Persistent remodeling and neurodegeneration in late-stage retinal degeneration

Rebecca L. Pfeiffer[a,b,**], Robert E. Marc[a,b], Bryan William Jones[a,b,*]

[a] Dept of Ophthalmology, Moran Eye Center, University of Utah, Salt Lake City, UT, USA
[b] Interdepartmental Program in Neuroscience, University of Utah, Salt Lake City, UT, USA

A B S T R A C T

Retinal remodeling is a progressive series of negative plasticity revisions that arise from retinal degeneration, and are seen in retinitis pigmentosa, age-related macular degeneration and other forms of retinal disease. These processes occur regardless of the precipitating event leading to degeneration. Retinal remodeling then culminates in a late-stage neurodegeneration that is indistinguishable from progressive central nervous system (CNS) proteinopathies. Following long-term deafferentation from photoreceptor cell death in humans, and long-lived animal models of retinal degeneration, most retinal neurons reprogram, then die. Glial cells reprogram into multiple anomalous metabolic phenotypes. At the same time, survivor neurons display degenerative inclusions that appear identical to progressive CNS neurodegenerative disease, and contain aberrant α-synuclein (α-syn) and phosphorylated α-syn. In addition, ultrastructural analysis indicates a novel potential mechanism for misfolded protein transfer that may explain how proteinopathies spread. While neurodegeneration poses a barrier to prospective retinal interventions that target primary photoreceptor loss, understanding the progression and time-course of retinal remodeling will be essential for the establishment of windows of therapeutic intervention and appropriate tuning and design of interventions. Finally, the development of protein aggregates and widespread neurodegeneration in numerous retinal degenerative diseases positions the retina as a ideal platform for the study of proteinopathies, and mechanisms of neurodegeneration that drive devastating CNS diseases.

1. Introduction

Negative plasticity as a consequence of photoreceptor degeneration has been chronicled in the literature for nearly a century (Kolb and Gouras, 1974; Lewis et al., 1998; Wolff, 1935), with substantial additions to the literature in the 1980s through the early 2000s (Coblentz et al., 2003; Erickson et al., 1983, 1987; Fariss et al., 2000; Fisher and Lewis, 2003; Lewis et al., 1989, 1998; Li et al., 1995; Marc et al., 1998a; Santos et al., 1997; Strettoi and Pignatelli, 2000; Strettoi et al., 2002). In 2003, all of these associated processes of plasticity were consolidated into a single term: retinal remodeling (Jones et al., 2003; Marc and Jones, 2003). It has since become widely recognized as an integral component of pathology in retinal degeneration, regardless of the precipitating insult (Fisher et al., 2005). Retinal remodeling is a complex process that involves multiple mechanisms. Glial hypertrophy and metabolic dysregulation (Jones et al., 2011; Pfeiffer et al., 2016) are fundamental components of retinal remodeling. In addition, existing neurons extend new, synaptically active, aberrant processes that alter the circuitry of the retina in a process termed "rewiring" (Jones et al., 2003, 2012; Lewis et al., 1998). Phenotypic switching of bipolar cell classes via alterations of glutamate receptors on existing cells results in "reprogramming" of neural circuits (Marc et al., 2007). Translocation of neuronal somas alters the lamination of the retina (Jones et al., 2003), and the eventual cell death of many neurons of all types within the inner retina modifies the signal processing network, likely corrupting it.

Understanding the process of retinal remodeling and its progression will guide the vision research community towards windows of opportunity for vision rescue therapies following photoreceptor loss (e.g. in retinal degenerative diseases such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP)) (Marc et al., 2014). Furthermore, evaluation of retinal remodeling, its components, and their origins provides insight into neural plasticity.

Early evaluation of human retinas with photoreceptor degeneration demonstrated neuronal loss in the inner retina and gross changes of retinal lamination (Kolb and Gouras, 1974; Wolff, 1935). Later work (Lewis and Fisher, 2005; Santos et al., 1997; Sethi et al., 2005) and our

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more recent results in human tissue demonstrate not only inner retinal neuronal loss, but also plasticity in the adult retina (Jones et al., 2016a, 2016c). Retinal remodeling as a consequence of photoreceptor degeneration has been well described in animal models as well (Jones et al., 2003, 2011). After prolonged retinal remodeling, we speculated that the associated plasticity would enter a plateau phase, perhaps in a predictable and pseudo-stable state. We were incorrect. Retinas engaged in remodeling continue to progress to a new phase of inner retina neurodegeneration with features consistent with proteinopathies. For brevity, neurodegeneration in the retina is referring specifically to inner retinal neurodegeneration, degeneration of the photoreceptors will be specified as photoreceptor degeneration. This review reassesses our understanding of retinal remodeling, including impacts on the outer and inner retina from a histological and ultrastructural perspective, as well as presents evidence for wide-spread retinal neurodegeneration, and discusses the role of proteinopathies in retinal degeneration.

It is our conclusion that neurodegeneration is an additional component of retinal remodeling, with a distinct etiology from reprogramming, rewiring, or currently known metabolic alterations, and is under active study. We will discuss these processes as a product of photoreceptor degeneration, will address the implications for therapeutics aimed at restoring vision, and close by discussing opportunities and advantages of using the retina to explore neurodegeneration and proteinopathies.

2. Retinal anatomy

The functional neuroanatomy of the retina has been studied since the earliest days of neuroscience through the work of Ramón y Cajal, who illustrated the basic anatomy and principles of information flow through the retina, from photoreceptors to ganglion cells. The retina is a thin, organized, multilaminar strip of nervous tissue along the posterior surface of the eye, which developmentally originates from the frontal cortex. It is subdivided into six major histological layers: the photoreceptor layer (which may be further subdivided into the outer segment, inner segment, and outer nuclear layer), the outer plexiform layer (OPL), the inner nuclear layer (INL), the inner plexiform layer (IPL), the ganglion cell layer (GCL), and the nerve fiber layer (NFL) (Fig. 1A). It is composed of five major neuronal cell types: photoreceptors, horizontal cells, bipolar cells, amacrine cells, and ganglion cells (Marc, 1999). These cells working together play important roles in processing color, motion, intensity, and directionality from visual stimulus (Masland, 2012). The retinal circuitry is, in its simplest terms, divided into two major pathways: vertical and horizontal. The vertical pathway is the path from the photoreceptors, bipolar cells, and ganglion cells, which ultimately project axons into the brain (Inner retina pathways illustrated in Fig. 1B). It is primarily thought of as an amplification pathway, though the presence of ON and OFF cells permits the first level of light-detection processing, and ON-OFF motifs are preserved from bipolar cells through processing in the brain. The horizontal pathway tunes signals from the vertical pathway from being extremely broad regions of light detection to more defined regions of higher light intensity with less light intense regions surrounding, and consists of amacrine and horizontal cells (Fig. 1C). The higher intensity regions of focus are termed *centers* while the surrounding regions are aptly named the *surround*. Together, the vertical and horizontal pathways provide initial processing of visual information, prior to action potentials relaying signals to the brain. For a more comprehensive review of visual functioning in the retina see Marc, (2009) (Marc, 2009).

3. Retinal degeneration

Photoreceptor degeneration can be caused by numerous mechanisms including hereditary diseases directly affecting the photoreceptors such as retinitis pigmentosa (RP) and rod-cone dystrophies, diseases affecting the RPE such as Lebers Congenital Amaurosis (LCA) and age-

related macular degeneration (AMD), or physical trauma leading to retinal detachment. Despite the variable mechanism of photoreceptor loss between cases, the ultimate outcome is the same: extensive loss of photoreceptors, leaving a deafferented neural retina followed by extensive remodeling, and eventually, neurodegeneration. The following subsections briefly describe the most common means of photoreceptor degeneration to introduce the reader to these concepts, but are not intended to be a comprehensive list of all photoreceptor degenerations.

3.1. Retinitis pigmentosa

Retinitis pigmentosa (RP) refers to a range of hereditary disorders, which onset with degeneration of the photoreceptors, commonly rod photoreceptors (Hamel, 2006). The name retinitis pigmentosa originates from the ophthalmoscopic observation of exposed pigmentation in the neural retina, arising from a presumed migration of pigmented RPE cells into the neural retina (Jones and Marc, 2005). The prevalence of RP is approximately 1 in 4000, with varying modes of inheritance where 50–60% of cases are inherited autosomal-recessive, 30–40% autosomal-dominant, and 5–15% X-linked. RP is known to arise from approximately 100 gene defects,[1] which are subclassified by their genetic component, mode of inheritance, and whether the defect is constrained to the eye or is syndromic and affects nonocular tissues (Dias et al., 2018). Examples of associated syndromic diseases are Bardet-Biedl syndrome and Usher syndrome, which are both autosomal-recessive. Bardet-Biedl syndrome, in addition to photoreceptor loss, is associated with polydactyly, truncal obesity, renal dysfunction, and learning difficulties (Suspitsin and Imyanitov, 2016) while Usher syndrome is associated with hearing-loss in addition to RP (Mathur and Yang, 2015).

The speed of vision loss and the mechanism causing the photoreceptor degeneration varies widely across RP diseases. Some individuals will experience vision loss early in life, while others will remain relatively asymptomatic until adulthood. Despite the many modes of inheritance and genes involved with RP, rod photoreceptors degenerate in a non-uniform fashion across the periphery of the retina, followed by cone loss. In most cases, RP patients are legally blind by their mid-forties, and photoreceptor degeneration continues until the retina is completely devoid of photoreceptors, leaving patients completely unable to perceive light for years to decades of life (Hartong et al., 2006).

3.2. Age-related macular degeneration

Age-Related Macular Degeneration (AMD) predominantly affects people over the age of 50, and is the leading cause of vision loss in elderly individuals. The risk of AMD increases with age.[2] Though 52 genetic variants have been linked to AMD, environmental factors such as smoking and diet can greatly increase an individual's risk, with smoking being the single largest risk factor, aside from age (Al-Zamil and Yassin, 2017; Fritsche et al., 2014; Lim et al., 2012).

AMD is associated with loss of proper function of the retinal pigment epithelium (RPE), which leads to photoreceptor death. The RPE separates the retina from the choroid and is a critical component of the retinoid cycle and photoreceptor maintenance. The RPE is essential for photoreceptor metabolism and phagocytosis of outer photoreceptor segments shed from photoreceptors in a circadian fashion. Histologically, dry AMD commonly presents with photoreceptor outer segment shortening and loss, drusen (lipid deposits above and below the RPE) separating the photoreceptors from RPE or from the choroid, and metabolic alterations of RPE cells that may predict progression of disease (Jones et al., 2016b). Regardless, loss of proper RPE function
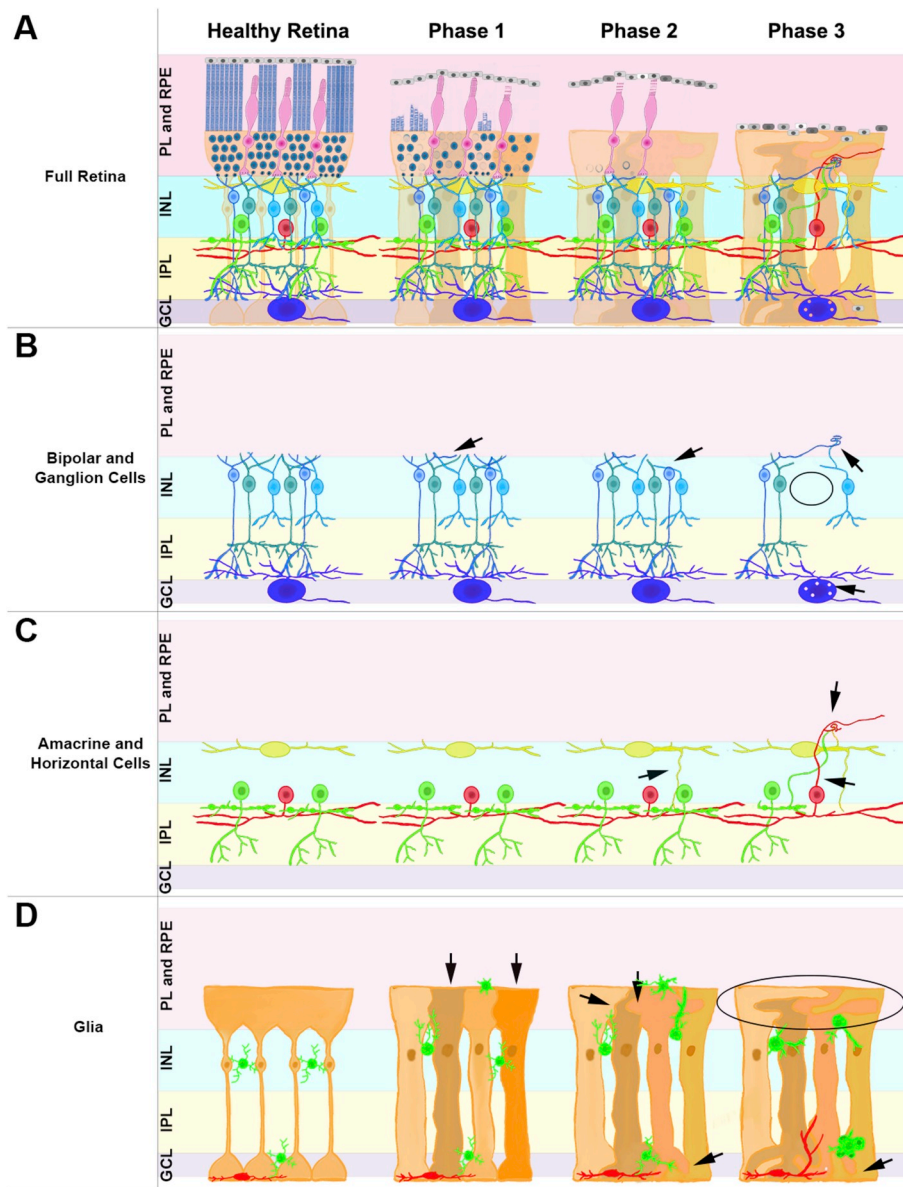

Fig. 1. Phases of remodeling. (A) Combined phases of remodeling including all cell types. (B) Phases of remodeling in ganglion and bipolar cells. Arrows indicate neurite sprouting, circle highlights cell loss. (C) Phases of remodeling in amacrine and horizontal cells. Arrows indicate neurite sprouting and microneuroma formation. (D) Phases of remodeling in glia. Arrows indicate metabolic variation. The oval indicates a region of muller cell entanglement.

and/or death leads to the death of photoreceptors, principally with the loss of central cone vision and often followed by the loss of peripheral rod vision. The wet form of AMD arises from new blood vessel formation (neovascularization) in the choroid, neural retina, subretina and vitreous, leading to subsequent leakage of blood and serum which is damaging to the neural retina (Wong et al., 2008). Currently, there are only treatments for wet forms of AMD to prevent further neovascularization through anti-VEGF treatments. However, the AREDS study suggests a prophylactic effect of supplements in warding off dry forms of AMD (Age-Related Eye Disease Study Research, 2001a, b). In wet and dry forms, affected individuals often complain about blurriness in their central vision, which progresses to a loss of central vision and advances outward towards the periphery.

3.3. Injury-induced retinal degeneration

Both retinal detachment and light-induced retinal degeneration (LIRD) induce photoreceptor degeneration with subsequent retinal remodeling in the absence of genetic involvement in humans and animal models. Clinically, retinal detachment has been described for nearly a century (Jeremy, 1922). Following detachment, the patient commonly experiences photopsias and progressive loss of sight in the affected eye, though the exact presentation varies with the cause of the detachment. Experimentally, retinal detachment and LIRD are excellent models to explore the responses of the outer and inner retina to the specific insult of photoreceptor degeneration. Retinal detachment studies observed that the loss of photoreceptors leads to a number of deleterious changes within the inner retina, that were subsequentially found also be present in genetic models (Erickson et al., 1987; Fisher et al., 1995; Lewis et al., 1989, 1994, 1998; Marc et al., 1998b). LIRD was documented to involve ultrastructural alterations to the RPE (Grignolo et al., 1969) alterations in photoreceptor outer segment lipids and proteins (Organisciak et al., 1989b) and induces photoreceptor degeneration (Organisciak et al., 1989a), and later was found to progress into remodeling (Jones et al., 2006). Following detachment or light-damage, photoreceptor outersegments degenerate, while

vacuolization of the soma and mitochondrial stress become evident by day 3 (Erickson et al., 1983). Glial involvement is evident via cell division, nuclear translocation, and protein changes in Muller cells of retinas detached for a prolonged period (Erickson et al., 1987; Lewis et al., 2010). Changes in metabolic signatures are also evident in both retinal detachment (Marc et al., 1998a) and LIRD (Marc et al., 2008). Finally, rewiring is evident in the inner retina of both models following photoreceptor degeneration (Jones et al., 2006; Lewis et al., 1998). The fact that these degenerations provoke features of remodeling consistent with genetic disease models indicates the loss of photoreceptors is the primary insult leading to remodeling.

4. Retinal remodeling

Retinal remodeling is a phenomenon consequent to photoreceptor degeneration consisting of a series of alterations in retinal metabolism, receptor expression, neuronal network topologies, and eventual cell death. Retinal remodeling has been described as phases, characterized by the progression from photoreceptor stress through photoreceptor degeneration and neural retinal involvement (Fig. 1). Phase 0 is the healthy retina, wherein no photoreceptor stress or degeneration is observed. Phase 1 is characterized in by initial stress and degeneration of photoreceptors along with the emergence of neural reprogramming and glial responses. Phase 2 of remodeling is defined by the progressive loss of remaining photoreceptors, particularly cones. Phase 2 is maintained as long as remnant cones persist in the retina, widespread rewiring and cell death of phase 3 is held at bay. Phase 3 follows the complete loss of photoreceptors. At this point in degeneration, deafferentation of the retina is complete and leads to neurite outgrowth by all cell classes, followed by widespread cell death.

In the following sections we will refer to phases of remodeling, describing the discrete etiologies of the main processes of remodeling: reprogramming, rewiring, glial responses, and formally introduce the next phase of retinal remodeling in section 4: neurodegeneration. In short, regardless of the primary insult, the neural retina undergoes a series of increasingly deleterious changes in response to loss of photoreceptors. These processes will likely have an impact on any therapeutic scheme introduced to restore/preserve vision once remodeling is initiated, and more comprehensive understanding of precipitating factors will provide future targets. Understanding these components will be essential to recommending the best potential therapeutic for different stages of remodeling (Marc et al., 2014).

4.1. Reprogramming

Photoreceptor input to bipolar cells is conveyed via graded glutamate release, dependent on light levels, which acts upon receptors of differing kinetics. In bipolar cells which depolarize in response to light (ON-BCs), the responsible receptor is metabotropic glutamate receptor 6 (mGluR6). In bipolar cells which depolarize in response to a decrease in light (OFF-BCs), the responsible receptors are ionotropic kainite and AMPA sensitive glutamate receptors (iGluRs). During phase 1 remodeling, ON-BCs change expression of their receptor phenotypes and become pharmacologically consistent with OFF-BCs. In healthy primate, the ratio of OFF-BC: ON-BC: RodBC is 40:30:30. In an RP affected retina, the ratio shifts to 70:20:05 (Fig. 2)(Jones et al., 2016a; Marc et al., 2007). These results were confirmed in rabbit retina with a shift of OFF-BCs from approximately 30-40% of the retina to over 56% of identifiable bipolar cells in a rabbit model of RP (Fig. 2) (Jones et al., 2011, 2012). In phase 2 remodeling, the shift of mGluR to iGluR expression in bipolar cells continues, in addition to mislocalization of mGluR receptors. As dendrites degenerate and disappear, mislocalized mGluR6 expression occurs in axons of RodBC (Strettoi and Pignatelli, 2000; Strettoi et al., 2002). In phase 3 remodeling, both mGluRs and iGluRs are functionally absent in all bipolar cells, though iGluRs persist in amacrine and ganglion cells (Marc et al., 2007). This end phenotype

of remodeling might be due to prolonged lack of afferent input to bipolar cells by photoreceptors, but the precise mechanism of down-regulation is unknown. It is worth noting however, that iGluR functional expression persists in retinal regions containing remnant cones, granted it is unclear what signaling remnant cones are doing. The persistence of iGluRs downstream of bipolar cells in phase 3 remodeling suggests that some sort of bipolar input to amacrine and ganglion cells is still present, yet it is currently unknown what initiates that signaling. We believe that answer lies in the rewiring component of remodeling.

4.2. Rewiring

Precise synaptic organization between neurons is central to proper neural network function. Corruption of neural wiring from disease or trauma alters how information is processed and complicates therapies designed to replace neurons lost through disease. Following insult, the central nervous system (CNS) is known to undergo rewiring events in epilepsy (Morimoto et al., 2004), Alzheimer's disease (Agosta et al., 2010), Parkinson's disease (Guo et al., 2015), and others. The retina is no different. The normal topology of retinal circuitry is disrupted during and following photoreceptor insult. In phase 1 remodeling, rod photoreceptors extend axonal processes beyond the OPL into the inner retina, in some cases extending to the inner limiting membrane (Fariss et al., 2000; Li et al., 1995; Sethi et al., 2005),. Simultaneously, RodBCs and rod-contacting horizontal cells retract their dendrites from rod spherules and a subset extend neurites towards cone pedicles (Linberg et al., 2006; Peng et al., 2000), making peripheral contacts (Fig. 1 B + C). In phase 2 remodeling, degeneration continues with photoreceptor cell death progression, with the end of phase 2 being marked by the absence of all photoreceptors. Bipolar cells continue to remodel their dendrites as their normal inputs disappear, before becoming completely deafferented once photoreceptors are gone (Strettoi and Pignatelli, 2000; Strettoi et al., 2003). Horizontal cells sprout neurites that extend into the IPL (Strettoi and Pignatelli, 2000; Strettoi et al., 2002, 2003), though their contacts, if any, are unknown. Amacrine cells and ganglion cells also initiate sprouting, creating new synaptic contacts in regions of novel neuropil (Jones et al., 2003). In phase 3 remodeling, the complete loss of afferent input leads to widespread neurite sprouting of all remaining retinal neurons (Jones et al., 2003; Marc and Jones, 2003; Marc et al., 2003). Extended neurites may coalesce together forming microneuromas, which are ultrastructurally found to contain ribbon synapses, vesicle clouds, and post-synaptic densities consistent with synaptic activity (Jones et al., 2003). Other neurites, and an allocation of entire neurons, have been found to escape the neural retina and extend within the choroid (Jones et al., 2003), or infiltrate epiretinal membranes caused by Muller cell extensions that break through the inner limiting membrane into the vitreous (Lewis et al., 2007). Mechanistically, neurite sprouting has been associated with retinoic acid (Lin et al., 2012a) and growth associated protein 43 (GAP43)(Coblentz et al., 2003). Due to the extensive neurite sprouting, the precise topology of novel circuits formed during remodeling are still under active investigation in our lab (Pfeiffer et al., 2018).

4.3. Glial responses

In addition to neurons, the retina also has numerous glial cells: astrocytes, microglia, and Müller cells, each providing critical functions in the retina (Fig. 1D). Each of these glia serves specific roles in the maintenance of the retina and proper neural signaling and become reactive early in remodeling. These roles and reactive states caused by remodeling are expounded below.

4.3.1. Astrocytes

Astrocytes are a class of glial cell found throughout the CNS, with well characterized roles in neuronal metabolism, formation and maintenance of the blood-brain-barrier, and stress response. In the brain,
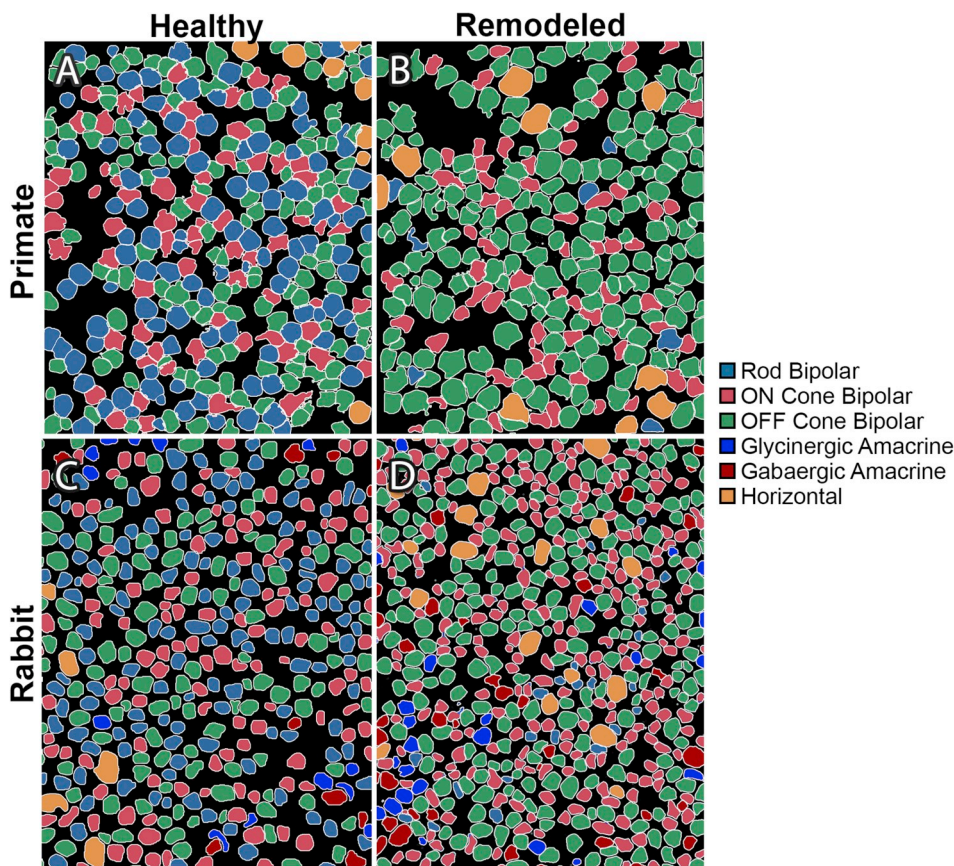
Fig. 2. Reprogramming *Adapted with permission from* Marc et al., (2007) *and* Jones et al., (2011) Theme maps of horizontal sections through the inner nuclear layer generated by cluster analysis of Kainic Acid driven (25 μM) signaling in normal and degenerate retinas. (A) Normal baboon retina, (B) Human RP retina, (C) Healthy rabbit retina, (D) Degenerate rabbit retina from a 10-Month Tg P347L rabbit.

■ Rod Bipolar
■ ON Cone Bipolar
■ OFF Cone Bipolar
■ Glycinergic Amacrine
■ Gabaergic Amacrine
■ Horizontal

they anatomically tile with one another forming distinct spatial domains (Bushong et al., 2002; Ogata and Kosaka, 2002). In vascularized retinas, they are less prevalent and their localization is generally associated with the optic nerve head and blood vessels, with a minimal overlap tiling observed (Jammalamadaka et al., 2015). Retinal astrocytes have a distinct morphology of small processes which make broad flat contacts with blood vessels, as well as smaller contacts with ganglion cells (particularly their axons), and other astrocytes (Luna et al., 2016). Astrocyte responses to photoreceptor degeneration has been a difficult phenomenon to study. In the retina, Müller cells are the most common macroglia, which in the healthy retina can be quickly differentiated from astrocytes based on glial fibrillary acidic protein (GFAP) expression. As we will discuss below, Müller cells express low levels of GFAP under conditions of low stress, while astrocytes express high GFAP. In retinal degeneration however, Müller cells begin to increase their GFAP expression making astrocyte responses difficult to differentiate. Luna and colleagues (Luna et al., 2016) evaluated astrocyte response to retinal detachment in multiple species using dye filling strategies in mouse (where Müller glial up-regulation of GFAP is less pronounced), finding distinct morphologies associated with detachment. Following detachment, and the associated photoreceptor degeneration, astrocytes become more diffuse in their GFAP labelling combined with greater branching and dispersed contacts with blood vessels. Following prolonged detachment, astrocytes are found to extend processes into the inner retina. In human AMD, the regular appearance of astrocytic processes bordering ganglion cell axons also becomes irregular (Luna et al., 2016). The exact progression of astrocytic response to photoreceptor degeneration in remodeling remains to be clarified. Nevertheless, it is clear that astrocytes alter their normal morphology and clear contacts with blood vessels in retinal detachment and human AMD.

4.3.2. Microglia

Microglia are the resident macrophage cells of the CNS, including the retina. They play a central role in CNS maintenance, development, and plasticity through remodeling of synapses, the clearance of cellular debris, pathogens, and apoptotic cells (Sominsky et al., 2018). In the retina, microglia cell bodies are found in the plexiform layers (Karlstetter et al., 2015) from where they continuously extend and retract processes as they surveil their surroundings in healthy retina (Nimmerjahn et al., 2005). In phase 1 remodeling in RP, as rods begin to become stressed, microglia ramify and extent processes towards the photoreceptor layer where they phagocytize apoptotic rods (Gupta et al., 2003). In AMD, microglia are attracted to drusen (Killingsworth et al., 1990), and once photoreceptors begin to degenerate, microglia are involved in their clearance. In retinal detachment, microglia also rapidly migrate from the IPL to the ONL in response to photoreceptor degeneration (Lewis et al., 2005). Microglia are not restricted to phagocytosis of apoptotic cells and have been implicated in the degeneration of neighboring, otherwise healthy photoreceptors (Gupta et al., 2003). This, in addition to the secretion of cytokines, leads to bystander killing by microglia, likely advancing photoreceptor cell death and potentially impacting other cell classes in retina (Langmann, 2007). In phase 3 remodeling microglia are found to become less ramified and settle into an in between morphology suggesting a chronic para-inflammatory state (Karlstetter et al., 2015).

4.3.3. Müller Cells

Müller cells are the primary macroglia of the retina that function in amino acid and ion homeostasis, water regulation, provide trophic and structural support, and play a central role in glutamate metabolism. In retinal degeneration, Müller cells are among the first to respond to stress. In phase 1, as the photoreceptors begin to become stressed and outer segments shorten and begin to degenerate, Müller cells begin to alter their metabolic signatures, then begin to hypertrophy and change

their protein expression including upregulation of GFAP, (Erickson et al., 1987; Roesch et al., 2012), decrease in glutamine synthetase (GS) expression, and decreased cellular retinaldehyde-binding protein (CRALBP) expression (Lewis et al., 1994). The normal homogeneous signature unique to Müller cells: high glutamine and taurine (> 10 mM) and a low concentration of glutamate (< 0.1 mM) (Marc et al., 1995); become less stable and more heterogeneous. Müller cells begin to demonstrate global glutamine elevation (Jones and Marc, 2005), though local metabolic signatures begin to differ among neighboring Müller cells in regions of photoreceptor degeneration (Jones et al., 2011). Ultrastructurally, Müller cells demonstrate greater overlap and interdigitation of their endfeet while also demonstrating heterogeneity in their osmication affinity (Pfeiffer et al., *In Press*). In phase 2, Müller cells continue to hypertrophy and begin to form a glial seal between the inner retina and the RPE, as photoreceptors continue to degenerate (Jones and Marc, 2005). Metabolically, the increase in glutathione concentration in Müller cells along with variability in glutamate, glutamine, and taurine levels between individual cells suggests these cells are undergoing oxidative stress (Jones et al., 2016a, 2016b). In phase 3, Müller cells complete the glial seal, isolating the inner retina from the RPE and choroid. The glial seal is a combination of Muller cell apical processes and Muller cells which have delocalized their nuclei into the OPL and undergone division (Lewis et al., 2010). Müller cell protein expression becomes increasingly altered with high levels of GFAP expression and decreasing levels of glutamine synthetase (Jones et al., 2016a). These changes persist long term following the photoreceptor degeneration (Lewis et al., 1989). As glutamine synthetase expression decreases, the levels between individual Müller cells becomes increasingly chaotic until glutamine synthetase expression completely collapses (Jones et al., 2016a; Pfeiffer et al., 2016). Fig. 3 demonstrates features of long-term remodeling progression to neurodegeneration in the Tg P347L rabbit. Recently, we discovered that the extracellular matrix (ECM) can be visualized by tomato lectin (TL) immunoprobing to facilitate understanding of the topological morphology changes that are occurring in retinal degeneration and remodeling. An added benefit is that TL markers with this approach are also compatible with ultrastructural analysis, as evidenced by its clean staining of glutaraldehyde fixed tissues (Fig. 3, column 1). Computational Molecular Phenotyping (CMP) analyses of retinas from 2 to 6 year old Tg P347L rabbits show continued pathologic neurite and glial remodeling, progressive neurodegeneration, neuronal loss and anomalous, and chaotic metabolic reprogramming of Müller cells (MCs) (Fig. 3, column 2) (Pfeiffer et al., 2016); Of note, severe, progressive loss of MC GS occurs as previously noted, (Fig. 3, column 3), which is essential for retinal glutamate-glutamine recycling and consistent with that seen in humans (Jones et al., 2016a). Glial revision in phase 3 remodeling continues until MCs have no distinct metabolic signature and exhibit highly disorganized morphologies. MCs transform into thick, overlapping blocks of glia with processes invading debris-like assemblies in large areas of the remnant retina (Fig. 3, column1).

5. Phase 4: Progressive neurodegeneration in retinal degenerations

Retinal remodeling after photoreceptor loss is common to all retinal degenerations in humans (Jones et al., 2016a, 2016b), carnivores (Marc et al., 1998a), rodents (Jones et al., 2003; Strettoi et al., 2003) and lagomorphs (Jones et al., 2011), independent of the primary insult inducing photoreceptor degeneration. However, throughout much of the literature, short-lived rodent models have been used to characterize and quantify the nature, extent and mechanisms of remodeling (Chang et al., 2002). This creates a misinterpretation of the process of retinal degeneration and creates a disconnect between the biology described by the use of experimental rodent models of vision rescue, spanning less than a hundred days of degeneration, and the ultimate goal of restoring sight in humans who display severely remodeled retinas following

decades of disease.

After continued monitoring of retinas and samples from human disease, we have identified a fourth phase of retinal remodeling: Progressive neurodegeneration that extends beyond simple cell loss to resembling proteinopathies observed in other forms of neurodegeneration, like Alzheimer's, Parkinson's, and others.

5.1. Neurodegeneration in humans

The hallmark of dry AMD and RP in humans is degeneration of photoreceptors, prompting numerous studies into the causes and progression of photoreceptor loss (Cuenca et al., 2014). Beyond photoreceptor loss, we know that retinal degeneration associated cell death is common in geographic atrophy, which follows late stage AMD and becomes progressively more severe with time. Geographic atrophy is characterized by a regional loss of RPE, photoreceptors, and the choriocapillaris following neovascularization of the retina. In addition to the loss of these outer retinal structures, neurons of the inner retina have also demonstrated signs of metabolic stress (Fig. 3)(Jones et al., 2016b) and cell death (Ramkumar et al., 2018). Retinal remodeling in humans and animal models of RP demonstrates the neural retina is not immune to cell death that occurs coincident and subsequent to photoreceptor stress and loss. Studies of post mortem RP eyes demonstrate loss of neurons in the inner retina (Jones et al., 2003, 2016a), including within the more preserved macula, with 70% loss of ganglion cells (Santos et al., 1997).

5.2. Animal models of RP

Extensive reorganization of the retina is associated with phase 3 retinal remodeling and has been described in numerous animal models as well as in human (Figs. 4 and 5) (Han et al., 2013; Jones and Marc, 2005; Jones et al., 2003, 2016a; Kalloniatis et al., 2016). Although not absolute, many rodent models of RP eventually demonstrate inner retinal cell death, particularly after prolonged loss of cone photoreceptors (Fig. 4). This occurs in a discontinuous fashion across the surface of the retina and is consistent with the regional retinal degeneration and the associated neuronal loss observed in humans. The key element leading to observable neurodegeneration is time. The rhodopsin transgenic (Tg) P347L rabbit permits evaluation of retinal remodeling over many years, recapitulating retinal remodeling observed in humans (Kondo et al., 2009), and also serving as a model for progressive neurodegeneration and proteinopathy as we discuss below. At 10 months old, the Tg P347L rabbit retina is largely devoid of rod and cone outer segments with a reduced electroretinogram (80% scotopic a and b-wave reduction, 70% photopic a and b wave reduction) reflecting the loss of photoreceptor input (Kondo et al., 2009). Over the following 1–2 years the sensory retina loses photoreceptors in a patchy fashion, until cone photoreceptors are lost, leading to phase 3 remodeling of the neural retina (Fig. 3) and (Jones et al., 2011). Following the complete loss of photoreceptors, widespread neural degeneration and remodeling is progressive and affects neurons of all classes (Jones et al., 2003). Loss of neuronal tissue as a percent of total tissue in the P347L rabbits is substantial. By 2 years there is ~40% cell loss and by 4 years–55%. In our 6-year TgP347L rabbit, the best-preserved region suffered ~78% loss, while the more degenerate regions showed > 99% neuronal loss.

6. Ultrastructural characterization of photoreceptor degeneration, retinal remodeling, and neurodegeneration

Electron microscopy has played an important role in our current understanding of many components of nervous system structure and function including synaptic architecture, cellular organization (Palay and Palade, 1955), and recently through connectomics efforts, neural network architecture (Marc et al., 2013). In addition, ultrastructural analysis, particularly transmission electron microscopy (Eskelinen,
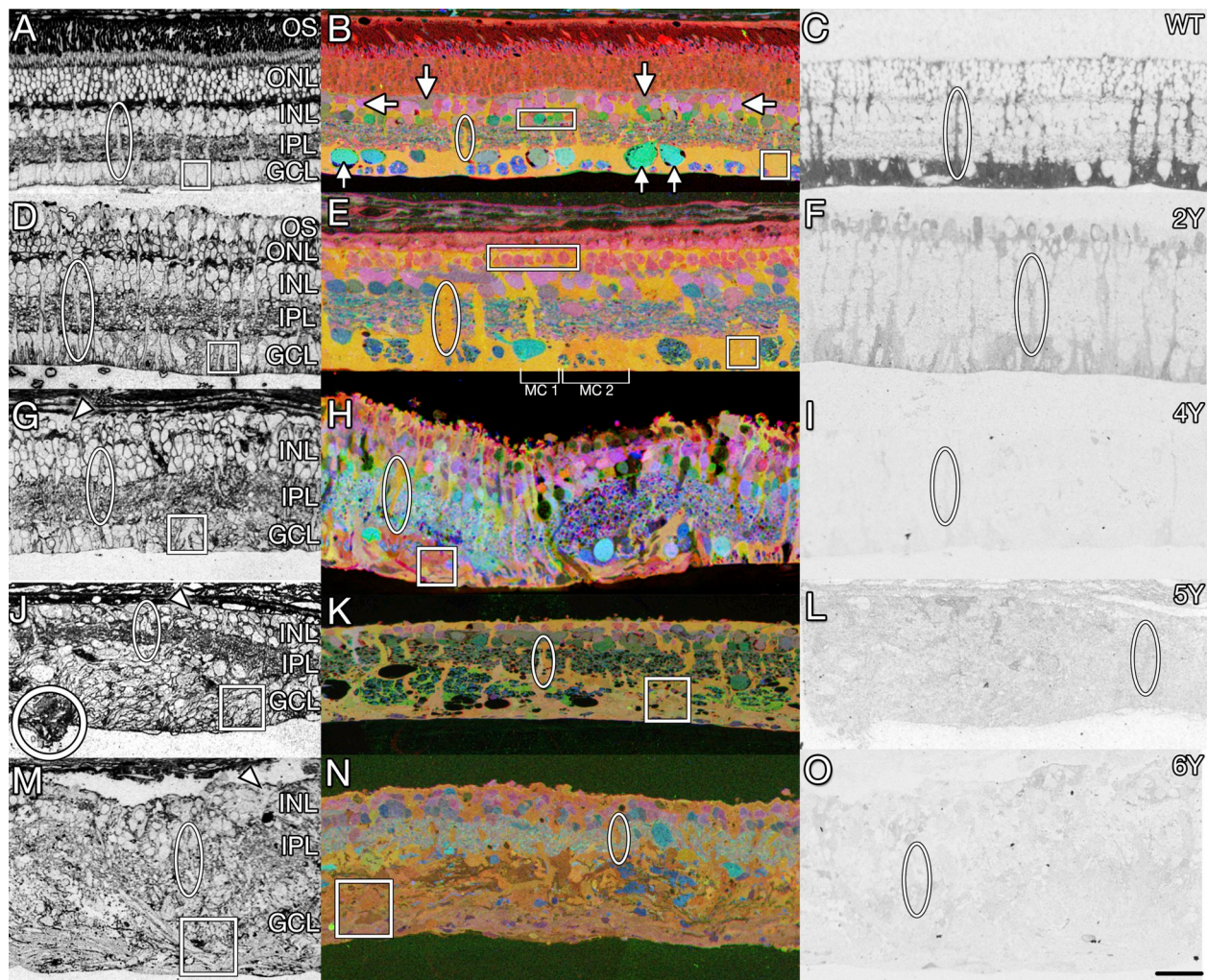
Fig. 3. Muller glial changes in remodeling. Transition from normal (A–C) to remodeled (D–I) and neurodegenerative retina (J–O) in WT (A–C) versus 2yr (D–F), 4yr (G–I), 5yr (J–L), and 6yr (M–O) Tg P347L rabbits. Representative Müller cell columns and endfeet are highlighted with ovals and squares, respectively. Retinas probed for tomato lectin (left column) display extracellular matrix and cell patterning. White circle (J) marks Müller cell eruption through the basement membrane. Small molecule sCMP mapping (middle column) with τQE (taurine, glutamine, glutamate) > RGB differentiates major cell types as colored metabolite mixtures: Normal Müller cells, yellow-orange (ovals); ganglion cells, teal (up arrows); amacrine cells, pink or green (rectangles); bipolar cells, pink (down arrows), horizontal cells, dull green (side arrows. Metabolically anomalous Müller Cells are indicated by brackets (E). Protein CMP of glutamine synthetase (right column) reveals declining expression over disease duration. Scale bar 30 μm.

2014; Klionsky et al., 2008) is the gold standard in the identification of cellular pathologies such as autophagy and necrosis. Clear descriptions of ultrastructural phenomena observed throughout retinal degeneration highlights multiple avenues of investigation for not only the progress of retinal degeneration, but also reveals pathological indications typical of multiple neurodegenerative diseases.

6.1. Early retinal degeneration

Early retinal degeneration is characterized by phase 1 remodeling (onset of photoreceptor stress and the beginnings of outer segment shortening). Some early studies of retinal degeneration explored advanced retinal degeneration in human tissues (phase 3 + remodeling), but most studies have been carried out in transgenic animal models which permit the evaluation of disease progression in the earliest phases. RP has been widely studied thanks to the large number of genetic mutations that lead to rod degeneration in models of RP. Fewer models are available for the study of AMD for a variety of reasons from genetic complexity to rodents' lack of anatomical foveas resembling human and primate foveas. Among the over 100 genetic mutations associated with RP, the most common is the P23H mutation in

rhodopsin used in many animal models including zebrafish (Tam and Moritz, 2006), mouse (Naash et al., 1993), rat (LaVail et al., 2018), and pig (Ross et al., 2012). This mutation, and others including the P347L mutation, causes degeneration of the photoreceptors, initiating with the loss of rods, leading to night blindness, with progressive tunnel vision prior to complete vision loss. Most ultrastructural studies of animal RP models are focused on photoreceptor structural anomalies associated with photoreceptor degeneration. These studies, like much of the AMD literature describe photoreceptor outer segment disorganization and degeneration (Asakawa et al., 2015; Jones et al., 2011), mitochondrial disorganization, swelling of endoplasmic reticulum or golgi apparatus (Blanks et al., 1982), and autophagic compartments in the photoreceptors (Bogea et al., 2015).

6.2. Advanced retinal degeneration

Early electron microscopy studies were typically of patients with advanced RP that demonstrated extensive loss of photoreceptors, with loss or irregular organization of outer segments in the foveal cones and widespread loss of photoreceptors in the periphery (Kolb and Gouras, 1974; Mizuno and Nishida, 1967). The RPE also demonstrates
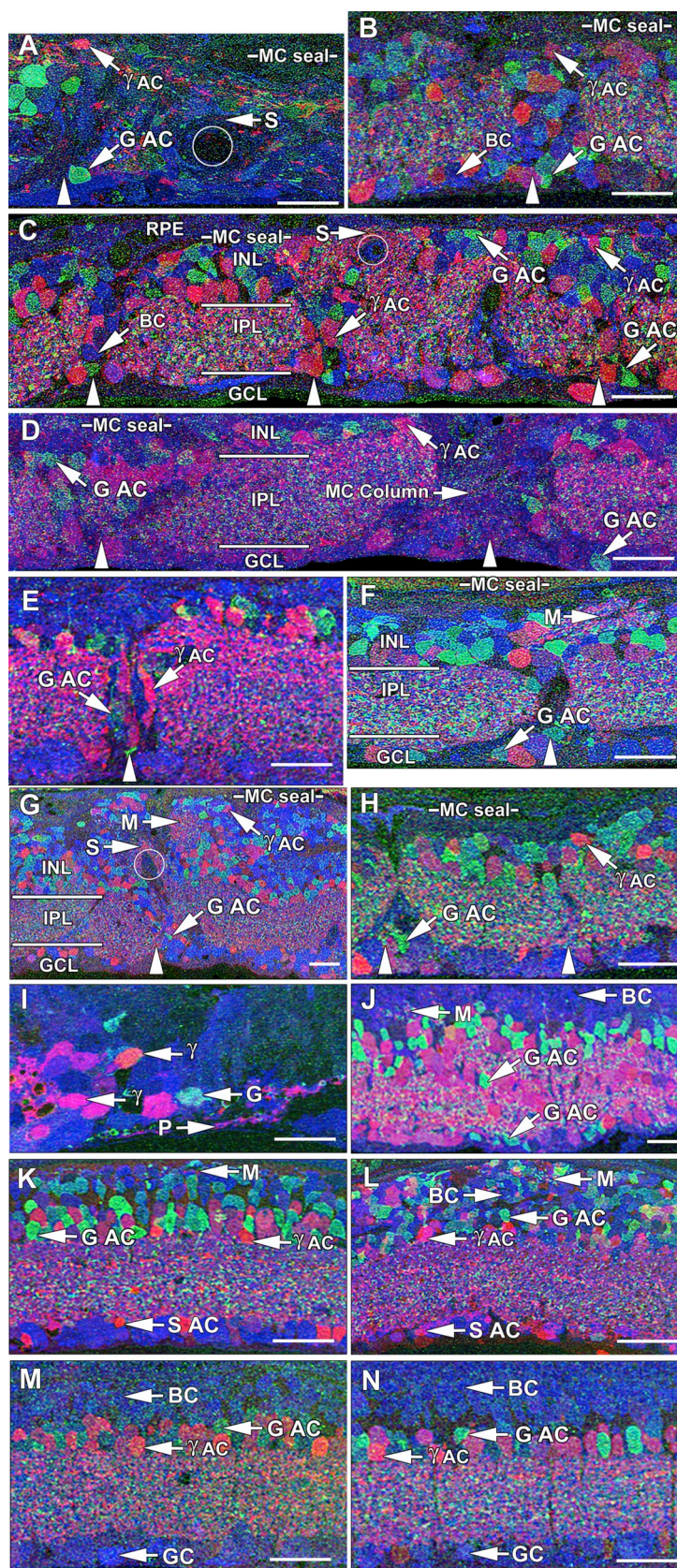
Fig. 4. Retinal remodeling in animal models and humans. *Reprinted with permission from* Jones et al., 2003. Representative γGE → rgb mappings of retinal degeneration models. Downward arrows indicate inversions from the inner nuclear layer (INL) to the ganglion cell layer (GCL); upward arrows indicate eversions from the inner nuclear layer to the distal margin of the remnant retina; vertical arrowheads indicate glial columns; circles denote blood vessels. Abbreviations: M, inner nuclear layer microneuroma; S, stricture; P, neuropil patch; γ. GABA; G, glycine Scales, 20 μm. (A) Human RP retina, FFB accession #378, 76 year old female, 2 h post-mortem, RP diagnosed at age 33, no vision at death. This vertical image demonstrates massive cell loss typical of late stage RP, with complete loss of the inner nuclear and ganglion cell layers at the right margin. A column of apparent neuronal migration is bordered by glycinergic amacrine cells (GAC) in the ganglion cell layer and GABAergic amacrine cells (γAC) at the distal margin of the remnant. Strictures distort the remaining inner plexiform layer and a Müller cell (MC) fibrotic seal separates the retina from the choroid/retinal pigmented epithelium. (B) *rd1* mouse, pnd 630. A large column of neurons bridges the depleted inner nuclear layer, displaying inverted amacrine and bipolar cells (BC) and everted amacrine cells. (C) RCS rat retina, pnd 900. This image shows three columns of neuronal migration (vertical arrowheads) where bipolar and amacrine cells are displaced from their proper locations. Distorted regions of the inner plexiform layer often pass through strictures as small as 5 μm. (D) S334ter rat, pnd 363. This image shows two glial columns (vertical arrowheads), with right column exhibiting Müller cell hypertrophy breaking up the normal tiling of the retina. Everted and inverted glycinergic amacrine cells are abundant. (E) P23H rat, pnd 372. A glial column (vertical arrowhead) traverses the inner plexiform layer accompanied by migrating glycinergic and GABAergic amacrine cells. (F) GHL mouse, pnd 746. A broad glial column (vertical arrowhead) serves as a pathway for migration for amacrine and bipolar cells into the ganglion cell layer. A microneuroma has formed distal to the heavily depleted inner nuclear layer. (G) TG9N mouse, pnd 160. An oblique column forms a neuron migration path with both inverted and everted cells. Strictures deform the inner plexiform layer and microneuromas form in the midst of the inner nuclear layer, but a mere 5 μm from the distal glial seal. (H) *nr* mouse, pnd 720. Two columns of neuronal migration are indicated, with inversion and eversion of amacrine cells. The inner nuclear layer is thinned to less than half its normal thickness. (I) *chx10* mouse, pnd 365. Few neurons survive in this defect, and only in small clusters with tiny patches of apparent neuropil surrounded by massive fields of apparent Müller cells. (J) *Chx10/P27^{Kip1} − / −* hypocellularity rescue mouse, pnd 60. This model initially displays roughly normal lamination, but with few bipolar cells and severely reduced photoreceptor numbers. However, even in the absence of clear glial columns or seals, microneuromas emerge and columns of neurons strung through the inner plexiform layer are common, as are misplaced amacrine cells in the ganglion cell layer. (K) RKO mouse, pnd 365. No neuron migration has emerged, and positions of amacrine cells, including presumed starburst amacrine cells (S AC), are normal. Microneuromas are forming next to the glial seal. (L) RhoΔCTA mouse, pnd 541. Migration across the inner plexiform layer has not begun, but microneuromas are emerging and the entire inner nuclear layer displays disordering of neurons, with everted amacrine cells and bipolar cells moving into the former amacrine cell layer.(M) *pcd* mouse, pnd 321. At this age, retinal lamination appears normal and no microneuromas have emerged and proper localization of ganglion cells (GC) is observed.(N) *rd2* mouse, pnd 151. At this age, retinal lamination appears normal and no microneuromas have emerged. These image data will be available for public access at http://www.marclab.org.

disorganization with pigmented cells present throughout the inner retina (Jones et al., 2016a), characteristic and likely the cause of pigmented bone spicules associated with advanced RP. In human eyes affected by advanced AMD, cone outer segments are largely degenerated (where still present), with shortened inner segments and swollen mitochondria (Litts et al., 2015), commonly associated with cell stress. Light microscopic approaches through computational molecular phenotyping demonstrate conclusive cell stress in both Müller
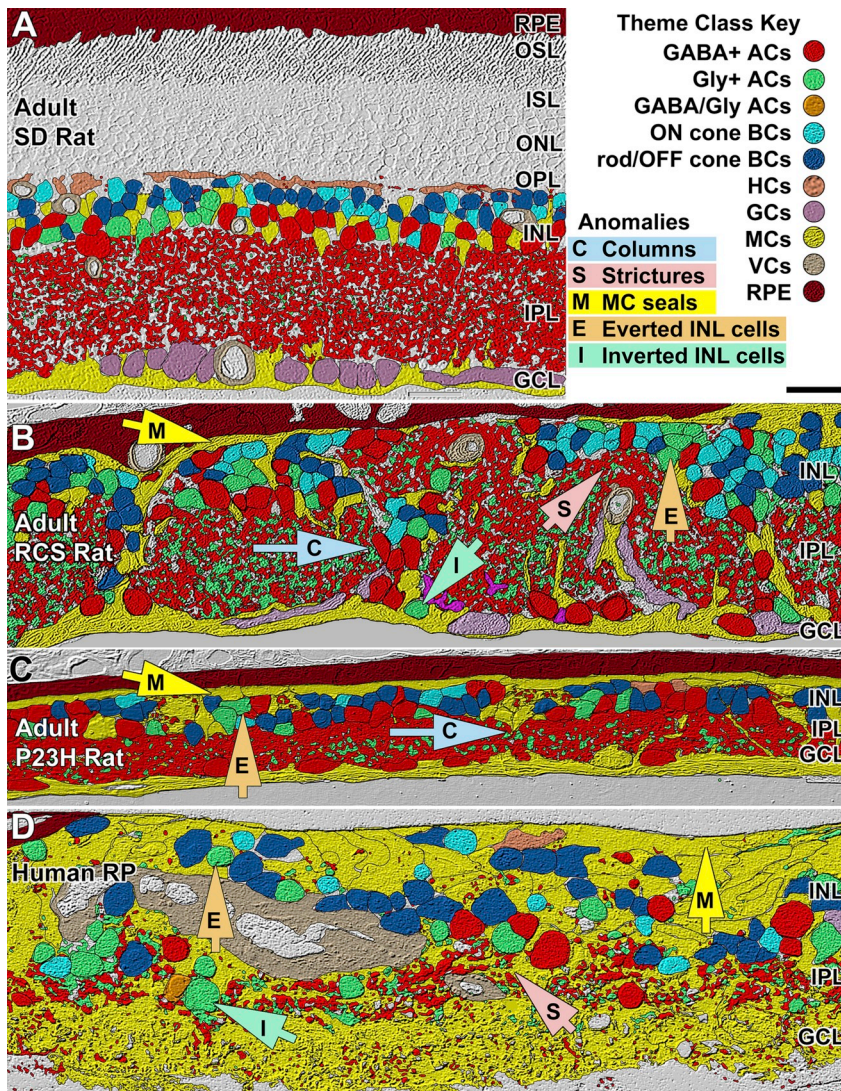
Fig. 5. Theme maps of remodeling *Reprinted with permission from* Jones et al., 2003 Theme maps of (A) normal pnd 700 Sprague-Dawley (SD) rat, (B) pnd 900 RCS rat, (c) P372 P23H line 1 transgenic rat, and (d) human RP (Foundation Fighting Blindness accession #133-OD, 67 year-, female, advanced RP, simplex, fixed 2.5 h post mortem). In normal retina, cell layers are precisely defined. Remodeling clearly disrupts lamination via migration on Müller glia columns (C), yielding eversion (E) of GABAergic and glycinergic amacrine cells to the distal Müller glial seal (M) and inversion of amacrine and bipolar cells (I) to the ganglion cell layer. Glial hypertrophy and neuronal movement can be so extensive that the inner plexiform layer is segmented, distorted and forced through strictures (S) as small as 10 μm.

cell populations as well as neuronal and photoreceptor populations (Jones et al., 2011, 2016a; Pfeiffer et al., 2016).

6.3. Effects of retinal degeneration on the inner retina

Over the past couple of decades, a few labs have worked to characterize the ultrastructural characteristics of the inner retina during retinal degeneration. A primary characteristic of remodeling in advanced retinal degeneration is the presence of microneuromas, where processes of numerous classes of neurons coalesce and run together, in some cases for many microns. These novel neuropil structures contain ultrastructural evidence of active synapses (Jones et al., 2003, 2012). Data show that Müller cells become and remain hypertrophic throughout the progression of remodeling, in addition to demonstrating evidence of variable hyper osmication both within cells and between Müller glia (Jones et al., 2011; Pfeiffer et al., *In Press*). In advanced aged models of retinal degeneration, many remnant ganglion cells somas and processes display severe cytopathologies (Asakawa et al., 2016), and extensive "internal whorl" structures, believed to be associated with ER or mitochondrial stress and autophagy (Fig. 6B and C), similar to pathologies found in CNS neurodegenerations (Hall et al., 1997; Park et al., 2014). Despite substantial neuronal loss following photoreceptor death, the retina continues to maintain synaptic structures (Fig. 6E and F).

6.4. Autophagy in retinal degenerations

The role of autophagy in retinal degeneration is a matter of ongoing discussion (Boya et al., 2016). Autophagy is the process of degrading and recycling cellular components intracellularly, by way of lysosomes (Dodson et al., 2013). In healthy tissue, this is an important part of cell maintenance, particularly among non-mitotic cells such as neurons. In diseased tissue, the role of autophagy becomes more complex. Autophagy is important for both the removal of damaged mitochondria (mitophagy) and the removal of other cellular debris including damaged proteins. Studies with genetically modified animals to inhibit autophagy found increased rod photoreceptor cell death, in addition to an accumulation of the protein transducin (a G-protein associated with phototransduction). These features combined, indicate a pro-survival or maintenance effect of autophagy in retinal degeneration (Yao et al., 2016; Zhou et al., 2015). It may also serve as a metabolic source when metabolic resources are scarce (Dodson et al., 2013).

Conversely, autophagy may initiate apoptosis in cells. In the retina, autophagy occurs in the developing retina as a component of programmed cell death. In the adult autophagy may be elicited through numerous mechanisms including genetic disorders, following trauma, or light damage of the photoreceptors. Autophagic compartments and oxidative stress are observed in photoreceptors following light damage in electron micrographs, in addition to an increase in LC3 expression (associated with autophagic activity (Kunchithapautham and Rohrer,
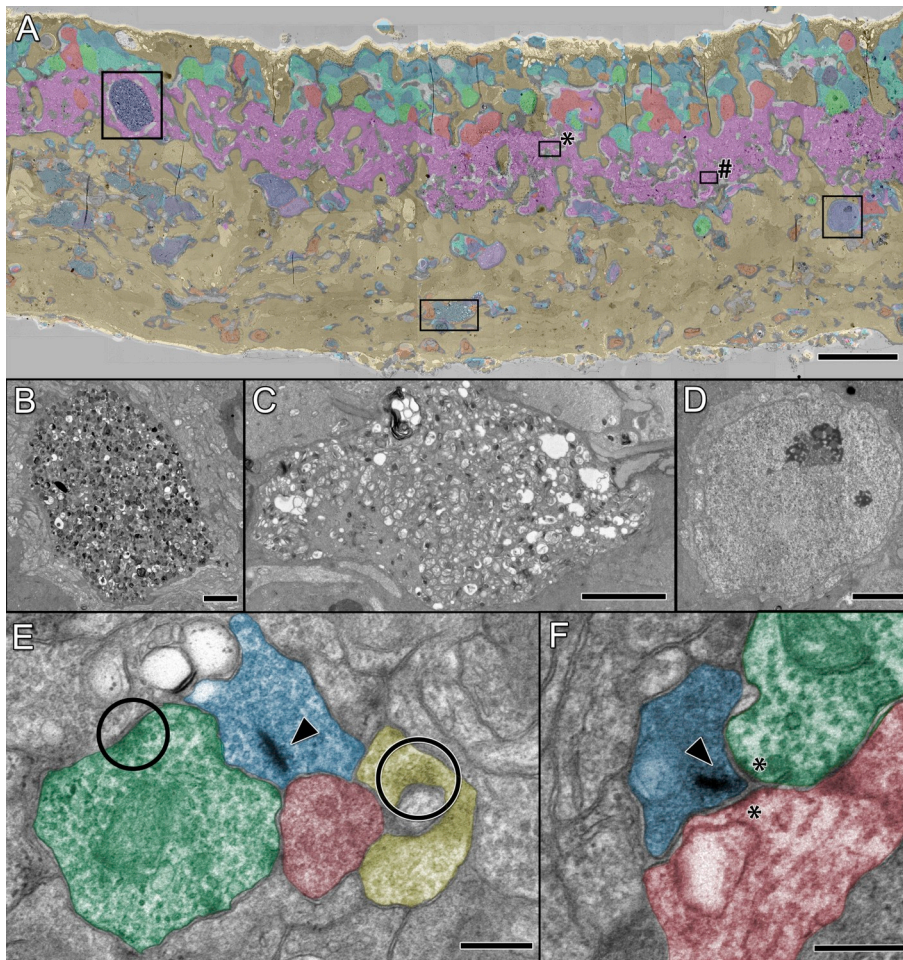
Fig. 6. TEM of remodeling and neurodegeneration in P347L rabbit. (A) Theme map overlay generated via k-means clustering of 7 yr Tg P347L rabbit retina using E, Q, J, D, G, γ, τ, and GS signals. Gold, MCs; magenta, IPL; salmon and green, amacrine cells; cyan and teal, bipolar cells; blue and purple, ganglion cells, scale 25 μm. (B) Large ganglion cell containing autophagic inclusions, scale 2.5 μm (C) Ganglion cell process filled with autophagic structures, scale 2.5 μm. (D) Ganglion cell without autophagic structures, scale 2.5 μm. (E) Conventional (circles) and ribbon (arrowhead) synapses in neurodegenerative retina (region * in A); scale, 300 nm. (F) Ribbon synapse (arrowhead) and typical post-synaptic densities (asterisks) persist (region # in A); scale, 300 nm.

2007; Tanida et al., 2008)). Autophagic structures are also found in photoreceptors of transgenic animals preceding photoreceptor cell death (Bogea et al., 2015). Work in our lab using large-scale ultrastructural connectomics finds autophagic structures, multivesicular bodies, and endosomes are distributed throughout the inner retina in both human and animal retinal degenerations (Fig. 7). Some of these structures are likely associated with standard homeostasis, however the increase in prevalence of these structures and the subsequent decrease in neuronal numbers found in adult tissue reveals autophagy as a key component of neurodegeneration resulting from retinal degenerations.

6.5. Possible contributions of debris exocytosis

A recent study by Meletijevic et al. (Melentijevic et al., 2017) described a novel mechanism by which neurons may respond to an increase in misfolded proteins. They find that adult neurons extrude misfolded proteins and pathologic mitochondria via novel structures, termed *exophers*. Exophers are large, complex, membrane enclosed structures associated with lysosomal autophagy. They are exported from within their origination neuron and may be taken up by a neighboring cell. This is proposed as a mechanism of misfolded protein transfer, that has been described in multiple neurodegenerative diseases (Lee et al., 2010). In addition, recent work by Fertig et al., has demonstrated extracellular vesicles extrusion of multivesicular bodies from teleocytes (Fertig et al., 2014). Our connectomics efforts with volumes of reconstructed serial section electron microscopy (Anderson et al., 2011a, 2011b) of pathological retina (unpublished), has revealed numerous instances of whorls and swollen multivesicular debris that are extruded from one cell and encapsulated by a neighboring cell,

either neuron (Fig. 8A) or Müller cells (Fig. 8B). While these extrusions are inconsistent with apoptotic blebbing or typical autophagy, these whorls and endocyte-like structures are often found associated with swollen mitochondria. Although inconsistent with the assumption that cells degrade their own organelles, transcellular debris degradation is not without precedence, in fact the potential for neurons to retain a capacity for phagocytosis has been previously described (Bowen et al., 2007). In the optic nerve head, it has been shown that mitochondria originating from ganglion cell axons can be transferred to neighboring astrocytes and degraded (Davis et al., 2014). Based on this, we propose that these structures are associated with debris removal from stressed cells, potentially similar to the above described mechanisms or via an unknown mechanism of cell-to-cell transfer of debris. Discussed below, these structures may provide a mechanism for the spread of progressive neural degenerative disease. Further investigation is required to determine the origins, implications, molecular biology and functional consequences of these structures.

7. Protein aggregation contributes to retinal neurodegeneration

The neurodegeneration found in retinal degenerations, including pronounced cell death, metabolic deviation, and debris accumulation, is reminiscent of CNS neurodegenerative diseases. Protein aggregates are a common pathology associated with neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Pick's disease, Huntington's disease (Waelter et al., 2001), and multiple types of dementia. In retinal degeneration, protein aggregates have been attributed to components of cell death, predominantly mechanisms of photoreceptor cell death (Illing et al., 2002; Saliba et al., 2002). Here, we
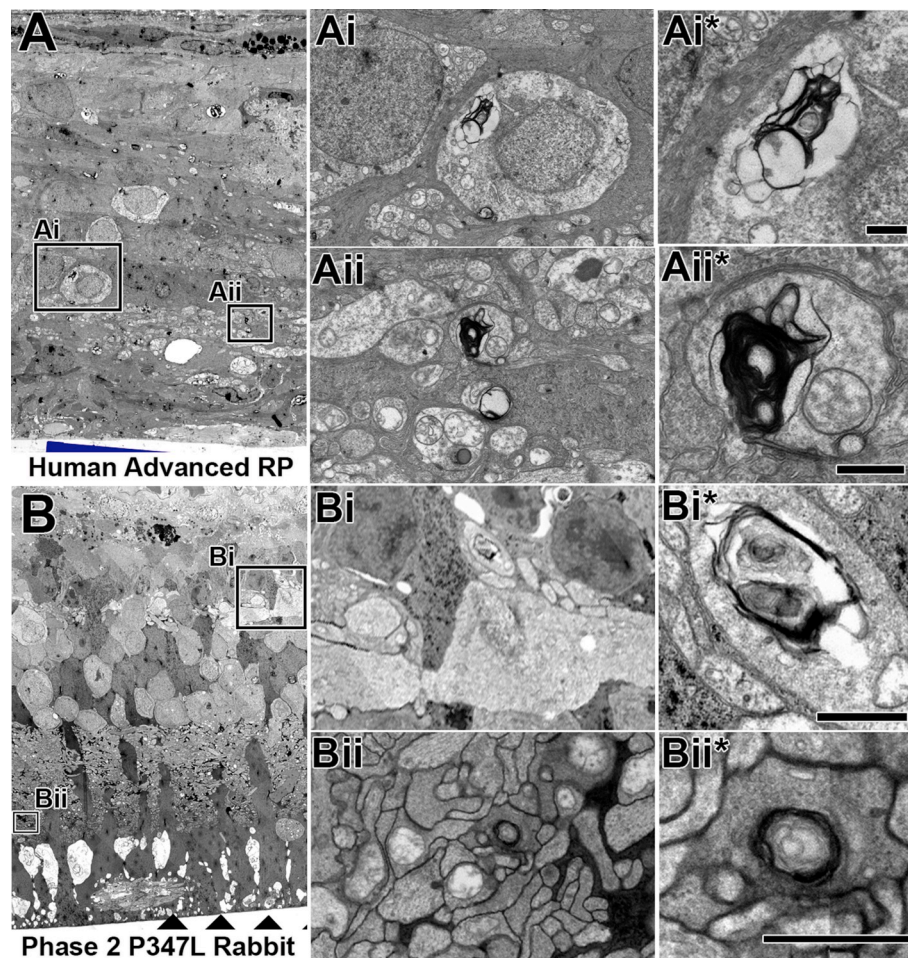
Fig. 7. TEM of internal whorl structures associated with neurodegeneration. (A) Human retina from 77yo male diagnosed with RP. (Ai and Aii) Regions of higher magnification from A containing whorl structures. (Ai* and Aii*) High resolution images of whorl structures. (B) Retina from a 2yo female P347L rabbit. (Bi and Bii) Regions of higher magnification from B containing whorl structures. (Bi* and Bii*) High resolution images of whorl structures. Scale bars 500 nm.

make a case for protein aggregates playing a role in the widespread neuronal loss associated with late-stage retinal degeneration in a manner consistent with that seen in other CNS diseases. This is not meant to imply that all initiating factors are the same. Clearly the precipitating factors (genetics, trauma, environmental factors, or a combination thereof) are unique in the onset of these disorders, nonetheless the final outcome of neurodegeneration is the same. Here we simply describe common proteins whose aggregates appear to be involved in the final neurodegeneration processes of the retina and brain.

7.1. Protein aggregation in AMD

In AMD, amyloid-beta (Aβ), the protein commonly associated with Alzheimer's disease, has been associated with AMD pathology (Ratnayaka et al., 2015). Aβ is a monomeric peptide produced by γ- and β-secretase cleavage of the amyloid precursor protein (APP) (Dawkins and Small, 2014). APP is a type I membrane glycoprotein with multiple spliced forms. Multiple factors including mutations in APP encoding genes and post-translational modifications of Aβ lead to greater self-association and the formation of amyloid fibrils and oligomers. These structures are associated with neurodegeneration (Lambert et al., 1998). APP is found in cells of the RPE, inner nuclear layer, and ganglion cells (Wang et al., 2011). Aβ has been identified in drusen deposits from eyes with AMD (Dentchev et al., 2003; Johnson et al., 2002). In addition to Aβ in drusen, Aβ depositions increase in the RPE with age, while levels of neprilysin (the enzyme responsible for clearing Aβ) are decreased, indicating a contributing mechanism of Aβ

accumulation with age (Wang et al., 2012). These Aβ structures of varying sizes have been reported in drusen post-mortem in humans with a correlation of a greater number associated with more advanced AMD (Yoshida et al., 2005), however the identification appears to be highly dependent on the antibody used for detection (Anderson et al., 2004). These observations led to investigation of the contributions of Aβ to retinal stress and degeneration. In animal models, various forms of Aβ and Aβ oligomers were injected into the eye or exposed to cell culture leading to an increase in pro-inflammatory cytokines (Kurji et al., 2010; Liu et al., 2012) and oxidative stress responses (Bruban et al., 2009). Combined, these studies indicate a primary contribution of proteinopathy-associated oligomers contributing to AMD and a potential additional pathway to address the complex progression of AMD.

7.2. Protein aggregation in RP

Protein aggregation is not restricted to AMD as a mechanism of retinal degeneration progression. One common type of autosomal dominant RP is the P23H single-base substitution mutation of rhodopsin that leads to progressive rod death followed by secondary cone loss. In this mutation, the rhodopsin protein is misfolded, leading to ER stress and activation of the unfolded protein response (Gorbatyuk et al., 2010), and has been shown to aggregate (Saliba et al., 2002). These protein aggregates are found to be highly ubiquitinylated, and over time leads to an impairment of the ubiquitin proteasome system (Illing et al., 2002).

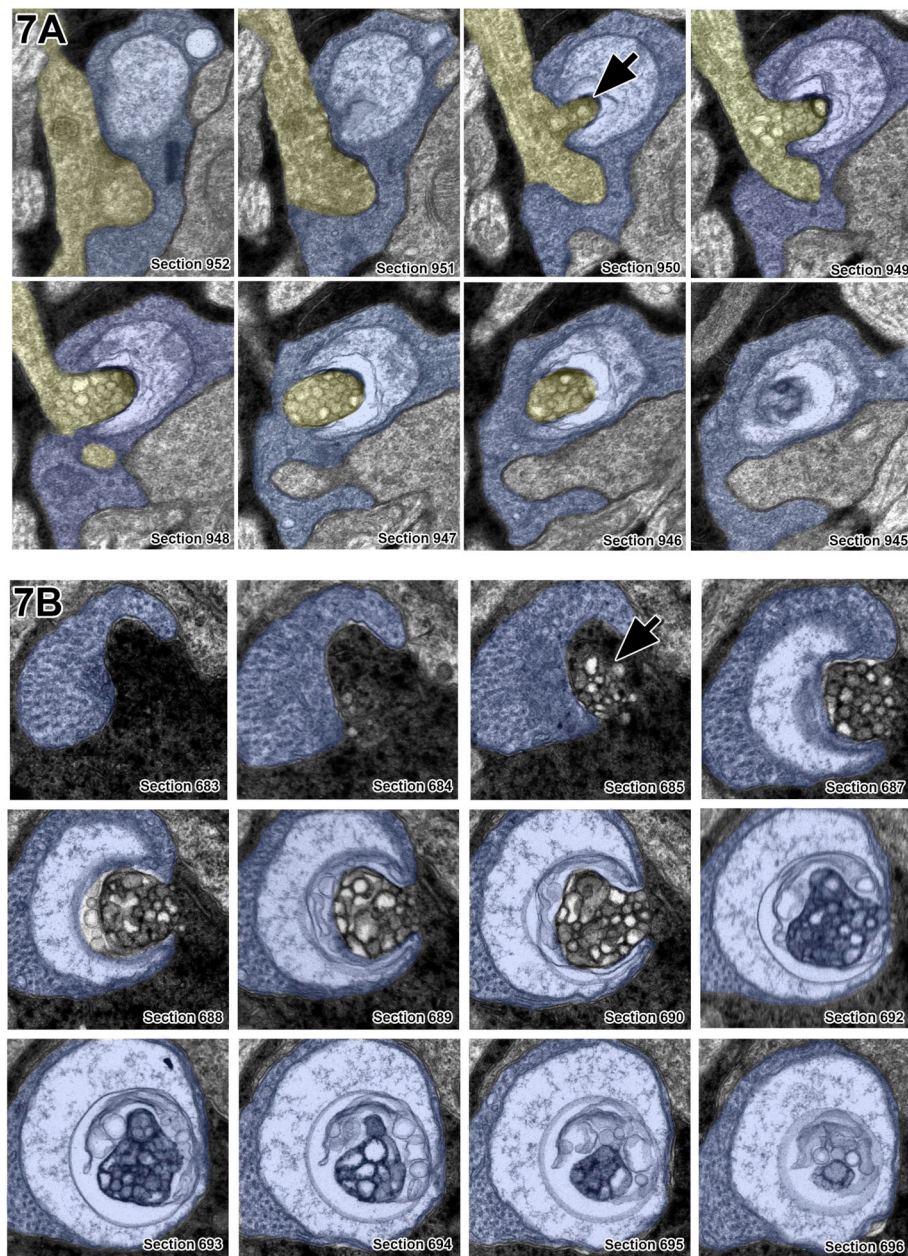Members of the synuclein family are another proposed protein

Fig. 8. Cell to cell transfer of debris-like structures in TEM serial sections. (A) Serial sections of an amacrine cell (yellow) extruding a region of multiple large vesicles (indicated by arrow) into a bipolar cell (blue) near a potential lysosome. (B) Serial sections of apparent engulfment of a multivesicular structure (indicated by arrow) in a Muller cell (darker) by a bipolar cell (blue) near an apparent lysosome.

aggregate found in RP (Surguchov et al., 1999). The most well-known member of this family is alpha-synuclein (α-syn), the protein which, when mutated, is associated with Parkinson's disease (Polymeropoulos et al., 1997). In the nervous system, α-syn is found enriched at synaptic terminals associated with the SNARE-complex (Burre et al., 2010). Mutant forms of α-syn, however, are prone to pathologic aggregations as oligomers, β-sheets, and Lewy Bodies, which are associated with neurodegeneration (Burre et al., 2015). α-Syn is found throughout the retina, with higher levels found in rod outer segments and the ONL (Martinez-Navarrete et al., 2007). Phosphorylation of the serine at position 129 of α-syn (Pα-syn) is a specific marker of α-syn lesions and is associated with an increased propensity to form aggregates (Fujiwara et al., 2002). We evaluated the distribution of α-syn in healthy retina and across aging timepoints in the degenerate retina of the P347L rabbit to better understand the potential contribution of protein aggregates in RP. In Tg retinas, the levels of both α-syn and Pα-syn vary with age and

severity of retinal remodeling (Fig. 9). Although signals may vary depending on the level of remodeling, the basic pattern is as follows: Early in degeneration (3mo-1.5yrs), Pα-syn is increased in horizontal cells, along with a subtle uniform increase in the INL, IPL, and GCL (Fig. 9E). Higher levels of α-syn are found in the outer segments of degenerating rods and lower levels throughout neurons of the outer and inner retina (Fig. 9F). By ~2yrs the thinned ONL shows extracellular aggregation of Pα-syn around and within some ganglion cells (Fig. 9H). High levels of α-syn are observed, with increased concentrations in the inner retina as well. Of note, at this stage the α-syn in ganglion cells appears to no longer be uniformly distributed, but rather is aggregated along the outer cell membrane (Fig. 9I). At ~4yr degeneration the ONL is largely absent and Pα-syn levels are two-fold higher than α-syn throughout neurons of the inner retina. Pα-syn also begins to aggregate inside neurons, particularly ganglion cells (Fig. 9K). α-Syn is distributed in the neuronal nuclei of the inner retina, with some punctate staining
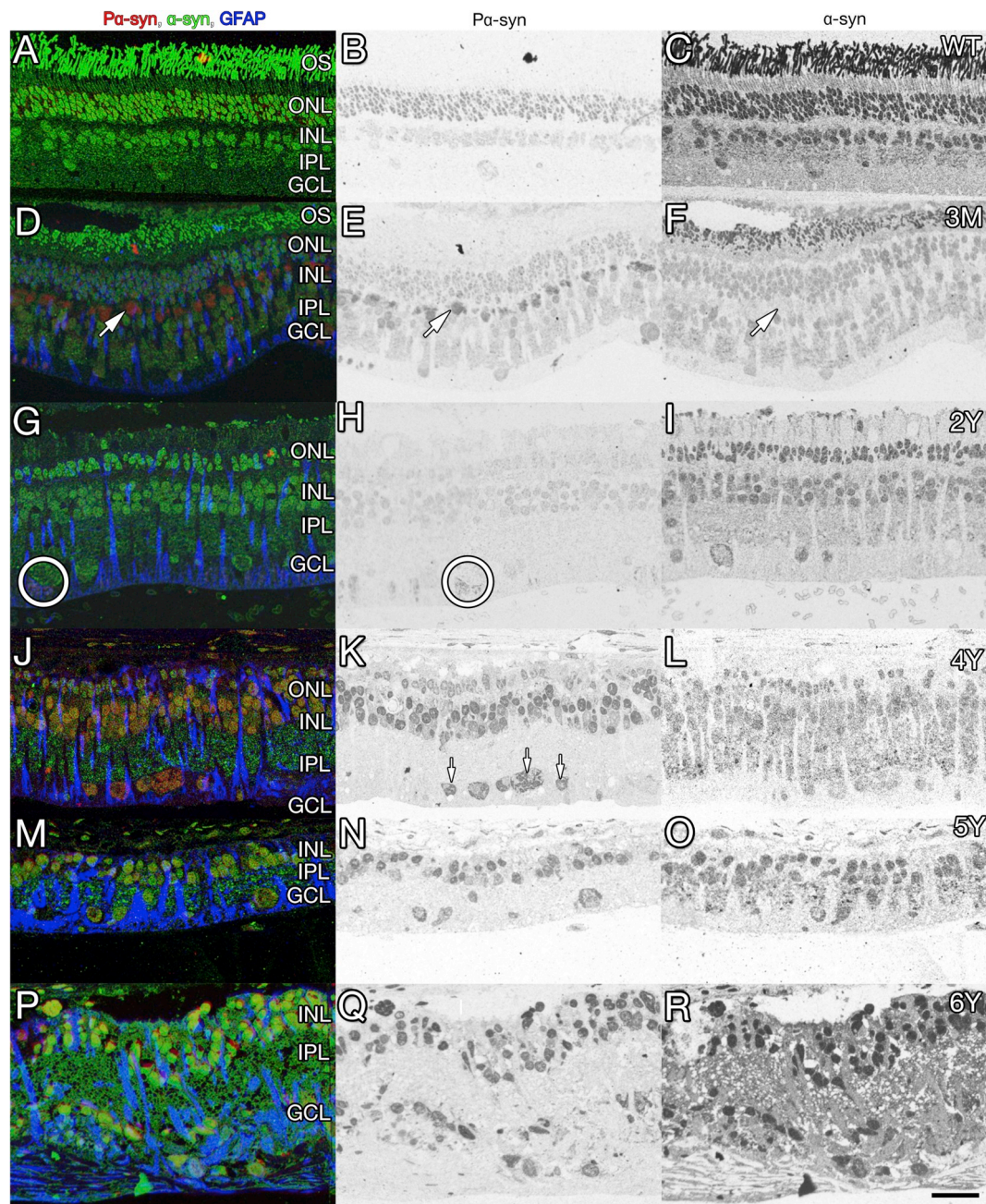
Fig. 9. Patterning of phosphorylated α-synuclein (Pα-syn), full α-synuclein (α-syn), and GFAP in normal WT (A–C) versus 3 mo, 2y, 4y, 5y, and 6y Tg rabbits (D–R). Left column: pCMP mapping of Pα-syn, α-syn, GFAP > rgb. Middle column: grayscale density mapped Pα-syn channel. Right column, grayscale density mapped Pα-syn channel. (A–C) Normal retina has highest Pα-syn and α-syn levels in photoreceptors. (D–F) In early degeneration, Pα-syn but not total α-syn is transiently elevated in horizontal cells (arrows). (G–I) As retinal degeneration progresses, Pα-syn but not α-syn debris accumulates around ganglion cells (circle). (J–L) In advanced disease, circumscribed extracellular and intracellular Pα-syn aggregates become common in the ganglion cell layer. (M–R) In advanced neurodegenerative phases, both Pα-syn and total α-syn levels become elevated in virtually all survivor neurons. Scale, 30 μm.

distributed within the IPL, presumably at large synapses (Fig. 9L). At 5 yr, Pα-syn continues to aggregate within ganglion cells in displaced neurons found within the IPL, and is found at high concentrations in many INL neuronal soma (Fig. 9N). α-Syn is found highly expressed in all remaining neurons and is predominantly colocalized with Pα-syn, with an exception of punctate levels in the IPL, as IPL staining is unique to the full protein (Fig. 9O). By 6–7yrs the structure of the retina is severely decimated. Pα-syn is not only ubiquitous in the remaining neurons but is also found in aggregates in the cellular debris found distributed among the region of remodeled glial endfeet (Fig. 9Q). α-Syn is distributed widely throughout remnant neurons and processes of the retina (Fig. 9R). Combined, these studies suggest a role of the

synuclein family, including α-syn and Pα-syn in retinal neurodegeneration, particularly during remodeling.

7.3. Ubiquitin proteasome system

In addition to the autophagy-lysosome system, a common pathway involved in neurodegenerative disease is the ubiquitin-proteasome system (UPS) (Zheng et al., 2016). The UPS is responsible for approximately 80% of intracellular protein degradation in eukaryotes, where ubiquitin tagged proteins are targeted for degradation by the 26S proteasome in an ATP dependent manner (Glickman and Ciechanover, 2002). Proteasome end products are short peptides, which may be
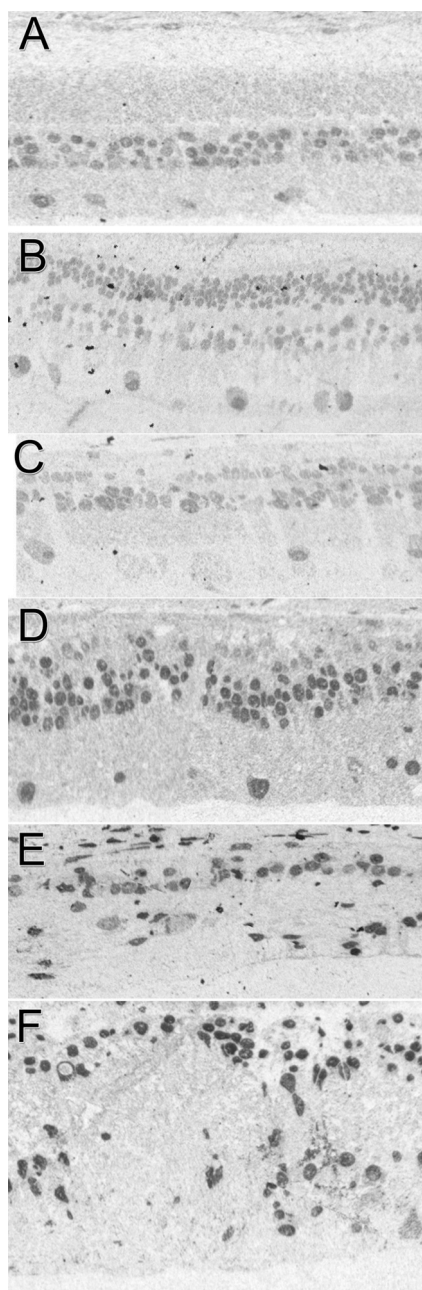
Fig. 10. Grayscale ubiquitin labelling in rabbit retinas. (A) WT P347L littermate control demonstrating light ubiquitin immunoreactivity in INL and GCL. (B) 3 mo Tg P347L rabbit retina demonstrating slight accumulation in soma of INL and focal increases in GCL Somas. (C) 2 yr Tg P347L rabbit retina with continued focal increases in soma of INL and GCL. (D) 4 yr Tg P347L rabbit retina. Levels of ubiquitin have risen in some soma. (E) 5 yr Tg P347L rabbit retina, demonstrating variable level of ubiquitin across all cell types with punctate increase in some soma. (F) 6 yr Tg P347L rabbit retina. The remaining somas have varying levels of ubiquitin with extra cellular increases in unknown processes.

further degraded in lysosomes to single amino acids (Schreiber and Peter, 2014). However not all substrates degraded by lysosomes are first processed via the UPS. In healthy cells, the UPS system helps to maintain proteostasis by rapidly degrading redundant or mutated proteins. Subsequentially, the UPS can be impeded by protein aggregates (Bence et al., 2001). In neurodegenerative diseases, despite differing aggregate forming proteins, ubiquitin inclusions are a common feature (McKinnon and Tabrizi, 2014).

In the retina, the UPS is associated with retinal disease (Campello

et al., 2013). An example of this in RP, is P23H rhodopsin aggregation associated with UPS impairment, where the impairment of degradation of the mutant rhodopsin leads to aggresome formation near the cellular centrosome (Illing et al., 2002). In the P347L rabbit, ubiquitin levels and localization as a measure of protein degradation and aggregation were mapped, revealing increased levels in neuronal somas soon after the onset of outer segment stress and degeneration. Focal increases were also found within ganglion cells underlying regions of photoreceptor stress (Fig. 10A–C). Later timepoints demonstrate increased levels of ubiquitin distributed throughout neuronal somas, with increases found throughout the retina at later time points (Fig. 10D and E). By 6 years, we see elevated ubiquitin levels in all remaining neurons, in addition to aggregation outside of somas (Fig. 10F). Combined, these data document protein aggregation and a disrupted UPS as components to retinal neurodegeneration in remodeling.

8. Implications for therapeutic interventions

RP is relatively rare, affecting 1 in 4000 people, however, AMD is the third leading cause of blindness worldwide and is expected to become more prevalent as the population over 65 increases. Because of this, a primary interest for current vision research is the advancement of new therapies for the treatment of photoreceptor-associated vision loss. Therapies including small electrode array implants to stimulate remaining neurons, optogenetic approaches involving the transfection of specialized opsins into remnant neurons, and a number of genetic and cellular based approaches are currently being investigated (Lamba et al., 2009; Petrs-Silva and Linden, 2014). All these interventions require a nominally intact retina with a stable retinal metabolic environment to either reactivate or repopulate neurons (Marc et al., 2014). The impact of proteinopathy and extensive neurodegeneration interferes with stable retinal environments conducive to proper function, and therefore needs to be addressed in any therapeutic intervention that hopes to have long-lasting function.

8.1. Optogenetics

The fundamental concept behind optogenetics as a treatment for retinal degenerative disorders is to engineer another cell class to genetically respond to light, restoring vision due to photoreceptor loss. Early studies demonstrated algal channelrhodopsin-2 (ChR2) when inserted into the membrane of mammalian cells, will induce a depolarization event in response to light (Nagel et al., 2003). Other studies have explored Archean halorhodopsin (NpHR) to induce hyperpolarization in response to light (Han and Boyden, 2007; Schobert and Lanyi, 1982; Zhang et al., 2007). Therefore, by genetically inserting these apoproteins into neurons, any neuron could be made light sensitive (Boyden et al., 2005). The idea that neurons of the retina could be given new light detecting capabilities following the loss of photoreceptors was proposed and successfully implemented by (Bi et al., 2006). However, which class of cell should be the appropriate recipient of the optogenetic therapy to induce, or restore, light-sensitivity? One early avenue was to restore light-sensitivity to cone somas, following the loss of outer segments with the goal of preserving native processing in the retina (Busskamp et al., 2010; Busskamp and Roska, 2011). As discussed above, in many forms of retinal degeneration, cone cell death occurs relatively early in the progression of the disease in humans, resulting in early alterations that may preclude or at least complicate potential treatments. Later work targeted the neurons of the inner retina to compensate for the complete loss of photoreceptors, either through a broadly delivered intravitreal injection approach, which predominantly targets ganglion cells (Greenberg et al., 2011; Tomita et al., 2009, 2010; Zhang et al., 2009), or through targeted delivery to specific cells of the inner retina (Doroudchi et al., 2011; Lagali et al., 2008). The discussion in the literature is still unresolved as to which cell is best for inducing light sensitivity, in what combination, and which

promoters are best for cell-specific targeting. Another major problem with algal and protozoan opsins is their very low photosensitivity, requiring extremely bright light displays to generate responses (Marc et al., 2014). This hurdle is rapidly being overcome as more recent work has demonstrated opsins transduced into mouse bipolar cells offer improved performance (Ganjawala et al., 2019; Gaub et al., 2015). Others have successfully transduced melanopsin into retinas, but the time course of melanopsin signaling is so far, much too slow to provide functional vision (Lin et al., 2008). Recent work has also made advancements in targeting opsins in healthy retinas of humans and non-human primates, furthering the feasibility of this type of therapeutic intervention (Chaffiol et al., 2017; Khabou et al., 2018; Sengupta et al., 2016).

8.2. Chemical photoswitches

Another approach is temporarily inducing photosensitivity in neurons through the application of chemical photoswitches. These photosensitive small molecules regulate neuronal electrical activity by transiently blocking ion channels. An early study used the photochemical AAQ (acrylamide-azobenzene-quaternary ammonium), which in its *trans* form blocks K^+ channels, thereby increasing excitability, and in its *cis* form unblocks K^+ channels. AAQ photoisomerizes from its *trans* to *cis* conformation in the presence of short wavelength (~380 nm) light, which unblocks K^+ channels and decreases excitability. Relaxation from *cis* to *trans* occurs slowly in darkness, or reisomerization can be rapidly induced using long wavelength (~540 nm) light (Polosukhina et al., 2012), allowing potentially rapidly gating, bi-directional optical control. Polosukhina et al. unexpectedly found that 380 nm light elicited action potentials, despite K^+ channels becoming unblocked at that wavelength. This turned out to be the result of AAQ primarily effecting amacrine cells, causing ganglion cells to fire due to disinhibition. A distinct problem with AAQ is the necessity of high intensity UV light for isomerization which itself could be oxidatively damaging to retinal tissues if administered post cornea and lens. Another chemical photoswitch is DENAQ (diethylamino-azobenzene-quaternary ammonium) (Tochitsky et al., 2014). DENAQ is also a K^+ channel photoswitch that blocks K^+ channels in its *trans* confirmation and unblocks in *cis*. The main difference is that DENAQ is red-shifted and photoisomerizes *trans* to *cis* within the visible spectrum (450–550 nm) then rapidly relaxes back to the *trans* conformation in the dark (within ~600msec). Also, DENAQ has been shown to be responsive to lower intensity light than either AAQ or many optogenetic strategies. Recently investigators have begun exploring new photoswitches capable of acting in AMPA receptors, via the photoswitchable excitatory amino acid (ATA) (Stawski et al., 2012). ATA is active in the dark, and photoisomerizes from *trans* to *cis* in blue light (480 nm). The distribution of AMPA receptors causes a group of RGCs to respond to blue light, while another group fires in response to darkness (Laprell et al., 2016). A combination of specific photoswitches may facilitate restoring ON-OFF responses, though remodeling leading to altered glutamate receptor expression levels (Marc et al., 2007, Jones et al., 2012) will likely be of concern (Lin et al., 2012b) as it would complicate the normal programming that photoswitches would depend upon. Photoswitches also demonstrate a shorter lifespan than optogenetics, making them a potential diagnostic tool (Marc et al., 2014).

8.3. Cellular replacement strategies

Typically, in mammalian CNS, once a neuron dies it is not replaced. This is certainly the case in mammalian retina. The advent of stem cell techniques promises the ability to differentiate new cells *in vitro*, with the hope of replacement of cells or entire organs grown specifically for an individual. Because the death of photoreceptors is the precipitating feature of all retinal degenerative diseases, photoreceptor replacement strategies are being investigated as a potential treatment. Photoreceptor

transplants have had early success with surviving, for at least a few weeks, and have been found to generate synapses in the neural retina (Barber et al., 2013; MacLaren et al., 2006; Pearson et al., 2012; Santos-Ferreira et al., 2016a). It has been shown following introduction of embryonic stem cell derived photoreceptors, that pupillary responses are increased in visually deficient mice (Singh et al., 2013), though it is unclear whether this is due to photoreceptor signaling or a change in the response of intrinsically-photosensitive retinal ganglion cells (ipRGCs). Research continues to determine the long-term viability of transplanted cells and their functionality in the context of the total retina (Pearson et al., 2014; Santos-Ferreira et al., 2016b). In addition, cellular replacement strategies involving RPE transplantation and implantation of full retinal sheets are also being explored. RPE transplant efforts have progressed to human trials in numerous RPE affecting disorders (Lu et al., 2017), following extensive validation in animal models (Khristov et al., 2018). These studies in humans have shown that RPE transplants are more effective in treating hemorrhagic AMD than choroidal neovascular membrane excision alone (Lu et al., 2017). Retinal transplants have been performed in mice (Arai et al., 2004; Radner et al., 2002), rats (Foik et al., 2018; Seiler and Aramant, 2012; Seiler et al., 2017), non-human primates (Tu et al., 2019), and current clinical trials are underway in humans. A study from earlier this year found that retinas derived from human induced pluripotent stem cells (iPSCs) are capable of surviving in light-damaged primate host retinas and have indications of restoring light responses (Tu et al., 2019). Further exploration and technological development into these transplants are necessary, as retinal detachments is a common side effect. However, we have also found that transplantation of fetal retina induces remodeling that occurs as fast as, or potentially faster than, that seen in degenerate retina without intervention (Seiler et al., 2012).

8.4. Bionic implants

Beyond the biologic interventions currently proposed, another methodology aims to intervene using principles similar to the widely successful cochlear implant; in this case, the retinal implant. For a more extensive review of retinal implants see: (Yue et al., 2016). There are multiple approaches to retinal implants: subretinal, epiretinal, and intrascleral (Bareket et al., 2017). A subretinal implant is surgically implanted under the retina between the photoreceptor layer (or former photoreceptor layer in the case of retinal degenerations) and the RPE, and uses microelectrodes to generate light responses to be processed through the remnant neural retina (Zrenner, 2002). An epiretinal implant is surgically placed along the vitreal surface, next to the ganglion cell layer of the retina, which does not require detachment of the retina from the RPE and generates action potentials in the associated ganglion cells, bypassing neural retina processing (Radner et al., 2002). Each approach has advantages and disadvantages.

The subretinal implant has the advantage of being a simpler more compact design. Some technologies are also including photodiodes with sensing and stimulating elements on one chip surface, to allow the wearer to preserve normal eye movements to shift visual attention (Stingl et al., 2013). The final advantage is that subretinal implants in theory have the capacity to utilize any circuitry remaining in the neural retina; however, as discussed in the remodeling section, it is likely that the circuitry of late retinal degenerations is corrupted.

Epiretinal implants, such as the Argus II are placed next to the ganglion cell layer in the vitreous, and stimulate nearby neurons to fire action potentials in a pattern controlled by a video camera headset. This approach has the potential to provide for coarse vision, allowing increased independence and mobility among individuals affected by retinal degenerations (Ahuja et al., 2011; da Cruz et al., 2013; Dorn et al., 2013). These results have been mostly maintained in long-term 5 year follow up studies, though 23% of individuals implanted had a serious side effect within the first 3 years (da Cruz et al., 2016).

All three methodologies are in clinical development. The epiretinal

Argus II is approved for clinical use in Europe (2011), the United States (2013) and in Canada (2015). Another epiretinal stimulation device is the IRIS system (Pixium Vision), which is currently in clinical trials in Europe (NCT03333954) and US (NCT03392324). For subretinal stimulation, the Alpha IMS and AMS systems (Retina Implant AG) have been leading the field with numerous clinical trials in the United States (NTC03629899), Europe (NTC02720640 and NCT01024803) and Hong Kong (NCT01497379)(Kitiratschky et al., 2015; Stingl et al., 2015, 2017). For suprachoroidal implants a group out of Australia is leading this effort (NCT03406416 and NCT01603576)(Ayton et al., 2014; Petoe et al., 2017; Shivdasani et al., 2014, 2017; Slater et al., 2015)

These implants have all had early success in stimulating neurons and generating light mediated responses in patients with profound outer retinal degeneration. That said, complications are not uncommon. Epiretinal implants have a high rate of subsequent retinal detachment of 24%, while subretinal implants have a 22% rate of retinal breaks (Kitiratschky et al., 2015). In addition, a recent report from the Alpha AMS/IMS group demonstrated issues with changes in microchip positioning in clinical trials (Kuehlewein et al., 2019). Glial scarring is also a common issue with retinal implants, as this can reduce efficacy and lead to the implant being effectively "welded" to the scar. Further exploration into more biocompatible implants and further tuning of the stimulation is ongoing. This includes intrascleral (or suprachoroidal) implants which require greater stimulation to activate neurons within the retina, and these currents are not well defined for the number and types of retinal cells that may be activated.

8.5. Genetic approaches

Among therapeutic interventions for vision loss, genetic approaches are especially favored in cases where a specific gene defect is known to be the direct cause of vision loss. Leber's Congenital Amaurosis (LCA) is the most notable example, in which one form is specifically caused by a loss of function mutation in the RPE specific gene *RPE-65*. LCA is an early onset retinal degeneration, where affected individuals typically experience severe vision loss in the first few years of life. Gene-replacement therapy delivered via adeno-associated viruses (AAVs) has been used to introduce functional *RPE-65*, and has shown promise in restoring proper RPE function in animal models, especially the Briard dog (Acland et al., 2001; Le Meur et al., 2007), and human patients (Cideciyan et al., 2009a, 2009b; Jacobson et al., 2015b; Sahel and Roska, 2013), gaining FDA approval in late 2017. Other gene therapies for replacing defective genes have been tested with x-linked mutations leading to RP with successful prevention of much of the early photoreceptor loss (Beltran et al., 2015).

A primary difficulty for the exclusive use of gene therapy to prevent or slow vision loss is the wide array of genetic defects that can lead to inherited retinal degenerations and the multiple environmental factors that contribute to the generation of AMD (Armstrong and Mousavi, 2015). Because of the diversity of potential defects, all gene therapies for retinal degenerative diseases, aside from perhaps AMD, will be orphan diseases. More importantly, intercession in most cases of recessive disease must occur perinatally, posing severe challenges for the medical ethics of early genetic manipulation. Also, many diseases are autosomal dominant in which a single defective gene can override the function of a normal gene and lead to photoreceptor death. Approaches to these disorders require suppression of the defective gene with methods such as shRNA targeting or new CRISPR/Cas9 gene editing methods, making a therapeutic path for human autosomal disease unclear. While autosomal diseases tend to progress more slowly, extending into adulthood (via unknown mechanisms), it is also not clear that the critical defect leading to widespread degeneration is operation of the defective gene or accumulation of toxic protein will not continue to complicate therapy, in which case late intervention will be of little use, and early intervention may be compromised. It is also important to note that despite the success of *RPE65* gene therapy, the treated individuals still

experience progressive cell death and slow rod kinetics (Jacobson et al., 2015a), illustrating that understanding the mechanisms behind retinal remodeling and plasticity requires more work before gene therapy can be deemed a full rescue.

8.6. Requirements for therapeutic interventions to be effective

There are many approaches to therapeutic interventions and treatment for photoreceptor-initiated vision loss. All are lofty and worthy goals. Unless you bypass the retina entirely, all therapeutic interventions involving the eye require a functional neural retina, or at least the preservation of ganglion cells and their axonal projections to LGN and brain.

Therapies that hope to utilize the neural processing afforded by the inner retina have a number of difficult problems to overcome. Cell-replacement therapies are unlikely to result in long-term vision restoration or preservation unless the initial insult leading to photoreceptor degeneration is also directly treated. It has not been shown that synapses made by newly introduced photoreceptors produce the same visual acuity as native photoreceptors (even within an order of magnitude), nor have photoreceptors been shown to persist. For most therapeutics targeted at stimulation of bipolar cells to be effective, regardless of whether via optogenetics, photoswitches, or subretinal implant, the primary circuitry of the retina must remain intact in addition to the metabolic support of surrounding glia. The basic idea that an epiretinal implant only stimulates ganglion cells, or that ganglion cells transduced by optogenetics or photoswitches could function independently is complicated by extensive coupling between ganglion cells and amacrine cells, as well as penetration of currents deep into retinal tissue. Previous data indicate that alterations in circuitry are present early in remodeling and it is unclear to what extent this affects the signals that are communicated to ganglion cells. We certainly know that retinal ganglion cells begin to display massive uncorrelated spiking in late phase 2 remodeling (Euler and Schubert, 2015; Margolis et al., 2008; Menzler and Zeck, 2011; Stasheff, 2008). In addition, other attributes of remodeling, such as, the metabolic variation of Müller cells during remodeling (Pfeiffer et al., 2016) and how it will affect the metabolic support provided by Müller cells (Bringmann et al., 2013; Reichenbach and Bringmann, 2010, 2013), remain to be explored in the context of therapeutic interventions.

The presence of neurodegeneration as a component of remodeling will present a difficult hurdle to overcome in implementing therapeutic interventions in especially advanced retinal degenerations. However, there are likely windows of opportunity during earlier stages of remodeling (Cuenca et al., 2014; Jones and Marc, 2005) and models of retinal degeneration are an ideal model system to evaluate the efficacy of neuroprotective compounds that could also be used for other neurodegenerative diseases.

9. Opportunities for retina as a model of CNS neurodegenerative disease

Retinal remodeling, specifically neurodegeneration and proteinopathy components, discussed above exhibit unmistakable correlates with CNS progressive neurodegenerative disease processes and illustrate the potential of the retina as a model for CNS neurodegenerative disease. The retina has been previously proposed for studying numerous brain disorders due to some features of those diseases manifesting in the retina during the course of the disease (London et al., 2013; Veys et al., 2019). While interesting and diagnostically useful, this underestimates the utility of specifically using the retina as a model for investigating mechanisms of neurodegeneration. Inner retinal neurodegeneration is a consequence of photoreceptor degeneration, and there is strong evidence for the role of protein aggregates being a causative factor in progressive retinal neurodegeneration. In addition, the retina has the advantage of being more accessible for evaluation of disease

progression, and retina contains in a compact space, entire circuitries that are better understood in terms of organization and topology than most other regions of CNS(Marc et al., 2013).

Alzheimer's Disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) are all progressive neurodegenerative diseases that initially result in miswiring, followed by neuronal cell death and proteinopathy alterations that have correlates in retina. Following insult, the CNS is known to undergo rewiring events in epilepsy (Morimoto et al., 2004), AD (Agosta et al., 2010), PD (Guo et al., 2015), and others. The retina is no different.

9.1. Protein changes

In AD, the predominating causative hypothesis is the amyloid hypothesis, wherein amyloid (specifically amyloid-β) plaque accumulation is responsible for the progressive neurodegeneration observed in AD (Hardy and Higgins, 1992), granted that more recent studies indicate a potentially greater role of phosphorylated tau in the degree of cognitive decline (Hardy and Selkoe, 2002). In addition, Aβ oligomers have been shown to also be major contributors to neurodegeneration preceding much of the hallmark plaque and tangle formation (Jeong, 2017). In PD, second in neurodegenerative disease prevalence only to AD (Sarkar et al., 2016) the primary pathological characteristic is Lewy bodies, which are made up of tangles of α-synuclein, synphilinin-1, and ubiquitin. Of these proteins, α-synuclein (α-syn) has been specifically studied due to its role in the emergence of clinical symptoms when it is misfolded (α-synucleinopathies) (Burre et al., 2015). Other proteins have been associated with PD, including phosphorylated tau (Sarkar et al., 2016). HD is another progressive neurodegeneration associated with the aggregation of mutant protein (Ross and Tabrizi, 2011). Perhaps uniquely, Huntington's has a single genetic cause (though diseases with similar symptoms have been identified (Govert and Schneider, 2013)). The huntingtin (HTT) gene, which is inherited in an autosomal dominant fashion and the length of the resultant polyglutamine stretch is predictive of disease onset (Li and Li, 2004).

AD, PD, and HD are by no means the only protein aggregation associated neurodegenerative diseases, as there are many more including those where protein aggregation is a secondary effect following the initial insult (i.e. traumatic brain injury, epilepsy, etc.). However, beyond protein aggregation, there are a number of other unifying characteristics observed in all of these disorders and in retinal neurodegeneration, which may ultimately reveal central mechanisms of neurodegeneration for broadly applicable therapeutics.

9.2. Receptor changes

As described in section 4.1, reprogramming is a key component of retinal remodeling. During this process, the loss of metabotropic-type glutamate receptors and a phenotypic switching to kainate and AMPA receptors provides a basis for beginning to untangle the changes in retinal physiology observed in degeneration. The simultaneous changes in NMDA receptors are interesting in different respects. First, the loss of NMDA receptors is a common thread between multiple neurodegenerations. In RD, a decrease in NMDA receptor expression has been demonstrated through both immunohistochemical (Grunder et al., 2001) and pharmacological approaches (Jones et al., 2011; Marc et al., 2007). In Parkinson's Disease (PD), an increase in α-syn is associated with internalization of surface NMDA receptors (Chen et al., 2015) In Alzheimer's disease (AD), expression of surface NMDA receptors are downregulated by Aβ oligomers leading to inhibition of long-term potentiation (Lacor et al., 2007). The loss of NMDA receptors appears in all cases to precede the gross cell death associated with each of these neurodegenerations, and understanding the mechanisms of this may help to provide treatments to delay memory loss in AD and PD, while preserving proper retinal signaling in RD. These results also conflict with the hypothesis of NMDA mediated neurotoxicity contributing to cell death in all of these degenerations.

9.3. Mitochondrial stress

Mitochondrial stress is a key feature found in numerous pathological CNS processes including neurodegeneration (Chaturvedi and Flint Beal, 2013; El-Hattab and Scaglia, 2016). Mitochondria play an important role in calcium buffering and cell metabolism, including energy production via oxidative phosphorylation and are central to the Krebs cycle. In addition to their roles in metabolism, they are found to be key regulators in cell death pathways, including apoptosis, autophagy, and necrosis. Reactive oxygen species (ROS) are a direct product of oxidative phosphorylation, and are normally found in tissues, but in large quantities can induce oxidative damage, which in turn activates autophagic pathways (Moreno et al., 2018). This phenomenon has been observed in RD (Moreno et al., 2018), AD (Hirai et al., 2001; Wang et al., 2014), PD (Ganguly et al., 2017; Liu et al., 2018), Huntington's Disease (HD)(Jodeiri Farshbaf and Ghaedi, 2017), and other neurodegenerative disease (Vazquez et al., 2012), and is thought to be a mechanism of cell death in each of these diseases. In addition to ROS, mitochondrial dysfunction can lead to improper calcium handling, which can be especially damaging to neurons (Willems et al., 2008). In retinal degeneration, we observe mitochondrial swelling in addition to disorganized cristae, especially within cells that contain autophagic whorls. The increase in oxidative stress in RD is further supported by the observed increases in glutathione in RP and AMD retinas (Jones et al., 2016a, 2016b).The common thread of mitochondrial stress in neuronal degeneration has made treatments directed at mitochondria an attractive target for therapies and ongoing research in this may help to prevent neurodegeneration in a variety of diseases (Suliman and Piantadosi, 2016).

9.4. Autophagy

As described in section 6.4, autophagy is an important component of cell maintenance, but can also lead to cell death through mechanisms of autophagy mediated cell death and apoptosis (for a comprehensive review of autophagy see (Ravanan et al., 2017)). In neurodegeneration, autophagy is commonly implicated in the progression of neurons from healthy to stressed, and eventually to cell death. Autophagy is complex, and has many contributing factors, some of which are directly related to other components of neurodegeneration progression (e.g. mitochondrial stress, protein misfolding/aggregation, etc.). Although autophagy appears to be beneficial in many ways, impairment leading to degeneration (Ghavami et al., 2014) and increased autophagy leading to longer lifespan (Zhang et al., 2014), it has also been associated with production of extracellular Aβ plaques. A full description of all of the pathways leading to autophagy and its role in neurodegeneration diseases (including RD), is the subject of numerous reviews (Boya et al., 2016; Menzies et al., 2017; Moreno et al., 2018). Autophagy is a clear component of cell stress and progressive neurodegeneration, indicating the further evaluation of these pathways may uncover unified targets to prevent or delay neurodegeneration.

9.5. Ubiquitin-proteasome system

In addition to autophagy, the ubiquitin-proteasome system is important for regulating the catabolism of proteins when they are obsolete, damaged, or are misfolded (for a comprehensive review see (Glickman and Ciechanover, 2002)). This mechanism, as described in section 7.3 is affected by RD. In addition to its role in the neurodegeneration observed in RD (Campello et al., 2013), there is evidence for UPS disruption in other neurodegenerative diseases, especially involving those associated with protein aggregation (Bence et al., 2001; McKinnon and Tabrizi, 2014; Zheng et al., 2016). The proteins involved in aggregation vary depending upon the disease, but ubiquitin is a
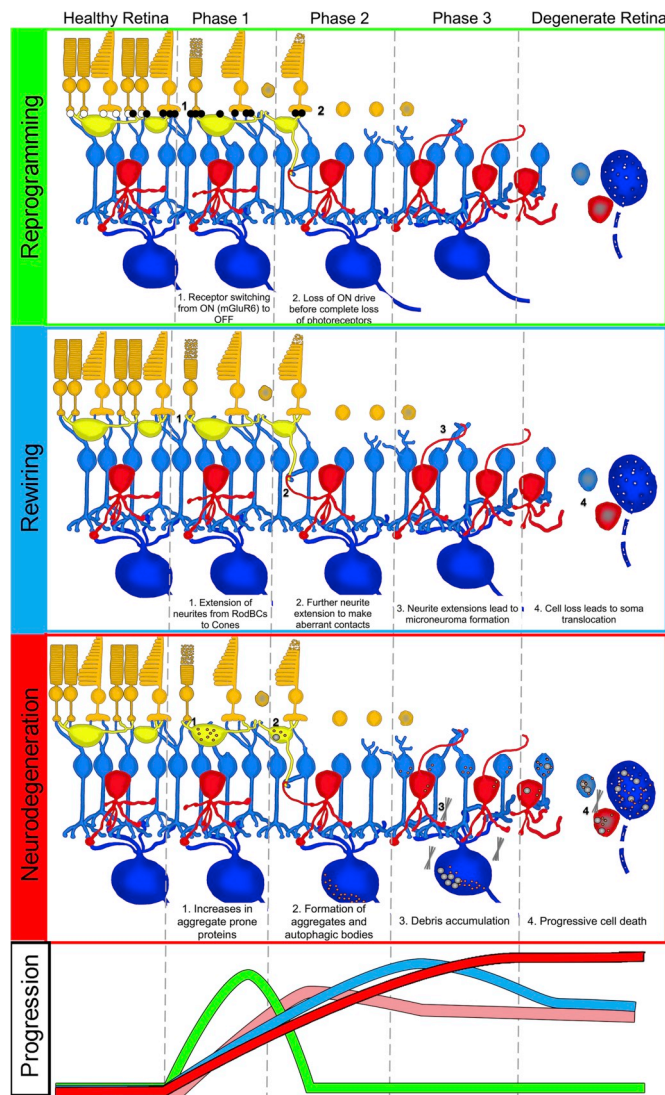
Fig. 11. Components of remodeling. Progression panel at bottom represents relative timescale for the initiation and maximal contributions of each component of remodeling: Reprogramming (green), Rewiring (blue), Neurodegeneration (red), and Glial contributions (pink).

common component of the aggregates. This indicates the UPS may be a targetable pathway to reduce protein aggregation and prevent neurodegeneration in these diverse diseases (Harrigan et al., 2018; Opoku-Nsiah and Gestwicki, 2018).

10. Conclusions and future directions

Retinal remodeling as a clear consequence of retinal degenerative disease has been a growing field over the last two decades. Moreover, many of its features have been alluded to in the literature for almost a century. We have consolidated evidence for inner retinal neurodegeneration as a primary component of remodeling (likely arising from proteinopathy mechanisms), which occurs along with the other previously described features of remodeling: reprogramming, rewiring, and glial responses. All four of these processes occur as a result of deafferentation, or in the case of retina, photoreceptor degeneration, though their time-course and etiologies vary (Fig. 11). Ultimately, the end-state of remodeling is wide-spread neurodegeneration.

Beyond rewiring, reprogramming, and glial components of retinal remodeling; the presence of retinal neurodegeneration, and the evidence for a proteinopathy further complicates therapeutics for

restoration of vision loss. All therapeutics directed at the retina require at a minimum, ganglion cells capable of transmitting signals to appropriate brain regions and metabolic support of these cells (effected by glial alterations), with others requiring specific intact neural network architectures (affected by rewiring), or predictable gene expression (affected by reprogramming). Therefore, it is reasonable to conclude the best time to intervene in retinal degenerations is earlier, prior to the more deleterious aspects of remodeling. This is not always possible meaning the path forward will require strategies to arrest, compensate for, or potentially reverse many aspects of retinal remodeling. This is not a small task. However, it is necessary for long-term effectiveness of each intervention. In addition, the lessons learned from attempting to restore vision will likely be instructive for future therapeutics in the rest of the CNS, especially in regards to neurodegenerative diseases.

Neurodegenerative diseases associated with protein aggregation are an active area of neuroscience research with widespread impact, particularly as a large portion of the population ages. Clearly, progressive neuronal cell death over a long period of time is a common thread, but underlying mechanisms provide cohesive targets for broad interventions. The relationship of protein aggregation and neurodegeneration associated with specific proteins such as amyloid-beta, alpha-synuclein, and tau were initially thought to be confined to specific diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and others. Further research finds protein aggregation to be a commonality between numerous neurodegenerations, with multiple modes of onset including trauma (Acosta et al., 2015), epilepsy (Yang et al., 2006), and retinal degeneration (Anderson et al., 2004). Of these neurodegenerations, retinal degeneration is an ideal system for studying the progression and mechanism of cell death in neurodegenerative proteinopathies. The retina is unrivaled by any other area of the CNS in its accessibility and our understanding of the associated metabolism and circuitry. These factors combined make the remodeled retina an attractive candidate tissue for the discovery of pathways leading to neurodegeneration and evaluating potential interventions.

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Conflicts of interest

Drs. Rebecca L. Pfeiffer and Bryan William Jones have no competing or conflicting interests to declare.

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