antibody therapy with rituximab. Although rituximab has gained increasing use in the therapy of extranodal marginal zone lymphomas of MALT type, the curative potential of this modality is unknown. Further studies are necessary to advance our understanding of the role of antibiotic or antiviral therapy for this entity.

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Inflammation in the pathogenesis of age-related macular degeneration

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Degenerative diseases of the retina can have a devastating impact on quality of life and constitute a major cause of untreatable blindness in developed countries. Age-related macular degeneration (AMD) stands out among these, as it leads to visual dysfunction in a significant fraction of the elderly population worldwide. AMD primarily affects the macular region of the retina; early signs of the disease include the appearance of soft drusen and regions of altered pigmentation in the retina, whereas advanced stages exhibit choroidal neovascularisation or atrophy of photoreceptors and the retinal pigment epithelium (RPE).[1–3] Diverse cellular processes have been implicated in AMD pathogenesis, including inflammation, oxidative stress, altered cholesterol metabolism and/or impaired function of the RPE.[3–6] It is widely believed that manifestation of distinct disease characteristics in AMD is the result of a complex interplay among genetic and environmental factors.[7 8] Although the casual pathways underlying AMD are not fully understood, this multifactorial neurodegenerative disease has received considerable attention in the last few years, as rapid advances in genetics and genomics have provided insights into the underlying pathophysiology, potentially opening avenues for new treatment paradigms.

On the basis of the presence of immune response proteins in drusen of post-mortem AMD retinas, Hageman and colleagues were the first to suggest a link between inflammation and AMD.[9 10] However, direct evidence for the role of immunoregulatory molecules came from genetic studies that identified strong association of AMD with variants in complement factor H (CFH).[8 11–14] This association is now firmly established

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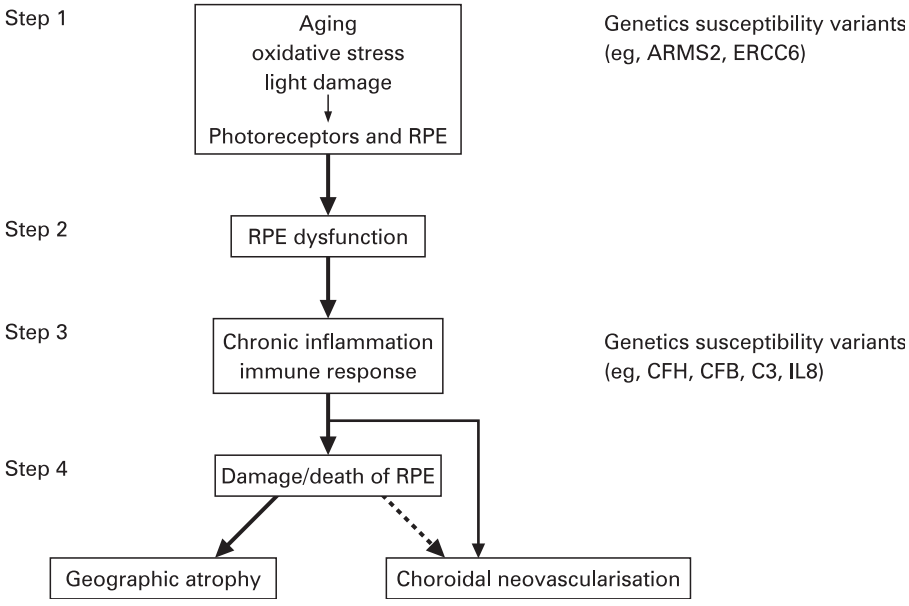

Figure 1 Proposed steps in the pathogenesis of age-related macular degeneration (based on recent genetic studies and Zarbin[3] and Zonoso *et al*[10]). RPE, retinal pigment epithelium.

through replications in numerous independent cohorts.[15–17] The strong link between AMD and CFH polymorphisms provided an impetus for the careful assessment of genetic variation in other complement pathway genes. AMD susceptibility variants have now been identified in complement component 2 (CC2) and complement factor B (CFB)[18 19] and complement component 3 (C3).[20 21] Association with AMD has also been suggested in chemokine (C-X3-C motif) receptor 1 (CX3CR1), Toll-like receptor 4 (TLR4) and major histocompatibility complex class I (HLA) genes.[22–24]

In this issue, Goverdhan and colleagues[25] report their study of genetic variants in four cytokine genes (including the pro-inflammatory interleukin (IL)1b, IL6, IL8 and anti-inflammatory IL10) (***see page 537***). They suggest that the −251A allele (rs4073) of the *IL8* promoter is more prevalent in AMD cases than controls ($p = 0.037$). As with all initial reports of association, this signal must be confirmed in larger samples before a definite link between *IL8* polymorphism and AMD can be confidently identified. Nevertheless, this possibility is mechanistically very interesting. IL8, a potent chemo-attractant and activator of neutrophils, is primarily involved in the initiation and amplification of acute inflammatory reactions and in chronic inflammatory processes. It can be produced by a variety of cell types, including macrophages, neutrophils and endothelial cells, in response to inflammatory stimuli.[26] Tentative associations between the rs4073 single-nucleotide polymorphism and inflammatory, gastric and neurodegenerative diseases have previously been reported, and this variant appears to enhance IL8 production in vivo.[27] In the context of AMD pathogenesis, the response to reactive oxygen species in photoreceptor outer segments or inflammatory injury can lead to increased expression and secretion of IL8 and monocyte chemotactic protein-1 from RPE cells[28] (S Miller, personal communication). It is tempting to speculate that even a slight increase in IL8 expression in individuals carrying the rs4073 variant may exacerbate RPE damage and favour progression towards advanced AMD.

Aging-associated changes, together with photo-oxidative stress, in photoreceptors and RPE appear to be the initial triggers of maculopathy, and the subsequent cellular damage is amplified in time by inflammation/immune response (fig 1). Susceptibility variants in genes that modulate stress and inflammatory responses may therefore influence the clinical presentation of AMD. Disease onset and severity are also likely to be affected by environmental factors (such as smoking). Variants in and around *CFH* at chromosome 1q31 and in *ARMS2/LOC387715* at chromosome 10q26 are so far the strongest AMD susceptibility alleles.[8 11–16 29] CFH and neighbouring genes regulate complement pathway by promoting the decay of C3 convertase and by acting as a cofactor for factor I-medicated proteolysis of C3b. Experiments are underway to characterise how genetic polymorphism in CFH leads to increased susceptibility to AMD. Furthermore, the concentrations of C-reactive protein, a systemic marker of subclinical inflammation, are increased in eyes that are homozygous for one of the CFH-associated susceptibility variants, Y402H.[11] In addition, IL10 has been shown to regulate macrophage function and alter ocular angiogenesis in older mice, indicating an additional link of inflammatory response to aging and disease process.[30]

Taken together, current evidence suggests that anomalies in inflammatory immune responses may trigger progression of maculopathy towards advanced clinical features (eg, choroidal neovascularisation or geographic atrophy; fig 1). This link and other processes underlying AMD will continue to become clearer as genetic and biochemical studies yield novel insights. We expect that more clues will be forthcoming in the next year, permitting us to better understand the clinical aspects of this debilitating blinding disease.

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