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.

Keywords: 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.

References

1. Hageman, G.S.; Anderson, D.H.; Johnson, L.V.; Hancox, L.S.; Taiber, A.J.; Hardisty, L.I.; Hageman, J.L.; Stockman, H.A.; Borchardt, J.D.; Gehrs, K.M.; et al. A common haplotype in the complement regulatory gene factor h (hf1/cfh) predisposes individua1. hageman, g. s. et al. a common haplotype in the complement regulatory gene factor h (hf1/cfh) predisposes individuals to age-related macular degeneration. Proc. Natl. Acad. Sci. USA 2005, 102, 7227–7232.
2. Hageman, G.S.; Luthert, P.J.; Victor Chong, N.H.; Johnson, L.V.; Anderson, D.H.; Mullins, R.F. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the rpe-bruch's membrane interface in aging and age-related macular degeneration. Prog. Retin. Eye Res. 2001, 20, 705–732.
3. Parsons, N.; Annamalai, B.; Obert, E.; Schnabolk, G.; Tomlinson, S.; Rohrer, B. Inhibition of the alternative complement pathway accelerates repair processes in the murine model of choroidal neovascularization. Mol. Immunol. 2019, 108, 8–12.
4. Geerlings, M.J.; de Jong, E.K.; den Hollander, A.I. The complement system in age-related macular degeneration: A review of rare genetic variants and implications for personalized treatment. Mol. Immunol. 2017, 84, 65–76.

5. Park, D.H.; Connor, K.M.; Lambris, J.D. The challenges and promise of complement therapeutics for ocular diseases. Front. Immunol. 2019, 10, 1007.
6. Mullins, R.F.; Aptsiauri, N.; Hageman, G.S. Structure and composition of drusen associated with glomerulonephritis: Implications for the role of complement activation in drusen biogenesis. Eye 2001, 15, 390–395.
7. Bora, N.S.; Matta, B.; Lyzogubov, V.V.; Bora, P.S. Relationship between the complement system, risk factors and prediction models in age-related macular degeneration. Mol. Immunol. 2015, 63, 176–183.
8. Van Lookeren Campagne, M.; Strauss, E.C.; Yaspan, B.L. Age-related macular degeneration: Complement in action. Immunobiology 2016, 221, 733–739.
9. Anderson, D.H.; Radeke, M.J.; Gallo, N.B.; Chapin, E.A.; Johnson, P.T.; Curletti, C.R.; Hancox, L.S.; Hu, J.; Ebright, J.N.; Malek, G.; et al. The pivotal role of the complement system in aging and age-related macular degeneration: Hypothesis re-visited. Prog. Retin. Eye Res. 2010, 29, 95–112.
10. Korb, L.C.; Ahearn, J.M. C1q binds directly and specifically to surface blebs of apoptotic human keratinocytes: Complement deficiency and systemic lupus erythematosus revisited. J. Immunol. 1997, 158, 4525–4528.
11. Taylor, P.R.; Carugati, A.; Fadok, V.A.; Cook, H.T.; Andrews, M.; Carroll, M.C.; Savill, J.S.; Henson, P.M.; Botto, M.; Walport, M.J. A hierarchical role for classical pathway complement proteins in the clearance of apoptotic cells in vivo. J. Exp. Med. 2000, 192, 359–366.
12. Kuraya, M.; Ming, Z.; Liu, X.; Matsushita, M.; Fujita, T. Specific binding of l-ficolin and h-ficolin to apoptotic cells leads to complement activation. Immunobiology 2005, 209, 689–697.
13. Nauta, A.J.; Raaschou-Jensen, N.; Roos, A.; Daha, M.R.; Madsen, H.O.; Borrias-Essers, M.C.; Ryder, L.P.; Koch, C.; Garred, P. Mannose-binding lectin engagement with late apoptotic and necrotic cells. Eur. J. Immunol. 2003, 33, 2853–2863.
14. McGrath, F.D.G.; Brouwer, M.C.; Arlaud, G.J.; Daha, M.R.; Hack, C.E.; Roos, A. Evidence that complement protein c1q interacts with c-reactive protein through its globular head region. J. Immunol. 2006, 176, 2950–2957.
15. Kumar-Singh, R. The role of complement membrane attack complex in dry and wet amd-from hypothesis to clinical trials. Exp. Eye Res. 2019, 184, 266–277.
16. Hänsch, G.M.; Seitz, M.; Betz, M. Effect of the late complement components c5b-9 on human monocytes: Release of prostanoids, oxygen radicals and of a factor inducing cell proliferation. Int. Arch. Allergy Appl. Immunol. 1987, 82, 317–320.
17. Lueck, K.; Wasmuth, S.; Williams, J.; Hughes, T.R.; Morgan, B.P.; Lommatzsch, A.; Greenwood, J.; Moss, S.E.; Pauleikhoff, D. Sub-lytic c5b-9 induces functional changes in retinal pigment epithelial cells consistent with age-related macular degeneration. Eye 2011, 25, 1074–1082.
18. Kunchithapautham, K.; Rohrer, B. Sublytic membrane-attack-complex (mac) activation alters regulated rather than constitutive vascular endothelial growth factor (vegf) secretion in retinal pigment epithelium monolayers. J. Biol. Chem. 2011, 286, 23717–23724.
19. Ambati, J.; Ambati, B.K.; Yoo, S.H.; Ianchulev, S.; Adamis, A.P. Age-related macular degeneration: Etiology, pathogenesis, and therapeutic strategies. Surv. Ophthalmol. 2003, 48, 257–293.
20. Colijn, J.M.; Buitendijk, G.H.S.; Prokofyeva, E.; Alves, D.; Cachulo, M.L.; Khawaja, A.P.; Cougnard-Gregoire, A.; Merle, B.M.J.; Korb, C.; Erke, M.G.; et al. Prevalence of age-related macular degeneration in europe: The past and the future. Ophthalmology 2017, 124, 1753–1763.
21. Vingerling, J.R.; Dielemans, I.; Hofman, A.; Grobbee, D.E.; Hijmering, M.; Kramer, C.F.L.; de Jong, P.T.V.M. The prevalence of age-related maculopathy in the rotterdam study. Ophthalmology 1995, 102, 205–210.
22. Wong, W.L.; Su, X.; Li, X.; Cheung, C.M.G.; Klein, R.; Cheng, C.Y.; Wong, T.Y. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. Lancet Glob. Heal. 2014, 2, e106–e116.
23. Kay, P.; Yang, Y.C.; Paraoan, L. Directional protein secretion by the retinal pigment epithelium: Roles in retinal health and the development of age-related macular degeneration. J. Cell. Mol. Med. 2013, 17, 833–843.
24. Kevany, B.M.; Palczewski, K. Phagocytosis of retinal rod and cone photoreceptors. Physiology 2010, 25, 8–15.
25. Sparrow, J.R.; Hicks, D.; Hamel, C.P. The retinal pigment epithelium in health and disease. Curr. Mol. Med. 2010, 10, 802–823.
26. Bird, A.C.; Bressler, N.M.; Bressler, S.B.; Chisholm, I.H.; Coscas, G.; Davis, M.D.; de Jong, P.T.V.M.; Klaver, C.C.W.; Klein, B.E.K.; Klein, R.; et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration. Surv. Ophthalmol. 1995, 39, 367–374.

27. Klaver, C.C.; Assink, J.J.; Van Leeuwen, R.; Wolfs, R.C.; Vingerling, J.R.; Stijnen, T.; Hofman, A.; de Jong, P.T. Incidence and progression rates of age-related maculopathy: The rotterdam study | iovs | arvo journals. Investig. Ophthalmol. Vis. Sci. 2001, 42, 2237–2241.

28. Davis, M.D.; Gangnon, R.E.; Lee, L.Y.; Hubbard, L.D.; Klein, B.E.K.; Klein, R.; Ferris, F.L.; Bressler, S.B.; Milton, R.C. The age-related eye disease study severity scale for age-related macular degeneration: Areds report no. 17. Arch. Ophthalmol. 2005, 123, 1484–1498.

29. Klein, R.; Meuer, S.M.; Myers, C.E.; Buitendijk, G.H.S.; Rochtchina, E.; Choudhury, F.; De Jong, P.T.V.M.; McKean-Cowdin, R.; Iyengar, S.K.; Gao, X.; et al. Harmonizing the classification of age-related macular degeneration in the three-continent amd consortium. Ophthalmic Epidemiol. 2014, 21, 14–23.

30. Sallo, F.B.; Peto, T.; Dandekar, S.; Leung, I.; Bird, A.C. The international classification system and progression of amd. Investig. Ophthalmol. Vis. Sci. 2003, 44, 1811.

31. Ishibashi, T.; Patterson, R.; Ohnishi, Y.; Inomata, H.; Ryan, S.J. Formation of drusen in the human eye. Am. J. Ophthalmol. 1986, 101, 342–353.

32. Lorés-Motta, L.; Paun, C.C.; Corominas, J.; Pauper, M.; Geerlings, M.J.; Altay, L.; Schick, T.; Daha, M.R.; Fauser, S.; Hoyng, C.B.; et al. Genome-wide association study reveals variants in cfh and cfhr4 associated with systemic complement activation: Implications in age-related macular degeneration. Ophthalmology 2018, 125, 1064–1074.

33. Schuman, S.G.; Koreishi, A.F.; Farsiu, S.; Jung, S.H.; Izatt, J.A.; Toth, C.A. Photoreceptor layer thinning over drusen in eyes with age-related macular degeneration imaged in vivo with spectral-domain optical coherence tomography. Ophthalmology 2009, 116, 488–496.

34. Gass, J.D.M. Drusen and disciform macular detachment and degeneration. Arch. Ophthalmol. 1973, 90, 206–217.

35. Labardini, C.P.; Blumenthal, E.Z. Causative pathogens in endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. Rambam Maimonides Med. J. 2018, 9, e0032.

36. Daien, V.; Nguyen, V.; Essex, R.; Morlet, N.; Barthelmes, D.; Gillies, M.; Hunt, A.; Dayajeewa, C.; Hunyor, A.; Fraser-Bell, S.; et al. Incidence and outcomes of infectious and noninfectious endophthalmitis after intravitreal injections for age-related macular degeneration. Ophthalmology 2018, 125, 66–74.

37. Mullins, R.F.; Russell, S.R.; Anderson, D.H.; Hageman, G.S. Drusen associated with aging and age-related macular degeneration contain proteins common to extracellular deposits associated with atherosclerosis, elastosis, amyloidosis, and dense deposit disease. FASEB J. 2000, 14, 835–846.

38. Johnson, L.V.; Leitner, W.P.; Staples, M.K.; Anderson, D.H. Complement activation and inflammatory processes in drusen formation and age related macular degeneration. Exp. Eye Res. 2001, 73, 887–896.

39. Anderson, D.H.; Mullins, R.F.; Hageman, G.S.; Johnson, L. V A role for local inflammation in the formation of drusen in the aging eye. Am. J. Ophthalmol. 2002, 134, 411–431.

40. Van Der Schaft, T.L.; Mooy, C.M.; De Bruijn, W.C.; De Jong, P.T.V.M. Early stages of age-related macular degeneration: An immunofluorescence and electron microscopy study. Br. J. Ophthalmol. 1993, 77, 657–661.

41. Johnson, L.V.; Ozaki, S.; Staples, M.K.; Erickson, P.A.; Anderson, D.H. A potential role for immune complex pathogenesis in drusen formation. Exp. Eye Res. 2000, 70, 441–449.

42. Mullins, R.F.; Schoo, D.P.; Sohn, E.H.; Flamme-Wiese, M.J.; Workamelahu, G.; Johnston, R.M.; Wang, K.; Tucker, B.A.; Stone, E.M. The membrane attack complex in aging human choriocapillaris: Relationship to macular degeneration and choroidal thinning. Am. J. Pathol. 2014, 184, 3142–3153.

43. Mullins, R.F.; Dewald, A.D.; Streb, L.M.; Wang, K.; Kuehn, M.H.; Stone, E.M. Elevated membrane attack complex in human choroid with high risk complement factor h genotypes. Exp. Eye Res. 2011, 93, 565–567.

44. Chirco, K.R.; Flamme-Wiese, M.J.; Wiley, J.S.; Potempa, L.A.; Stone, E.M.; Tucker, B.A.; Mullins, R.F. Evaluation of serum and ocular levels of membrane attack complex and c-reactive protein in cfh-genotyped human donors. Eye 2018, 32, 1740–1742.

45. Clark, S.J.; Perveen, R.; Hakobyan, S.; Morgan, B.P.; Sim, R.B.; Bishop, P.N.; Day, A.J. Impaired binding of the age-related macular degeneration-associated complement factor h 402h allotype to bruch's membrane in human retina. J. Biol. Chem. 2010, 285, 30192–30202.

46. Ebrahimi, K.B.; Fijalkowski, N.; Cano, M.; Handa, J.T. Decreased membrane complement regulators in the retinal pigmented epithelium contributes to age-related macular degeneration. J. Pathol. 2013, 229, 729–742.

47. Hecker, L.A.; Edwards, A.O.; Ryu, E.; Tosakulwong, N.; Baratz, K.H.; Brown, W.L.; Issa, P.C.; Scholl, H.P.; Pollok-Kopp, B.; Schmid-Kubista, K.E.; et al. Genetic control of the alternative pathway of complement in humans and age-related macular degeneration. Hum. Mol. Genet. 2010, 19, 209–215.

48. Reynolds, R.; Hartnett, M.E.; Atkinson, J.P.; Giclas, P.C.; Rosner, B.; Seddon, J.M. Plasma complement components and activation fragments: Associations with age-related macular degeneration genotypes and phenotypes. Investig. Ophthalmol. Vis. Sci. 2009, 50, 5818–5827.
49. Heesterbeek, T.J.; Lechanteur, Y.T.E.; Lorés-Motta, L.; Schick, T.; Daha, M.R.; Altay, L.; Liakopoulos, S.; Smailhodzic, D.; den Hollander, A.I.; Hoyng, C.B.; et al. Complement activation levels are related to disease stage in amd. Investig. Ophthalmol. Vis. Sci. 2020, 61, 18.
50. Scholl, H.P.N.; Issa, P.C.; Walier, M.; Janzer, S.; Pollok-Kopp, B.; Börncke, F.; Fritsche, L.G.; Chong, N.V.; Fimmers, R.; Wienker, T.; et al. Systemic complement activation in age-related macular degeneration. PLoS ONE 2008, 3, e2593.
51. Altay, L.; Sitnilska, V.; Schick, T.; Widmer, G.; Duchateau-Nguyen, G.; Piraino, P.; Jayagopal, A.; Drawnel, F.M.; Fauser, S. Early local activation of complement in aqueous humour of patients with age-related macular degeneration. Eye 2019, 33, 1859–1864.
52. Loyet, K.M.; DeForge, L.E.; Katschke, K.J.; Diehl, L.; Graham, R.R.; Pao, L.; Sturgeon, L.; Lewin-Koh, S.C.; Hollyfield, J.G.; van Lookeren Campagne, M. Activation of the alternative complement pathway in vitreous is controlled by genetics in age-related macular degeneration. Investig. Ophthalmol. Vis. Sci. 2012, 53, 6628–6637.
53. Schick, T.; Steinhauer, M.; Aslanidis, A.; Altay, L.; Karlstetter, M.; Langmann, T.; Kirschfink, M.; Fauser, S. Local complement activation in aqueous humor in patients with age-related macular degeneration. Eye 2017, 31, 810–813.