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Structure, Function, and Molecular Landscapes of the Aging Retina

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Abstract

Because the central nervous system is largely nonrenewing, neurons and their synapses must be maintained over the lifetime of an individual to ensure circuit function. Age is a dominant risk factor for neural diseases, and declines in nervous system function are a common feature of aging even in the absence of disease. These alterations extend to the visual system and, in particular, to the retina. The retina is a site of clinically relevant age-related alterations but has also proven to be a uniquely approachable system for discovering principles that govern neural aging because it is well mapped, contains diverse neuron types, and is experimentally accessible. In this article, we review the structural and molecular impacts of aging on neurons within the inner and outer retina circuits. We further discuss the contribution of non-neuronal cell types and systems to retinal aging outcomes. Understanding how and why the retina ages is critical to efforts aimed at preventing age-related neural decline and restoring neural function.

OVERVIEW

Neurons face the extraordinary challenge of maintaining and repairing their dendritic, axonal, and synaptic compartments throughout our lifetimes. They accomplish all of this while continuing to function, a feat akin to replacing the engine of an airplane while in flight. It is thus not surprising that repairs do not always go as planned. Decreases in sensory and cognitive performance are well documented as central causes of age-related morbidity (for reviews, see Burke & Barnes 2006, Di Iorio et al. 2006). Similar to other sensory modalities, the visual system begins to show functional loss in the fifth decade, and these changes are of significant clinical importance. Aging alters many aspects of vision, including visual acuity and motion discrimination (Spear 1993). In parallel, there is a rise in the risk of visual disease, such as age-related macular degeneration.

In this review, we discuss the processes and pathways that underlie aging in the retina as a framework in which to understand neural aging more broadly. As in the brain, aging in the retina does not appear to be associated with large-scale neural death (Dickstein et al. 2007, Morrison & Hof 1997, Samuel et al. 2011). While the retina appears to thin in old age (Aggarwal et al. 2007, Gao & Hollyfield 1992, Katz & Robison 1986, Weisse 1995), this is offset by an increase in total retinal area. As a consequence, total retinal volume is maintained in aging, but the density of neurons decreases (Samuel et al. 2011). Flow cytometry assays confirmed no change in the numbers of any of the major retinal neuron types in old age in rodent models (Samuel et al. 2011). These results are consistent with reports of reduced neuron density (Aggarwal et al. 2007, Harman et al. 2000), increased retinal area, and decreased macula thickness (Eriksson & Alm 2009) in old humans.

These results indicate that the predominant impact of aging in retinal neurons is at the levels of structure and function. At the cellular level, changes that occur in the aged retina parallel those documented in the brain: The number of synapses decreases, dendrite architecture remodels, and neural function is compromised (Burke & Barnes 2006, Morrison & Baxter 2012, Samuel et al. 2011) (**Figure 1**). These alterations are associated with many distinct molecular changes, several of which may be neuron subtype dependent. For example, age alters gene expression, increases oxidation and damage of both mitochondrial and cellular DNA, and modulates calcium homeostasis (Foster 2007, Taylor & Turnbull 2005, Trifunovic et al. 2004, Zahn & Kim 2007). The events that instigate these changes may be extrinsic to the nervous system (i.e., inflammation) or occur within neurons themselves. Once nervous system damage occurs, it can initiate downstream events that compound these alterations. Thus, if we are to meaningfully prevent or reverse age-related neural decline, we must understand the cellular and molecular programs through which diverse neuron types maintain their connectivity and function over time. In this review, we outline the features and events that contribute to neural aging in the outer retina, highlight parallels within the inner retina circuitry, and consider extrinsic vascular and glial impacts on neural outcomes.

AGE-RELATED DEFECTS IN THE OUTER RETINA

Of all the cell types in the retina, the most is known regarding age-related changes to photoreceptors and their synaptic partners, bipolar cells, and horizontal cells. There are several practical reasons for this. First, all outer retina types have been identified, and their connectivity has largely been mapped, making it possible to identify age-related cellular alterations with single-synapse precision (Behrens et al. 2016, Sanes & Zipursky 2010). Rod and cone photoreceptors are found in the outer nuclear layer (ONL). Rods respond to dim light and are responsible for monochromatic night vision, while cones are active under photopic conditions and are responsible for daylight vision and color discrimination (Ingram et al. 2016). Light detected by photoreceptors is converted into electrical signals that are detected by horizontal and bipolar cells found in the inner nuclear

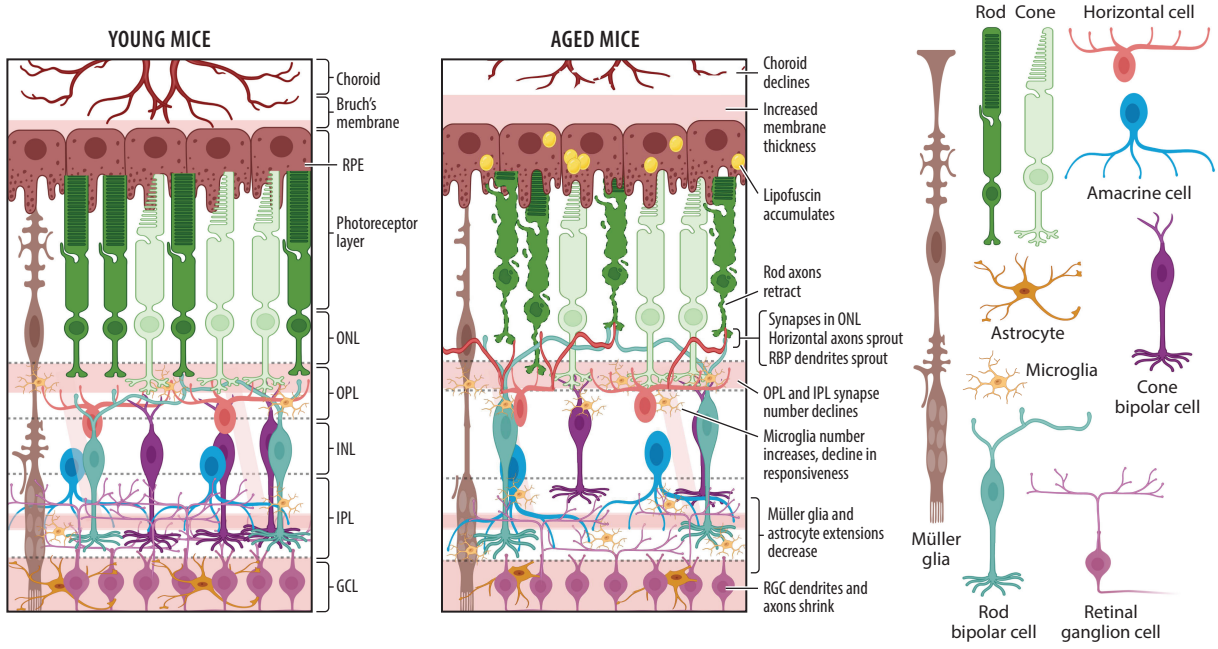

Figure 1

Structural impacts of aging in the retina. Shown is a schematic of retinal neuron organization in young and aged mice. In young animals, the outer nuclear layer (ONL) contains rods (*dark green*) and cones (*light green*) that form connections in the outer plexiform layer (OPL) with rod bipolar cells (*teal*), cone bipolar cells (*purple*), and horizontal cells (HCs; *red*) found in the inner nuclear layer (INL). Also present in the INL are amacrine cells (*blue*) that form connections in the inner plexiform layer (IPL). They do so together with bipolar cell axons, which connect with retinal ganglion cell (RGC) dendrites (*magenta*). RGC cell bodies reside in the ganglion cell layer (GCL). Müller glia (*brown*) span the length of the outer retina, astrocytes (*orange*) reside in the GCL, and microglia (*yellow*) processes are largely restricted to the synaptic layers. Three intraretina vascular layers also interdigitate the GCL, IPL, and OPL. In the aged retina, several of these organizational features are altered. In the outer retina, supporting retinal pigment epithelium (RPE) cells accumulate lipofuscin, and Bruch's membrane appears to thicken. Rod photoreceptors retract into the ONL, accompanied by misplaced synapses, while cones are structurally less affected. Postsynaptic HC axons and rod bipolar dendrite cells extend neurites into the ONL to maintain contact with retracting rods. These changes are accompanied by synapse misorganization and loss. In the inner retina, the total number of synapses in the IPL decreases, and RGC dendritic arbors decrease in size. Microglia increase in number and become less reactive in injury, while the processes of both Müller glia and astrocytes are attenuated. Vascular function can also decline in both the choroid and the inner retina. Figure adapted from images created with BioRender.com.

layer (INL) through a thin band of synapses in the outer plexiform layer (OPL). Second, synapses in the outer retina are large and relatively easy to visualize and quantify and form among a limited number of neuron types. This enables direct measurements of age-related changes to connectivity at the structural and functional levels. Finally, age-related structural changes to outer retina synapses appear to be conserved in humans and mice, suggesting that molecular studies of this circuit in rodents may prove useful for uncovering conserved aging mechanisms (Eliasieh et al. 2007, Liets et al. 2006, Samuel et al. 2011). We discuss the impact of aging on each outer retina neuron type in turn.

STRUCTURAL HALLMARKS OF THE AGING OUTER RETINA

Normal aging in mice (Samuel et al. 2011, 2014) and humans (Eliasieh et al. 2007, Liets et al. 2006) results in outer retina neuron structural defects that appear to drive OPL synapse changes and age-related functional decline. Rods, in particular, play a key role. In mice, approximately half

of aging rods retract their axons from the OPL into the ONL, a process that is accompanied by synapse misplacement in the ONL and postsynaptic horizontal and bipolar cell neurite sprouting (Eliasieh et al. 2007; Liets et al. 2006; Samuel et al. 2011, 2014) (**Figure 2**). In addition, aged rods have been shown to have shorter outer segments and reduced levels of opsin than young rods (Kolesnikov et al. 2010). Notably, cones appear to be spared from age-related changes to their axons or pedicles (Samuel et al. 2011, 2014). Consistent with this, rod bipolar, but not cone bipolar, cells extend accompanying sprouts that contact mislocalized rod terminals. Single-cell reconstructions show that rod-targeting horizontal cell axons, but not cone-targeting dendrites, also remodel, and these processes cofasciculate with rod bipolar cell sprouts to target mislocalized rod terminals (Samuel et al. 2014). It is unclear whether cone telodendria, which also contact rod terminals, remodel to accompany rod synapses as they retract. Functional defects accompany these structural alterations. Visual acuity and contrast sensitivity are reduced twofold in aged mice (Kolesnikov et al. 2010). Scotopic electroretinogram recordings show reduced amplitudes of both a- and b-waves in aged mice, while aged rods show decreased sensitivity in single-cell recordings (Kolesnikov et al. 2010). Despite the lack of structural alterations in cones, these cells do display age-related functional decline in humans and mice (Gresh et al. 2003, Li et al. 2001, Williams & Jacobs 2007). The cause of age-related cone functional decline remains unclear, as the numbers of cones do not change in mice or humans (Gresh et al. 2003, Li et al. 2001, Williams & Jacobs 2007), but it is possible that some cone subsets may show selective vulnerability to aging (Cunea et al. 2014).

MOLECULAR DRIVERS OF OUTER RETINA AGING

What molecular alterations drive rod aging? While mutations in several synapse proteins cause similar structural alterations to those observed in aging (for a review, see Burger et al. 2021), to date, the only protein family that has been causally tied to rod aging is the serine threonine kinase LKB1 and its target, AMPK, a crucial energy sensor. In old age, while the levels of LKB1 itself decrease only modestly, the ability of LKB1 to phosphorylate AMPK decreases by approximately 80% (Samuel et al. 2014). These results are consistent with decreased AMPK activation in aging in other model systems (Reznick et al. 2007). Samuel et al. (2014) showed that this decrease appears to drive rod aging. Deletion of AMPK or LKB1 results in age-related changes in young adult mice. Conversely, increasing active AMPK directly, with a constitutively active form of the enzyme, or indirectly, through caloric restriction, reduced the number of ectopic synapses in old animals. This signaling pathway appears to be specific, as alterations to other LKB1 targets (e.g., SADA and SADB) did not affect outer retina organization, nor did the activation levels of these kinases differ in old age. Why might aging impact the ability of LKB1 to activate AMPK? It is possible that LKB1 might be mislocalized or hindered in its ability to interact with its obligate cofactors (Alessi et al. 2006). Alternatively, alterations in the levels of AMP and ATP might affect the ability of AMPK to serve as a substrate for LKB1. Future studies may shed light on these alternatives.

The results of these genetic studies are consistent with those of RNA and genome-wide profiling efforts in aging rods. For example, Corso-Diaz et al. (2020) showed that aged rods display differential methylation and that targeted regions tend to cluster at chromosomal locations associated with energy metabolism and respiration. Similar results have been observed in transcriptomic studies (Parapuram et al. 2010). Relatedly, improving cellular metabolism can delay cone death in a mouse model of retinitis pigmentosa (Punzo et al. 2009). Finally, AMPK and other energy homeostasis signaling networks have been shown to modulate global aging rates in other model systems (Apfeld et al. 2004, Burkewitz et al. 2014, Ulgherait et al. 2014). Together, these results suggest that metabolic alterations are key hallmarks and causal features of structural and functional alterations to the aging outer retina.

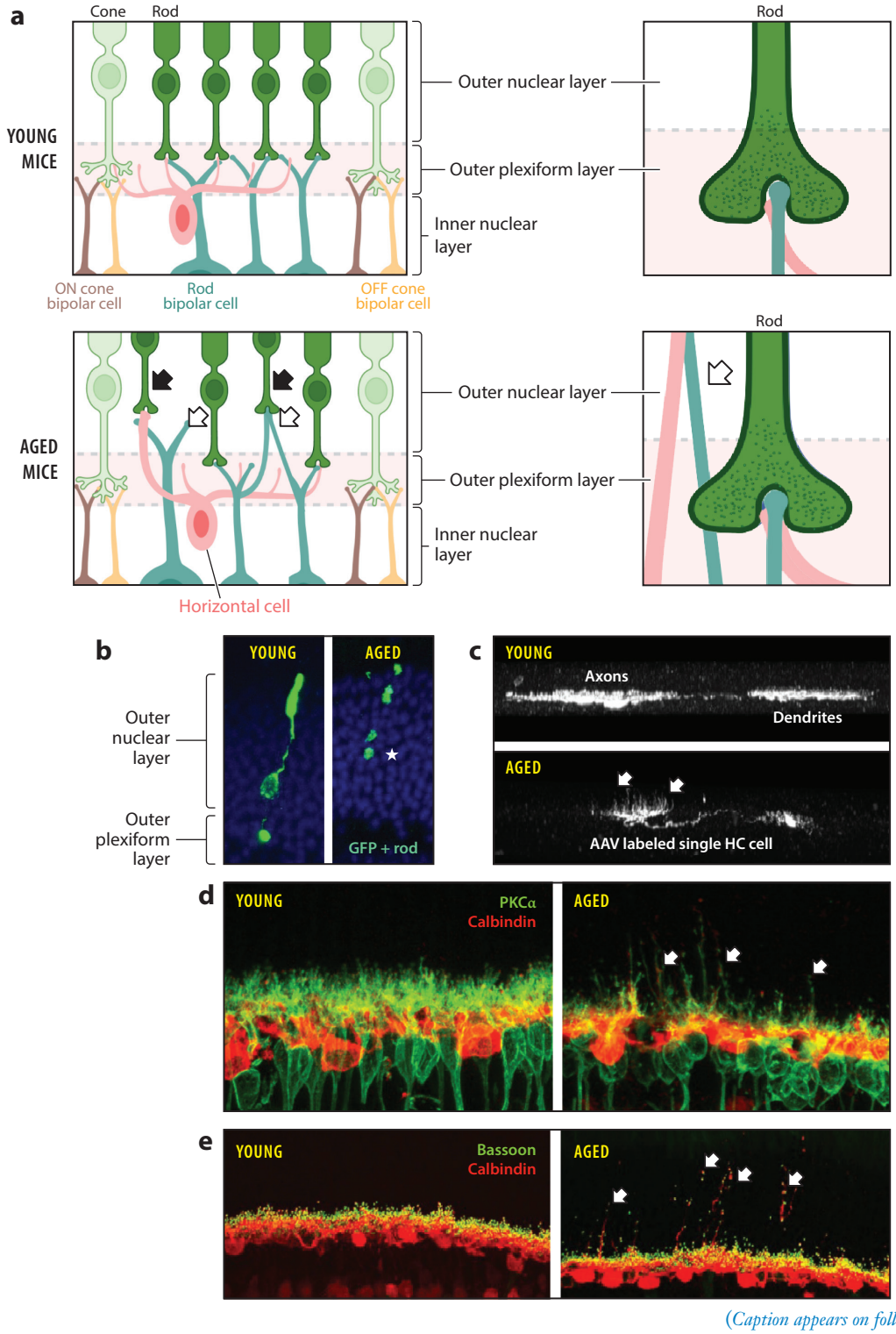

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Figure 2 (*Figure appears on preceding page*)

Age-related changes to cell types of the outer retina. (*a*) Schematic and representative histology images from young (2 months) and aged (24 months) mice. In the young retina, all rod and cone terminals reside in the outer plexiform layer, where they contact the dendritic terminals of bipolar cells and the axons and dendrites of horizontal cells (HCs), which also remain restricted to this region. With age, photoreceptor density is reduced, and approximately half of rod axons retract their terminals into the outer nuclear layer (*black arrows*), accompanied by HC and rod bipolar spouting (*white arrows*). (*b–c*) Histological studies of (*b*) single rod photoreceptors or (*c*) single HCs labeled with AAV-GFP confirm these alterations, with rod axons retracting (*white star*), accompanied by sprouting of HC axons (*white arrows*), but not dendrites. Cones do not undergo similar changes. (*d*) HC axons (Calbindin, *red*) and rod bipolar cell dendrites (PKCα, *green*) sprout far into the outer nuclear layer (*white arrows*). (*e*) These changes are accompanied by synapse remodeling (*white arrows*; Bassoon, *green*; Calbindin, *red*). Figure adapted from images created with BioRender.com.

Significantly less clear is how changes to metabolic function cause rod axon remodeling. One potential explanation is that these pathways converge on synapse transmission, which in turn may regulate axonal structure and location. Consistent with this, mutations of many genes implicated in photoreceptor synaptic transmission cause changes that parallel those observed in normal aging. For example, loss of the OPL organizers Bassoon, RIBEYE, 4.1G, CAST, Retinoschisin, or piccolino results in retraction of rod terminals, remodeling of interneuron neurites, and reduced function (Maxeiner et al. 2016, Mukherjee et al. 2010, Sanuki et al. 2015, Sato et al. 2008, Takada et al. 2008, tom Dieck et al. 2012). It is possible that decreased AMPK activity may act in part by lowering synaptic transmission from rods to their targets. Supporting this idea, synaptic transmission from rods decreases in old age (Kolesnikov et al. 2010), and AMPK affects neuron excitability and firing rates (Ikematsu et al. 2011).

CELLULAR DRIVERS OF OUTER RETINA AGING

Are changes to rods a cause or a consequence of postsynaptic remodeling? Data published to date are most consistent with a causal model (Samuel et al. 2014). First, deletion of either LKB1 or AMPK in rods alone is sufficient to phenocopy all of the outer retina structural alterations seen in old age. Second, when LKB1 or AMPK was deleted from only a few rods, horizontal and bipolar cell processes sprouted in direct apposition to the retracted rod terminals, suggesting that upstream events in single rods are causal to postsynaptic changes (Samuel et al. 2014). While these results do not rule out contributions from postsynaptic outer retina neurons, they do suggest that rods are central to maintaining outer retina integrity in old age. These data further suggest the interesting possibility that rod postsynaptic neurons might display protective or compensatory pathways that enable them to respond to presynaptic alterations. Alternatively, retracting rods could release a sprouting factor, as can occur in the peripheral nervous system (Brown et al. 1981), and interneuronal processes may remain adhesive to retracting photoreceptor terminals and thereby be pulled into the ONL. Finally, retracting rods may release less neurotransmitter, and this reduction may lead to postsynaptic partner sprouting. Horizontal cells in particular are a good candidate for promoting OPL maintenance, as deletion of horizontal cells from adult retina results in photoreceptor degeneration (Sonntag et al. 2012). Given these data, it would be interesting to identify the compensatory molecular pathways in aging postsynaptic outer retina neurons and determine whether these properties can be transferred to other neuron types to modulate circuit repair.

AGE-RELATED DEFECTS IN THE INNER RETINA

Unlike photoreceptors, retinal ganglion cells (RGCs) in the inner retina fire action potentials downstream of exhibitory and inhibitory inputs that they receive from diverse populations of

bipolar cells and amacrine cells (Carras et al. 1992, Velte & Masland 1999). These inputs are in part determined by RGC laminar targeting in the inner plexiform layer (IPL) and mosaic patterning across the retinal surface. Where an arbor projects determines the potential synaptic partners from which a neuron can choose. Thus, even modest alterations to presynaptic arrangements or postsynaptic dendritic or axonal arrangement could alter RGC signal integration and ultimately impact visual function. Indeed, visual defects are typical of old age and include reductions in visual acuity, motion perception, and visual processing speed (Spear 1993). Below, we highlight structural, molecular, and cellular drivers of aging in the inner retina (**Figure 3**) and discuss them in the context of age-related alterations to visual function.

STRUCTURAL HALLMARKS OF AGING IN RETINAL GANGLION CELLS

Aging increases retinal area but not neuron numbers, so old neurons would presumably need to expand their arbors to maintain connectivity given the same distribution of presynaptic partners. Instead, dendritic arbors of most or all RGCs shrink with age (Samuel et al. 2011), consistent with similar observations in aged brain neurons (Burke & Barnes 2006, de Brabander et al. 1998, Grill & Riddle 2002). However, RGC dendrites do not appear to alter their laminar targeting, nor is sublaminar organization of the IPL obviously affected in aging. The visual receptive fields of direction-selective RGCs are also not altered in old age (Samuel et al. 2011). These results suggest that age-related changes to IPL circuitry do not occur above the threshold needed to detect alterations in the electrophysiological parameters tested to date.

Less clear is whether visual signals processed in the retina are effectively conveyed to retina-recipient areas in the brain. RGC axons target at least 50 different retinorecipient areas, some in an RGC type–specific manner (Martersteck et al. 2017, Morin & Studholme 2014). While the impact of aging on RGC innervation in most of these regions is unknown, axons target the correct lamina in at least one retinorecipient region, the superior colliculus (SC). However, the total area of RGC arbor fields decreases by 30% with age, and the density of axon terminal branches is also reduced. These declines were observed both in molecularly identified RGC types and in a sampling of diverse RGC subtypes, suggesting that they may be a common feature of RGC aging (Samuel et al. 2011). When these changes begin and whether some RGC types are more or less resilient over time are unknown. It will also be interesting to determine whether particular RGC target regions in the brain show selective vulnerability, particularly in regions associated with functional decline in aging.

STRUCTURAL HALLMARKS OF AGING IN INTERNEURONS

Neuron subtype–specific labeling of interneurons in aged retina suggests that distinct populations are likely differentially susceptible to aging. For example, while many amacrine subtypes remain to be analyzed, dendritic arbor size and laminar targeting did not change significantly in subtypes that have been examined to date (AII, Starburst, VGLUT3, and TH) (Samuel et al. 2011). Rod bipolar and other bipolar subtypes that sporadically connect with rods (e.g., type 3a and type 4; Wassle et al. 2009) show a different pattern. While their dendrites sprout into the photoreceptor layer (Eliasieh et al. 2007, Liets et al. 2006, Samuel et al. 2011, Terzibasi et al. 2009), their axons show no obvious alterations (Samuel et al. 2011). As noted above, the opposite pattern is observed in horizontal cells, where rod-contacting axons sprout, but cone-contacting dendrites do not (Samuel et al. 2014). These data show that even within the same neuron, different compartments can show distinct morphological responses to old age.

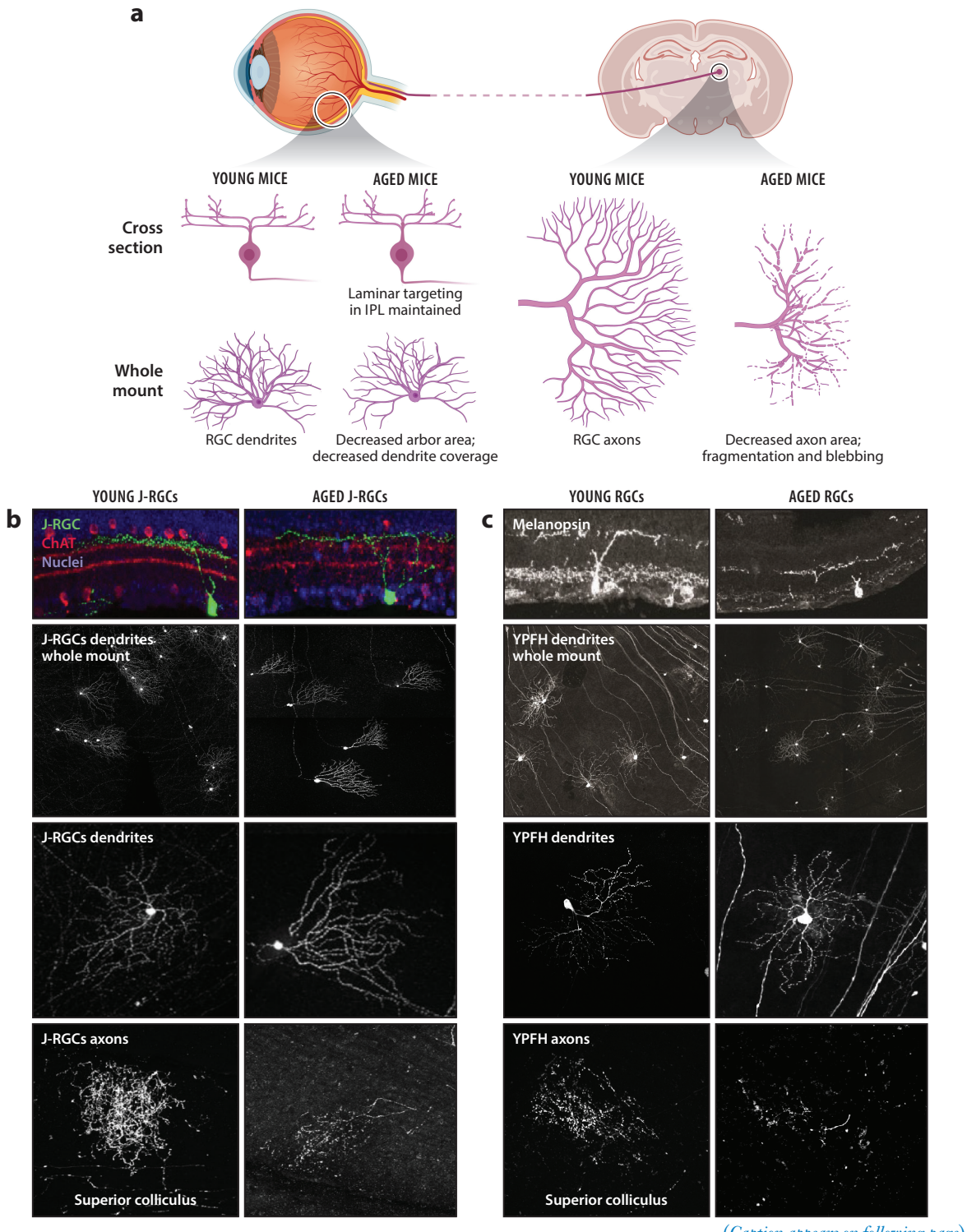

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Figure 3 (*Figure appears on preceding page*)

Age-related changes to cell types of the inner retina. (*a*) Schematic and representative histology images from young (2 months) and aged (24 months) mice are shown. In the young retina, retinal ganglion cells (RGCs) target distinct lamina in the inner plexiform layer (IPL) and have normal dendrite and axon areas in the retina and brain, respectively. With age, RGC laminar targeting is maintained, but both dendritic and axon arbor areas are reduced, with the greatest impact on arbor size in the brain (approximately 30% reduction). (*b–c*) Representative cross section (*upper panel*) and whole mount images (*lower panels*) of age-related alterations to RGC dendrites and axons in young (2 months) and aged (>2 years) mice are shown. These images highlight that changes occur both (*b*) in genetically identified RGC subtypes, such as cells that express Junction Adhesion Molecule B (JAM-B), called J-RGCs (see Kim et al. 2008), and (*c*) in RGC types more generally labeled in the YFPH line in which YFP is driven by elements of the Thy1 promotor (see Feng et al. 2000). Figure adapted from images created with BioRender.com.

MOLECULAR DRIVERS OF RETINAL GANGLION CELL DENDRITE AGING

The molecular programs that drive age-related decreases in RGC dendrite area are not clear, but some clues to their identity may be gleaned from development. For example, intrinsic transcriptional programs, signals from neighboring cells, and activity-dependent remodeling in vertebrates all contribute to the development of RGC dendrites (Lefebvre et al. 2015). One candidate pathway of potential relevance to RGC aging is that between Brain Derived Neurotrophic Factor (BDNF) and its receptor Tropomyosin receptor kinase B. This well-described dendrite regulator is generally decreased in the aging nervous system (Croll et al. 1998, Silhol et al. 2005), and normal levels are required for maintenance of RGCs (Gupta et al. 2014). Because BDNF can both promote and inhibit RGC primary dendrite extension, branching, and overall complexity depending on where it is produced in the visual system (Lom et al. 2002), it is plausible that decreased BDNF production in aging could impact dendritic structures. In support of this idea, elevating BDNF protein or activity appears to rescue some changes in Alzheimer's models in culture and in vivo, but whether these protective effects extend to humans remains uncertain. Initial clinical trials focused on this pathway have not shown benefits (for a review, see Lu et al. 2013).

Another potential candidate modulator of RGC dendrite aging is the transcriptional regulator Special AT-rich sequence binding protein 1 (Satb1). This factor is required for developmental patterning of ON-OFF direction-selective RGC dendrites (ooDSGCs) (Peng et al. 2017). Satb1 regulates the expression of Contactin-5 (Cntn5), an adhesion molecule expressed on ON starburst amacrine cells. Notably, Satb1 expression declines with biological aging in small model organisms like *Caenorhabditis elegans*; conversely, ectopic expression of SATB1 is associated with increased *C. elegans* lifespan (Zhang et al. 2009). In both human stem cell–derived dopaminergic neurons and mice, loss of SATB1 causes activation of a senescence transcriptional program in dopaminergic neurons via regulation of the prosenescence factor p21 (Riessland et al. 2019). Consistent with these data, genome-wide association study analyses have shown that mutations in CNTN5 are associated with an increased risk of late-onset Alzheimer's disease (Harold et al. 2009). Given that expression of these two molecular candidates decrease with age, it would be interesting to test whether aging particularly destabilizes ooDSGC dendrites.

Finally, metabolism and energy homeostasis pathways may also contribute to dendrite aging. In particular, AMPK activation during energetic stress inhibits dendrite outgrowth of cultured hippocampal neurons (Burkewitz et al. 2014, Ramamurthy et al. 2014). Because *Prkaa1* (AMPKα1) is widely expressed by most RGC subtypes (Tran et al. 2019), it has the potential to impact RGC function in aging and age-related disease. In support of this idea, AMPK activation is increased compared to controls in RGCs from human glaucoma patients and in mouse models of glaucoma and is associated with dendrite retraction and synapse loss. Conversely, AMPK depletion was protective against these changes (Belforte et al. 2021). Mechanistically, AMPK is a potent inhibitor of mTORC1 (Gwinn et al. 2008), a key regulator of RGC dendritic morphology (Morquette et al.

2015). Restoration of mTOR activity following acute neural injury extended RGC survival and ameliorated dendritic arbor retraction (Morquette et al. 2015), suggesting that mTORC1 inhibition is a potential mechanism for dendritic arbor maintenance. Additional studies will be needed to resolve the cell type–specific roles for AMPK in the inner retina, given that its role in aging appears to vary across cell types.

MOLECULAR DRIVERS OF RETINAL GANGLION CELL AXON AGING

Recent single-cell sequencing experiments that differentiated injury-resilient from injury-susceptible RGC populations may help shed light on potential RCG axonal aging candidates (Tran et al. 2019). Resilient RGCs (αRGCs type OFF transient and ooDSGCs) expressed a set of candidates absent from susceptible RGC subtypes [e.g., OPN4+ intrinsically photosensitive RGCs (ipRGCs) types 2 and 4 and αRGC types OFF and ON sustained]. These included genes previously documented to be projective (*Igf1*, *Opn4*, and *Spp1*), as well as new candidates. For the latter, gain- and loss-of-function studies showed that several improved RGC survival, including (*a*) urocortin (*Ucn*); (*b*) corticotropin releasing hormone binding protein (*Crhbp*), a secreted glycoprotein that inhibits UCN activity; (*c*) tissue inhibitor of metalloproteinase 2 (*Timp2*), an inhibitor of matrix metalloproteinases; (*d*) matrix metalloproteinase 9 (*Mmp9*), a target of *Timp2*; (*e*) neuron-derived neurotrophic factor (*Ndnf*); and (*f*) peripherin (*Prph*), which encodes a neurofilament protein. The protective effects of these proteins can be RGC subtype specific (Tran et al. 2019). Similarly, some modules of RGC injury–associated genes can impact RGC survival, while others can improve axon regeneration (Jacobi et al. 2022). At least some of these protective pathways are conserved in other neuron subtypes. For example, Timp2 has been characterized as a youth-associated bloodborne factor capable of revitalizing hippocampal function in aged mice (Castellano et al. 2017). Additional potential candidates include those implicated in axonal development, maintenance, and resistance to injury or disease. For example, local translation of extranuclear Lamin B appears to be required for the maintenance of *Xenopus* RGC axons after targeting has occurred (Yoon et al. 2012). Roles for canonical axon growth and targeting molecules, including Ephrins and their Eph receptors (Petros et al. 2010, Williams et al. 2003), neuronal cell adhesion molecules (Zelina et al. 2005), and cadherins (Inoue & Sanes 1997, Takeichi 2007), may also extend to maintenance. While direct studies of these pathways in RGC aging have not been completed, results to date are consistent with the idea that RGC subtypes may have unique regulatory networks that may determine their susceptibility to aging.

AGE-RELATED CHANGES IN VISUAL AND NONVISUAL RETINA FUNCTIONS

The visual system has two global functions. The first is imaging forming vision via RGC innervation of the lateral geniculate nucleus (LGN) and SC, which relay information to the visual cortex. The second is detection of global luminance levels that help entrain the biological clock via specialized RGC innervation of the suprachiasmatic nucleus (SCN), the master regulator of the circadian rhythm. The diverse cellular changes reported in aged retinas may drive functional alterations to both modalities. For example, electroretinographic responses decline in aged retinas (Jackson et al. 2002), as does sensitivity to contrast (Elliott et al. 1990) and adaptation to darkness (Jackson et al. 1999). Among these changes, visual acuity defects have been the most widely documented with age in both humans (Gittings & Fozard 1986, Jay et al. 1987, Weale 1975) and animal models (Kolesnikov et al. 2010, Ordy et al. 1980). However, the cause of these defects remains unclear. Optical factors (i.e., decreased pupil size and increased light scatter from lens opacification) are insufficient to account for acuity declines, implicating changes in retinal and other neurons

(Weale 1975). Two neuronal mechanisms have been suggested: neuronal loss and structural alternations. Given that levels of age-related cell death appear modest, but decreases in RGC dendritic field area are apparent, these alterations could lead to gaps in coverage of the visual field by individual RGC subtypes, perhaps contributing to decreased acuity. Additional studies will be needed to clarify the role of RGC dendrite and axon changes in age-related functional decline.

Nonvisual functions controlled by the retina have also been reported to decline in normal aging. For example, the circadian rhythm exhibits progressively decreased amplitude, phase advancement, and shorter periods in aged individuals (Cajochen et al. 2006, Myers & Badia 1995), while pupil constriction is defective in several age-related retinal diseases, including glaucoma (Feigl et al. 2011), diabetic retinopathy (Feigl et al. 2011), retinitis pigmentosa (Kawasaki et al. 2012), and age-related macular degeneration (Maynard et al. 2015). In addition to central defects, age-related changes to circadian rhythm–entraining neurons in the retina may also be key drivers of these alterations. These cells are called ipRGCs (Schmidt et al. 2014), and within this population, there are six identified cellular subtypes in mice (M1–M6) and two to four subtypes in human and primate retinas (for a review, see Sondereker et al. 2020). Populations of M1-ipRGCs negative for the RGC marker Brn3b regulate mood and circadian photoentrainment (Chen et al. 2011, Fernandez et al. 2018). M1-ipRGCs positive for Brn3b project to the olivary pretectal nucleus and drive the pupillary light reflex. Functions of other ipRGC subtypes are currently unknown (Chen et al. 2011). In aged human retina, the number of ipRGCs appears to decline by approximately 30% in subjects over 70 years old based on total population counts (Esquiva et al. 2017). The remaining ipRGCs displayed decreased dendrite branching (Esquiva et al. 2017). Thus, while ipRGCs are more resilient than other RGC types in injury models in mice, they do appear susceptible to age-related loss in humans. Whether additional changes occur in aged ipRGC axons in the SCN that contribute to either functional compensation or pathology is unclear. ipRGC loss has also been reported in humans with age-related neurological diseases in which circadian rhythm is disrupted, such as Alzheimer's disease (La Morgia et al. 2016) and Huntington's disease (MS Lin et al. 2019). It will be interesting to determine the functional role of ipRGCs in these conditions and to determine whether circadian dysfunction is a cause or a consequence of disease progression.

NON-NEURONAL CONTRIBUTIONS TO RETINAL AGING

As in other brain regions, non-neuron cells in the retina significantly modulate and contribute to retina function. These include retinal pigment epithelium (RPE) cells, which are specialized to support photoreceptor health and function, and glial populations (Müller glia, astrocytes, and microglia) that modulate connectivity, signaling, and neuron function. In addition, the mouse retina, like the human retina, is supported by a trilaminar intraretina vascular network critical for neuron function. We discuss how aging impacts each of these important compartments below.

AGE-RELATED CHANGES TO THE RETINAL PIGMENT EPITHELIUM

The RPE is comprised of a mononuclear cell layer that is interdigitated by photoreceptor outer segments. RPE function is critical for photoreceptor health and signaling. The RPE governs retinoid metabolism, outer segment phagocytosis, neuroretinal adhesion, and interphotoreceptor metabolism via transport of nutrients and metabolites to photoreceptors (Curcio et al. 1990). The RPE is a key site of age-related structural and molecular changes that may predispose the retina to disease, and RPE changes are often considered to be aging biomarkers (Eldred & Lasky 1993, Feeney-Burns et al. 1984). These changes include the loss of melanin granules (Sarna et al. 2003) and the accumulation of lipofuscin (a mixture of lipids and some proteins). RPE changes

can be progressive and lead to the formation of drusen, extracellular deposits that arise between Bruch's membrane and the RPE (Gu et al. 2012). Bruch's membrane itself appears to thicken and become disorganized (Gu et al. 2012, Sarna et al. 2003). Lipofuscin granules first appear in the basal portions of RPE cells of young eyes as early as the first decade of life, and accumulation is progressive such that lipofuscin granules fill the entire RPE cytoplasm by the ninth decade (Wing et al. 1978). These components are thought to originate from incomplete digestion of photoreceptor outer segments and can contribute to RPE and photoreceptor death, especially in disease conditions (Zarbin 2004). Both the mechanisms that lead to accumulation and the reasons that such deposits trigger RPE death are areas of active investigation. For the latter, lipid-triggered apoptosis (Sparrow & Cai 2001) or lysosomal dysfunction (Pan et al. 2021) may contribute. Less clear, however, is whether or how RPE changes drive disease-free features of normal aging, such as rod axon retraction. It will be interesting to explore whether rejuvenation of the RPE could mitigate these changes.

IMPACTS OF AGING ON RETINA GLIAL POPULATIONS

The retina contains three glia populations, Müller glia, astrocytes, and microglia. Unlike astrocytes and microglia, which migrate into the retina from the periphery, Müller glia are derived from the same retinal progenitor population as retinal neurons (Cepko 2014). Müller glia are the most numerous retinal glia type, and their soma reside in the inner retina. They possess a bipolar morphology in which a vertical stock traverses the entire depth of the retina and gives rise to horizontal branches (Dreher et al. 1992, Reichenbach & Wohlrab 1983). Like astrocytes in the brain, Müller glia have diverse functions, including regulation of synapse development, neurovascular coupling, and cellular metabolism (for a review, see Tworig & Feller 2021). In zebrafish, these cells can also regenerate neurons to repair adult damaged retinas, but in humans and mice, they cannot, due in part to Hippo pathway repression of transcriptional responses needed for dedifferentiation (Rueda et al. 2019). Müller glia can also be reprogrammed to undergo direct transdifferentiation via overexpression of neuron-specifying factors (Jorstad et al. 2017, Yao et al. 2018). Given their diverse roles and regenerative potential, Müller glia are poised to influence retinal function in aging. However, relatively little work has been completed in this area. We do know that Müller glia numbers are not altered by aging in animal models (Martins et al. 2022), but they may structurally and functionally decline. For example, in old zebrafish, Müller glia may show disruptions in their branching patterns in the IPL and basal lamina (Martins et al. 2022). In addition, relatively few transcriptional or DNA methylation changes occur in aged Müller glia relative to young counterparts (S Lin et al. 2019). Finally, aging is insufficient to stimulate Müller glia proliferation and regeneration in zebrafish, and aged Müller glia retrained their full proliferative potential following retinal damage (Martins et al. 2022). This is encouraging given efforts aimed at targeting Müller glia to repair neural circuits in age-related retinal diseases.

Astrocytes reside in the retinal nerve fiber layer lining the inner surface of the retina. This cell type has been historically understudied relative to other retina cell types, but emerging reports suggest that astrocytes have key biological functions that may impact retina aging. First, these cells drive vascular patterning of the superficial layer in part through their production of vascular endothelial growth factor-A (Fruttiger et al. 1996, Rattner et al. 2019). Ablating astrocytes before vessel development prevents vessels from entering the retina at all (O'Sullivan et al. 2017, Tao & Zhang 2016). The addition of astrocytes accelerated revascularization in a hypoxic retina model (Dorrell et al. 2010). Whether astrocytes play similar roles in maintaining retina vessels in aging is unknown, but human histological data suggest that astrocytes experience some age-related structural alterations that could impact their function. These include lipofuscin deposits and a

significantly lower number of processes surrounding blood vessels (Ramirez et al. 2001). Finally, increased astrocyte reactivity has been implicated in aging (Ramirez et al. 2001) in the brain and retina, primarily though alterations in labeling for glial fibrillary acidic protein (for a review, see Palmer & Ousman 2018). Whether or how these changes impact astrocyte function in the retina is unknown.

AGE-RELATED CHANGES TO MICROGLIA

Microglia are motile cells with macrophage-like properties that reside within the retina. They display diversity in their functional and molecular states during retina development and in the context of age-related retinal diseases, indicating that their state changes are likely critical for disease responses (He et al. 2021, Kumari et al. 2022, Menon et al. 2019, O'Koren et al. 2019, Wang & Cepko 2022, Yu & Saban 2019). Accordingly, phagocytic states have been implicated in nearly all major retina disorders. These include retinal degeneration, glaucoma, diabetic retinopathy, age-related macular degeneration, uveitis, and retinal detachment (Combadiere et al. 2007; Gupta et al. 2003; Madeira et al. 2015; Okunuki et al. 2018, 2019; Rashid et al. 2019; Yuan & Neufeld 2001; Zeng et al. 2008). Microglia engulfment can also limit success in retina neuron transplantation efforts (Kramer et al. 2019, Li et al. 2016, Singhal et al. 2008). A detailed understanding of the regulation of microglial states and heterogeneity will thus be important for improving new therapies, and some progress has been made toward this goal.

A large body of evidence suggests that microglia phagocytic states are key to developmental and age-related disease outcomes (for a review, see Paolicelli et al. 2022). In particular, microglia are highly phagocytic during neuronal refinement but become less phagocytic as neurons mature (Li et al. 2019). Phagocytic microglia states re-emerge in the context of retinal degeneration, glaucoma, and diabetic retinopathy, and disease severity is reduced in several ocular models when microglia or related engulfment pathways are removed (Bodea et al. 2014, Bosco et al. 2008, Combadiere et al. 2007, Howell et al. 2012, Ma et al. 2019, Okunuki et al. 2019, Peng et al. 2014, Schwarzer et al. 2020, Wang et al. 2014). What drives these alterations to phagocytic state? Spatially and temporally restricted cues appear to play a role (Anderson et al. 2019, 2022; Jiang et al. 2022; Li et al. 2019; O'Koren et al. 2019; Punal et al. 2019; Silverman & Wong 2018; Wang et al. 2016). For example, whereas microglia in the uninjured adult retina largely occupy a single state, the developing retina contains microglia in at least 10 different transcriptionally defined states (Anderson et al. 2022). Several of these states bear transcriptional hallmarks of phagocytosis that correspond with morphological changes indicative of engulfment (Anderson et al. 2019, 2022; Silverman & Wong 2018). In addition, environmental signals, such as the presence of apoptotic neurons, can directly impact retina microglia states (Anderson et al. 2019, 2022; Jiang et al. 2022). In turn, microglia in particular states can directly alter the fate, function, and connectivity of retinal cells (Anderson et al. 2019, 2022; Jiang et al. 2022; O'Koren et al. 2019; Punal et al. 2019; Wang et al. 2016). Similar alterations may occur in aging, as microglia number increases, and motility rates decrease, in aged mice. Aged microglia are also less responsive to injury (Damani et al. 2011). Thus, the function and phagocytic state of microglia are modulated across the retina lifespan, and these states temporally align with distinct cellular outcomes.

Some progress has also been made in elucidating pathways that control microglia state and function. For example, several types of immune-related proteins and pathways can affect microglia engulfment by serving as so-called "eat me" or "don't eat me" signals (Butler et al. 2021, Frost & Schafer 2016, Li et al. 2019, Salter & Stevens 2017). While a comprehensive review of these molecules is outside the scope of this article, we highlight a few findings with direct relevance to the retina. Among the "eat me" signals, complement proteins have been implicated in retina

development, maintenance, and disease. The largest body of work focuses on eye-specific refinement of RGC axons in the LGN, which requires complement (Schafer et al. 2012, Stevens et al. 2007). In the retina itself, C1q regulates horizontal cell refinement (Burger et al. 2020). The complement system has also been implicated in the maintenance of retina structure and function; multiple knockouts of proteins in the complement cascade (e.g., C1q, C3, C5) showed reduced retina function at 6 months but not 6 weeks of age (Mukai et al. 2018). The role of complement in retinal diseases in which aging is a risk factor (e.g., glaucoma, age-related macular degeneration, and diabetic retinopathy) is also quite well documented (for a review, see Borucki et al. 2020). Finally, polymorphisms in several complement proteins, including factors H, B, and C3, are associated with increased age-related macular degeneration risk (for a review, see Borucki et al. 2020), and several preclinical and clinical studies show that inhibiting specific complement pathways is protective (Bosco et al. 2018, Liao et al. 2020).

In line with these data, our group recently identified an important role for the immune molecule signal regulatory protein alpha (SIRPα) via a surprising mechanism (Jiang et al. 2022). In the periphery, professional phagocytes such as macrophages can express SIRPα, and binding of its receptor CD47 on host cells serves as a "don't eat me" signal that reduces phagocytosis (Gardai et al. 2005; Oldenborg et al. 2000, 2001). However, in the brain and in the retina, SIRPα is present on both neurons and microglia (Barclay & Brown 2006, Chuang & Lagenaur 1990, Jiang et al. 1999, Kharitonenkov et al. 1997, Mi et al. 2000, van Beek et al. 2005), while high amounts of CD47 are present on neurons throughout development. Microglia are highly phagocytic during this period, despite the presence of inhibitory CD47 (Lehrman et al. 2018). Jiang et al. (2022) showed that neuronal but not microglia SIRPα is necessary for microglia phagocytosis and synapse refinement, indicating that neuronal SIRPα is an important permissive cue for microglia engulfment activity. Neuronal SIRPα appears to be prophagocytic because it prevents CD47 from accessing microglial SIRPα, thus acting as a decoy receptor. This suggests a novel cellular mechanism by which neurons modulate microglial states by blocking "don't eat me" signals. As vulnerable synapses in the outer retina appear to maintain high SIRPα levels, ongoing studies will address whether modulating SIRPα can impact synapse aging and loss.

NEUROVASCULAR COUPLING AS A CONTRIBUTOR TO AGING

Significant evidence suggests that cerebrovascular alterations are associated with both normal aging and age-related central nervous system diseases in the brain and the eye (Kisler et al. 2017, Sweeney et al. 2018, Wei et al. 2017). This is perhaps not surprising given that the retina is one of the most energetically demanding parts of the body and relies on real-time delivery of nutrients via the intraretinal vasculature. The relationship that enables this feat is called neurovascular coupling (Iadecola 2017). Vasculature alterations often occur early in retinal and brain disease, before symptom onset, and can lead to vessel remodeling, reduced blood flow, blood barrier alterations, tropic failure, and reduced pathogenic protein clearance (Iadecola 2017, Montagne et al. 2020).

What are the mechanisms that drive vessel declines in retinal aging and disease? While relatively little is known regarding vessel maintenance, cues that regulate the development of the retinal vasculature have been described and may be relevant to aging. In the mouse, as in humans, retinal neurons are supported by a trilaminar intraretinal vascular network. The vascular layers consist of the superficial plexus, which interdigitates the ganglion cell layer; the intermediate plexus, which ascends into the IPL; and the deep plexus, which interleaves the OPL. Local blood flow varies in accordance with regional demand and is directly driven by neuron signaling to vasculature cells, including endothelial cells and pericytes (Paredes et al. 2018, Selvam et al. 2018). Aging induces dysfunction and loss in both of these cell types, so changes to neurovascular

coupling via neuronal signaling or vascular responses could modulate neural decline in old age (Bhattacharya et al. 2020, Herrera et al. 2010, Nortley et al. 2019). From the neuronal perspective, both particular neuron types and particular types of neuron activity can influence vessels. For example, removing amacrine cells specifically reduced the growth of the intermediate layer (Usui et al. 2015), while RGCs are required to template astrocytes, which in turn guide developing vessels (O'Sullivan et al. 2017). In addition, cholinergic signaling via cholinergic waves (Weiner et al. 2019) and retinal dopamine (Nguyen et al. 2019) regulate vessel growth and the retraction of hyaloid vessels, respectively. Because dopamine and dopamine receptor levels can decline in old age (Palmer & DeKosky 1993), and dopaminergic neuron subsets can be lost in age-related disease in humans and mice (Cordella et al. 2018, Nobili et al. 2017, Pan et al. 2019), dopamine is a particularly interesting therapeutic target for modulating vessel aging phenotypes.

CONCLUSION

In this review, we discuss the impact of aging on the cellular, synaptic, and molecular programs that underlie visual function. We compare these features from the perspective of cells that connect in the outer retina and in the inner retina and describe contributions from non-neuronal cells. While in some cases the field has pinpointed causal molecular drivers of aging in particular cell types, the majority of studies in disease-free aging are comparative. Thus, many important areas of future research remain. These include (*a*) determining the causal role of non-neuronal contributions to retinal neuron aging, (*b*) decoding the molecular drivers of dendritic and axonal maintenance defects in particular RGC types, (*c*) determining whether plasticity in neuron structure and connectivity is conserved in old neurons in the inner retina, and (*d*) testing whether maintenance pathways can be manipulated for therapeutic outcomes in efforts to generate or transplant new retinal neurons. The last point, in particular, speaks to the importance of understanding adult circuit regulators, as any efforts to repair connectivity in disease must consider that new neurons will be attempting to integrate with established ones. Several candidates identified from developmental and injury models provide good starting points for mechanistic studies. With appropriate tools and biomarker readouts, such as high-throughput genetic manipulation of adult neurons and measures of RGC axon integrity, the field now has the resources to make headway in these areas. Finally, the argument for increased efforts to understand where and when circuits remain flexible in adulthood extends to the field's efforts to prevent, treat, and even reverse visual and brain diseases. Aging remains the largest risk factor for every major life-threatening adult disease, including those in the nervous system. Our inability to date to cure these diseases could reflect our insufficient understanding of the fundamental impacts of aging on cell biology and function. It is our hope that continued study of the retina will answer fundamental questions in neural aging and thus improve clinical outcomes.

DISCLOSURE STATEMENT

M.A.S. is the owner of a provisional patent on compositions and methods for altering microglia phagocytic capacity to modify central nervous system diseases. The other authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

AUTHOR CONTRIBUTIONS

Q.A., J.D.Z, and M.A.S. designed and generated the figures. M.A.S. conceived and wrote the paper with significant input from J.D.Z. and S.P.T.

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