**The role of glial cells and the complement system in retinal diseases and Alzheimer’s disease: common neural degeneration mechanisms**

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**Abstract**

Many age-related degenerative diseases of the central nervous system (CNS) increasingly appear to have similarities in their underlying causes. By applying knowledge between disorders, and in particular between degenerative diseases of different components of the CNS (e.g. the eye and the brain) we can begin to elucidate general mechanisms of neural degeneration. Age-related macular degeneration and glaucoma, two diseases of retinal neurons, which have recently been discussed in view of their common mechanisms with Alzheimer’s disease, highlight this perspective. This review discusses the common roles of the complement system (an immunological system) and glial cells (providing, amongst other functions, trophic support to neurons) in these three disorders. A number of facets of these systems would seem to be involved in mechanisms of degeneration in at least two of the three diseases considered here. Regulatory proteins of the complement system (such as factor H), neurotrophin levels, and the interaction of microglia with the complement system in particular may be general to all three presentations of neural degeneration. Investigating the functioning of these fundamental systems across different diseases exemplifies the importance of considering advances in knowledge across a wider base than specific disease pathology. This may give insights both for understanding the function of these supporting systems and providing an avenue for developing future therapeutic targets general to neural degenerative diseases.

**Keywords:** Complement system; Glia; Alzheimer’s disease; Age-related macular degeneration; Glaucoma; Neurodegeneration

**The role of glial cells and the complement system in retinal diseases and Alzheimer’s disease: common neural degeneration mechanisms**

Cell death, and the mechanisms which guide it, is an important part of normal physiological function in the central nervous system (CNS) (Strasser, et al. 2000). However, as the CNS ages it becomes increasingly likely that cell death will occur for healthy cells, leading to a breakdown of some aspect of perceptual or cognitive function; as illustrated by the numerous age-related diseases, including retinal diseases age-related macular degeneration (AMD) and glaucoma, and the neurodegenerative Alzheimer’s disease (AD). Although these diseases may have very different symptoms (primarily central and peripheral vision loss in AMD and glaucoma respectively, and significant cognitive impairment in AD), there is mounting evidence that they may result from similar mechanisms (e.g. McKinnon 2003; Ohno-Matsui 2011; Sivak 2013). This may be further supported by evidence for some degree of co-morbidity (i.e. combined prevalence of a higher level than expected by chance) between these disorders (Bayer et al. 2002; Roca-Santiago et al. 2006; Gonzalez 2012). These apparent common causal mechanisms suggest that neural degeneration in diverging situations (with apparently different causes and outcomes) may be underpinned by widely applicable principles, which may therefore be able to be exploited to better understand such disorders by applying existing knowledge about one to others.

This type of approach may be particularly useful for applying knowledge of retinal diseases to neurological problems, as the eye is clearly a more accessible target than the brain, being the only component of the central nervous system that can currently be directly imaged *in vivo* (Cordeiro et al*.* 2004). The mechanisms discussed here are therefore specifically chosen to highlight areas for which there would seem to currently be more advanced understanding in the retinal diseases (AMD and glaucoma) than for AD. Previous reviews of the literature (e.g. McKinnon 2003; Ohno-Matsui 2011) have looked at these links but the body of literature on mechanisms of all three disorders considered here (AMD, glaucoma, and AD) is always growing, and these previous reviews have tended to focus more on applying knowledge from the neurological to ocular. This is perhaps understandable, as in some areas (as in the role of amyloid beta peptides in pathogenesis) the work on AD is considerably more advanced compared to ocular diseases, however there are some areas in which research into these ocular diseases may be applied to AD. This has been explored to some extent in a recent review by Sivak (2013), however this article took more of a bidirectional perspective, and focussed mostly on the areas of amyloid beta deposition and oxidative stress (two of the clearest and most thoroughly researched common mechanisms of degeneration in these diseases). The focus here is on mechanisms which may be triggered by amyloid beta and oxidative stress pathology (amongst other factors), which may be implicated as playing common causal roles in each disease, based on the research. Specifically we will consider the effect of these factors within an immunological system known as the complement system, and their effect on the glial cell network: two systems which typically function to protect and support healthy neural functioning.

**Background and definitions**

***Age-related macular degeneration***

In age-related macular degeneration (AMD), the cells of the high-acuity macular area (specifically the retinal pigment epithelium (RPE) and photoreceptor cells, Fig. 1) undergo degeneration, resulting in a gradual loss of vision in this central area of the retina (as photoreceptors are crucial for absorbing and transducing light for transmission to visual processing areas in the brain, and RPE cells support photoreceptors trophically and in replenishing pigment (Strauss 2005)). The early stages (prior to degeneration) of the disease are characterised by the build-up of an amyloid beta (Aβ)-based deposit known as drusen (Ambati and Fowler 2012). This occurs specifically in the photoreceptor layer and between the retinal pigment epithelium layer and Bruch’s membrane (the blood-retina barrier), and seems to originate from RPE cells (Johnson et al. 2002; Kam et al. 2010). One of the main components of drusen is the amyloid beta (Aβ) peptide, a molecule synthesised by a gene known as the amyloid precursor protein (APP). Amyloid beta exists in a number of forms, the most common of which in normal physiology is a neurotrophic form (sAPPα) (Lukiw et al. 2012). However, formation of drusen results from the production of a neurotoxic form (Aβ1-42), resulting from a decrease in production in of sAPPα leaving more APP free for production of Aβ1-42 (Lukiw et al*.* 2012). Neurotoxicity from Aβ1-42 and other molecules that also begin to accumulate in the formation of drusen (for a discussion of these see e.g. Buschini, Piras, Nuzzi, Vercelli 2011; Crabb et al. 2002; Ding, Patel, Chan 2009) eventually leads to degeneration of RPE and photoreceptor cells (as discussed in *Common causal mechanisms*), in some cases resulting in the weakening of Bruch’s membrane (the blood-retina barrier), allowing choroidal neovascularisation (where blood vessels from the vasculature behind the retina grow through this membrane; Ambati and Fowler 2012) and possible rupture of Bruch’s membrane (Mousa et al.1999); both of which result in bleeding into the retina (a progression of the condition to the form known as ‘wet’ AMD). These processes result in a loss of central vision, of varying distribution and denseness (i.e. the impairment may be focussed over part of or the whole of the central part of vision, and may either be absolute or more diffuse).



**Figure 1 –** a schematic illustration of the structure of the retina

***Glaucoma***

Unlike in AMD, the primary class of cells affected by glaucoma is that of retinal ganglion cells. Retinal ganglion cells (RGCs) are responsible for integrating information from multiple photoreceptor cells in order to convey this information to the brain for processing (Curcio and Allen 1990); degeneration of these cells therefore may include degeneration from their origin in the retina through to their terminations (largely) in the lateral geniculate nucleus, leading to involvement of this area, and, even further along the processing stream, the primary visual cortex, in the pathology of glaucoma (Yücel and Gupta 2008). The most commonly identified trigger for the mechanisms of glaucoma is increased pressure within the eye (intraocular pressure) due to damage to the trabecular meshwork structure at the junction of the cornea and iris, covering the aqueous drainage canal (either simply by ‘wear and tear’ or build-up of material on the trabecular meshwork due to growth factor dysfunction (Sihota et al. 2001; Wordinger et al*.* 2007)). This leads to impaired drainage of nutritious fluid from the eye, raising pressure (Kwon et al. 2009). This increase in pressure has then been implicated in the initiation of a number of molecular mechanisms (such as oxidative stress, discussed further in *Mechanisms*) that may result in the death of retinal ganglion cells. In terms of the perceptual impact of this condition, glaucoma can be conceived of as somewhat opposite to AMD: peripheral vision is usually affected in the first instance in this condition (as opposed to central vision in AMD), with retinal ganglion cells tending to receive inputs from greater numbers of photoreceptors in the peripheral retina (and thus degeneration of peripheral ganglion cells affects larger proportions of the peripheral visual field; e.g. Gellrich and Gellrich 1996), and an apparent particular vulnerability of larger retinal ganglion cells (more commonly found in the peripheral retina) to degeneration (Glovinsky, Quigley, Pease 1993; Laquis, Chaudhary, Sharma 1998).

***Alzheimer’s disease***

Alzheimer’s disease is characterised by neurotoxic Aβ1-42 accumulations (known as senile plaques; as in the drusen associated with AMD) and the formation of fibrous tangles of another protein, tau, within neurons. The presence of these features is proposed to lead to death of both neurons themselves and also glial support cells (Pak et al. 2003) in diverse areas of the brain including the neocortex, hippocampus, and basal forebrain nuclei (Selkoe 2002). The degeneration of neurons in these areas leads to cognitive impairment, most prominently progressive memory loss. The association of the pathology of AD specifically with amyloid beta is supported by the strong link between Down Syndrome and AD (insofar as those with Down Syndrome almost always develop a form of AD (Lott and Head 2005)). This is significant in that Down Syndrome is specifically associated with trisomy (triplication) of chromosome 21, on which APP is located. This therefore supports a theory of increased availability of APP products for synthesis to neurotoxic forms (Aβ1-42) (Lukiw et al*.* 2012) as an important causal factor in AD. Tau tangles are thought to build up in a similar way, with accumulation of normal tau precursors triggered by adverse cell conditions leading to aggregation of a pathological form of tau which results in impairment of axonal transport (see Ballatore et al. 2007); the role of tau in the disease pathology is discussed no further in this review as the role of this in AMD and glaucoma is not so clear as that of Aβ.

***Complement system***

The first system that will form a large part of discussion here is the complement system, which will thus first be described in terms of its typical function, in order to provide context for its involvement in disease pathogenesis. The complement system is an important part of the normal immune system which primarily acts to eliminate microbes via proteins (complement factors) located either in cells or embedded in the membranes of cells, leading to lysis (other-mediated cell breakdown) or cell death via destruction of important structures within the cells (Fishelson et al. 2001). This may occur via three separate pathways: the classical pathway, the alternative pathway, or the lectin pathway. The classical pathway functions by binding of the complement factor C1q to invading bodies which have been stabilised by antibodies; the alternative pathway is activated by fragments of dead cells (typically bacterial); and the lectin pathway works by binding of a protein called mannose-binding lectin to carbohydrate groups typically found on the surface of bacterial cells. These three pathways all converge in function by initiating a cascading response leading to the cleavage of complement factor C3, resulting in the activation of the membrane attack complex, a molecule which primarily induces necrosis (unprogrammed cell death) via attack on mitochondria (Rus et al. 2005). These responses are shut down either when the targeted microbe is destroyed, or, if attached to an antibody, when it is inhibited by a regulatory protein designed to prevent the host antibody from being destroyed itself (Abbas et al. 2007). The complement system may also induce apoptosis (programmed cell ‘suicide’): although activation of the membrane attack complex to a level insufficient to cause necrosis does not seem to be sufficient for initiation of apoptosis, investigation of the dead cells after activation of the membrane attack complex indicates that the mechanism of death for these cells may be combined necrotic and apoptotic mechanisms. Furthermore, complement factors prior to this stage in the complement cascade (such as factor C3) have been implicated in initiation of apoptosis in cells prior to the onset of membrane attack complex activity (Fishelson et al*.* 2001).

Alternatively, studies have indicated that apoptosis initiated by some other mechanism may activate the complement cascade. Apoptosis of a cell leaves waste product known as apoptotic bodies; the activation of the complement system may occur following apoptosis for clearance of these bodies, possibly by the activation of the complement factor C3b by a molecule produced by apoptotic cells (phosphatidylserine) (Mold and Morris 2001). This activation of the complement system clearly imparts a risk of the initiation of further activation and thus the death of healthy tissue. This is typically regulated by the complement regulatory proteins previously mentioned (largely the complement factor H in this case) (Fishelson et al*.* 2001); however these may become compromised in degenerative diseases, providing a mechanism for degeneration. This is discussed further in *Common causal mechanisms.*

***Glial cells***

The other focus of this review is the glial cell network (both in interaction with and independently of the complement system). There are three main types of glial cells found generally in the central nervous system: astrocytes, oligodendrocytes, and microglia. These provide a range of support roles to neurons, including providing nutrition, maintenance, and regulation (mostly astrocytes), as well as clearing of debris (microglia), and insulation (oligodendrocytes) (Jessen 2004). In the retina there are few astrocytes and no oligodendrocytes (as the neurons are sufficiently short as to not require insulation to function efficiently), but an additional group of glial cells: Müller cells. These are involved in nutrition and maintenance of neurons, and also perform clearing functions similar to microglia (Newman and Reichenbach 1996).

**Common causal mechanisms**

One of the most obvious similarities between AMD and AD is the presence of deposits of neurotoxic amyloid-beta peptides in the retina (drusen) and the brain (plaques) respectively. Less well documented, but nevertheless apparent, is the involvement of a similar deposit in RGCs in glaucoma (McKinnon 2003). Specifically, deposits of Aβ are found in AMD between the RPE and Bruch’s membrane (Johnson et al*.* 2002), co-localised with degenerating RGCs in glaucoma (Guo et al*.* 2007), and as plaques in the hippocampus and cortex of AD patients (Atwood et al. 2002). An argument has been advanced by some researchers using detailed cellular imaging methods that, in particular with drusen and AD plaques, these deposits are of limited morphological similarity, and therefore caution should be taken in attributing too much significance to the common occurrence of such deposits in these different diseases (Anderson et al. 2004). However, this has limited relevance to the discussion here as (a) this review does not focus in detail on the role of protein deposits specifically, highlighted here only to provide relevant background for their possible role in the initiation of later degenerative mechanisms, and (b) whether or not the morphology of the deposits is the same, their importance seems to particularly rest on the constituent parts; i.e. amyloid beta. This would seem to be supported by the attention in recent years by some researchers beyond the actual deposits of Aβ to a less easily detected form of these peptides; soluble oligomers (composed of several Aβ peptides bonded together) (Barghorn et al*.* 2005; Glabe 2006; LaFerla et al. 2007; Esparza et al*.* 2013). Some work of particular interest has suggested that in fact these oligomers are more important than the deposits (Esparza et al*.* 2013), (see also evidence for oligomers in AMD and glaucoma (Luibl et al. 2006; Yin et al. 2008)), potentially explaining cases in which deposits of Aβ are evident, but the disease has not manifested (e.g. Kam et al*.* 2010; Esparza et al*.* 2013).

One way in which the accumulation of amyloid beta may lead to degeneration is by a process known as oxidative stress; whereby molecules such as DNA and proteins are damaged due to excessive oxidation resulting from an imbalance of the activity of oxidants and antioxidants (Chandra et al. 2000). This imbalance may occur via the oxidising properties of the amyloid beta peptide, which is thought to produce hydrogen peroxide (an oxidant; Behl et al. 1994), and has also been shown to induce the accumulation of a toxic molecule known as a reactive oxygen species (reactive because it holds ‘spare’ electrons therefore rendering it readily able to form bonds with other molecules, resulting in their oxidation) (Mattson and Goodman 1995). Reactive oxygen species may also be increased in response to iron deposits, a feature of all three diseases (LeVine 1997; Farkas et al*.* 2004; Dunaief 2006), and in glaucoma and AD may lead to a self-propagating mechanism of degeneration involving the glutamate cycling system; oxidative stress increases levels of glutamate to a neurotoxic amount, causing damage of mitochondria via dysfunction of the calcium signalling system, resulting in production of reactive oxygen species which then clearly increases oxidative stress (Walton and Dodd 2007; Chrysostomou et al. 2012). Oxidative stress then may initiate apoptosis in cells via the activation of caspases (a class of enzymes which produce energy for the breakdown of proteins such as DNA). Although apoptosis is typically a useful process (e.g. for healthy brain development, eliminating neurons inappropriate to the developing region-specific morphology and of abnormal neurons which may otherwise become problematic) (Roth and D’Sa 2001), in degenerative disorders as discussed here apoptosis occurs in healthy cells, thus interfering with function. The roles of amyloid beta peptides and oxidative stress in each of the three disorders discussed here have been covered at length in previous reviews (e.g. Sivak 2013). However, this brief introduction allows discussion of events that may be triggered by these factors, and demonstrates a higher level commonality between the three disorders in particular which are considered here.

***Complement system***

One such mechanism which has been linked to amyloid beta neurotoxicity (Chiu, Chan, Wu, Leung, So, Chang 2012) and has received less attention in previous reviews, and which has been demonstrated to play a role in cell degeneration in all three disorders, is the complement system (Tichaczek-Goska 2012). As previously mentioned (see *Background and definitions: Complement system)*, the complement system may be activated in response to apoptosis in order to clear the waste resulting from this cell death, initiated by the complement factor C3b (Mold and Morris 2001). In normal function, complement activity is shut off after the waste is cleared by regulatory proteins such as complement factor H; however, there is evidence for reduced plasma levels of factor H in AMD and AD coupled with upregulation of factor H-suppressing microRNAs which bind to the untranslated portion of factor H-producing mRNA and prevent its synthesis (Lukiw et al. 2008; Lukiw et al*.* 2012; Tichaczek-Goska 2012) , and for down-regulation of factor H activity due to oxidative stress in glaucoma (Tezel et al*.* 2010) (a mechanism which may presumably also exacerbate the problem in AMD and AD), therefore providing a potential mechanism of cell death in these (i.e. with apoptosis, initiated by oxidative stress resulting from factors such as neurotoxic amyloid beta accumulations, leading to complement activation which then cannot be inhibited, and therefore results in widespread activation of a greater complement response and thus cell death). Further to this, a particular variant of the gene regulating synthesis of complement factor H, the Y402H polymorphism, has been identified for AMD (Hecker et al*.* 2010). Y402H is proposed to lead to alterations in the structure of factor H, resulting in difficulty in binding to certain targets (including necrotic cells; Day et al. 2011). This variant has also been found by some studies to be associated with AD (e.g. Zetterberg et al. 2008; although see Le Fur et al*.* 2010 for contradictory evidence). This therefore provides another mechanism by which the pathogenesis of these diseases may be caused. Another regulatory protein (i.e. which typically controls the activity of the complement system) to consider is CD59, the deficiency of which has been implicated in cell death in AD (Yang et al. 2000). There seems to be no definitive research of AMD implicating CD59 in the pathogenesis of this disease, however studies which have induced similar symptoms in mice have observed down-regulation of this factor, indicating that this could also be a possible mechanism of complement-related cell death in AMD (Jha et al. 2007).

In addition to these regulatory proteins, there is evidence for up-regulation of the complement factor C1q, the initiating factor for the classical pathway of the complement system, in glaucoma (Stevens et al*.* 2007) and in AD (Fischer et al. 1995). This may be as a result of the role of C1q in clearance of waste following necrosis of cells (Gaipl et al. 2005), however once present it is proposed that C1q also has a role in ‘tagging’ synapses for destruction (Stevens et al*.* 2007). There does not seem to be a particularly significant increase in C1q in AMD, although it has been noted as a constituent of drusen and therefore may be assumed to play some role in this disorder (van der Schaft et al. 1993).

Complement factor H and factor C1q are mostly associated with the alternative and classical pathways of complement activation respectively (CD59 regulates all three pathways; Rus et al*.* 2005), however there is also some evidence for the involvement of the lectin pathway in AMD and AD in particular. As previously noted, the lectin pathway is activated by the recognition of specific carbohydrate groups that are typically found on the surface of bacterial cells (Rus et al*.* 2005). These are specifically two carbohydrate groups called mannose and N-acetylglucosamine, and, importantly, have been identified to be present in drusen (Mullins and Hageman 1999). This is proposed to result from the degradation of the pigment-containing RPE cells, as mannose and N-acetylglucosamine are two of the main constituents of larger carbohydrate complexes which compose one of the main human pigments, rhodopsin; leaving mannose and N-acteylglucosamine molecules when this is broken down (Cingle et al. 1996). This therefore provides another source of complement activation in AMD, supported by the presence of the protein mannose-binding lectin (the complement factor of the lectin pathway) in drusen (Anderson et al*.* 2010). There appears to be less research centred around the presence of these carbohydrates for AD. However, Lanzerein and colleagues (1998) suggested that lower concentrations of mannose-binding lectin in the cerebrospinal fluid of patients with AD was suggestive of lectin pathway complement activation in this condition, which may indicate some similar process here as in AMD, and a modified form of N-acetylglucosamine has been associated with the stabilisation of Aβ plaques in AD (e.g. Griffith et al. 1995), implying that the unaltered form is also likely present in some measure.

***Glia***

The complement system may also be implicated in the dysfunction of support cells, another problem seen in various forms in AMD, glaucoma, and AD (e.g. Streit 2005; Bhutto et al*.* 2006; Qu et al. 2010). There are extensive support cell systems in the eye and the brain (e.g. glial cells) providing, amongst other functions, neurotrophic and immunological support to these areas (e.g. Kumar et al. 1993; Holtkampet al*.* 2001; Strauss 2005; Farina et al. 2007). The role of microglia in particular in the pathogenesis of these diseases has been linked with the complement system, with suggestions that one mechanism of the activation of the microglial system may be the detection of complement activation, and that this may then lead to the widespread proliferation of microglia seen in all three diseases (Yuan and Neufeld 2001; Gupta et al. 2003; Khoury and Luster 2008; Lucin and Wyss-Coray 2009). Studies of the role of microglia in age-related neurodegeneration suggest that such proliferation may become problematic as a stronger and more prolonged inflammatory response is produced than in younger organisms, resulting (as with the complement response described previously) in loss of healthy cells and an associated functional impairment (Wong, 2013). Microglia are known to be able to produce complement factors (Gasque et al. 2000), therefore this may also contribute to the over-activation of the complement response in these diseases, possibly exacerbated by changes in the expression of regulatory complement factors (including reduced expression of complement factor H, discussed previously; Ma et al. 2013). These changes were explained by Ma and colleagues (2013) in a study of AMD-affected retinas by another of the neurotoxic constituents of drusen, lipofuscin; a molecule which has also been noted in both AD and glaucoma (de Castro et al 2013; Dowson 1982; Ma et al 2013).

Further insight into the particular contribution of microglia to the progression of degenerative diseases may come from research into glaucoma, indicating an early increase followed by progressive reduction in the inhibition of microglial immunological function (Taylor et al. 2011). This is consistent with the progression of such diseases, with an initial accumulation of matter (such as the amyloid beta deposits seen in AMD, AD, and glaucoma) clearly not destroyed by immunological responses as it should be, followed by a strong immunological response on native cells (resulting in the observed cell death). In addition to the other mechanisms which may contribute to this response (such as oxidative stress as discussed previously), it has also been proposed that the presence of amyloid beta may elicit microglia to produce C3, the immediate precursor to the necrosis-inducing membrane attack complex in the complement cascade (Walker et al. 1995) and the resulting death of cells may elicit the migration of further microglial cells to the affected area to clear the debris produced by cell death, thus also becoming activated and attacking further native cells (Gupta et al*.* 2003). Both of these components (C3 and the membrane attack complex) are found in drusen (Anderson et al. 2004), glaucomatous retinal ganglion cells (Tezel et al. 2010) and senile plaques (Webster et al. 1997). A further role for microglia may be in the destruction of synapses ‘tagged’ by the complement system (see *Common causal factors: Complement system;* Stevens et al*.* 2007).

Astrocytes and Müller cells are also able to produce complement proteins (Gasque et al*.* 2000; Stasi et al*.* 2006) and therefore may contribute to degeneration in similar ways. However, these cells may also promote degeneration in other ways than via the complement system. For instance, Tezel and Wax (2000) demonstrated that retinal glia produce a substance called tumor necrosis factor-α (a pro-apoptotic factor), which leads to apoptosis of cells via the binding of this substance to specialised receptors. These receptors are found to be up-regulated in glaucoma (Tezel et al. 2001). Evidence from AD suggests that the level of tumor necrosis factor- α is also increased in the pathology of this disease (Fillit et al*.* 1991); however there seems to be less detailed evidence of the possible contribution of this for AD compared to glaucoma. A similar situation also seems to exist for nitric oxide. In typical function, nitric oxide acts as a neurotransmitter, generated by neurons and implicated in functions such as synaptic plasticity and gene expression regulation (Dawson and Dawson 1996); however evidence suggests that, in glaucoma, astrocytes in the optic nerve head region produce a toxic quantity of nitric oxide (Morgan et al. 1999), leading to interference with cell respiration and damage to DNA (Bredt and Snyder 1994; Zhang et al. 1994). This upregulation occurs in response to increased intraocular pressure (Neufeld 1999; Liu & Neufeld 2001), possibly as an attempt at neuroprotection as the vasodilatory effect of nitric oxide in normal physiological function can help to reduce intraluminal pressure (Nathanson & McKee 1995; relevant here in relation to the increased intraocular pressure implicated in the most common form of glaucoma). Similarly to tumor necrosis factor- α, a role for nitric oxide has also been proposed for AD (Law et al. 2001), but again has been less detailed, with more focus in the literature on dysfunctional glutamate cycling (Caraci et al*.* 2012), an area which is perhaps more developed for AD than for glaucoma (Kuehn et al. 2005), for which a mechanism may be mediated by nitric oxide production (Dawson and Dawson 1996). However, as in glaucoma, nitric oxide may be released in an attempt to counteract dysfunction – in the case of AD reduced cerebral blood flow (Girouard, Iadecola 2006) – with this ultimately becoming counterproductive as a neurotoxic level of NO is produced.

There are also further mechanisms by which support cell dysfunction may be problematic in ocular and neurodegenerative diseases. For instance, one important function of glia is their trophic support of neurons. The significance of this can be seen in glaucoma, in the loss of cells of the lamina cribrosa. The lamina cribrosa consists of glial cell columns joined by tissue plates, and forms part of the optic nerve head; its cells are therefore damaged in the pathogenesis of glaucoma (by tumor necrosis factor- α, discussed previously (Taylor et al*.* 2004)). These cells are known to provide trophic support to RGCs via production of neurotrophins including nerve growth factor and brain-derived neurotrophic factor (proteins which support the development and survival of neurons) (Lambert et al. 2001). The loss of these cells therefore removes important trophic support from RGCs, increasing the likelihood of cell death. This is particularly problematic in glaucoma as a secondary source of neurotrophins, visual processing areas of the brain such as the superior colliculus, are prevented from providing this support due to blockage of axonal transport from these areas by the increased intraocular pressure associated with this condition (Quigley et al*.* 2000). There is similarly some evidence for reduced neurotrophin levels in AD; Connor and colleagues (1997) found reduced levels of brain-derived neurotrophic factor in the hippocampus and temporal cortex, a finding which has been attributed by some to interference in axonal transport of this substance (as in glaucoma), in this case by the formation of Tau tangles in neurons (Schindowski et al. 2008).

**Evidence from the results of therapeutic applications**

Further evidence may be seen for the existence of these common neural degeneration mechanisms by looking at existing therapeutic targets in the three diseases considered here, how these overlap, and where there is scope to explore potential targets which are as yet not being considered, based on the application of this knowledge. This approach may allow a practical way to understand how far it is useful to understand degeneration mechanisms in the way discussed in the previous section: a treatment targeting a mechanism thought to be common to the diseases should produce a positive effect in each if there is true pathological similarity. From the current evidence presented below (Table 1) this would seem to be the case for the mechanisms discussed here. However, two potential caveats need to be considered of the evidence presented in the following section: firstly, some of the models of disease used to assess potential therapeutic targets do not include all of the mechanisms discussed in the previous section. This is particularly the case in much of the therapeutic work on AMD using rodent choroidal neovascularisation models, which emulate the ‘wet’ form of AMD but often do not include many of the features discussed previously in relation to AMD (notably drusen is not present). However, although this is a clear limitation, these models are widely used in the literature for primary assessment of possible targets, and many of the mechanisms implicated in the diseases as discussed previously (as arising from processes e.g. as associated with the presence of drusen and seen also in the earlier ‘dry’ form of AMD) are seen in these models (e.g. down-regulation of the complement regulatory protein CD59) (Bora et al. 2007). Secondly, some of the potential targets discussed here have not yet been shown to be effective in humans, with current research restricted to animal models of the diseases: randomised control trials in humans would be needed to verify these findings, and similarly any of the findings from preliminary open-label trials in humans.

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| **System** | **Target** | **AMD** | **Glaucoma** | **AD** |
| **Complement system** | Complement factor H | Injected (rat model; Kim et al*.* 2013); patented for treatment (Binder & Weismann 2013); mediating factor in other treatments (e.g. Brantley et al*.* 2009; Nischler et al*.* 2011) | Theoretical only (Tezel et al*.* 2010) | Theoretical (e.g. Lukiw, Zhao, Cui 2008) Patented for treatment (Binder & Weismann 2013) |
| CD59 | Injected (mouse model; Bora et al*.* 2007)Gene therapy (mouse model; Cashman et al*.* 2011) | n/a | Theoretical only (Yang et al. 2000) |
| C1q | n/a | Progesterone treatment (may reduce C1q; Posthumus 1952; Paulssen et al*.* 2008); patented for treatment (Shepard et al*.* 2009) | Injection (rat model; Sárvári et al*. 2*003) |
| Mannose-binding lectin  | Theoretical only (Anderson et al*.* 2010) | n/a | Theoretical only (Lanzerein et al. 1998) |
| **Glia** | Microglia | Theoretical only (Gupta et al. 2003) | Inhibition of microglia (Bosco et al*.* 2008) | Theoretical only (Khoury & Luster 2008) |
| Tumor necrosis factor-alpha | n/a | Inhibitors (Roh et al*.* 2012); open-label trials (Theodossiadis et al*.* 2007); RCT for related condition (Saurenmann et al*.* 2006) | Open-label trial (Tobinick 2007) |
| Nitric oxide | n/a | Inhibitor (Neufeld et al*.* 1999); inhibition of precursor (Liu et al*.* 2006) | Two approved pharmacological treatments targeting a precursor (Wang et al*.* 2012) |
| Neurotrophins | Secreting implant (Emerich & Thanos 2008; Goldberg 2012) | Injection (rat model (Mey & Thanos 1993); gene therapy (rat model; Pease et al*.* 2009); secreting implant (Emerich & Thanos 2008; Goldberg 2012) | Injection (mouse model; Garcia et al*.* 2010) |

**Table 1** – Possible therapeutic targets and current available evidence for efficacy in age-related macular degeneration, glaucoma, and Alzheimer’s disease. Theoretical only refers to cases where the underlying mechanisms have been described in theoretical investigations of the disorders but no attempts to address the therapeutic feasibility have been made so far.

***Complement system therapeutic targets***

*Complement Factor H*

Complement factor H is an important regulatory factor of the complement system, found to be reduced or mutated to a non-functional form in AMD, glaucoma, and AD (Zetterberg et al*.* 2008; Hecker et al*.* 2010; Tezel et al*.* 2010; Lukiw et al*.* 2012). Recent work has demonstrated some evidence of the efficacy of injection of complement factor H for improving outcomes in a rat model of AMD (Kim et al*.* 2013). This therefore provides proof of principle for complement factor H as a potential therapeutic target, further confirming its role in the disease pathogenesis; similar experiments for AD to investigate whether this finding is also true here (as the evidence discussed previously suggests it should be). A patent has been filed in the US for the use of complement factor H as a treatment for a clinical samples with a variety of diseases including AMD and AD (Binder and Weismann 2013), which indicates that clinical trials may begin for this target for both diseases in the near future. Alternatively, an *in vitro* model of oxidative stress in human neural cells resulting in lowered levels of CFH demonstrated that anti-microRNA injection is able to counteract this reduction, providing another possible way to target CFH (Lukiw et al. 2008).

An additional way in which knowledge from AMD about complement factor H may be able to contribute to understanding of AD is through the knowledge that, in AMD, it has been found that the Y402H polymorphism for complement factor H mediates treatment outcome for other treatments (e.g. Brantley et al*.* 2009; Nischler et al*.* 2011). This may therefore be applied to AD through an investigation of how different polymorphisms of the factor H gene may interact with different treatments and levels of treatment.

*CD59*

A deficit in complement regulatory protein CD59 also leads to cell death by allowing the complement immune response to be too prolonged and too strong. Evidence from research using a common mouse model of AMD (laser-induced choroidal vascularisation) has indicated that injection of a CD59 solution into the abdominal cavity or into the eye prevented formation of the membrane attack complex (the pro-necrotic end-product of the complement cascade) and reduced levels of growth factors which contribute to vascular problems (Bora et al*.* 2007). CD59 would therefore seem to be a possible target for Alzheimer’s treatment, potentially providing a way to prevent, or at least slow, cell death, via the reduction of complement-mediated cell death.

However, Bora and colleagues (2010) reported increased apoptosis of some cells in another study of this CD59 solution in their AMD mouse model. The specific cells affected in this way for this study were of a problematic cell complex which contributes to choroidal vascularisation (problematic overgrowth of blood vessels) in AMD, therefore providing a good outcome for the affected mice; this therefore might indicate that CD59, if correctly targeted, may similarly be able to affect problematic cells in AD. However, whereas in AMD this choroidal neovascular complex is created by cell proliferation (i.e. new cells), most of the problems in AD are created by extracellular events such as the build-up of Aβ1-42, and intracellular events such as the formation of Tau fibrils occur within existing cells (Selkoe 2002) and thus apoptosis of these cells would be damaging, not therapeutic. However, Bora and colleagues (2007; 2010) clearly show that a CD59 solution may have some therapeutic value, and, given that CD59 has been identified to have a role in the pathogenesis of AD, research would be needed to see how this form and other possible reformulations may affect disease progression for AD. This could be further supported by more recent work by another research group exploring the possibility of another form of CD59 treatment, delivered using gene therapy techniques, which, further to confirmation of the results of Bora and colleagues (2007; 2010), indicated that RPE cells may be protected from complement-mediated attack (Cashman et al. 2011). This therefore suggests that CD59 could, in the right form, be a suitable target to encourage neuroprotection of cells in Alzheimer’s disease. Exploration of this possibility would increase knowledge about the precise role of CD59 in AD.

*C1q*

Complement factor C1q is a key component of the classical pathway of the complement immune response (Gaipl et al*.* 2005). There seems not to be any research directly looking at the impact of C1q inhibitors on outcomes in any of the three disorders discussed here. However, the hormone progesterone, which has been shown to have some effectiveness in treatment of glaucoma (e.g. Posthumus 1952), has been demonstrated in other diseases to reduce production of C1q (Paulssen et al. 2008). This link may provide some support for the use of more targeted C1q inhibitors. A patent has been published for this, however no clinical trials seem to be forthcoming at this time (Shepard et al. 2009). Research in a rat model of AD indicating that a C1q inhibitor was able to prevent complement-mediated damage to hippocampal cells (Sárvári et al*.* 2003) provides preliminary support for clinical use in this disease; clinical trials are thus now needed for both glaucoma and AD.

*Mannose-binding lectin*

The lectin pathway of the complement system is implicated in AMD and possibly AD. No research seems to have been carried out specifically to investigate if mannose-binding lectin inhibitors could help treat either of these diseases, however evidence from oxidative stress-related complement activation following tissue damage in rats indicate that inhibition of this component could help reduce complement activation in a situation of oxidative stress (a significant factor in both AMD and AD (Collard et al*.* 2000; Nunomura et al. 2006; Ambati and Fowler 2012)). More specific trials focussing on mannose-binding lectin inhibitors would help to evaluate the role of the lectin pathway in AMD and AD.

***Glial therapeutic targets***

*Microglia*

Microglia are involved in clearing of debris in intracellular space (Jessen 2004). There is some evidence that reducing activity of microglia in a mouse model of glaucoma improves outcomes (Bosco et al*.* 2008; although see Howell et al. 2010). Research in AD has indicated a pro-inflammatory role for microglia in this disease (i.e. promoting immune response against native cells (Tan et al. 2012)); clinical trials may help confirm this if inflammation was shown to be reduced in response to therapeutic targeting.

*Tumor necrosis factor-α*

Tumor necrosis factor- *α* is a pro-apoptotic agent produced by glial cells implicated in degeneration (e.g. Fillit et al*.* 1991; Tezel and Wax 2000). Recent evidence from a rat model of glaucoma has supported the targeting of this molecule by inhibitors, reducing degeneration of RGCs and proactive degeneration of axons to the visual processing areas of the brain (Roh et al*.* 2012). Clinically, the use of antagonists for the receptors of this molecule (as up-regulated in glaucoma; Tezel et al*.* 2001) has been supported by a number of open-label (i.e. non-blinded, non-controlled) studies, showing improved outcomes in a number of ophthalmic diseases (Theodossiadis et al. 2007). There is also evidence from randomised control trials with childhood uveitis, an ophthalmic condition which often leads to glaucoma in later life, that inhibitors of tumor necrosis factor- *α* may be beneficial in reducing the likelihood of glaucoma developing (e.g. Saurenmann et al*.* 2006); although this is clearly not ideal, and a randomised control trial of such inhibitors for glaucoma itself would be desirable, this does lend further support for the use of such treatments.

An inhibitor of tumor necrosis factor *α* has also been investigated forAD (Tobinick 2007; Tobinick and Gross 2008), indicating improvement in cognitive measures in an open-label trial. More rigorous randomised control trials with such a control and with patient and assessor blinding to which condition the patients were in would be desirable for AD (and for glaucoma), however this does indicate some preliminary support for tumor necrosis factor- *α* inhibitors as a viable therapeutic strategy for AD, and thus supports the view that this factor is common to degeneration in both disorders.

*Nitric oxide*

The production of neurotoxic levels of nitric oxide by glia has been proposed as a mechanism of degeneration in glaucoma (Morgan et al*.* 1999). Neufeld and colleagues first demonstrated in a rat disease model that a substance which inhibits the production of nitric oxide (aminoguanidine) reduces retinal ganglion cell degeneration (Neufeld et al. 1999). Furthermore, additional work by the same group indicated another target (epidermal growth factor receptor) which may also inhibit the production of the enzyme contributing to the synthesis of nitric oxide in glaucoma (Liu et al. 2006). Treatment of Alzheimer’s disease appears to have overtaken glaucoma somewhat for this target in recent years, with two approved pharmacological treatments targeting EGFR available to treat this condition (Wang et al*.* 2012): together with the evidence from glaucoma again supporting the idea of common degeneration mechanisms in both disorders. Nevertheless, as previously discussed, it would appear from the literature that the theoretical research around nitric oxide as a causal agent in neurodegeneration is more advanced for glaucoma than for AD, therefore reciprocal consideration of the knowledge surrounding nitric oxide by those working on glaucoma and AD may be beneficial for both diseases.

*Neurotrophins*

Glia produce neurotrophins to promote neuron growth, maintenance, and survival (Lambert et al*.* 2001).The use of neurotrophins as a therapeutic strategy has been supported in glaucoma in animal models, with reduced RGC loss in with glaucomatous rats following injection of brain-derived neurotrophic factor and ciliary neurotrophic factor (Mey and Thanos 1993). More recently, gene therapy conveying ciliary-derived neurotrophic factor has also been shown to be beneficial using a similar paradigm (Pease et al*.* 2009). A further treatment possibility currently being investigated is a ciliary-derived neurotrophic factor-secreting implant (NT-501), which has, in preliminary investigations, shown some degree of success in not only glaucoma but also AMD and other ophthalmologic conditions (Emerich and Thanos 2008; Goldberg 2012). These strategies may therefore also be interesting possibilities to pursue for the treatment of AD, supported by findings that ciliary-derived neurotrophic factor improves outcomes in a mouse model of this disease (Garcia et al*.* 2010). This evidence again provides good preliminary support for the idea of common degenerative mechanisms, with animal model evidence for the efficacy of targeting neurotrophins available for all three disorders discussed here, and additionally successful clinical trials for the ophthalmic disorders.

**Conclusion**

It is increasingly clear the degeneration of cells which takes place in retinal diseases such as age-related macular degeneration and glaucoma and in neurological conditions such as Alzheimer’s disease may occur by similar mechanisms. The discussion here has focused on dysfunction of the immunological complement system and support cells such as glia, with support from both basic and applied studies for common roles of these systems in the degeneration seen in AMD, glaucoma, and AD. This suggests a similarity of functional properties in both the complement system and the glial cell system in the retina and brain, with implications for degeneration and normal function.

It should be noted that these systems clearly provide a potentially problematic target for treatment as they are adaptive mechanisms in normal physiology to protect the individual; shutting them down entirely is thus clearly not a practical solution, even if this could be technically feasible, as this may result in problems such as increased susceptibility to disease (e.g. Sohn et al. 2007). This therefore is something that would need to be addressed in evaluating the usefulness of any therapy targeted at these systems. However, given the apparent overlaps in mechanisms of degeneration in these diseases there is clear support for the idea of common neural degeneration mechanisms across retinal and other CNS processes. This principle also clearly extends beyond the specific diseases and mechanisms discussed here, and may be applied both in the other direction (i.e. treatments of Alzheimer’s disease investigated for use in glaucoma and age-related macular degeneration; as discussed in reviews e.g. Sivak 2013), and for other disorders (e.g. Parkinson’s disease, amyotrophic lateral sclerosis, etc.). The discussion in the section *Evidence from the results of therapeutic applications* illustrates the importance of researchers being aware of this general applicability in some areas, and thus of being aware of advances in knowledge in related fields; it is clear both here and from evidence presented elsewhere (e.g. in Ohno- Matsui 2011) that there is an unfortunate and avoidable pattern of discoveries in both retinal and brain function which are subsequently rediscovered in the other system up to decades later; for instance neurotrophin injections have proved beneficial both in a rat model of glaucoma and in a mouse model of AD, but with a 17 year gap between these findings (Mey and Thanos 1993; Garcia et al*.* 2010). Although many of the possible links in degeneration mechanisms between the diseases discussed here are still somewhat tentative, and more work is clearly needed to corroborate the full extent of the viability of such a paradigm, the evidence presented seems promising in this regard. This would have implications not only for treatment of such diseases (with increasing prevalence and thus both human and economical costs necessitating exploration of any such possibilities; Skurla et al. 1988; Wittchen et al*.* 2011), but also for understanding of normal CNS function, with dysfunction serving as a useful proxy by which to study this.

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