AMD and the Complement System

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Wet age-related macular degeneration (wAMD) is characterized by choroidal neovascularization (CNV), and it is the leading cause of blindness affecting elderly in the Western world. AMD is a complex disease that has strong associations with the complement system. All three initiating complement pathways may be relevant in CNV formation, but most evidence indicates a major role for the alternative pathway (AP) and for the terminal complement complex, as well as certain complement peptides generated upon complement activation. Since the complement system is associated with AMD and CNV, a complement inhibitor may be a therapeutic option for patients with wAMD. The aim of the review is to **(i)** reflect on the possible complement targets in the context of wAMD pathology, **(ii)** investigate the results of prior clinical trials with complement inhibitors for wAMD patients, and **(iii)** outline important considerations when developing a future strategy for the treatment of wAMD.

age-related macular degeneration | complement system | choroidal neovascularization | anti-complement therapy | complement inhibition

1. Introduction

Age-related macular degeneration (AMD) is a multi-factorial retinal disease with a significant inflammatory contribution, which is presently being explored. Several recent findings have strongly associated AMD with the complement system [1][2][3][4][5][6][7][8][9], thereby pinpointing the pivotal role of complement factors in the development of AMD. The complement system is a part of the innate immune system and is activated by either pathogens or damaged host cells. The initiating pathways of complement activation are the lectin pathway (LP), classical pathway (CP), and alternative pathway (AP), which all revolve around the cleavage of complement component 3 (C3). It is still uncertain which pathways are involved in the pathophysiology of the more severe wet form of AMD (wAMD). However, the amplification ability of the AP seems to be crucial. Since the retina has high metabolic demands, its tissue is particularly vulnerable to oxidative damage, and a small local injury may be sufficient for amplification of the complement response and the development of AMD.

AMD is the leading cause of age-related blindness in the Western world [10]. AMD affects ~10% of Europeans above the age of 85 [11] and 1.7% of Dutch individuals between the ages of 55 and 98 [12]. The prevalence of AMD is predicted to increase worldwide because of a shift toward aging populations [13]. In patients suffering from wAMD, neovascular vessels develop beneath the RPE or penetrate into the subretinal space, a process known as choroidal neovascularization (CNV).

2. AMD and associations to the complement system

Importantly, several clues indicate the essential role of the complement system in the pathogenesis of ARM and AMD [1][2][3][4][5][6][7][8][9]: **(i)** the presence of complement components in drusen, such as the complement peptide C3a and factor H (FH) [1][2][14][15][16][17][18], **(ii)** single nucleotide polymorphisms (SNPs) in genes encoding components and regulators of the complement system are associated with an increased risk of ARM and AMD [19], **(iii)** higher levels of the terminal complement complex (the membrane attack complex, MAC) in the retinas of ARM and AMD patients [20], especially in those with an FH risk variant [1][21][22], **(iv)** fewer or dislocated regulatory complement proteins in the eyes of ARM and AMD patients [23][24], **(v)** increased levels of systemic and active complement proteins in AMD patients compared to the controls [25][26][27][28], and **(vi)** elevated levels of local complement proteins in aqueous humor samples and the vitreous humor of AMD patients compared to the controls [29][30][31]. A recent genome-wide association study (GWAS) showed that multiple complement variants affect systemic complement activation. However, only some of these variants are associated with AMD and local disease in the retina, suggesting tissue-specific effects [32]. These findings have led to the hypothesis that AMD is a local manifestation of chronic low-grade systemic complement activation in aging patients with risk variants [27].

3. Genetic polymorphisms in complement genes found in AMD patients

Several genetic linkage analyses in large family-based studies [33][34][35][36][37] and subsequent GWAS focusing on AMD [38][39][40][41][32][42] established the significant associations between AMD and specific genomic regions, particularly in chromosomes 1 and 10. Genetic polymorphisms in two specific genomic regions were found to be major risk factors for developing AMD: 1q32 comprising the *FH* gene and 10q26 comprising the *ARMS2*/*HTRA1* gene [39][43]. Subsequently, genetic variation in other complement genes was associated with AMD development and progression [44], such as the genetic variants found in the genes *C3* [45], *FI* [46], *C2*/*FB*, *FH*-related genes [4], and *C9* [46]. The many variants found in the genes related to the complement system [4][9][43][44][47] highlight the importance of this immunologic pathway in AMD etiology.

The Y402H mutation in *FH* (rs1061170) is the most strongly associated common risk variant of ARM and AMD [44]. The SNP was found to yield an increased likelihood of developing wAMD of 1.9–2.34 per allele [48], and homozygous individuals were found to have an increased likelihood of 5.78 [49]. With the expression of the Y402H allele, the binding of the FH Y402H to GAGs in Bruch's membrane is impaired [23][50][51][52], which leaves some individuals more prone to AMD — e.g., deposited MAC is found to be increased by >60% in the choroids of 402H homozygous individuals compared to 402Y homozygous individuals [21].

A nonsense mutation in *C9* (rs121909592) holds a 4.7-reduced likelihood of developing wAMD [53], substantiating the role of the MAC in AMD. R32Q (rs641153) and R32W (rs12614) are variants of *FB* associated with protection against wAMD, as R32Q and R32W FB relate to reduced binding to C3b. Moreover, an SNP (R102G, rs2230199) in the gene of *C3* was associated with an increased risk of AMD [45], which may be accounted for by a decreased binding affinity of C3b toward FH [44]. This may yield reduced FH-dependent degradation of C3b, an extended

lifetime of the convertases, and, consequently, enhanced AP activation. Together, these findings suggest that genetic variants that hinder the negative regulation of the complement system promote AMD development and that the variants inhibiting activation are protective.

4. Complement therapeutics for AMD patients

A complement inhibitor may be most efficient if delivered directly to the outer retina, where local disease develops and is continuously amplified. Inhibitors of the complement system can be recombinantly made or, for long-term management, encoded in viral vectors delivered to retinal target cells. The drug should be able to cross retinal cell layers and Bruch's membrane but, at the same time, must remain locally at a therapeutic concentration, requiring a certain molecular structure and size of the inhibitor. In the context of wAMD, all complement pathways seem relevant in preclinical trials of CNV formation, and important roles are played by MAC, the AP, and C3a and C5a, yielding several possible therapeutic targets. Several clinical trials with complement inhibitors have been initiated during the last decade based on the association between AMD and the complement system. Unfortunately, the results have, so far, not been successful. This apparent lack of success does not have one distinct cause but is most likely due to a combination of the chosen site of delivery, the concentration and the structure of the drug in the context of reaching the target tissue, the diffusion of the drug to the systemic circulation, the complement target, the stage of disease when treated, the skewed patient population, the targeting of only one pathway, and the outcome measures. Moreover, the physiological differences between studies done in vitro and preclinically, and the clinical trials may have been too large. However, surveying ongoing and future trials will be intriguing and relevant in the process of developing effective therapeutic strategies for these patients.

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