the ferroptosis-sensitising effect of its inhibitor brequinar having been attributed to the off-target inhibition of FSP1 [62]; and GTP cyclohydrolase 1 produces tetrahydrobiopterin, which, with GCH1-driven lipid remodelling and endogenous CoQ10 synthesis, selectively preserves phospholipids bearing two polyunsaturated acyl tails [63]. Dietary vitamin E (α-tocopherol) is the physiological radical-trapping antioxidant of membranes, and its depletion unmasks ferroptosis where GPX4 is deficient [64,65]. Ferrostatin-1 and liproxstatin-1 act by the same mechanism with far higher potency in membranes, which is why they outperform α-tocopherol in cell-based assays [66].

Transcriptionally, these defences converge on nuclear factor erythroid 2-related factor 2 (Nrf2), which induces SLC7A11, the glutathione-synthesising enzymes, ferritin, ferroportin and haem oxygenase-1, and is the dominant transcriptional determinant of anti-ferroptotic capacity in epithelia [67]. One element is directionally ambiguous: because HMOX1 liberates iron from haem, strong HO-1 induction can be pro-ferroptotic rather than protective [68]. Nrf2 output should therefore be read as net antioxidant capacity rather than as the sum of its individual targets. Nrf2 signalling is suppressed by PM2.5 and modulated by ozone in the nasal mucosa of AR mouse and rat models [69,70], and influenza virus induces ferroptosis of nasal mucosal epithelial cells by disabling the Nrf2–KEAP1–GCLC axis, which demonstrates that the Nrf2–ferroptosis link operates in nasal epithelium specifically [71].

2.5. Ferroptosis as a Flexible Constellation

Ferroptosis is best regarded not as a single linear pathway but as a family of related mechanisms whose dominant driver varies with cell type and context [72]. A tissue may be vulnerable because its membranes are PUFA-rich, because it expresses a lipoxygenase–PEBP1 complex, because it carries a large labile iron pool, because its GPX4 or selenium supply is marginal, or because Nrf2 output is suppressed. This has two consequences for

AR: findings in bronchial epithelium cannot be assumed to hold in the nose without being tested, and the nasal epithelium—with its type 2-induced ALOX15 and ACSL4, its NOX/DUOX enzymes and its direct exposure to pollen oxidases and metal-rich particulates—has several independent reasons to be ferroptosis-prone. Figure 4 summarises the machinery as it applies to a nasal epithelial cell.

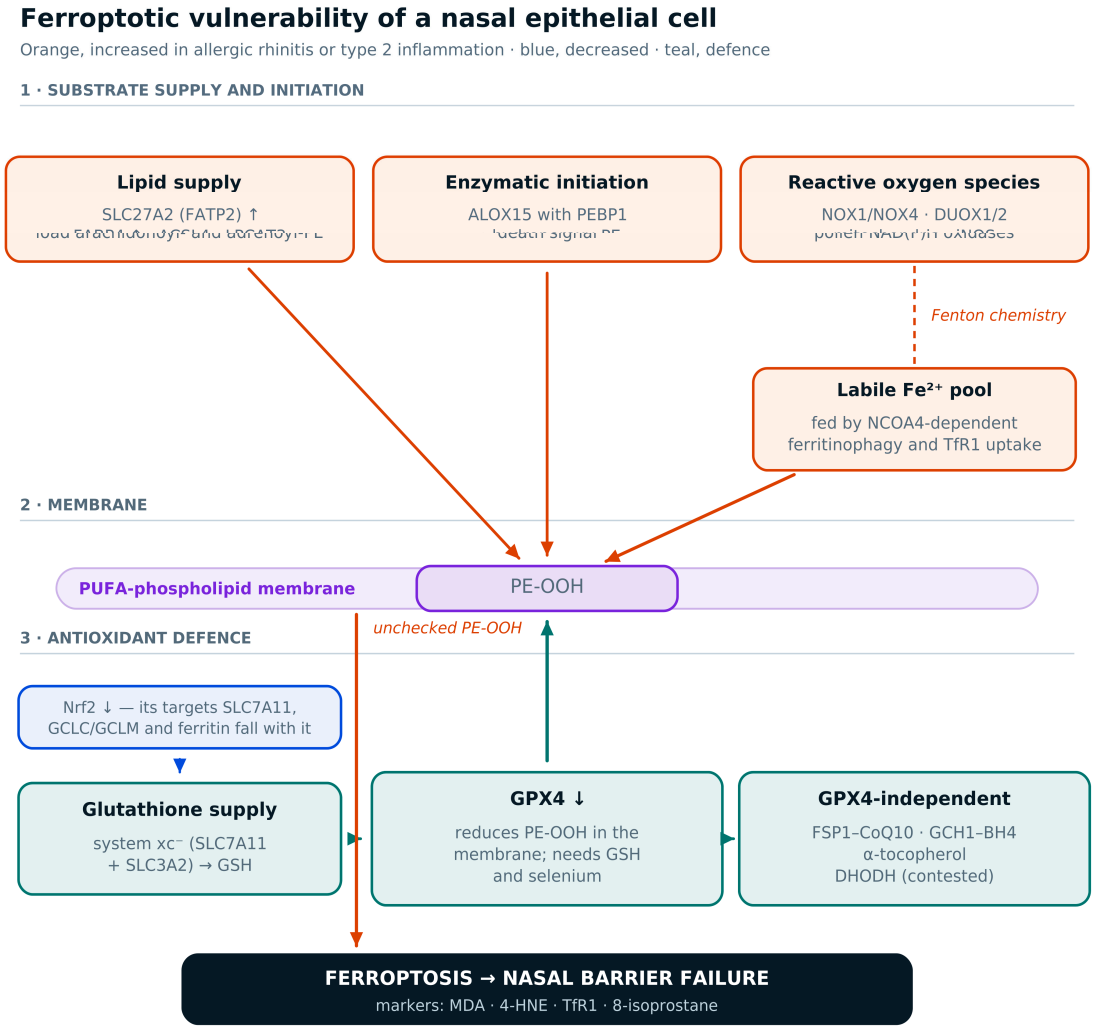

Figure 4. Molecular determinants of ferroptotic vulnerability in a nasal epithelial cell. Polyunsaturated fatty acids imported through SLC27A2 (FATP2) and chaperoned by FABP4 are activated by ACSL4 and incorporated into phosphatidylethanolamine (PE) by LPCAT3, generating the substrate for peroxidation. Initiation proceeds enzymatically through the ALOX15–PEBP1 complex or non-enzymatically through reactive oxygen species from NOX1/NOX4, DUOX1/2, mitochondria, inducible NO synthase and pollen-borne NAD(P)H oxidases, with labile Fe^{2+} released by NCOA4-dependent ferritinophagy accelerating chain propagation through Fenton-type chemistry. Lipid hydroperoxides (PE-OOH) are reduced by GPX4, which requires glutathione (GSH; synthesised from cystine imported by system xc^-) and selenium; FSP1–CoQ10 and GCH1–BH4 provide GPX4-independent radical trapping, and α-tocopherol is the physiological membrane antioxidant. Nrf2 transcriptionally coordinates SLC7A11, GCLC/GCLM, ferritin and ferroportin, together with HMOX1, whose induction is directionally ambiguous because haem catabolism releases iron. Unchecked peroxidation yields the electrophilic aldehydes malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE), which adduct cellular proteins, and the F_2-isoprostanes, which mark the process in nasal fluids; junctional proteins such as occludin are themselves redox-sensitive targets. Elements shown in red have been reported as up-regulated, and those in blue as down-regulated, in allergic rhinitis models or type 2-inflamed nasal tissue (Section 5). Abbreviations are listed at the end of the article.

https://doi.org/10.3390/antiox15121544

3. The Nasal Epithelial Barrier in Allergic Rhinitis: Architecture, Failure and Redox Control

3.1. Architecture of the Barrier

The nasal epithelial barrier is a composite of physical, chemical, immune and microbial layers. Its physical core is the apical junctional complex: tight junctions assembled from claudins, occludin and the junctional adhesion molecules, anchored to the actin cytoskeleton by the zonula occludens scaffold proteins ZO-1, ZO-2 and ZO-3, and underlain by E-cadherin-based adherens junctions and desmosomes [73–75]. Tight junction composition and function in human nasal epithelium are modulated by growth factors, Toll-like receptor ligands and cytokines, and differ in AR and viral infection [76]. Above the junctions sit the mucus gel, the glycocalyx with membrane-tethered mucins such as MUC1, and the mucociliary escalator; beneath them lie basal progenitor cells that retain an "allergic inflammatory memory" after type 2 stimulation and that regenerate the surface epithelium [77–79]. Dendritic cells extend processes beyond the tight junctions in human AR mucosa, providing the anatomical route for transepithelial antigen sampling [80].

3.2. Evidence of Barrier Failure in Patients with AR

The pivotal clinical demonstration came from nasal biopsies of patients with HDM-induced AR, in which transepithelial electrical resistance was reduced, paracellular permeability increased, and occludin and ZO-1 expression decreased compared with controls [81]. The same group subsequently showed that histamine, IL-4 and the Th1 mediators IFN-γ and TNF-α each increase nasal epithelial permeability; that the Th1- and Th2-driven defects are reversed by anti-TNF-α and anti-IL-4Rα, respectively; and that histone deacetylase activity sustains the defect, so that HDAC inhibition restores epithelial integrity in patient-derived cultures and in mice [17,82]. That non-type 2 mediators disrupt the barrier as effectively as type 2 ones is itself informative, and bears on the endotype question raised in Section 6.3. Nasal mucus proteomics in AR patients independently reflects increased epithelial permeability [83], and MUC1 deficiency promotes barrier dysfunction in AR, linking the glycocalyx to junctional integrity [78]. Causality in the other direction has also been established: experimentally induced nasal barrier disruption increases sensitisation and mast cell degranulation in mice even in the absence of pre-existing allergic inflammation, so barrier failure can precede and drive the allergic response rather than merely follow it [84].

3.3. What Disrupts the Barrier

Allergen proteases were the first disruptors identified. The HDM cysteine protease Der p 1 cleaves tight junction proteins and facilitates transepithelial allergen delivery [85], and in patient-derived nasal epithelial cultures it produces a transient, dose-dependent fall in transepithelial resistance with claudin-1 cleavage and IL-6 release, although paracellular flux was not always measurably changed—a nuance worth preserving when the barrier argument is made [86]. HDM also triggers calcium signalling that disrupts cell–cell contacts more readily in epithelium from allergic than from healthy donors [87]. Pollen grains release proteases on hydration that detach airway epithelial cells and open tight junctions [88,89], although differentiated bronchial epithelium exposed to timothy grass pollen extract retained its physical barrier while altering mediator release, so pollen's direct barrier toxicity should not be overstated [90]. Environmental particulates are potent disruptors: diesel exhaust particles, but not ragweed pollen, disrupted nasal tight junctions in vivo and exacerbated AR in mice [91], and PM2.5 at non-cytotoxic doses increased permeability and degraded ZO-1, occludin and claudin-1 in the human nasal RPMI 2650 cell line, an effect largely abolished by N-acetylcysteine, which establishes that the

junctional damage is proximately oxidative [92,93]. Among the alarmins, thymic stromal lymphopoietin paradoxically strengthens tight junctions in human nasal epithelial cells, so the alarmin–barrier relationship is bidirectional [94]. Collectively the inhaled exposome and the type 2 milieu act on the barrier through convergent routes, and the barrier defect itself amplifies both [15,95–98].

3.4. Redox Sources and Redox Targets in the Allergic Nasal Mucosa

The nasal mucosa of patients with AR is an oxidising environment. NOX1 and NOX4 protein, mRNA and superoxide are overexpressed in allergic mucosa, localised to surface epithelium, submucosal glands, endothelium and inflammatory cells [44]; NOX4 mediates hydrogen peroxide-driven MUC5AC overexpression in nasal epithelial cells [46]; and DUOX1/2 are abundant at the apical surface, where they generate hydrogen peroxide in response to allergens and microbes [45]. Mitochondrial ROS are elevated in peripheral blood mononuclear cells of patients with persistent AR and drive NLRP3-dependent IL-1β release [99], and oxidant damage to mitochondrial complex III increases allergic airway inflammation in vivo [47]. Pollen grains and sub-pollen particles deliver their own NAD(P)H oxidase activity, generating ROS in airway lining fluid within minutes of deposition; removing this oxidase activity or scavenging ROS blocks the augmentation of allergic inflammation, and ozone exposure increases the oxidase activity of ragweed pollen [12–14,100]. Lactoferrin, but not iron-saturated lactoferrin, suppresses pollen-induced ROS and eosinophilic inflammation, an early hint that iron availability conditions the oxidant response to allergen [101]. Nasal nitric oxide is consistently higher in AR than in healthy controls or non-allergic rhinitis [48,49].

The junctions themselves are redox targets. Occludin oligomerisation depends on the redox state of its cysteine residues and is altered by pro- and anti-oxidant conditions [102], and the PM2.5 experiments cited above show that ROS precede junctional protein degradation [92]. The counter-regulatory arm is Nrf2: PM2.5 suppresses Nrf2 activity, raises MDA and lowers superoxide dismutase and haem oxygenase-1 in the nasal lavage of AR mice while activating NF-κB [69], ozone alters Nrf2 and its target genes in the nasal mucosa of AR rats [70], and N-acetylcysteine blocked both the diesel-exhaust-induced disruption of nasal tight junctions and the increase in sneezing in ragweed-sensitised mice [91,98]. Oxidative stress also disrupts autophagy and mitophagy in airway epithelium, which, as Section 2.3 explains, feeds the labile iron pool through ferritinophagy [103].

3.5. Cell Death Modalities of the Nasal Epithelium

Reviews of programmed cell death in AR nasal epithelium have concentrated on apoptosis, autophagy and pyroptosis and link their dysregulation to barrier damage, immune imbalance and cytokine excess [104,105], although autophagy is better regarded as a regulator of cell death than as a death pathway in its own right, and is treated as such throughout this review. The most complete mechanistic chain of this kind joins PM2.5 exposure, an AhR/CYP1A1/ROS axis, NLRP3-dependent pyroptosis and nasal epithelial barrier dysfunction in AR [106]. Ferroptosis entered this list only in 2025, when the first experimental study of ferroptosis in nasal epithelium under type 2 stimulation appeared [29], although ferroptosis had been connected to AR susceptibility and to AR immune cells two years earlier [107,108], and had been demonstrated in non-allergic nasal epithelial injury in the same year [71,109]; the studies that placed it there are the subject of Section 5. Figure 5 summarises how exposome and type 2 inputs converge on redox imbalance and barrier failure in the nasal epithelium.

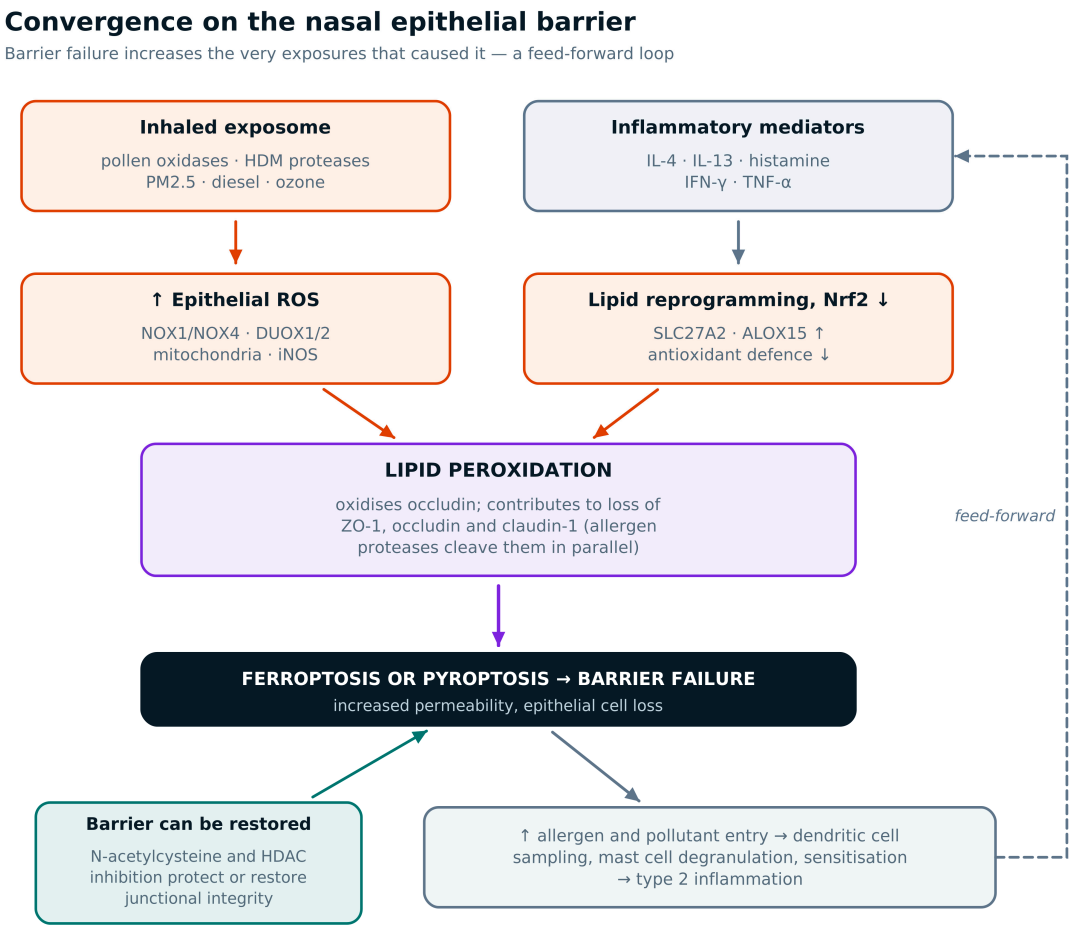

Figure 5. Convergence of exposome and type 2 signals on redox imbalance and barrier failure in the nasal epithelium. Inhaled exposures (pollen grains and sub-pollen particles carrying NAD(P)H oxidases, house dust mite proteases, PM2.5 and diesel exhaust particles, ozone, and tobacco smoke) and endogenous mediators (IL-4, IL-13, histamine, and the Th1 cytokines IFN-γ and TNF-α) increase epithelial reactive oxygen species through NOX1/NOX4, DUOX1/2, mitochondrial complex III and iNOS, reprogram lipid metabolism (ALOX15, ACSL4, FABP4, SLC27A2) and suppress Nrf2. The resulting lipid peroxidation oxidises occludin, contributes to the degradation of ZO-1, occludin and claudin-1 and, in the extreme, kills epithelial cells by ferroptosis or pyroptosis; allergen proteases act in parallel by cleaving junctional proteins directly. Loss of barrier integrity increases allergen delivery to subepithelial dendritic cells, alarmin release and mast cell degranulation, which in turn sustain type 2 inflammation and histamine release, closing a feed-forward loop. Interventions shown in green (N-acetylcysteine and histone deacetylase inhibition) have been shown to protect or restore barrier parameters in nasal or airway epithelium [82,91,92].

4. Lipid Peroxidation and Antioxidant Status in Patients with Allergic Rhinitis: What Has Actually Been Measured

The clinical biomarker literature on oxidative stress in AR is older, larger and more heterogeneous than the ferroptosis literature, and it has never been read with ferroptosis in mind. Table 1 summarises the studies by compartment. Three features emerge: measurements made in the airway compartment are far more consistent than measurements made in blood; thiol oxidation is the most reproducible systemic signal; and no study has yet measured a ferroptosis-specific readout in nasal tissue.

4.1. Systemic Markers in Adults

Early case–control studies reported higher serum MDA with lower vitamin A, vitamin E and total antioxidant capacity in AR [110], and higher erythrocyte lipid peroxidation with depleted plasma vitamin C, ceruloplasmin and total antioxidant activity in perennial AR [111]. These results were not uniformly replicated. In a Chinese cohort serum nitric oxide and the iNOS/total NOS ratio were elevated while MDA was unchanged or even lower [112], and in Turkish adults, erythrocyte CuZn-superoxide dismutase was reduced but glutathione peroxidase and MDA did not differ from controls [113]. The composite Erel assays have been more consistent: total oxidant status (TOS) and the oxidative stress index (OSI) are higher in AR, with TOS discriminating patients from controls with an area under the curve of 0.99 in a recent cohort, whereas total antioxidant status (TAS) is unchanged in adults [114]. The same study found that TOS and OSI correlated negatively with eosinophil counts and did not differ by asthma comorbidity or sensitisation pattern, which argues against a purely eosinophil-driven oxidant burden.

The disagreement over serum MDA is systematic rather than random, and four explanations account for most of it. First, the analyte: most of these studies measure MDA as TBARS, which cross-reacts with other aldehydes, sugars and bilirubin and is sensitive to the storage time, freeze–thaw history and iron content of the sample [37], so between-laboratory values are not commensurable. Second, timing: AR is episodic, and studies that sampled outside the pollen season or did not report season are comparing patients in remission with controls, which biases towards the null, whereas the airway-compartment studies that report positive findings were mostly performed during exposure. Third, the comparator: control groups differ in smoking, obesity, diet and antioxidant supplement use, each of which moves systemic peroxidation markers at least as much as AR does. Fourth, the compartment itself: a nasal mucosal process need not raise circulating MDA at all, and the composite Erel indices behave more consistently than MDA precisely because they integrate many oxidant species rather than one labile aldehyde. This pattern is the main reason we read the airway compartment as the informative one and treat serum MDA as an unreliable proxy for nasal lipid peroxidation.

4.2. Thiol/Disulphide Homeostasis

Dynamic thiol/disulphide homeostasis has provided the most reproducible systemic signature. In seasonal AR, disulphide levels and the disulphide/thiol ratios rise during symptomatic pollen exposure and normalise in the asymptomatic phase, showing that the oxidative shift tracks allergen exposure rather than a fixed trait [115]. Native thiol and the reduced/oxidised thiol ratio are lower in larger adult cohorts [114,116], the pattern is reproduced in children sampled during an attack, together with zinc deficiency [117], and two months of medical treatment restores native thiol and lowers disulphide in persistent AR [118]. Because glutathione is the dominant low-molecular-weight thiol and GPX4 is absolutely glutathione-dependent, a systemic shift towards disulphide is the clinical parameter most directly related to the anti-ferroptotic reserve, even though it is measured in plasma rather than in epithelium.

4.3. The Paediatric "High Oxidant, High Antioxidant" Paradox

Paediatric studies have repeatedly found that both TOS and TAS are elevated in AR. Three case–control studies found both raised, with AR the only independent predictor of TOS in one and the oxidative stress index high despite abundant water-soluble antioxidants in another [119–121]; in a prospective cohort of 226 schoolchildren, TAS but not TOS was independently associated with symptom duration beyond six months per year, suggesting compensatory up-regulation of antioxidant capacity in chronic disease [122]. Against this apparent compensation, specific lipid-phase defences are depleted: serum

vitamin E is lower in children with AR and correlates inversely with specific IgE [123], plasma paraoxonase-1—the HDL-bound enzyme that hydrolyses oxidised phospholipids—is lower and tracks symptom severity inversely [124], and serum albumin is lower and ferritin higher in children with AR [125]. Population data add that higher plasma carotenoids and γ-tocopherol inversely associated with AR and sensitisation, and dietary vitamin C with fewer symptoms [126,127], although a composite "oxidative balance score" was paradoxically associated with higher AR prevalence, probably through reverse causation [128]; markers of DNA rather than lipid oxidation track sensitisation and FeNO rather than the disease label [129,130]. The lesson is that the lipid-phase, chain-breaking defences (vitamin E, paraoxonase, thiols), rather than the Erel serum total antioxidant status—which is unchanged or paradoxically raised—are the parameters that move in blood, which is precisely the pattern ferroptosis biology would predict. In the nasal compartment itself, aggregate antioxidant capacity does fall [131].

4.4. The Airway Compartment: Nasal Lavage and Exhaled Breath Condensate

Measurements made where the disease is located are more informative. Nasal lavage 8-isoprostane and leukotriene B_4 are raised in seasonal AR during the pollen season irrespective of smoking, and nasal 8-isoprostane rises with natural pollen exposure alongside symptoms and eosinophilia and is elevated in children with persistent AR, although it does not correlate with eosinophil counts, which cautions against its use as a stand-alone marker [132–134]. Exhaled breath condensate 8-isoprostane shows the same pattern and falls with intranasal corticosteroids and outside the pollen season [135], and condensate from children with AR contains more MDA and less glutathione than controls [136]. In adolescents, nasal lavage TOS and OSI were higher and TAS lower than in controls, and the nasal OSI independently predicted small-airway resistance [131]. Two panel studies in Chinese adults with AR linked personal PM2.5 constituents to nasal oxidative stress: polycyclic aromatic hydrocarbons, sulphate and ammonium and the elements vanadium, chromium, copper, arsenic, selenium, cadmium and lead were associated with higher nasal lavage MDA, while vanadium, manganese, iron, zinc, arsenic and selenium were associated with lower nasal lavage SOD, in parallel with worse symptom and quality-of-life scores [137,138]. These are the only human data that connect redox-active metal exposure to nasal lipid peroxidation in AR, and they sit naturally beside the PM2.5–ferroptosis experiments in nasal epithelium discussed in Section 5.5.

4.5. Tissue and Lipoprotein Evidence

Direct tissue measurements are scarce. The immunohistochemical demonstration of NOX1, NOX4 and superoxide in allergic nasal mucosa remains the principal human tissue study of oxidant generation in AR [44]. At the lipoprotein level, HDL from patients with AR has reduced antioxidant capacity, lower paraoxonase and cholesteryl ester transfer protein activity, higher lipoprotein-associated phospholipase A_2 activity and a lysophosphatidylcholine-enriched composition, defining a pro-oxidant lipoprotein phenotype that would favour lipid peroxidation at mucosal surfaces [139].

4.6. Iron Status

Because ferroptosis is iron-dependent, iron epidemiology in AR deserves mention even though it is indirect. Claims-based analyses associate AR with iron-deficiency anaemia in children and anaemia in adults, with a gradient by number of atopic diagnoses, although survey data are mixed [140–142]. Premenopausal women with AR show functional iron deficiency—iron stores present but poorly available—that associates with stronger symptoms after nasal allergen provocation [143], and iron deficiency is more frequent in severe than in mild paediatric AR [144]. The mechanistic framework proposed by Roth-Walter is that iron

restriction primes innate immunity towards type 2 responses and that allergen delivery of iron (iron-loaded lipocalins) is tolerogenic [145]. At first sight, iron deficiency sits awkwardly with an iron-dependent death mechanism; the apparent contradiction dissolves once it is recognised that ferroptosis depends on the intracellular labile iron pool, which is governed by ferritinophagy, transferrin receptor expression and ferroportin export rather than by systemic iron stores, and that functional iron deficiency in inflammation reflects sequestration of iron within cells, which is where ferroptosis occurs.

Figure 6 sets the iron findings against the iron-handling machinery of the epithelial cell.



Figure 6. Iron handling in the nasal epithelial cell, and the apparent paradox of iron status in allergic rhinitis. Transferrin-bound iron enters through transferrin receptor 1 and is reduced and released into the labile iron pool, which is the catalytically active, ferroptosis-relevant compartment; non-transferrin-bound iron from inhaled particulate matter enters directly. Iron is stored safely in ferritin and exported through ferroportin, both of which are Nrf2-regulated, and is liberated from ferritin by NCOA4-dependent ferritinophagy. Inhaled metal-rich particulates, cigarette smoke and allergen exposure increase the labile pool, whereas ferritin sequestration and export reduce it. The apparent paradox of allergic rhinitis is that patients show markers of functional iron deficiency and raised ferritin, which the model reads not as a lower ferroptotic risk but as intracellular sequestration with a potentially enlarged labile pool; this remains untested, since nasal ferritin, NCOA4 and transferrin receptor expression have not been compared between patients and controls (Section 9).

4.7. Effects of Treatment on Oxidative Markers

Treatment studies, although small, show that the oxidant burden of AR is modifiable. Intranasal corticosteroids lowered exhaled 8-isoprostane in adults [135] and serum peroxides

in children, in whom the antioxidant potential fell in parallel [146]; combined intranasal mometasone and rupatadine lowered TOS, whereas intranasal steroid alone had little systemic effect [147]; two months of medical treatment restored thiol/disulphide balance [118]; a topical superoxide dismutase formulation lowered serum MDA alongside symptom improvement in a small pilot [148]; and an eight-week randomised trial of the probiotic *Weizmannia coagulans* BC99 reduced serum MDA, raised glutathione, improved symptom and quality-of-life scores and shifted serum unsaturated fatty acid metabolism [149].

Table 1. Human studies of oxidative stress, lipid peroxidation and antioxidant status in allergic rhinitis, by compartment.

Compartment/Study	Design and Population	Lipid Peroxidation and Oxidant Markers	Antioxidant Markers	Not Measured (Ferroptosis-Relevant)
Serum/plasma, adults				
Akbay et al. 2007 [110]	Case–control, 40 AR vs. 40 controls	Serum MDA ↑	Vitamins A and E ↓, total antioxidant capacity ↓	4-HNE, GPX4, iron indices
Sequeira et al. 2012 [111]	Case–control, 39 PAR vs. 53 controls	Erythrocyte TBARS ↑	Vitamin C ↓, ceruloplasmin ↓, total antioxidant activity ↓; SOD ↑; GSH, catalase =	Isoprostanes, selenium
Jiao et al. 2010 [112]	Case–control, 48 AR vs. 23 controls	Serum NO ↑, iNOS ratio ↑; MDA =	GPx ↑, SOD =	Lipid-phase antioxidants
Sağdıç et al. 2011 [113]	Cross-sectional, 22 AR, 36 asthma, 36 controls	MDA =	Erythrocyte CuZn-SOD ↓, GPx =; plasma copper ↑, zinc =	Selenium-dependent GPX4
Ulusoy et al. 2016 [115]	32 SAR (symptomatic vs. asymptomatic) vs. 32 controls	Disulphide ↑ and disulphide/thiol ratios ↑ only when symptomatic	Native thiol/total thiol ↓ when symptomatic	GSH/GSSG in nasal compartment
Savaş & Günizi 2022 [116]	Case–control, 130 adults	Thiol oxidation ratio ↑	Native and reduced thiol ↓, copper ↓	Lipid peroxidation products
Gürpınar & Karaoğlanoğlu 2026 [114]	Case–control, 31 AR vs. 31 controls	TOS ↑ (AUC 0.99), OSI ↑ (AUC 0.91); disulphide ↑	TAS =; total and native thiol ↓	MDA/4-HNE, iron
Trakaki et al. 2019 [139]	Case–control, 43 AR vs. 20 controls	Lp-PLA2 activity ↑, lysoPC-enriched HDL	HDL antioxidant capacity ↓, PON1 ↓	Oxidised phospholipid species
Shi et al. 2018 [99]	Ex vivo PBMC, 45 PAR vs. 23 controls	Mitochondrial ROS ↑, NLRP3/IL-1β ↑	—	Lipid peroxidation
Serum/plasma, children				
Emin et al. 2012 [119]	Case–control, 106 AR vs. 70 controls	TOS ↑	TAS ↑	Vitamin E, PON1
Özkaya et al. 2013 [124]	Case–control, 66 HDM-AR vs. 40 controls	TOS ↑, correlates with symptom score	PON1 ↓, inversely with symptom score	MDA/4-HNE
Sim et al. 2015 [120]	Propensity-matched, 90 AR vs. 90 controls	TOS ↑, OSI ↑	TAS slightly ↑	Lipid-phase antioxidants
Moon et al. 2021 [122]	Prospective, 226 schoolchildren with AR, no control group	TOS not related to symptom duration	TAS ↑ with symptoms >6 months/year (adjusted OR 1.66)	Lipid-phase antioxidants
Arnaudova Danevska et al. 2023 [121]	Case–control, 30 AR vs. 30 controls (probably the same cohort as [146])	d-ROMs/oxidative stress index ↑	Water-soluble antioxidants ↑	Lipid-phase antioxidants
Günizi et al. 2022 [117]	Case–control, 35 PAR (during attack) vs. 35 controls	Disulphide ↑	Total and native thiol ↓, zinc ↓	—
Wang et al. 2020 [123]	Cross-sectional, 65 AR vs. 48 controls	—	Serum vitamin E ↓, inversely with specific IgE	Lipid peroxidation products

Bakkeheim et al. 2011 [125]	Cross-sectional, 102 schoolchildren	—	Albumin ↓; ferritin ↑ in AR	Lipid peroxidation products
Chen et al. 2020 [129]	Nested case–control, 400 preschool children	Urinary 8-OHdG not associated with AR	—	Lipid peroxidation
Airway compartment (nasal lavage/EBC)				
Tanou et al. 2009 [132]	40 SAR (in season) vs. 30 controls	Nasal lavage 8-isoprostane ↑, LTB4 ↑	—	GSH, MDA in lavage
Ciebiada et al. 2014 [133]	Within-subject, 21 grass-pollen AR	Nasal 8-isoprostane ↑ in season; no correlation with eosinophils	—	—
Gratziou et al. 2008 [135]	11 SAR, 12 SAR + asthma, 16 controls; INCS follow-up	EBC 8-isoprostane ↑, LTB4 ↑; 8-isoprostane ↓ with INCS and out of season	—	Nasal fluid markers
Profita et al. 2010 [134]	93 children with AR ± asthma	Nasal 8-isoprostane ↑, PGE2 ↑	—	—
Çelik et al. 2012 [136]	145 children with asthma and/or AR vs. 74 controls	Nasal and oral EBC MDA ↑	EBC GSH ↓	4-HNE, isoprostanes
Köksal et al. 2023 [131]	70 adolescents with AR vs. 30 controls	Nasal lavage TOS ↑, OSI ↑ (predicts small-airway resistance)	Nasal lavage TAS ↓	MDA/4-HNE
Li et al. 2023, 2024 [137,138]	Panel, 49 AR adults, repeated visits (same cohort)	Nasal lavage MDA ↑ with PAHs, sulphate, ammonium, V, Cr, Cu, As, Se, Cd, Pb	Nasal lavage SOD ↓ with V, Mn, Fe, Zn, As, Se	Iron in lavage, 4-HNE
Nasal tissue				
Moon et al. 2009 [44]	Allergic mucosa vs. controls (IHC, RT-PCR)	Superoxide ↑ (DHE)	—	GPX4, 4-HNE, TfR1, ACSL4
Treatment studies				
Kahveci et al. 2021 [147]	84 adults, mometasone ± rupatadine, 1 month	TOS ↓ with combination; INCS alone =	TAS =	—
Göker et al. 2022 [118]	35 PAR adults, 2 months treatment	Disulphide ↓	Native thiol ↑	—
Arnaudova Danevska et al. 2023 [146]	30 children, INCS 8 weeks	Serum peroxides ↓	Antioxidant potential ↓	—
Guo et al. 2016 [148]	Pilot, TAT-SOD cream at LI20 acupoint	Serum MDA ↓	SOD, catalase, GPx =	—
Li et al. 2025 [149]	RCT, 78 adults, *W. coagulans* BC99, 8 weeks	Serum MDA ↓	GSH ↑, SOD stabilised	Nasal compartment

Studies are grouped by the compartment sampled. Direction of change is given relative to healthy controls unless a within-subject design is specified. AR, allergic rhinitis; SAR, seasonal AR; PAR, perennial/persistent AR; MDA, malondialdehyde; TBARS, thiobarbituric acid reactive substances; TOS/TAS/OSI, total oxidant status/total antioxidant status/oxidative stress index (Erel assays); PON1, paraoxonase-1; SOD, superoxide dismutase; GPx, glutathione peroxidase; EBC, exhaled breath condensate; INCS, intranasal corticosteroid; ↑ increased; ↓ decreased; = unchanged; — not measured or not reported. The last column lists lipid-phase or ferroptosis-relevant parameters that were not measured.

4.8. What the Clinical Literature Does Not Contain

Two recent reviews have stressed that most human biomarker evidence in AR comes from peripheral blood rather than nasal mucosa, that cohorts are small and incompletely phenotyped, and that MDA data in rhinitis are fewer and less consistent than in asthma

[19,150]. From the standpoint of this review, the gaps are specific: we identified no study that has measured 4-HNE adducts, oxidised phosphatidylethanolamines, GPX4 expression, transferrin receptor 1 or labile iron in allergic nasal mucosa or lavage; none that has examined whether allergen immunotherapy alters redox markers; and no AR-specific meta-analysis of lipid peroxidation or antioxidant-status biomarkers—nasal nitric oxide is the only redox parameter to have been meta-analysed in AR [48]. These are the measurements that would convert the clinical and the mechanistic literatures into a single testable model, and Section 9 sets them out.

Figure 7 shows what has been measured in each compartment and where the gap lies as presented in the evidence Table 1.

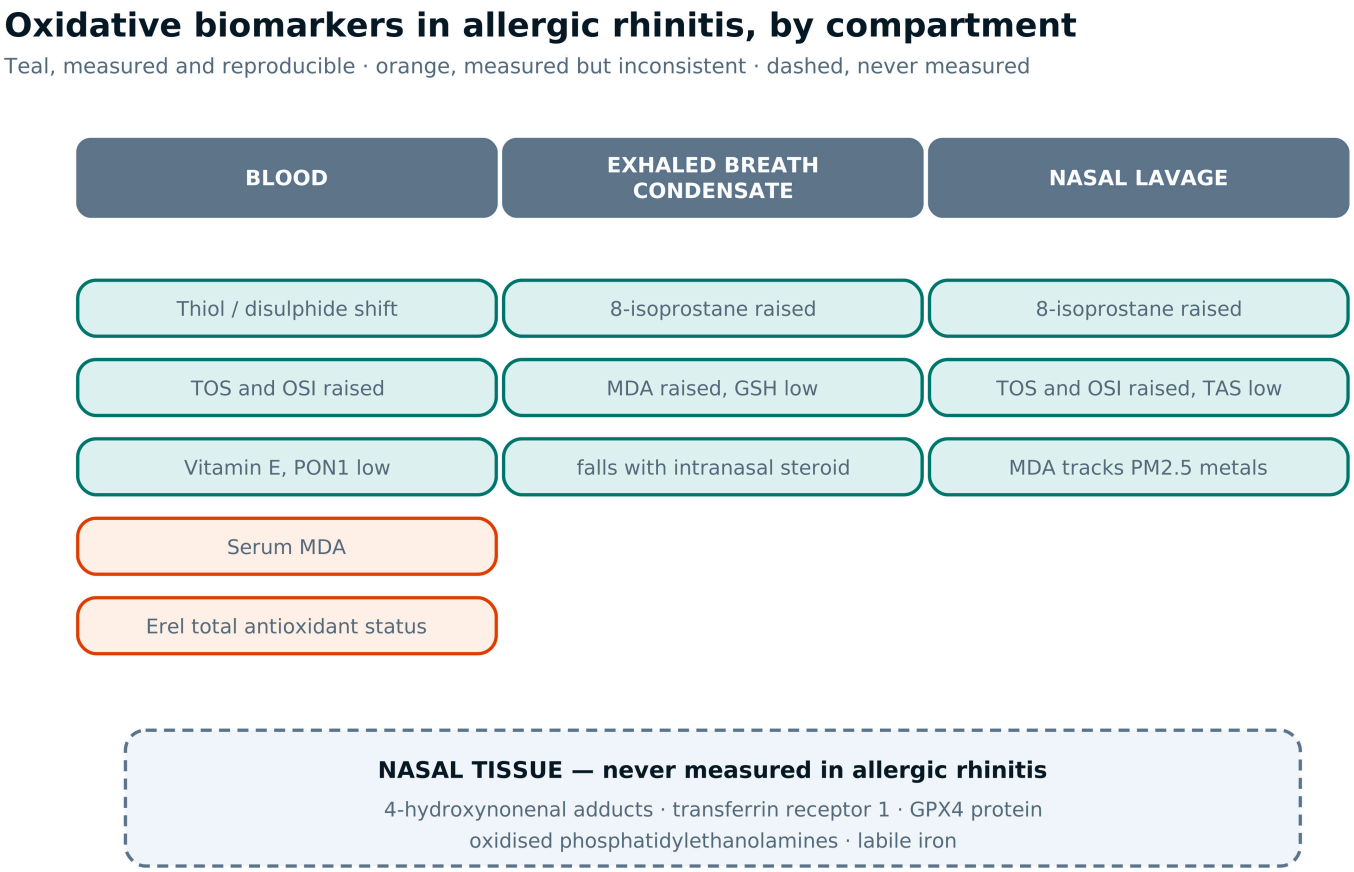

Figure 7. Oxidative-stress and lipid-peroxidation biomarkers measured in allergic rhinitis, by compartment, and the measurement that has never been made. Blood is the most heavily sampled compartment and the least consistent: malondialdehyde and total oxidant status are variably raised, total antioxidant status is raised in children and lowered in adults, and thiol oxidation is the single reproducible systemic signal. Exhaled breath condensate and nasal lavage are sampled less often but agree more closely, with 8-isoprostane, leukotrienes and malondialdehyde consistently raised and total antioxidant capacity reduced in the airway lumen. Nasal tissue has been examined in only one study of oxidant sources, and no study in allergic rhinitis has measured a ferroptosis-specific readout—transferrin receptor 1 with malondialdehyde adducts, 4-hydroxynonenal adducts, oxidised phosphatidylethanolamine species or labile iron—in nasal tissue. That gap, shown as the dashed panel, is the single most consequential absence in the clinical literature and the first item of the research agenda (Section 9). Colour and marking coding: teal, measured and reproducible; orange, measured but inconsistent; dashed line, never measured.

5. Direct Evidence for Ferroptosis in Allergic Rhinitis

The AR-specific ferroptosis literature consists, at the time of writing, of one human genetic association study, four experimental studies in nasal epithelial cells and murine models, one study in immune cells, one in silico analysis and one earlier narrative review that anticipated the m6A–ferroptosis connection. Table 2 summarises these studies with their models, readouts and limitations; Table 3 lists the adjacent nasal studies—chronic rhinosinusitis, pollutant, viral and smoke injury—one of which demonstrates ferroptosis of human nasal epithelium in vivo, while the rest establish the pathway in nasal epithelial cells or in mice but not in AR.

5.1. Genetic Susceptibility

The only human genetic evidence is a candidate-gene association study evaluating variants in ferroptosis-related genes against the risk of house dust mite-induced AR [107]. Its published abstract does not report the individual genes or effect estimates, so the study is cited here only for the association it tests, but it does show that the hypothesis of ferroptotic susceptibility in AR was already being tested in patients in 2023, before any mechanistic study had been published.

5.2. Ferroptosis of the Nasal Epithelium: Three Regulatory Axes

The most complete AR study, and the only one to include patient tissue, used HDM-exposed human nasal epithelial cells and RPMI-2650 cells, HDM-sensitised mice and nasal mucosal samples from patients [28]. HDM exposure induced lipid peroxidation-driven ferroptosis together with barrier damage; GPX4 was protective, in that its inhibition aggravated and its overexpression alleviated the injury; growth arrest-specific 1 (GAS1) promoted ferroptosis by suppressing GPX4, and GAS1 knockdown protected HDM-exposed mice; and the GAS1–GPX4 relationship depended on METTL3-mediated N6-methyladenosine (m6A) methylation of *GPX4* mRNA at a defined site. This is the single most important paper for the present review because it links an allergen, lipid peroxidation, the canonical ferroptosis brake and the barrier in one system that includes patient tissue. Its limitation, as published, is that the abstract establishes barrier damage without naming the junctional proteins or resistance measurements involved, so the nature of the barrier defect in this model remains unspecified.

A second m6A-dependent axis has been described in IL-13-stimulated primary human nasal epithelial cells and ovalbumin-sensitised mice [29]. METTL3 promoted m6A-dependent expression of the RNA-binding protein PTBP1, and PTBP1 and thioredoxin-interacting protein (TXNIP) rose and fell together; nasal mucosa showed reduced GPX4, Nrf2 and MnSOD with increased ACSL4, decreased glutathione and SOD activity and increased MDA, and METTL3 knockdown reversed these changes together with symptom scores, goblet cell hyperplasia and collagen deposition. Ferrostatin-1 restored antioxidant capacity when PTBP1 or TXNIP were overexpressed. The PTBP1→TXNIP step was not tested directly, however, and the mechanism the authors invoke from other tissues—PTBP1-mediated decay of *TXNIP* mRNA—predicts the opposite direction, so this limb of the axis should be treated as correlative. The involvement of TXNIP is nonetheless notable because resveratrol, the polyphenol with the strongest clinical record in AR (Section 8.3), was earlier shown to act through inhibition of the TXNIP–oxidative stress pathway in a mouse model of AR [151]. Neither tight junction proteins nor transepithelial resistance were measured, ferrous iron was not quantified, and the direction of the Nrf2 finding differs between the results and the discussion of the paper.

The third axis places the lipoxygenase at the centre. In ovalbumin-sensitised mice and in human nasal epithelial cells stimulated with IL-4 and IL-13, the transcription factor

FOXP1 transcriptionally up-regulated succinate dehydrogenase assembly factor 2 (SDHAF2), which bound ALOX15 and increased its expression; SDHAF2 knockdown reduced Fe^{2+}, ROS, MDA, lipid peroxides and inflammation and improved nasal pathology, restoring ALOX15 reversed the protection conferred by SDHAF2 knockdown, and the ferroptosis inducer erastin partly reversed its benefit in vivo [30]. Independently, a molecular docking-guided study in IL-13-stimulated JME/CF15 nasal epithelial cells identified ALOX15 as the target of the isoflavone formononetin, which reduced lipid ROS, Fe^{2+} accumulation, glutathione loss, ferroptosis and NLRP3-mediated pyroptosis; ALOX15 knockdown reproduced and ALOX15 overexpression abolished the protection [152]. Taken together with the up-regulation of ALOX15 transcripts in type 2-inflamed human nasal epithelium in chronic rhinosinusitis with nasal polyps [42], these studies make ALOX15 the most promising candidate executioner of lipid peroxidation in the allergic nasal epithelium, mirroring the 15LO1–PEBP1 biology established in asthmatic bronchial epithelium (Section 6.1)—although one is a paywalled single-group study and the other an in vitro, docking-led report in a low-visibility journal.

Alongside these three axes, the substrate-supply limb has been examined in human nasal tissue: type 2 inflammation up-regulates the fatty acid transporter SLC27A2 (FATP2) and the lipid peroxidation program in nasal epithelial cells, and FATP2 inhibition reverses it (Section 5.5). Because SLC27A2 and ACSL4 determine how much peroxidisable polyunsaturated phospholipid a cell carries (Section 2.2), this places a druggable node upstream of all three axes.

Figure 8 sets the three axes side by side.

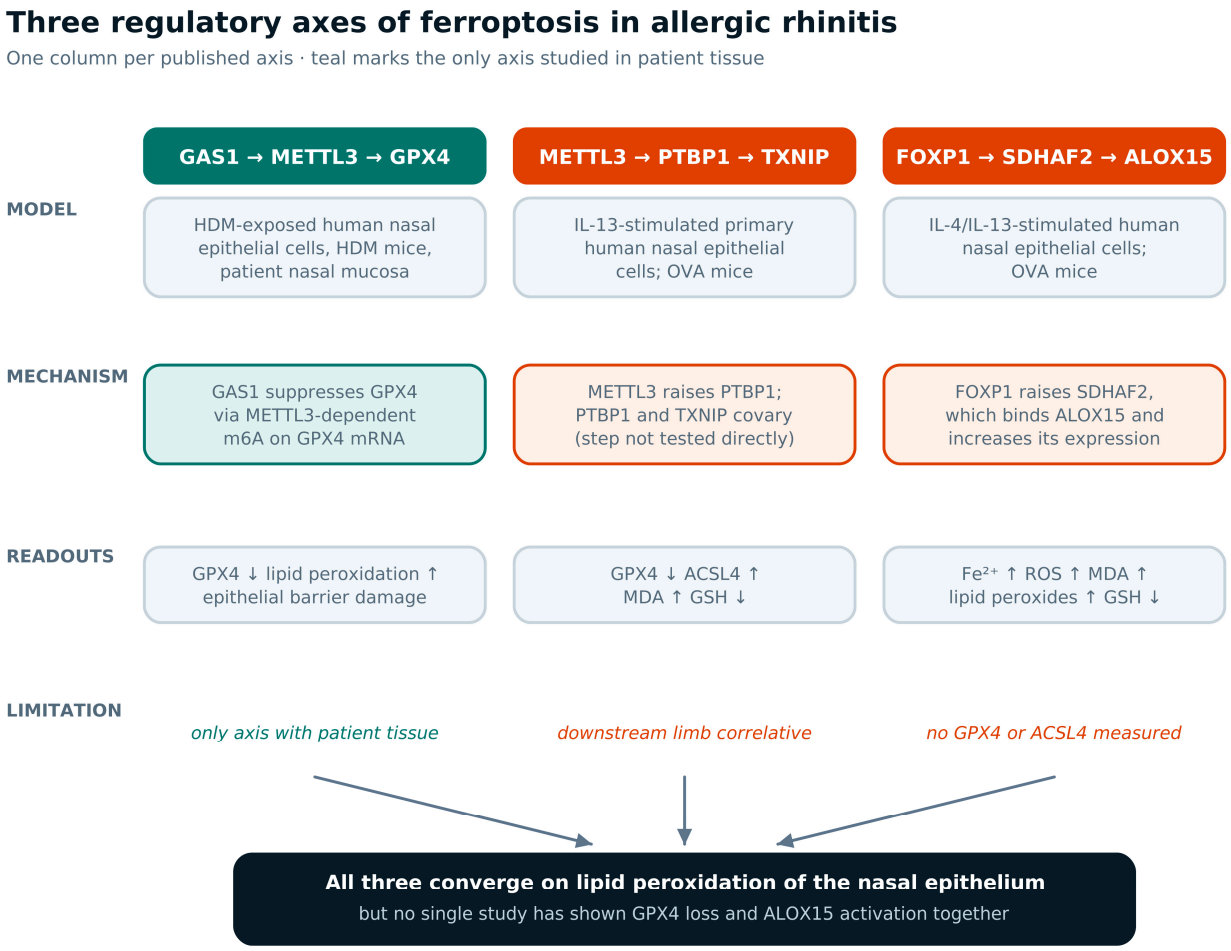

Figure 8. The three regulatory axes linking allergic inflammation to ferroptosis of the nasal epithelium. Each axis was defined in a separate study and converges on the same end point. In the first,

house dust mite exposure raises GAS1, which increases METTL3-dependent m6A methylation and suppresses GPX4, the only axis so far linked to a barrier outcome [28]. In the second, IL-13 stimulation drives METTL3-dependent methylation of PTBP1 with downstream involvement of TXNIP [29]; the step from PTBP1 to TXNIP is inferred rather than demonstrated, and is marked accordingly. In the third, FOXP1 induces SDHAF2 and ALOX15, placing the lipoxygenase at the centre and reversing the phenotype with erastin [30]. Two of the three converge on METTL3, which is the most striking feature of the small AR literature, and all three were demonstrated in the same two model systems, which is its main limitation (Section 5.6).

5.3. Ferroptosis in Immune Cells: The Other Direction

Ferroptosis in AR is not confined to epithelium, and in immune cells it may be therapeutic rather than pathogenic. Dietary lecithin-bound iodine, an agent approved in Japan for allergic disease, attenuated ovalbumin-induced AR in mice by reducing allergen-specific IgE through dampened germinal-centre reactions; in vitro, potassium iodide drove activated B cells towards ferroptosis by raising ROS and ferrous iron, and iodine-fed mice showed increased ROS in germinal-centre B cells [108]. This is a rare example of deliberate ferroptosis induction in a pathogenic cell population as an AR treatment, and it is the mirror image of the epithelial protection strategy. The tension between the two is examined in Section 6.2.

5.4. In Silico Studies

A GEO-based differential expression analysis of ferroptosis genes in AR, combined with network pharmacology and molecular docking of the traditional formula Bu-Zhong-Yi-Qi decoction, predicted ferroptosis-related targets of the formula without wet-laboratory validation [153]. An earlier Chinese-language review had already proposed that m6A regulation and ferroptosis intersect in combined AR and asthma in children, so the hypothesis subsequently confirmed by the GAS1–METTL3 and METTL3–PTBP1 studies was in circulation before either was published [154].

5.5. Adjacent Evidence: Ferroptosis Occurs in Human Nasal Epithelium

Three kinds of study outside AR demonstrate that the nasal epithelium can die by ferroptosis in vivo. In acute PM2.5 injury, ferroptosis of nasal epithelial cells was driven through AMPK-mediated autophagy in vitro and in vivo, with GPX4, SLC7A11 and lipid peroxidation among the indexed readouts [109]; H1N1 influenza induced ferroptosis of nasal mucosal epithelial cells through the Nrf2–KEAP1–GCLC pathway [71]; and in patients with nasal polyps, in whom epithelial lipid peroxidation was increased in both eosinophilic and non-eosinophilic disease, cigarette-smoke-induced epithelial ferroptosis—driven by transferrin receptor 1-dependent iron loading—promoted CXCL8 release and neutrophil influx, with deferoxamine protective in smoke-exposed mice [155]. This is the clearest evidence that nasal epithelial ferroptosis occurs in human tissue and that it can bias the downstream infiltrate. In chronic rhinosinusitis, STAT1-induced IL-36γ increases the sensitivity of human nasal epithelial cells to ferroptosis [156], ALOX5 has been nominated as a ferroptosis-associated driver of epithelial barrier dysfunction in nasal polyps [157], ZFP36L1 promotes ferroptosis by destabilising *CAMK2A* mRNA [158], and several bioinformatic ferroptosis signatures have been reported [159–162]. Most relevant to AR is the demonstration, by single-cell sequencing and air–liquid interface cultures of patient-derived nasal epithelium, that type 2 inflammation up-regulates SLC27A2 together with ALOX15, DUOX1, NOS2 and POR in nasal epithelial cells, with ACSL4 and LPCAT3 enriched in SLC27A2-positive cells but not correlated with IL-4/IL-13 pathway genes; that the FATP2 inhibitor lipofermata lowers this programme in polyp-derived but not healthy-derived cultures; and that dupilumab treatment was associated with reduced expression

of these genes in a reanalysis of a public single-cell dataset [42]. Ferroptosis itself was not measured as an endpoint in that study—lipid peroxidation was assessed by C11-BODIPY on tissue sections—but its substrate biology was.

Table 2. Primary studies of ferroptosis in allergic rhinitis.

Study	Model(s)	Regulatory Axis	Ferroptosis Readouts	Barrier Readout	Rescue/Reversal	Main Limitation
Lin et al. 2026 [28]	HDM-exposed HNEpC and RPMI-2650; HDM mice; patient nasal mucosa	GAS1 → METTL3-m6A of *GPX4* mRNA → GPX4 ↓	Lipid peroxidation; GPX4 inhibition/overexpression	Barrier damage reported; proteins not specified in abstract	GPX4 overexpression; GAS1 knockdown in vivo	Pharmacological inhibitor not reported in abstract
Liu et al. 2025 [29]	IL-13-stimulated primary HNEpC; OVA mice	METTL3-m6A → PTBP1; PTBP1 and TXNIP covary	GPX4 ↓, Nrf2 ↓, MnSOD ↓, ACSL4 ↑, GSH ↓, MDA ↑	Not measured	Fer-1; METTL3 knockdown; m6A inhibitor	PTBP1 → TXNIP step untested and direction conflicts with the cited mechanism; no barrier or Fe^{2+} data; Nrf2 direction inconsistent within the paper
Deng et al. 2026 [30]	IL-4/IL-13-stimulated HNEpC; OVA mice	FOXP1 → SDHAF2 → ALOX15	Fe^{2+} ↑, ROS ↑, MDA ↑, lipid peroxides ↑, GSH ↓	Not measured	SDHAF2 knockdown; erastin reversal; Fer-1	No GPX4 or ACSL4 measured; single-group study
Li et al. 2026 [152]	IL-13-stimulated JME/CF15 nasal epithelial cells	ALOX15 (formononetin target)	Lipid ROS, Fe^{2+}, GSH; pyroptosis also reduced	Not measured	Formononetin; ALOX15 knockdown/overexpression	In vitro; journal metadata to confirm
Nakamura et al. 2023 [108]	OVA mice fed lecithin-bound iodine; B cells in vitro	Iodine → ROS/Fe^{2+} → ferroptosis of activated B cells	ROS, ferrous iron in B cells	Not applicable	Ferroptosis *induced* therapeutically	Immune-cell, not epithelial, mechanism
Yang et al. 2023 [107]	Candidate-gene association, HDM-induced AR	Variants in ferroptosis-related genes	Not applicable	Not applicable	Not applicable	Individual genes and effect sizes not reported in the abstract
Cen et al. 2024 [153]	GEO transcriptomes; network pharmacology; docking	Predicted ferroptosis targets of Bu-Zhong-Yi-Qi decoction	In silico	Not applicable	None	No experimental validation

HNEpC, human nasal epithelial cells; HDM, house dust mite; OVA, ovalbumin; Fer-1, ferrostatin-1; m6A, N6-methyladenosine; ↑ increased; ↓ decreased; → denotes the direction of a regulatory step (A → B: A acts on or leads to B) rather than a change in level. "Barrier readout" records whether junctional proteins or permeability were measured. Evidence tier: AR-direct (obtained in AR patients, AR models or nasal epithelial cells under type 2 stimulation).

Table 3. Adjacent evidence: ferroptosis and lipid peroxidation in nasal epithelium outside allergic rhinitis.

Study	Setting	Key Finding	Relevance to AR
Gu et al. 2023 [109]	PM2.5 acute nasal epithelial injury, in vitro and in vivo	Ferroptosis via AMPK-mediated autophagy; GPX4/SLC7A11 pathway	Pollutant trigger shared with AR exacerbation; links autophagy to ferroptosis in nasal cells
Liu et al. 2023 [71]	H1N1 infection of nasal mucosal epithelium	Ferroptosis through Nrf2–KEAP1–GCLC inhibition	Shows the Nrf2–glutathione–ferroptosis axis operates in nasal epithelium
Pan et al. 2025 [155]	Patients with nasal polyps; cigarette smoke; mice	TfR1-dependent iron loading drives epithelial ferroptosis and CXCL8 release with neutrophil influx; deferoxamine protective in mice	Ferroptosis of human nasal epithelium in vivo; shows the infiltrate can be biased by epithelial ferroptosis
Park et al. 2025 [42]	CRSwNP scRNA-seq; patient-derived ALI cultures	Type 2 inflammation up-regulates SLC27A2, ALOX15, DUOX1, NOS2, POR; lipofermata lowers them in polyp-derived cultures; dupilumab association from reanalysis of a public dataset. Ferroptosis not a measured endpoint	Substrate and initiator program of lipid peroxidation induced by IL-4/IL-13 in human nasal epithelium
Fan & Li 2026 [156]	CRS; HNEC	STAT1 → IL-36γ increases ferroptosis sensitivity	Ferroptotic sensitivity of nasal epithelium is tunable by cytokines
Huang et al. 2026 [157]	CRSwNP multi-omics and machine learning	ALOX5 as ferroptosis-associated driver of barrier dysfunction	Lipoxygenase–barrier link in human nasal disease
Xiong et al. 2026 [158]	CRS; knockout mice; patient tissue	ZFP36L1 destabilises *CAMK2A*, impairs mitochondrial quality control, promotes ferroptosis	Mitochondrial control of nasal epithelial ferroptosis
Huang & Liu 2023; Guo et al. 2024; Li et al. 2025; Lv & Jiang 2025 [159–162]	CRSwNP/CRS transcriptomic signatures	Ferroptosis- and iron-related gene sets distinguish disease from control	Hypothesis-generating only

CRS, chronic rhinosinusitis; CRSwNP, CRS with nasal polyps; HNEC, human nasal epithelial cells; ALI, air–liquid interface; → denotes the direction of a regulatory step (A → B: A acts on or leads to B). Evidence tier: nasal-adjacent (human nasal tissue or nasal epithelial cells, but not allergic rhinitis).

5.6. Critical Appraisal

Several limitations apply to the AR-specific studies as a group (Table 2 and Table 3). All four epithelial studies rely on the same two stimuli—IL-13 or IL-4/IL-13 stimulation of nasal epithelial cells, and ovalbumin or HDM sensitisation of mice—and one of them [152] has no in vivo arm at all, so the convergence of their findings is partly a convergence of their methods. Only one study [28] included patient tissue, and only that study reported a barrier outcome, describing epithelial barrier damage without naming the junctional proteins involved. Ferroptosis was identified by marker panels (GPX4, ACSL4, MDA, Fe^{2+}, lipid ROS, glutathione) and by rescue with ferrostatin-1 or reversal with erastin, which is the accepted standard, but no study used transferrin receptor or 4-HNE adduct immunohistochemistry on tissue sections, which would allow ferroptosis to be sought in archival nasal biopsies. No study examined eosinophils, mast cells or ILC2 in nasal tissue, and no study addressed whether ferroptosis is a cause of epithelial loss in chronic AR or an epiphenomenon of severe experimental sensitisation. Finally, the reviews that have covered ferroptosis in AR cite, between them, fewer than ten AR-specific primary papers [31–34],

which confirms that the field is young. These limitations define the research agenda in Section 9; they do not undermine the central point, which is that three independent regulatory axes—GAS1–METTL3–GPX4, METTL3–PTBP1–TXNIP and FOXP1–SDHAF2–ALOX15—converge on lipid peroxidation of the allergic nasal epithelium. Table 2 and Table 3 collect, respectively, the AR-specific studies appraised above and the adjacent nasal evidence of Section 5.5. Figure 9 maps the entire evidence base by the system in which each finding was obtained.

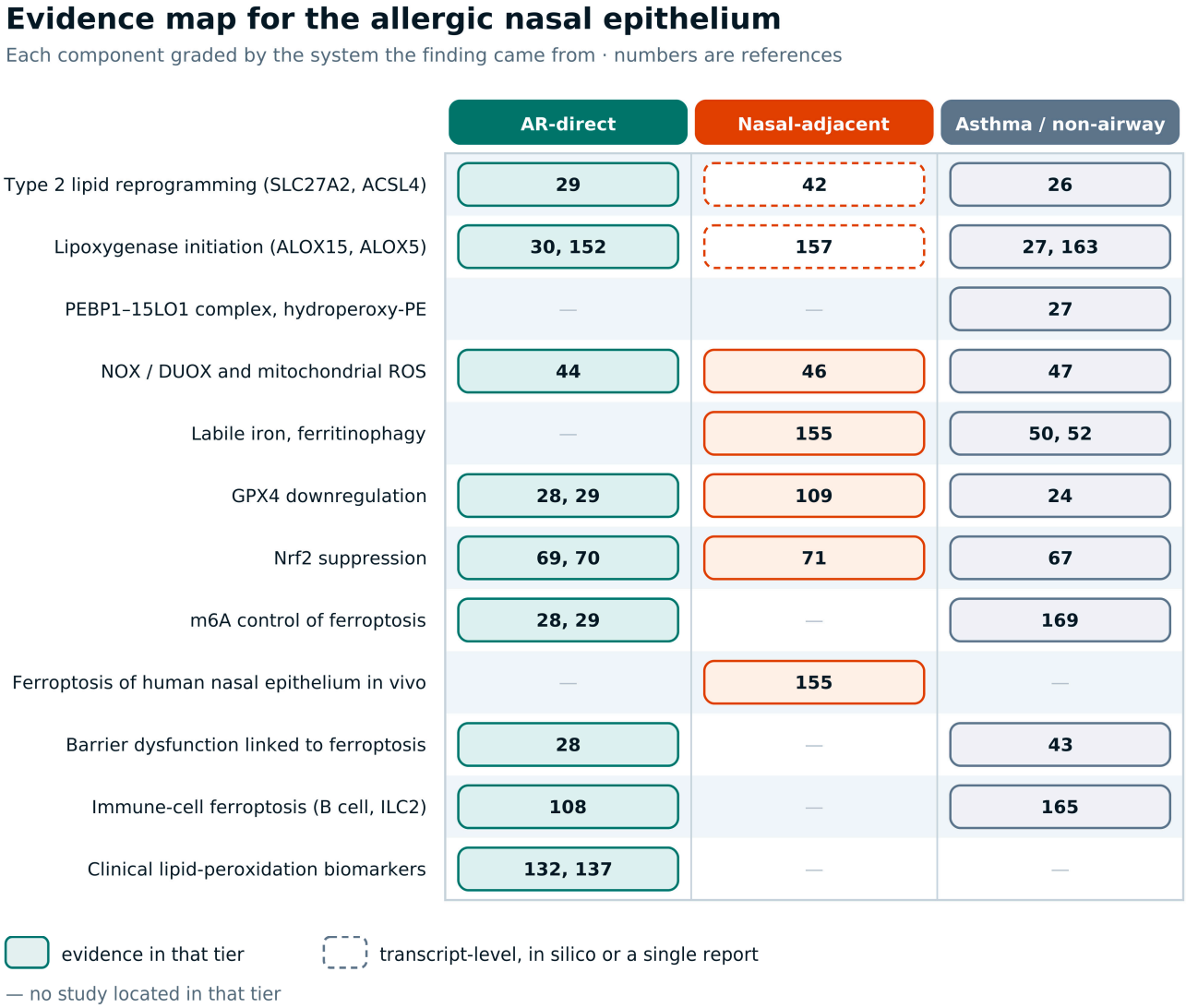

Figure 9. Evidence map for lipid peroxidation and ferroptosis in the allergic nasal epithelium, graded by the system in which each finding was obtained. Each row is a component of the proposed mechanism; each column is an evidence tier. Filled cells indicate at least one study supporting the component in that tier: AR-direct (allergic rhinitis patients, AR animal models or nasal epithelial cells under IL-4/IL-13 or allergen stimulation); nasal-adjacent (chronic rhinosinusitis, pollutant-, virus- or smoke-injured nasal epithelium); and lower-airway/asthma or non-airway systems. Hatched cells denote evidence limited to transcript level, in silico analysis or a single study whose full text could not be verified. The map makes explicit that the lipid-handling and lipoxygenase components are supported in AR, that ferroptosis of human nasal epithelium in vivo has so far been shown only in nasal polyp tissue, and that the ferritinophagy and PEBP1 components remain extrapolated from the lower airway, while the immune-cell evidence rests on a single AR model alongside one asthma study. Numbers in cells refer to the reference list.

6. Extrapolated Evidence from Asthma and Type 2 Immunity, and Where It Breaks Down

Because the AR-specific literature is small, much of the mechanistic richness of the ferroptosis story in allergic airway disease comes from asthma and lower-airway models. Borrowing from them is legitimate only if the borrowing is made explicit and its limits stated. This section sets out the extrapolations the review relies on and the three places where they are known to break down.

6.1. The 15-Lipoxygenase–PEBP1 Axis

The strongest mechanistic thread runs through 15-lipoxygenase. The PEBP1–15LO1 complex that generates the hydroperoxy-PE ferroptotic signal was demonstrated in airway epithelial cells from patients with asthma [27], and in human asthmatic airway epithelium IL-13 drives 15LO1 expression and lowers the glutathione redox ratio, with the lower ratio tracking worse lung function [43]. Luteolin attenuates asthma by inhibiting ALOX15-mediated bronchial epithelial ferroptosis in HDM/LPS models [163], and GPX4 restrains airway inflammation partly by suppressing 5-lipoxygenase [164]. The nasal counterpart of this axis is now partly in place: ALOX15 is up-regulated at transcript level in type 2-inflamed human nasal epithelium [42], the FOXP1–SDHAF2–ALOX15 axis drives ferroptosis in AR nasal epithelial cells and mice [30], and formononetin protects IL-13-stimulated nasal epithelial cells by inhibiting ALOX15 [152]. What has not been shown in the nose is the specific PEBP1–15LO1 protein complex or the hydroperoxy-PE product itself; the nasal evidence is for ALOX15 expression and function, not for the PEBP1 scaffolding mechanism. That gap should be stated whenever the asthma 15LO1 work is cited in an AR context.

6.2. Ferroptosis Can Be Protective or Pathogenic Depending on the Cell

The most important recent qualification comes from immunometabolism. In allergic airway inflammation, pathogenic type 2 lymphocytes acquire tolerance to ferroptosis, and that tolerance is what permits the lipid-handling program sustaining type 2 immunity; in other words, ferroptosis resistance in immune cells, not ferroptosis sensitivity, is pathogenic in that compartment [165]. The point is sharper than it first appears, because the resistance of pathogenic ILC2 and Th2 cells depends on cystine-fuelled glutathione together with GPX4 and thioredoxin reductase 1, and ILC2-specific deletion of GPX4 or TXNRD1—or pharmacological TXNRD1 inhibition—reduces ILC2 accumulation. GPX4 is therefore simultaneously the protective target in epithelium [28] and a pathogenic dependency in ILC2s, and the paper's own translational proposal is to inhibit, not support, the anti-ferroptotic machinery. This cuts directly against a naive reading of the epithelial data, in which ferroptosis is uniformly harmful and should be blocked. The resolution is cell-type specificity: protecting the epithelial barrier from ferroptosis and deleting pathogenic immune cells by ferroptosis are not contradictory goals but complementary ones, provided an intervention can be targeted to the right compartment. The lecithin-bound iodine study, which induces ferroptosis in activated B cells to lower IgE [108], and the epithelial-protection studies [28–30] therefore describe two faces of the same biology. Any therapeutic proposal in AR must declare which compartment it intends to act on, and systemic radical-trapping antioxidants, which cannot distinguish the two, may be a blunt instrument for exactly this reason (Section 8).

Figure 10 states the consequence for therapy.

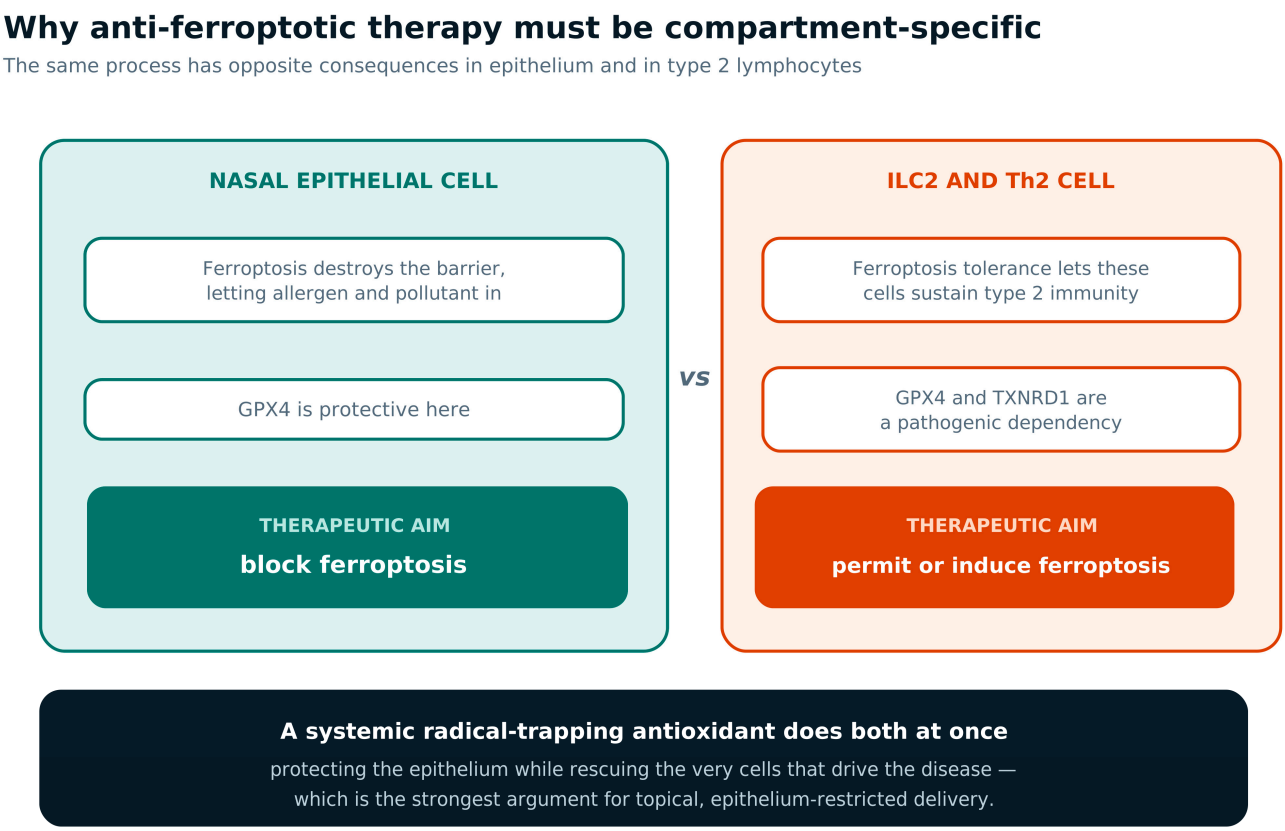

Figure 10. Why anti-ferroptotic therapy in allergic rhinitis must be compartment-specific. The same biochemical process carries opposite consequences in the two cell populations that matter. In the nasal epithelial cell, ferroptosis destroys the barrier and admits allergen and pollutant, so GPX4 is protective and the therapeutic aim is to block ferroptosis. In group 2 innate lymphoid cells and Th2 cells, resistance to ferroptosis is what allows the pathogenic population to persist, so GPX4 and TXNRD1 constitute a dependency and the therapeutic aim is the reverse—to permit or induce ferroptosis, as the lecithin-bound iodine study did in activated B cells [108,165]. A systemic radical-trapping antioxidant would do both at once, protecting the epithelium while rescuing the very cells that drive the disease, which is the strongest available argument for topical, epithelium-restricted delivery (Section 8.7).

6.3. What Epithelial Ferroptosis Does: Inflammation, Barrier and Endotype

Two questions follow from the preceding sections: whether ferroptosis of the nasal epithelium promotes or restrains inflammation, and whether it damages the barrier. On the first, the available evidence points one way. Ferroptosis is an immunogenic death: loss of membrane integrity releases HMGB1 and other damage-associated molecular patterns [23], and the oxidised phospholipids and 4-HNE generated during the process are themselves signalling species that recruit and activate leucocytes. In nasal tissue, the polyp smoke study showed epithelial ferroptosis driving CXCL8 release and neutrophil recruitment [155], and in the lower airway ferroptotic epithelium amplifies allergen-driven inflammation rather than limiting it [52,166]. We found no report in which epithelial ferroptosis restrained allergic inflammation; the only clearly anti-inflammatory role of ferroptosis in this disease lies in the immune compartment, where deleting pathogenic cells is beneficial (Section 6.2). On the second question, the single AR study that examined the barrier found it compromised when ferroptosis was induced and preserved when ferroptosis was blocked [28], which is consistent with the mechanism—peroxidation destroys the lipid bilayer in which tight junctions are anchored—but it is one study, and none of the AR studies reported a quantitative barrier measurement. The honest statement is that

epithelial ferroptosis is pro-inflammatory on present evidence and barrier-damaging on a single demonstration.

The nasal polyp smoke study showed that epithelial ferroptosis drove CXCL8 release and neutrophil recruitment, without testing an eosinophilic output [155], and the newest asthma review stresses that ferroptosis contributes to eosinophilic, neutrophilic and steroid-resistant endotypes differently [35]. AR is predominantly a type 2, eosinophil-rich disease, but it has neutrophilic and mixed endotypes, is frequently complicated by chronic rhinosinusitis, and is exacerbated by pollutants and smoke that themselves bias towards neutrophilic inflammation. The downstream immunological meaning of nasal epithelial ferroptosis in AR therefore cannot be assumed from the asthma literature and may depend on the patient's endotype and exposures. This is a second reason to grade the evidence rather than merge it.

6.4. Allergen, Iron and Ferritinophagy

The clearest extrapolated therapeutic signal concerns iron. In HDM-induced asthma, allergen exposure increases unbound iron and lipid peroxidation in airway epithelial cells through NCOA4-dependent ferritinophagy, and both the iron chelator deferoxamine and the radical-trapping antioxidant ferrostatin-1 reduce epithelial damage in vitro and airway inflammation in vivo [52,166]. The same allergen (HDM) and the same cell type (airway epithelium) are involved, which makes this the most transferable of the asthma studies, but the experiment has not been repeated in nasal epithelium, and no AR study has measured ferritinophagy, NCOA4 or the labile iron pool. The human iron epidemiology in AR (Section 4.6) is consistent with disordered iron handling but does not establish ferritinophagy in the nasal mucosa. Iron chelation and ferritinophagy inhibition are therefore hypotheses for AR, not established strategies.

6.5. Other Lower-Airway and Pollutant Models

A broader set of asthma and pollutant studies supplies supporting detail: ferroptosis signatures in HDM-sensitised mouse lung [167]; the ferroptosis–autophagy crosstalk in asthma [168]; METTL3-driven m6A control of mitophagy-dependent ferroptosis in PM2.5 lung injury (mechanistically parallel to the m6A axes found in AR) [169]; RNF8–AKT–Nrf2 protection of airway epithelium [170]; cold exposure exacerbating allergic airway inflammation via ferroptosis with ferrostatin-1 rescue, published in this journal [171]; and a review of environmental-pollutant-induced ferroptosis across pulmonary disease [172]. These are coherent with the AR data but are, without exception, lower-airway or non-allergic systems. They are cited in this review as mechanistic context and are labelled as such; none should be read as evidence that the mechanism operates in the human nose.

7. An Integrative Model of Ferroptotic Vulnerability of the Nasal Epithelial Barrier

The clinical and mechanistic literatures, read together, support a coherent working model that is testable and that makes explicit predictions. The model is summarised in Figure 11 and can be stated as five linked propositions, each annotated with its current evidence tier.

First, the allergic nasal epithelium is primed for lipid peroxidation. Type 2 cytokines IL-4 and IL-13 reprogram its lipid metabolism, up-regulating the fatty acid transporter SLC27A2 (FATP2) and the lipoxygenase ALOX15, with ACSL4 and LPCAT3 co-enriched in the same cells, so that its membranes are predicted to accumulate the polyunsaturated phosphatidylethanolamines that ferroptosis consumes [42]. The substrate limb is supported in human nasal tissue at transcript level in chronic rhinosinusitis, which is a nasal-

adjacent tier, and directly in AR by the raised ACSL4 reported in IL-13-stimulated nasal epithelial cells [29]; it has not been shown at protein level in allergic nasal mucosa.

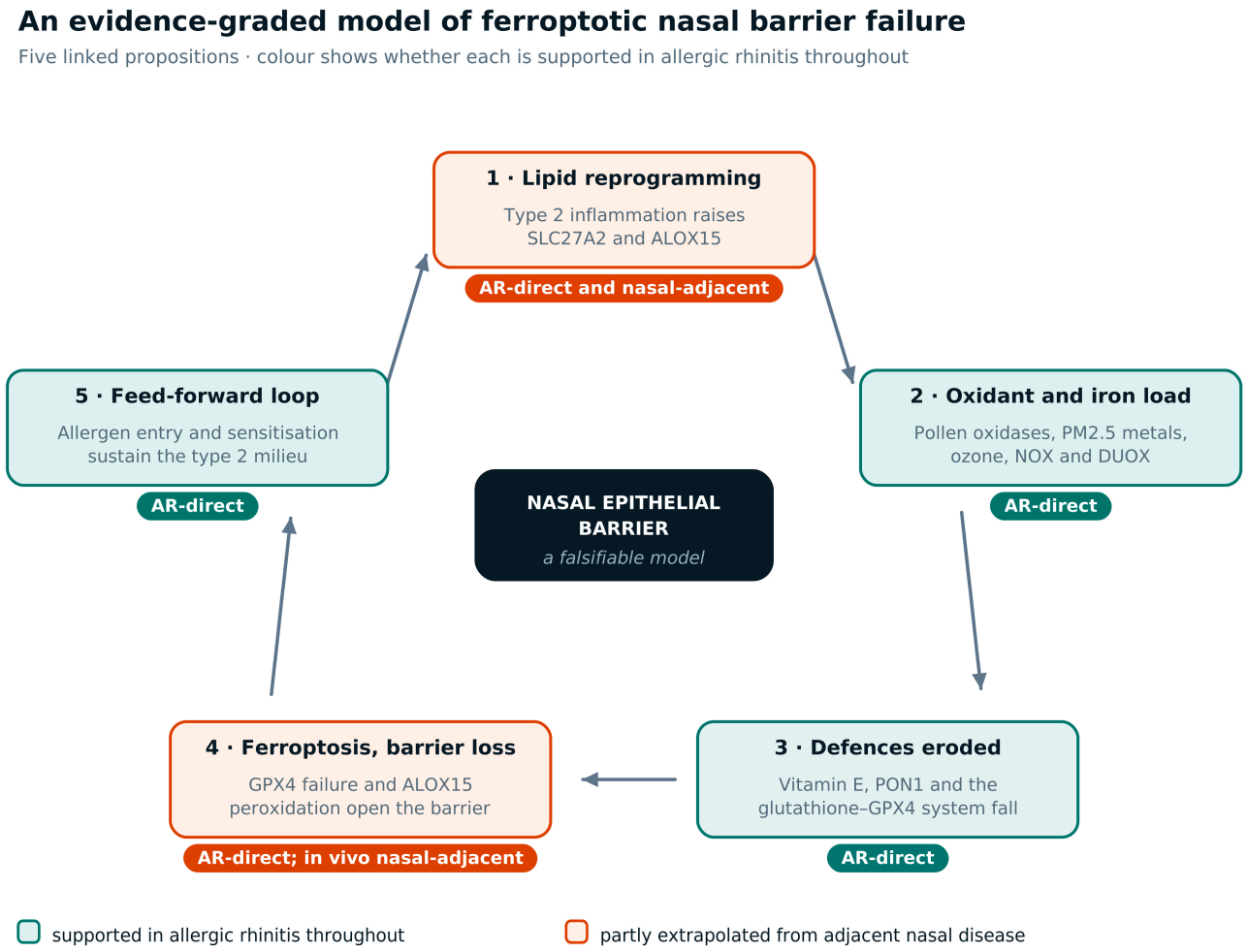

Figure 11. An integrative, evidence-graded model of ferroptotic vulnerability of the nasal epithelial barrier in allergic rhinitis. The five propositions of the model are shown as a cycle. (1) Type 2 inflammation reprograms epithelial lipid metabolism towards peroxidation-prone membranes (SLC27A2 and ALOX15 up; ACSL4 and LPCAT3 co-enriched). (2) Inhaled oxidants and iron (pollen NAD(P)H oxidases, PM2.5 metals, ozone) and epithelial NOX/DUOX raise the peroxidation load. (3) Lipid-phase antioxidant defences (vitamin E, PON1, GSH–GPX4) are selectively eroded while aggregate antioxidant capacity in blood is preserved or raised, although in nasal lavage it falls. (4) GPX4 failure and ALOX15-driven peroxidation cause ferroptosis of nasal epithelial cells and barrier damage. (5) Barrier failure increases allergen/pollutant entry, alarmin release and sensitisation, sustaining the type 2 milieu and closing the loop. Each proposition is tagged with its evidence tier on the scale defined in the Scope and Literature Search section. Only two tiers appear in the figure: every proposition in the model has at least AR-direct support, and propositions 1 and 4 rest partly on nasal-adjacent evidence as well, so no proposition of the model is supported by extrapolation from asthma or non-airway systems alone. The model also simplifies in one respect that should be read alongside it: ferroptosis does not operate in isolation in this tissue. It is regulated by autophagy—NCOA4-dependent ferritinophagy supplies the labile iron that drives proposition 4—and it interacts with pyroptosis, since iron overload also activates gasdermin D and the PM2.5–AhR–NLRP3 axis drives pyroptotic barrier damage in the same epithelium [54,106]. Autophagy is shown here as a regulator of ferroptosis rather than as a death pathway in its own right, autophagy-dependent cell death not having been demonstrated in nasal epithelium. Testable predictions arising from the model are listed in the outer boxes and expanded in Section 9.

Second, the same tissue faces an exceptional oxidant load. It is the first-pass filter for pollen-borne NAD(P)H oxidases, metal-rich fine particulates and ozone, and it expresses high levels of NOX1, NOX4 and DUOX, so that reactive oxygen species and labile iron are delivered to or generated within precisely the membranes made vulnerable by the first proposition [12,44,137]. This is supported in AR patients (nasal lavage metal–MDA associations) and in AR models.

Third, antioxidant defences in AR are selectively eroded rather than globally depleted. In blood, aggregate antioxidant capacity measured as the Erel total antioxidant status is often preserved or even raised, while the lipid-phase, chain-breaking defences that specifically restrain membrane peroxidation—vitamin E, paraoxonase-1 and the glutathione–thiol system that feeds GPX4—are the parameters that fall [115,123,124], with Nrf2 output suppressed in pollutant-exposed AR animal models [69]; in the nasal compartment itself, aggregate antioxidant capacity falls too [131]. This pattern, drawn from the clinical biomarker literature and, for Nrf2, from AR models, is exactly what the ferroptosis framework predicts and is the review's main reinterpretation of two decades of oxidative-stress data in AR.

Fourth, when peroxidation outstrips these defences, nasal epithelial cells undergo ferroptosis, and this contributes to barrier failure. Two of the three regulatory axes converge on reduced GPX4 [28,29], and the third on increased ALOX15-dependent peroxidation [30], in nasal epithelial cells and murine nasal mucosa; no single study has yet shown both limbs together. The one axis studied with a barrier readout showed barrier damage relieved by GPX4 restoration [28]. Ferroptosis of human nasal epithelium in vivo has been demonstrated directly only in nasal polyp tissue [155]. This proposition is therefore AR-direct for the cellular mechanism but rests, for the in vivo human endpoint, on nasal-adjacent evidence.

Fifth, barrier failure closes a feed-forward loop. Loss of tight junction integrity increases allergen and pollutant access to subepithelial dendritic cells and mast cells, augments alarmin release and sensitisation, and sustains the type 2 cytokine milieu that drove the lipid reprogramming in the first place [17,81,84]. Because barrier disruption can precede sensitisation [84], ferroptotic epithelial injury is positioned as a potential initiator of this loop, not only a consequence of it—though this causal ordering has been shown for barrier disruption in general and not specifically for ferroptotic barrier injury in AR.

The model's value is that it is falsifiable. It predicts that allergic nasal mucosa should contain ferroptosis-specific markers (4-HNE and MDA protein adducts, transferrin receptor 1, reduced GPX4) co-localised with junctional protein loss; that nasal lavage lipid peroxidation should track barrier permeability and symptom scores within patients; that interventions restoring GPX4 or trapping lipid radicals in the epithelium should preserve the barrier; and that the lipid-phase antioxidant deficit, not aggregate antioxidant capacity, should predict disease activity. Section 9 translates these predictions into specific measurements, several of which are feasible with nasal lavage and routine biopsy material.

8. Therapeutic Implications: Antioxidant and Anti-Ferroptotic Strategies Against the Level of Evidence Available

The model above identifies several intervention points: reducing the oxidant and iron load, replenishing lipid-phase antioxidants, restoring GPX4 and Nrf2, and inhibiting the peroxidation enzymes. For each, we distinguish strategies with randomised clinical evidence in AR from those supported only by AR models or by asthma, because the gap between the two is where most antioxidant trials in airway disease have failed.

8.1. The Cautionary Baseline: Systemic Antioxidants

The most instructive negative result predates the ferroptosis era. In a four-week randomised trial in 54 allergic adults (36 supplement, 18 placebo), a combination of β-carotene, vitamins C and E, zinc, selenium and garlic significantly raised serum vitamin C, vitamin E, β-carotene and selenium but changed neither serum antioxidant capacity nor plasma F_2-isoprostanes, exhaled nitric oxide or allergen-specific immune responses [173]. This is the single most important translational caveat in the field: flooding the circulation with antioxidants does not necessarily lower a lipid peroxidation biomarker, let alone reach the nasal epithelium. The ferroptosis framework explains why—radical trapping must occur within the membrane phospholipid bilayer of the target cell, and systemic water-soluble antioxidants are poorly positioned to do so—and it predicts that route and lipophilicity matter more than dose. Any future AR trial should therefore favour lipophilic agents, topical (intranasal) delivery, and biomarker-defined patient selection over systemic megadosing (Figure 12).

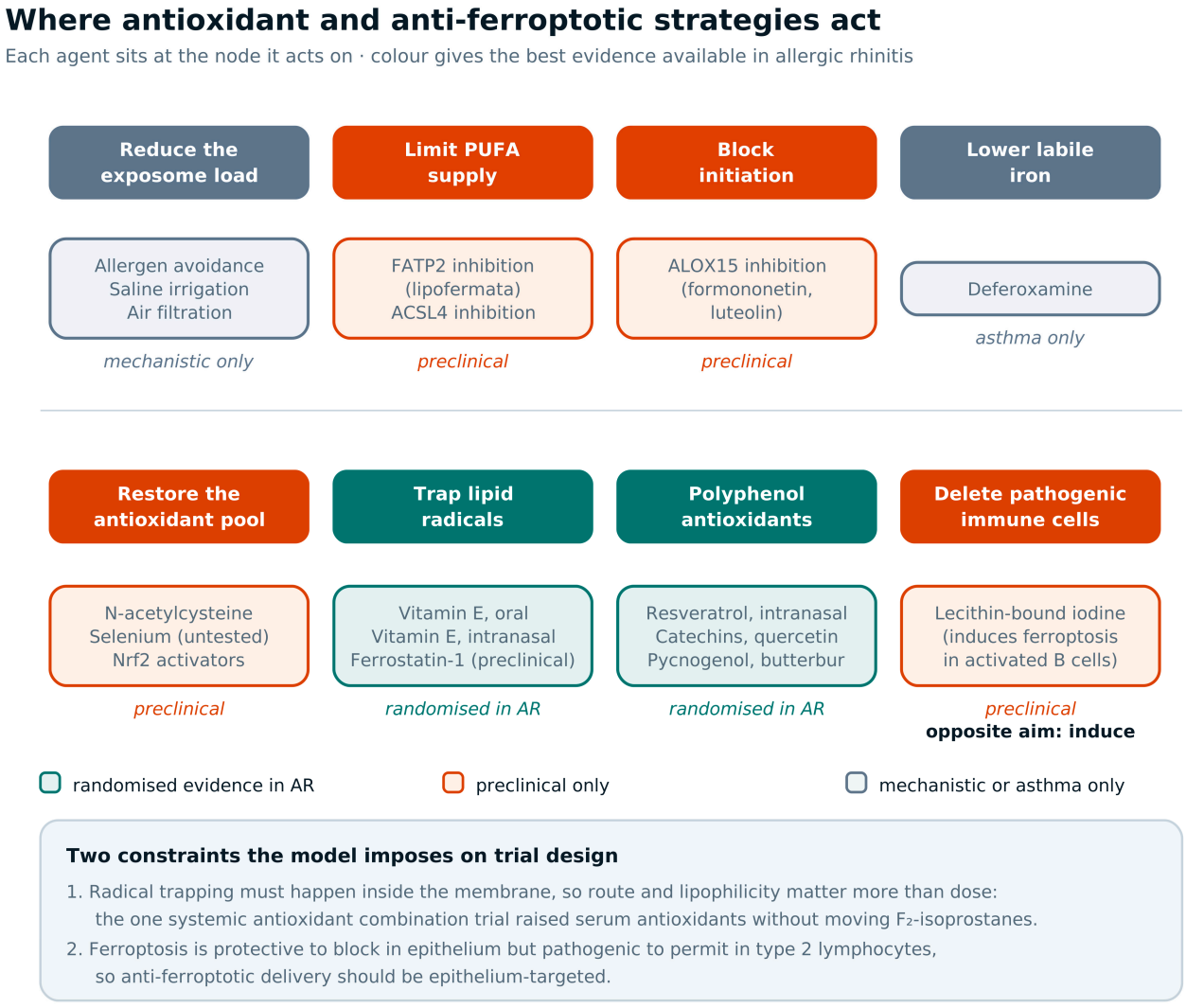

Figure 12. Where antioxidant and anti-ferroptotic strategies act on the pathway, with the level of evidence available in allergic rhinitis. Each node is a point at which the pathway can be interrupted, and the agents beneath it are placed by mechanism rather than by drug class. Colour gives the best level of evidence available in allergic rhinitis: randomised evidence in AR patients, preclinical evidence only, or evidence that is purely mechanistic or confined to asthma. Only two nodes—lipid-phase radical trapping and polyphenol antioxidants—are supported by randomised trials in AR, and the enzyme and iron nodes predicted by the model are the least developed. The lecithin-bound

iodine node is marked separately because its aim is the opposite of the others: it induces rather than blocks ferroptosis, in activated B cells. The two constraints shown beneath follow from the model and bear directly on trial design (Sections 8.1 and 8.7).

8.2. Replenishing Lipid-Phase Antioxidants: Vitamin E, Intranasally

Vitamin E (α-tocopherol) is the physiological membrane radical-trapping antioxidant whose depletion unmasks ferroptosis (Section 2.4), and serum vitamin E is low in children with AR (Section 4.3). It has been given both orally and topically. In a double-blind placebo-controlled trial in 112 patients with seasonal AR, oral α-tocopherol 800 mg/day added to standard therapy reduced nasal symptom scores but did not affect ocular symptoms, the proportion of days with severe symptoms, or rescue-medication use [174]. More relevant to the model, vitamin E has been delivered directly to the nasal mucosa: a randomised saline-controlled trial in 106 adults with AR found that a liposomal nasal spray combining vitamins A and E improved visual analogue scores, SNOT-22 and nasal inflammatory cell counts over 30 days [175], and a controlled observational study compared an α-tocopherol acetate nasal spray with beclomethasone and loratadine in pollen-induced AR [176]. Neither trial measured an oxidative endpoint. Intranasal vitamin E is nonetheless the clinical intervention most precisely predicted by the lipid-peroxidation model, and it is a plausible anchor for a mechanism-driven trial that measures nasal lavage 8-isoprostane and MDA as well as symptoms.

8.3. Polyphenols, Especially Intranasal Resveratrol

Resveratrol has the strongest clinical record of any antioxidant-class agent in AR. A double-blind trial in 151 adults compared intranasal resveratrol with placebo and with budesonide; resveratrol improved obstruction, itching, sneezing and rhinorrhoea and lowered blood IgE, IL-4, TNF-α and eosinophils [177]. In children, intranasal resveratrol combined with carboxymethyl-β-glucan reduced nasal symptoms in pollen-induced AR and respiratory infections in children with AR [178,179], as summarised in reviews and a Delphi consensus [180,181]. Mechanistically, resveratrol acts in a mouse AR model through the TXNIP–oxidative stress pathway [151]—the very node downstream of METTL3–PTBP1 in the ferroptosis axis of Liu et al. [29]—which provides a direct, if preliminary, link between the best clinical antioxidant in AR and one of the three ferroptosis axes. A systematic review and meta-analysis of 13 randomised trials in 823 patients found a pooled improvement in total nasal symptom score (standardised mean difference 0.73; sneezing 0.57; nasal obstruction 0.50) but no significant effect on quality of life, at low to very low certainty of evidence [182]. Other polyphenol and natural-product agents (O-methylated catechin green tea, Pycnogenol, butterbur, curcumin, baicalein and luteolin) have clinical or preclinical support that is summarised in Table 4 and in recent natural-product reviews [183–187]. Plant essential oils have been screened as a further source of such agents: in a comparison of commercial lemongrass, sea buckthorn and basil oils, lemongrass oil showed radical-scavenging activity in the DPPH assay approaching that of ascorbic acid (91.68% versus 97.04%), although both the antioxidant and the cytotoxicity readouts in that work were obtained in a colorectal cancer cell line rather than in airway epithelium [188].

8.4. Restoring Nrf2 and GPX4

Nrf2 signalling is suppressed in the nasal mucosa of pollutant-exacerbated AR models [69,70], and the Nrf2–ferroptosis link operates in nasal epithelium in a viral model [71]; whether restoring Nrf2 protects the allergic nasal barrier has not been tested. Classical Nrf2 activators (sulforaphane, dimethyl fumarate, bardoxolone) have not been studied in AR or nasal epithelium, so their inclusion here is as a mechanistic hypothesis only. GPX4

is selenium-dependent, but selenium status has not been properly assessed in AR—the one paediatric study that measured serum selenium found no association [125]—and we found no selenium supplementation trial in patients with AR; the one randomised antioxidant trial that included selenium was the negative systemic study discussed above [173]. N-acetylcysteine, which supplies cysteine for glutathione synthesis and so supports GPX4 indirectly, protected ZO-1, occludin and claudin-1 against PM2.5 in nasal epithelial cells [92] and reduced oxidative stress in a rat AR model after PM2.5 exposure [189], and in asthma an intranasal curcumin-plus-NAC combination attenuated airway inflammation specifically by targeting the Nrf2/GPX4–SLC7A11 ferroptosis axis [190]. These agents are attractive because they are inexpensive, available and amenable to intranasal delivery, but their AR evidence is preclinical.

8.5. Targeting the Peroxidation Enzymes and Iron

The enzyme inhibitors predicted by the model are the least clinically developed. ALOX15 (15-lipoxygenase) is inhibited by formononetin in nasal epithelial cells [152], by luteolin in bronchial epithelium [163], and by baicalein and ML351 in other systems, but none has an AR trial. ACSL4 and FABP4 inhibition are supported only by cancer and metabolic literature, with no study in nasal epithelium. FATP2 (SLC27A2) inhibition by lipofermata reduced the lipid peroxidation program in patient-derived nasal polyp epithelium [42]. Ferrostatin-1 has been used as a mechanistic probe in AR, restoring antioxidant capacity in nasal epithelial cells and in murine models [29,30], though never as a candidate therapy with clinical endpoints. Liproxstatin-1 and the iron chelator deferoxamine, by contrast, have in vivo efficacy in HDM and cold-exposure asthma models [52,171] but have not been studied in AR or nasal epithelium; nanoparticle formulations of ferroptosis inhibitors for airway delivery remain at the preclinical stage. Iron chelation in AR remains a hypothesis grounded in the iron epidemiology of Section 4.6 and the ferritinophagy biology of Section 2.3.

8.6. Reducing the Upstream Load

The model also legitimises interventions that lower the oxidant and iron input rather than scavenging downstream. Intranasal corticosteroids lower exhaled and systemic lipid peroxidation markers (Section 4.7), which may be part of how they work, although their effect in the nasal compartment itself has not been measured; allergen avoidance, nasal saline irrigation and air filtration reduce the exposome load that drives epithelial peroxidation; and allergen immunotherapy, by reducing the type 2 drive, should in principle reverse the lipid reprogramming, although we identified no study that has measured redox or ferroptosis markers before and after immunotherapy. Delivery is a recurring theme, and it is less simple than topical access suggests.

The nasal mucosa is directly accessible, but mucociliary clearance removes most of an aqueous spray within fifteen to twenty minutes [191], and that residence time is shorter still in the inflamed, hypersecretory nose of symptomatic AR. A lipophilic radical-trapping antioxidant therefore has to be formulated for retention if it is to act on the epithelium at all, which is the likeliest reason the liposomal vitamin spray [175] performed better than a simple solution would be expected to. Three approaches are plausible: mucoadhesive hydrogels and in situ gelling systems, which prolong contact by binding mucin; liposomes and lipid nanocarriers, which additionally carry lipophilic agents into the membrane phase where ferroptosis occurs; and plant-derived nanovesicles, which have shown mucosal delivery in other tissues. Advances in intranasal formulation of natural antioxidants make this technically feasible [191]. None of these has been tested with an anti-ferroptotic agent in AR, however, and none has been tested against a lipid peroxidation endpoint in the nose, so the evidence tier for all three is mechanistic. A second caution is more

fundamental: topical administration is not the same as epithelium-restricted exposure. The nasal mucosa is richly vascularised and absorbs small lipophilic molecules efficiently [191], so any agent intended to act on the epithelium alone must be shown to do so, with measurement of epithelial concentration and of systemic exposure rather than assumption from the route. This matters particularly here, where Section 6.2 predicts that systemic exposure would act against the intended effect.

Table 4. Antioxidant and anti-ferroptotic strategies in allergic rhinitis, mapped to target and level of evidence.

Strategy/Agent	Route	Target in the Model	Best Evidence in/Near AR	Tier
Avoidance, saline irrigation, air filtration	Topical/behavioural	Reduce exposome oxidant and iron load	Standard of care; pollutant exposure drives nasal lipid peroxidation in AR [91,137]	Mechanistic
Intranasal corticosteroid	Intranasal	Reduce inflammation-driven ROS	Lowers exhaled 8-isoprostane and serum peroxides [135,146,147]	Clinical-AR
Allergen immunotherapy	SC/SL	Reduce type 2 lipid reprogramming	Mechanistically predicted; redox endpoints not measured	Mechanistic
Vitamin E (α-tocopherol), intranasal	Intranasal	Lipid-phase radical trapping	Randomised saline-controlled trial of liposomal vitamin A + E spray, 106 adults [175]; controlled observational study of α-tocopherol acetate spray in pollen AR [176]; no oxidative endpoints	RCT-AR
Vitamin E (α-tocopherol), oral	Oral	Lipid-phase radical trapping	Double-blind RCT, 112 patients, 800 mg/day: nasal but not ocular symptoms improved [174]	RCT-AR
Resveratrol (±carboxymethyl-β-glucan)	Intranasal	Polyphenol antioxidant; TXNIP pathway	RCTs in adults and children [177–179]; mechanism via TXNIP [151]	RCT-AR
Polyphenols (catechins, quercetin)	Oral/intranasal	Radical trapping; Nrf2	SR/MA, 13 RCTs: nasal symptoms improved, quality of life not [182]; green tea catechin RCT [183]	RCT-AR
Pycnogenol, butterbur	Oral	Antioxidant; leukotriene inhibition	RCTs in seasonal AR [184,185]	RCT-AR
Vitamin D (adjuvant)	Oral	Indirect redox/immune	SR/MA as adjuvant in AR [192]; a paediatric SR/MA could not pool its four AR trials [193]	RCT-AR
Spirulina	Oral	Antioxidant	RCT vs. cetirizine [194]	RCT-AR
Probiotics (*W. coagulans* BC99)	Oral	Lower systemic MDA, raise GSH	RCT with oxidative endpoints [149]; a second probiotic RCT in children measured no redox endpoint [195]	RCT-AR
N-acetylcysteine	Intranasal/oral	Cysteine → GSH → GPX4	Protects nasal junctions vs. PM2.5 [92]; rat AR model [189]	Preclinical-AR
Curcumin, berberine, CoQ10	Oral/systemic	Antioxidant; Nrf2	Rat AR models [186,196]	Preclinical-AR
Nrf2 activators (sulforaphane, DMF)	—	Restore Nrf2 anti-ferroptotic program	None in AR	Mechanistic
Selenium	Oral	GPX4 cofactor	No AR trial found; serum selenium not associated with AR [125]; included in the negative systemic RCT [173]	Mechanistic

Formononetin (ALOX15 inhibitor)	In vitro	Inhibit ALOX15 peroxidation	IL-13-stimulated nasal epithelial cells [152]	Preclinical-AR
Luteolin (ALOX15/ALOX15)	Systemic	Inhibit ALOX15 peroxidation	Bronchial epithelium, HDM/LPS asthma model [163]; none in AR	Preclinical-asthma
Baicalein, ML351 (ALOX15/ALOX15)	—	Inhibit ALOX15 peroxidation	No airway or AR study located	Mechanistic
FATP2/SLC27A2 inhibition (lipofermata)	In vitro	Limit PUFA supply	CRSwNP nasal epithelium [42]	Preclinical (nasal-adjacent)
Ferrostatin-1	Systemic	Radical trapping	Mechanistic probe in AR nasal epithelial cells and murine AR [29,30]; not tested as therapy	Preclinical-AR
Liproxstatin-1	Systemic	Radical trapping	Cold-exposure asthma model [171]; none in AR	Preclinical-asthma
Deferoxamine (iron chelation)	Systemic	Lower labile iron	HDM asthma model [52]	Preclinical-asthma
Lecithin-bound iodine	Oral	Induce ferroptosis in activated B cells	OVA mouse AR; ferroptosis shown in vitro, ROS in germinal-centre B cells in vivo [108]	Preclinical-AR

Evidence tier: RCT-AR, randomised controlled trial in AR patients; clinical-AR, non-randomised clinical study in AR; preclinical-AR, AR animal or nasal epithelial cell model; preclinical-asthma, asthma or lower-airway model only; mechanistic, proposed from the pathway with no AR or airway study. NAC, N-acetylcysteine. Agents are grouped by mechanism of action in the model (Figure 11). These tiers grade the strength of therapeutic evidence and are distinct from the AR-direct, nasal-adjacent and asthma/non-airway tiers used for mechanistic provenance in Figures 9 and 11; both scales are defined, and their relationship set out, in the Scope and Literature Search section.

8.7. A Compartment-Specific Caveat

Section 6.2 shows that inhibition of ferroptosis is protective in the epithelium but that resistance to ferroptosis in type 2 lymphocytes is pathogenic, and that inducing ferroptosis in activated B cells can lower IgE [108,165]. A systemic anti-ferroptotic agent would protect the epithelium and simultaneously rescue the pathogenic immune cells that depend on ferroptosis tolerance—working against itself. This is a strong argument for topical, epithelium-restricted delivery of any anti-ferroptotic strategy in AR, and against systemic radical-trapping antioxidants, and it reinforces the lesson of the negative systemic trial in Section 8.1.

9. A Research Agenda: Measurements That Would Test the Model

The model in Section 7 is only useful if it can be falsified, and most of the measurements it requires are feasible with material already collected in rhinology practice. We group them by increasing difficulty; Figure 13 sets out the most immediately feasible of them as a workflow.

The most immediate priority is to look for ferroptosis in nasal tissue that patients and clinicians already provide. Inferior turbinate and nasal polyp specimens, and the mucosal biopsies taken in research settings, can be stained for transferrin receptor 1 together with MDA protein adducts—the validated tissue signature of ferroptosis [53]—and for 4-HNE adducts, GPX4, ACSL4 and ALOX15, with co-staining for ZO-1, occludin and claudin-1 to test the central prediction that ferroptotic markers co-localise with junctional loss. No such study has been done in AR, and it requires no new sampling. It is important to be clear about what such a study could and could not conclude. A marker panel of this kind is necessary but not sufficient: TfR1 accumulation, MDA and 4-HNE adducts and loss of GPX4 are consistent with ferroptosis but individually occur in other forms of oxidative

injury, and none demonstrates that cells died by an iron-dependent mechanism. Confirmation requires functional evidence in a system where it can be obtained—iron dependence shown by chelation, and rescue by ferrostatin-1 or liproxstatin-1 or by manipulation of GPX4 or ACSL4—together with the exclusion of the competing modalities discussed below. In human tissue, where intervention is impossible, the strongest available evidence is convergence: the marker panel together with the lipidomic signature. A parallel, equally feasible step is to extend the nasal lavage biomarker work beyond 8-isoprostane and MDA to 4-HNE adducts, labile iron and, where instrumentation allows, the ferroptosis-associated oxidised phosphatidylethanolamine species themselves—the 15-hydroperoxy- and 15-hydroxy-arachidonoyl- and adrenoyl-PE products—by targeted liquid chromatography–tandem mass spectrometry, which is the one measurement that distinguishes ferroptotic peroxidation from oxidative stress in general, and to correlate these within patients against objective disease readouts (nasal nitric oxide, peak nasal inspiratory flow), direct barrier measurements where available (transepithelial electrical resistance or paracellular flux) and symptom scores across and outside the allergen season.

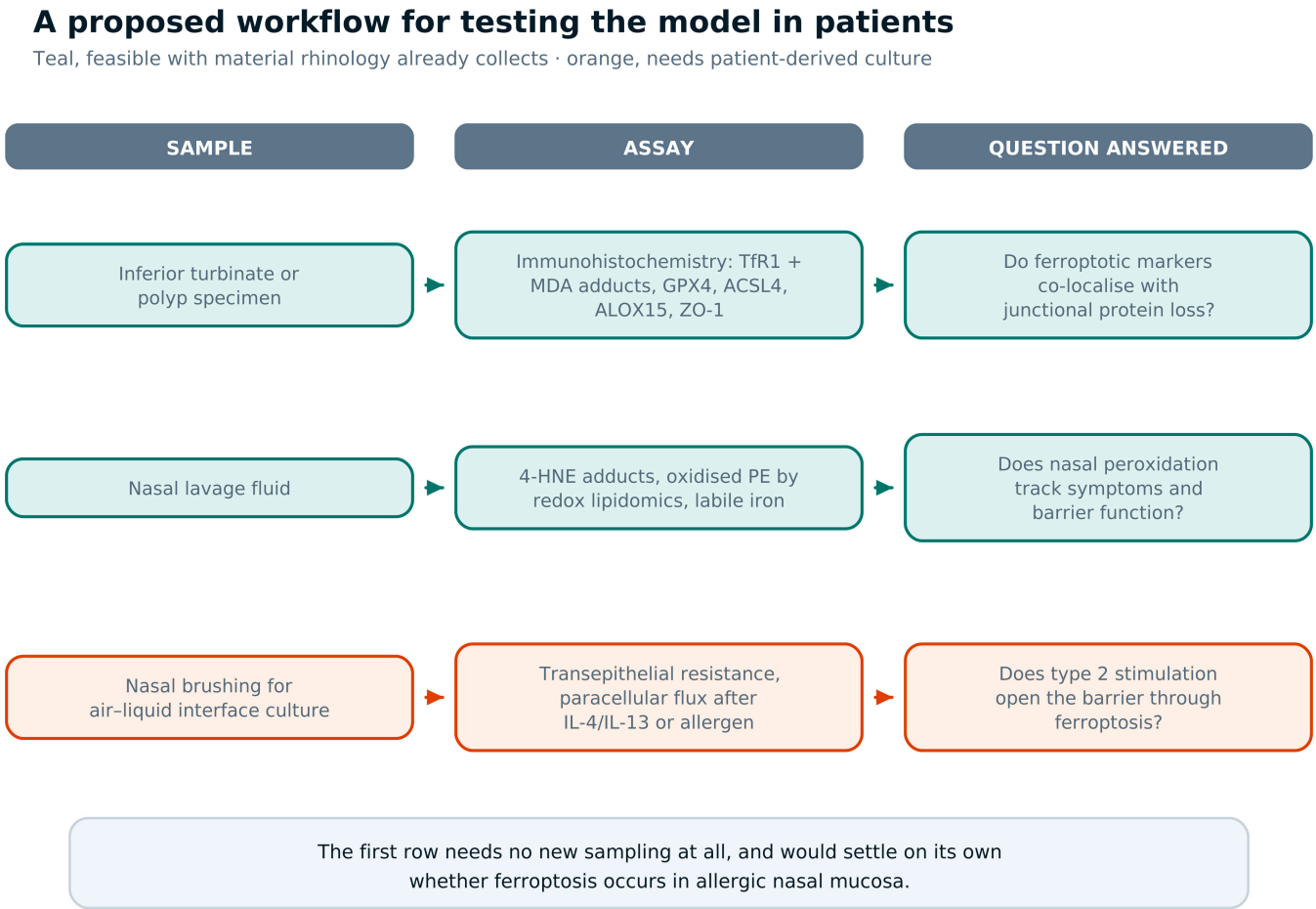

Figure 13. A proposed workflow for testing the model in patients, using material that rhinology practice already generates. Each row pairs a specimen that is already obtained in routine or research rhinology with the assay to be performed on it and the question that assay would answer. Inferior turbinate or polyp tissue stained for transferrin receptor 1 with malondialdehyde adducts, GPX4, ACSL4 and ALOX15, co-stained for ZO-1, occludin and claudin-1, would test whether ferroptotic markers co-localise with junctional loss. Nasal lavage extended beyond 8-isoprostane to 4-hydroxynonenal adducts, oxidised phosphatidylethanolamine species by redox lipidomics and labile iron would test whether nasal peroxidation tracks symptoms and barrier function. Nasal brushings

grown at air–liquid interface and stimulated with IL-4/IL-13 or allergen, assayed for transepithelial electrical resistance and paracellular flux, would supply the quantitative barrier readout that none of the existing AR studies reported. None of this requires new sampling. The first row alone would establish whether the tissue signature of ferroptosis is present in allergic nasal mucosa, which no study has yet shown; establishing that ferroptosis is actually occurring requires, in addition, functional evidence of iron-dependent death and rescue by a ferroptosis inhibitor or by genetic manipulation of the pathway, which the second and third rows are designed to supply.

A second priority is to resolve the substrate and defence biology in human nasal epithelium directly. Air–liquid interface cultures of patient-derived nasal epithelial cells—already used in chronic rhinosinusitis [42] and in AR [86]—can be stimulated with IL-4/IL-13 or allergen and assayed for the full ferroptosis panel together with transepithelial resistance and paracellular flux, closing the single largest gap in the current AR studies, none of which reported a quantitative barrier measurement. The same system can test whether the PEBP1–15LO1 complex and hydroperoxy-PE products that define the asthma axis actually form in nasal cells, which is currently assumed rather than shown (Section 6.1).

Junctional readouts need to be specified with more care than the existing literature has used. Staining or blotting for ZO-1, occludin and claudin-1 reports protein abundance; confocal imaging of the same proteins reports whether they remain at the junction or have been internalised; and neither is the same as showing that the protein has been chemically attacked. Direct oxidative modification requires detection of 4-HNE or MDA adducts on the junctional proteins themselves, by immunoprecipitation followed by adduct blotting or by redox proteomics, and loss through degradation requires a separate demonstration—cleavage fragments, or rescue by calpain or proteasome inhibition. These three mechanisms carry different therapeutic implications and are routinely conflated. Whichever is demonstrated, it should be anchored to a functional measurement in the same experiment: transepithelial electrical resistance for ionic barrier integrity and flux of a labelled dextran for the paracellular pathway, measured in parallel with the ferroptosis panel, so that a molecular change is shown to carry a functional cost rather than merely to accompany one.

A third priority is clinical–epidemiological. We identified no AR-specific meta-analysis of lipid peroxidation or antioxidant-status biomarkers—nasal nitric oxide is the only redox parameter meta-analysed in AR to date [48]—and one is overdue and should stratify by compartment (blood versus airway), by age (the paediatric high-TAS paradox needs explanation), and by lipid-phase versus aggregate antioxidant parameters, because the model predicts that the former, not the latter, track disease activity. Iron handling deserves dedicated study in order to determine whether functional iron deficiency in AR [143] reflects intracellular sequestration that raises the labile iron pool and so ferroptotic risk, and to determine whether nasal ferritin, NCOA4 and transferrin receptor expression differ between patients and controls.

A fourth priority is interventional and mechanism-anchored. The intranasal vitamin E and resveratrol trials already performed [175–177] should be repeated or extended with lipid peroxidation and, where tissue is available, ferroptosis endpoints, so that symptom benefit can be tied to the proposed mechanism; this would also test the prediction that topical lipophilic antioxidants succeed where the systemic antioxidant combination trial failed to shift lipid peroxidation [173]. Whether allergen immunotherapy reverses the epithelial lipid-reprogramming signature is an open and tractable question. Finally, the compartment-specificity problem (Section 8.7) should be addressed head-on in animal models by comparing epithelium-targeted anti-ferroptotic delivery against systemic delivery, given the evidence that ferroptosis tolerance in type 2 lymphocytes is itself pathogenic [165].

Two cross-cutting cautions apply. Marker panels and ferrostatin-1 rescue, though standard, do not distinguish ferroptosis from the apoptosis and pyroptosis that also operate in AR nasal epithelium [105,106,152], so studies should measure the competing death modalities in parallel. Autophagy belongs in such panels for a different reason: it is a regulator of ferroptosis through ferritinophagy rather than a death modality competing with it, and should be reported as such unless autophagy-dependent cell death is specifically demonstrated. In addition, the direction of causation—whether ferroptotic barrier injury initiates sensitisation or results from established inflammation—can only be settled by longitudinal or interventional designs, since the one study showing that barrier disruption precedes sensitisation did not use a ferroptotic stimulus [84].

10. Conclusions

Allergic rhinitis has a two-decade clinical literature showing that lipid peroxidation is elevated in the nasal secretions and exhaled breath of patients, and inconsistently so in blood, and a three-year experimental literature showing that nasal epithelial cells can die by ferroptosis when exposed to house dust mite or type 2 cytokines. This review has argued that these are two descriptions of one process, and that reading them together reframes oxidative stress in AR from a non-specific accompaniment of inflammation into a targetable mechanism of epithelial barrier failure. The reframing rests on three AR-direct observations—the GAS1–METTL3–GPX4, METTL3–PTBP1–TXNIP and FOXP1–SDHAF2–ALOX15 axes—supported by human nasal tissue evidence, obtained in nasal polyp disease rather than AR, that type 2 inflammation reprograms epithelial lipid metabolism and that nasal epithelium can ferroptose in vivo, and it reinterprets the clinical finding that in blood it is the lipid-phase antioxidants, rather than aggregate antioxidant capacity, that fall in AR.

The honest limits are equally clear. The AR-specific evidence base is small, built on two recurring models, and thin on barrier measurements; direct demonstration of ferroptosis in human allergic nasal mucosa in vivo is still lacking, resting on nasal polyp tissue; much mechanistic depth is borrowed from asthma and must be labelled as borrowed; and the one systemic antioxidant combination trial to use a lipid peroxidation endpoint in allergic adults moved neither antioxidant capacity nor F_2-isoprostanes, a warning that mechanism does not guarantee therapeutic translation. Ferroptosis is also not uniformly harmful in allergy—its tolerance in type 2 lymphocytes is pathogenic—so the therapeutic logic is compartment-specific and favours epithelium-targeted, topical delivery over systemic antioxidant supplementation.

What makes the model worth publishing now is that it is testable with material rhinologists already handle. Staining nasal biopsies for transferrin receptor 1, 4-HNE adducts and GPX4 alongside junctional proteins, extending nasal lavage biomarkers to ferroptosis-specific species, and anchoring intranasal antioxidant trials to lipid peroxidation endpoints would, within a few years, either support or substantially weaken the case for ferroptosis as a driver of nasal barrier dysfunction in AR. Either outcome would be informative, and both are within reach.

Author Contributions: Conceptualization, A.M.S., I.-C.M., A.-A.N., I.-D.H. and R.A.M.; methodology, A.M.S., V.-C.I. and A.-A.N.; validation, A.-A.N., C.P. and R.A.M.; formal analysis, A.M.S. and V.-C.I.; investigation, A.M.S., V.-C.I., I.-C.M. and C.P.; resources, I.-C.M., C.P. and I.-D.H.; data curation, V.-C.I.; writing—original draft preparation, A.M.S., V.-C.I., I.-C.M., A.-A.N. and C.P.; writing—review and editing, I.-C.M., A.-A.N. and R.A.M.; visualization, A.M.S., V.-C.I. and A.-A.N.; supervision, R.A.M.; project administration, I.-C.M., I.-D.H. and R.A.M.; funding acquisition, I.-D.H. and R.A.M. All authors have read and agreed to the published version of the manuscript.

Funding: We would like to acknowledge "Victor Babeș" University of Medicine and Pharmacy for their support in covering the costs of publication for this research paper.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analysed in this study. Data sharing is not applicable to this article.

Acknowledgments: Financial support from the Doctoral School is gratefully acknowledged. This work was carried out within the DOCTOMED project (COD SMIS 350965). During the preparation of this manuscript, the authors used Anthropic Claude (model version Fable 5.1) for the purposes of organization of source material and figure preparation. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

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