Chapter 5

Alzheimer's-Related Amyloid Beta Peptide Aggregates in the Ageing Retina: Implications for Sight Loss and Dementia

J. Arjuna Ratnayaka and Savannah Lynn

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/64790

Abstract

Although visual problems are reported by patients with Alzheimer's disease and dementia, studies into this particular aspect of neuropathology are scarce. The growing awareness of complex pathological processes in the ageing retina and brain, however, enables us to consider this from a new perspective. Here we discuss the latest findings on the wide-ranging visual defects experienced by those suffering from Alzheimer's disease and dementia. We propose that events leading to chronic degeneration of the retina and the brain in fact share many striking similarities. In particular, we discuss the role of the Alzheimer's-related amyloid beta (Aβ) group of peptides that has been shown to accumulate in senescent retinas, correlated with increased risk of retinal degeneration. The high photo-oxidative retinal environment creates ideal conditions for Aβ aggregation, evidenced by high Aβ loads reported in aged and donor eyes from patients with age-related macular degeneration. Consequently, longitudinal and non-invasive retinal assessments may provide invaluable information on incipient pathology and disease progression in the retina as well as the senescent brain. Such insights may not only lead to identifying new pathogenic mechanisms in the retina with implications for understanding Alzheimer's disease but reveal the underlying causes of visual abnormalities reported in patients with dementia.

Keywords: amyloid beta, retina, degeneration, Alzheimer's, age-related macular degeneration

1. Introduction

Dementia poses a significant risk to those over the age of 65, affecting up to 46.8 million individuals globally, a number that is expected to increase to approximately 131 million by 2050 [https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf]. Currently, no reliable treatments exist, although it has been estimated that slowing disease progression by just 5 years would reduce the number of dementia-related deaths by almost half [https://www.alzheimers.org.uk]. Alzheimer's disease (AD) is an age-related neurodegenerative disorder of the brain, and the most common cause of dementia amongst the elderly [1]. AD is typified by progressive memory loss and significant cognitive decline amongst other complications that ultimately leads to death [2].

A major pathological feature of AD is misfolding and aggregation of the naturally occurring amyloid beta (Aβ) family of proteins. A variety of different Aβ peptides are generated by successive proteolytic cleavage of the amyloid precursor protein (APP). These accumulate as large insoluble aggregates in AD brains and are referred to as 'senile plaques'. The amyloid cascade hypothesis proposes that Aβ plays a central role in AD [2]. However, AD and dementia are complex diseases, and the role of Aβ and other disease factors are still incompletely understood. Studies are also hampered by the brain's relative inaccessibility, and clinical diagnosis typically occurs many years after disease onset [3]. Consequently, there is considerable impetus towards developing non-invasive, reliable and cost-effective diagnostic methods so those at risk may be identified at relatively early stages to maximise the chances of clinical intervention. Most studies into AD and dementia are primarily focused on memory loss and cognitive decline [4, 5]. However, many AD patients are also reported to suffer from a variety of visual complications, which by contrast has received comparatively little attention. The recent discovery that Aβ deposits in the ageing human retina correlate with complex retinopathies such as age-related macular degeneration (AMD) has given support to the hypothesis that shared pathologies may exist between the brain and senescent retina.

In this chapter, we provide a comprehensive review of the latest findings reporting visual abnormalities in patients with AD and dementia. The methodology for this review is based on searches conducted in the NCBI PubMed (http://www.ncbi.nlm.nih.gov/pubmed) database using keywords 'dementia and retina' (396 articles) and 'AD and retina' (457 articles) in June 2016. These numbers contrast starkly with larger numbers of studies in areas related to memory loss and cognitive decline. For example, use of keywords 'dementia and memory loss' (12,383 articles) or 'AD and cognitive impairment' (19,883 articles) yield many more citations; highlighting the as yet limited interest in systematically reporting visual abnormalities in AD and dementia patients. Additionally, we used keywords such as 'retina and Aβ' (111 articles) and 'retinal pigment epithelium (RPE) and amyloid' (59 citations) to include specific articles related to ophthalmology and dementia, and to describe studies in ex vivo and animal models that provide insights into Aβ-mediated pathogenesis. Centring on these articles, specific information in hyperlinks, as well as insights from our own work, we discuss the role of Aβ in driving retinal degeneration and neurodegeneration, and propose that the eye may provide a powerful model to study Aβ pathology. We suggest that the retina may act as an anatomical

http://dx.doi.org/10.5772/64790

window into the Alzheimer's brain through which early stages of neurodegeneration could non-invasively be identified.

2. The ageing brain and retina: intimate connections

The neuroretina and the central nervous system (CNS) share common origins as both derive from the developing neural ectoderm and maintain a direct and permanent connection via the optic nerve [6]. The neuroretina may therefore be considered an extension of the brain that resides within a discrete compartment—the eye. In addition to this anatomical link, both the retina and tissues of the CNS exhibit similar structural and functional arrangements. These include specialised structural adaptations such as surface infolds, postmitotic neuronal and epithelial cells, immunologically privileged compartmentalisation via a blood-brain/retinal barrier, as well as more importantly, similar patterns of damage with increasing age [7]. It is therefore possible that common disease mechanisms may also be involved in diseases of the ageing eye and brain.

Gathering of visual information first occurs when light enters the eye's anterior pole and is projected to the neuroretina. Here, incident light is converted by specialised photoreceptors in the neuroretina into electrical impulses which are subsequently relayed to second- and third-order neurons [8] (**Figure 1**). Axons of retinal ganglion cells (RGCs) then convey these signals to the brain. The synaptic arrangement in the neuroretina comprises of three sequential neuronal layers: photoreceptors, bipolar, and RGCs (referred to as the three neuron links) [9]. Neuronal cell bodies and processes exist in alternate layers giving rise to the laminated structure of the retina where cell bodies typically exist within the inner and outer nuclear layers, whereas processes and synapses of retinal neurons reside within the inner and outer plexiform layers [10]. In addition to these cell types, specialised neurons referred to as amacrine and horizontal cells facilitate the parallel processing of information [9]. Furthermore, a highly specialised monolayer of epithelial cells which originates from the neuroectoderm referred to as the RPE forms the margins of the outer retina and the interface with the outer vasculature (**Figure 1**) [11]. Here, within this strategic position, the RPE performs many critical metabolic and supportive functions for the overlying neuroretina. These include the absorption of stray light, phagocytosis of shed photoreceptor outer segments (POS) as part of the daily visual cycle, maintenance of the blood-retinal barrier (BRB), ion homeostasis as well as playing a role in retinal adhesion [11, 12]. The normal function of the RPE monolayer is therefore critical to maintain healthy vision in old age.

The arrangement of the mammalian retina is such that light must first traverse the entire length of the retina before reaching the photoreceptors. Two distinct types of photoreceptors exist which may be categorised according to histological morphology and which are each specialised for a specific function. Rod photoreceptors constitute 95% of all photoreceptors, express the photopigment rhodopsin and are responsible for scotopic (low light) visual processes [13]. Cone photoreceptors on the other hand encompass a highly invaginated membrane to provide an optimal surface area for phototransduction and are responsible for photopic (normal/high

light) visual processes, the perception of colour and visual acuity. Colour vision is achieved through expression of the photopigment opsin, which, depending on the structure of the molecule, confers sensitivity to varying wavelengths of light [9]. Cone photoreceptors typically concentrate within the fovea—an area corresponding to 1.5 mm in diameter at the centre of the human retina where light from the central visual field is focused and which is responsible for high visual acuity and detailed image perception [14]. Within this area, the retina is devoid of the inner retinal layers and retinal vasculature, which ensures minimal interference to focused light when creating a clear foveal image [9]. The region peripheral to the fovea is termed the macula which has a high proportion of cones that extends to a radius of 5.5 mm in diameter [14].

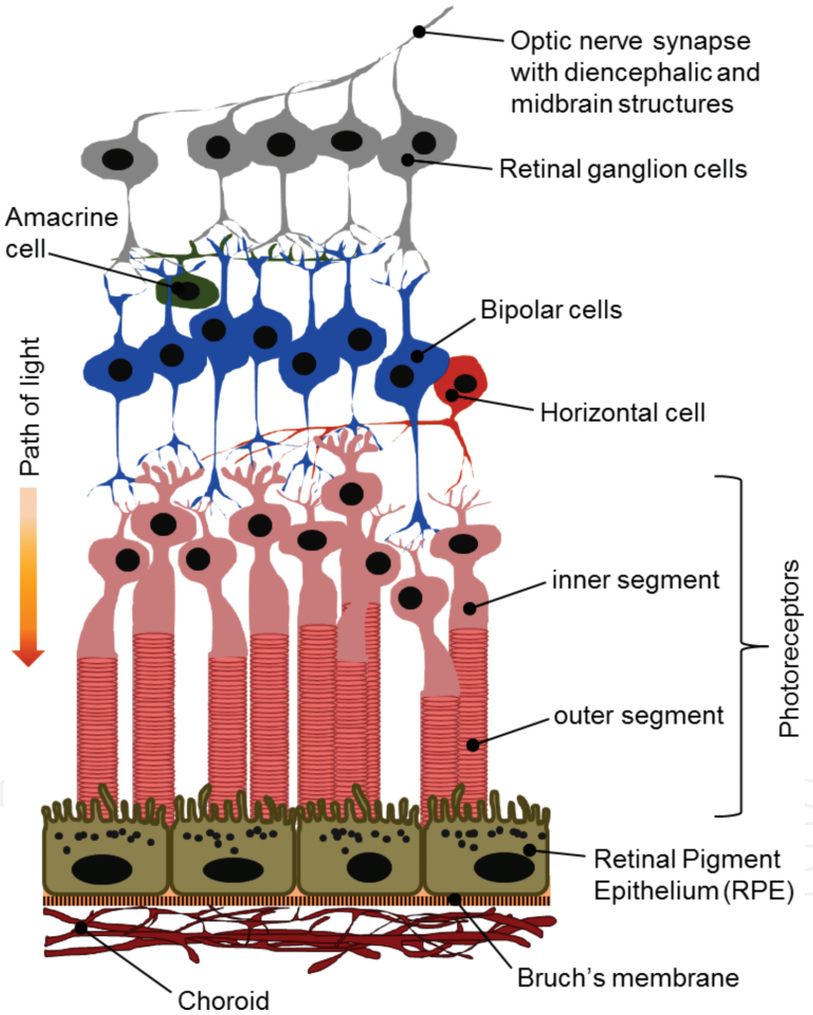

Figure 1. Synaptic arrangement of the neuroretina and associated layers. Diagram illustrating the inverted arrangement of the human neuroretina with light-sensitive photoreceptors forming intimate associations with the underlying retinal pigment epithelium (RPE).

The axons of the RGCs converge at the centre of the retina where they exit the eye through the optic disc and maintain a permanent connection with the brain via the optic nerves (**Figure 2**) [15]. The optic nerve (also referred to as the second cranial nerve) enters the cranial cavity via

http://dx.doi.org/10.5772/64790

the optic canal where it runs parallel to the middle cranial fossa in close proximity to the pituitary gland. Anterior to the stalk of the pituitary gland, an anatomical crossroad exists known as the optic chiasm, where optic nerves unite and axons from RGCs that reside within the nasal side of both left and right retinas connect with the opposing hemisphere of the brain (**Figure 2**). Conversely, temporal RGC axons project to its corresponding cerebral hemisphere. Soon after exiting the optic chiasm, the RGC axons converge to form the optic tract which predominantly synapses with the lateral geniculate nucleus (LGN), a relay centre for the visual pathway that resides within the thalamus. The internal structure of the LGN comprises several layers which function as maps of visual space and which segregate information according to axonal origin. As the LGN receives information from the right and left visual fields, visual input from the opposing hemisphere is kept separate from that of the corresponding eye. This information is then passed to the visual cortex within the posterior brain for processing via optic radiations formed by the axons of the LGN neurons (**Figure 2**). Here, segregation of visual information is maintained according to the location in the retina from which information was perceived. For example, information derived from the fovea occupies a significant area of the posterior visual cortex, whereas progressively more anterior regions of the visual cortex represent visual perceptions from the periphery of the retina. Several other regions of the brain are innervated from the visual cortex including the occipital, parietal and temporal lobes. These areas are linked with visuoperceptual and visuospatial aspects of vision, as well as visual acuity and the recognition of familiar objects [16, 17].

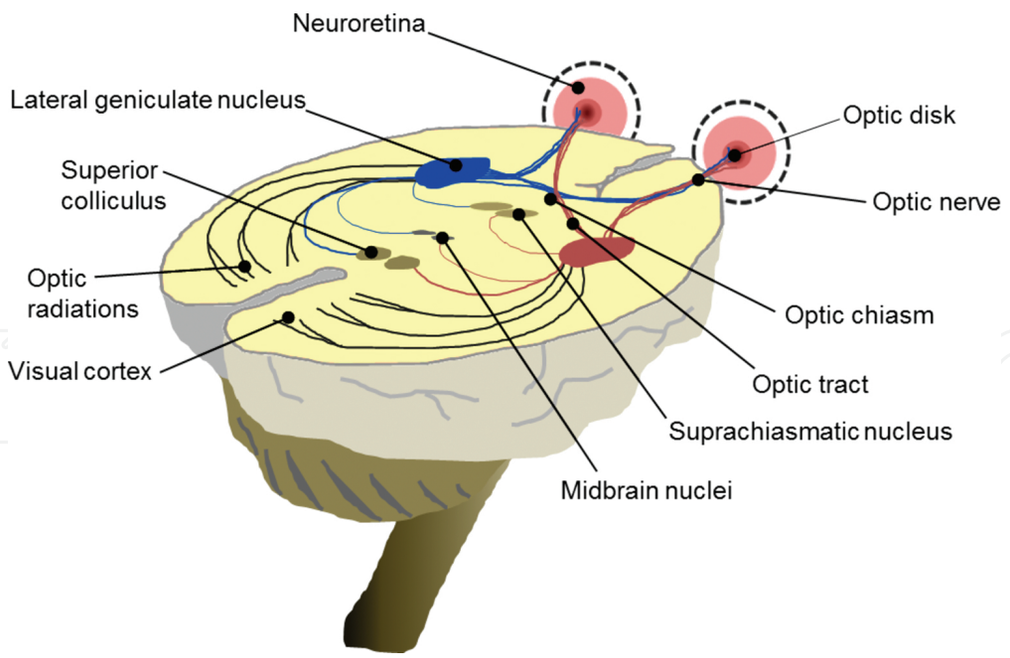

Figure 2. Synaptic terminals of the optic nerve and visual pathway in the brain.

RGC axons within the optic tracts also connect with several diencephalic and midbrain structures. These include the superior colliculi (SC), also termed the optic tectum which is

situated on the roof of the midbrain and is involved in controlling eye movement; the suprachiasmatic nucleus (SCN) which is a small, wing-shaped structure within the hypothalamus located directly above the optic chiasm that is involved in circadian rhythm; and nuclei within the midbrain that are implicated in controlling pupil diameter (**Figure 2**). Of note, several of these aforementioned visual centres have been associated with AD pathology. For instance, the SC has been shown to progressively accumulate both Alzheimer-associated senile plaques as well as neurofibrillary tangles (NFT). AD-linked changes have also been reported in the SCN including a reduction in the size, cell number and accumulation of NFTs, which may collectively contribute to the wide range of visual complications reported in these patients [15, 17].

3. Visual abnormalities in Alzheimer's disease and in patients with dementia

A variety of visual abnormalities have been reported in patients with AD ranging from visuo-constructional and visuo-perceptual dysfunctions, object agnosia, prosopagnosia to visual hallucinations as well as simultanagnosia [5, 18, 19]. Patients with posterior cortical atrophy (PCA), which is associated with degeneration of the posterior cortex, also report particular difficulties with visual tasks often presenting with visual agnosia, visual neglect and visual hallucinations [20, 21]. However, compared to memory loss, visual deficits have received little attention and are thus poorly understood. Patients in the spectrum of, and leading to, clinical AD show marked reductions in the number of RGC [22], narrowing of venous blood column diameter and reduced venous blood flow rates [23], as well as optic nerve abnormalities such as loss of axonal densities [24], RGCs [25] and increased receptor expression for advances glycation end products [26]. Abnormalities are also observed in regions of AD brains that synapse with the optic nerve and/or are associated with the visual processing pathway (**Figure 2**). Some examples include the loss of myelin, diminished nucleolar volume in the LGN, as well as accumulation of lipofuscin (autofluorescent pigment granules) [27]. AD brains also show the presence of NFT in the SC [28] (which receives ~10% of the RGC axons), as well as the presence of Aβ/neuritic plaques in regions of the brain that are implicated in visual attention and the control of eye movement. Aβ deposition has also been reported in the lens of AD patients [29]. Additionally, histopathological evidence from post-mortem brains reveals significant pathological changes in the visual processing regions of the brain including the loss of pyramidal cells and reduced myelin in the outer laminae of the visual cortex [30–33]. A comprehensive list of such neurological changes in areas of the brain associated with vision has been described by Armstrong (2009) indicating the extensive nature of psyco-visual abnormalities in patients with AD and dementia [29].

Not surprisingly, a large number of AD transgenic animal models also develop visual deficits and have therefore been used to investigate retinal pathologies. These include, but are not limited to, the Tg2576 [34], APPswe/$PS1_{M146L}$ and APPswe/PSΔE9 [35], 5xFAD [36, 37], and P301S [38] mice. A wide range of retinal changes have been documented in these animals,

http://dx.doi.org/10.5772/64790

including an age-dependent increase in APP/Aβ immunoreactivity in the neuroretina and associated vasculature, the accumulation of Aβ plaques/hyperphosphorylated tau in the nerve fibre layer (NFL) and RGC, thinning of the RGC, as well as glial cell-derived neuro-inflammatory responses within the retina [4]. Of importance, a number of these changes are common to well-established animal models of retinal degeneration that are widely used to study AMD [39, 40].

4. The degenerating retina: sight loss in old age

Despite the growing number of Alzheimer's patients reporting visual complications, this has received comparatively little attention. This may be due to several reasons including incomplete diagnosis, associated complications, old age and cognitive impairment of patients as well as lack of medical devices or tools to obtain a clear clinical diagnosis. Consequently, the breadth and diversity of visual abnormalities in AD and dementia patients is yet to be fully recognised. For example, analysis of published literature in NCBI PubMed using keywords such as 'vision and dementia' (without the inclusion of any further search parameters) yielded only 447 citations in a 10-year period (between 2006 and June 2016), which is surprisingly few given the frequency of visual abnormalities reported in these patients. In contrast, search terms such as 'memory loss and cognitive decline' yield 3062 citations over a similar period. Understanding how the ageing retina becomes susceptible to degeneration and how it may affect the visual pathway and/or perception by the brain could provide insights into the molecular and cellular basis underlying visual abnormalities in AD. Here then is an opportunity to gain further insights into how the world may be perceived by those suffering from AD and dementia. Patients with retinopathies not only have damaged retinal tissues but also show impairments in how visual information is relayed to and processed by the brain. For instance, visual hallucinations classified under the term Charles Bonnet syndrome have been reported in patients with late-onset visual disorders such as AMD [41]. Indeed, almost half of AMD patients experience visual hallucinations, whilst a third report hallucinations that are distressing, intrusive and interfere with daily activities [41, 42]. AMD affects approximately 50 million individuals globally [8, 43]. Unlike rare diseases caused by single-gene mutations, AMD is a complex multifactorial disease which in many ways shows striking parallels with AD [4, 44, 45].

AMD exhibits an age-dependent prevalence with one in three individuals exhibiting some sign of early disease by their seventh decade [43]. Currently, there are over half million AMD patients in the United Kingdom (source: Macular Society), with comparable incidence rates in Europe and other Western populations as reported by the European Eye Study (EUREYE) [46]. This puts a significant strain on national healthcare budgets with the direct annual cost of AMD exceeding US$254 billion globally [14]. This figure is predicted to rise three-fold over the next 20 years as a result of increased life expectancy and reduced mortality rates [43]. This common, irreversible blinding condition derives its name from the macula; the anatomical region affected in disease. This specialised region, which we have introduced earlier, resides at the

centre of the retina, temporal to the optic disk and is responsible for visual acuity and image resolution (mediating focused central vision). Patients with AMD therefore suffer loss of centrally mediated sight [45]. As the majority of patients are typically in the latter stages of life, this has a disproportionate social impact, similar to some social issues encountered by patients with AD and dementia [43].

The early stage of AMD is typically asymptomatic, and like AD, can remain so for many years before clinical diagnosis. Hence, most patients with early AMD exhibit few or no obvious visual symptoms [47], although a recent study found indications of early macular pathology even in those aged between 35 and 44 [48]. A major pathological hallmark of early AMD is the focal deposition of lipid-rich extracellular aggregates between the RPE and Bruch's membrane (**Figure 1**) [49]. With increasing age, such aggregates termed 'drusen' become common within the periphery of normal healthy retinas as hard structures with well-defined borders [50]. In contrast, patients with larger, soft drusen showing ill-defined borders (~125 μM) in the macula region are considered to be at a higher risk of developing AMD [51]. Late AMD presents as two distinct phenotypes; classified as geographic atrophy (dry) and neovascular (wet) AMD. If early stages of the disease are excluded, the numbers of dry and wet AMD patients are broadly similar [52]. Dry AMD is typified by gradual impairment of macular RPE cells and death of overlying photoreceptors. By contrast, wet AMD is characterised by growth of new leaky blood vessels from the underlying choroid (**Figure 1**). This results in accumulation of fluid/sub-retinal swelling and scaring of the macula due to disruption of the outer BRB [45]. The growth of new vessels in wet AMD may be managed in most cases through monthly intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors. In contrast, dry AMD which affects the majority of AMD patients currently has no effective treatment [8]. Significant advances have been made in recent years to identify the genetic landscape of AMD and related retinopathies [45]. However, this new knowledge has yet to provide insights into key disease mechanisms, or translate into effective treatments against advancing blindness. It is therefore vital to gain a better understanding of disease processes in the ageing retina before effective AMD treatments can be developed. The recent discovery of the Alzheimer's-associated Aβ peptide, a well-known neurodegenerative agent associated in key stages of AMD, has opened up the possibilities of studying sight loss from a novel perspective. Such studies in a highly accessible tissue such as the retina could lead to a better understanding of Aβ mechanisms as well as new insights into AD and dementia.

5. Age-related macular degeneration and Aβ

The healthy retina is constitutively exposed to Aβ. In fact, recent findings demonstrate that Aβ synthesis occurs at local sites within the retinal environment including the RPE and RGCs [53, 54]. The RPE is considered to be the principal source of Aβ in the posterior eye; a tissue which also expresses APP [55]. The RPE also expresses the necessary factors for regulating Aβ synthesis including β- and γ-secretase, as well as the Aβ-degrading enzyme neprilysin [56,

http://dx.doi.org/10.5772/64790

57]. Furthermore, studies of mouse and bovine ocular fluids show the presence of Aβ in picomolar to nanomolar quantities within both aqueous and vitreous humours [58].

The retina is a particularly useful tissue to study Aβ pathology as it is continuously exposed to high photo-oxidative stresses throughout life, an ideal environment for Aβ accumulation [44, 59, 60]. Hence, it is not surprising that the Aβ burden in the retina increases with advancing age. To date, age-dependent accumulation of Aβ has been shown in multiple retinal locations including photoreceptors, RPE, Bruch's membrane and within the inner and outer retinal vasculature [39, 55, 61, 62]. This pattern of Aβ accumulation has been reported both in rodent models and in donor human eyes. For instance, Aβ deposits on photoreceptor were shown to be abundant on mature POS or outer tips which are phagocytosed by RPE cells as part of the daily visual cycle. Studies in wild-type mice show such Aβ-enriched outer tips of photoreceptors to be enlarged, possibly due to impaired internalisation of POS by senescent RPE [39]. The use of antibodies that recognise Aβ as well as APP also show immunoreactivity within the cytoplasm of RPE cells that are adjacent to drusen [55]. Numerous studies also reveal the presence of Aβ within drusen, which links a key clinical hallmark of AMD with Aβ [44, 55, 61–63]. Aβ within drusen have been shown organised into assemblies of approximately 2–10 μm in diameter. These spheres referred to as 'amyloid vesicles' were shown to have a concentric ring-like interior, permeated with Aβ immunoreactivity [55].

Interestingly, studies of post-mortem tissues show that the ageing human retina plays host to a variety of Aβ assemblies. The use of various antibodies including 4G8, 6E10, WO1, WO2, OC, A11 and 82E1 has revealed the presence of non-fibrillar oligomers, protofibrils and mature amyloid fibrils [55, 61, 62]. Furthermore, different Aβ structures were evident in different locations within amyloid vesicles. For example, in studies using 4G8, 6E10, WO1 and WO2 (which specifically recognise mature Aβ assemblies including protofibrils and mature fibrils), immunoreactivity was typically observed within the outer shell of amyloid vesicles [55, 61, 63]. Conversely, studies investigating Aβ oligomers (antibodies A11 and M204) showed preferential accumulation at the centre of drusen in close proximity to the inner collagenous layer of Bruch's membrane. Here, Aβ oligomers constituted the most abundant Aβ assembly within drusen [39, 62]. Moreover, the presence of Aβ within drusen appeared to correlate with drusen load as well as increasing age [63]. One study using a small number of patient samples found that Aβ deposition were only present within drusen of AMD patients; supporting the likelihood that Aβ accumulation is associated with more advanced forms of AMD [64].

As the RPE monolayer, which is strategically juxtaposed between the neuroretina and the outer retinal vasculature (**Figure 1**), appears to be the main focus of Aβ deposition, it is not surprising that Aβ has profound effects on its function. Of critical importance is the role of the RPE in maintaining the immune-privileged state of the retina via the outer BRB. Oligomeric $A\beta_{1-42}$ has been shown to impair both early zonular occludens (ZO-1) and mid-to-late occludin tight junctions in the RPE as well as induce actin cytoskeletal disorganisation. This suggests that Aβ may compromise BRB integrity [65]. This is comparable to Aβ's mode of action in the AD brain which results in blood-brain barrier (BBB) disruption, increased BBB permeability and endothelial cell dysfunction [66]. In fact recent studies have also shown a downregulation of both ZO-1 and occludin upon application of Aβ to human cerebral microvascular endothelial

cells. Such insights reveal striking parallels between neurodegenerative processes between the ageing retina and brain, and how Aβ may play a key role in both pathologies [7, 66]. Similarly, oligomeric Aβ exposure causes an upregulation of VEGF in both the brain and retina which has been linked with AD and AMD. VEGF is essential in maintaining hippocampal plasticity as well as cognitive function. However, VEGF upregulation is correlated with $A\beta_{1-42}$ accumulation in AD brains resulting in neuronal cell death and BBB dysfunction [67]. In the eye, VEGF is primarily secreted by the RPE; the increased levels of which are correlated with the neovascular form of AMD [8]. Anti-VEGF inhibitors consequently form the current the mainstay of wet AMD treatments. Exposure of RPE cells to Aβ was shown to profoundly increase VEGF secretion, which may contribute to such an undesirable pro-angiogenic retinal environment [57].

Aβ also appears to play a central role in chronic inflammation of the ageing retina. Such pathology is similar to inflammatory conditions found in AD brains [68]. For example, transcriptome studies show enhanced complement gene expression in AD brains, particularly those of complement C1q and C3 proteins [69, 70]. AMD involves a similar chronic inflammatory response that is as yet incompletely understood. Here, compliment associated proteins deposit within drusen alongside Aβ including compliment factor C3, compliment factor H and the membrane attack complex, including its constituents C5, C6, C7 and C9 [55, 71]. Consequently, Aβ is thought to promote a pro-inflammatory retinal microenvironment where it co-localises with complement factor H (CFH) and iC3b to induce compliment activation. Studies have also shown the elevation of pro-inflammatory IL-1β, IL-6, IL-8, TNF-α and caspase-1 upon intravitreal Aβ injection in C57BL/6 J mice, as well as an increase in IL-8 and MMP-9 secretion levels by RPE upon exposure to $A\beta_{1-42}$ [72, 73]. Microglial activation and engulfment of Aβ have also been observed co-localised with retinal Aβ [39]. Similar pathology is also reported in the brains of patients with AD [68].

Unsurprisingly, key features of AMD observed in human donor eyes can be recapitulated by experimentally elevating retinal Aβ levels in wild-type mice. Our studies show that subretinal injection of human recombinant $A\beta_{1-42}$ at physiological doses (nM range) in C57BL/6 mice induces RPE pigment abnormalities, RPE plasticity as well as photoreceptor outer segment loss, hallmarks of AMD (**Figure 3**). Critically, using the 82E1 antibody specific to human Aβ, we found experimentally introduced Aβ to co-localise to multiple retinal locations corresponding to points of Aβ immunoreactivity reported in eyes of both AD [74, 75] and AMD patients/mouse models [55, 61–63]. Hence, Aβ was shown to localise to RGC, the outer nuclear layer, photoreceptors as well as the RPE-Bruch's membrane interface [39]. Attempts by others to elevate $A\beta_{1-42}$ levels in the rodent vitreous resulted in apoptotic cells in photoreceptor and nuclear layers as well as a significant reduction in RGC [76, 77]. However, our method of elevating the retinal Aβ load via subretinal injection appears to mimic the senescent eye more accurately (**Figure 3**), as the resulting phenotype certainly bears closer resemblance to human AMD [55, 63, 64]. Additional evidence for ocular Aβ pathology comes from studies implicating Aβ in other eye diseases such as supranuclear cataracts and glaucoma of which the latter is common amongst AD patients [4].

http://dx.doi.org/10.5772/64790

6. Similarities between AD and AMD

Degenerative processes in the ageing retina and brain share many common features. A major pathological hallmark common to both AD and AMD is the formation of insoluble extracellular aggregates that share several histochemical and compositional properties. Proteomic analyses of the molecular components of senile plaques and drusen, for instance, has revealed common proteins including tau, clusterin, vitronectin, apolipoprotein E (ApoE), serum amyloid P (SAP), Aβ, metal ions, as well as pro-inflammatory factors and components of the compliment cascade [4, 44, 78]. Histochemically, such deposits also stain with thioflavin T and Congo red which confirms the presence of misfolded or amyloid proteins. However, there appears to be differences between Aβ structures found in senile plaques and drusen. For instance, whilst

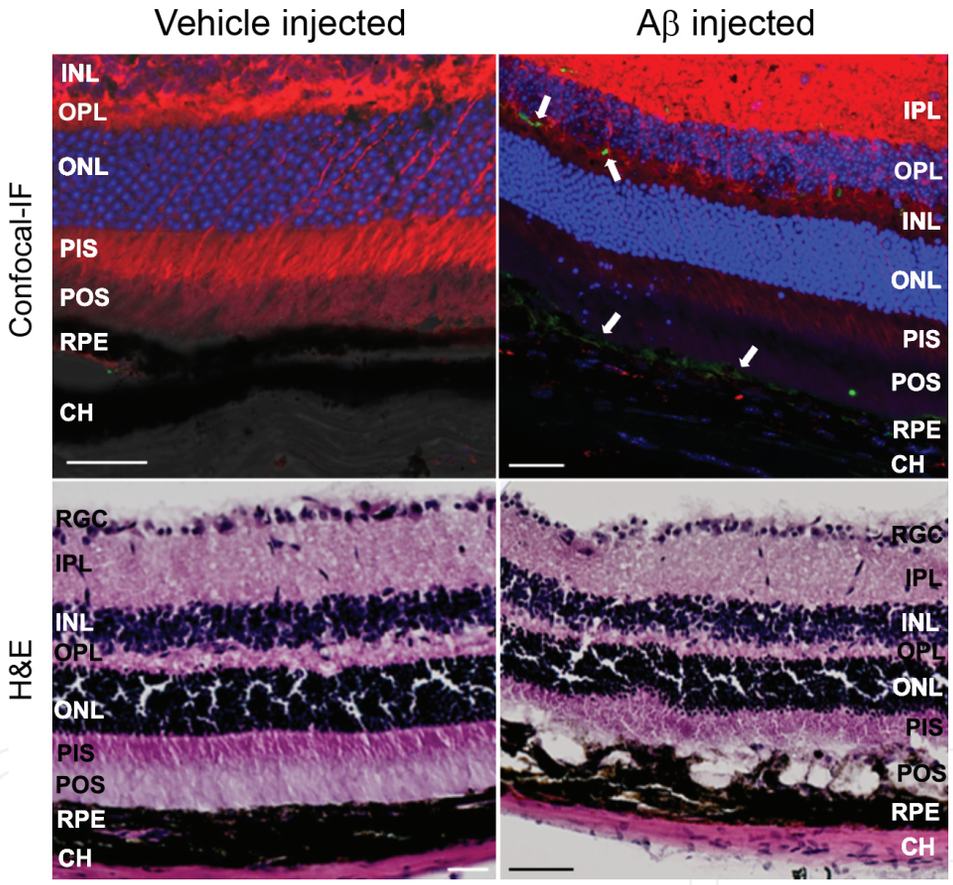

Figure 3. Subretinally injected Aβ in our mouse model recapitulates key aspects of retinal degeneration observed in age-related macular degeneration (AMD). Wild-type C57BL/6 mice injected with nM concentrations of recombinant human $A\beta_{1-42}$ recapitulated key features of AMD. At 8 days post-injection, retinas contained RPE pigment abnormalities, RPE hypertrophy as well as photoreceptor outer segment loss, in contrast to healthy retinas of vehicle injected mice. Confocal-immunofluorescence using the human Aβ-specific antibody 82E1 revealed focal Aβ deposits (green) in the inner nuclear layer and in the RPE-Bruch's membrane interface (arrows) corresponding to areas of Aβ synthesis/accumulation reports in aged human retinas. RGC, retinal ganglion cells; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; PIS, photoreceptor inner layer; POS, photoreceptor outer segments; RPE, retinal pigment epithelium; BM, Bruch's membrane; CH, choroid. DAPI (blue). Scale bar corresponds to 100 μm.

both types of extracellular protein deposits stain for Congo red, only senile plaques are positive for the apple green birefringence dye specific for anti-parallel β-pleated sheets [49, 63].

Commonalities between AD and AMD are also observed in the manner in which highly localised and significant damage occurs to lysosomes and mitochondria. In AD brains, these include substantial increases in the size/number of endosomes, autophagosomes and lysosomes; accumulation of lysosomal dense bodies in dystrophic neurites, as well as changes in expression of lysosomal hydrolases such as cathepsins [2, 79]. Our studies as well as those of others have shown selective permeabilisation of lysosomal membranes and release of lytic content into the cytosol as a precursor to neuronal death, indicating a mechanism of early cellular compromise correlated with a specific vulnerability in certain neurons [2, 79, 80]. Analysis of fixed tissues from AMD patients show extrudes of senescent RPE cytoplasm with reactive lysosomes into the underlying Bruch's membrane, and the accumulation of incompletely digested POS from overlying photoreceptors as lipofuscin within lysosomes [14]. Senescent postmitotic RPE cells with lipofuscin-filled lysosomes are a characteristic feature of the ageing retina, and it accounts for as much as 20% of the cytoplasmic volume by the age of 80. Experiments using cell lines show the toxic nature of lipofuscin and its derivative N-retinylidene–N-retinylethanolamine (A2E) that disrupts the phagocytic mechanisms of RPE cells, impairs lysosomal proteases, inhibits the lysosomal ATPase proton pump and causes leakage of lysosomal contents into the cytosol [81]. Dysfunctional lysosomes with lipofuscin/A2E also generates reactive oxygen species (ROS), modify lipid peroxidation and forms high molecular weight components that are stable within lysosomes. Moreover, A2E causes detergent-like membrane disruption and inhibits lytic function. Healthy macula RPE cells contain high levels of lysosomal enzymes acid phosphatase and cathepsin D, relative to lysosomes from RPE cells in the nasal/mid-zone and peripheral retina [82]. Lysosomal enzyme activity decreases by up to 50% when exposed to lipofuscin [83], indicating the regional vulnerability of the macula in early AMD. Lysosomal damage may be further exacerbated by the highly photoxidative RPE environment, providing ideal conditions for ROS generation [84].

Mitochondria also show early damage in AD. Hence, post-mortem AD brains show significantly fewer mitochondria, abnormally enlarged as well as exceptionally small mitochondria, damaged cristae, changes to organelle physiology, fission/fusion rates and transport defects [85]. Mitochondrial abnormalities have also been linked to AMD primarily using studies of cell lines showing a decrease in the number/area of RPE mitochondria, changes in redox components and proteins involved in mitochondrial trafficking, increase in mitochondrial DNA repair and decreased RPE mitochondrial respiration. A2E specifically damages mitochondria inducing RPE apoptosis [60]. Our previous studies of a variant form of cystatin C associated with AMD revealed a striking endoplasmic reticulum (ER)/Golgi to mitochondria mis-localisation, which may have long-term consequences for RPE mitochondria [86, 87]. Recently, a strong association between the mitochondrial ARMS2 variant protein and AMD was reported which appeared to drive AMD towards a neovascular phenotype [8].

Genetic risk factors between AMD and AD also indicate evidence of a shared aetiology. For instance, studies have revealed a substantial link between allelic variants encoding compo-

http://dx.doi.org/10.5772/64790

nents of the alternative compliment cascade and the risk of developing AMD including factor H, factor B and C3 [88–91]. Evidence for a similar genetic predisposition in AD has been reported where polymorphisms within the CFH allele have been linked with an increased risk of AD [92]. The large number of compliment cascade components that have been reported within drusen and senile plaques, as well as the fact that chronic inflammation is a key driver in both AD and AMD indicates that similar inflammatory responses may be involved in the aetiologies of both AD and AMD. A strong genetic link has also been associated with ApoE, a polymorphic gene encoding proteins ApoE2, ApoE3 and ApoE4 involved in lipid metabolism. Amongst these, ApoE4 is somewhat confusingly associated with a lower risk of developing AMD, whilst conferring an increased susceptibility to AD. Although the reason for this is not clear, the positively charged nature of ApoE4 is speculated to interact somewhat differently with Bruch's membrane in the outer retina compared to its behaviour in the brain [93, 94]. The opposite holds true with regard to ApoE2, which is protective in AD but is associated with a higher risk of developing AMD. The reason for this also remains elusive [4]. Collectively, it appears that ApoE dysregulation may affect Aβ metabolism/clearance in the retina and brain in somewhat different ways, but which nonetheless triggers or drives pathology in these respective tissues [93, 95, 96]. Several environmental factors are also shared between AD and AMD that are thought confer increased susceptibility. These include cigarette smoking and diet, as well as conditions such as high blood pressure, heart disease, stroke, diabetes, high cholesterol levels and obesity [97–99]. In fact, a recent study conducted by the World Health Organisation (WHO) revealed that smoking, which is the most prominent environmental risk factor for AMD, almost doubled the risk of developing dementia [http://www.who.int/tobacco/publications/en/]. The growing awareness of these shared pathologies in the senescent brain and retina as well as the increasing sophistication of detection methods are beginning to uncover closer links between AD and AMD. For instance, a recent study revealed the increased risk of AMD amongst AD patients [100].

Collectively, this body of evidence strongly suggests a significant overlap between the aetiologies of AMD and AD. This is not surprising, given the extensive visual complications being reported in patients with AD and dementia. Initial detection typically relies on self-diagnosis and/or observations by friends and family and is therefore often inconsistent, adding to the potential delay in recognising these neuropathological conditions in a timely manner. Hence, ocular studies have been proposed alongside studies to identify common biomarkers so that those at greater risks may be identified relatively early before progressing to more advanced stages.

7. Conclusions: amyloid beta and the retina as a biomarker for Alzheimer's disease

With increased sophistication of new imaging methods and related technologies, there is a growing interest in developing reliable and cost-effective methods of identifying those at greater risk of developing AD. These advances are welcome as current diagnostic techniques

such as magnetic resonance imaging (MRI) do not always provide sufficient image resolution to detect incipient brain pathology, whilst positron emission tomography (PET) is prohibitively expensive and is not widely available [4]. Consequently, the most conclusive diagnosis of AD is only made following a brain autopsy, which is of little use as a predictor of disease. Various studies have explored the possibility of measuring peripheral Aβ in the blood or cerebrospinal fluid (CSF) as prognostic markers of disease. CSF as a biomarker has consistently been shown to provide an accurate indication of underlying AD pathology but is an invasive and costly procedure [4]. In contrast, plasma Aβ presents a more cost-effective and a less invasive method of diagnosis, but has proved less successful in identifying those at higher risk [101]. Interestingly, a recent study revealed that plasma Aβ levels accurately correlated across progressive stages of AMD [102]. Nonetheless, inconclusive data from other studies, as well as evidence from AD patients, suggest that such approaches require a more rigorous level of standardisation and further fine-tuning before clinical application [101].

In summary, we propose that the eye is not only a useful organ to study Aβ pathology but that a better understanding of retinal dystrophies may reveal insights into AD and dementia. The eye is amiable to manipulation and study in a way that the brain is not, thus providing a powerful diagnostic tool or an anatomical window to detect potential brain pathology. Consequently, non-invasive retinal imaging techniques may be exploited to measure the retinal Aβ burden and thus identify potential individuals at risk of developing AD. Such methods have already been demonstrated by those using retinal photography, scanning laser ophthalmoscopy (SLO), Doppler blood flowmetry and optical coherence tomography (OCT) to assess retinas of AD and dementia patients [23, 103, 104]. For example, funduscopy is widely used to assess the retina, which often detects the first clinical signs of AMD such as macular drusen. Using such an apparatus, a pilot study found a significant correlation between the appearance of peripheral retinal drusen and AD [103]. Furthermore, Doppler blood flowmetry has been used to measure retinal blood vessel diameters in AD patients. These studies show that decreased vessel diameter correlated with disease progression alongside impaired retinal blood-flow and circulation abnormalities [23]. Advances in OCT were also used to demonstrate NFL abnormalities in patients with open-angle glaucoma [104]. However, this may be of limited value as an early-disease indicator since NFL thinning only becomes apparent in advanced AD [23]. SLO, another non-invasive approach, is used to reliably assess optic nerve-head damage and optic disc topography in glaucoma patients [105], pathologies that are also evident in some AD patients [24]. Finally, trials have been undertaken in AD rodent models using systemic injections of the naturally occurring food ingredient curcumin, which fluoresces when bound to retinal Aβ [74]. Use of this compound has the added advantage of being able to traverse the BRB and BBB, demonstrating successfully use of a non-invasive retinal imaging in AD-Tg mice which correlated the extent of retinal Aβ with plaque load and disease. Curcumin labelling of retinal Aβ deposits in these mice was detected as early as 2.5 months, whereas Aβ deposition in the brain was only apparent after 5 months [74] supporting the idea that the aged eye may function as an early warning system for incipient brain pathology. As curcumin has also been shown to reliably label Aβ deposits/structures in post-mortem human retinas [74], its use could easily be extended to non-invasively detecting retinal Aβ in AD clinics. Hence, there is considerable interest in the pharmaceuticals industry to identify both

http://dx.doi.org/10.5772/64790

natural compounds as well as synthetic agents capable of reliably binding Aβ [106, 107]. Such studies will be highly informative in providing further insights into the role of Aβ in the ageing retina and brain, and help extend current understanding of shared pathologies in these intimately linked tissues.

Acknowledgements

We thank Mr Thomas Freeman and Ms Rosie Munday for their work on the Aβ-induced retinal degeneration mouse model, and Dr David A Johnston (Biomedical Imaging Unit, University of Southampton) for his expertise in imaging. We would also like to thank Dr Helen S.K Ratnayaka (Sussex Community NHS Foundation Trust) for reading the manuscript. SAL is funded by the National Centre for the Replacement Refinement & Reduction of Animals in Research (NC3R: grant # NC/L001152/1). This work was also supported by Fight for Sight (grant # 1485), the Gift of Sight Appeal and the Hampshire and Isle of Wight Community Foundation.

Author details

J. Arjuna Ratnayaka* and Savannah Lynn

*Address all correspondence to: J.Ratnayaka@soton.ac.uk

Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, SGH, Southampton, UK

References

[1] Castellano JM, Kim J, Stewart FR, Jiang H, DeMattos RB, Patterson BW, et al. Human apoE isoforms differentially regulate brain amyloid-beta peptide clearance. Science Translational Medicine. 2011;3(89):89ra57.

[2] De Strooper B. Proteases and proteolysis in Alzheimer disease: a multifactorial view on the disease process. Physiological Reviews. 2010;90(2):465–94.

[3] Bradford, A, Kunik ME, Schulz P, Williams SP, Singh H. Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. Alzheimer Disease and Associated Disorders. 2009;23(4):306–14.

[4] Sivak JM. The aging eye: common degenerative mechanisms between the Alzheimer's brain and retinal disease. Investigative Ophthalmology & Visual Science. 2013;54(1): 871–80.

[5] Kirby E, Bandelow S, Hogervorst E. Visual impairment in Alzheimer's disease: a critical review. Journal of Alzheimer's Disease. 2010;21(1):15–34.

[6] Gilbert SF. Developmental Biology. 6th ed. Sunderland, MA: Sinauer Associates, Inc.; 2000.

[7] Nag S, Walker JM, editors. The Blood-Brain and Other Neural Barriers: Reviews and Protocols. Toronto, ON: Springer; 2011.

[8] Fritsche LG, Fariss RN, Stambolian D, Abecasis GR, Curcio CA, Swaroop A. Age-related macular degeneration: genetics and biology coming together. Annual Review of Genomics and Human Genetics. 2014;15:151–71.

[9] Purves D, Augustine, GJ Fitzpatrick D, Hall WC, LaMantia AS, McNamara JO, White LE. Vision: The Eye. Neuroscience. 4th ed. Sunderland, MA: Sinauer Associates, Inc.; 2008. p. 253–88.

[10] Sanes JR, Zipursky SL. Design principles of insect and vertebrate visual systems. Neuron. 2010;66(1):15–36.

[11] Strauss O. The retinal pigment epithelium in visual function. Physiological Reviews. 2005;85(3):845–81.

[12] Rizzolo LJ. Barrier properties of cultured retinal pigment epithelium. Experimental Eye Research. 2014;126:16–26.

[13] Saade CJ, Alvarez-Delfin K, Fadool JM. Rod photoreceptors protect from cone degeneration-induced retinal remodeling and restore visual responses in zebrafish. Journal of Neuroscience. 2013;33(5):1804–14.

[14] Khandhadia S, Cherry J, Lotery AJ. Age-related macular degeneration. Advances in Experimental Medicine and Biology. 2012;724:15–36.

[15] Besharse JC, Bok D. Information Processing: Ganglion Cells. The Retina and It's Disorders. Oxford, UK: Elsevier; 2011.

[16] Snell RS, Lemp MA. Clinical Anatomy of the Eye. 2nd ed. Oxford, UK: Wiley; 1998. p. 379–412.

[17] Purves D, Augustine GJ, Fitzpatrick D, Hall WC, LaMantia AS, McNamara JO, White LE. Central Visual Pathways. Neuroscience. 4th ed. Sunderland, MA: Sinauer Associates, Inc.; 2008. p. 289–311.

[18] Tzekov R, Mullan M. Vision function abnormalities in Alzheimer disease. Survey of Ophthalmology. 2014;59(4):414–33.

[19] Valenti DA. Alzheimer's disease: visual system review. Optometry (St Louis, MO). 2010;81(1):12–21.

[20] Kirshner HS, Lavin PJM. Posterior cortical atrophy: a brief review. Current Neurology and Neuroscience Reports. 2006;6:477–80.

[21] Josephs KA, Whitwell JL, Boeve BF, Knopman DS, Tang-Wai DF, Drubach DA, Jack CR Jr, Petersen RC. Visual hallucinations in posterior cortical atrophy. Archives of Neurology. 2006;63:1427–32.

[22] Blanks JC, Torigoe Y, Hinton DR, Blanks RH. Retinal pathology in Alzheimer's disease. I. Ganglion cell loss in foveal/parafoveal retina. Neurobiology of Aging. 1996;17(3):377–84.

[23] Berisha F, Feke GT, Trempe CL, McMeel JW, Schepens CL. Retinal abnormalities in early Alzheimer's disease. Investigative Ophthalmology & Visual Science. 2007;48(5): 2285–9.

[24] Sadun AA, Bassi CJ. Optic nerve damage in Alzheimer's disease. Ophthalmology. 1990;97(1):9–17.

[25] Syed AB, Armstrong RA, Smith CU. A quantitative analysis of optic nerve axons in elderly control subjects and patients with Alzheimer's disease. Folia Neuropathologica/ Association of Polish Neuropathologists and Medical Research Centre, Polish Academy of Sciences. 2005;43(1):1–6.

[26] Wang MY, Ross-Cisneros FN, Aggarwal D, Liang CY, Sadun AA. Receptor for advanced glycation end products is upregulated in optic neuropathy of Alzheimer's disease. Acta Neuropathology. 2009;118:381–9.

[27] Scholtz CL, Swettenham K, Brown A, Mann DM. A histoquantitative study of the striate cortex and lateral geniculate body in normal, blind and demented subjects. Neuropathology and Applied Neurobiology. 1981;7:103–14.

[28] Parvizi J, Van Hoesen GW, Damasio A. The selective vulnerability of brainstem nuclei to Alzheimer's disease. Annals of Neurology. 2001;49:53–66.

[29] Armstrong RA. Alzheimer's disease and the eye. Journal of Optometry. 2009;2(3):103–11.

[30] Hof PR, Morrison JH. Quantitative analysis of a vulnerable subset of pyramidal neurons in Alzheimer's disease: II. Primary and secondary visual cortex. The Journal of Comparative Neurology. 1990;301(1):56–64.

[31] Armstrong RA, Nochlin D, Sumi SM, Alvord EC. Neuropathological changes in the visual cortex in Alzheimer's disease. Neuroscience Research Communication. 1990;6:163–71.

[32] Armstrong R. Visual field defects in Alzheimer's disease patients may reflect differential pathology in the primary visual cortex. Optometry and Vision Science. 1996;73:677–82.

[33] Baker DR, Mendez MF, Townsend JC, IIsen PF, Bright DC. Optometric management of patients with Alzheimer's disease. Journal of the American Optometric Association. 1997;68:483–94.

[34] Liu B, Rasool S, Yang Z, Glabe CG, Schreiber SS, Ge J, et al. Amyloid-peptide vaccinations reduce {beta}-amyloid plaques but exacerbate vascular deposition and inflammation in the retina of Alzheimer's transgenic mice. The American Journal of Pathology. 2009;175(5):2099–110.

[35] Ning A, Cui J, To E, Ashe KH, Matsubara J. Amyloid-beta deposits lead to retinal degeneration in a mouse model of Alzheimer disease. Investigative Ophthalmology & Visual Science. 2008;49(11):5136–43.

[36] Park SW, Kim JH, Mook-Jung I, Kim KW, Park WJ, Park KH, et al. Intracellular amyloid beta alters the tight junction of retinal pigment epithelium in 5XFAD mice. Neurobiology of Aging. 2014;35(9):2013–20.

[37] Oakley H, Cole SL, Logan S, Maus E, Shao P, Craft J, et al. Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2006;26(40):10129–40.

[38] Gasparini L, Crowther RA, Martin KR, Berg N, Coleman M, Goedert M, et al. Tau inclusions in retinal ganglion cells of human P301S tau transgenic mice: effects on axonal viability. Neurobiology of Aging. 2011;32(3):419–33.

[39] Hoh Kam J, Lenassi E, Jeffery G. Viewing ageing eyes: diverse sites of amyloid Beta accumulation in the ageing mouse retina and the up-regulation of macrophages. PloS One. 2010;5(10):1–12.

[40] Pennesi ME, Neuringer M, Courtney RJ. Animal models of age related macular degeneration. Molecular Aspects of Medicine. 2012;33(4):487–509.

[41] Vojnikovic B, Radeljak S, Dessardo S, Zarkovic-Palijan T, Bajek G, Linsak Z. What associates Charles Bonnet syndrome with age-related macular degeneration? Collegium Antropologicum. 2010;34(Suppl. 2):45–8.

[42] Cox TM, Ffytche D. Negative outcome Charles Bonnet syndrome. British Journal of Ophthalmology. 2014;98(9):1236–9.

[43] Gehrs KM, Anderson DH, Johnson LV, Hageman GS. Age-related macular degeneration—emerging pathogenetic and therapeutic concepts. Annals of Medicine. 2006;38(7):450–71.

[44] Ohno-Matsui K. Parallel findings in age-related macular degeneration and Alzheimer's disease. Progress in Retinal and Eye Research. 2011;30(4):217–38.

[45] Lotery A, Trump D. Progress in defining the molecular biology of age related macular degeneration. Human Genetics. 2007;122(3–4):219–36.

[46] Augood CA, Vingerling JR, de Jong PT, Chakravarthy U, Seland J, Soubrane G, et al. Prevalence of age-related maculopathy in older Europeans: the European Eye Study (EUREYE). Archives of Ophthalmology (Chicago, IL: 1960). 2006;124(4):529–35.

[47] Khandhadia S, Cipriani V, Yates JR, Lotery AJ. Age-related macular degeneration and the complement system. Immunobiology. 2012;217(2):127–46.

[48] Korb CA, Kottler UB, Wolfram C, Hoehn R, Schulz A, Zwiener I, et al. Prevalence of age-related macular degeneration in a large European cohort: results from the population-based Gutenberg Health Study. Graefe's Archive for Clinical and Experimental Ophthalmology. 2014;252(9):1403–11.

[49] Mullins RF, Russell SR, Anderson DH, Hageman GS. 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 Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2000;14(7):835–46.

[50] Bonilha VL. Age and disease-related structural changes in the retinal pigment epithelium. Clinical Ophthalmology (Auckland, NZ). 2008;2(2):413–24.

[51] Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology. 1992;99(6):933–43.

[52] Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. British Journal of Ophthalmology. 2012;96(5):752–6.

[53] Wang J, Ohno-Matsui K, Morita I. Elevated amyloid beta production in senescent retinal pigment epithelium, a possible mechanism of subretinal deposition of amyloid beta in age-related macular degeneration. Biochemical and Biophysical Research Communications. 2012;423(1):73–8.

[54] Dutescu RM, Li QX, Crowston J, Masters CL, Baird PN, Culvenor JG. Amyloid precursor protein processing and retinal pathology in mouse models of Alzheimer's disease. Graefe's Archive for Clinical and Experimental Ophthalmology. 2009;247(9): 1213–21.

[55] Johnson LV, Leitner WP, Rivest AJ, Staples MK, Radeke MJ, Anderson DH. The Alzheimer's A beta—peptide is deposited at sites of complement activation in pathologic deposits associated with aging and age-related macular degeneration. Proceedings of the National Academy of Sciences of the United States of America. 2002;99(18): 11830–5.

[56] Ratnayaka JA, Serpell LC, Lotery AJ. Dementia of the eye: the role of amyloid beta in retinal degeneration. Eye (London, England). 2015;29(8):1013–26.

[57] Yoshida T, Ohno-Matsui K, Ichinose S, Sato T, Iwata N, Saido TC, et al. The potential role of amyloid beta in the pathogenesis of age-related macular degeneration. The Journal of Clinical Investigation. 2005;115(10):2793–800.

[58] Prakasam A, Muthuswamy A, Ablonczy Z, Greig NH, Fauq A, Rao KJ, et al. Differential accumulation of secreted AbetaPP metabolites in ocular fluids. Journal of Alzheimer's Disease. 2010;20(4):1243–53.

[59] Kaarniranta K, Hyttinen J, Ryhanen T, Viiri J, Paimela T, Toropainen E, et al. Mechanisms of protein aggregation in the retinal pigment epithelial cells. Frontiers in Bioscience (Elite edition). 2010;2:1374–84.

[60] Jarrett SG, Lin H, Godley BF, Boulton ME. Mitochondrial DNA damage and its potential role in retinal degeneration. Progress in Retinal and Eye Research. 2008;27(6):596–607.

[61] Luibl V, Isas JM, Kayed R, Glabe CG, Langen R, Chen J. Drusen deposits associated with aging and age-related macular degeneration contain nonfibrillar amyloid oligomers. The Journal of Clinical Investigation. 2006;116(2):378–85.

[62] Isas JM, Luibl V, Johnson LV, Kayed R, Wetzel R, Glabe CG, et al. Soluble and mature amyloid fibrils in drusen deposits. Investigative Ophthalmology & Visual Science. 2010;51(3):1304–10.

[63] Anderson DH, Talaga KC, Rivest AJ, Barron E, Hageman GS, Johnson LV. Characterization of β amyloid assemblies in drusen: the deposits associated with aging and age-related macular degeneration. Experimental Eye Research. 2004;78(2):243–56.

[64] Dentchev T, Milam AH, Lee VMY, Trojanowski JQ, Dunaief JL. Amyloid-β is found in drusen from some age-related macular degeneration retinas, but not in drusen from normal retinas. Molecular Vision. 2003;9:184–90.

[65] Bruban J, Glotin AL, Dinet V, Chalour N, Sennlaub F, Jonet L, et al. Amyloid-β (1-42) alters structure and function of retinal pigmented epithelial cells. Aging Cell. 2009;8:162–77.

[66] Liu W, Cai H, Lin M, Zhu L, Gao L, Zhong R, et al. MicroRNA-107 prevents amyloid-beta induced blood-brain barrier disruption and endothelial cell dysfunction by targeting endophilin-1. Experimental Cell Research. 2016;343(2):248–57.

[67] Dal Pra I, Armato U, Chioffi F, Pacchiana R, Whitfield JF, Chakravarthy B, et al. The Abeta peptides-activated calcium-sensing receptor stimulates the production and secretion of vascular endothelial growth factor-A by normoxic adult human cortical astrocytes. Neuromolecular Medicine. 2014;16(4):645–57.

[68] Wyss-Coray T, Rogers J. Inflammation in Alzheimer disease—a brief review of the basic science and clinical literature. Cold Spring Harbor Perspectives in Medicine. 2012;2(1); 1–23.

[69] Blalock EM, Geddes JW, Chen KC, Porter NM, Markesbery WR, Landfield PW. Incipient Alzheimer's disease: microarray correlation analyses reveal major transcrip-

tional and tumor suppressor responses. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(7):2173–8.

[70] Katsel P, Tan W, Haroutunian V. Gain in brain immunity in the oldest-old differentiates cognitively normal from demented individuals. PloS One. 2009;4(10):e7642.

[71] Johnson LV, Leitner WP, Staples MK, Anderson DH. Complement activation and inflammatory processes in drusen formation and age related macular degeneration. Experimental Eye Research. 2001;73(6):887–96.

[72] Liu RT, Gao J, Cao S, Sandhu N, Cui JZ, Chou CL, et al. Inflammatory mediators induced by amyloid-beta in the retina and RPE in vivo: implications for inflammasome activation in age-related macular degeneration. Investigative Ophthalmology & Visual Science. 2013;54(3):2225–37.

[73] Cao L, Wang H, Wang F, Xu D, Liu F, Liu C. Aβ-Induced senescent retinal pigment epithelial cells create a proinflammatory microenvironment in AMD. Investigative Ophthalmology & Visual Science. 2013;54(5):3738–50.

[74] Koronyo-Hamaoui M, Koronyo Y, Ljubimov AV, Miller CA, Ko MK, Black KL, et al. Identification of amyloid plaques in retinas from Alzheimer's patients and noninvasive in vivo optical imaging of retinal plaques in a mouse model. NeuroImage. 2011;54(Suppl. 1):S204–17.

[75] Guo L, Salt TE, Luong V, Wood N, Cheung W, Maass A, et al. Targeting amyloid-beta in glaucoma treatment. Proceedings of the National Academy of Sciences of the United States of America. 2007;104(33):13444–9.

[76] Walsh DT, Montero RM, Bresciani LG, Jen AY, Leclercq PD, Saunders D, et al. Amyloid-beta peptide is toxic to neurons in vivo via indirect mechanisms. Neurobiology of Disease. 2002;10(1):20–7.

[77] Walsh DT, Bresciani L, Saunders D, Manca MF, Jen A, Gentleman SM, et al. Amyloid beta peptide causes chronic glial cell activation and neuro-degeneration after intravitreal injection. Neuropathology and Applied Neurobiology. 2005;31(5):491–502.

[78] Catchpole I, Germaschewski V, Hoh Kam J, Lundh von Leithner P, Ford S, Gough G, et al. Systemic administration of Abeta mAb reduces retinal deposition of Abeta and activated complement C3 in age-related macular degeneration mouse model. PLoS One. 2013;8(6):e65518.

[79] Nixon RA, Cataldo AM, Mathews PM. The endosomal-lysosomal system of neurons in Alzheimer's disease pathogenesis: a review. Neurochemical Research. 2000;25(9–10):1161–72.

[80] Soura V, Stewart-Parker M, Williams TL, Ratnayaka A, Atherton J, Gorringe K, et al. Visualization of co-localization in Abeta42-administered neuroblastoma cells reveals lysosome damage and autophagosome accumulation related to cell death. The Biochemical Journal. 2012;441(2):579–90.

[81] Sundelin S, Wihlmark U, Nilsson SE, Brunk UT. Lipofuscin accumulation in cultured retinal pigment epithelial cells reduces their phagocytic capacity. Current Eye Research. 1998;17(8):851–7.

[82] Boulton M, Moriarty P, Jarvis-Evans J, Marcyniuk B. Regional variation and age-related changes of lysosomal enzymes in the human retinal pigment epithelium. The British Journal of Ophthalmology. 1994;78(2):125–9.

[83] Shamsi FA, Boulton M. Inhibition of RPE lysosomal and antioxidant activity by the age pigment lipofuscin. Investigative Ophthalmology & Visual Science. 2001;42(12):3041–6.

[84] Khandhadia S, Lotery A. Oxidation and age-related macular degeneration: insights from molecular biology. Expert Reviews in Molecular Medicine. 2010;12:e34.

[85] Silva DF, Selfridge JE, Lu J, Lezi E, Cardoso SM, Swerdlow RH. Mitochondrial abnormalities in Alzheimer's disease: possible targets for therapeutic intervention. Advances in Pharmacology (San Diego, Calif). 2012;64:83–126.

[86] Ratnayaka A, Paraoan L, Spiller DG, Hiscott P, Nelson G, White MR, et al. A dual Golgi- and mitochondria-localised Ala25Ser precursor cystatin C: an additional tool for characterising intracellular mis-localisation leading to increased AMD susceptibility. Experimental Eye Research. 2007;84(6):1135–9.

[87] Paraoan L, Ratnayaka A, Spiller DG, Hiscott P, White MR, Grierson I. Unexpected intracellular localization of the AMD-associated cystatin C variant. Traffic (Copenhagen, Denmark). 2004;5(11):884–95.

[88] Edwards AO, Malek G. Molecular genetics of AMD and current animal models. Angiogenesis. 2007;10(2):119–32.

[89] Spencer KL, Olson LM, Anderson BM, Schnetz-Boutaud N, Scott WK, Gallins P, et al. C3 R102G polymorphism increases risk of age-related macular degeneration. Human Molecular Genetics. 2008;17(12):1821–4.

[90] Yates JR, Sepp T, Matharu BK, Khan JC, Thurlby DA, Shahid H, et al. Complement C3 variant and the risk of age-related macular degeneration. The New England Journal of Medicine. 2007;357(6):553–61.

[91] Liao X, Lan CJ, Cheuk IW, Tan QQ. Four complement factor H gene polymorphisms in association with AMD: a meta-analysis. Archives of Gerontology and Geriatrics. 2016;64:123–9.

[92] Zetterberg M, Landgren S, Andersson ME, Palmer MS, Gustafson DR, Skoog I, et al. Association of complement factor H Y402H gene polymorphism with Alzheimer's disease. American Journal of Medical Genetics Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics. 2008;147b(6):720–6.

[93] Holz FG, Pauleikhoff D, Spaide RF, Bird AC. Age-related Macular Degeneration.2nd ed. Heidelberg, Germany:Springer;2013

[94] Giau VV, Bagyinszky E, An SSA, Kim SY. Role of apolipoprotein E in neurodegenerative diseases. Neuropsychiatric Disease and Treatment. 2015;11:1723–37.

[95] Ricciarelli R, Canepa E, Marengo B, Marinari UM, Poli G, Pronzato MA, et al. Cholesterol and Alzheimer's disease: a still poorly understood correlation. IUBMB Life. 2012;64(12):931–5.

[96] Pikuleva IA, Curcio CA. Cholesterol in the retina: the best is yet to come. Progress in Retinal and Eye Research. 2014;41:64–89.

[97] Panpalli Ates M, Karaman Y, Guntekin S, Ergun MA. Analysis of genetics and risk factors of Alzheimer's disease. Neuroscience. 2016;325:124–31.

[98] Klein R, Cruickshanks KJ, Nash SD, Krantz EM, Nieto FJ, Huang GH, et al. The prevalence of age-related macular degeneration and associated risk factors. Archives of Ophthalmology (Chicago, IL: 1960). 2010;128(6):750–8.

[99] Hogg RE, Woodside JV, Gilchrist SE, Graydon R, Fletcher AE, Chan W, et al. Cardiovascular disease and hypertension are strong risk factors for choroidal neovascularization. Ophthalmology. 2008;115(6):1046–52.e2.

[100] Frost S, Guymer RH, Aung KZ, Macaulay SL, Sohrabi HR, Bourgeat P, et al. Alzheimer's disease and the early signs of age-related macular degeneration. Current Alzheimer Research. 2016[Epub ahead of print].

[101] Toledo JB, Shaw LM, Trojanowski JQ. Plasma amyloid beta measurements—a desired but elusive Alzheimer's disease biomarker. Alzheimer's Research & Therapy. 2013;5(2): 8.

[102] Guymer R, Cipriani T, Rittenhouse KD, Lim L, Robman LD, Li W, et al. Plasma levels of amyloid beta and other proinflammatory mediators in patients with age-related macular degeneration. Graefe's Archive for Clinical and Experimental Ophthalmology. 2015;253(8):1347–54.

[103] Aslam A, Peto T, Barzegar-Befroei N, Gregory S, Morrison G, Ritchie C, Lengyel I, editors Assessing Peripheral Retinal Drusen Progression in Alzheimer's Dementia: A Pilot Study Using Ultra-Wide Field Imaging. The Association for Research in Vision in Opthalmology. Orlando, FA: IOVS; 2014.

[104] Moschos MM, Georgopolous G, Chatziralli IP, Koutsandrea C. Multifocal VEP and OCT findings in patients with primary open angle glaucoma: a cross-sectional study. BMC Opthalmology. 2012;12(34):1–5.

[105] Danesh-Meyer HV, Gaskin BJ, Jayusundera T, Donaldson M, Gamble GD. Comparison of disc damage likelihood scale, cup to disc ratio, and Heidelberg retina tomograph in the diagnosis of glaucoma. British Journal of Opthalmology. 2006;90(4):437–41.

[106] Koronyo Y, Salumbides, BC, Black KL, Koronyo-Hamaoui M. Alzheimer's disease in the retina: imaging retinal aβ plaques for early diagnosis and therapy assessment. Neurodegeneration Diseases. 2012;10(1–4):285–93.

[107] Park YD, Park JH, Hur MG, Kim SW, Min JJ, Park SH, et al. Fluorescent 2-styrylpyridazin-3(2H)-one derivatives as probes targeting amyloid-beta plaques in Alzheimer's disease. Bioorganic & Medicinal Chemistry Letters. 2012;22(12):4106–10.

IntechOpen