Role of inflammation in the pathogenesis of age-related macular degeneration


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This article aims to review the role of inflammation in the pathogenesis of age-related macular degeneration. Besides environmental factors, a direct link to genetics in general and/or genetics of inflammatory pathways could be shown to contribute to both the initiation and propagation of the disease. The complement system with the Y402H variant of the complement factor H gene as one of the key factors plays a central role. A defect in the control leads to an activation in genetically predisposed individuals. The LOC387715/SARM1 and HTRA1 genes, as well as certain chemokines and their receptors, especially the CX3CR1 chemokine receptor and the Toll-like receptors, are associated with the development of age-related macular degeneration. Among all inflammatory cells and mediators, macrophages deserve special attention. They have been shown to express both proinflammatory and angiogenic factors, such as VEGF and many others that have been identified in choroidal neovascularization membranes. However, there are controversial reports on the actual role of these inflammatory cells, as well as on the role of C-reactive protein. An additional mechanism that is directly related to inflammation is oxidative stress via the release of oxygen free radicals—a phenomenon that, to a certain extent, occurs in every mammalian organism—which may be increased in the aging body, thereby leading to oxidative tissue damage. This damage seems to be a crucial trigger for age-related macular degeneration via both direct damage of unsaturated fatty acids and activation of inflammatory pathways. Polysaturated fatty acids, major molecules of the photoreceptor outer segments, are highly susceptible to oxidation processes.

Keywords: complement system • C-reactive protein • inflammatory cell • polymorphism • Y402H

Age-related macular degeneration (AMD) is the leading cause of blindness in individuals aged 55 years or older in the Western world. In Europe, 1.7% of all individuals over the age of 55 years have AMD. With life expectancy progressively rising, its prevalence is steadily increasing. Before the year 2020, there will be a 50% increase in the incidence of AMD [1]. The disease is reported to account for 54% of the cases of blindness among the white population in the USA [2]. By 2020, the number of people affected could increase by as much as 70% [2]. A European study with patients enrolled in several countries has reported that 2.3% of the population over the age of 65 years have wet AMD [3]. In the late 1990s, photodynamic therapy was introduced. The progress of AMD could finally be arrested or significantly slowed down, even leading to some improvement in visual acuity in a small percentage of the treated patients [4]. In the last decade, a whole new class of agents, the anti-VEGF drugs, have been introduced. These drugs are not only capable of stopping the process of the development of choroidal neovascularization (CNV), but they also restore a significant amount of lost vision in many patients. However, in most cases, more than one injection is needed during the course of the disease owing to a time-limiting effect of these drugs.

Among the risk factors, genetics, environmental and health factors play a central role in the pathogenesis. Numerous studies have identified factors such as advanced age, diabetes mellitus, smoking, systemic hypertension, cardiovascular disease, race, diet and obesity as being strongly associated with the onset of AMD. The most established factors are advanced age, diet, smoking and race [5]. Several studies have investigated smoking as a risk factor and found a statistically significant association with the development of AMD [6]. The possible mechanisms include impairment in antioxidants...
(e.g., plasma vitamin C and carotenoids), production of reactive oxygen species, induction of hypoxia, alteration of the choroidal blood flow [9] and an effect on the immune system [10].

With the improvements in medical science and healthcare delivery in most countries of the Western world, life expectancy will steadily increase in the next few decades, meaning that AMD will certainly become a greater burden, both for the affected individuals, as well as financially for the healthcare systems and insurance companies across the world.

However, the pathogenesis of AMD, which is more complex than initially assumed, is far from being understood in every detail. Taking into account the huge amount of scientific work carried out over the last decade, key questions of the pathogenesis still remain unanswered, and it is likely that many years, maybe decades, will pass until this huge puzzle has been completed.

The challenge of understanding this disease is that it affects the center of the macula, is associated with age, and has a clear genetic predisposition in at least 50% of cases. The paradox of AMD is that it is hard to understand how an acquired disease associated with senescence can also have a hereditary component. One theory is that the immune system responds to epigenetic changes in the proteome of the retina.

This paper will review the role of inflammatory processes in the physiological and pathological changes that occur during the course of AMD.

**AMD & the aging eye**

Age-related macular degeneration is a disease of the aging eye in patients aged 50 years or older, showing the typical findings in most cases. It is possible that the process begins with a subclinical inflammation and takes years, or even decades, before any clinical findings and/or symptoms manifest.

A patient's genetic profile, oxidative stress and light damage play significant roles in the complex pathogenetic mechanisms of AMD [11]. The aging process in every human eye may include oxidative stress to a different degree. Nevertheless, some people develop AMD while others do not. Therefore, a direct link between these risk factors must exist, determining the point in time when the disease begins to develop. A trigger for this process might be inflammation. Whether the inflammation erupts and leads to the full manifestation of AMD could depend on the patient's genetic status [11].

A major factor in the pathogenesis of AMD seems to be an imbalance in the defense mechanisms of the eye. A number of inflammatory stimuli affect the aging eye, usually causing subclinical outcomes. However, if the patient has inherited certain polymorphisms of specific inflammatory mediators, the inflammatory response will be altered and follow an entirely different course, leading to tissue damage. If the patient has not inherited these specific polymorphisms, they might just experience certain age-dependent alterations in the retinal tissue, but AMD might not develop.

Several 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. These changes do not follow a specific pattern of sequence, so there is no typical step-by-step progress of the disease with the alterations presenting either concurrently or consecutively [11].

**Drusen formation**

Drusen presents one of the typical findings in AMD, with their number and size being important risk factors for developing CNV. They form between Bruch’s membrane and the retinal pigment epithelium (RPE) and consist of more than 24 known proteins and molecular components [11].

The main part of the material accumulating in the RPE/Bruch’s membrane space consists of fragments of degenerated RPE cells [12], including melanin granules, lipofuscin granules, membranous materials and recognizable organelles. They cannot diffuse through Bruch’s membrane [4]. Drusen consist of debris of by-products, several inflammatory mediators and materials of the choroidal circulation. At the early stage, they do not represent a risk factor for the patient. Certain RPE cells containing specific drusen-related molecules in their cytoplasm have been identified [12]. These specific RPE cells may play more of a role than others in the formation of drusen. The cells have been described as having a 'compromised RPE phenotype' [13]. Further components of drusen are degraded RPE cells, cytoplasmic fragments of retained basal lamina [14] and different types of lipids [15].

Markers of lipid peroxidation have been detected in drusen, indicating a direct link between oxidative stress and lipid peroxidation. Carboxymethyl lysine, a product of lipoprotein peroxidation, has been found in the neovascular tissue taken from cadavers with AMD, but it could not be detected in eyes of healthy donors [16,17]. Carboxymethyl lysine has also been found in soft drusen and in RPE tissue of patients with AMD [17]. Another hypothesis might be that the formation of drusen is a result of dendritic cells that are recruited by injured or locally damaged RPE cells, which die as a result of ischemia, oxidative stress or other causes and accumulate in the RPE/Bruch’s membrane space [18].

**Changes in choriocapillaris**

Changes in the anatomical and biochemical structure of the choriocapillaris might be another factor that may lead to cell death and/or an inflammatory response. The results are changes in blood flow, increased oxidative stress, accumulation of lipids in Bruch’s membrane, and ultimately, the destruction of the architecture of the membrane.

These changes include a decrease of the density and lumen diameter, as well as of the thickness of the choriocapillaris [19]. A hypoxic condition for the RPE cells and the photoreceptors, which consume approximately 90% of oxygen delivered by the choriocapillaris, develops, resulting in a dysfunction or damage of the RPE causing a secondary degeneration of the photoreceptors [20,21]. The ischemic condition in the macula leads to oxidative stress, triggering an inflammatory reaction. The consequence is a degradation of the RPE, with the degraded material accumulating in the RPE/Bruch’s membrane space, creating the basis for drusen formation.
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Changes in Bruch’s membrane

Bruch’s membrane is a barrier between the choriocapillaris and the RPE, permitting an unobstructed flow of material from the retina to the choriocapillaris and vice versa. Aging changes involve an increase in the thickness of the membrane by 135% from 2.0 to 4.7 μm up to the age of 90 years [19]. As a result, water and material conductivity decreases, leading to the accumulation of debris in the subretinal space.

The complement system

Complement components & functions

An inflammatory process involving the complement system has been proposed to play an important role in the development of AMD. Numerous proteins of the complement system, as well as their activation products and regulators, have been detected in drusen and nearby RPE in patients with AMD [19,22-26]. These include, among others, the complement factors three (C3) and five (C5), the membrane attack complex C5b–C9, and the complement factor H (CFH).

Two studies strengthened the evidence for a key role of the complement system in the development of AMD, showing that in laser-induced CNV in mice, intact C3 and C3a/R/C5aR receptors are required [26,27]. Several complement factors could have been shown to be elevated in patients with AMD.

The complement system contains at least 30 proteins (enzymes and regulators) providing an immune defense mechanism for the human organism. It is activated by immune complexes, residues on microbial cell surfaces, and several other triggers. Complement activation involves three principle pathways: classic, alternative, and lectin (common) pathways. All three pathways join at the point of the activation of C3. C3 is then cleaved into C3a and C3b by the C3 convertase. This enzyme initiates the C5 convertase that catalyzes the formation of the membrane-attack complex with its end components C5b–C9. Another function of the activated complement system is the release of chemokines, mediating the recruitment of inflammatory cells and an enhancement of capillary permeability [28,29]. Complement activity is vital for the immune response of the human organism against pathogens and dying cells. A disregulation of the system can result in an overactivation, with healthy tissue damage.

Complement factor H gene & Y402H variant

Heredity factors have been proven to play an important role in the development of AMD. Several studies have identified the CFH as one of the responsible genes. CFH is a soluble protein, synthesized predominantly in the liver, but also, to a certain extent, by the RPE cells. It is encoded within the interval of chromosome 1q23–32. CFH is an important negative regulator of the complement system, inhibiting the alternative and classical pathways and regulating (indirectly inhibiting) the common pathway. The main function, however, is the control of the activation of the alternative pathway in blood plasma, the host tissue and sites of inflammation. It preferentially binds to C3b and inactivates this molecule. Consequently, the enzymes C3 convertase in the alternative pathway and C5 convertase in the common pathway cannot be produced. Furthermore, CFH acts as a cofactor for the Factor-I-mediated proteolytic inactivation of C3b into iC3b and C3dg. As a result, progression of the entire cascade is inhibited. It has been proposed that an impaired complement inhibitory activity by CFH plays an important role in the pathogenesis of AMD.

The strongest AMD-associated single nucleotide polymorphism (SNP) is the CFH Y402H (tyrosine to histidine substitution at amino acid 402) variant, which is located within a binding site for C-reactive protein (CRP) [29-33]. Alterations of the CFH gene among people with the Y402H variant could increase the level of inflammation and promote the progress of AMD [33,34]. This means that a certain activation of the complement system by a defective control of the cascade in individuals who are genetically predisposed initiates the release of proinflammatory and angiogenic mediators and complement cleavage products, and consequently enhances the development of AMD.

It has been reported that the CFH Y402 variant reduces the binding affinity to CRP, meaning that reduced binding of CRP by CFH might lead to an impaired targeting of CFH to cellular debris and an accumulation of CRP in the choroid [9]. Another possibility might be that a persistent chronic inflammation, as the result of impaired complement inhibitory activity, may occur in patients with CFH Y402H. A proinflammatory state develops, leading to the accumulation of CRP rather than an impaired binding by CFH [9]. In addition to CFH Y402H, five further SNPs have been reported to have an association with AMD, indicating that multiple SNPs that have an influence on CFH function might play a role in the pathogenesis of AMD [9].

Other complement components

Several additional complement components have been linked with the pathogenesis of AMD. Two variants of C2 (1QH BF/E818D and R32Q BF/intron) have a protective influence on AMD [35], possibly due to the BF variant being a complement activating factor. A decreased complement activation by BF might explain the protective effect. C7 is reported to be protective against AMD as well [36]. The SNP variant rs251989, which is located in the SERPING1 gene encoding the C1 inhibitor, has been found less frequently in patients with AMD compared with the control group [37].

LOC387715/ARMS2 & HTRA1 genes

Single nucleotide polymorphisms in chromosome 10q26 are associated with the risk for having dry and wet AMD, as shown in numerous studies [38-45]. The LOC387715/ARMS2 and HTRA1 genes play an important role in the pathogenesis of the disease [40,41,44,46]. The HTRA1 gene encodes a heat shock serine protease that is expressed in the retina and can regulate TGF-β signaling [44,46]. The LOC387715/ARMS2 gene encodes a putative 12-kDa protein. Although it has been suggested that LOC387715/ARMS2 may not actually encode a protein, recent data have shown that it encodes a mitochondrial outer membrane protein that is also expressed in the retina [45].
The a169T SNP on LOC387715 resulted in a 7.6-times increased risk for developing AMD in individuals homozygous for this change [47]. Furthermore, evidence has been found for a gene–gene interaction between CPH and LOC387715, further increasing the risk of AMD [48].

Other associations
Chlamydia pneumoniae infections have been suggested to be linked with increased risk in AMD development. Increased serum anti-
C. pneumoniae antibodies have been detected in AMD patients [99], and C. pneumoniae has been found in neovascular membranes [98]. C. pneumoniae is a trigger for the alternative pathway of the complement system and might induce an overactivation. This hypothesis has been strengthened by a study showing that the presence of a high C. pneumoniae antibody titer and the CPH Y402 variant significantly increases the risk of AMD [51].

Smoking is one of the high-risk factors for AMD, as confirmed in several studies. The risk of macular degeneration is two- to three-fold higher in current smokers compared with never smokers [52]. There is evidence that the likelihood of developing AMD will reduce if a smoker were to quit smoking. After 1 year of nonsmoking, the likelihood reduces by 6.7% [53]. After another 5 years of nonsmoking, the risk is further reduced by another 5%, and after yet another 5 years, by an extra 4.2% [53].

Correlations between smoking and the development of late AMD could be found for the LOC387715 polymorphism [54] and for CPH genotypes. It is estimated that CPH, LOC387715 and cigarette smoking together explain 61% of the population-attributable risk of AMD. The adjusted population-attributable risk percentage estimates are 20% for smoking, 36% for LOC387715 and 43% for CPH [53].

C-reactive protein
C-reactive protein, a cytokine, is an acute phase reactant and systemic marker of subclinical inflammation, and is involved in the acute phase response of the human immune system to infections. The detection of inflammatory molecules in the plasma or serum of patients with AMD [55,57] lead to the assumption that a chronic inflammation could be part of the disease. Moreover, genetic studies showed that the Y402H variant of CPH, which is located on the binding site for CRP, is an important risk factor for early and late AMD, with the association being stronger in advanced stages of AMD [55,58]. However, lack of agreement exists regarding the role of CRP in the pathogenesis of AMD. A study from The Netherlands reported that CRP haplotypes associated with a high systemic CRP level can decrease or increase the risk for AMD, depending on the CPH Y402H genotype of the patient [59]. The Physicians Health Study, on the other hand, did not find an association between common genetic variation in CRP and the risk of AMD, even for the CPH Y402H genotype [60].

A study was initiated employing a direct sequencing approach to encompass both sets of SNPs previously evaluated in the two studies mentioned earlier for their association with the risk for AMD [58]. Disease status alone, history of smoking, BMI or CPH genotype have been considered. No evidence for a statistically significant association between any of the SNPs identified in the CRP gene and wet AMD could be found [58]. Higher levels of CRP have been found to be linked with advanced AMD [60]. If elevated levels of CRP are associated with the risk of developing AMD, the reason is not to be found in a genetic variation within CRP. Another study could confirm an association of the Y402H variant of CPH and risk of AMD, similar to several previous studies, but may not prove a significant association between common genetic variations in CRP and the risk of AMD [61]. It has been proposed that CRP might play a direct role in the pathophysiology of AMD via an activation of the alternative pathway of the complement system [62].

Chemokines & chemokine receptors
Chemokines bind to their receptors on immune cells, such as macrophages, and promote their recruitment to inflamed tissues. The CX3CR1 chemokine receptor has been linked with the pathogenesis of AMD in recent times. The V249I and T280M CX3CR1 SNPs are associated with an increased risk for AMD [63]. Homozygosity for the CX3CR1 allele has been reported to be associated with AMD [64]. CX3CR1 is expressed in all retinal cells, but solely on the retinal microglia cells. Cells that are positive for CX3CR1 and accumulate in the macular subretinal space may play a central role in the development of AMD [65].

The Toll-like receptors (TLRs) differentiate between microbial molecules and induce an immune response by tissue and inflammatory cells. The L4H2F variant of the TLR3 gene could have a protective effect against dry AMD [66]. TLR4 and TLR8 have been investigated and are unlikely to play a role in AMD pathogenesis [67].

Inflammatory cells & mediators
It is recognized that inflammation plays a central role in the pathogenesis of AMD. A downregulatory immune environment exists in the eye, meaning that the natural environment of the eye downregulates inflammation [68]. Any defect in this downregulatory immune environment should, therefore, trigger an increased immune response.

Macrophages are likely to have a significant role in AMD, as reported in numerous studies over the last decade. They have been detected in neovascular membranes in wet AMD [67] and have shown to express proinflammatory and angiogenic factors, such as VEGF [68]. The actual role of the macrophages, however, has not yet been verified, and controversial reports exist. At the site of laser-induced CNV in mice, a decreased macrophage accumulation correlated with a lesser severity of the neovascularizations [69]. Therefore, it has been concluded that macrophages might induce the development of CNV. On the other hand, it is reported that macrophages play a protective role in CNV. In IL-10-deficient mice, an increased recruitment of macrophages was associated with less severe laser-induced CNV [70]. Two possible explanations for this controversy may exist. First, it would be possible that the less severe CNV reported in the first study might follow a direct injury to the endothelium of the neovascularizations, rather than the depletion of macrophages reported in the second study. The second possibility might be that macrophages are a heterogeneous group of inflammatory cells with different effects. Two types of
macrophages exist, the M1, which are proinflammatory, and the M2, which are anti-inflammatory. These M2 macrophages might play a protective role in the early stages of the disease by clearing deposits and drusen. The M1 type could induce the inflammation caused by the retinal injury due to the laser, promoting the development of the choroidal neovascularizations [7]. During the initial stages of AMD, there is an interaction between the RPE and macrophages with the RPE cells expressing monocyte chemotactic protein, a cytokine involved in macrophage recruitment. Another important role of macrophages is the secretion of tissue factor and VEGF, thus promoting the development of CNV [7].

Apart from macrophages, the microglial cells of the retina (expressing the CX3CR1 receptor as previously mentioned), which are responsible for neuronal homeostasis and immune defense, play a role in the pathogenesis of AMD [73]. They are activated when retinal injury or degeneration occurs. They proliferate, migrate to the altered area, phagocytize cell debris, and secrete proinflammatory cytokines and chemokines [79]. An accumulation of reactive microglia in the affected areas is a significant cellular event. It indicates the presence of neuroinflammation, as found in various diseases, such as Alzheimer's disease and Parkinson's disease, as well as glaucoma [74]. In the CNS, activated microglia play an important role in oxidative stress. Microglial cells produce large numbers of superoxide ions and release them into the surrounding tissue as an effective attack system [74].

Angiotensin II has been shown to augment inflammation. It increases the release of reactive oxygen species and activates neutrophils, inducing them to produce free radicals [75]. It enhances vascular inflammation, accelerates atherosclerosis, and downregulates PPAR-α and PPAR-γ mRNA and protein. Furthermore, it increases the transcription of MCP-1, E-selectin, ICAM-1, VCAM-1, inducible nitric oxide synthase and COX-2 [79].

**Oxidative stress**

Oxidative stress occurs to a different extent in every human organism as it ages. Oxidation is confined primarily to the macula because light, oxygen tissue damage and high-metabolite rate provide tissue tropism. Related tissue damage through the release of free oxygen radicals is a crucial trigger for AMD. Despite several protective mechanisms, mainly through antioxidant enzymes, such as superoxide dismutase, catalase, ascorbic acid and glutathione peroxidase, as well as antioxidants, such as vitamin C and E, oxidative stress has a cumulative influence on the human retina. Reactive oxygen species, such as the hydroxyl (OH), singlet oxygen (O₂), and the hydrogen peroxide (H₂O₂) radicals play the significant role in this complex mechanism. Factors that are known to stimulate the production of reactive oxygen species include irradiation, aging, inflammation, air pollutants, smoking and repertusion injury. The tissue primarily affected by oxidative stress is the RPE with the photoreceptors and the choriocapillaris suffering damage as a consequence [79]. In an aging eye, the plasma levels of vitamin C and E decrease. Lipid peroxidation, highlighted by the fact that approximately 50% of the outer membrane of the photoreceptors is comprised of polyunsaturated fatty acids, particularly docosahexaenoic acid, which is the most oxidizable of all fatty acids, increases. As a consequence, oxidative damage to the RPE cells rises. Docosahexaenoic acid is not only a target of peroxidation, but also of carboxyethylpyrrole formation. This epigenetic, post-translational oxidative modification initiates a macrophage-driven, antigen-specific immune response that is exacerbated by CFI polymorphisms that enable uncontrolled complement activation. Immunochemistry localized carboxyethylpyrrole to the outer segments of the photoreceptor rod and RPE in mouse retina, and demonstrated more intense carboxyethyl-pyrrole immunoreactivity in photoreceptors from a human AMD donor compared with healthy human retina [77]. Carboxyethyl-pyrrole has also been associated with deposition in Bruch's membrane from cadaver eyes with former AMD. Further supportive evidence is the importance of macrophages to the induction of neovascular AMD [67], the genetic association of CFI polymorphism to AMD [68,70,72], and, finally, the mouse model that mimics AMD [78].

In RPE cells, the density of the macular pigment decreases and the concentration of lipofuscin increases. One of its major components, N-retinyl-N-retinyliden-ethanolamin (AQ2), is a photosensitizer, which, induced by light (mostly the energetic blue and ultraviolet wavelengths), can produce reactive oxygen species. This mechanism is called photodynamic reaction type 2 [71]. The result is an impairment of lysosomal activity, leading to lipid peroxidation, reduced phagocytosis and, ultimately, RPE cell death [72].

Lipofuscin accounts for just 1% of the RPE cytoplasmic volume in the first decade of life, increasing to 19% in the eighth decade [74]. As lipofuscin increases, the RPE cytoplasmic volume decreases, consequently compromising RPE function, which may lead to photoreceptor cell death.

Reactive oxygen species are a by-product of cellular metabolism. Since the RPE and photoreceptors consume 50% of the O₂ from the choriocapillaris, the rate of metabolism and generation of metabolic by-products is high. A complex network of pathways exists, being responsible for the production of free radicals. In the xanthine oxidase pathway, ischemia triggers the production of hypoxanthine, xanthine and uric acid as well as the production of the O₂, which is consequently transformed into the H₂O₂, into the OH radical via an iron-dependent pathway.

In the myeloperoxidase metabolic pathway, arachidonic acid is converted through different reactions by cyclooxygenase and lipoxygenase. As a result, the OH and O₂ 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.

Phagocytes, activated either by the complement system, arachidonic acid or the oxidative tissue, damage themselves, producing H₂O₂, which is transformed, among others, into the OH radical or chlorozone, leading directly to oxidative tissue damage. Retinal hemorrhage (hemoglobin) induces the conversion of H₂O₂ into the OH radical via an iron-dependent pathway.

Since the histopathological changes in AMD are similar to those in atherosclerosis, it has been suspected that scavenger receptors for oxidized lipoproteins might be present in AMD lesions. These have finally been found in CNV membranes. This finding
supports the hypothesis that macrophages accumulate to ingest the oxidized low-density lipoprotein by scavenger receptors specific for oxidized lipoproteins in the early stages of AMD [79].

**Expert commentary**

The pathogenesis of AMD is more complex than initially assumed and is far from being understood. Inflammation seems to play a key role. A direct link to genetics in general and/or genetics of inflammatory pathways has been proven. In addition, several other risk factors, such as smoking and obesity, have been identified.

The complement system seems to play a central role in the AMD-related inflammatory cascades, with CFH being one of the key factors. A control defect may lead to an activation of the complement system in individuals who are genetically predisposed. This initiates the release of proinflammatory and angiogenic mediators, as well as complement cleavage products, and consequentially leads to the development of AMD. Furthermore, several other complement components are involved in cascades leading to AMD.

The **LOCR77751ARMS2** and **HTRA1** genes, and certain chemokines and their receptors, especially the **CX3CR1** chemokine receptor and the **TLRs**, are associated with the development of AMD. Among all inflammatory cells and mediators, macrophages deserve special attention. They have been detected in neovascular membranes of wet AMD patients. In addition, they have been shown to express proinflammatory and angiogenic factors such as VEGF and many others. However, there are controversial reports on the actual role of these inflammatory cells, as well as on the role of CRP.

In the last decade, the inflammatory arm in the pathogenesis of AMD has been targeted in general by intravitreal steroids or **NSAIDs**. Recently, an indirect inhibition of inflammation could be achieved with the introduction of the anti-VEGF drugs. Future therapeutic developments should consider the role of inflammation in the pathogenesis of AMD and possibly target other factors that also play a key role in the development of AMD. So far, oxidative stress, which occurs to a different degree in every human organism as it ages, has been identified to be closely related to the inflammatory cascade. Furthermore, related oxidative tissue damage seems to also be a crucial trigger for AMD.

**Five-year view**

The disease characteristics of patients suffering from AMD show an individual variability. Therapeutic approaches should consider these variations in order to meet the characteristics and the individual needs of the patients as well. The complicated pathways leading to AMD imply that monotherapies to treat wet AMD may be obsolete in the near future. A combination therapy including an anti-inflammatory drug seems to be the right and scientifically logical way of treating AMD. Recently, it could have been proven that combination therapy can reduce the rates of retreatment while improving visual acuity, similar to monotherapeutic approaches [10]. A further goal of future treatment strategies should be the limitation of treatment intervals by developing depot drugs, as well as improving the positioning of the drug directly to the macular region of the retina in order to achieve a better local effect.

**Financial & competing interests disclosure**

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**Key issues**

- Age-related macular degeneration (AMD) is the leading cause of blindness in individuals aged 55 years or older in the Western world. With life expectancy steadily growing throughout the world, the importance of AMD will rise even more in the next few decades.
- The pathogenesis of AMD, which is more complex than initially assumed, is far from being understood in every aspect.
- Apart from the most established risk factors, such as advanced age, diet, smoking and race, a patient's genetic profile, oxidative stress and light damage play significant roles in the complex pathogenetic mechanisms of AMD.
- A major factor in the pathogenesis of AMD seems to be an imbalance in the defense mechanisms of the eye. In patients with inherited variations of specific inflammatory mediators in the complement system, the immune response can be altered, leading to tissue damage.
- Hereditary factors have been proven to play an important role in the development of AMD. Several studies have identified the complement factor H as one of the genes responsible. The main function, however, is the control of the activation of the alternative pathway in blood plasma, the host tissue and sites of inflammation. It has been proposed that an impaired complement inhibitory activity by complement factor H plays an important role in the pathogenesis of AMD.
- The role of the cytokine C-reactive protein, a systemic marker of subclinical inflammation, remains controversial.
- Inflammatory cells, such as macrophages, play another key role in AMD. However, their actual effect can either be preventing or enhancing choroidal neovascularization. This may be owing to the fact that there are two different types of macrophages: M1, which are proinflammatory, and M2, which are anti-inflammatory.
- Certain chemokines and their receptors, especially the CX3CR1 receptor and the Toll-like receptors, are associated with the development of AMD.
- Oxidative stress occurs to a different extent in every human organism as it ages. Related tissue damage through the release of free oxygen radicals is a crucial trigger for AMD.
References
Papers of special note have been highlighted as:
• of interest
** of considerable interest
** Significant paper describing basic knowledge of molecular pathology and age-related macular degeneration (AMD).
** Important paper describing basic knowledge on AMD.
** Important paper that reports the association of immunology and drusen biogenesis.
** Important paper reporting the association of immunology and drusen biogenesis.
** Important paper detailing the complement system and the association between drusen formation and AMD.
** Describes the association between the complement system and choroidal neovascularization.
** Important paper reporting the association between the complement system and choroidal neovascularization.
** Describes the basic knowledge of the complement system.
** Describes the basic knowledge of the complement system.
** Explains the basic knowledge on complement factor H.
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• Explains basic knowledge on complement factor H.


• Reports the association between SERPING1 and AMD.


• Describes basic knowledge of HTRA1.


• Important paper that explains the basics of genetics and AMD.


• Explains the basics of genetics and AMD.


• Significant paper describing the basic knowledge on genes, inflammation and AMD.


• Highlights the importance of understanding the association between AMD, smoking and genes.


• Significant paper describing the basic facts between smoking and AMD, as well as their association with each other.


• Reports the basic knowledge and the association between C-reactive protein and AMD.


• Provides a summary of AMD, risk factors, genes and inflammatory factors.


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• Important paper that explains the association between genes, C-reactive protein and AMD.

• Reports the association between MAD and macrophages.

Important paper that explains the role of microglia in AMD pathogenesis.

• Important paper that reports the association between inflammation, the complement system and AMD.


Website
101 QLT announces positive results from the evaluation of Vidiyne® combination therapy. QLT Inc. 2 June 2009 www.reuters.com/article/pressRelease/idUSI02111102-Jun-2009+PRN20090602

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