A Review on the Alzheimer Disease Animal Models and Retinal Degeneration

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***Abstract*—Alzheimer's disease (AD) is a chronic neurodegenerative disease, serving as the most common form of dementia among the elderly population. AD targets various neurological processes in humans such as the visual pathway and hence resulting in various forms of visual abnormalities. Several studies have reported the loss of retinal ganglion cells, reduced thickness of nerve fibre layers (NFL) and damage of the optic nerve head and fiber layers. These findings suggest a putative link between AD and visual function deficits.**

As genetic defects have been found to be associated with AD, it is possible to experimentally mimic this condition in animal models. AD gene mutations discovered in human amyloid precursor protein (APP), presenilin 1/2 (PS1/PS2) and microtubule-associated tau protein have been used to engineer AD animal models.

In this review, we discuss the underlying molecular mechanisms of AD in terms of amyloidogenesis and tauopathies, as well as explain the pathological changes leading to vision loss in AD patients. Subsequently, the biology of the genes/proteins which have a causative link to AD, including APP, PS1 and PS2 will be discussed. Several recent reports of retinal degeneration in AD transgenic mouse models are selected to examine the relationship between AD and visual disturbance. We believe that a well-established method to generate transgenic mice will enhance our understanding of AD pathology and its correlation with retinal degeneration, leading to possible detection and treatment methods for AD.

I. Introduction

ALZHEIMER'S disease (AD) is a chronic neurodegenerative disease, serving as the most common form of dementia among the elderly population. Recently, findings of people carrying the AD mutated gene, such as those afflicted with Familial Alzheimers Disease (FAD), have an early onset of AD at around 40 years of age [1], [2]. AD is characterized by insidious onset of progressive decline in cognitive function [3], [4]. Patients diagnosed with AD tend to have pathological features of neuronal loss, neurofibrillary tangles (NFT) and neuritic plaques [5], [6]. Characteristic lesions in AD are senile or neuritic plaques, consisting of amyloid-β (Aβ) deposition, NFT, that associate with tau protein pathology, which all lead to the degeneration of neurons and synapses in the brain [2], [4], [7].

One of the first symptoms AD patients tend to report is visual abnormalities. Indeed, it is common for AD patients or people who suffer from other neurodegenerative diseases to have deficits in visual functions [1], [8]. A possible cause could be the accumulation of Aβ peptide that has been observed in the lens fibre cells of AD patients. Tauopathy in retinal degeneration is also suspected as a contributor. Clinical data has indicated that glaucoma patients who have a decrease of overall tau protein level in the retina still have increased amounts of abnormal hyperphosphorylated tau [9]–[11]. Patients with elevated amounts of both Aβ42 and tau due to glaucoma and diabetic retinopathy also have elevated levels of tau in the vitreous body [12]. Studies have indicated links between ocular diseases, such as glaucoma and AD [8], [13], [14]. Studying these ocular diseases may provide more information on the vision deficits in AD patients. Furthermore, the characteristics and relationship of AD in neural pathology of the brain and retinal pathology of the eye may be uncovered.

II. Pathology of AD and Biological Mechanisms of Neurodegeneration in AD

A. Aβ and its precursor form

Aβ peptides and amyloid plaques are pathological signatures of AD and have been studied in-depth for decades. Amyloid plaques are composed of Aβ and non-Aβ components such as ubiquitin and alpha-synuclein [14]. These elements are found to accumulate around meningeal and cerebral vessels and in the gray matter [15]. Since Aβ is produced by the cleavage of amyloid precursor protein (APP), different groups of enzymes responsible for this cleavage are key factors to the expression of Aβ in the cell tissues. The cleavage of APP can undergo two different pathways - a non-amyloidogenic pathway and an amyloidogenic pathway.

The non-amyloidogenic pathway cleavage is completed by α-secretase followed by γ-secretase, cleaving APP into sAPP α amino (N) terminal extodomain and the non-pathogenic P3 fragment. The cleavage of APP by α-secretase prevents the formation of Aβ [15]. On the other hand, the cleavage of

APP by β- and then γ -secretases through the amyloidogenic pathway contributes to the formation of Aβ. The first cleavage conducted by β-secretase releases sAPP β, which undergoes further deletion by the γ-secretase enzyme complexes to produce Aβ [15].

In amyloidogenic pathway, two types of Aβ, Aβ40 and Aβ42, can be generated by the cleavage of γ-secretase. Different forms of Aβ have different effects. Aβ40 isoform prevents the formation of deposits, whereas Aβ42 has the opposite effect [16]. Recent research has indicated that the hydrophobic nature of Aβ42 may be prone to aggregation which leads to the formation of Aβ deposits and plaques in brain tissues [15]. According to the review of Morrissette et al, 2008, the transgenic AD animal models demonstrated similar plaque formation with Aβ42 accumulation supporting the neurotoxic function of Aβ42. Interestingly, it is thought that the amount of oligomeric Aβ formation is not proportional to the degree of cognitive dysfunction, but rather the onset of the cognitive decline precedes the formation of plaques [16].

1) APP mutant genes: Genes implicated in AD include APP and presenilin 1/2 (PS1/PS2), among others. Carriers of genetic defects often develop AD at an earlier stage of life than those AD patients who do not have genetic defects, although the familial forms of AD are uncommon; two known forms of APP mutation are the London and Swedish mutations [15], [17]. The London mutation is a missense mutation of codon 717 with valine replaced by isoleucine, which enhances fibrillogenic Aβ42 production. The Swedish double mutations at codons 670 and 671 increase Aβ40 and 42 formation. Other missense mutations targeting the pathway of Aβ production often result in more Aβ42 than Aβ40 [17]. The discovery of mutations that appear causal to AD has enabled the engineering of transgenic animal models to study the pathogenesis of AD in a more effective way (see below).

2) Presenilins PS1 & PS2 mutations: The hydrophobic nature of Aβ42 may be prone to aggregation which leads to the formation of Aβ deposits and plaques in brain tissues [15]. In this sense, the mutation of γ-secretase enzyme complexes can trigger the mass deposition of Aβ plaques. The components of γ-secretase complex include PS1, PS2, nicastrin, anterior pharynx defective and presenillin enhancer 2 [15]. Mutations of PS1 and PS2 are found on chromosomes 14 and 1, respectively. The presenilin gene mutations are autosomal dominant. PS1 mutations are associated with early onset of familial Alzheimers disease (FAD) whereas PS2 mutations are involved in the late onset of sporadic AD. Although the mutations differ on AD onset, they both increase the production of Aβ42 [18].

PS1 and PS2 mutations in transgenic mice are believed to interfere with the homeostasis of calcium [17]. Calcium release is up-regulated by elevating Inositol trisphosphate (IP3), leading to an increase in neuronal calcium. IP3 is a secondary messenger molecule used in signal transduction and lipid signalling. This directly affects the synaptic plasticity, which may trigger AD and memory deficit [18]. In addition, mutated human PS1 transgene appears to alter fast axonal transport and induce tau hyperphosphorylation [18]. Intracellular Aβ in the soluble form rather than the insoluble was found to be responsible for synaptic dysfunction by interfering with the intracellular calcium homeostasis and by interacting with abnormal tau [18]. By looking into presenilin mutant genes, we can further investigate the responsibility of the intracellular calcium in AD pathology.

B. Tau

1) Functions of Tau: Another hallmark of the AD is neurofibrillary tangles (NFT), of which tau is a major component. Tau is one of the families of microtubule-associated proteins (MAP), important in axonal transport. Disregulation of tau leads to neurodegenerative disorders caused by the disruption of the communication paths between neuronal cells. Thus, understanding the mechanisms and the factors inducing tauopathy is essential for the development of treatments for neurodegenerative disorders.

A variety of tau isoforms can be found in the human brain. Different types of tau are produced by alternative splicing, in which select exons of genes are expressed or skipped, translating into different isoforms of the protein product. Six different forms (ranging from 45 to 65 kDa) can be found in human tau [19]. Owing to different conformations, such as the alternative splicing of exon 10, tau isoforms are expressed with specific functions in different regions [19]. Tau proteins help to maintain the integrity of microtubule network in neurons. The N-terminal of tau projected from the microtubule surface interacts with other cytoskeletal components [20] and the C-terminal regulates the microtubule polymerization [21]–[24]. Therefore, the multi-binding sites of tau may be of great importance in stabilization, organization, axonal transport and the communication within the neuronal cells.

Apart from the brain tissues, depositions of NFT are also found in other regions of the body such as the heart, skeletal muscles, lungs and kidneys in rats as well as in human fibroblasts [25] and pancreas [26]. Indications show that AD can be triggered by inflammations and other risk factors not localized in the CNS but in peripheral areas.

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2) Hyperphosphorylated tau and tauopathies: In a neurodegenerative condition like Alzheimers disease, the neuronal cells undergo an irregular cellular cycle leading to neuronal cell apoptosis and potentially neurodegeneration. The abnormal cell cycle may result from extrinsic sources like mitogen factors and oxidative stress, which affect phosphorylation

cascades [11], [27], [28]. The phosphorylation of tau is regulated by various cascade signalling pathways [27], with Tau serving as a possible endpoint to these cascades. Abnormal hyperphosphorylation of tau is crucial in the pathogenesis of AD.

NFT deposition is first found in the hippocampus structures before the cortex in AD patients [28]. However, it seems that the development of the NFT has no correlation with the memory dysfunction. The improvement of cognitive function after the suppression of transgene irrespective of the NFT involves neuronal remodelling like improved synaptic function and decreased synaptic loss in Tauopathy [29]. As a consequence, the role of hyperphosphorylated tau in neuropathy is still unknown.

C. Correlation of Aβ with tau

Various hypotheses have been established regarding Aβ and amyloid plaque in relation to hyperphosphorylated tau. One popular hypothesis is the amyloid cascade. It has been suggested that Aβ is the triggering point of inducing AD, with the downstream regulation of tauopathy and cognitive deficit.

It is believed Aβ formation precedes other factors like tauopathy. This is supported by results in transgenic mice that over-expression of APP leads to the hyperphosphorylation of tau [16]. The suppression of tau can improve the cognitive functions even with APP overexpression [16]. This suggests that both Aβ and tau contribute to cognitive impairment in AD. It has been noted that the specific time and period to suppress the mutated tau in Tg4510 strain mice may provide clues regarding the onset of the cognitive dysfunction [30]. Aβ prohibiting the function of proteasome may affect the clearance of the aggregated tau and NFT [16]. Moreover, the phosphorylation of tau and its microtubule binding ability are regulated by different signalling pathways and Aβ is found exerting its effect on the glycogen synthase kinase 3β and the cyclin-dependent kinase 5 [16]. All evidence points to the fact that tau can be the mediator for the regulation of Aβ under a feedback mechanism with Aβ.

III. Vision problem/loss for AD patient

A. Aetiology of vision loss in AD patients

Neurodegenerative disease patients such as AD, often suffer from some form of vision deficit due to pathological changes in the retina. Currently, there are three potential mechanisms of vision loss reported by AD patients. These three mechanisms have been termed: 1) the broad-band pathway [31], 2) glaucoma [32], [33]; and 3) the ventral and dorsal streams of vision [13]. These mechanisms have been the focus of researches attempting to link AD and the deficit in vision.

These three mechanisms can be understood by considering the interplay between the eye and the brain. Like other regions of the brain, the retina is derived from the neural tube. The retina is an integral part of the central nervous system by generating neural signals when light is detected. The signals are passed into the optic nerve which is directly connected to the visual cortex in the brain. The first two mechanisms are linked to the initial reception of the light in the retina while the third mechanism correlates directly to the visual cortex in the brain.

The broad-band pathway and glaucoma mechanisms share similar aetiologies. The broad-band pathway is one of the two traditional pathways of the pre-cortical visual system [34], [35]. This broad-band pathway is the magnocellular pathway, which originates in the magnocellular retinal ganglion cells (M-cells) [34], [35]. The theory behind the broad-band pathway suggests that the degeneration of the M-cells is responsible for the visual impairment in AD. With new technological techniques, studies have shown a decline in retinal ganglion cells (RGC) in AD patients. There is evidence suggesting that the reduction of RGCs is parallel with severity of AD [5], [36], however, specific loss of M-cells in AD appears to be weakly supported. To date, only one study by Sadun et al [13] has shown support for the degeneration of M-cells being linked with AD vision impairment.

Glaucoma, the second mechanism, is thought to be similarly connected to AD as the broad-band pathway. Glaucoma is one of the worlds leading causes of vision loss [9]. It is characterized by the loss of RGC and cupping of the optic nerve head caused by increased intraocular pressure due to the buildup of aqueous humor leading to swelling and a reduced total number of axons in the optic nerve. Studies noted that AD patients have a 25% higher glaucoma rate compared to 6% in control group. Biological similarities have been noted between glaucoma and AD, with many studies showing the loss of RGCs in AD patients with some levels of M-cell loss which are thought to be the first cells to die in glaucoma [9], [10]. Other similarities exist but RGC loss is reported as the primary similarity between these conditions [10] however there is no definite study showing that the underlying causes of the diseases are the same [10].

The third mechanism being suggested is the ventral and dorsal pathways. The ventral and dorsal pathways are the what, where and how of the visual cortex. The ventral pathway is the what, responsible for object recognition and color stimuli. The dorsal pathway is the where and how, responsible for perception and motion [37]. Deficits in both ventral and dorsal pathways have been observed in patients with AD, with evidence that impairment of both pathways occurs in AD patients. However, methodological issues may have been biased in the findings of the impairment and hence no firm conclusion can be drawn relating AD vision deficit with dorsal and ventral pathways.

All three mechanisms have supporting experimental evidence, however none are conclusive. As such, it is important to study the pathological changes more precisely in order to determine the correct mechanisms involved in the vision loss of AD patients. More likely, the visual loss is a combination of all three mechanisms, but this is only speculative, as all three mechanisms contribute to the visual abnormalities reported by AD patients.

1) Clinical findings of AD patients related to broad-band pathway: Retinal abnormalities observed in AD patients were first noted by Hinton et al. [38] and later confirmed by Blanks et al. [5], [6], [36]. The abnormalities involve RGC loss, reduction of nerve fibre layer (NFL) thickness and more

recently, tau pathology. These changes could be related to the characteristic lesions seen in the brains of AD patients, such as Aβ plaques and NFT, however, little is known about the proposed relation.

Sadun et al. [13] also found similar results where AD patients had a reduced axonal density and RGC count than the elderly controls. However, this was contradicted by Curcio et al [39] and Davies et al [40] showing no evidence of significant abnormalities between axonal density and RGCs between AD and the elderly controls. A recent study by Bersha et al [26] found that patients with AD showed a significant narrowing of the venous blood column and a significantly reduced blood flow to the retinal veins. Studies also showed differences in the optic nerve fibre density. Some findings showed a reduced density while others showed no difference [39].

2) Clinical findings of AD patients related to glaucoma: As mentioned before, many studies have also shown a link between glaucoma and AD. Chandra et al [15] found that an increased risk of glaucoma existed in patients with AD after studying the contributory causes of death in AD patients. Bayer et al [33] supported this by reporting that AD patients had a 25% rate of glaucoma as compared to a 6.5% in the controls (n=186). Another study supported this finding which found a 25% rate of glaucoma in AD patients as compared to 5.2% in the control group (n=116). However, other studies have shown no association between the two diseases. In a large scale glaucoma study (n=15000+), there was no evident increase in the rate of AD among the glaucoma patients [41]. Another study found that only 1 out of 38 AD patients had glaucoma, which contradicts the association between the diseases [42].

3) Clinical findings of AD patients related to dorsal and ventral pathways: Several studies have reported the impairment of object and facial recognition and color and pattern processing [13], [34], [41], [43]–[46] in AD patients. A few studies have shown deficits with visio-spatial processing, motor coordination and motion perception [26], [34], [47]. Many studies have placed a higher importance on the ventral pathway rather than the dorsal pathway, as most studies showed a higher impairment rate with skills related to the ventral pathway. Bouras et al [48], Arnold et al [37] and Van et al [49] found that NFT formed in higher density in the ventral stream as compared to the dorsal stream, signifying a higher degree of damage in the ventral pathway. However, Cronin-Golomb et al [44] showed that while AD patients had difficulty with visual tasks, the backward pattern masking performance could explain 50% of the variance in the participants cognitive performances.

The three possible mechanisms discussed above, show contradictory results. This could be related to the inconsistency between the methodologies and study groups. Many factors also have an impact to the findings, such as the level of education, age, gender and sample size. All these factors contribute to the results reported by the separate investigative studies. As it is nearly impossible to completely standardize the factors and methodologies in a study like this, a more effective and efficient technique to study this link should be investigated. To do this, it is often advisable to utilize appropriate animal models, in order to solve the questions of what mechanism links the visual deficit to AD.

IV. AD ANIMAL MODELS (TRANSGENIC MICE) FOR STUDYING VISION LOSS IN AD PATIENTS

Studying AD in human subjects has many severe restrictions that hamper the study process. These restrictions range from ethical approval to patient consent. They also include the time frame of AD onset in humans, the sample sizes and the unpredictability of human pathology. Even after ethical approval and patient consent, studying AD in the brain and retina currently requires post-mortem samples, which are difficult to obtain. With these restrictions, researchers have turned to alternative means to study AD. Mouse models are widely used for their rapid onset of the disease process and are relatively easy to engineer with current transgenic technology. Researchers commonly use transgenic animal models to mimic AD in humans. Several designs of AD animal models are used, ranging from the single transgenic to triple transgenic (3xTg) mouse models. Not only do these models offer clues about the neurodegenerative diseases, but are also comparatively more cost and time effective. These models have played an important role in many advances in AD pathology.

A. Transgenic mice -APP mutant gene

One of the mouse models well-utilized for studying AD was developed by Karen Hsiao Ashe [20]. The behaviours and histopathology observed in Tg2576 mice have shown similarities to those found in AD. Some studies have indicated that the impairment in learning and memory in spatial reference and alternation was in correlation with the amounts of Aβ and the formation of amyloid plaques. The degree of impairment was obvious in 9-month mice with robust increase of the amount of Aβ and plaque. The more neurotoxic Aβ42 was found to be substantially increased [16]. Other studies suggested that the concentration of Aβ did not proportionally increase with the APP expression with age [20].

The ages of AD onset were variable among studies in Tg2576 mice, with the earliest onset being 3 months and the latest at 15 months of age [40], [43], [44], [50], depending on the targets focused and the protocols used. The soluble oligomic Aβ has been found as early as 2 months of age with synaptic dysfunction occurring before the concrete Aβ deposition existed [17]. Therefore, transgenic APPswe mice have the AD onset of about 6 to 10 months of age together with a surge in the diffuse and oligomeric Aβ. They may be essential tools for studying the onset of AD.

B. Double Transgenic mice - APP and PS1/2 mutant genes

Several types of transgenic mutant mice were manipulated to carry a single mutated PS1 or PS2 gene. Though overproduction of Aβ42 occurred in this kind of single mutant mice, no lesions were observed in brain tissues [17]. On the contrary, the construct of human mutated PS1 or PS2 with additional types of mutated genes seems to reinforce the pathogenesis of AD by increasing opportunities of proteolysis of

APP via the amyloidogenic pathway. Various transgenic mice expressing different kinds of mutated PS1 and mutated APP genes were engineered and different levels of Aβ expressions were observed.

The APPswe mouse model Tg2576 crossed with human mutation gene PS1M146V can produce Aβ deposits at the age of 6 months, which is around 3 months earlier than Tg2576 mice. It appears that the more mutated genes inserted in the construct of the transgenic animal models, the earlier the occurrence of the Aβ peptide and Aβ plaque accumulation. Other Tg mice with Swedish, Dutch and London mutations also have elevated intraneuronal Aβ accumulation in the hippocampus and cortical pyramidal neurons before the existence of the Aβ plaques [32]. The PS1 knockin mice models also expressed similar results. The aggregation of N-modified Aβ 42 in neurons and the axonal degeneration at the age of 2 months were observed in the APP/PS1KI mice models. The loss of CA1 neurons with working memory deficits and reduction of motor performance were found at the age of 6 months [32]. As a consequence, presenilin mutation together with APP mutation can increase the accumulation of Aβ peptide and plaques.

C. Triple transgenic mice APP, PS1 and tau mutant genes

The transgenic mice with mutated APP gene expression may be a more appropriate AD mouse model to mimic the development of AD occurrence in humans. The triple transgenic mice model expressing PS1M146V, APPswe, and tauP301L transgenes was proven to be a promising mouse model producing plaques and tangles in the brain tissues. The PS1 knockin mouse originated from a hybrid 129/C57BL6, is utilized for generation of the triple transgenic mice [51].

Specific regions of human APP and tau transgene expressed in 3xTg mice were found to be the same as AD human brain regions including hippocampus and cerebral cortex [52]. The distribution of intraneuronal Aβ in the 3xTg mices brain tissues resembles AD brains found in human. Aβ is first discovered in the neocortical regions and it later spreads to CA1 pyramidal neurons of the hippocampus of 3xTg mice at 6 months of age [52]. The aggregated tau was first found within pyramidal neurons of CA1 subfield of hippocampus in the 3xTg mice [53]. Therefore, 3xTg mouse model may be a good model mimicking tau and later NFT formation and the pathway of distribution among the human brain regions. However, tau and hyperphosphorylated tau did not co-exist with Aβ at the same age of mice. Tau formation was first observed in the 6-month-old mice, but the abnormal human hyperphosphorylated tau exists later in older mice. It can then be found in both hippocampus and cortical regions by the age of 15 months [52].

V. Retinal Degeneration in AD Mouse Models

In this part, we will review and examine recent research utilizing AD animal models to study AD and retinal degeneration. Recent findings can be grouped into three main categories -neuronal cell loss, neuronal signal interruption and tau pathology. The four studies below are collectively used to show the relationships between retinal degeneration and AD in mouse models.

Recent studies on animal models have shown that retinal abnormalities in AD are associated with amyloidosis. Aβ accumulation in the retinal vasculature can lead to activation of apoptosis in neurons, recruitment of MCP-1 and activation of microglia cells. Tau filament formation has also been observed in the retina, but it is independent of axonal degeneration. Studies also show that Aβ and APP accumulation in the retina is age dependent and the formation of Aβ plaques occurs earlier in the brain than it does in the retina. This gives rise to the idea that APP is processed differently in the brain than in retina; APP appears approximately at the same time period in these areas, but Aβ plaques occur at different times.

Ning et al., (2008) using two strains of double transgenic mice (Table I) have produced results showing accumulation of amyloid-β in the retina of the these transgenic mice. Aβ was absent in young mice, indicating that Aβ deposits were formed later than 7.8 months of age but before 27 months as the Aβ was strongly reactive in the older mice. Presence of APP was significantly stronger in aged mice compared to younger mice, representing age dependent amyloidosis. The outer nuclear layer (ONL) was negative for APP while the inner plexiform layer (IPL) and inner nuclear layer (INL) were strongly reactive to the presence of APP. Microglia was detected in surrounding cells in ganglion cell layer (GCL), IPL and OPL of the older mice. Microglias act as an immunodefense system in the CNS to clean up possible harmful factors in the CNS. MCP-1, which is responsible for the recruitment of T-cells, monocytes and dendrite cells to sites of injury, was present in the cytoplasmic compartment in the GCL, but not outside GCL. Together with the presence of microglia and MCP-1 in the GCL, a significant increase in Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) positive cells were detected in the transgenic mice.

Perez et al., (2009) found that plaques were first formed in the retina at approximately 12 months in Tg mice and were observed to affect the retinal structure. The distribution of important membrane associated SNAP receptor protein syntaxin 1 was disrupted. The interference of syntaxin 1 could be one of the causes leading to visual impairment in AD. Microglia activity was detected with a significant increase in the retina between the Tg and non-Tg mice in all ages. ERG detected a significant decrease in alpha and beta waves of Tg and non-Tg mice at low light intensities, representing retinal degeneration of some forms. The difference of alpha and beta waves may be correlated with the Aβ plaques and increased microglia activities, interfering retinal neuronal transmission and disrupting the normal physiology of the retina.

Dutescu et al., (2009) studied the differences and connections between the brain and retina of two AD double Tg mice models (Tg2576 and APP/PS1 double transgenic mice model). Expression of APP was detected at the age of 14 months in Tg2576. Along with APP; Aβ was also detected in Tg2576 at the same age as non-Tg mice. Detection of positive Aβ in peripheral retina of vacuolar structures of the GCL indicted damages to capillaries in both mice models. The double Tg mice model revealed Aβ labeling in the cytoplasmic

Title	Year & Authors	AD Animal Model	Age	Significance
β-Amyloid Deposition and Functional Impairment in Retinal of APPswe/PS1E9 Tg model of AD	2008, Ning et al	APPswe/ PS1 E9	12-16 months and 19-21 months	Aβ interferes with neuronal signal transmission, no direct observation of neuronal cell loss
Amyloid-B deposits lead to retinal degeneration in a mouse model of Alzheimer's Disease	2009, Perez et al	Strain 1: APP/PS1, Strain 2: APPswe /PS1 DeltaE9	Strain 1: 7.8 and 27 months Strain 2: 10.5 months	A plaques detected in retina lead to apoptosis of neural cells, causing neuronal cell loss
Amyloid Precursor Protein Processing and Retinal Pathology in Mouse models of Alzheimer's Disease	2009, Dutescu et al	Strain 1:Tg2576, Strain 2: APP-swe/ PS1-dE9	Strain 1: 6-12 months, Strain 2: 2-18 months	APP processing is different between the brain and retina of different Tg mice
Tau inclusions in retinal ganglion cells of human P301S tau Tg Mice, effects on axonal viability	2009, Gasparini et al	P301S	1-6 months	Tau pathology increases rate of axonal pathology

TABLE I
SUMMARY OF RETINA AND AD RESEARCH

compartment of RGC and INL cells similar to those labeled in the single transgenic model - Tg2576. Analysis of Aβ40 and Aβ42 showed significantly higher concentrations in Tg mice as compared to their non-Tg age group in the retina. Furthermore, the onset of Aβ and APP was different between the brain and retina of AD mice models, suggesting formation of Aβ was earlier in the brain.

Gasparini et al., (2009) studied the tau pathology in the retina of AD mouse models. Tau was hyperphosphorylated in the Tg mice and the reactivity was consistent with tau pathology in the brain. Hyperphosphorylated tau was positive in cell bodies, axons and proximal dendrites in RGC of Tg mice, but immunoreactivity studies were positive for filamentous tau associated with degenerated axons and dendrites. Abnormal axon swellings were observed in the RGC. These observations revealed that axonal pathology occurs before tau accumulation, meaning that axonal degeneration is independent of tau filament formation in the retina.

A. Discussion

In summary, APP is the precursor of Aβ and its concentration is age dependent. Aβ is considered here as a possible mechanism that stimulates the activation and presence of microglia and MCP-1 in the retina. This is thought to cause apoptosis as shown by the significant increase in TUNEL positive cells of Tg mice.

APP processing is believed to be different between the brain and retina due to discrete time periods of Aβ formation. Retina of Tg2576 showed a significant difference between α- and β-secretase in the retina while the brain had an equal amount. Double transgenic strain APP/PS1, showed minimal of both α- and β-secretase in the retina, suggesting the differences lay in APP processing. Formation of tau filaments in the retina is also believed to be one of the causes of the neuronal loss or disruption in retinal degeneration. However, Gasparini (2009) revealed that axonal degeneration was independent of tau filament formation, suggesting that tau filament increased the rate of axonal degeneration but was not responsible for the onset.

AD animal models used to study retinal degeneration have produced a variety of results. Each AD animal model is unique depending on its mutation (Ex. Tg2576 single transgenic and APP/PS1 double transgenic), resulting in slightly different outcomes such as the detection of α- and β- secretase in Tg2576 but not in the double transgenic model. However, all the models produce similar results such as the measurements of Aβ formation and increased microglia activity. These results lead to the thought that vision impairment is partly due to the interference effect leading to disrupted neuronal transmission or neuronal cell loss. Current models contribute their own part to AD pathology, but vary in many measures. A more complete and comparable animal model design may connect the critical but subtle differences between the models. This will lead to a more comprehensive understanding of AD.

VI. IMPLICATIONS FOR FUTURE RESEARCH

AD animal models for AD in humans, differs substantially due in part to unique evolutionary pressures. Being genetically, biochemically and biophysically different, means animal models can only contribute in a limited capacity. Despite this, animal models have contributed much to our understanding of AD pathology. This may ultimately lead to the detection and treatment of AD one day. Contradictory and different findings in studies using mouse models may result from both the identity and quantity of mutation genes that mimic the pathology of AD in humans. Greater number of transgenes incorporated, appears to increase the variety of abnormalities seen. As most models used for studying AD and retinal degeneration relationships differ in the results, researchers should select the model that best suit their pathway of interest.

Increasing evidence links AD with retinal degeneration. This represents significant progress in understanding AD and serves as a possible early detection method of AD and other neurodegenerative diseases. Recent studies looking at retinal degeneration diseases such as glaucoma and AMD, suggest neuronal losses are due to Aβ or Aβ like deposits leading to neuronal loss in the retina. Despite anatomical and physiological differences, animal models have contributed and will continue to contribute to the key understanding of neurodegenerative diseases.

Studying the relations of retinal degeneration and AD is an easier task in animal models than in humans. The time and cost is significantly reduced when compared to studying the relation in humans. This will increase the output of research correlating AD with vision loss and hence will increase the

chance that a correct link will be established between retinal degeneration and AD.

Determining the correct mechanism and link between the two will introduce a whole new direction of research into treatment, intervention and early detection of AD or retinal degeneration. Vision loss is often one of the first symptoms most apparent in AD and other neurodegenerative diseases. Eyes are being viewed as a possible window into the brain and a model to develop treatment for neurodegenerative diseases such as AD. Although AD has been known for a century now, early and accurate diagnosis of still remains a big challenge [50].

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