Chapter 2
The Role of Complement in AMD

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Abstract  Age related macular degeneration (AMD) is a common form of blindness in the western world and genetic variations of several complement genes, including the complement regulator Factor H, the central complement component C3, Factor B, C2, and also Factor I confer a risk for the disease. However deletion of a chromosomal segment in the Factor H gene cluster on human chromosome 1, which results in the deficiency of the terminal pathway regulator CFHR1, and of the putative complement regulator CFHR3 has a protective effect for development of AMD. The Factor H gene encodes two proteins Factor H and FHL1 which are derived from alternatively processed transcripts. In particular a sequence variation at position 402 of both Factor H and FHL1 is associated with a risk for AMD. A tyrosine residue at position 402 represents the protective and a histidine residue the risk variant. AMD is considered a chronic inflammatory disease, which can be caused by defective and inappropriate regulation of the continuously activated alternative complement pathway. This activation generates complement effector products and inflammatory mediators that stimulate further inflammatory reactions. Defective regulation can lead to formation of immune deposits, drusen and ultimately translate into damage of retinal pigment epithelial cells, rupture of the interface between these epithelial cells and the Bruch’s membrane and vision loss. Here we describe the role of complement in the retina and summarize the current concept how defective or inappropriate local complement control contributes to inflammation and the pathophysiology of AMD.

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1 Age-Related Macular Degeneration

1.1 The Disease

Age related macular degeneration (AMD) is the leading cause of blindness in the elderly population, especially in the Western World. Today, more than 20 Mio individuals over 50 years of age show early signs of this sight-threatening disease (Congdon et al. 2004; Pascolini et al. 2004). The actual demographic development predicts an increase in the number of elderly people and thus a higher number of people at risk by about 50 % (Friedman et al. 2004).

In the early stage of the disease immune deposits, which are termed drusen, develop between the Bruch’s membrane (BM) and adjacent retinal pigment epithelial cell (RPE) layer (Bird et al. 1995). Ongoing progression of the inflammatory reactions and the disease enhances size and the number of drusen and result in two severe forms: geographic atrophy (GA) leads to death of macula surrounding photoreceptors that overly degenerated RPE cells. Choroidal neovascularisation (CNV) is characterized by the growth of blood vessels into the retinal layer which leak fluid or bleed. Both forms result in a complete loss of central vision (de Jong 2006).

AMD is a multifactorial disease which is caused by several genetic factors, by environmental factors and disease susceptibility is also influenced by age and ethnic background (Vingerling et al. 1995; Klein et al. 2004).

1.2 AMD: A Chronic Inflammatory Disease

The pathogenesis of AMD is subject of intensive research and recent reports showed that early as well as advanced stages of AMD are caused by defective complement activation and local inflammation (Johnson et al. 2001). At present additional concepts for AMD pathophysiology are discussed, which however are not exclusive to the initial complement and inflammation hypothesis. These explanations are based on inefficient or defective transport/diffusion of nutrients from the choroids via the Bruch’s membrane to the photoreceptors, or inappropriate reverse transport of waste products from photoreceptors to the choroids (Zarbin 1998). Consequently debris may accumulate along the interface of the RPE cells and the Bruch’s membrane, providing an activator surface that allows complement activation. Also in this concept defective or inefficient complement regulation may cause further amplification of the complement cascade and inflammation. Both concepts may explain how inappropriate control and inhibition of spontaneous or triggered complement activation causes progression and amplification of the complement cascade and consequently the generation of inflammatory activation compounds in form of C3a and in particular of the potent inflammatory marker C5a (Scholl et al. 2008). If low level complement activation persists over weeks, months and even years, already a minor change in the composition of one regulatory component may
cause deregulation and damage. This continuous imbalance can then progress into pathophysiology, in manifestation of drusen and degeneration of the RPE cell layer and of the overlying photoreceptors.

AMD is associated with complement activation or deregulation of the spontaneously initiated alternative complement pathway leading to local release of inflammatory activation products and to local inflammation, which relate to the pathogenesis of the disease (Donoso et al. 2006). This concept is further confirmed by immunohistochemical analyses and proteome assays, which identified proteins and components associated with complement activation and inflammation in drusen. Multiple complement components, regulators, complement activation products and inflammatory proteins are identified in drusen, including C3, C3d, the terminal components C5, C6, C7, C8 and C9, terminal complement regulators vitronectin and clusterin, apolipoproteins apoA1, apoA4 and apoE as well as thrombospondin, serum amyloid A (SAP-A) and SAP-P (Anderson et al. 2002; Crabb et al. 2002; Li et al. 2006a). This composition demonstrates the association of complement and complement regulators in the process of drusen formation and likely also in the associated inflammatory reactions. The activated complement systems triggers further events and which ultimate cause formation of drusen, cell damage of the RPE cells and visual loss (Hageman et al. 2001).

Most or all of these proteins that are identified by immunohistochemistry and proteome analyses are expressed locally, e.g. by RPE cells and are present in the choroids. Thus explaining or confirming a local role of complement and inflammation in the pathogenesis of AMD. Immunohistochemical analyses also identified the inflammatory marker C-reactive protein (CRP) in drusen and in deposits formed along the Bruch’s membrane (Anderson et al. 2002; Laine et al. 2007; Skerka et al. 2007). Based on immunoblot assays the local level of C-reactive protein (CRP) in the choroidal stroma was about 2.5-fold higher in individuals with the Factor H risk variant (Johnson et al. 2006). These increased CRP levels in the choroids of individuals at risk are indicative for a chronic inflammation. Upon inflammation, infection or tissue damage CRP plasma levels increase substantially, from minimal, undetectable levels to plasma concentrations of more than 500 mg/l (Pepys and Hirschfield 2003). CRP, is a member of the pentraxin protein family and this 125 kDa is composed of five identical subunits, which are stabilized by calcium ions (Volanakis 2001; Casas et al. 2008). In addition a monomeric 25 kDa form of CRP exists (Potempa et al. 1987; Ji et al. 2007; Mihlan et al. 2009). The exact biological functions of pCRP and mCRP are currently unclear.

2 Age-Related Macular Degeneration: A Genetic Disorder

Population based analyses, twin studies (Hammond et al. 2002; Seddon et al. 2005) and familial aggregation analyses (Seddon et al. 1997) suggested that AMD is a heritable disease and that the majority of late AMD cases has a specific genetic background. Over the last years evidence accumulated that AMD is caused by
genetic factors. Initiated by the Human Genome Project in 2005, four independent genome-wide linkage studies identified two major chromosomal loci that confer major risk for this retinal disease and that account for approximately 50% of cases (Edwards et al. 2005; Haines et al. 2005; Klein et al. 2005; Rivera et al. 2005). One chromosomal region is located in human chromosome 1q31, which includes the Factor H gene cluster, and the second region is located on human chromosome 10q26 which covers the two closely located genes ARMS2 (age-related maculopathy susceptibility 2) and HTRA1 (high-temperature required factor A1) (Dewan et al. 2006; Yang et al. 2006).

The region on human chromosome 1q31 includes the gene representing the complement regulator Factor H and the five CFHRs (Complement Factor H Related genes) CFHR1 to CFHR5 (Rodriguez de Cordoba et al. 2004). Within the Factor H gene numerous relevant single nucleotide polymorphisms (SNPs) were identified by SNP genotyping, including regions within the promoter-, the coding- and also within the non coding intronic regions (Li et al. 2006b). The major risk variant SNP rs1061170 is located in exon 9, and translates on the protein level at position 402 of both Factor H and FHL1 in the exchange of the amino acid tyrosine (Y) to the risk variant histidine (H). The H402 variant increases the risk for AMD about twofold to fourfold for heterozygote cases and about threefold to sevenfold for homozygote individuals. Subsequent genetic studies confirmed the high association of the Y402H polymorphism in population and different ethnic groups worldwide (Souied et al. 2005; Okamoto et al. 2006; Seitsonen et al. 2006; Simonelli et al. 2006), and revealed that the H402 risk variant confers a similar risk for development of drusen, and the two severe forms of GA and CNV (Magnusson et al. 2006). Additional SNPs associated with exudative age related macular degeneration were identified in the promoter region of Factor H (position -257; SNP rs3753394); in exon 2, resulting in the exchange at residue 62 of isoleucine (I) to valine (V) (I62V; SNP rs800292), in exon 7 changing the codon but maintaining the alanine (A) residue (A307A; SNP rs1061147) and two which are located within the intervening sequence between exon 15 and exon 16 (SNPs rs380390 and rs1329428) (Chen et al. 2006).

A Chromosomal deletion of a 84-kbp fragment directly downstream of the Factor H gene, that includes the genes coding for CFHR1 and CFHR3 has a protective effect in AMD (Hughes et al. 2006; Spencer et al. 2008a; Schmid-Kubista et al. 2009). Case control studies revealed the complete absence of both genes comprise 0.8–1.1% of cases and 2.6–5.7% of the age-matched controls (Hageman et al. 2006).

Additional complement genes associated and linked to AMD include the classical pathway component C2, as well as the alternative pathway protein Factor B which are both located in close arrangement on human chromosome 6p21 (Gold et al. 2006). The L9H and R32Q variant in Factor B are in nearly complete linkage disequilibrium with the E318D or rs547154 SNP9 in intron 10, respectively of C2. All four polymorphisms are highly protective for AMD. In addition a common polymorphism, i.e. rs2230199 in the C3 gene, which is encoded on chromosome 19p13 is strongly associated with AMD (Yates et al. 2007; Spencer et al. 2008b). This variation of C3 that results on the protein level in an arginine (R) to glycine (G) exchange
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at position 102 (R102G) increases the risk for AMD about twofold for heterozygote and about threefold for homozygote individuals. The association of complement genes in the pathogenesis of AMD further strengthens the concept that the human complement system is involved in the pathogenesis of AMD (Fig. 1).

The second disease associated locus on human chromosome 10q26 includes two separate genes. ARMS2 (also termed LOC387715) which encodes a hypothetical protein. The AMD-associated SNP rs10490924 on exon 1 of the ARMS2 gene reveals an estimated risk of 2.6 for heterozygous and 7.0 for homozygous individuals (Rivera et al. 2005). The SNP results in a non-synonymous A69S alteration in the corresponding protein (Fritsche et al. 2008). Recent studies confirmed that this polymorphism in the ARMS2 gene is highly associated with AMD. The second high-susceptibility gene within the 10q26 region comprises the SNP rs11200638 within the HTRA1 gene that is suggested to present a promoter variant of the heat shock serine protease (Dewan et al. 2006; Yang et al. 2006).
3 Effect of the Reported SNPs for Protein Function

3.1 Factor H and Other Complement Proteins

The genetic associations summarized above demonstrate that Factor H, FHL1, CFHR1, CFHR3, C2, Factor B and C3 are involved with AMD development and they show that complement plays a key role in the disease. Obviously sequence exchanges in complement genes and in the encoded complement proteins and regulators disturb the delicate balance of complement activation vs. inhibition and result in activation and inflammation (Zipfel and Skerka 2009).

3.1.1 Factor H and FHL1

The human Factor H gene encodes two proteins, Factor H, which is composed of 20 SCR domains, and the Factor H-like protein (FHL1) (Zipfel and Skerka 1999; Jozsi and Zipfel 2008). FHL1 is derived from an alternatively spliced transcript and the secreted protein is composed of the first seven N-terminal domains of Factor H including codon 402 in SCR 7 and exhibits a unique C-terminal extension of four amino acids (Misasi et al. 1989). Both Factor H and FHL1 are complement regulators that act on the level of C3 convertase and control formation and fate of C3 and C3 convertase C3bBb (Pangburn et al. 1977; Kuhn and Zipfel 1996). Both regulators have multiple binding sites for C3b, Heparin, C-reactive protein (CRP) and binding sites for cellular and biological surfaces. In this context SCR 7 mediates binding to heparin, cell surfaces and CRP (Jarva et al. 1999; Giannakis et al. 2003).

The AMD-associated tyrosine to histidine exchange at position 402 of both Factor H and FHL1 affect the binding intensity to heparin and CRP (Clark et al. 2006; Laine et al. 2007; Sjoberg et al. 2007; Skerka et al. 2007; Yu et al. 2007; Ormsby et al. 2008). The protective variants of both Factor H and FHL1, carrying Y402, bind stronger and the risk variants with H402 bind with lower affinity to their ligands. This differences in binding are explained by the alteration of the distribution of positively charged amino acids by the H402 which are essential for a proper heparin binding over SCR 7 (Prosser et al. 2007; Ormsby et al. 2008). However, differences in heparin affinity of the two allotypes were not reported consistently, what is explained to be glycosaminoglycan specific (Herbert et al. 2007).

The reduced heparin binding of the risk variant translates into lower binding to cellular surfaces, e.g. of RPE cells and results in an inefficient complement regulation at the cell surface (Skerka et al. 2007).

The exchange at amino acid position 402 also affects interaction with the inflammatory marker CRP. Using either intact Factor H, recombinant FHL1 or recombinant fragment SCRs 6–8 the protective variants always showed stronger binding, and the risk variants showed consistently reduced binding to CRP. Individuals who are homozygous for the risk form H402 show 2.5-fold elevated CRP immunoreactivity throughout the choroid and extracellular deposits along the Bruch’s membrane as
demonstrated by immunohistochemistry (Johnson et al. 2006). Conversely, AMD patients that carry the protective Y402 phenotype show lower CRP immunoreactivity in the choroidal stroma, drusen as well as basal deposits. Deposition of CRP in drusen or subRPE deposits is a biomarker for chronic inflammation in RPE/chroid complex (Ross et al. 2007). This suggests that the Y402H polymorphism affects Factor H-mediated CRP function and plays a role in local ocular inflammation and cellular injury of RPE cells provoked by complement activation.

One major function of the activated complement system is to identify and tag modified self-cells such as apoptotic particles and necrotic cells, to allow non-inflammatory clearance (Zipfel and Skerka 2009). CRP marks damaged cells and tissues by binding to constituents such as DNA or phosphocholine that are exposed on injured cells. CRP binds the inhibitor Factor H (Ji et al. 2006a, b). Binding of this central soluble complement regulator is relevant on the surface of apoptotic and necrotic cells. CRP activates the classical complement pathway resulting in formation of the C3 convertase which generates C3b and causes C3b surface deposition and opsonization. However, by binding the inhibitor Factor H further progression of the cascade, amplification, C5 convertase formation and terminal pathway activation is inhibited (Gershov et al. 2000; Mihlan et al. 2009). Recently we showed that the monomeric form of CRP, mCRP binds Factor H and increases Factor H inhibitory action on the surface of apoptotic self cells (Mihlan et al. 2009). Factor H has three binding sites for mCRP and one binding site is located in the AMD-associated SCR 7 of both Factor H and FHL1 (Mihlan et al. 2009). Consequently uptake and removal of apoptotic particles was enhanced and bound Factor H showed a potent anti-inflammatory effect.

Recently also a functional difference was reported for the N-terminal located isoleucin (I) to valine (V) exchange at amino acid position 62 of Factor H and FHL1. The I62 variant is associated with the protective form for AMD and most likely has a higher thermal stability (Hocking et al. 2008). In addition Tortajada et al. showed that the protective I62 variant exhibits an increased affinity for C3b and enhanced cofactor activity in the Factor I-mediated cleavage of fluid phase and surface bound C3b (Tortajada et al. 2009). However in the structural model of the co crystal generated with the N-terminal region of Factor H and C3b, residue 62 in SCR 1 of Factor H is positioned outside the interaction interface of the two proteins (Wu et al. 2009).

3.1.2 Complement Factor H Related Proteins

Deletion of an 84-kbp fragment in the human Factor H gene cluster, which is positioned directly downstream of the Factor H gene has a protective effect for AMD development. The homozygous deletion of the chromosomal fragment results in the complete absence of the two plasma proteins CFHR1 and CFHR3 (Zipfel et al. 2007). CFHR1 is a regulator of both the C5 convertase and of the terminal pathway and thus controls reactions downstream of the C3 convertase, which is controlled by Factor H (Heinen et al. 2009). A CFHR1 related function is proposed for the CFHR3 protein (Hellwage et al. 1999).
CFHR1 and Factor H share almost identical C-termini. The three C-terminal domains of CFHR1 (i.e. SCRs 3–5) and that of Factor H (i.e. SCRs 18–20) show sequence identity of >98% (Skerka et al. 1991). The C-terminal region of Factor H is central for surface recognition and cell binding and this activity is shared by CFHR1 (Jozsi and Zipfel 2008). In consequence CFHR1 and Factor H bind simultaneously to the same sites on the cell surface. In the situation of CFHR1 deficiency more binding sites for Factor H are available and accessible (Heinen et al. 2009) (Fig. 2).

**Fig. 2** Factor H and CFHR1 have identical C-terminal surface binding regions and bind to the same sites on the cell surface. (a) Factor H is composed of 20 SCR domains and CFHR1 by five domains. The three C-terminal SCRs of Factor H and that of CFHR1 (shown in blue color) show almost sequence identity and bind to the same ligands on the cell surface. Both proteins are present in plasma and vitreous fluid and bind simultaneously to the same sites and surfaces. The relevant amino acid exchange at position 402 of Factor H is in domain 7 and is indicated in the Factor H model. (b) Genetic data show that chromosomal deletion of the CFHR1 gene, which results in the absence of CFHR1 in vitreous fluid and in plasma has a protective effect in AMD. In the absence of CFHR1 more binding sites for Factor H are available on the surface of retinal pigment epithelial cells, resulting in increased Factor H binding and in a stronger local protection.

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### 3.1.3 Other Complement Proteins Associated with AMD:

**C2, Factor B and C3**

Polymorphisms in complement component **C2** (E318D) and **Factor B** (L9H, R32Q) are protective for AMD development (Gold et al. 2006). C2 is a component of the classical complement pathway, and Factor B is involved in alternative pathway.
activation. C2 as well as Factor B are expressed in the neural retina, RPE and choroid. Factor B is also identified in ocular drusen. Genetic and functional data suggest that the protective effect is most likely mediated by mutations in the Factor B gene than mutations in the C2 gene. While the AMD associated C2 variants are either conservative change or an intronic SNP, the Q32 variant of Factor B has reduced hemolytic activity (Lokki and Koskimies 1991). Furthermore is the L9H exchange located within the signal peptide and may affect secretion and processing of Factor B. The AMD associated Factor B variants modulate activation of the alternative complement pathway and therefore may lead to an overall complement deregulation.

The AMD-associated polymorphism in C3 results in exchange of arginine (R) to glycine (G) at amino acid position 102 (Yates et al. 2007). This exchange affects the mobility of the protein and results in a “fast” C3F (fast) and a “slow variant” C3s (slow) (Botto et al. 1990). C3F, the risk variant for AMD, is also associated with renal disease including IgA nephropathy, as well as MPGN-II (Wyatt et al. 1987; Abrera-Abeleda et al. 2006) and has been reported to influence long-term success of renal transplants (Brown et al. 2006). R102 forms together with neighbord or adjacent amino acid residues a positively charged spot on the surface of the C3 molecule, which in C3b is in close proximity with negatively charged amino acids close to the thioester-containing domain (Janssen et al. 2006; Yates et al. 2007). Substitution of positively charged R102 to neutral G102 likely weakens the interaction between charged surfaces and potentially influences thioester activity. Therefore the AMD associated risk variant G102 may affect C3b-Factor H complex formation resulting in less efficient C3b inactivation on (retinal) surfaces. Consequently C3 convertase action is increased and more activations products in form of C3b, iC3b, C3d are deposited onto ocular cell surfaces and generate more anaphylatoxin C3a (Johnson et al. 2001; Nozaki et al. 2006).

3.2 Gene Products of the Chromosome 10q26: ARMS-2 and HRTA1

Chromosome 10q26 encodes two genes that are not related to complement and that are strongly associated with risk for AMD development. The AMD-associated polymorphisms of ARMS2 (rs10490924; A69S) and HTRA1 (rs11200638, promoter polymorphism) are in strong linkage disequilibrium that their possible effects are indistinguishable in statistical analysis (Jakobsdottir et al. 2005). Apparently the SNP in the ARMS2 genes shows stronger association with AMD than the HTRA1 gene. This may explain the high association of chromosome 10q26 with AMD (Kanda et al. 2007).

The ARMS gene has an open reading frame which encodes an evolutionary new protein of 12 kDa with so far unknown biological function. A deletion–insertion polymorphism resulting in loss of the polyadenylation signal in ARMS2 RNA is strongly associated with AMD and directly affects transcript formation. Consequently in homozygous individuals no ARMS mRNA is detected. In individuals with the
protective A69 variant the protein is expressed in the retina, placenta and weakly also in the kidney, lung and heart. The exact localization of AMRS2 is still not defined. Different studies report either a cytosolic or mitochondrial localization within retinal cells (Kanda et al. 2007; Fritsche et al. 2008; Wang et al. 2009). The ARMS2 protein seems associated with microtubules of the cytoskeleton and with mitochondrial outer membranes. However independent of the exact cellular location of ARMS2, the S69 variant seems not expressed and the absence of this protein leads to progression of AMD. Thus, identification of the functional biological role of ARMS2 will provide new insights in AMD development.

The HTRA1 gene on chromosome 10q26 encodes a serine protease that is expressed in murine and human RPE cells (Oka et al. 2004). HTRA1 likely regulates degradation of extracellular matrix proteoglycans. This activity can facilitate access of other degradative matrix enzymes, such as collagenases and matrix metalloproteinases, to their substrates (Grau et al. 2006). The SNP rs11200638 within the promoter region of the HTRA1 gene is strongly associated with development of CNV. Apparently the risk variation affects expression levels of the protein and in eyes of donors, homozygous for the risk variant RPE show increased expression by factor of 1.7, as compared to the protective variant (Dewan et al. 2006; Yang et al. 2006). Such higher HTRA1 protein levels may alter the integrity of Bruch’s membrane, favoring invasion of choroid capillaries across the extracellular matrix, as described for the wet form of AMD. Together, these findings suggest a potential new mechanism for AMD pathogenesis, independent of the complement-mediated AMD progression.

4 Lessons Learned from Rare Disorders (HUS, MPGN)

Defective and inappropriate complement regulation can cause AMD. In addition to this frequent retinal disease AMD, two rare kidney disorders, in from of atypical Hemolytic Uremic Syndrome (aHUS) and Membrano Proliferative Glomerulonephritis (MPGN II, also termed dense deposit disease) are also associated with Factor H gene mutations, CFHR1/CFHR3 deficiency as well as mutations/polymorphisms in genes coding for complement regulators C3, Factor B and Factor I (Thurman and Holers 2006; Zipfel et al. 2006). Thus related genetic defects suggest similar or highly related pathophysiological mechanisms. Thus defective local complement activation results in related local damaged, which however manifest in different organs (Zipfel 2009).

Gene mutations have been reported for the rare renal disorders aHUS (Perez-Caballero et al. 2001) and MPGN II (Appel et al. 2005). Very related mechanisms can affect the endothelial lining of the glomerulus (aHUS) or the glomerular basement membrane, as well as the retinal cell and surface layer the Bruch’s membrane. This similarity suggests that the fine tuned, coordinated action of multiple complement components is essential to maintain the delicate balance of the complement system and to prevent inflammation and cell damage. An exchange of one single residue
in the DNA, RNA or amino acid sequence can already affect protein expression and protein function. Such an exchange can affect the coordinated action and the progression of the cascade and the delicate balance between activation and inhibition of the complement cascade (Skerka and Zipfel 2008).

The knowledge how gene defects in complement components are translated into local defective complement regulation allowed defining appropriate therapy for these rare disorders aHUS and MPGN II. The related pathomechanisms of AMD, atypical HUS and MPGN II is relevant to design and use complement and other anti-inflammatory agents to locally control complement activation in these different organs.

5 Outlook

Based on genetic, functional, and immunohistological data evidence has accumulated that AMD is caused by deregulated local complement activation which develops into chronic inflammation. As related mechanisms of defective complement control results in damage of renal tissues a common link between diseases is emerging which were initially considered unrelated disorders. This allows prediction of additional disease associated genes and allows defining novel targets for complement inhibition.

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