REVIEW ARTICLE

The significance of the complement system for the pathogenesis of age-related macular degeneration — current evidence and translation into clinical application

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Abstract

Background Dysregulation of the complement system has been shown to play a major role in the pathogenesis of age-related macular degeneration (AMD).

Methods The current evidence from human studies derives from immunohistochemical and proteomic studies in donor eyes, genetic association studies, and studies of blood complement protein levels. These lines of evidence are corroborated by in vitro and animal studies.

Results In AMD donor eyes, detection of complement proteins in drusen suggested local inflammatory processes involving the complement system. Moreover, higher levels of complement proteins in the Bruch's membrane/choroid complex could be detected in AMD donor eyes compared to controls. A large number of independent genetic studies have consistently confirmed the association of AMD with risk or protective variants in genes coding for complement proteins, including complement factor H (CFH), CFH-related proteins 1 and 3, factor B/C2, C3 and factor I. Another set of independent studies detected increased levels of complement activation products in plasma of AMD patients, suggesting that AMD may be a systemic disease and the macula a vulnerable anatomic site of minimal resistance to complement activation. Genotype–phenotype correlations, including the impact of genetic variants on disease progression, gene–environment and pharmacogenetic interactions, have been investigated. There is evidence that complement gene variants may be associated with the progression from early to late forms of AMD, whereas they do not appear to play a significant role when late atrophic AMD has already developed. There are indications for an interaction between genetic variants and supplementation and dietary factors. Also, there is some evidence that variants in the CFH gene influence treatment effects in patients with neovascular AMD.

Conclusions Such data suggest that the complement system may have a significant role for developing new prophylactic and therapeutic interventions in AMD. In fact, several compounds acting on the complement pathway are currently in clinical trials. Therapeutics that modulate the complement system need to balance inhibition with preservation of sufficient functional activity in order to maintain adequate immune responses and tissue homeostasis. Specifically, targeting the dysfunction appears more adequate than a global suppression of complement activation in chronic diseases such as AMD.

Keywords Age-related macular degeneration · Pathogenesis · Complement system · Genotype · Gene–environment interaction · Pharmacogenetics · Therapy

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Age-related macular degeneration (AMD), the leading cause of blindness in western societies, is a complex disease with genetic, environmental and demographic risk factors [1–4]. In recent years, there has been growing evidence that inflammatory processes, including dysregulation of the complement system, play a major role in the pathogenesis of AMD. The discovery of genetic poly-

morphisms in genes coding for complement proteins that affect patients' susceptibility to AMD propelled research into establishing the complement system as a key component in the pathogenesis of AMD [1–5].

However, translation from the bench to the bedside is a complex process, and our understanding of the role of the complement system in AMD is still at a distance from the bedside. This review aims to discuss the significance of the complement system for the pathogenesis of AMD, and the resulting implications for current and future clinical application.

First, a brief overview of the complement system is provided, along with evidence of its role in AMD pathogenesis. *Second*, the clinical relevance of polymorphisms of the complement genes is addressed. This includes associations of the genetic variants with alterations of complement activation or with certain AMD subtypes, as well as their possible influence on AMD progression, response to treatment (pharmacogenetics), or interference with known modifiable risk factors for AMD (gene-environment interaction). *Third*, we summarize approaches that might provide us with future treatment options.

The complement system and its role in AMD pathogenesis

Based on specificity and immediacy, immune processes have been discerned into two main effector systems. Both, the adaptive and the innate immune system are tightly interconnected. The adaptive immune system is built around B- and T-lymphocytes which allow antigen-specific recognition and immunological memory. In contrast, the innate immune system acts less specifically but more instantaneously. One of its main effectors is the complement system, which encompasses more than 30 plasma proteins with a combined concentration of more than 3 g/l [6, 7]. The evolutionary preservation of this ancient immune system is a reflection of its biological importance for the integrity of the organism [6].

The complement system can be activated via three different pathways: the classic, lectin or alternative pathway.

In each, a proteolytic cascade is amplified and eventually leads to the activation of a central protein, C3. Downstream from C3 activation, the effectors of the complement system may be classified as anaphylatoxins (C3a, C5a; leading to inflammation), the membrane attack complex (MAC; leading to cell lysis), and opsonins (leading to opsonization).

The classic pathway is activated when the complement protein C1q binds to antibodies attached to antigen. In contrast, the lectin pathway uses pattern recognition receptors (PRRs) such as mannose-binding lectin (MBL) to recognize pathogen-associated molecular patterns (PAMPs). The alternative pathway of complement (APC) will be described in greater detail, as current evidence suggests that it is the most important in relation to the pathogenesis of AMD. For more in-depth information on the complement system, the reader is referred to excellent reviews [6, 7].

The APC (Fig. 1) is initially activated by a constant low-level spontaneous hydrolysis of C3. Binding of C3 to factor B allows factor D to cleave factor B into Ba and Bb. One of the resulting products, C3bBb, is a C3 convertase that initiates an amplification loop, producing more C3b and C3a from C3. Uncontrolled activation of the APC would lead to self-tissue damage. Therefore, regulators are necessary to prevent the inappropriate activation and action of the APC [6]. Such regulators may accelerate the decay of preformed C3 convertases, e.g., decay-accelerating factor (DAF; CD55), complement receptor 1 (CR1), complement factor H (CFH), or prevent convertases to form by degrading their constituents such as C3b [6]. The latter is a function of factor I, which requires other complement regulators (CR1, CFH, membrane cofactor protein [MCP; CD46]) as cofactors. Both processes ultimately limit further complement activation. Other regulators may inhibit MAC-mediated cell lysis (CD59, vitronectin, S protein) or may cleave anaphylatoxins (carboxypeptidase N, B and R). The regulators of complement may further be classified as cell-bound (e.g., MCP, CR1, DAF, CD59) or as being located in the fluid phase (CFH, vitronectin, S protein). CFH is the most important regulator of the latter group.

Fig. 1 Proteins of the alternative complement cascade are typed in *black* (see text). In *red* font are therapeutic agents currently in clinical trials. For further explanation of the therapeutic agents, see main text
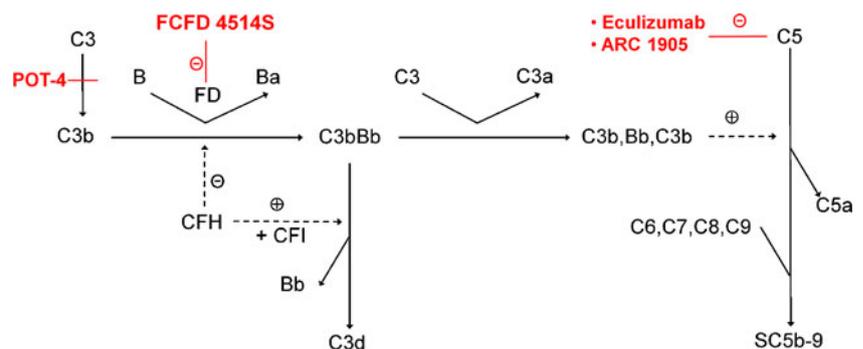
Evidence for involvement of the complement system
in AMD pathogenesis

There are currently three separate lines of evidence from
human studies that support the involvement of the
complement system in AMD pathogenesis (Fig. 2):

- Immunohistochemical and proteomic studies in donor eyes
- Genetic association studies
- Studies of complement protein levels in peripheral blood

The first line of evidence derives from immunohisto-
chemical detection of proteins of the complement
cascade, its regulators and other inflammatory markers.
These were increased in donor eyes from AMD patients
compared to controls and characteristically localized in
drusen, the hallmark clinical finding of early AMD [5,
8–13]. Further supporting evidence came from a quanti-
tative proteomics analysis of the macular Bruch's mem-
brane/choroid complex. In AMD donor eyes, many
complement proteins were elevated compared to control
eyes [14]. Complement proteins such as CFH are also
present in normal eyes [15], and may therefore have a
physiological function. The disease-associated variant of
CFH was shown to have a lower affinity to Bruch's
membrane [16], which might lead to an uncontrolled and
thus increased local activation of the alternative comple-
ment cascade.

Evidence for a genetic component of AMD susceptibility
arises from twin and family studies that have consistently
shown increased susceptibility in individuals with positive
family history [17–23]. In 2005, genetic association studies
revealed significant associations of polymorphisms in the
complement factor H (CFH) gene with an increased or
decreased risk for AMD [15, 24–26]. The significance of

the complement system was further substantiated by the
identification of additional genes coding for proteins of the
complement system and their association with an increased
or decreased risk to develop AMD. These include genes
coding for complement factor B/C2 (CFB) [27–29], C3
[30–32], factor I (FI) [33, 34], and CFH-related proteins 1
and 3 [35, 36]. The associations between these variants and
AMD, however, appear to be substantially weaker than for
variants in CFH. A large number of independent studies
have since consistently confirmed the association of AMD
with risk-modifying complement gene polymorphisms. For
a more in-depth discussion of genetic AMD susceptibility,
the reader is referred to other recent thorough reviews [1,
37–40].

The third line of evidence derives from studies of blood
complement protein levels. The data show that AMD
patients have increased systemic complement activation as
measured in peripheral blood (see next section) [41–43].

The evidence from human studies is supported by a large
number of in vitro and animal studies. Notably, subsequent
functional in vitro analysis provided evidence for a
biological relevance of CFH variants. The altered protein
structure of the CFH Y402H "at risk" variant results in a
decreased binding affinity to target molecules such as C-
reactive protein and heparin to cell surfaces and Bruch's
membrane [16, 44–50]. In contrast, the protective CFH
V62I variant has been found to be a stronger inhibitor of C3
convertase formation [51]. Furthermore, it has been shown
that constituents of lipofuscin, the accumulation of which is
part of the disease process in AMD, may activate
complement [52]. Also, smoking as well as a low-grade
immunoresponse against carboxyethylpyrrole (CEP)
adducts that accumulate in the subretinal space may result
in complement activation at the ocular fundus in mouse
models [53, 54]. The transcriptional profiles of the RPE/

Fig. 2 Three lines of evidence
from human studies supporting
involvement of the complement
system in the pathogenesis of
age-related macular degeneration.
An increased local (demonstrated
by immunohistochemical) and
systemic (demonstrated by
plasma protein studies) comple-
ment activation may be due to a
genetic risk profile, and is
possibly affected by various
additional factors
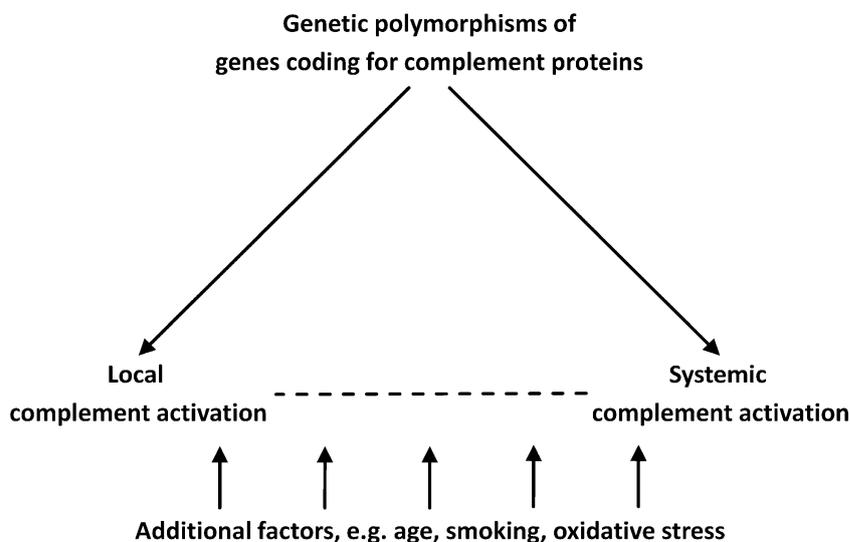
choroid complex in aged (compared to young) mice showed a marked increase in proteins of the complement pathway [55]. Thus, major risk-conferring factors for AMD development, such as oxidative stress, ageing and smoking, have been linked to an activation of the complement system. Moreover, the RPE physiology is affected by complement activation, and the RPE is also capable of modulating its own complement protein production, suggesting that RPE cells may play an important role in regulating complement activation in the retina [56–59]. A *CFH-/-* mouse model has been described which develops a retinal phenotype in old age [60].

Clinical relevance of variations of complement genes

Systemic complement activation in AMD patients

Immunohistochemical studies on AMD donor eyes and data from genetic studies suggest that AMD pathogenesis involves mainly the APC. This led to the hypothesis that the relevant genetic polymorphisms, if biologically meaningful for AMD pathogenesis, would result in measurable differences in the activation status of the complement cascade. Indeed, the first study that comprehensively assessed plasma concentrations of APC proteins in AMD patients and controls found higher levels of activation products in the AMD cohort [41]. Specifically, all tested activation products (Ba, C3d, MAC, C3a, C5a), especially the markers of chronic

complement activation (Ba and C3d; $p<0.001$), were significantly elevated. Similar alterations were observed in the activating regulator factor D, but not in C3, C4 or CFH. The increased concentration of protein markers of the APC correlated with CFH haplotypes in patients and controls, suggesting a genetically controlled activation of the APC. A subsequent study in a larger independent cohort of patients and controls essentially confirmed these results, showing that both plasma protein levels and genetic markers were individually predictive of having AMD [43]. A one standard deviation change in levels of complement substrate (factor B), regulator (factor D), and activation products (Ba and C3d) was associated with an approximately 5-fold increase in AMD risk (Fig. 3).

Support for these observations comes from biochemical in vitro studies already mentioned, which may explain the variable concentration of activation products downstream from CFH due to a difference in biological activity related to the CFH variant. The study by Hecker et al. furthermore revealed an association of complement activation with genetic polymorphisms in *CFB*, and suggested that activation of the APC in blood increases with age [43]. A trend was observed for greater increases in plasma protein levels of factor D, factor B, Ba and C3d in advanced subtypes of AMD, suggesting that complement activation in the blood could be associated with progression of AMD. A third study focussing on patients with advanced AMD also found an increased complement activation in AMD patients: studying a slightly different set of complement proteins,

Fig. 3 Prediction of AMD and impact of plasma complement levels on AMD risk. Shown are the odds ratios for each combination of a one standard deviation change in plasma levels of factor D, factor B, C3d, and Ba on the risk to develop AMD relative to a reference group (R) having mean levels of all four proteins. Numbers on the x and y axes represent standard deviation changes above (1), changes below (−1), and at the mean (0) of the corrected and standardized plasma levels for each protein. From Hecker et al. [43]; by permission of Oxford University Press
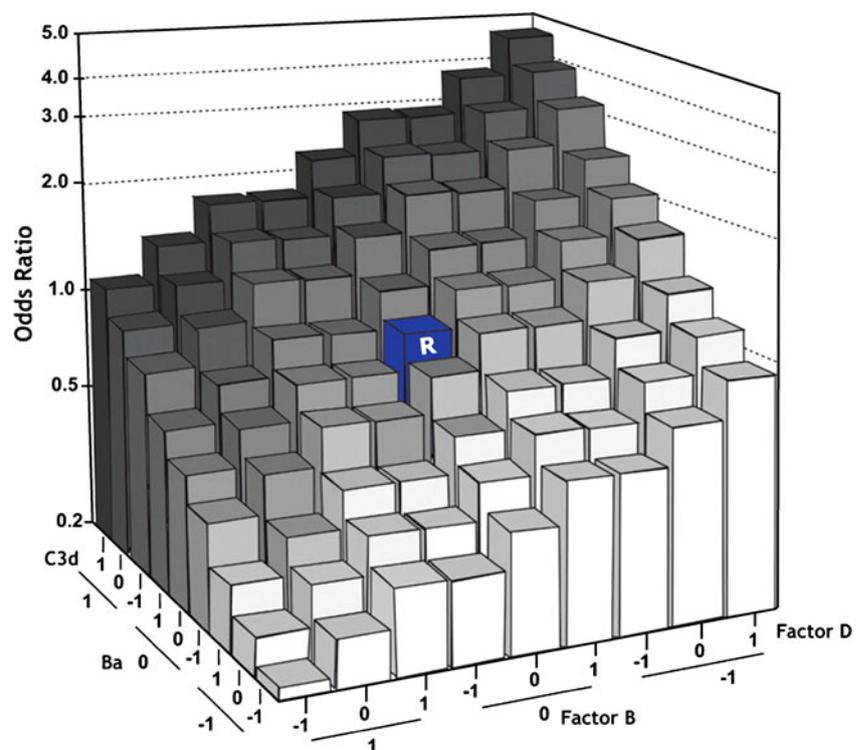
Reynolds and co-workers found an increased plasma concentration of C5a and Bb, independent of genotype. The group had also found decreased CFH plasma concentration in patients with geographic atrophy, a finding not reported by the two other studies. Furthermore, the study provided evidence for an association of increased body mass index with complement activation fragments [42].

Further support for the suggested association between abnormal complement activation and AMD came from a large case control study that revealed an association of AMD with diseases known to be associated with systemic complement activation [61]. AMD patients were found to have systemic lupus erythematosus (confounder adjusted OR=1.83) and glomerulonephritis (adjusted OR=1.46) more often than controls. Moreover, patients with membranoproliferative glomerulonephritis (MPGN) type 2, a disease with uncontrolled complement activation [62], may show a phenocopy of the retinal findings, such as drusen, that are usually observed in patients with AMD [63–66].

Notably, these studies provide a rationale for future clinical trials that aim at a systemic modulation of complement activation in order to prevent AMD. However, evidence available so far relates to the link between complement activation and the risk to develop the disease. Currently, there is no evidence from human studies that complement activation is still pivotal when late forms of AMD have already developed.

Complement gene variants and AMD subtypes

To date, none of the associated complement gene variants have shown a clear pattern of preference for the development of either choroidal neovascularisation (CNV) or geographic atrophy [67–71]. This may suggest that complement variants are equally important for the development of both forms of late AMD, and additional genetic and/or environmental factors may be required to determine if either geographic atrophy or CNV develops. It remains conceivable that all previous studies have not been sufficiently powered in order to detect an effect, in that most studies are biased towards CNV patients. Further studies have analyzed a potential correlation between the CFH-risk allele Y402H and specific subtypes of neovascular AMD [72–75]. Due to the heterogeneous results in those studies, clear conclusions with regard to a preferential occurrence of classic or occult neovascular membranes can currently not be drawn. Possibly, severity and age of onset of neovascular membranes in AMD patients may be influenced by the genetic background, as suggested by Leveziel et al. [76]. Shuler et al. analyzed phenotypic characteristics in a cohort of 956 AMD patients, and identified only peripheral reticular pigmentary change as a phenotypic feature associated with the common Y402H risk variant [71].

The phenotype of basal laminar drusen ("cuticular drusen") is similar to, yet distinct from AMD. Basal laminar drusen have also been shown to be associated with CFH variants [66]. The Y402H variant may be present in up to 70% of patients with basal laminar drusen [77], which is higher than usually observed in populations with typical AMD. Early-onset basal laminar drusen were reported to be associated with heterozygous nonsense, missense or splice-variants of CFH in combination with the Y402H variant [78].

Polypoidal choroidal vasculopathy (PCV) has been described as a separate clinical entity differing from neovascular AMD and other diseases associated with subretinal neovascularization [79], and it remains controversial as to whether or not PCV represents a sub-type of neovascular AMD [80]. Patients with PCV tend to be younger, the disease is more prevalent in Oriental races, and eyes with PCV lack drusen as a characteristic sign of early AMD. In a comprehensive examination of the CFH gene, Kondo and co-workers found a strong association with the I62V variant in a cohort of 130 Japanese PCV patients [81]. Notably, they found no significant association of the Y402H variant with PCV, which contrasts with its marked effect on AMD susceptibility in Caucasians. Similar conclusions were derived from a study by Lee et al. in a Chinese population [82]. However, a recent and better powered study (408 patients with typical AMD, 518 patients with PCV, 1,351 control samples) also identified an association of PCV with the Y402H allele in addition to the association with the I62V variant [83]. Gotoh et al. found no difference in incidence of the CFH Y402H genotype between patients with exudative AMD and PCV, and a recent study on a Caucasian population with PCV and AMD also suggested that both diseases are genetically similar on the CFH and CFB/C2 locus [84]. The latter study included the Y402H but not the I62V variant. These genetic studies provide evidence for a similar pathogenetic background of the two phenotypically similar diseases, namely an involvement of the complement system. Different polymorphisms may have different functional consequences on the protein level, and might at least in part account for the different phenotype. The eventual disease phenotype may furthermore be determined by additional genetic and/or environmental factors. Only few data are available on the association of retinal angiomatous proliferation (RAP) with polymorphisms in genes coding for complement proteins. In a Japanese population, a correlation with RAP was found for the CFH I62V variant but not for the Y402H variant [83], while in an Austrian population, an association of RAP was found for the Y402H variant [72].

Complement gene variants and progression of AMD

In two independent cohorts, Magnusson and co-workers showed that the Y402H variant conferred a similar risk of

early and late AMD [68]. Also, Farwick and colleagues reported the *CFH* variants to be significantly related to the development of early but not with progression to late AMD [85]. This suggested that additional factors may be required to explain disease progression. However, data from the population-based Rotterdam study revealed an increasing odds ratio with more progressed disease stages [86], and two further studies found an increased risk to progress from early to later disease stages in patients with the *CFH* [87–89] and *C3* [89, 90] risk genotypes. Results for the *C2/CFB* locus were inconsistent, possibly due to different single nucleotide polymorphisms (SNPs) tested [89, 90].

It should be noted, however, that none of these studies has addressed the question of whether genetic variants are associated with disease progression once late AMD has developed. Nevertheless, it is the progression of the two late forms, geographic atrophy and choroidal neovascularisation, which are probably the most important with regard future therapeutic intervention. This issue was recently addressed in a longitudinal association study investigating variants in *CFH*, *C3* and *ARMS2*, and progression of geographic atrophy in a large cohort of AMD patients with pure bilateral geographic atrophy [91]. It was found that all genetic risk variants were strongly associated with the risk of developing geographic atrophy, whereas there was no association with disease progression once geographic atrophy had already developed. It is suggestive that other susceptibility factors may influence disease progression in geographic atrophy [91]. This was very recently confirmed in a study of Klein et al. where — at least for variants in the complement genes — there was no association with the progression of geographic atrophy [92].

Gene-environment interaction: nutrition, supplementation and smoking

The only protective factor for AMD known to date are antioxidants. The randomized clinical Age-Related Eye Disease Study (AREDS) showed that a combination of zinc, β-carotene, vitamin C, and vitamin E reduced the risk of progression from intermediate to advanced AMD by 25% [93]. There is also preliminary evidence of a protective effect of omega-3 fatty acids [94–96].

Data on the interaction between nutrition or supplementation and genetic variants in regard to the risk to develop AMD has been limited, but recently two large studies, the Age-Related Eye Disease Study (AREDS), being clinic-based, and the Rotterdam study, being population-based, provided evidence for an interaction.

In the AREDS, Klein and co-workers studied a subset of 876 participants who were considered at high risk of progressing to advanced AMD [97]. They found a treatment interaction of the *CFH Y402H* polymorphism

with the AREDS medication. Interestingly, supplementation resulted in a 68% reduction in the rate of progression in the subgroup with the homozygous non-risk genotype, compared to a reduction of only 11% in the subgroup with the homozygous risk genotype. Thus, the data suggest reduced benefit of AREDS supplementation for patients with the *CFH Y402H* risk genotype. Further sub-analysis found the genotype–treatment interaction to be explained by the zinc component, since an interaction was observed in the groups taking zinc versus those taking no zinc, but not for groups taking antioxidants compared with groups taking no antioxidants. No significant *CFH* genotype–treatment interaction effects on progression were observed when the analysis additionally included patients with an earlier disease stage (AREDS category 2) [87].

Conflicting results were recently reported by Ho et al. investigating 2,167 individuals from the Rotterdam Study at risk of AMD [98]. They assessed biological interaction with genetic variants by calculating the synergy indices. In a mean follow-up period of 8.6 years, 517 participants developed early AMD. Significance of the synergy index supported the possibility of biological interaction between *CFH Y402H* and zinc, β-carotene, lutein/zeaxanthin, and eicosapentanoic/docosahexaenoic acid (EPA/DHA). Homozygotes for *CFH Y402H* with dietary intake of zinc in the highest tertile reduced their hazard ratio of developing early AMD from 2.25 to 1.27. For intakes of β-carotene, lutein/zeaxanthin, and EPA/DHA, these risk reductions were from 2.54 to 1.47, 2.63 to 1.72, and 1.97 to 1.30, respectively [98].

The discrepancies between the two studies may be explained by the different design: AREDS is clinic-based, and thus the study population is affected by early or late AMD at baseline, whereas the cohort of the Rotterdam study consisted of participants without any sign of AMD. Consequently, the outcome event was different: for AREDS it was the progression from early to late AMD or from unilateral to bilateral late AMD, whereas in the study of Ho et al. it was incident early AMD.

Smoking is by far the strongest environmental risk factor of AMD susceptibility. Smoking increased the risk of AMD additive to the genetic predisposition due to variants in the CFH gene [86, 99–101]. Smoking as well as an increased body mass index (BMI) were independently related to advanced AMD, controlling for the genotype [70]. Smoking and having the *CFH 402H* variant independently increase risk of neovascular AMD [102, 103]. Smoking increased the odds of disease progression due to the *CFH* [87, 89] and other genetic risk variants [89]. Smoking was independently related to AMD, with a multiplicative joint effect with genotype on AMD risk [89]. Therefore, there appears to be no interaction between smoking and *CFH* genotypes.

Variations of complement genes and response to treatment: pharmacogenetics

Intravitreal injections of vascular endothelial growth factor (VEGF)-A inhibitors have recently revolutionized the therapy of neovascular AMD [104]. There are, however, surprisingly few data on the interaction of treatment effect and genetic variants. A retrospective analysis of 86 patients treated with intravitreal bevacizumab revealed a significantly worse visual acuity outcome in patients with the CFH Y402H risk genotype (CC) compared with those with the TC and TT genotypes [105]. The same researchers retrospectively investigated the pharmacogenetic interaction between CFH variants and the treatment effect of ranibizumab [106]. In their cohort of 156 patients, there was no effect for the primary outcome measure, visual acuity. However, the data suggested that patients homozygous for the Y402H risk allele may have a higher risk of requiring more ranibizumab injections. The authors hypothesized that the higher inflammatory activity found in genetically predisposed patients could favor recurrence of neovascularization or reduce its response to anti-VEGF treatment. Obviously, further studies are needed to explore significant interaction between genetic variants and anti-VEGF-A treatment effects.

Several studies assessed a potential association between the CFH Y402H genotype and response to photodynamic therapy (PDT) [107–110]. The largest study included 273 patients treated with PDT and a median follow-up time of 19.8 months. There was no significant difference in genotype distribution between a PDT-positive and a PDT-negative response group (the latter being defined as visual acuity of <6/60 or loss of 3 lines of vision at final visit) [109]. Similar results were presented in a Finnish study with 88 participants [111]. There was also no significant difference in number of PDT treatments needed depending on genotypes. Two smaller studies with shorter follow-up times suggested either a worse [107] or a better [108] outcome (visual acuity) in the patient group homozygous for the CFH Y402H risk allele. A recent study from Japan found an association of CFH variants with the mean time interval from the initial treatment to the time of recurrence [110]. These overall conflicting results may simply be due to limitations in statistical power.

It is likely that pharmacogenetic studies will play a more important role when testing compounds that target and modulate the complement system. AMD patients with "at-risk" genotypes might be more responsive to such interventions and therefore, specific genetic markers will probably impact on a meaningful allocation of specific treatments. As an alternative to genetic testing, protein-based methods have now been developed that make it possible to distinguish CFH risk variants in plasma [112, 113].

Emerging pharmacological intervention

Since the link between complement activation and AMD susceptibility has unequivocally been established, modulation of the complement system appears to be a reasonable strategy for reducing the risk of developing AMD, for preventing progression from early to late forms of AMD, for treating late AMD, or for optimizing currently available treatments such as VEGF-A inhibition.

Several compounds are currently in phase 1 or 2 clinical trials (see Fig. 1; clinicaltrials database accessed August 4, 2010).

POT-4 (Potentia Pharmaceuticals/Alcon) is an analogue of the small cyclic synthetic peptide compstatin, an inhibitor of the central complement protein C3. A sustained release formulation aims at providing therapeutic drug concentrations for several months after intravitreal injection. A prospective, uncontrolled, non-randomized, dose-escalating, pilot phase 1 safety study in AMD patients with subfoveal CNV has been completed (ClinicalTrials.gov Identifier: NCT00473928).

Eculizumab (Soliris®, Alexion Pharmaceuticals) is a monoclonal antibody inhibiting C5. The drug is approved as systemic treatment for paroxysmal nocturnal hemoglobinuria (PNH), a disease characterized by the absence of CD59 expression of erythrocytes. Eculizumab is currently being investigated in a phase 2 trial (ClinicalTrials.gov Identifier: NCT00935883) in patients with non-exudative AMD (drusen or geographic atrophy). In the randomized, double-arm, double-masked study, patients receive the drug via an intravenous infusion. Primary outcome measures are the growth of geographic atrophy and the change in drusen volume, respectively.

ARC1905 (Ophthotech Corporation) is an anti-C5-aptamer that is injected intravitreally with currently two registered phase 1 clinical trials. ARC1905 is meant to bind C5 to prevent its interaction during activation of the complement cascade. In one clinical trial, ARC1905 is used for neovascular AMD in combination therapy with either multiple doses or with only one induction dose of intravitreal ranibizumab in a non-randomized, open-label, uncontrolled, safety study (ClinicalTrials.gov Identifier: NCT00709527). The second trial (ClinicalTrials.gov Identifier: NCT00950638), a randomized, open-label, dose comparison study, aims at elucidating the safety profile of intravitreal ARC1905 application in dry AMD (drusen and/or geographic atrophy).

FCFD4514S (Genentech / Roche) is an anti-complement factor D antibody fragment that is injected intravitreally. Similarly to ARC1905, its safety is currently in evaluation in a phase 1 trial in patients with dry AMD (geographic atrophy; ClinicalTrials.gov Identifier: NCT00973011).

Several other compounds are currently being tested in a pre-clinical phase that aims either at inhibiting the effect of

activated complement proteins or at normalizing an increased activation of the complement cascade.

Conclusions

There is strong evidence from human immunohistochemical, genetic and proteomic studies supporting a major role of the complement system in AMD pathogenesis, and this is further supported by a large number of in vitro and animal studies. Genetically controlled systemic complement activation may have a major impact on the macula as a "locus minoris resistentiae". Moreover, altered complement proteins may have specific local effects such as an impaired control of complement activation at the level of the RPE and Bruch's membrane.

Therapeutics that aim at modulating processes of the complement cascades will need to balance the beneficial effects of inhibition with the preservation of sufficient functional activity for immune responses and tissue homeostasis [114]. This appears most important in chronic diseases such as AMD where long-term treatment appears essential to prevent vision loss due to conversion from early into late disease stages. Ideally, the pharmacological effect would act on the key dysregulated elements of AMD pathophysiology, leaving the remaining complement system largely unaffected.

There is still a lack of knowledge about the impact of individual elements of the complement system on AMD development, phenotypic variability and progression. It would be desirable to target mechanisms that are involved in disease progression and not merely in disease susceptibility. Moreover, there is as yet insufficient evidence to determine if dysregulation of either the systemic or the local complement components or both are the major contributors in AMD pathogenesis. Such knowledge would probably affect the preferred route of drug administration. A more detailed summary on potential and current strategies of therapeutic complement inhibition is provided elsewhere [114, 115].

Due to the rather low yearly progression rate from early to late AMD stages, large patient cohorts may have to be studied over many years to detect a prophylactic effect of any intervention on conversion rates to late disease stages. The AREDS has shown that early AMD patients with a high risk of progression must be identified to provide sufficient power to detect a prophylactic effect.

In emerging treatment trials, adequate disease monitoring will be essential. Compounds targeting the complement system might be most beneficial in early AMD stages where treatment effects are likely to be subtle. Biomarkers such as drusen volume have not been unequivocally qualified as meaningful surrogate endpoints. Thus, high resolution multi-modal functional and/or morphological assessment strategies may be needed in order to identify and correctly interpret possible treatment effects [116].

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