Review

THE PATHOPHYSIOLOGY OF GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION AND THE COMPLEMENT PATHWAY AS A THERAPEUTIC TARGET

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Purpose: Geographic atrophy (GA) is an advanced, vision-threatening form of age-related macular degeneration (AMD) affecting approximately five million individuals worldwide. To date, there are no approved therapeutics for GA treatment; however, several are in clinical trials. This review focuses on the pathophysiology of GA, particularly the role of complement cascade dysregulation and emerging therapies targeting the complement cascade.

Methods: Primary literature search on PubMed for GA, complement cascade in age-related macular degeneration. ClinicalTrials.gov was searched for natural history studies in GA and clinical trials of drugs targeting the complement cascade for GA.

Results: Cumulative damage to the retina by aging, environmental stress, and other factors triggers inflammation via multiple pathways, including the complement cascade. When regulatory components in these pathways are compromised, as with several GA-linked genetic risk factors in the complement cascade, chronic inflammation can ultimately lead to the retinal cell death characteristic of GA. Complement inhibition has been identified as a key candidate for therapeutic intervention, and drugs targeting the complement pathway are currently in clinical trials.

Conclusion: The complement cascade is a strategic target for GA therapy. Further research, including on natural history and genetics, is crucial to expand the understanding of GA pathophysiology and identify effective therapeutic targets.

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Geographic atrophy (GA) is an advanced, vision-threatening form of age-related macular degeneration (AMD). This degenerative disease occurs with progressive loss of areas of the retinal pigment epithelium (RPE), photoreceptors, and underlying choriocapillaris.[1] Loss of visual function because of GA is considered irreversible and usually bilateral, with half of patients developing GA in both eyes within seven years of the initial GA diagnosis.[2]

An estimated 973,000 people in the United States[3] and approximately 5 million globally[4,5] have GA in at least one eye. In the United Kingdom, GA is estimated to account for 26% of legal blindness.[6,7] The incidence of advanced AMD increases exponentially with age, with the two forms of advanced AMD, GA and neovascular AMD, occurring with roughly equal prevalence.[4,5,8] As the population ages, the prevalence of advanced AMD is expected to rise from 9.64 million to 11.26 million in 2020 and 18.57 million in 2040.[5]

Currently, there is no efficient prevention, individual risk estimation, or reliable prognostic evaluation available, and, most importantly, there are no therapeutics approved for the treatment of GA. However, a number of drugs are in clinical trials. In particular,

several of these target the complement cascade, a part of the innate immune system that can cause inflammation and cell death. Dysregulation of the complement cascade has been implicated in multiple chronic progressive diseases, including GA,[9,10] and complement inhibition has been identified as a likely candidate for efficient therapeutic intervention. This review will focus on the pathophysiology of GA, particularly the role of complement cascade dysregulation and emerging therapies targeting the complement cascade.

Pathology of Geographic Atrophy

Early stages of AMD are characterized by the presence and accumulation of drusen, extracellular deposits of cellular debris including protein and lipid aggregates, which appear clinically as yellowish dots at the posterior pole of the retina. Two large epidemiologic studies, Age-Related Eye Disease Study (AREDS) and Beaver Dam Eye Study, demonstrated that appearance and growth of drusen deposits are prognostic for GA. Eyes with multiple large drusen (>125 μm) are significantly more likely to develop GA than eyes with small drusen (<63 μm) (15-year odds ratio [OR], 14.5, 95% confidence interval [CI], 5.9–35.7[11]; 10-year rate in 75 to 80 year olds, 26%[12]). Similarly, eyes with soft indistinct drusen (15-year OR, 14.6, 95% CI, 6.8–31.1) or pigmentary abnormalities (15-year OR, 15.2, 95% CI, 7.3–31.6) are also more likely to develop GA.[11]

Imaging of Geographic Atrophy

Geographic atrophy can be imaged and monitored by multiple modalities, such as color fundus photography (CFP), fluorescein angiography (FA), fundus autofluorescence (FAF), red-free (RF) imaging, near

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infrared-wavelength FAF (NIR-FAF), and spectral-domain optical coherence tomography (SD-OCT) (Figure 1).[13] Atrophic patches appear as generally well-demarcated areas, and choroidal vessels are increasingly visible in the absence of the overlaying RPE. Each imaging modality provides insight into different aspects of GA pathology and progression.

Fundus autofluorescence imaging detects the autofluorescence of lipofuscin, thought to be incompletely degraded photoreceptor outer segments and visual cycle by-products such as A2E, which accumulate within RPE cells.[14,15] Complete absence of lipofuscin, appearing as dark, hypofluorescent regions, is used as a quantitative assessment of RPE cell death and an indirect measure of overlying photoreceptor loss.

Recent advances in high-resolution imaging techniques such as SD-OCT and adaptive optics scanning laser ophthalmoscopy (AOSLO) have allowed improved imaging of retinal features.[16,17] Adaptive optics scanning laser ophthalmoscopy technology provides sufficient resolution to enable *en face* visualization of individual cone photoreceptors. Using this technique, structural changes in cone photoreceptors have been reported over drusen and at GA lesion boundaries.[17] The cross-sectional images produced by SD-OCT allow detailed imaging of all retinal layers, including photoreceptors, RPE, and choroid. Comparative studies have shown generally high agreement between SD-OCT and FAF.[16] However, SD-OCT offers clear advantages compared with *en-face* FAF as it allows a three-dimensional visualization of neurosensory atrophy, RPE alteration at the junctional border of GA lesions and central RPE loss, and choriocapillary thinning and choroidal enhancement because of increased light transmission resulting from melanocyte loss.[18,19] In particular, foveal integrity is only reliably detected by SD-OCT and correlates tightly with visual function.[19] The presence, number, and change in axial distribution of discrete hyperreflective loci on SD-OCT, thought to represent RPE cell migration from their native location in the outer retinal layer to ectopic locations in the inner retinal layers, have been recognized as a potential biomarker for progression from intermediate AMD to GA.[20] Analysis of retinal layers on SD-OCT has led to the description of an early form of drusen-associated atrophy, termed "nascent GA," which is associated with the subsidence of the outer plexiform layer and inner nuclear layer.[21] Further analysis of these pathognomonic features of GA by SD-OCT may provide additional insight into the pathophysiology of GA.

Polarization-sensitive OCT (PS-OCT) is an advanced SD-OCT modality that selectively visualizes the RPE through the intrinsic polarization of incident light by RPE-specific melanocytes. This allows for the
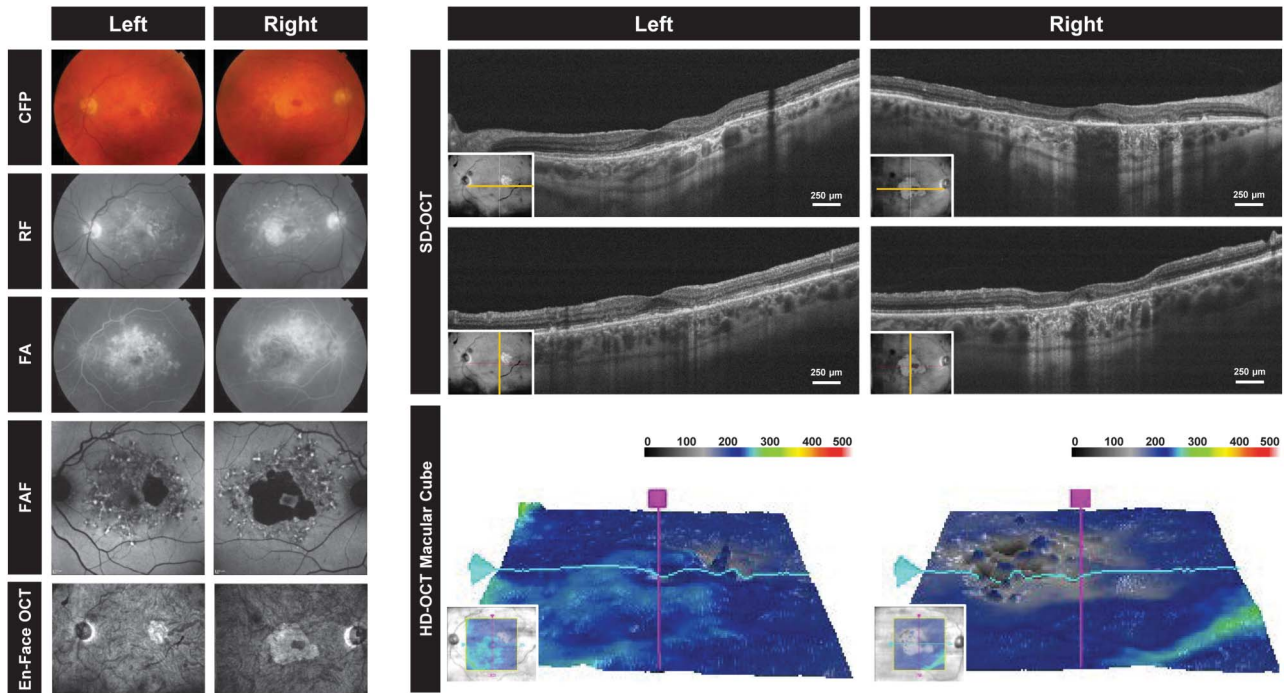
Fig. 1. Multimodal imaging of geographic atrophy. Images of geographic atrophy (GA) from both eyes of one patient using color fundus photography (CFP), red-free imaging (RF), fluorescein angiography (FA), fundus autofluorescence (FAF), near-infrared fundus autofluorescence (NIR-FAF), and spectral domain optical coherence tomography (SD-OCT) (*en face,* cross-sectional, and macular cube images shown).

detection of discrete RPE changes in early AMD as well as a precise qualitative and quantitative evaluation of advanced GA lesions.[22,23] For example, PS-OCT has identified additional features of drusen morphology, such as nonhomogeneity,[24] which may correlate with RPE degeneration.[25]

Patterns of Disease Progression

Geographic atrophy is a progressive disease,[26,27] and progression rates can vary depending on baseline size,[2,26–30] atrophy location,[31] and the patterns of autofluorescence surrounding atrophic areas on FAF images (Figure 2).[28] Geographic atrophy lesions are often multifocal, and the total atrophic area in eyes with multifocal lesions has been reported to grow faster than in eyes with unifocal lesions.[30,32,33] With the exception of very large and very small GA lesions, atrophic patches generally grow linearly over time[2,34]; a square root transformation can be used to normalize enlargement rates to account for differences in baseline size in a population.[30,34]

Geographic atrophy is often bilateral; in AREDS, the cumulative probability of having bilateral GA at first GA development was 0.07 (95% CI, 0.05–0.09), increasing to 0.62 (95% CI, 0.52–0.72) at 10 years with a median time of 7 years (95% CI, 6.0–10.0 years) to progression to bilateral GA.[2] In addition, there is a high degree of concordance between eyes with regard to GA incidence, progression, and area.[2,27,35,36]

The foveal-sparing growth patterns of GA suggest that the fovea is less susceptible to atrophy than extrafoveal regions.[31,37] In an early study, foveal sparing was reported until about >1 disc area (DA) of atrophy was present,[37] and recently, it was demonstrated that GA progression toward the periphery is 2.8 times faster than toward the fovea.[38] This can result in a horseshoe- or ring-shaped area of GA surrounding the fovea.[39] Based on this characteristic location and growth pattern, it is hypothesized that rods are preferentially, though not exclusively, affected over cones in GA; this is also supported by compromised scotopic retinal sensitivity in eyes with AMD.[40,41]

In AREDS GA progressed from noncentral to central GA, defined as definite GA involving the center point of the fovea, in a median 2.5 years following any GA diagnosis, with 35% of participants presenting with center-involved GA at the initial diagnosis.[2] In the Beaver Dam Eye Study, 50% presented with foveal involvement at first diagnosis.[32]

Functional Impact of Progression of Geographic Atrophy

Only a few studies have evaluated long-term GA progression patterns (≥2 years),[2,27,32,42] and data on
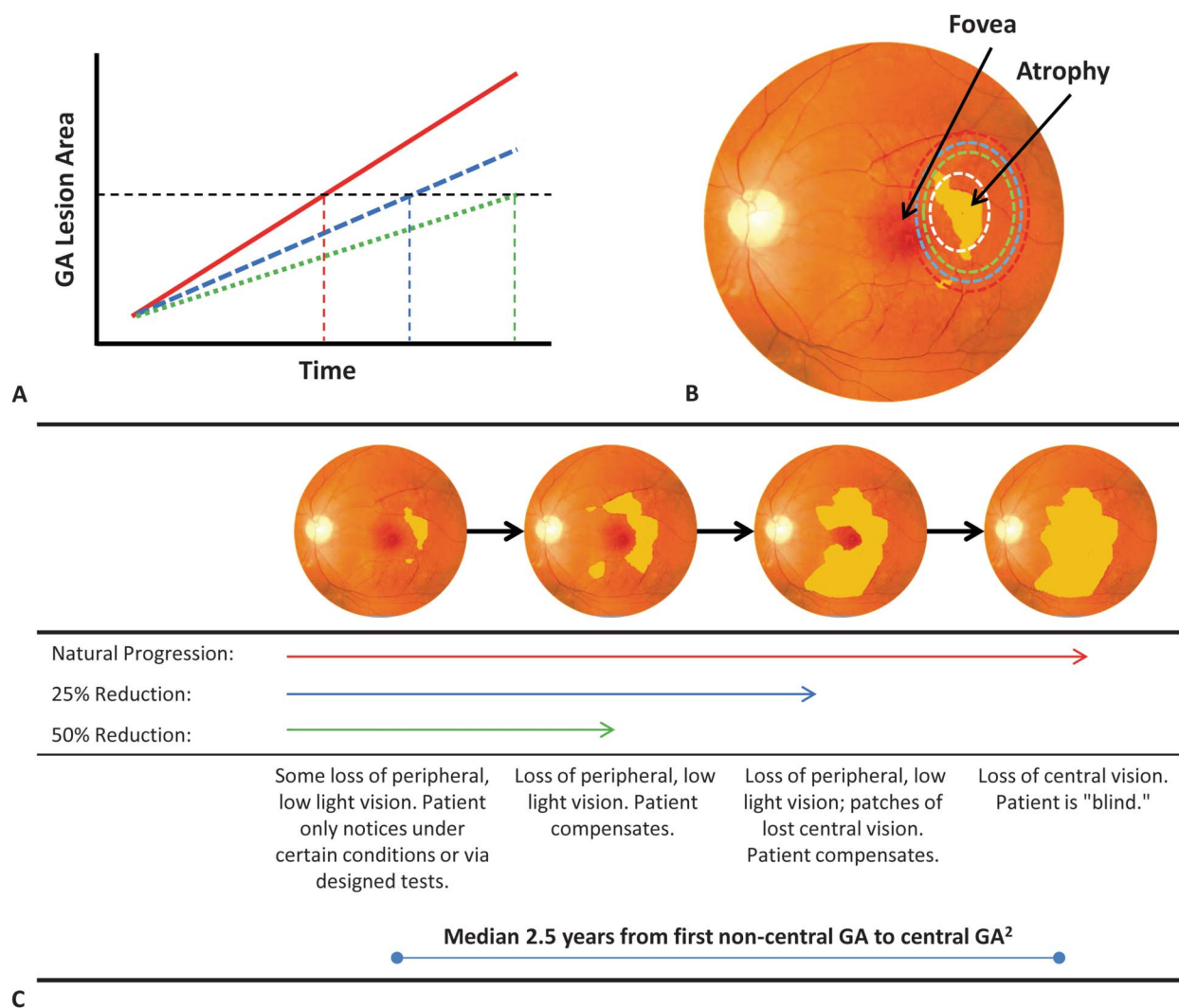
Fig. 2. Impact of geographic atrophy progression on patient vision. As geographic atrophy (GA) progression usually begins outside of the fovea, decreasing the rate of GA area progression by 25% to 50% can potentially delay progression to the fovea by years, particularly if intervention is started early. Red: Natural progression; blue: 25% reduction; green: 50% reduction. **A.** GA progression over time; vertical reference lines note the time differences in atrophy progression to a given GA lesion size under these three scenarios. **B.** Illustration of GA area growth over time. Dotted circles represent expected GA growth per expected natural history (red) or with reduced speed of progression (blue, green). The rate of atrophy progression may be faster toward the periphery than toward the fovea. **C.** Example of progression of a GA lesion and its effect on patient vision. Central vision is largely preserved until atrophy encroaches on the fovea, though tasks requiring full-field vision, such as reading, can be impaired as peripheral vision is lost.

visual function in particular are sparse. Three natural history studies reported losses of more than three Early Treatment Diabetic Retinopathy Study (ETDRS) lines in best-corrected visual acuity (BCVA)[2] in 4[39] or 5[2,32] years; however, some central GA was already present in all[2] or many[11,39] of these eyes at the baseline measurement. As GA impacts the visual field to varying degrees depending on lesion location, tasks dependent on full-field central vision such as reading[39,43–45] may be impaired to a greater extent than is apparent from BCVA. Maximum reading rate correlates with the size of the atrophic area[44] and is a significant risk factor for subsequent visual acuity loss.[39,45]

Patients with early/intermediate AMD and GA experience increased visual impairment under low-light conditions. Deficits in visual acuity under reduced illumination (low luminance visual acuity; LLVA) may precede and be larger than losses in BCVA under normal illumination.[39,45–47] The low-luminance deficit, or difference between LLVA and BCVA, is potentially predictive of subsequent visual acuity loss and GA progression.[39,48] Conversely, patients with early AMD who report better night vision are less likely to develop GA.[49] Quantitative analysis of dark adaptation has shown that dark adaptometry has high sensitivity and specificity for diagnosing AMD, which may be of clinical utility considering

the short time required to perform the measurement (≤6.5 minutes).[50] While the utility of this technique in the assessment of GA lesion progression remains to be studied, impairments in dark adaptation have been shown to be positively correlated with age, worse visual acuity, presence of reticular pseudodrusen, AMD severity, and subfoveal choroidal thinning.[51]

Microperimetry, which maps a patient's threshold light sensitivity onto the retina, provides a link between retinal function and anatomy; areas where the patient cannot detect light of the highest testable intensity indicate scotomas. Decreases in retinal sensitivity over time correlate with GA progression,[52] morphological alterations on SD-OCT,[53] increased fluorescence on FAF,[54] and decreases in LLVA.[47] Similar to LLVA, functional mapping by microperimetry reveals greater visual deficits under scotopic conditions in early stages of AMD, and absolute defects once GA has become manifest. Microperimetry may also detect more widespread decreases in retinal sensitivity in the perilesional areas.[52]

In later stages of GA, large central scotomas develop, effectively resulting in legal blindness. Upon progression of GA to the fovea, central fixation is lost and an extrafoveal preferred fixation locus may develop.[43]

Pathogenesis of Geographic Atrophy

The pathogenesis of GA is multifactorial and is generally thought to be triggered by intrinsic and extrinsic stressors of the poorly regenerative RPE, particularly oxidative stress caused by the high metabolic demand of photoreceptors, photo-oxidation, and environmental stressors such as cigarette smoke. With aging, the damage caused by these stressors accumulates, resulting in the appearance of drusen (extracellular) and lipofuscin (intracellular) deposits.[55] Components of drusen (cellular debris, lipids, lipoproteins, amyloid deposits) and lipofuscin (by-products of photoreceptor outer-segment degradation, A2E), as well as other products of oxidative stress such as advanced glycation end products, are thought to trigger inflammation via multiple pathways, such as the complement cascade and the NLRP3 inflammasome. When the regulatory components in these pathways are compromised, as is the case with several GA-linked genetic risk factors in the complement cascade, this inflammation can ultimately lead to the retinal cell death characteristic of GA.

The Complement Cascade

A leading contributor to the pathogenesis of AMD is inappropriate complement cascade-mediated inflam-mation.[10,56] The complement cascade is primarily involved in the detection and removal of foreign pathogens such as bacteria.[9,57–62] Involving more than 30 known cell-associated and systemically circulating proteins, activation of the complement cascade can lead to inflammation, opsonization, phagocytosis, and cell death through the formation of the membrane attack complex (MAC).

The complement cascade consists of three separate pathways, each activated by different factors: antigen–antibody complexes (classical complement pathway), polysaccharides on microorganisms (lectin complement pathway), and pathogen cell surfaces (alternative complement pathway) (Figure 3). In addition, the alternative complement pathway continuously undergoes spontaneous low-level activation. These different pathways converge with the cleavage of complement factor C3 into C3a and C3b, which induce inflammation and label (opsonize) cells for phagocytosis, respectively. On host cells, endogenous factors shut down the complement cascade. On pathogens, the complement cascade continues with the cleavage of complement factor C5, which triggers cell death via phagocytosis, inflammation, and ultimately MAC activation. Of note, genetic variants associated with GA risk strongly implicate the alternative complement pathway in disease pathogenesis.[63,64] An overview of the complement cascade and a summary of key evidence supporting its role in GA pathogenesis follows.

Initiation. The three complement pathways are initiated by different factors, each resulting in the cleavage of complement factor C3.

Classical. The classical complement pathway is activated when the C1 complex binds specific antigen–antibody complexes, often immunoglobulin M (IgM), IgG3, or IgG1. This induces a conformational change in the C1 complex, allowing it to cleave C4 and C2 to generate the C4bC2b complex. C4bC2b acts as the C3 convertase of the classical pathway, cleaving C3 into C3a and C3b.

Lectin. The lectin complement pathway is activated when mannose-binding lectin (MBL) binds mannose-containing polysaccharides on microorganisms, initiating the cleavage of C4 and C2 by the MBL–MBL-associated serine protease (MASP) complex. As in the classical pathway, the C4bC2b complex forms the C3 convertase of the lectin pathway.

Alternative. The oldest evolutionary signaling pathway of the three, the alternative complement pathway acts both independently of, and as an amplification loop for, the classical and lectin pathways.[60] The alternative complement pathway undergoes low-level *self-*
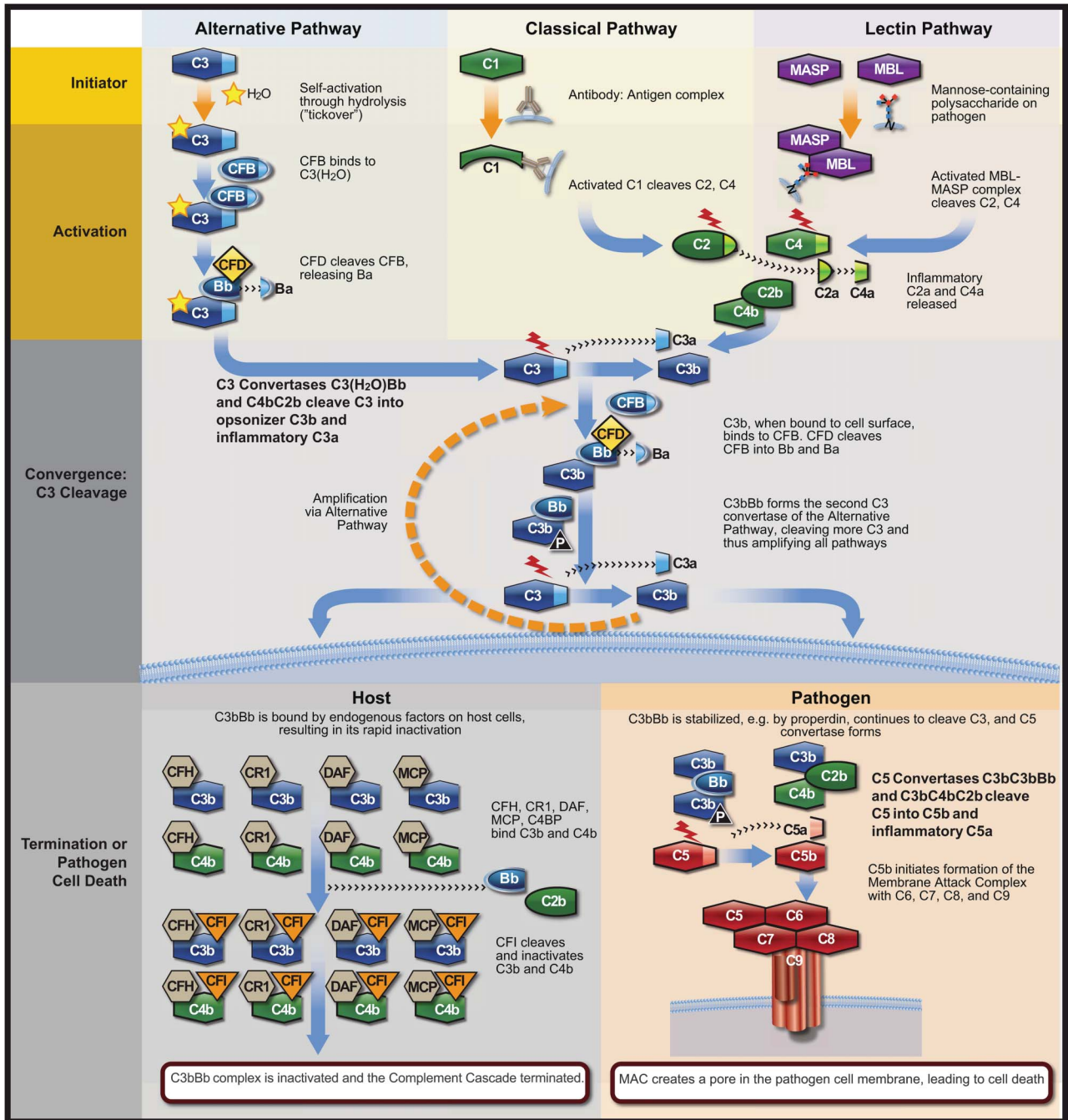
Fig. 3. The complement cascade. CFB, complement factor B; CFD, complement factor D; CFH, complement factor H; CFI, complement factor I; CR1, complement receptor 1; DAF, decay accelerating factor; MAC, membrane attack complex; MASP, MBL-associated serine protease; MBL, mannose binding lectin; MCP, membrane cofactor protein.

activation through the slow, spontaneous hydrolysis of C3 termed "tickover." Once hydrolyzed, C3(H$_2$O) binds complement factor B (CFB), which is subsequently cleaved by complement factor D (CFD) into C3(H$_2$O)Bb, forming the initial C3 convertase of the alternative complement pathway.

Complement factor D is the rate-limiting enzyme in alternative complement pathway activation.[65] Increas-ing concentrations of CFD, which circulates only in an active form, can directly enhance complement cascade activity.[66]

Amplification via the alternative complement pathway. Cleavage of C3 by any of the C3 convertases exposes a thioester group on C3b, through which C3b can covalently bind to the surface of pathogen or host cells via hydroxyl groups on carbohydrates.[67] C3b then binds

to CFB, which is cleaved by CFD into Bb and Ba. This forms the primary C3 convertase of the alterative pathway, C3bBb, which continues to cleave C3 and thus amplifies complement cascade activation. In this manner, amplification via the alternative complement pathway may account for more than 80% of total complement activation.[68,69]

Host cells: termination of the complement cascade. On host cells, endogenous factors including regulatory proteins inactivate the C3 convertases, terminating the complement reaction. C3b and C4b are bound by endogenous regulators of complement activation such as complement receptor 1 (CR1), decay accelerating factor (DAF/CD55), complement Factor H (CFH; primarily C3b), C4-binding protein (C4BP; primarily C4b), and membrane cofactor protein (MCP/CD46), which displace Bb or C2b (DAF, CR1) and/or act as cofactors for complement factor I (CFI)-mediated cleavage and inactivation of C3b and C4b.

Rapid inactivation of the complement cascade is critical to localize the reaction to pathogens and prevent complement attack of host cells. Notably, CFI is a rate-limiting enzyme of complement termination; increasing CFI concentration by just 25% can effectively shut down alternative complement pathway activation in *in vitro* experiments.[60,70] This implies that a small change in CFI activity or abundance may have significant effects on complement cascade activity.

Pathogens: stabilization and amplification of the complement cascade. On pathogens, the C3 convertase complexes are stabilized on the cell surface, while the absence of endogenous regulatory proteins prevents inactivation. In the alternative complement pathway, properdin (complement factor P) binds to and stabilizes C3bBb on the cell surface.

Formation of the C5 convertase, inflammation, phagocytosis, and the membrane attack complex. The classical, lectin, and alternative complement pathways converge with the cleavage of C3 into C3a and C3b and the subsequent formation of the C5 convertase complexes of C4bC2bC3b (classical, lectin pathways) or C3bC3bBb (alternative complement pathway). These C5 convertase complexes cleave C5 into C5a and C5b, initiating the final steps of the complement cascade.

Inflammation is initiated by C3a, C4a, and C5a, which induce smooth muscle contraction, increase vascular permeability, and control migration of neutrophils and monocytes. C3a and C5a activate mast cells to release histamine, tumor necrosis factor (TNF)-α, and other inflammatory factors, further recruiting antibody, complement, and phagocytic cells to the site of complement activation.

Pathogen cell death is ultimately accomplished by the MAC, a complex of C5b, C6, C7, C8, and the C9 polymer, initiated by C5b. The MAC creates pores in the pathogen cell surface, destroying the lipid bilayer, disrupting proton gradients, and allowing penetration of enzymes, resulting in pathogen or cell destruction.

Role of Complement in Health and Disease

Although the complement cascade is traditionally considered part of the immune system, and therefore charged with protecting against foreign pathogens, complement activity also has important roles in maintaining healthy tissue. Clearance of apoptotic cells is facilitated by the complement pathway, which opsonizes the cells for removal via phagocytosis.[62] Apoptotic cells shed membrane-bound complement regulators such as MCP/CD46 and CD59,[71] while the presence of circulating complement regulators, for example, CFH, prevents the reaction from escalating and affecting nearby cells.[61] Additional nonimmunological physiological roles for complement activity include neuronal synapse remodeling,[72,73] lipid metabolism,[74] and bone remodeling.[75]

When the function or expression of complement regulators is compromised, otherwise healthy cells can become susceptible to complement attack (Figure 4). This loss of appropriate complement regulation is thought to underlie a number of diseases, including AMD.[9] As discussed below, genetic variations in complement proteins, such as in C3, CFH, and CFI, decrease complement inactivation, thus rendering cells vulnerable to inappropriate complement attack.

Evidence for Complement Cascade Dysfunction in Geographic Atrophy

The case for complement cascade dysfunction in AMD is supported by three key lines of evidence. Landmark genome-wide association studies (GWAS) identified AMD-associated variants in complement factor genes, particularly those such as *CFH* that promote alternative complement pathway termination on host cells.[63] In addition, patients with GA exhibit alterations in complement cascade components both systemically and locally within the eye. Finally, these observations are supported by preclinical research *in vitro* and in mice, which have demonstrated that complement dysfunction is associated with GA-like pathology.[76] Evidence supporting the role of complement cascade dysfunction and the pathogenesis of GA is discussed in detail below.

Genetic evidence for complement cascade dysfunction in geographic atrophy. Development of advanced AMD is strongly influenced by genetics. Early
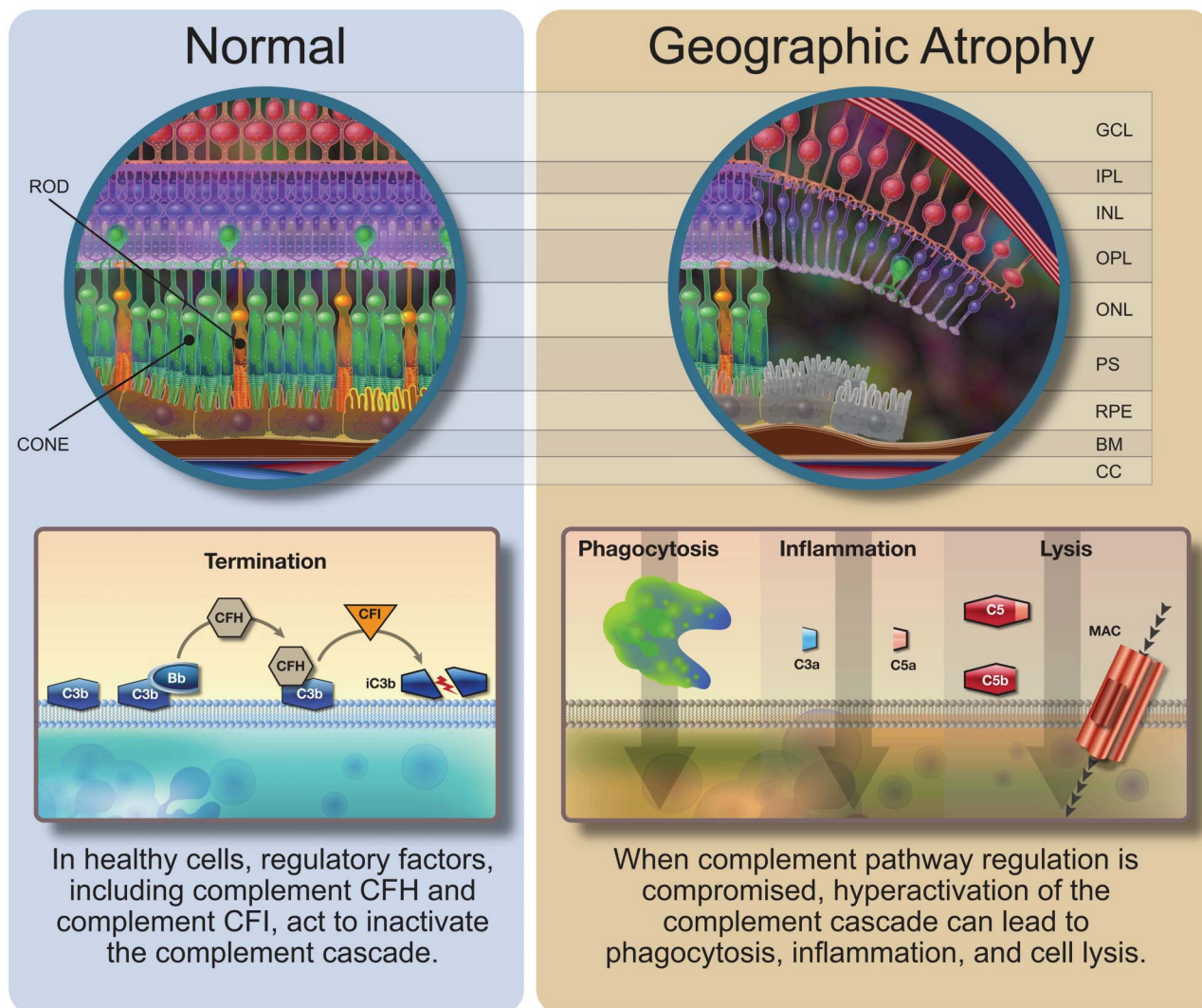
Fig. 4. Pathophysiology of geographic atrophy. Retinal layers: BM, Bruch's membrane; CC, choriocapillaris; GCL, ganglion cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; MAC, membrane attack complex; ONL, outer nuclear layer; OPL, outer plexiform layer; PS, photoreceptor segment (inner and outer); RPE, retinal pigment epithelium.

genome-wide and targeted sequencing studies identified a common variant in the *CFH* gene associated with AMD risk (CFH Y402H)[77–80] estimated to account for nearly half of AMD risk.[78–80] More recently, a meta-analysis and validation sequencing of GWAS data by the AMD Consortium, which evaluated >17,100 advanced AMD cases and >60,000 controls for common AMD risk variants, identified 19 single nucleotide polymorphisms (SNPs), of which four are contained within complement cascade genes (*CFH, CFI, C3, C2/CFB*).[81] Other identified SNPs are associated with genes involved in lipid metabolism, extracellular matrix remodeling, and angiogenesis.[81] In addition, individually rare coding variants have been identified in *CFI, CFH, C3*, and *C9*.[82–87]

Many of these variants are predicted to increase activation or decrease inactivation of the complement cascade, thereby altering the physiological balance toward increased inflammatory processes, supplying perhaps the strongest evidence for the involvement of complement in AMD. Each of the CFH Y402H, CFH R1210C, and C3 K155Q variants are predicted to reduce the interaction between CFH and C3b, thus diminishing complement cascade inactivation and potentially increasing feedback amplification of the alternative complement pathway.[79,82,84,87–89] Of note, the rare, highly penetrant CFH R1210C variant is associated with a 6-year earlier onset of AMD[83] and is also a risk allele for rare glomerulopathies linked to inappropriate alternative complement pathway regulation.[90,91] Patients with these glomerulopathies also

display phenotypic changes consistent with early AMD.[90] Similarly, many of the rare *CFI* risk variants are predicted to be damaging to CFI function and thus decrease complement cascade inactivation.[84,85,92] The rare CFI G119R variant, which reduces CFI expression and C3b degradation, confers a particularly high risk of AMD (OR, 22.20; 95% CI, 2.98–164.49).[85]

Physiological evidence for complement cascade dysfunction in geographic atrophy. In addition to the strong genetic association, complement cascade dysfunction has been detected both systemically and in human donor eyes of patients with advanced AMD, including GA. Complement activation products, such as C3d (a breakdown product of C3b after cleavage by CFI), C3a, Ba, Bb, and C5a, are elevated in plasma of patients with AMD[93] and GA[94]; alterations in levels of plasma CFD[93,95] and CFI[92,96] have also been reported. Drusen derived from human donor eyes contain complement factors C3,[97,98] C5,[98–100] CFH,[80,101] and activated MAC.[99,100] Transcriptome profiling of AMD versus control retinal tissue demonstrated upregulation of complement pathway genes.[102] Bruch's membrane/choriocapillaris extracts from advanced AMD eyes contained elevated CFB, C3, C3a, and CFD levels compared with eyes lacking macular drusen,[97] and MAC is elevated in the choriocapillaris of eyes with the high-risk *CFH* allele.[103,104] Reductions in MCP/CD46, a cofactor for CFI-mediated cleavage of C3b and C4b, were observed in early AMD and GA donor eyes, preceding atrophy and correlating with disease severity.[105,106]

Evidence of systemic complement cascade dysfunction has also been found in patients with AMD-associated variants in complement factor genes. The GA-associated *CFH* variant has been reported to be associated with elevated choroidal[101] or systemic[107–109] markers of inflammation, higher levels of oxidized phospholipids in plasma,[110] and increased presence of complement activation products.[93,103,111] Similarly, individuals with advanced AMD and rare *CFI* variants had significantly lower serum CFI levels compared with those without AMD; lower CFI serum levels were associated with a greater risk of advanced AMD among those with (OR, 13.6; $P = 1.6 \times 10^{-4}$) and without (OR, 19.0; $P = 1.1 \times 10^{-5}$) a rare *CFI* variant.[92]

Preclinical research on complement dysfunction in geographic atrophy. A number of preclinical studies provide proof-of-concept support and mechanistic insight into complement dysfunction and GA pathogenesis.

Studies in mouse models of complement dysregulation support a causal role for complement in retinal pathology.[112] In the absence of a specific environ-mental or immune challenge, *CFH* deficiency in mice is sufficient to cause age-related decreased visual acuity, reduced photoreceptor activity under scotopic conditions, altered retinal autofluorescence, and increased C3 deposition in the retina.[113] The phenotype can be rescued by expression of human *CFH*.[114] Transgenic mice expressing the human CFH Y402H risk variant, which may better mimic complement dysregulation in human disease, develop an AMD-like pathology including subretinal drusen-like deposits, accumulation of subretinal macrophage/microglia, basal laminar deposits, and increased numbers of lipofuscin granules.[115] In addition, C3 overexpression leads to retinal pathology,[116] while conversely, *CFD*-deficient mice are protected against photoreceptor loss from chronic light exposure compared with wild-type mice.[117] Recently, alternative complement pathway activation was implicated in photoreceptor cell death following retinal detachment,[118] further emphasizing a role for this pathway in photoreceptor degeneration.

It is believed that environmental risk factors and oxidative stress, coupled with genetic risk factors, can trigger complement-induced retinal cell death. In a proof-of-concept study, an immune response to carboxyethylpyrrol (CEP), an oxidation fragment of the polyunsaturated fatty acid docosahexaenoic acid (DHA) abundant in the outer retina, was sufficient to cause complement C3d deposition in Bruch's membrane and AMD-like lesions in mice.[76] Photo-oxidation products of A2E, a component of lipofuscin, can trigger CFB-dependent complement activation in RPE cells.[119,120] In mice, chronic exposure to cigarette smoke led to reduced photoreceptor function and complement C3d deposition at the RPE/Bruch's membrane and choroid, while *CFB*-deficient mice were protected against similar retinal damage.[121]

NLRP3 Inflammasome

Other pathways, such as inflammasome activation, have also been implicated in GA pathogenesis. The NLRP3 inflammasome is a multiprotein scaffold consisting mainly of NLRP3, the adaptor molecule ASC, and caspase-1. Activation of the NLRP3 inflammasome can lead to caspase-mediated processing of the cytokines interleukin (IL)-1β and IL-18, key mediators of innate and adaptive immunity, and cleavage of gasdermin D that drives pyroptosis, a lytic type of cell death.[122] While inflammasome activation has been associated with loss of RPE cells,[123–125] the molecular mechanism of inflammasome-mediated RPE cell death has yet to be defined. Research continues in effort to determine pathways that trigger the NLRP3 inflammasome either via activation (stimulation of inflammasome

complex signaling) or priming (upregulation of inflammasome-related genes). One trigger appears to be accumulation of RNA. A GA-like model of RPE degeneration in mice can be initiated by downregulation of the RNA processor enzyme *DICER1,* which leads to RNA accumulation and cell death via NLRP3 inflammasome activation.[123,126] Decreased *DICER1* expression and the resulting accumulation of RNA have been found in human donor eyes with GA.[126]

Drusen components also trigger the inflammasome. It has been demonstrated that when drusen are excised from donor eyes and then added in vitro to macrophages and dendritic cells, the ASC inflammasome component becomes activated and IL-1β/IL-18 production occurs.[125] Similarly, when individual drusen components such as A2E (the major fluorophore of lipofuscin) are added in vitro to cultured RPE cells, these cells then secrete IL-1β via inflammasome activation in response to the A2E insult.[127] In a mouse model, intravitreal injection of the drusen component amyloid-β led to genetic upregulation of inflammasome components in the neuroretina and corresponding increased levels of IL-1β and IL-18.[128]

C1q is one of several complement system factors found in drusen, and the addition of C1q to macrophages induces in vitro inflammasome component activation and production of IL-1β.[125] Exogenous administration of other complement components such as C3a,[129] C5a,[130] and MAC[131,132] also activates the NLRP3 inflammasome. Thus, current in vitro studies indicate that activation of the complement system has the downstream effect of inflammasome-mediated cytokine signaling through IL-1β and IL-18. The interaction between complement and inflammasome pathways is an emerging area of research, and as in vitro findings are further explored through in vivo studies, the roles these two systems play in the pathophysiology of GA will be more clearly understood.

The overall role of the inflammasome on neovascular AMD pathogenesis is a subject of active debate.[133,134] Inflammasome-mediated production of IL-18 has been shown to protect against neovascularization,[125,133,135] and intravitreal administration of IL-18 is being explored as a therapy for neovascular AMD.[133] Additional mechanistic studies are required to shed light on this controversy.

Natural History Studies in Geographic Atrophy

Studies on the natural history of GA and age-related macular degeneration have provided much valuable information regarding the progression, epidemiology, and environmental risk factors of

GA.[2,11,12,27,28,32,136–138] However, there are still gaps in our understanding of the natural history of the disease, which ongoing and upcoming studies aim to address. Two studies, SIGHT (NCT02332343) and DSGA (NCT02051998) will investigate differential patterns of atrophy progression in the retina, namely foveal sparing and directional spread of atrophic areas, respectively. Three other studies will study GA using different types of retinal imaging, namely FAF (NCT00393692), OCT (NCT01712841), and AOSLO (NCT01866371).

Proxima, a large natural history study program with a global enrollment target of 560 patients, is evaluating the relationship between GA progression and visual function outcomes as well as the prognostic nature of the *CFI* biomarker. Proxima consists of two cohorts: Proxima A (NCT02479386), designed to have a population similar to the Phase 3 Chroma and Spectri trials (see below), will include patients with bilateral GA; while Proxima B (NCT02399072) will include a broader cohort of patients, that is, those generally excluded from Phase 3 trials (unilateral GA, GA with choroidal neovascularization [CNV] in the fellow eye). Patients will be followed every 6 months, and assessed outcomes will be similar to those of Chroma and Spectri.

Clinical Development of Potential Pharmacotherapies

Although no drugs are currently available in clinical practice for the treatment of GA, a number of therapeutics are at various stages of clinical development. Among these are six drugs that target the complement cascade (Table 1), including three targeting C5, one targeting C3, and one targeting the alternative complement pathway (Figure 5). To date, limited information is available for LFG316 (anti-C5; Novartis International AG, Basel, Switzerland), Zimura (C5 inhibitor; Ophthotech Corporation, New York, NY), and CLG561 (anti-properdin; Novartis and Alcon Inc, Hünenberg, Switzerland). APL-2 (C3 inhibitor; Apellis Pharmaceuticals, Crestwood, KY), eculizumab (anti-C5; Alexion Pharmaceuticals, Inc, Cheshire, CT), and lampalizumab (anti-CFD; Genentech, Inc, South San Francisco, CA and F. Hoffmann-La Roche AG, Basel, Switzerland), which have completed Phase 2 trials, are discussed below.

Beyond the complement cascade, therapies are in development to target other GA-implicated pathways such as anti-inflammatory agents, amyloid-β scavengers, choroidal perfusion enhancers, serotonin receptor agonists, and stem cell therapies; discussion

Table 1. Complement Inhibitors in Clinical Trials for the Treatment of Geographic Atrophy (GA)

Drug	Target	Administration	Company	Status	Primary Outcome	ClinicalTrials.gov
APL-2 (AL-78898A; POT-4)	C3; peptide inhibitor	Intravitreal	Apellis (molecule formerly with Alcon Research/Potentia Pharmaceuticals)	Phase 2 ongoing	Phase 2: square root of GA area change at 12 months	NCT01603043; NCT02503332 (FILLY)
CLG561	Properdin; fully-humanized antigen binding fragment (Fab)	Intravitreal	Alcon Research, Novartis Pharmaceuticals	Phase 1 complete; Phase 2 recruiting; monotherapy and in combination with LFG316	Phase 2: GA area change at day 337	NCT02515942
Eculizumab	C5; monoclonal antibody	Intravenous	Alexion Pharmaceuticals	Phase 2 complete[48]; no further development[145,146]	GA growth at 26 weeks	NCT00935883 (COMPLETE)
Lampalizumab (FCFD4514S, anti-factor D)	Complement factor D; monoclonal antigen-binding fragment (Fab)	Intravitreal	Genentech, Hoffmann-La Roche	Phase 2 complete; Phase 3 ongoing	Phase 2: GA area change at 18 months; Phase 3: GA area change at 48 weeks	NCT00973011; NCT01229215 (MAHALO); NCT01602120 (MAHALO open-label extension); NCT02247479 (Chroma); NCT02247531 (Spectri); NCT02288559
LFG316	C5; monoclonal antibody	Intravitreal	Novartis Pharmaceuticals	Phase 2 monotherapy complete; Phase 2 in combination with CLG561 recruiting	Phase 2 monotherapy: GA growth at 12 months; Phase 2 with CLG361: GA area change at day 337	NCT01527500; NCT02515942
Zimura (ARC1905)	C5; aptamer	Intravitreal	Ophthotech Corporation	Phase 1 complete	Safety	NCT00950638
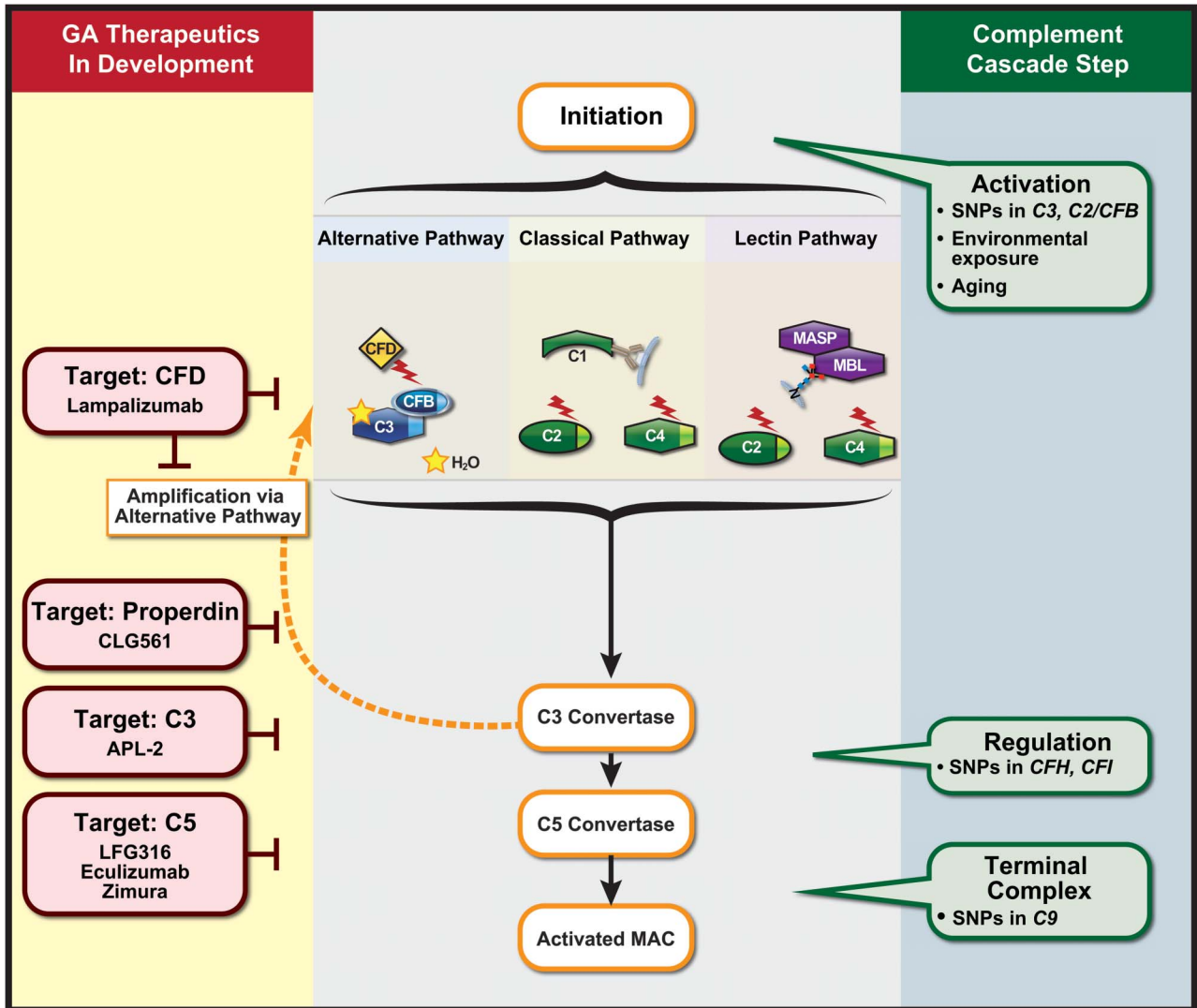
Fig. 5. Geographic atrophy (GA) therapeutics in development targeting the complement cascade. Several GA therapeutics (left) targeting different components of the complement cascade (center) are in Phase 2 or Phase 3 clinical trials. Also shown are factors such as the identified genetic variations (SNPs) that can affect complement cascade activity (right). CFB, complement factor B; CFD, complement factor D; CFH, complement factor H; CFI, complement factor I; MAC, membrane attack complex; SNP, single nucleotide polymorphism.

of these agents can be found in other recent reviews.[1,139,140] Other approaches in preclinical development include nucleoside reverse transcriptase inhibitors (NRTIs), which are already approved for the treatment of HIV infection,[141] and a modulator of the innate inflammatory profile (TMi-18; Translatum Medicus Inc, Toronto, ON, Canada).[142]

APL-2 (POT-4/AL-78898A, Apellis Pharmaceuticals) is an intravitreally administered peptide inhibitor of C3. Phase 2 trials of POT-4/AL-78898A were terminated before primary endpoint, and therefore no efficacy data are currently available (NCT01603043). APL-2 is a modified version of POT-4 designed to have a longer half-life.[143] The Phase 2 FILLY trial (NCT02503332) of APL-2 in patients with GA is currently ongoing.

Eculizumab (Soliris, Alexion Pharmaceuticals, Inc) is an intravenously (IV) administered humanized monoclonal antibody targeting C5, approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of two rare genetic deficiencies of complement inhibition, atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria.[144] Eculizumab binds to C5, inhibiting its cleavage into C5a and C5b, thereby preventing MAC formation.

The Phase 2 COMPLETE trial (NCT00935883) evaluated eculizumab in 30 eyes of 30 patients with eligible GA lesion area from 1.25 to 18 mm^2 who received high-dose eculizumab (n = 10; IV 900 mg for 4 weeks followed by 1,200 mg every 2 weeks until

week 24), low-dose eculizumab (n = 10; IV 600 mg for 4 weeks followed by 900 mg every 2 weeks until week 24), or placebo (n = 10) over 24 weeks.[48] The primary efficacy endpoint was change in GA area assessed by SD-OCT at 26 weeks, with additional follow-up at 52 weeks. However, GA enlargement from baseline was similar at each time point between eculizumab and placebo groups (change from baseline of mean square root of GA area ± standard deviation [SD]: 26 weeks, 0.19 ± 0.12 vs. 0.18 ± 0.15 mm, respectively, $P = 0.96$; 52 weeks, 0.37 ± 0.21 vs. 0.37 ± 0.22 mm, respectively; $P = 0.93$). No drug-related adverse events (AEs) were reported in COMPLETE patients through 12 months.

While the study was powered to only detect at least a 55% difference in GA progression, the lack of any trend toward efficacy with eculizumab led the study authors to conclude that "after 26 weeks we can say definitively that the treatment failed to meet this endpoint." Eculizumab for GA is no longer listed among Alexion's pipeline therapeutics.[145,146] At this time, it is not clear whether the failure of eculizumab was because of the choice of C5 as a target, insufficient ocular bioavailability in systemic (vs. intravitreal) administration, study design, or other factors.[48] For example, inhibiting C5 does not block the actions of C3 (e.g., C3a-induced inflammation and C3b/iC3b-mediated opsonophagocytosis).

Lampalizumab (FCFD4514S/anti-factor D, Genentech, Inc and F. Hoffmann-La Roche AG) is an intravitreally administered antigen-binding fragment (Fab) of a humanized monoclonal antibody targeting CFD. Lampalizumab binds to CFD, preventing CFD-mediated activation of C3bBb and effectively terminating activation and amplification of the alternative complement pathway.[147]

As discussed above, CFD is the rate-limiting enzyme of the alternative complement pathway and is present in low serum concentrations relative to other complement factor proteins.[93,96] Inhibiting CFD decreases, but does not eliminate, classical and lectin-activated complement initiation.[68,69] Intravitreal clinically relevant doses were demonstrated to have minimal systemic inhibition of the alternative complement pathway in pharmacokinetic studies in monkeys[148,149] and in subjects participating in the Phase 1 and Phase 2 lampalizumab trials (NCT00973011; NCT01229215).[150,151] The low levels of lampalizumab in systemic circulation resulting from intravitreal administration are not expected to affect systemic alternative complement pathway activity.[148]

The MAHALO Phase 2 study (NCT01229215) evaluated lampalizumab in patients with GA secondary to AMD and the results have been submitted for publication (Yaspan et al). Confirmatory Phase 3 trials

Chroma (NCT02247479) and Spectri (NCT02247531) are ongoing. Chroma and Spectri are identically designed double-masked, multicenter, randomized, sham injection-controlled trials enrolling 936 participants each across more than 20 countries. Each study arm will contain patients positive and negative for the *CFI* biomarker. Patients are being randomized 2:1:2:1 to 10 mg lampalizumab every 4 weeks, sham injection every 4 weeks, 10 mg lampalizumab every 6 weeks, and sham injection every 6 weeks. The primary efficacy endpoint is the mean change in GA area at 1 year, and the overall study duration is 2 years. Additional visual function secondary endpoints include reading speed, Patient Reported Outcome (PRO) Visual Function Questionnaire (VFQ)-25, microperimetry, LLVA, and BCVA.

Conclusion

Dysregulation of the complement cascade has emerged as a key contributor to the pathophysiology of GA, supported by a number of genetic, histological, and preclinical studies. With several Phase 2 and 3 clinical trials already in progress, there is at present a significant impetus toward identifying complement targets that may prove effective at limiting retinal cell death in patients with GA. Continued research, including studies on the initial development of GA, GA lesion progression, genetics, and the contribution of each to subsequent visual function decline, is crucial to further our understanding of GA pathophysiology and to identify additional potential therapeutic targets.

Key words: age-related macular degeneration, atrophy, complement, eculizumab, geographic atrophy, lampalizumab.

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