



Perspective

Pathophysiology of Geographic Atrophy: RPE or Choroid as the Primary Culprit?

Victor Chong

UCL Institute of Ophthalmology, University College London, 11-43 Bath Street, London EC1V 9EL, UK;
victor@eretina.org

Abstract

Age-related macular degeneration (AMD) remains the leading cause of irreversible, severe visual loss among elderly populations in industrialized nations. The clinical spectrum ranges from early forms, characterized by the accumulation of extracellular deposits known as drusen, to advanced, vision-threatening late stages. While anti-vascular endothelial growth factor (anti-VEGF) therapy for neovascular AMD is the standard of care, geographic atrophy has remained a progressive condition. Geographic atrophy is a chronic neurodegenerative disease defined pathologically by the concurrent, progressive loss of the retinal pigment epithelium (RPE), the overlying photoreceptors, and the underlying choriocapillaris. Historically, the diagnosis and monitoring of GA relied on color fundus photography, which identified the lesions as sharply demarcated, well-circumscribed round or oval areas of depigmentation through which underlying choroidal vessels became clinically visible. However, the advent of high-resolution multimodal imaging—particularly fundus autofluorescence (FAF) and optical coherence tomography (OCT)—has necessitated a modernization of this terminology. Despite the imaging consensus, the fundamental pathophysiology of GA remains the subject of intense academic and clinical debate. The controversy focuses on identifying the primary cellular culprit responsible for initiating the cascade of degeneration. The “top-down” hypothesis suggests that intracellular metabolic failure, oxidative stress, and senescence within the RPE trigger the secondary dysfunction and death of the adjacent photoreceptors and choriocapillaris. Conversely, the “bottom-up” vascular hypothesis argues that age-related and complement activation-driven hemodynamic insufficiency, ischemic dropout, and structural involution of the choriocapillaris precede RPE dysfunction, creating a hypoxic microenvironment that drives the subsequent epithelial collapse. This narrative review scrutinizes the exact molecular, genetic, and structural mechanisms governing the expansion of geographic atrophy. By dissecting the evidence supporting both the RPE and the choriocapillaris as primary instigators, this analysis explores the paradigm that GA represents a synergistic failure of the outer blood–retinal barrier—a symbiotic trophic unit highly dependent on precise vascular and epithelial crosstalk, tightly regulated complement cascades, and extracellular matrix integrity.



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1. Introduction to the Pathobiology of Geographic Atrophy

Age-related macular degeneration (AMD) remains the leading cause of irreversible, severe vision loss among elderly populations in industrialized nations [1,2]. Driven by shifting global demographics and increasing life expectancies, epidemiological projections

estimate that 288 million individuals will be affected by the disorder by the year 2040 [1]. The disease exists on a clinical spectrum ranging from early forms, characterized by the accumulation of extracellular deposits known as drusen, to advanced, vision-threatening late stages [1,2]. Late AMD manifests in two distinct phenotypes: the exudative or neovascular (wet) form, defined by aberrant choroidal neovascularization (CNV), and the non-neovascular (dry) form, which culminates in geographic atrophy (GA) [1,3]. While anti-vascular endothelial growth factor (anti-VEGF) therapeutics have transformed the prognosis for neovascular AMD, geographic atrophy has historically remained an untreatable, relentlessly progressive condition [3,4].

Geographic atrophy is a chronic neurodegenerative disease defined pathologically by the concurrent, progressive loss of the retinal pigment epithelium (RPE), the overlying photoreceptors, and the underlying choriocapillaris [3,5]. Historically, the diagnosis and monitoring of GA relied on color fundus photography, which identified the lesions as sharply demarcated, well-circumscribed round or oval areas of depigmentation (measuring at least 175 μm in diameter) through which underlying choroidal vessels became clinically visible [6]. However, the advent of high-resolution multimodal imaging—particularly fundus autofluorescence (FAF) and optical coherence tomography (OCT)—has necessitated a modernization of this terminology [6,7].

To standardize clinical and research definitions, the Consensus on Atrophy Meeting (CAM) group established OCT-based criteria for defining atrophy [6]. The CAM group introduced the umbrella term “macular atrophy” to describe atrophy occurring across various retinal diseases, defining it by three primary OCT criteria: loss of the outer retina, loss of the RPE, and the presence of choroidal hypertransmission [6]. Within this framework, the term “geographic atrophy” is strictly reserved to describe macular atrophy occurring exclusively secondary to non-neovascular AMD [6]. Furthermore, the CAM group differentiated the progression of the disease into incomplete RPE and outer retinal atrophy (iRORA) and complete RPE and outer retinal atrophy (cRORA) [7]. The transition from iRORA—characterized by choroidal hypertransmission, attenuation of the RPE, and photoreceptor degeneration—to cRORA, where the zone of disrupted RPE exceeds 250 μm , serves as a critical prognostic biomarker for disease expansion [7].

Despite precise imaging consensus, the fundamental pathophysiology of GA remains the subject of intense academic and clinical debate. The central inquiry focuses on identifying the primary cellular culprit responsible for initiating the cascade of degeneration. The “top-down” hypothesis posits that intracellular metabolic failure, oxidative stress, and senescence within the RPE trigger the secondary starvation and death of the adjacent photoreceptors and choriocapillaris [3,8]. Conversely, the “bottom-up” vascular hypothesis argues that age-related hemodynamic insufficiency, ischemic dropout, and structural involution of the choriocapillaris precede RPE dysfunction, creating a hypoxic microenvironment that drives the subsequent epithelial collapse [5,9].

This comprehensive review scrutinizes the exact molecular, genetic, and structural mechanisms governing the expansion of geographic atrophy. By dissecting the evidence supporting both the RPE and the choriocapillaris as primary instigators, this analysis explores the contemporary paradigm that GA represents a synergistic failure of the outer blood–retinal barrier—a symbiotic trophic unit highly dependent on precise vascular and epithelial crosstalk, tightly regulated complement cascades, and extracellular matrix integrity.

2. The Case for the Retinal Pigment Epithelium as the Primary Culprit

The retinal pigment epithelium is a highly specialized, polarized monolayer of pigmented hexagonal cells strategically positioned between the neurosensory retina and the

vascular choroid [3]. The morphology of these cells adapts to their topographical location; in the fovea, RPE cells are narrow and tall, measuring approximately 14 μm in diameter and 10 to 15 μm in height, whereas in the peripheral retina, they broaden to 60 μm in diameter while flattening to 7.5 μm in height [3].

The RPE performs multiple physiological functions essential for visual preservation. These include the formation of the outer blood–retinal barrier via tight junctions, the absorption of scattered light, the recycling of visual cycle retinoids, the secretion of vital neurotrophic and angiogenic factors, and the daily phagocytosis of shed photoreceptor outer segments [3]. The “top-down” pathogenic model argues that the extraordinary, unyielding metabolic demands placed upon the RPE eventually outpace its intracellular clearance mechanisms, leading to primary senescence and cell death [3,8].

2.1. Oxidative Stress, Lipofuscin Accumulation, and Phototoxicity

The environment of the outer retina is subjected to immense oxidative stress, driven by continuous exposure to visible light, the high partial pressure of oxygen supplied by the choroid, and the massive generation of reactive oxygen species (ROS) that occurs during the phagocytosis of lipid-rich photoreceptor outer segments [3,8]. Chronic photo-oxidation of polyunsaturated fatty acids within shed outer segments under high oxygen tension steadily increases the intracellular burden of peroxidized lipids over time [10]. Over decades of life, the RPE’s lysosomal degradation pathways undergo a gradual decline in efficiency. This failure leads to the intracellular accumulation of lipofuscin—an autofluorescent, heterogeneous matrix of oxidized lipids, cross-linked proteins, and undegradable cellular waste [3,8].

A primary fluorophore and highly toxic constituent of lipofuscin is N-retinylidene-N-retinylethanolamine (A2E), a bis-retinoid byproduct of the visual cycle [3]. The accumulation of A2E within the RPE exerts profound phototoxic effects. Upon exposure to ambient blue light, A2E acts as a powerful photosensitizer, triggering the generation of massive quantities of ROS, specifically singlet oxygen and superoxide radicals [8,11]. These free radicals inflict direct, irreversible damage to nuclear DNA, cellular lipid membranes, and, critically, mitochondrial DNA (mtDNA) [8,12]. Furthermore, A2E directly destabilizes lysosomal membranes and inhibits vacuolar H⁺-ATPase, which elevates cytosolic pH and further impairs enzymatic waste clearance [11]. As lipofuscin physically occupies increasing cytosolic volume and actively disrupts lysosomal function, the RPE is pushed toward a state of chronic, insurmountable oxidative stress [3].

2.2. Mitochondrial Dysfunction and Autophagic Failure

Mitochondrial dysfunction has emerged as a central pillar in the primary RPE failure hypothesis. Mitochondria in the RPE must meet immense ATP demands to sustain ion pumps and molecular transport across the outer blood–retinal barrier [12]. Because mtDNA lacks the protective histones found in nuclear DNA, it is exceptionally vulnerable to the localized oxidative stress generated by A2E and lipofuscin [8,12]. Direct measurements of mitochondrial bioenergetics in primary RPE cultures isolated from human donors with AMD demonstrate significantly reduced baseline oxygen consumption rates, diminished spare respiratory capacity, and compromised oxidative phosphorylation compared to healthy age-matched controls [12–14].

Under physiological conditions, the RPE utilizes master transcription factors to regulate antioxidant defenses and mitochondrial biogenesis. Nuclear factor-erythroid 2-related factor-2 (NFE2L2/Nrf2) and peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1 α) govern the expression of vital clearance systems and antioxidant enzymes, such as manganese superoxide dismutase (MnSOD, or SOD2) [8]. Experimental models con-

firm that the ablation of these pathways replicates GA pathology. The targeted, RPE-specific knockout of the SOD2 gene results in swollen, electron-lucent mitochondria with disorganized cristae, a forced metabolic shift toward glycolysis, and profound RPE senescence [8]. Similarly, the dual global knockout of Nrf2 and PGC-1 α disrupts autophagic flux, resulting in the intracellular accumulation of damaged mitochondria (marked by Pink1/Parkin), the formation of drusen-like deposits, and the infiltration of Iba-1-positive immune cells, perfectly mimicking the dry AMD phenotype [8].

RPE cells harboring high-risk alleles for Complement Factor H (CFH Y402H) or ARMS2/HTRA1 exhibit significantly higher levels of mtDNA damage, decreased antioxidant capacity, and heightened susceptibility to oxidative apoptosis, firmly linking systemic genetic risk to localized mitochondrial collapse [3,12,15,16].

Autophagy—the lysosomal degradation of damaged organelles—is initially upregulated in early AMD as a cytoprotective response, mediated by AMPK (AMP-activated protein kinase) and the scaffolding protein p62 [8]. However, in advanced disease, the autophagic machinery becomes overwhelmed and dysfunctional, failing to clear the immense burden of peroxidized lipids and defective mitochondria [8,17,18]. When defective mitophagy fails to remove ROS-generating mitochondria, a self-amplifying loop of mtDNA damage and bioenergetic crisis ensues, and this autophagic arrest serves as a terminal tipping point for RPE viability [8,16].

2.3. Lysosomal Destabilization, the NLRP3 Inflammasome, and Pyroptosis

As the RPE's internal clearance mechanisms fail and lipofuscin burden reaches critical thresholds, the mechanisms governing cell death shift from immunologically silent apoptosis toward highly pro-inflammatory pathways. Central to this transition is the nucleotide-binding oligomerization (NOD)-like receptor protein 3 (NLRP3) inflammasome [3].

The NLRP3 inflammasome consists of NLRP3, the adaptor molecule ASC, and caspase-1. Upon activation, the NLRP3 multiprotein scaffold assembles, leading to the autoproteolytic cleavage of pro-caspase-1 into its active form, caspase-1 (CASP1) [3]. CASP1 cleaves pro-IL-1 β and pro-IL-18 into mature, active interleukins that are secreted into the subretinal space, recruiting macrophages and microglia cells and promoting chronic inflammation [3]. At the same time, CASP1 cleaves gasdermin D [3]. The N-terminal fragment of gasdermin D oligomerizes and inserts into the RPE plasma membrane, forming massive pores that disrupt osmotic homeostasis. This process results in “pyroptosis,” a rapid, lytic form of programmed cell death forcing neighboring RPE cells into the same inflammatory death spiral [3].

Recent evidence also implicates a non-canonical inflammasome pathway in GA. The accumulation of Alu RNA elements within the RPE can trigger intracellular detection via cyclic GMP–AMP synthase (cGAS) and caspase-4/caspase-5 (or caspase-11 in murine models) [19], which directly activates gasdermin D, entirely bypassing canonical caspase-1 to force RPE pyroptosis [3]. The convergence of these pathways underscores how internal RPE stress acts as the primary spark for macroscopic retinal atrophy.

2.4. The “Oil Spill” Hypothesis: ApoB Lipoproteins and the Lipid Wall

While intracellular lipofuscin and mitochondrial failure lead to RPE cell death from within, the RPE simultaneously initiates extracellular changes through the active secretion of lipids into Bruch's membrane (BrM). Termed the “Oil Spill” hypothesis by Curcio, this model argues that the RPE is the primary, autonomous source of the lipid deposits that form drusen and isolate the outer retina [20].

The RPE processes large quantities of lipids derived from the daily phagocytosis of photoreceptor outer segments. To clear this lipid burden, the RPE constitutively assembles

and secretes apolipoprotein B (ApoB)-containing lipoprotein particles from its basal surface directly into Bruch's membrane [20]. These lipoprotein-like particles (LLPs) and small granules (SGs), typically 60 to 80 nanometers in diameter, are rich in unesterified cholesterol (UC) and esterified cholesterol (EC) [20]. The concentration of esterified cholesterol is exceptionally high, reaching levels sevenfold greater in the macula than in the peripheral retina [20].

In early adulthood, these secreted lipoproteins gather sparsely among the fibrils of the outer collagenous layer and the elastic layer of BrM [20]. However, as age increases, these particles progressively fill the inner collagenous layer. Eventually, they densely pack to form a continuous, highly concentrated stratum located precisely between the RPE basal lamina and the inner collagenous layer—a pathogenic structure termed the “lipid wall” [20].

The lipid wall represents the earliest structural precursor to basal linear deposits (pre-BLinD) [20]. Once established, this wall exerts devastating physical and biochemical effects. Physically, the highly hydrophobic lipid wall drastically increases the hydraulic resistance of Bruch's membrane, creating an impermeable barrier that blocks the bidirectional transport of essential nutrients, oxygen, and water from the choroid to the RPE, while simultaneously trapping metabolic waste within the sub-RPE space [20].

Biochemically, the apolipoprotein components of these trapped lipids undergo oxidative and non-oxidative degradation over time [20]. This degradation causes the uniform lipoprotein vesicles to fuse, forming pools of lipoprotein-derived debris and macroscopic esterified cholesterol lakes [20]. This debris transitions into overt basal linear deposits (BLinD) and soft drusen [20]. The heavily peroxidized lipids within these lesions act as profound pro-inflammatory and pro-angiogenic triggers, eliciting complement activation and further damaging the RPE [3,20]. As this entire extracellular cascade is driven by RPE-derived cholesterol and ApoB secretion, it provides a compelling argument that the primary pathobiological defect in GA originates entirely within the RPE itself.

3. The Case for the Choriocapillaris as the Primary Culprit

Despite the extensive evidence detailing RPE failure, a robust counter-paradigm exists: the “bottom-up” or vascular hypothesis. This model argues that the RPE is merely a victim of ischemia, and that the primary initiating event in geographic atrophy is the age-related involution, hemodynamic failure, and vascular dropout of the choriocapillaris from complement activation [5,9], with ghost vessel formation [21].

3.1. Hemodynamic Vulnerability and Histopathological Evidence

The choroid requires the highest rate of blood flow per unit of tissue mass in the human body, a unique physiological necessity required to meet the extreme metabolic demands of the photoreceptor-RPE complex and to act as a heat sink, dissipating the thermal energy generated by light absorption [5]. The choriocapillaris itself is organized in a dense, highly fenestrated lobular pattern immediately abutting the outer aspect of Bruch's membrane [5].

Histopathological studies of human donor eyes reveal that normal aging is characterized by a gradual decline in choriocapillaris density, a reduction in luminal diameter, and a progressive loss of choroidal endothelial cells [5]. In the context of early and intermediate AMD, however, this vascular dropout becomes severely pathological [5]. Morphometric analyses indicate that the vascular density of the choriocapillaris is inversely proportional to the cross-sectional area of sub-RPE drusen deposits; indeed, the density of the choriocapillaris directly beneath isolated soft drusen is up to 45% lower than in adjacent, drusen-free regions [5].

Crucially, researchers have identified the presence of “ghost vessels”—capillary tubes that have entirely lost their functional endothelial lining but still retain their pericyte wrapping and basement membrane architecture—in the early stages of AMD [5]. The prevalence of these ghost vessels strongly indicates that primary endothelial cell death and capillary retraction occur significantly early in the disease timeline, long before the structural collapse or macroscopic death of the overlying RPE [5]. In this model, the resulting chronic hypoxia and restricted nutrient delivery force the RPE into a state of metabolic crisis, acting as the upstream trigger for subsequent drusen biogenesis, lipofuscin accumulation, and eventually, geographic atrophy [5,9].

3.2. Insights from Optical Coherence Tomography Angiography (OCTA)

The clinical validation of the vascular hypothesis has been greatly accelerated by Optical Coherence Tomography Angiography (OCTA). By detecting the decorrelation of OCT signals caused by moving erythrocytes, OCTA provides non-invasive, high-resolution, three-dimensional mapping of the retinal and choroidal microvascular networks in vivo [9,22].

In eyes exhibiting active geographic atrophy, OCTA demonstrates profound choriocapillaris flow deficits (CC FDs)—areas where blood flow is undetectable—that colocalize exactly with areas of RPE loss [9,22]. More importantly, OCTA reveals significant perfusion anomalies in areas where the RPE remains structurally intact. Studies have consistently identified an annular zone of severe CC flow impairment in the para-atrophic and peri-atrophic margins immediately surrounding the borders of existing GA lesions [22]. The spatial distribution and magnitude of these regional flow voids are highly predictive of disease behavior; regions demonstrating significant CC FDs at baseline exhibit a markedly higher probability of transitioning into complete atrophy over subsequent months, strongly suggesting that a leading edge of ischemia drives the expansion of the GA lesion [22].

The specific AMD phenotype also dictates the severity of this vascular dropout. When comparing standard AMD-related GA to Extensive Macular Atrophy with Pseudodrusen-like Appearance (EMAP), OCTA reveals that EMAP exhibits significantly higher CC FDs both at the margin of the atrophy ($p < 0.05$) and beyond the margin ($p < 0.01$) [22]. This indicates a more aggressive vascular compromise in EMAP, emphasizing that widespread CC impairment dictates the velocity and clinical severity of the atrophic spread [22].

3.3. The 2025 OCTA Longitudinal Debate: Defining the Exact Sequence of Loss

While cross-sectional data clearly link CC loss to GA, the exact temporal sequence—whether CC dropout initiates RPE loss or strictly follows it—remains highly controversial. This debate is epitomized by two landmark longitudinal OCTA studies published in 2025, which utilized differing analytical methodologies and reached opposing conclusions.

The Johari Moghadam et al. (2025) Study (The Vascular Primacy Model) [9]:

Published in *Clinical Ophthalmology*, this retrospective longitudinal cohort study analyzed 68 eyes from 50 patients with intermediate AMD (iAMD) over a 24-month period [9]. The study compared eyes that progressed to GA (7 eyes) against those that remained stable. The findings strongly supported the “bottom-up” hypothesis:

- **Baseline Ischemia Predicts Atrophy:** At baseline, well before the clinical onset of GA, eyes that eventually progressed to atrophy exhibited a significantly larger total area of choriocapillaris flow deficits ($469,815.6 \mu\text{m}^2$ vs. $131,335.2 \mu\text{m}^2$ in stable eyes; $p = 0.013$) and a significantly higher proportional area of non-perfusion (36.0% vs. 12.5%; $p = 0.013$) [9].
- **Delayed Retinal Vascular Decline:** At baseline, there were no significant differences in retinal superficial capillary plexus vessel density (VD) or foveal avascular zone (FAZ) metrics between the progressor and stable cohorts [9]. Significant decreases in

retinal VD (parafoveal $p = 0.026$; full macular $p = 0.019$) occurred exclusively after the 24-month onset of GA [9].

- *Conclusion:* The authors concluded that global CC ischemia is a primary initiator that is detectable prior to GA onset. They proposed that primary CC damage starves the RPE, leading to outer retinal atrophy, which subsequently lowers the metabolic demand of the overlying retina, thereby triggering secondary retinal vasoconstriction and VD loss [9].

The Beqiri et al. (2025) Study (The Epithelial Primacy Model) [22]:

Conversely, Beqiri and colleagues utilized swept-source OCTA to challenge the primacy of the ischemic insult [22]. Instead of measuring global macular ischemia, this study tracked 27 eyes with iAMD by monitoring the exact topographic grid locations where new, large choroidal hypertransmission defects (hyperTDs)—the definitive OCT biomarker for cRORA—subsequently emerged [22].

- *Lack of Preceding Local Flow Deficits:* Tracking the specific grid sites where hyperTDs eventually formed, the researchers found absolutely no marked change in CC FD (above a 5% test–retest variability threshold) prior to the onset of the hyperTD [22].
- *Post-Onset Ischemia:* Significant increases in CC FDs within those specific grid targets were only detected after the structural emergence of the hyperTD [22].
- *Conclusion:* The authors concluded that highly localized loss of choriocapillaris perfusion does not precede RPE death (hyperTD formation). Rather, the RPE fails first, and the underlying choriocapillaris subsequently atrophies due to the loss of RPE-derived trophic support, though the resulting post-onset ischemia may still govern the continued radial expansion of the lesion [22].

The discrepancies between these two high-level studies underscore the profound technical challenges of OCTA. Precise quantification of CC FDs requires advanced compensation strategies (such as Phansalkar local thresholding) to mathematically mitigate signal attenuation and shadowing artifacts caused by overlying drusen, hyperreflective foci, and calcifications [9,22]. The divergence in findings largely rests on the scale of analysis.

Study	Cohort & Modality	Primary Analytical Metric	Key Baseline Finding	Pathobiological Conclusion
Johari Moghadam et al. (2025) [9]	68 eyes (iAMD); 24-month longitudinal OCTA.	Global macular CC flow deficits & Retinal VD.	Progressing eyes had ~3.5× larger CC FD area ($p = 0.013$) long before clinical GA onset.	Bottom-Up: Widespread CC ischemia precedes GA. Retinal VD drops post-GA due to reduced metabolic demand.
Beqiri et al. (2025) [22]	27 eyes (iAMD); multi-year swept-source OCTA.	Localized CC FD changes exactly where hyperTDs emerge.	No marked (>5%) local CC FD change observed prior to the emergence of the hyperTD.	Top-Down: Localized CC loss does not precede local RPE death, but follows it, subsequently influencing lesion growth.

4. The Symbiotic Unit: RPE-Choriocapillaris Crosstalk and Synergistic Failure

In light of compelling, yet seemingly contradictory evidence supporting both the RPE and the choriocapillaris as primary culprits, contemporary pathology increasingly rejects a mutually exclusive binary. Instead, geographic atrophy is now recognized as a disease of the entire outer blood–retinal barrier. The RPE, Bruch’s membrane, and the choriocapillaris function as a highly interdependent, symbiotic “trophic unit” [5,23]. The survival of one layer is absolutely contingent upon continuous biochemical and structural crosstalk with the others; when this dialogue is disrupted, a cascade of synergistic failure ensues [5].

4.1. Vascular Endothelial Growth Factor (VEGF) and Trophic Support

The absolute cornerstone of this symbiotic relationship is Vascular Endothelial Growth Factor-A (VEGF-A) [23]. While extensively targeted for its pathological role in driving choroidal neovascularization in wet AMD, physiological, constitutive levels of VEGF are absolutely vital for the survival, differentiation, and fenestration of the healthy choriocapillaris [23].

The RPE is the primary source of this constitutive VEGF [23]. As the RPE is physically separated from the choriocapillaris by the acellular Bruch’s membrane, the VEGF it secretes must be highly diffusible to successfully cross the extracellular matrix and reach the endothelial VEGF Receptor 2 (VEGFR2) [23].

The necessity of this pathway was demonstrated in a landmark transgenic study by Saint-Geniez et al. Researchers engineered a conditional mouse model (VEGF188/188) that was genetically restricted to producing only the sequestered, non-diffusible VEGF188 isoform [23]. These mice exhibited entirely normal embryonic and early adult choriocapillaris development. However, beginning at 7 months of age, the inability of the sequestered VEGF to reach the choroid precipitated a rapid, progressive degeneration and atrophy of the choriocapillaris [23]. This primary, engineered vascular loss was immediately followed by massive structural abnormalities in the RPE—including extensive vacuolization and regression of basal infoldings—culminating in widespread RPE loss, the accumulation of membranous debris, and extreme photoreceptor apoptosis [23].

However, while this transgenic mouse model provides invaluable proof-of-concept regarding the spatial diffusibility requirements of VEGF isoforms across extracellular boundaries, these findings must be interpreted with anatomical caution when extrapolating directly to human geographic atrophy. Rodents inherently lack a specialized anatomical macula and possess a choriocapillaris architecture that differs markedly from the human outer retina in terms of thickness, lobular vascular organization, and hemodynamic properties. Therefore, characterizing the resulting mouse histopathological phenotype as virtually indistinguishable from human GA represents an oversimplification of complex human maculopathy.

Furthermore, proposing the RPE as the exclusive or sole clinically significant source of retinal and choroidal VEGF overlooks the dynamic cellular heterogeneity of the aging eye. During intermediate AMD and GA progression, multiple other cell types actively contribute to the localized VEGF pool. Infiltrating choroidal macrophages and mononuclear phagocytes secrete substantial quantities of VEGF and pro-angiogenic cytokines in response to sub-RPE debris and localized hypoxia [24,25]. Choroidal endothelial cells themselves utilize autocrine VEGF signaling to maintain vascular tube integrity [26]. Additionally, retinal glial cells—including Müller cells and astrocytes—and even choroidal mast cells contribute measurable amounts of VEGF during chronic retinal stress and neurovascular inflammation [27,28]. Thus, while RPE-derived soluble VEGF is unquestionably essential

for baseline choriocapillaris fenestration, microvascular survival in GA is governed by a complex, multi-cellular cytokine network.

4.2. The VEGF and PEDF Counterbalance

The RPE’s maintenance of the choroidal microenvironment requires a delicate equilibrium of opposing signaling molecules. While the RPE secretes VEGF from its basal aspect to sustain the choriocapillaris, it simultaneously secretes Pigment Epithelium-Derived Factor (PEDF), primarily from its apical surface [23]. PEDF serves dual functions as a robust neuroprotectant for photoreceptors and a potent anti-angiogenic factor that prevents the dense choroidal vessels from aggressively breaching Bruch’s membrane [23].

In normal aging and particularly in AMD pathogenesis, the expression of PEDF in the RPE, the basal lamina, and the choroidal stroma is significantly downregulated. If the local microenvironment experiences hypoxia due to early choriocapillaris dropout, the surviving RPE cells upregulate Hypoxia-Inducible Factor 1-alpha (HIF-1α), leading to a massive overexpression of VEGF [23]. In geographic atrophy, the terminal senescence of the RPE results in a complete cessation of both VEGF and PEDF secretion, leading to the collapse of both the epithelial and vascular compartments [5,23].

5. Intersecting Pathologies: Complement Dysregulation and Extracellular Barriers

Beyond autonomous cellular senescence and the withdrawal of trophic support, the pathophysiology of geographic atrophy is linked to systemic immune dysregulation and the structural degradation of the extracellular matrix.

5.1. The Complement Cascade and MAC Deposition

The complement system—a highly conserved component of innate immunity—serves as the primary bridge linking systemic genetic risk factors to localized retinal degeneration [1,3]. The cascade is activated via three distinct pathways, classical, lectin, and alternative, all of which converge on the enzymatic cleavage of Complement Component 3 (C3) into its active fragments, C3a and C3b [3]. This central cleavage event ultimately initiates the terminal complement pathway, resulting in the assembly of the Membrane Attack Complex (MAC, or C5b-9), a cylindrical pore-forming structure that inserts directly into target cell membranes, disrupting osmotic homeostasis and causing rapid cell lysis [3,29] (Table 1).

Table 1. The role of target molecules of the complement pathway and their mechanism of action in the pathogenesis of geographic atrophy.

Target Molecule	Mechanism of Action	Pathological Outcome in Geographic Atrophy
C3 (Complement Component 3)	Central convergence point for classical, lectin, and alternative pathways. Cleaves into C3a and C3b.	Unregulated cleavage amplifies the cascade, leading to massive downstream MAC assembly.
C5 (Complement Component 5)	Cleaved by C5 convertase into C5a (anaphylatoxin) and C5b (initiates terminal MAC).	C5a recruits macrophages; C5b acts as the foundation for the pore-forming MAC.
MAC (C5b-9)	Terminal pore-forming complex that inserts into lipid bilayers.	Directly causes osmotic lysis and necrosis of RPE cells and choroidal endothelium.
CD46, CD55, CD59	Membrane-bound complement regulatory proteins (mCRPs) expressed by healthy RPE.	Early downregulation removes autologous protection, making RPE susceptible to MAC lysis.
CFH (Complement Factor H)	Soluble inhibitor of the alternative complement pathway.	Genetic variants (e.g., Y402H) impair inhibition, driving systemic and local hyper-inflammation.

The RPE and the choroid are major localized producers of complement proteins [3]. To prevent autologous complement-mediated destruction, healthy RPE cells densely express membrane-bound complement regulatory proteins (mCRPs), specifically CD46 (Membrane Cofactor Protein), CD55 (Decay-Accelerating Factor), and CD59 [3]. In patients with geographic atrophy, there is an early disease-related downregulation of both CD46 mRNA and cell-surface protein expression on the RPE [3].

Simultaneously, the systemic regulation of the alternative pathway is frequently compromised by genetic polymorphisms [30]. The most notable of these is the Y402H variant of Complement Factor H (CFH), as well as rare variants in Complement Factor I (CFI), which critically impair the body's ability to inhibit alternative pathway overactivation [3]. The metabolically stressed RPE serves as a potent, highly localized complement activator [3,20]. Without the protection of CD46 and an uninhibited CFH environment, the RPE and the adjacent choriocapillaris endothelium become primary targets for unregulated MAC deposition [3]. This unchecked complement-mediated lysis accelerates both the RPE pyroptosis and the choriocapillaris endothelial necrosis that drives the leading edge of GA expansion [3,12].

5.2. Age-Related Changes in Bruch's Membrane: Calcification, ECM Cross-Linking, and Diffusion Barriers

The structural and biochemical state of Bruch's membrane represents a critical mediator in the synergistic failure of the outer retina. Functioning as the molecular sieve between the RPE and the choroidal vasculature, its permeability is an absolute requirement for visual health [20]. As previously discussed, the deposition of RPE-derived ApoB lipoproteins to form the "lipid wall" creates a formidable hydrophobic barrier within the membrane [20].

A profound mechanistic insight into the lethality of structural barrier formation is derived from the pathology of Pseudoxanthoma Elasticum (PXE). PXE is an autosomal-recessive systemic disorder caused by mutations in the ABCC6 gene, leading to abnormally low systemic levels of inorganic pyrophosphate, a potent natural inhibitor of ectopic calcification [31]. In the eye, PXE results in the rapid, progressive, and extensive calcification of the elastic layer of Bruch's membrane [31]. This dense calcification shatters the transport capabilities of the membrane, inducing a sharply demarcated, bilateral macular atrophy that is phenotypically almost identical to AMD-driven geographic atrophy [31,32]. The PXE model provides undeniable evidence that an isolated physical failure of the extracellular matrix—completely independent of primary RPE senescence or primary capillary ischemia—is fully sufficient to induce the mutual starvation and death of both the RPE and the choriocapillaris [31].

In typical age-related macular degeneration, Bruch's membrane pathology is significantly more multifaceted than calcification alone, encompassing a broad spectrum of structural, biochemical, and cellular alterations. Over decades of life, non-enzymatic glycation and the accumulation of advanced glycation end-products (AGEs) induce extensive extracellular matrix (ECM) cross-linking of collagen fibrils within the inner and outer collagenous layers [33,34]. This cross-linking markedly increases mechanical stiffness and alters the structural integrity of the membrane. Simultaneously, the membrane undergoes a profound reorganization of ECM proteins, characterized by the fragmentation of the central elastic lamina, irregular collagen thickening, and aberrant deposition of adhesive glycoproteins such as fibronectin, laminin, and tenascin [34,35].

The combination of heavy lipid accumulation (the lipid wall), extensive ECM protein cross-linking, and structural reorganization results in a dramatic, age-dependent reduction in hydraulic conductivity [35,36]. This loss of fluid movement severely impedes the bidirectional transit of water, electrolytes, and micronutrients from the choriocapillaris

to the RPE, while preventing the clearance of metabolic waste products from the outer retina [36].

Furthermore, these extracellular matrix modifications act as potent chemoattractants that drive pathological immune-cell recruitment. Choroidal macrophages, dendritic cells, and microglial precursors migrate toward the basal aspect of Bruch's membrane in an attempt to phagocytose trapped lipids and proteinaceous debris [37]. This localized immune infiltration triggers extracellular protease activation, specifically the release of matrix metalloproteinases (such as MMP-2 and MMP-9) alongside altered expression of tissue inhibitors of metalloproteinases (TIMPs) [37,38]. Rather than successfully remodeling or restoring normal tissue architecture, this chronic, dysregulated proteolytic activity further degrades the functional elasticity and transport capacity of Bruch's membrane, chemically and physically isolating the RPE from its vascular lifeline and guaranteeing the eventual clinical manifestation of geographic atrophy.

6. Clinical Implications and Therapeutic Horizons

The evolving understanding of geographic atrophy as a multifactorial, synergistic collapse of the outer blood–retinal barrier has rapidly driven the development of targeted, disease-modifying therapeutics. Recognizing the central role of uncontrolled inflammation and MAC-induced cell lysis, the pharmacological inhibition of the complement cascade has successfully transitioned from theoretical models to clinical application [3,12].

Pegcetacoplan, a targeted C3 inhibitor, demonstrated significant efficacy in the Phase 3 OAKS and DERBY clinical trials, successfully slowing the anatomic growth rate of GA lesions compared to sham treatments [4]. Similarly, avacincaptad pegol, a targeted C5 inhibitor, demonstrated robust efficacy in the Phase 3 GATHER2 trial [39]. By halting the cleavage of C3 and C5, respectively, these therapeutics prevent the downstream generation of inflammatory anaphylatoxins (C3a, C5a) and block the ultimate assembly of the lytic MAC on the surfaces of the RPE and choroidal endothelium [4,12,39].

While the FDA approval of these agents marks a historic milestone, they are not curative; they solely decelerate the leading edge of atrophic expansion [4,39]. Furthermore, by fundamentally altering the delicate immune and angiogenic balance within the sub-retinal space, complement inhibitors carry a paradoxically increased, dose-dependent risk of inducing exudation [12].

Given the limitations of complement inhibition, future therapeutic paradigms are pivoting to address the metabolic and mitochondrial failures that initiate the cascade [8,12]. Simultaneously, the integration of advanced imaging modalities into clinical practice offers new avenues for preventative care. The early detection of choriocapillaris flow deficits using swept-source OCTA—particularly through the identification of global macular ischemia prior to localized RPE collapse, as outlined by Moghadam and colleagues—may allow clinicians to accurately stratify intermediate AMD patients at the highest risk of rapid progression [9]. Identifying these highly vulnerable phenotypes opens the window for early, prophylactic interventions aimed at preserving endothelial health, restoring vascular tone, and stabilizing the lipid wall before the irreversible structural collapse of the RPE and choriocapillaris occurs [9].

7. Conclusions

The quest to identify a single, isolated primary culprit—either the retinal pigment epithelium or the choriocapillaris—in the pathophysiology of geographic atrophy represents a historical oversimplification of a highly complex, intersecting neurovascular disease. The preponderance of modern evidence dictates that geographic atrophy is the terminal endpoint of a synergistic failure within a tightly integrated biological unit.

The “top-down” epithelial sequence is unequivocally supported by the relentless oxidative burden placed on the RPE, leading directly to mtDNA damage, lipofuscin phototoxicity, the pathological secretion of ApoB lipoproteins to form the impermeable lipid wall, and the explosive, lytic activation of the NLRP3 inflammasome. Conversely, the “bottom-up” vascular sequence is robustly validated by histopathological and advanced OCTA evidence demonstrating early hemodynamic insufficiency, physical vascular dropout, and profound choriocapillaris flow deficits that either precede or intimately drive RPE cell death.

These two cascades do not operate independently. The RPE relies on the choriocapillaris for metabolic sustenance, oxygenation, and heat dissipation, just as the choriocapillaris relies on RPE-derived soluble cytokines for its structural survival and high-density fenestration. A primary defect originating in either layer—whether induced by genetic complement dysfunction, cumulative oxidative stress, and/or the physical barricading of Bruch’s membrane via lipid deposition and calcification—inevitably triggers the rapid and irreversible failure of the other. The resulting destruction of the outer blood–retinal barrier drives the clinical characteristic of geographic atrophy. Future therapeutic paradigms must therefore transcend singular targets, aiming instead to develop combinatorial approaches that simultaneously quench complement-driven inflammation and support the delicate vascular–epithelial symbiosis before the tipping point of irreversible macular atrophy is reached.

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