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Age-Related Macular Degeneration: A Connection between Human Herpes Virus-6A-Induced CD46 Downregulation and Complement Activation?

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Viruses are able to interfere with the immune system by docking to receptors on host cells that are important for proper functioning of the immune system. A well-known example is the human immunodeficiency virus that uses CD4 cell surface molecules to enter host lymphocytes and thereby deleteriously destroying the helper cell population of the immune system. A more complicated mechanism is seen in multiple sclerosis (MS) where human herpes virus-6A (HHV-6A) infects astrocytes by docking to the CD46 surface receptor. Such HHV-6A infection in the brain of MS patients has recently been postulated to enable Epstein–Barr virus (EBV) to transform latently infected B-lymphocytes in brain lesions leading to the well-known phenomenon of oligoclonal immunoglobulin production that is widely used in the diagnosis of MS. The cellular immune response to HHV-6A and EBV is one part of the pathogenic mechanisms in MS. A more subtle pathogenic mechanism can be seen in the downregulation of CD46 on astrocytes by the infecting HHV-6A. Since CD46 is central in regulating the complement system, a lack of CD46 can lead to hyperactivation of the complement system. In fact, activation of the complement system in brain lesions is a well-known pathogenic mechanism in MS. In this review, it is postulated that a similar mechanism is central in the development of age-related macular degeneration (AMD). One of the earliest changes in the retina of AMD patients is the loss of CD46 expression in the retinal pigment epithelial (RPE) cells in the course of geographic atrophy. Furthermore, CD46 deficient mice spontaneously develop dry-type AMD-like changes in their retina. It is also well known that certain genetic polymorphisms in the complement-inhibiting pathways correlate with higher risks of AMD development. The tenet is that HHV-6A infection of the retina leads to downregulation of CD46 and consequently to hyperactivation of the complement system in the eyes of susceptible individuals.

Keywords: human herpes virus-6A, age-related macular degeneration, CD46, complement system proteins, autophagy, parainflammation, inflammaging

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INTRODUCTION

Many microorganisms use a survival strategy based on their interference with the immune system of their hosts. One way to do so is to acquire immune regulatory proteins from the host that subsequently protect them from immune-mediated attacks by the host. Examples are human immunodeficiency virus (HIV) (1) and cytomegalovirus (2) that both incorporate host cell-derived

complement control proteins like CD55 and CD59 to protect themselves against complement attacks by the host. Similarly, certain *Borrelia burgdorferi* strains arm themselves with the complement regulatory proteins FHL-1/reconectin and Factor H by using complement regulators acquiring surface proteins (3). Another strategy is to use cell surface receptors of host immune cells for infection and thereby directly interfering with immune functions. A well-known example is HIV that infects host T-helper cells using the CD4 receptor (4, 5).

Other pathogenic effects can be seen when viruses infect host cells and thereby change the cell functions without killing the cells in the process. In multiple sclerosis (MS), e.g., human herpes virus-6A (HHV-6A) infects astrocytes in the brain by docking to the CD46 molecules (6–11). One effect of such HHV-6A infection in MS patients has recently been postulated to interfere with Epstein–Barr virus (EBV) in latently infected B-cells in brain lesions (12). Consequently, B-cells would be transformed by EBV and produce clonal immunoglobulins that are common in MS patients and are used as diagnostic markers in the cerebrospinal fluid. In addition, cellular immune responses to HHV-6A and EBV would induce and sustain the inflammatory lesions in MS brains. Furthermore, the infection of astrocytes with HHV-6A also leads to downregulation of the receptor CD46 that was used for entering the cell (8). Since CD46 is important in limiting the activity of the complement system, the downregulation of CD46 leads to hyperactivity of complement (13). In recent years, it has become clear that complement activity in the brain itself is an important factor in the pathogenesis of MS (14).

Based on these observations, it is postulated here that similar HHV-6A/CD46/complement interactions are central in the development of age-related macular degeneration (AMD). In this article, pathogenic mechanisms in AMD as they are known today are summarized and then a link to HHV-6A *via* CD46 is proposed. Finally, the relation of AMD to MS and other diseases where HHV-6A infection plays a pathogenic role is explored.

HYPOTHESIS

Age-related macular degeneration, a degenerative disease of the retina, is the leading cause of irreversible central blindness in elderly people [for review, see Ref. (15)]. Although many risk factors are known [for review, see Ref. (16)], the etiology of AMD remains elusive. Based on known pathogenic mechanisms described below, it is proposed that HHV-6A is an etiologic agent for AMD.

Inflammation/Parainflammation/ Inflammaging

Inflammation plays an important role in the pathogenesis of AMD [for review, see Ref. (17–20)]; however, the exact inflammatory mechanisms involved remain unclear. Individuals with elevated C-reactive protein, a general systemic marker for inflammation, carry a higher risk of developing AMD (21). Locally in the retina, proinflammatory macrophages (M1) are enriched at the expense of scavenging and anti-inflammatory M2 macrophages (22). A chronic low-grade inflammation, called parainflammation, is generally considered a beneficial response to chronic insults also in AMD (23). A chronic, parainflammation characteristic for aging is called inflammaging [for review, see Ref. (24)]. Similar to age-related diseases in other organs, inflammaging is supposed to manifest itself also in AMD (25, 26).

Complement and CD46

A central role in the inflammatory pathogenesis of AMD is accredited to the regulation of the complement system [for review, see Ref. (27, 28)]. The strong genetic risk conferred by a polymorphism of complement factor H (29–33), but also polymorphisms of ARMS2/HTRA1 (34) support this notion. At present, the function of the ARMS2 protein and the biological consequences of the polymorphism are not completely unraveled, but it has recently been found that ARMS2 functions as surface complement regulator and that ARMS2 is involved in complement-mediated clearance of cellular debris (35).

The spectrum of complement activation in the retina of AMD patients ranges from beneficial to detrimental. Therefore, complement regulation plays a key role in the pathogenesis of AMD. Membrane cofactor protein (MCP, CD46) is a well-known regulatory membrane protein that guards cells from complement attack [for review, see Ref. (36)]. CD46 acts as a cofactor for complement factor I, which protects autologous cells against complement-mediated injury by cleaving C3b and C4b deposited on the cells surface. An intergenic single-nucleotide polymorphism just 3′ of complement factor I on chromosome 4 is indeed associated with risk of advanced AMD (37).

The importance of the complement regulatory CD46 is demonstrated by the finding that retinal pigment epithelial (RPE) cells lose their CD46 expression very early in the development of geographic atrophy even before any morphological change of RPE (38). The loss of CD46 makes the RPE vulnerable to complement. Furthermore, an additional role of CD46 in RPE seems to lay in the adhesion of the RPE to its basement membrane and Bruch's membrane, thereby safeguarding its integrity (39). The key pathogenic role of CD46 loss in AMD is also demonstrated by an experimental animal model in which *Cd46*$^{-/-}$ knockout mice develop a dry-type AMD-like phenotype (40).

Autophagy and CD46

Autophagy is a hot topic in AMD research (41) and it is likely to play an important role in the pathogenesis of AMD as a highly regulated clearance and recycling mechanism of cytoplasmic contents [for review, see Ref. (42, 43)]. Transforming growth factor β activated kinase 1 (TAK1), a key player in the regulation of autophagy, maintains the normal function of RPE cells (44, 45). Recently, it was discovered that autophagy is triggered, when pathogens are bound to CD46 (46). This may be a cellular adaptation to infection *via* CD46.

Chemokines and Chemokine Receptors

Associations of polymorphisms in the gene of chemokine (C-X3-C motif) receptor 1 (*CX3CR1*) with AMD susceptibility have been reported in several studies (47–49). The CX3CR1

TABLE 1 | Association of human herpes virus-6A (HHV-6A) and age-related macular degeneration (AMD) with AIDS, Hashimoto's thyroiditis (HT), and multiple sclerosis (MS).

Disease	Association with HHV-6A	Association with AMD
AIDS	HIV-1 infection is epidemiologically associated with HHV-6A infection (63, 64). Particularly, HHV-6 is found in demyelinating lesions in AIDS patients with cerebral involvement (65) and HIV-1 and HHV-6 antigens and transcripts are found in the retina of patients with AIDS (66)	Persons with AIDS appear to have an approximately 4-fold increased prevalence of intermediate-stage AMD when compared to a similarly aged human immunodeficiency virus (HIV)-uninfected population (67)
HT	The most frequent cause of hypothyroidism is HT. In a study examining thyroid fine needle aspirates (FNA) and peripheral blood mononuclear cells, HHV-6 DNA prevalence was much higher in HT (82%) than in controls (10%). and viral load was significantly increased in FNA from HT patients, and thyrocytes from HT FNA displayed a 100-fold higher HHV-6 DNA load compared to infiltrating lymphocytes (68). Variant analysis performed in 10 HT samples showed that all samples harbored HHV-6A. *In vitro* infection of thyrocytes with HHV-6A induces modulation of miRNAs considered markers of autoimmune thyroid disease *in vivo*. These alterations were not seen thyrocytes infected with HHV-6B or HHV-7 (69)	The association of AMD with thyroid function is somewhat controversial. In a study with 356 people with AMD 21% reported to have hypothyroidism compared to 11% of those 9,321 without AMD giving an odds ratio of 2.33 (70). On the other side, in a prospective population-based cohort study with 5,573 participants of age ≥55 years, higher free thyroxine (FT4) values were associated with a higher risk of AMD, odds ratio albeit being very small (1.35 for the highest quartile of FT4 levels) (71). However, participants with AMD at baseline ($N = 567$) were excluded from the study. Interestingly, another study found that thyroxine substitution, which can be considered a surrogate marker for hypothyroidism, also correlated with AMD (72). In a smaller study with 114 patients, an association of AMD with not further specified thyroidopathy was found (73).
MS	There is abundant evidence that HHV-6A has an etiopathologic role in MS [for review, see Ref. (74)]. HHV-6A infects astrocytes *via* the CD46, thereby interfering with complement regulation (13, 14), in much the same way as is proposed here for RPE cells. Furthermore, it has recently been postulated that HHV-6A also interacts with Epstein–Barr virus in the CNS of MS patients leading to B-cell transformation and production of oligoclonal immunoglobulins that are typical for MS (12)	Although there are no epidemiologic studies directly examining a possible association between MS and AMD, ocular pathology has been studied in MS patients (75). MS cases with variable clinical severity demonstrated evidence of retinal atrophy and prominent inflammation

polymorphisms result in decreased affinity for its ligand (CX3CL1, fractalkine), which in turn negatively affects microglial and macrophage migration (50). A chemotactic cytokine, RANTES or CCL5, produced by RPE cells also seems to regulate inflammatory cell migration (51).

HHV-6A: Regulating Complement, Autophagy, and Chemokines

Human herpes virus-6A uses the membrane protein CD46 as a receptor to enter cells (8, 52, 53). Such infection is followed by downregulation of CD46. Other viruses, like measles virus (CD46), HIV (CD4), and EBV (CD21), also follow similar strategies of receptor downregulation after infection (54). The CD46 downregulation by HHV-6A may functionally impair the protective effect of CD46 against the activation of autologous complement and the consequent cellular damage as shown *in vitro* using measles virus (55). In this way, HHV-6A would interfere with key pathogenic complement mechanisms in AMD when RPE cells are infected *via* CD46.

HHV-6 infection can also impair Toll-like receptor signaling by reducing TAK1 activity as shown in infected dendritic cells (56). When RPE cells are infected with HHV-6A, the essential role of TAK1 for maintaining normal function of RPE cells through regulation of autophagy would be impaired (44, 45).

HHV-6 expresses its own chemokine receptors encoded by the U12, and U51 genes. The open reading frame U12 functionally encodes a calcium-mobilizing receptor for the β-chemokines RANTES, MIP-1α and -1β, and MCP-1 (57, 58), thereby potentially interfering with RANTES regulation of inflammatory cell migration (51). In epithelial cells already secreting RANTES, U51 expression results in specific transcriptional downregulation of the cytokine (59).

Altogether, HHV-6A, infecting RPE cells *via* CD46, would have the potential to interfere on several levels with the parainflammatory mechanisms central to AMD pathogenesis.

Association of AMD with HHV-6A-Related Diseases

If HHV-6A has an etiologic role in the development of AMD, as hypothesized here, a higher prevalence of AMD would be expected in other diseases where HHV-6A infection is observed. In contrast to HHV-6B, which is the infectious agent of roseola in childhood, no definite clinical picture of acute HHV-6A infection could be established so far (60–62). On the other hand, HHV-6A infection has been associated with several chronic diseases like AIDS, Hashimoto's thyroiditis, and MS and their epidemiological association is summarized in **Table 1**.

CONCLUSION

Despite the fact that more and more molecular and genetic mechanisms involved in the pathogenesis of AMD are known today (76–79), the etiologic trigger of the disease has not been identified so far. Center stage is taken by the CD46 on RPE cells with its regulatory role in complement activation, autophagy, and the chemokine/cytokine network. Since CD46 is also the sole cellular receptor for HHV-6A, one is tempted to speculate that HHV-6A might be the trigger for AMD. Supporting evidence comes from the potential of HHV-6A to interfere with inflammatory mechanisms (62, 80). Indirect evidence comes from

epidemiological studies that link HHV-6A-related diseases with AMD (**Table 1**).

In order to substantiate the hypothesis, several approaches are possible:

- Looking for HHV-6A DNA, viral proteins, and HHV-6A-encoded miRNA in pathology samples of AMD.
- Studying experimental infection of RPE cells with HHV-6A *in vitro*.
- Further epidemiological studies evaluating HHV-6A infection and AMD.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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