Inflammation and the pathogenesis of age-related macular degeneration

Albert J Augustin† & Janna Kirchhof
Department of Ophthalmology, Staedtisches Klinikum Karlsruhe, Karlsruhe, Germany; Department of Ophthalmology, University of Mainz, Langenbeckstrasse 1, 55131 Mainz, Germany

Background: Age-related macular degeneration (AMD) is the leading cause of blindness in the Western world. Many changes occur in various areas of the eye as it ages. These include choroidal thinning, thickening of Bruch’s membrane and drusen formation. Each of these is associated with the onset of AMD. Methods: Recent findings on how those changes contribute to the pathogenesis of AMD with a focus on inflammation are examined. Results: There is evidence suggesting that all changes identified so far as being involved in the pathogenesis of AMD are not able to cause AMD alone. Instead, susceptibility genes, and in particular a coding variant of a gene on chromosome 1 result in dysfunction of the immune system. This leads to an inappropriate inflammatory response, which then sets the stage for AMD onset. Conclusions: It is now well-known that AMD is a multi-factorial disease, with environmental causes and genetics all playing a role.

Keywords: Bruch’s membrane, drusen, polymorphism, RPE dysfunction, Y402H


1. Introduction

Age-related macular degeneration (AMD) was first described in the medical literature well over a century ago [1,2] and yet it was not the late 1990s that a treatment was finally found which could arrest or significantly slow the progress of the disease. That treatment, photodynamic therapy with verteporfin, even led to some improvement in lost vision for a small percentage of patients [3,4]. In recent years, a whole new class of agents – VEGF inhibitors – has been introduced to the market. These drugs have been shown to be capable of restoring a significant amount of lost vision for many patients.

However, today, AMD still ranks as the leading cause of legal blindness among older individuals in the developed world. A 2004 study reported that among people over the age of 40 years, AMD and/or geographic atrophy were present in at least one eye in 1.47% of the population. On that basis, this would mean that 1.75 million Americans are currently affected. Moreover, it was predicted that as the population ages, there will be a 50% increase in the incidence of AMD before the year 2020 [5]. In another study, AMD was reported to account for 54% of the cases of blindness among the White population in the United States, and the number of blind people could increase by as much as 70% by 2020 [6]. Meanwhile, a multi-country European study has reported that 3.3% of the population over the age of 65 has grade 4 age-related macular degeneration, and 2.3% have choroidal neovascularization [7].

Both genetics and lifestyle factors play important roles in the development of AMD. Numerous studies have identified factors such as a history of diabetes, smoking, elevated blood pressure, cardiovascular disease and obesity as being strongly associated with the onset of AMD. Age and family history, however, are still the most consistently accurate risk factors for determining susceptibility to
age-related macular degeneration [8]. The condition is also thought to be more prevalent among Caucasians as compared with either African Americans or people of Hispanic origin.

With these data as a backdrop, and given the improvements in healthcare delivery in most countries of the Western world, which mean more people are living to an older age, we can see that AMD is certain to become a greater burden both for individuals, and for healthcare management in general.

2. A disease of the aging eye

AMD is a disease of the aging eye. So few people under the age of 50 show signs of developing the condition that most studies which have examined its demographics, prevalence or treatments have not included anyone under 50. In most cases, subjects have been 65 years of age and older. It is known that the disease does not begin with a virus, insult or injury. The process may start with a sub-clinical inflammation, but take decades before any clinical symptoms manifest themselves. Even then, many patients who exhibit warning signs of potential disease fail to develop the condition. Rodrigues, in 2007 [9] noted that investigators suspected 100 years ago that AMD begins with an inflammatory process. For unknown reasons, this hypothesis was ignored until fairly recently.

Smoking is one of the risk factors for macular degeneration. Several studies confirm a significant association between smoking and macular degeneration. The risk of macular degeneration is two- to three-fold higher in current-smokers compared with individuals who have never smoked [10]. There is evidence that the likelihood of developing macular degeneration will reduce if one were to quit smoking. If you quit smoking, then 1 year of non-smoking will reduce the likelihood of you developing macular degeneration by 6.7%. After another 5 years of non-smoking the risk is further reduced by another 5%, and after yet another 5 years of non-smoking by an extra 4.2%. The protective effect of quitting smoking seems to be somewhat more pronounced in the first years after stopping smoking [11].

Correlations between smoking and the development of late AMD could be found for the LOC387715 polymorphism [12] and for complement factor H (CFH) genotypes [13].

Although many recent studies have outlined genetic factors that play a role in the development of AMD, genes tell only part of the story. A patient’s genetic profile may represent a risk factor, but aging, oxidative stress and light damage, which are all associated with the onset of AMD, are risk factors as well. We believe that if a person lives long enough, the aging process in their eyes may include oxidative stress. Some people’s eyes will experience more oxidative stress than others. Many people will also experience some degree of light-induced damage to their eyes over their lifetimes. But why do some people develop AMD while others do not? We propose that there still must be a link that ties aging, oxidative stress and light exposure to the disease process. That trigger may be inflammation. Whether the inflammation erupts into full-blown AMD could be determined by the patient’s genetic makeup.

Chlamydia pneumoniae has also been associated with AMD. The mechanisms underlying how it may be involved in the etiology are poorly understood though. Most probably it triggers the alternative complement pathway, but the outcomes of studies so far should not be over-interpreted, as evidence for an association is contradictory.

This paper reviews the physiological and pathological changes that occur as the eye ages, and how the inflammatory process affects those changes. It also describes how molecular genetics comes into play, and determines who will develop AMD and who won’t.

A major factor in the pathogenesis of AMD is an imbalance in the innate defense mechanisms of the eye. A number of inflammatory stimuli affect the eye as it ages, usually causing subclinical outcomes. However, if the patient has inherited certain polymorphisms of specific inflammatory mediators, the inflammatory response will follow an entirely different course. This response ultimately leads to the most damaging part of the inflammatory process. If the patient has not inherited these specific polymorphisms, it is unlikely that AMD will develop.

The principal genetic variant occurs in the complement system – more specifically, within complement factor H (CFH). Such polymorphisms are known to increase the risk of AMD by several fold [14-17]. Without these polymorphisms, the patient would, in effect, have just an aging eye, and would not necessarily develop AMD or any other ocular pathology. However, not all individuals positive for CFH polymorphisms suffer from the disease. About 30% of exudative AMD patients are not carriers of CFH mutations.

3. Biological and histological changes

Numerous biological and histological changes take place in the aging eye, but not all of them induce an inflammatory response or lead to the development of AMD. Nor do these changes occur in any particular sequence, so there is not a step-by-step advancement in the pathogenesis of the condition. These processes may evolve concurrently or consecutively. Sometimes, the relationship between one and the other is not entirely clear.

Some of the changes that occur in the aging eye include (Figure 1):

- Oxidative stress and related tissue damage
- Drusen formation
- Thinning of the choriocapillaris
- Thickening of Bruch’s membrane
- Production of angiogenic factors.

Besides inflammation, oxidative stress and related tissue damage through the release of free oxygen radicals are crucial triggers for AMD (Figure 2). Several pathways, which are partially linked together, are known for the production of free radicals.
In the myeloperoxidase metabolic pathway, arachidonic acid is converted through different reactions by cyclooxygenase and lipoxigenase. As a result, hydroxyl and singlet oxygen radicals are produced, leading to oxidative tissue damage. Arachidonic acid is, among others, produced by phagocytes, activated by oxidative tissue damage and the complement system. Apart from that, the production of arachidonic acid is a self-energizing process.

In the xanthine oxidase mechanism, ischemia triggers the production of hypoxanthine, xanthine and uric acid as well as the production of the singlet-oxygen radical, which is consequently transformed into hydrogen peroxide or into the hydroxyl-radical via an iron-dependent pathway.

Activated phagocytes, produced by the complement system, by arachidonic acid or by the oxidative tissue damage itself, produce hydrogen peroxide, which is transformed into, among others, the hydroxyl-radical or chloroxide, leading directly to oxidative tissue damage.

Retinal hemorrhage (hemoglobin) induces the conversion of hydrogen-peroxide into the hydroxyl-radical via an iron-dependent pathway.

Oxidative stress occurs in all people as they get older, but not to the same extent in everyone. As the human eye ages, choroidal vascular atrophy leads to a metabolic breakdown. The choriocapillaries underlying the retinal pigment epithelium lose their ability to transfer oxygen and nutrients to the surrounding cells [18,19].

As the eye ages, plasma levels of vitamin C and E decrease [20,21] lipid peroxidation increases [22], and retinal pigment epithelium (RPE) cells become more prone to oxidative damage. Macular pigment density also decreases with age, which increases RPE cell lipofuscin content. Lipofuscin is a photosensitizer, and in animal studies [19], it has been shown that lipofuscin and light produce reactive oxygen species (this is called photodynamic reaction type 2) that compromise lysosomal activity, lead to lipid peroxidation, reduce phagocytosis and ultimately cause RPE cell death.

Feeney-Burns reported in 1984 [23] that lipofuscin accounted for just 1% of the RPE cytoplasmic volume in the first decade of life, but that this increases to 19% in the eighth decade. As the RPE cytoplasmic volume decreases, lipofuscin increases, which compromises RPE function and may lead to photoreceptor cell death.

In 1988, it was suggested that [24] the presence of lipofuscin in the RPE was an early indicator of RPE cell death. As the RPE cells took on more lipofuscin, there were accompanying abnormal excretions, which accumulated on the basal aspect of the cells and within Bruch's membrane. This process eventually resulted in the death of the RPE and visual cells, but also led to the build-up of dead cell residue between the RPE and Bruch's membrane. The widespread deaths of the RPE also led to wide openings between the cells, permitting neovascularization to emerge into the retina space and eventually into the vitreous humour.

In 1999 Winkler [25], and in 2000 Beatty et al. [19] described the process by which oxidative injury caused by free radicals affects primarily the RPE, the choriocapillaris, and the photoreceptor cells. Factors that are known to stimulate the production of reactive oxygen intermediates (ROI) include irradiation, aging, inflammation, air pollutants, cigarette smoke and reperfusion injury.

Figure 1. Changes that occur in the aging eye. Taken by themselves, these changes may not have a devastating effect. However, in the presence of Y402H polymorphism, dysfunction in the complement system occurs, leading to an inappropriate inflammatory response. This may lead to retinal pigment epithelium (RPE) dysfunction as well as tissue damage and remodelling which set the stage for the onset of choroidal neovascularization.
Figure 2. Modalities of free radical generation and inflammatory pathways leading to oxidative tissue damage. 1. Xanthine oxidase mechanism. 2. Iron-dependent production of oxygen radicals. 3. Phagocyte-activation-controlled pathways (Figure 3 shows the results of factor H dysfunction in the complement system, caused by the Y402H polymorphism or other susceptibility genes). 4. Oxidative tissue damage. 5. Myeloperoxidase (MPO) metabolic pathway. 6. Photodynamic processes.

HETEs: hydroxyeicosatetraenoic acids; HPETEs: hydroperoxyeicosatetraenoic acids; HMP: haemoglobin-like protein; HWR: Haber-Weiss reaction; LT4; Leukotriene A4; LT8; Leukotriene B4; PG: prostaglandin; SOD: superoxide dismutase.
Reactive oxygen species are a by-product of cellular metabolism and since the RPE and photoreceptors consume 90% of the O₂ from the choriocapillaris, the rate of metabolism and the generation of metabolic by-products is high.

Oxidative stress is considered to be involved in endothelial alteration.

It has been suggested that in essential hypertension oxidative stress should be associated with increased C-reactive protein (CRP) and endothelial activation, as can be evaluated by soluble intercellular adhesion molecule-1 (ICAM) and vascular adhesion molecule-1 (VCAM) plasma levels. In patients with Behçet's disease, a chronic inflammatory disease leading to uveitis, elevated mean values of CRP and erythrocyte sedimentation rate (ESR) as well as a strong positive correlation between these two parameters could be evaluated. It could be hypothesized, that CRP and ESR levels might be higher than laboratory reference levels in patients with AMD.

The Rotterdam Study [26] has shown that elevated baseline levels of high-sensitivity C-reactive protein (HsCRP) were associated with the development of early and late AMD. In this large population-based cohort, those patients with high blood levels of C-reactive protein at the study's start were most likely to have at least early-stage AMD. For instance, participants with the highest CRP levels at the study's start were 40% more likely to develop early-stage AMD during the study, compared with those with the lowest initial CRP levels.

Light irradiation also stimulates the upregulation of free radicals, and leads to oxidative stress and tissue injury. There is however, some debate over the effect of light irradiation on the development of AMD. Although many studies have looked at the association between light exposure and AMD, it is extremely difficult to quantify the total amount of light exposure over a lifetime, and therefore, no studies have yet proven a cause and effect relationship between exposure to ultra-violet light and this disease [27,28].

The outer retina and the outer segments of the photoreceptors themselves are also highly susceptible to oxidative damage. Approximately 50% of the outer membrane is comprised of polyunsaturated fatty acids, particularly docosahexaenoic acid (DHA), which is the most oxidizable of all fatty acids [19,29]. Together these factors combine to create a multi-faceted cascade of free radical production, leading to oxidative stress, which leads to RPE cell death, and in turn, leads to ROI up-regulation (Figure 2).

3.1 Changes to choroidal thickness

Another factor that may lead to cell death and/or an inflammatory response results from changes to the vascular network that feeds the eye. Distinct changes in the structure of the choriocapillaris begin around the fifth decade of life. They contribute to blood flow changes, increased oxidative stress, the progressive accumulation of lipids in Bruch's membrane, and ultimately, the destruction of the architecture of the membrane.

For example, the choriocapillaris density and lumen diameter decrease, and choroidal thickness decreases, from 200 μm at birth to around 80 μm at the age of 80 [30]. Therefore, the RPE and the photoreceptors, which consume approximately 90% of oxygen delivered by the choriocapillaries are deprived of the oxygen and nutrients they require for normal existence [31,32]. Marmorstein et al. [33] pointed out that there is a close association or intertwining between the nutritional demands, and the metabolic processes within the RPE and the photoreceptors. The ischemia-induced damage or dysfunction of the RPE causes a secondary degeneration of rods and cones. As can be seen in Figures 1 and 2, ischemia at the posterior segment leads to a cycle of oxidative stress, triggering an inflammatory reaction, which in turn leads to a degradation of the RPE. This causes degraded material being sloughed into the RPE/Bruch's membrane space, where it then creates the basis for drusen formation.

Thus we can see that while oxidative stress causes damage to the RPE and other structures within the eye, this stress is not caused by a single mechanism; it is multi-factorial. Some of these factors seem to operate independently of each other.

3.2 Changes to Bruch’s membrane

Several distinct changes take place within Bruch's membrane as the eye ages. Whether this is directly related to the onset of macular degeneration is not certain at this time.

Bruch's membrane is a basement membrane complex located between the RPE and the choroid, where it acts as a barrier between the choriocapillaris and the RPE. In normal healthy eyes, it permits an unobstructed 'flow' across the barrier between the RPE and other structures within the eye, this stress is not caused by a single mechanism; it is multi-factorial. Some of these factors seem to operate independently of each other.

3.3 Drusen formation

One of the hallmarks of AMD is the presence of drusen. Numerous studies have pointed to the number and size of drusen as important risk factors for developing choroidal neovascularization and subsequent vision loss.

The fact that drusen accumulate between Bruch's membrane and the RPE has been known for more than a century [35], but even today there is on-going debate as to whether drusen originate from degraded RPE cytoplasm, or are formed as the result of a secretion from an aged or injured RPE. These two points of view have been clarified in recent years, thanks to newer imaging techniques such as electron microscopy. The
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A list of proteins and molecular components now known to be present in drusen has grown to more than 24. Anderson and colleagues [36] have confirmed that much of the material sequestered in the RPE/Bruch's membrane space is, in fact, recognizable as fragments of degenerated RPE cells. Included are traces of melanin granules, lipofuscin granules, membranous materials and recognizable organelles. These by-products are shunted away from the RPE, but cannot cross Bruch's membrane [37]. This debris of by-products surrounds and eventually encapsulates drusen which, at this stage are still forming and present no risk for the patient. At this point, there is no indication that they will ever become threatening. It must also be said that this encapsulation does not consist exclusively of degraded RPE materials. A variety of other inflammatory mediators may be at play here, and may also include other cell types as well as materials extravasated from the choroidal circulation.

Anderson also identified certain RPE cells that contain specific drusen-related molecules in their cytoplasm, suggesting that these specific RPE cells may play more of a role than others in drusen biogenesis. Some of these molecules are indicative of abnormal cells, while others are histologically normal. Interestingly, although the cells that contain the drusen-related molecules in their cytoplasm appear abnormal and are about to die, they are not dying through a process akin to apoptosis, but rather through another pathway whereby their size multiplices out of control. Johnson and colleagues [38] described these cells as having a 'compromised RPE phenotype'.

Feeney-Burns and colleagues have also reported that this debris (the drusen) may consist of entrapped blebs of degraded RPE, as well as cytoplasmic fragments of retained basal lamina [23].

Bird and Marshall proposed that it is the lipids that are hydrophobic [39] and therefore unable to cross Bruch's membrane.

There are a number of studies showing that there is a direct link between oxidative stress and lipid peroxidation, and that markers of lipid peroxidation are found in drusen. Hammes and colleagues detected carboxymethyl lysine (CML), which is a product of lipoprotein peroxidation, in the neovascular tissue taken from cadavers with AMD, but it was not found to be present in eyes taken from healthy donors [40].

Ishibashi and colleagues [41] found this same CML in soft drusen and in RPE tissue of AMD eyes, but not in a group of control eyes.

Finally, Olin et al. [42] reported finding a surplus of thiobarbituric acid reactive substances (TBARS), which indicate oxidative damage and are also a marker for lipid peroxidation [43] in the eyes of elderly macaque monkeys which had > 10 drusen. The marker was not seen in monkeys of a similar age who did not have at least 10 drusen.

These findings indicate that there is a process of oxidative damage occurring, and that this tissue damage is creating a waste-product, or by-product that is either being deposited in the drusen, or is contributing to the formation of drusen.

Expanding this list of proteins found in drusen, regardless of whether they come from degraded RPE cells, has opened the door to another interesting theory behind macular degeneration. These proteins appear to be much the same as proteins found in the brains of patients with Alzheimer's disease (amyloid plaque) and in the arteries of patients with atherosclerosis and glomerular basement membrane disease [44].

Hageman and colleagues [45] have also presented a novel theory suggesting that drusen result from dendritic cells that are recruited by injured or locally damaged RPE cells. The RPE cells die as a result of ischemia, oxidative stress or other causes and are shunted into the RPE/Bruch's membrane space. Dendritic cells migrate through Bruch's membrane, toward dead and/or dying RPE cell fragments. Dendritic cells are known to be present in inflammatory lesions [46], and are recruited toward injured tissue by a series of cytokines, chemokines and heat shock proteins where they are eventually activated.

According to Hageman, ~ 40% of mature drusen have been found to have a 'core-like structure'. These structures began as dendritic cells that penetrated Bruch's membrane and attached themselves to drusen-associated cells. The dendritic cells were ultimately integrated into the growing drusen. These dendritic cells appear to be more common in smaller drusen or those with smaller height-to-width ratios.

4. Inflammation

Although human eyes age over time, and most will develop drusen to some extent, this does not mean all eyes will go on to develop AMD. Somehow, there is a trigger which will eventually lead to this sight-robbing disease in some patients, but not in others. This trigger, we believe, is an inflammatory response: specifically, the response of the body's own defense system to this inflammation.

Population-based studies looked at anti-inflammatory agents and AMD and found no link [47]. Nevertheless, there is study-based evidence suggesting the possibility of anti-inflammatory agents as a therapeutic strategy to suppress choroidal neovascularization (CNV)-associated wet AMD [48].

As stated previously, we believe that it is not the inflammation by itself that leads to the onset of AMD, but an inappropriate response by the body's defense system to this inflammation. The first point to address here is to explain the link between the damage to the RPE, whether caused by oxidative stress or other sources, and the inflammatory process.

Hollyfield and colleagues [29] identified carboxyethylpyrrole (CEP) as a potential initiating molecular signal that links the damaged RPE with the body's immune response, and leads to the onset of AMD.

They found that mice treated with CEP mouse serum albumin (CEP-MSA) generated a powerful antibody-mediated immune response, with titers of antibody that were 6 – 8 times
higher compared with those of control mice. Swelling of individual RPE cells and in adjoining cells, cell lysis and, in some mice, swelling of the overlying photoreceptor cells were also seen. There was a statistically significant relationship (p < 0.01) between the severity of the outer retina pathology, as measured by the number of lesions present in a given RPE sample, and the specific antibody titer.

This process was not observed in a cohort of mice that were recombinase activating gene (Rag)-deficient, indicating that the body must have a functioning immune system, with mature T- and B-cells, in order for this inflammatory response to take place.

Hollyfield concluded that mice immunized with CEP-MSA developed localized retinal lesions involving degeneration of the RPE, and changes to the photoreceptors that resembled geographic atrophy. Localized sub-RPE deposits resembling soft drusen were also seen.

So why does the body's defense system respond this way in some subjects, but not in others? We propose that it is related to a dysfunction in the body's immune response network – the complement system – and in particular to a component of the complement system known as complement factor H (CFH, or HF1). This is a powerful inhibitor of the complement system, and a regulatory molecule in the alternative complement and classic complement systems. The factor H gene was identified by Ripoche and colleagues in 1988 [49,50], and was found to be on chromosome 1, in an area populated by many other genes that are essential for complement regulation. But it's not the gene itself that concerns us, so much as it is the gene's coding variant, Y402H, which represents a tyrosine to histidine single-nucleotide polymorphism (SNP) at position 402. If this is present, it dramatically increases one's risk of developing AMD.

The complement system (see section 3 of Figure 2) comprises at least 30 inter-related proteins and is part of the body's innate defense system. Its purpose is to protect the body from invading pathogens, to augment cell-mediated immune responses, and finally, to help clear away by-products (phagocytosis) created in the defense of the host. The system (Figure 3) comprises three distinct pathways – the lectin, alternative and classic pathways – each with its own characteristics and its own initiating triggers. Each of these pathways contains a particular component, C3, and as the pathway is activated by an invading pathogen or by an injured cell, C3 is broken down into various by-products. One such by-product is C3b, which binds to the surfaces of both the host and invading cells. In normal eyes, CFH (or HF1), a regulator of the complement system, inactivates C3b that has been deposited on the host cells, so host cells are no longer targeted, but the cells of the invading pathogens are targeted. Drusenous debris, which the body recognizes as an invader, would be attacked, and phagocytes could digest the attacking bodies.

However, in some patients, the CFH cascade is not launched and both the host and the invaders are left with C3b on their membranes. Therefore, both are attacked and destroyed by the inadequately controlled complement components. The culprit here is a dysfunction in CFH caused by the Y402H polymorphism which allows the immune response system to run out of control, attacking the host tissues as well as diseased tissues.

In 2005, in separate investigations, Edwards reported that having the Y402H polymorphism increased the risk of AMD by 2.7-fold, and that this could account for up to 50% of the attributable risk for AMD [15]. Y402H polymorphism is located within short consensus repeat 7 (SCR7) which also contains overlapping binding sites for heparin and C-reactive protein. Edwards suggests that while CRP activates the complement cascade, it may also play a role in the development of AMD by directly binding to CFH. He did not rule out other coding variants of CFH that could have the same effect, and therefore modulate the risk of developing AMD.

Haines and colleagues, following much the same approach, reported that the presence of the coding variant Y402H increased the odds ratio for AMD between 2.45 and 5.57. This variant alone could explain 43% of cases of AMD in older Caucasians [16].

Similarly, Klein and colleagues reported that the risk of AMD increased by a factor of 7.4 when the individual was homozygous for the risk allele [14].

Finally, a paper by Hageman et al. [17], compared almost 1000 cadaver eyes with confirmed AMD against 400 eyes without AMD, and determined that AMD pathology is manifested primarily in the macula, and that complement activation at the level of Bruch's membrane is a key element in the process of drusen formation. Also, a specific common haplotype of the complement regulator HF1 predisposes individuals to AMD. The haplotype is present in 50% of AMD cases, and 29% of controls (OR = 2.46). Homozygotes for this haplotype account for 24% of AMD cases and 8% of controls (OR = 3.51). The results implicate abnormalities in HF1-mediated regulation of alternative pathway complement activation, and pathogenic agents that activate the system, in a substantial proportion of AMD cases.

5. Other associations

Numerous studies over the past decade have examined the association between other potential mediators of inflammation and AMD. These mediators appear to follow different pathways, and at this time, few links between the mediators and AMD have been proven. Those which show the strongest links are the pro-inflammatory cytokines IL-1, IL-6, and TNF-α, which are known to be released from the choroid of eyes with AMD [51]. Certain chemokines, including monocyte chemoattractant protein-1 (MCP-1), chemokine (C-C motif) receptor 2 (CCR-2), stromal cell derived factor 1 (SDF-1) and chemokine (C-X-C motif) receptor 4 (CXCR4) also have been shown to be expressed in the neuroretina [52].

Additional inflammatory cells that may exert an influence are from the myeloid and lymphoid families. Neutrophils,
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which are from the myeloid family, have been shown to induce CNV in an experimental mouse model, but no conclusions can be drawn about their eventual effect on early AMD [53]. Lymphoid cells, which include B-cell and T-cell lymphocytes have not been shown to play any role in either drusen biogenesis, or in AMD itself [9].

Through these studies, we can see that drusen gather these chemokines and cytokines, which then initiate the inflammatory response. In some cases, the inflammatory response is physiologically detectable, but does not lead to subsequent damage of tissue within the eye. In other cases, it stimulates the activation of pro-angiogenic growth hormones, in particular VEGF, which then leads to choroidal neovascularization.

Macrophages play a key role in the pathogenesis of AMD, stimulating aberrant angiogenesis in blinding eye diseases [54]. Impaired macrophage recruitment may lead to the accumulation of C5a and IgC, inducing the production of VEGF by the retinal pigment epithelium, possibly acting as a mediator for the development of CNV [55]. It could be shown that a generalized macrophage depletion reduced the size and leakage of laser-induced CNV [56]. Clodronate liposomes (CL(2)MDP-lip) can cause a depletion of monocytes in the blood and lymph node macrophages [57]. IL-10 regulates macrophage activity in the eye and could be an attractive therapeutic target in order to suppress or inhibit choroidal neovascularization in age-related macular degeneration [54]. Retinal microglial cells express CX3C chemokine receptor 1 (CX3CR1). Homozygosity for the CX3CR1 M280 allele, associated with impaired cell migration, increases the risk of AMD [58]. CX3CR1-deficient mice have abnormal microglial cells, that accumulate under the retina and contribute to the progression of age-related macular degeneration [59].

A novel theory which may show promise concerns the augmentation of dysfunctional CFH proteins with a more functional CFH-modifying protein. This could re-establish the appropriate regulation of the complement pathway system in affected individuals.

6. Conclusion

It is now well-known that AMD is a multi-factorial disease, with environmental causes (smoking, hypertension and obesity) and genetics all playing a role. In this paper, we have concentrated on a genetic susceptibility gene (i.e. a gene that leads to complement factor dysregulation).

As with all tissues contained within the human body, the eye experiences numerous physiological and pathological changes as it ages. The aging process, together with a lifetime
of exposure to light induces oxidative stress, which then leads to damage to the RPE, drusen formation and RPE dysfunction. Drusen, which accumulate between Bruch’s membrane and the RPE may become targets for activated dendritic cells. Drusen formation also initiates activation of the complement system, which under normal circumstances, would contain and destroy these invading pathogens. However, when a person is carrying the Y402H polymorphism, the complement system turns against the host tissue as well as the invading foreign bodies, and launches what amounts to an out-of-control inflammatory response. This inappropriate chain of events in the body’s immune response system then sets the stage for the process of neovascularization.

For the time being, the treatment options for age-related macular degeneration will remain limited, and will consist of inhibitors of neovascularization, mainly anti-VEGF compounds, as well as photodynamic therapy. However, understanding the mechanisms of the Y402H polymorphism, as well as other genetic pathways such as a common coding SNP in the LOC387715 gene, and an IL-8 promoter polymorphism known as 251 A/T, both of which are being investigated, may result in new platforms being developed for the management of macular degeneration. Genetic testing would enable clinicians to identify patients who are at the greatest risk of developing AMD. At the same time, new gene-based treatments may be designed which would prevent the early events that initiate inflammation in those patients, rather than treating a condition that is already in place and affecting the patient’s vision.

7. Expert opinion

All degenerative diseases of the retina which affect central vision may have a devastating effect on the quality of life. Besides diabetic retinopathy, AMD leads to visual dysfunction in a significant fraction of the elderly population worldwide, which is constantly growing due to an increase in life expectancy. Early signs of this disease entity include the appearance of soft drusen and regions of altered pigmentation in the retina. Advanced stages exhibit choroidal neovascularization or atrophy of photoreceptors and the RPE. Numerous pathways and alterations of physiological processes have been investigated.

Those include inflammation, oxidative stress and altered cholesterol metabolism. In the last two years inflammatory processes, namely alterations of the inflammatory pathway have been identified as being involved in the pathogenesis of AMD. However, at this time we only know about an enhanced risk in patients with a genetic variation of the complement system. In the future we may be able to target patients with this genetic risk factor for specific anti-inflammatory treatments, maybe with simple anti-inflammatory agents currently used for pain relief.

On the other hand, the contribution of the different inflammatory pathways has not been quantified. These consist of photodynamic reactions and a low grade inflammation in the area of drusen. In addition, there is little if any information on the role of systemic inflammation in this disease. We already know that inflammation occurs during various activities such as exercise and eating. The amount of inflammation correlates with the intensity of the exercise and the quality of the food. Thus, one consequence of these early and incomplete findings is the clear recommendation not to avoid exercise but to control the intensity of the exercise and to increase the quality of the food. However, the contrary is also true: High-quality food alone cannot compensate for an unhealthy way of life or a lack of activity.

Hopefully, in the future clinical trials will not only focus on complement but also investigate other sources of inflammation as well. This is especially important since they are easily accessible by anti-inflammatory drugs and/or nutrition behaviour.

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Declaration of interest

The authors have no relevant affiliation or financial involvement in any organization or entity, or a financial conflict of interest with the subject matter or with any of the material discussed in this paper.
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Affiliation
Albert J Augustin1,2 MD & Janna Kirchhof1 PhD
1Author for correspondence
2Department of Ophthalmology, Staatliches Klinikum Karlsruhe, Moltkestr. 90 76133 Karlsruhe, Germany
Tel: +49 721 974 2001; Fax: +49 721 974 2009; E-mail: albertjaugustin@googlemail.com

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