Neural and Müller glial adaptation of the retina to photoreceptor degeneration

Henri O. Leinonen1,*, Edward Bull1, Zhongjie Fu2,*

Abstract

The majority of inherited retinal degenerative diseases and dry age-related macular degeneration are characterized by decay of the outer retina and photoreceptors, which leads to progressive loss of vision. The inner retina, including second- and third-order retinal neurons, also shows aberrant structural changes at all stages of degeneration. Müller glia, the major glial cells maintain retinal homeostasis, activating and rearranging immediately in response to photoreceptor stress. These phenomena are collectively known as retinal remodeling and are anatomically well described, but their impact on visual function is less well characterized. Retinal remodeling has traditionally been considered a detrimental chain of events that decreases visual function. However, emerging evidence from functional assays suggests that remodeling could also be a part of a survival mechanism wherein the inner retina responds plastically to outer retinal degeneration. The visual system’s first synapses between the photoreceptors and bipolar cells undergo rewiring and functionally compensate to maintain normal signal output to the brain. Distinct classes of retinal ganglion cells remain even after the massive loss of photoreceptors. Müller glia possess the regenerative potential for retinal recovery and possibly exert adaptive transcriptional changes in response to neuronal loss. These types of homeostatic changes could potentially explain the well-maintained visual function observed in patients with inherited retinal degenerative diseases who display prominent anatomic retinal pathology. This review will focus on our current understanding of retinal neuronal and Müller glial adaptation for the potential preservation of retinal activity during photoreceptor degeneration. Targeting retinal self-compensatory responses could help generate universal strategies to delay sensory disease progression.

Key Words: bipolar cells; electroretinography; Müller glia; photoreceptors; plasticity; retinal degeneration; retinal neuron; retinal remodeling; retinal ganglion cells

Introduction

The immature retina undergoes dynamic changes in synaptic activity and connectivity during early development. The opening of the eye stimulates the maturation of retinal ganglion cells (RGCs). Light deprivation affects the stratification of RGC dendrites and results in permanent damage to visual responses (Tian and Copenhagen, 2001, 2003; Di Marco et al., 2009; Strettoi et al., 2022). In addition, mice with a loss of rod bipolar cells (RBCs) early in development were found to adjust synaptogenesis to preserve retinal function in dim light (Johnson et al., 2017). Similarly, the loss of a major cone bipolar cell (CBC) type can be fully compensated by other types of CBCs such that visual contrast and temporal frequency tuning is fully preserved by adulthood (Tien et al., 2017). The role of homeostatic plasticity in maintaining retinal function during development is further evidenced by the formation of synaptic connections between RBCs and cones in mice with neural retinal leucine zipper deficiency (Strettoi et al., 2004). This hypothesis is further supported by the preservation of retinal circuitry in mice with disproportionately large retinal neural cells induced by overexpressed antipoptotic gene Bcl-2 (Strettoi and Volpini, 2002). However, it is unclear if matured retinas demonstrate plasticity to maintain retinal function in degenerative diseases.

Photoreceptor degeneration causes visual dysfunction and ultimately blindness in retinal disorders across all age groups. Synaptic connectivity in the inner retina and Müller glia processes undergo robust structural changes in response to photoreceptor loss. However, it is poorly known how these structural changes manifest in retinal function and vision. Recent studies suggest that mammalian retinas possess the capability of undergoing adaptive changes to preserve neural function during photoreceptor degeneration in a mouse model of retinitis pigmentosa (RP) (Leinonen et al., 2020; Fu et al., 2021b; Tomita et al., 2021), a rare genetic disorder characterized by photoreceptor loss (> 150 causal genes identified so far) (Newton and Megaw, 2020). This phenomenon corresponds to clinical observations that normal vision can be maintained for years in patients with inherited retinal degenerative diseases. Current ophthalmological technologies allow minimally invasive, longitudinal investigation of retinal function and morphology.

Retinal Remodeling and Rewiring and Functional Consequences during Retinal Degeneration

RP, primarily characterized by rod cell death, loss of night vision, and visual field reduction, accounts for roughly half of inherited retinal degenerative diseases. Clinically prominent pathology in the central retina can be delayed by several years when secondary cone photoreceptor death ensues (Hartong et al., 2006). In the early stages of RP, the retinal neural connectivity may undergo remodeling in conjunction with progressive rod degeneration (Cuenca et al., 2014; D’Orazi et al., 2014; Pfeiffer et al., 2020; Strettoi et al., 2022). Retinal remodeling is characterized into Phases 0 to 3 (Pfeiffer et al., 2020). Phase 0 represents the healthy state of the retina. Phase 1 consists of initial photoreceptor stress, rod degeneration, glial activation, as well as emerging glial and neural remodeling characterized by sprouting of rod, RBC, and horizontal cell (HC) processes. Specifically, rod axons begin to sprout beyond the outer plexiform layer (OPL) into the inner retina and can reach the inner limiting membrane. RBCs and rod-contacting HCs retract their dendrites from rods and their dendrites may find new contacts with cone pedicles. The ON pathway, which activates at light onset, is particularly susceptible to remodeling, whereas the OFF pathway, responsible for light decrements,
appears less susceptible to these changes. Concurrent with dendritic retraction from the OPL, metabotropic glutamate receptor 6 is downregulated in ON-RBC dendrites and can mislocalize to the RBC soma and axons (Gargini et al., 2007; Barhoum et al., 2008). A large proportion of RBCs and ON-CBCs can become “OFF-BC-like” as they start to aberrantly express ionotropic glutamate receptors during progressive photoreceptor degeneration (Marc et al., 2007; Jones et al., 2011). In Phase 2, cone death occurs. BCs become completely deafferented. HCs can extend dendrites backwards into the inner plexiform layer, and even amacrine cells and RGCs initiate sprouting (Strettoi and Pignatelli, 2000; Strettoi et al., 2002; Jones et al., 2003; Pfeiffer et al., 2020). Phase 3 represents the most advanced stage when all photoreceptors have died, leading to neurite outgrowth by all retinal neuron classes and the inner retina functionally compensates for partial photoreceptor loss. In the retinas of ground squirrels subjected to photocoagulation (Beier et al., 2018), there is a remarkable capability of the adult retina for selective circuit repair, as expanded short-wavelength sensitive cone (S-cone) photoreceptors are recruited to regenerate broad spectral sensitivity of the retina. Retinal connections with local bipolar cells. The visual sensitivity of RGCs at the lesion site recovers to baseline levels after 2 months (Sher et al., 2013). Improved visual acuity and typical remodelling of the distal inner retina is corrected, and light sensitivity at RBCs and RGCs is significantly recovered, highlighting the capability of the adult retina for restorative synaptic plasticity.

The inner retina functionally compensates for partial photoreceptor loss

To further investigate how the adult retina functionally responds to partial rod or cone death, a selective cell ablation model using the cre-recombinase mediated diphtheria toxin receptor insertion technique has been applied (Care et al., 2019, 2020). Following the loss of half of the rod population in otherwise healthy adult mice, three possible functional outcomes have been hypothesized: (1) input loss from rods could directly propagate through the circuitry to a matching defect in retinal output; (2) functional reorganization could be exacerbated in downstream circuitry leading to an even larger decrease in retinal output as predicted from magnitude of rod loss; or (3) input loss could be compensated in downstream circuits. The magnitude of rod output is stronger than expected from the extent of rod loss (Care et al., 2020). Full-field ERGs and patch-clamp recordings at RBCs and RGCs have shown that hypothesis 3 is most likely. First, mean spiking activity recorded at RBCs increased to flashes of light induced by only 20% of rods in the experiment. However, A_{bmax}/A_{a} sensitivity to dim light flashes appears to increase compared to the values of normal controls. Second, scotopic ERG b-wave amplitude is much less reduced than the a-wave (Care et al., 2020). Rod responses from RBCs remain intact despite marked rod loss, which further confirms compensation occurring at the rod-RBC synapses. Compensatory changes and maintained visual function are also observed.
after the loss of half of the cone population in adult mice (Care et al., 2019; Lee et al., 2022). These latter reports are challenged by the findings that cone pathway function recovers to normal levels when half of the cones are ablated in adult mice at postnatal day (P)10, but not when the same procedure is performed in matured mice retinas at P30 (Shen et al., 2020). This highlights the well-known dogma of the lower capability for neuroplasticity in adulthood compared to juvenility, which is also recapitulated in retinal tissue. Therefore, while retinal remodeling is capable of adjusting to retinal degeneration in adult mice after postnatal development, the extent of this plasticity is variable.

High inner retina activation and visual responses can coincide with progressive retinal degeneration

The hypothesis of whether functional compensation in the retina could occur during progressive retinal degeneration has also been tested (Leinonen et al., 2022). ONL thickness and rod-driven ERG responses are lost by around 75% at 5 months of age in heterozygous P23H mice (Figure 2; Leinonen et al., 2020). Despite the robust ongoing rod degenerative disease occurring along with global retinal inflammation and oxidative stress (Leinonen et al., 2020; Fu et al., 2021b; Ortega et al., 2022), visual contrast sensitivity remains well-maintained up until 5 months of age (Leinonen et al., 2020). This is true even in P23H mice bred on a Gnat2 background that eliminates cone phototransduction and renders the mice reliant on their rod-function. Mass RBC responses derived from ex vivo ERG recordings showed increased relative sensitivity (Leinonen et al., 2020), which mirrors prior findings (Care et al., 2020). The functional compensatory changes in P23H mouse retinas are accompanied by transcriptomic profiles that indicate robust cellular restructuring and neural plasticity with “cell adhesion molecules”, “axon guidance” and “glutamatergic synapse” being among the top 10 most upregulated KEGG pathways. Importantly, the decorrelation of scotopic ERG a- and b-wave amplitudes, i.e., increased amplitude ratio of b/a, has also been observed in P23H rats (Machida et al., 2000; Aleman et al., 2001). However, visual performance in RP can decay nonlinearly as exemplified by abrupt loss of RBC responses and contrast sensitivity between 5 and 6 months in Gnat2+/− (P23H) mice (Figure 2: Leinonen et al., 2020). This needs to be taken into account when designing therapeutic interventions.

Behavioral vision in a genetic retinal degenerative diseases model has also been tested closer to the terminal disease stage. Peripherin-2 deficient Rds mice never generate fully formed photoreceptor outer segments and exist at approximately 3% of normal opsin content, which should lead to a similar extent of photon catch loss. However, ERG b-wave amplitudes are recorded at approximately 15% of normal levels, suggesting compensatory signal gain between photoreceptor and bipolar cells in these mice (Thompson et al., 2014). Although optokinetic tracking and visual water task behavior are severely compromised in Rds mice as expected, they still exhibit distinct and meaningful pattern vision despite minimal rod and cone function. In addition, RBCs display normal sensitivity to local application of exogenous glutamate in patch-clamp experiments in 2-month-old Rds10 retinas (Barhoum et al., 2008). This finding is remarkable as 2-month-old Rds10 mouse retinas are completely devoid of rods and show notable metabotropic glutamate receptor-6 downregulation in RBCs.

RGCs remain relatively stable during progressive retinal degenerative diseases, but several aspects of high-fidelity vision decline

In heterozygous P23H rats, receptive field strength declines immediately upon ONL degeneration (Sekirnjak et al., 2009, 2011). The rod-driven light responses in RGCs as well as receptive field size start to decline relatively late, only after P200, and RGCs spontaneous firing peaks at the same time. In Royal College of Surgeons rats at a disease stage with nearly all rods but most cones remain, RGC receptive field distortion is primarily linked with retinal remodeling (Yu et al., 2017). Importantly, all the functionally diverse RGCs characterized in the study persist after rod death. However, although direction-selective RGCs remain in Royal College of Surgeons rats, their direction tuning broadens and direction selectivity decreases.

Moreover, some electrophysiology studies focusing on the midbrain targeting the superior colliculus (SC), dorsal lateral geniculate nucleus, or primary visual cortex (V1) have suggested that RGCs’ operation mode during retinal degenerative disease directly propagates to these brain targets (Fransen et al., 2015; Procyk et al., 2019; Leinonen et al., 2022). Recordings from the P23H rat superior colliculus demonstrate the loss of light responsivity in ON cells that originally coincide with input loss (Fransen et al., 2015). In contrast, OFF responses become supernormal and progressively elevate above wild-type levels. Recordings of the dorsal lateral geniculate nucleus in 3–5-week-old Rd1 mice, at a disease stage with complete loss of rods and partial loss of cones, demonstrate diminished ON cell responses and slightly declined receptive field sizes (Procyk et al., 2019). However, cone contrast sensitivity remains intact at this relatively advanced disease stage. In 2-month-old 3334ter-3 rats at 1.5–3 months, most rods are dead but cones remain, even when responses to pattern stimuli recorded at V1 have declined at medium-to-high contrasts, the contrast sensitivity as measured by the CSO parameter shows no deterioration (Chen et al., 2020). Similarly, excellent pattern contrast sensitivity in V1 single-unit recordings in young adult P23H mice has been shown, although several other receptive field properties are altered compared to wild-type mice (Leinonen et al., 2022). In summary, RGC physiology inevitably changes during photoreceptor degenerative disease and functional consequences propagate into the visual areas of the brain. The adult human visual cortex may also be sufficiently plastic to adapt to altered visual inputs.

Does hyperexcitability in the inner retina counteract beneficial effects of rewiring?

A major issue that could discount the functional benefits of the apparent retinal adaptation to photoreceptor loss is the simultaneously increasing spontaneous neural activity that can worsen neural signal-to-noise ratio and mask light-responses. Characteristic of the severely degenerated retina is spontaneous, rhythmic oscillatory waves which physiological meaning has not yet been fully characterized. Although these oscillatory waves are generally recorded at the level of RGCs, they are not intrinsic to RGCs, but rather originate presynaptically (Borowska et al., 2011). They appear at two distinct, frequent domains. The less characterized are slow, sub-3 Hz oscillations that are believed to originate from spontaneous Ca2+ spikes in remnant cones as a direct consequence of synaptic remodeling and decreased negative feedback by HCs (Haq et al., 2014). The fast approximately 10 Hz oscillations arise from CBC-AII amacrine cell network activity, which is independent of input from the degenerating outer retina (Borowska et al., 2011) and is believed to be dependent on voltage-gated Na+ channels and gap junctional coupling (Trenholm et al., 2012). The increased spontaneous oscillations likely incur detrimental effects on vision as their pharmacologic suppression improves light responses and stimulation efficiency recorded at RGCs (Tocchiev et al., 2013; Barrett et al., 2015; Gehlen et al., 2020).
Moreover, inner retinal neurons can also increase spontaneous spiking (become hyperexcitable) during photoreceptor degeneration. This can occur early in disease progression and appears to propagate into the visual areas of the brain (Dhurandhar and Hubel, 1978; Leimert, et al., 2022). After investigation of RGC’s responses during RP progression in Rd1 and Rd10 mouse retinas, increased spontaneous RGC firing in parallel with decreased light responses was found (Tielas, et al., 2019). The light responses at RGCs are normal before degeneration onset in Rd10 mice, but RGC’s spontaneous firing increases by 2–3-fold and light-responses decrease by half. The hyperactivity in Rd10 mouse RGCs is intrinsic as blocking all synaptic drive to RGCs does not decrease hyperactivity. Based on an extensive series of pharmacological and genetic experiments that either increased or decreased retinoid acid signaling, the researchers have shown causative evidence that increased retinoic acid signaling in the retina could explain RGC hyperexcitability during progressive retinal degenerative diseases (Tielas, et al., 2019) and after laser-induced photoreceptor ablation (Close et al., 2005). Suppression of retinoic acid signaling remarkably improves luminance-detection and pattern vision in Rd10 mice (Tielas, et al., 2019, 2022), revealing a novel drug target to improve vision in RP.

An intriguing hypothesis is that increased retinal electrical activity upon photoreceptor degeneration is part of a survival mechanism, as loss of input is known to lead to neuronal death whereas increased activity enhances longevity (Corredor and Goldberg, 2009). Therefore, long-term effects of interventions aimed at either increasing or decreasing the electrical activity need to be carefully assessed. It will also be important for future studies to elucidate whether increased synaptic gain at the rod-RSC synapse and increased inner retina hyperexcitability in RP retinas share the same mechanistic origin, as it could have significant implications for prospective therapies.

Müller Glia-Derived Retina Adaptation during Photoreceptor Degeneration

Metabolic adaptation

Müller glia fill all retinal layers, providing structural and trophic support for neighboring neurons. In response to injury, Müller glia are activated and releases antioxidants and neurotrophic factors to preserve retinal function from further damage at early stages (Bringmann, et al., 2005). However, prolonged glialosis is detrimental as the ability of Müller glia to support retinal neurons becomes disrupted. Müller glia may also produce lactate, lipoproteins, and glutamine, which are then shuttled to photoreceptors for synaptic formation and energy production (Fu, et al., 2014). Proliferative Müller glia can convert pyruvate to acetyl-CoA (an intermediate in the TCA cycle), which may potentially cause metabolic switches in RPE and limit the fuel supply to photoreceptors. Further exploration of cellular interaction and metabolic alterations is needed. Better understanding of the molecular mechanisms may help prolong the beneficial effects of glial remodeling during photoreceptor degeneration.

In addition, Müller glia produce photoreceptor components such as 11-cis-retinol in the chicken retina and rhodopsin protein in mouse retina (Goel and Dinghra, 2012; Kaylor, et al., 2014). In P23H mouse retinas, there is co-expression of rod markers (Rho and Pde6b), cone markers (Opn1Lw and Opn1Sw), and Müller glial cell markers (Rbp4 and Slc3a1) in a cluster of cells identified with single-cell transcriptomics. Decreased expression of genes involved in phototransduction, inner and outer segment, photoreceptor cell cytoskeleton, and photoreceptor development are found in both rod and cone Muller cells in P23H mouse retinas (Tomita, et al., 2021). Müller glia may enhance the pathways involved in photoreceptor maintenance to compensate for those lost in rods and cones.

Collectively, Müller glia may support photoreceptor health by providing the necessary proteins lost during retinal degeneration, or that Müller glia may contribute to the regeneration of lost photoreceptors. Gene expression validation at translational and function levels is needed to test this hypothesis. However, Müller glia reprogramming, proliferation, and differentiation are well documented in zebrafish, but may not occur spontaneously in mammalian retinas (Salman, et al., 2021).

Reprogramming

Zebrafish possesses the ability to regenerate a damaged retina and restore vision (Goldman, 2014; Lahne, et al., 2020). In response to retinal injury, multiple extrinsinc signaling pathways could trigger Müller glial cell cycle-reentry (Figure 3A). Growth factors and cytokines such as insulin, FGF2 (Wan, et al., 2006) and heparin-binding epidermal-like growth factor (HBEGF) (Wan, et al., 2012), midkine (Naegashima, et al., 2020), and tumor necrosis factor-alpha (Nelson, et al., 2013; Iribarne, et al., 2019) activate the regenerative potential of Müller glia. Signaling pathways such as glycogen synthase kinase 3β/catenin, Mapk/Erk, P13k/Akt and Jak/signal transducer and activator of transcription 3 stimulates Müller glial reprogramming and retinal progenitor formation (Wan, et al., 2014). The downstream transcriptional factor achaete-scute complex-like 1a (Ascl1a) is a key regulator of genes involved in Müller glia–derived progenitor production, and zebrafish retina regeneration (Savino, et al., 2008; Ramachandran, et al., 2010, 2011). Ascl1a positively regulates Müller glial insulinoma-associated 1a, which in turn induces the expression of the cyclin-dependent inhibitors p57, and suppresses cell-cycle genes (such as ccn2, cdk1, and cdk2), thus stimulating cell cycle exit and neural differentiation (Ramachandran, et al., 2012). Insulinoma-associated 1a, via modulating the cone-rod homeobox (Crx, responsible for photoreceptor differentiation) and the nuclear receptor proliferation and quiescence (Figure 3B). However, Müller glia in mammalian retinas still hold regenerative potential as shown in zebrafish, modulating growth factors such as EGF and TGFβ also controls Müller glial reprogramming, proliferation, and differentiation in mammalian retinas (Wan, et al., 2014). Furthermore, inhibition of GABA or glutamate receptors also stimulates Müller glial proliferation in uninjured retinas (Rao, et al., 2017; Kent, et al., 2021). Although the role of these factors might be species-specific, some knowledge gained from zebrafish has promoted the study of induction of Müller glial reprogramming, proliferation, and differentiation in mammalian retinas.

Unlike those in zebrafish, the reactive Müller glial cells in mice will not protrude processes and instead reaccrete into the nuclear layer (Kaelin, et al., 2000; Goel and Dinghra, 2012). In P23H mouse retinas, Müller glia have a very homogenous metabolic supply to photoreceptors. Further exploration of cellular interaction and metabolic alterations is needed. Better understanding of the molecular mechanisms may help prolong the beneficial effects of glial remodeling during photoreceptor degeneration.
In vivo conditions, would benefit drug testing. This process can be suppressed by YAP inhibition (Hoang et al., 2020). Loss of Müller glial-specific Hippo pathway components, which suppress YAP receptor signaling, induces Müller glia to reprogram into highly proliferative overactivation of YAP (yes-associated protein), which interacts with EGF and HBEGF stimulate while TGF-β suppresses Müller glial proliferation in mammalian retinas. Manipulation of β-catenin, Nfia/b/x, Hippo, and YAP pathways stimulates Müller glia have been induced to differentiate into rod photoreceptors and cone-rod homeobox; EGF: epidermal-like growth factor; FGF2: fibroblast growth factor receptor (horizontal)” by BioRender.com (2022). Retrieved from https://app.biorender.com/ “retinal cell (ganglion 1)”, “bipolar neuron”, “retinal cell (amacrine)”, “retinal cell (horizontal)” by BioRender.com (2022). Retrieved from https://app.biorender.com/ “retinal cell (ganglion 1)”, “bipolar neuron”, “retinal cell (amacrine)”, “retinal cell (horizontal)” by BioRender.com (2022). Retrieved from https://app.biorender.com/ Nrl expression to generate Müller glial progenitor cells, which regenerate the injured retina. Growth factors and cytokines (such as FGF2, HBEGF, insulin, Midkine-a, TNFa) as well as Wnts positively stimulate the process. TGF-β, Notch, and neurotrophins and GABA, glutamate, gamma negatively regulate the process. Adapted and updated from Salman et al. (2021). (B) In mammalian retina, the generation potential of Müller glia is limited. The activated Müller glia may undergo metabolic adaptation and remodeling to preserve neural retinal function. Interestingly, EGF and HBEGF stimulate while TGF-β suppresses Müller glial proliferation in mammalian retinas. Manipulation of β-catenin, Nfia/b/x, Hippo, and YAP pathways stimulates the generation of Müller glial progenitor cells, which can be further differentiated into photoreceptors upon the subsequent activation of Obx2, Crx, and Nrl following the stimulation of the Wnt pathway by targeting β-catenin. The graph was adapted/reprinted from “retinal cell (Müller glial)”, “cone photoreceptor”, “rod photoreceptor”, “retinal cell (ganglion 1)”, “bipolar neuron”, “retinal cell (amacrine)”, “retinal cell (horizontal)” by BioRender.com (2022). Retrieved from https://app.biorender.com/ biorender-templates (license #HT240EXBM). Ascl: Achaete-scute complex-like 1; Crx: cone-rod homeobox; EGF: epidermal-like growth factor; FGF2: fibroblast growth factor 2; GABAA: gamma-aminobutyric acid; HBEGF: heparin-binding epidermal-like growth factor; Inr1a: insulina-associated 1a; Jakk斯塔3: janus kinase-signal transducer and activator of transcription 3; Mapk/Erk: mitogen-activated protein kinase/extracellular signal-regulated kinase; Nfia/b/x: nuclear factor I; Nrl: neuronal retina leucine zipper; Obx2: orthodenticle homebox 2; PINK/Atk: phosphatidylinositol-3-kinase/protein kinase B; TGF-β: transforming growth factor-β; TNFa: tumor necrosis factor α; YAP: yes-associated protein.

differentiate into rods and cones (Goel and Dhingra, 2021). These reports suggest distinct impacts of growth factors and neurotransmitters on Müller glial proliferation and retinal regeneration in mammalian retinas. Targeting signaling pathways is an intriguing intervention to trigger Müller glial reprogramming in mammalian retinas. Overexpression of Ascl1 in Müller glia in young mice stimulates the regeneration of amacrine and bipolar cells, as well as photoreceptors after N-methyl-D-aspartate or light injury (Ueki et al., 2015). However, this regenerative potential is dampened in adult mice. Müller glia have been induced to differentiate into rod photoreceptors and restore vision in retinal degenerative mice by firstly stimulating Wnt signaling (β-catenin) in 4-week-old mice and then transcriptional factors essential for rod induction (Crx, Obx2, and Nrl) 2 weeks later (Yao et al., 2018). In addition, overactivation of YAP (yes-associated protein), which interacts with EGF receptor signaling, induces Müller glia to reprogram into highly proliferative cells in adult mouse retinas (Hamon et al., 2019). Alternatively, the deletion of Müller glial-specific Hippo pathway components, which suppress YAP signaling, also results in a highly proliferative, progenitor-like cellular state (Rueda et al., 2019). Loss of Müller glial nuclear factor I factors a, b, x (Nfia/b/x), which maintains glial quiescent state, leads to Ascl1 up-regulation, Müller glial nuclear factor I suppression, and ultimately bipolar- and amacrine-like cell generation in adult mice after treatment with N-methyl-D-aspartate, FGF2 and insulin (Hoang et al., 2020). This process can be suppressed by YAP inhibition (Hoang et al., 2020). Targeting common signaling pathways may generate generic therapeutic potential for mammalian Müller glial reprogramming and retinal regeneration.

Conclusion

With these results taken together, the mature mammalian retina possesses some degree of plasticity that may help maintain vision during retinal degenerative diseases. Regarding the therapeutic potential of retinal glial cells, activated Müller glia benefit inner retinal neurons via producing trophic factors (Vecino et al., 2016). Müller glia could also enhance the pathways affected in photoreceptors as well as potentially improve photoreceptor energy supply in degenerative retinas. Supplementation of natural metabolic modulators that induce Müller glial remodeling helps preserve neural retinal function (Fu et al., 2021b). Better understanding the interaction between Müller glia and retinal neurons, as well as the underlying mechanisms, would greatly accelerate the field. Further studies regarding how to improve neuroplasticity during blinding diseases are warranted. Investigations targeting the cellular and molecular contributions to the compensatory neural signature is key to better understanding the disease pathogenesis. Further advancement of proteomics and metabolomics at a single cell level will further validate the results obtained from single-cell transcriptomics. The field could also be further advanced by the application of spatial transcriptomic genes that map the gene expression profile at specific locations within the retina. The application of the microfluidics 3D system, which better models the cell-cell interactions in in vivo conditions, would benefit drug testing. Continuous efforts will be necessary to explore this field as it could lead to novel therapeutic strategies that tackle the unmet medical need caused by retinal degeneration.

Acknowledgments: We thank Mr. Umar Seemab (University of Eastern Finland, Finland) for generating the UMAP graph in Figure 1J. We thank Ms. Nguyen Pham and Dr. Frans Vinberg (University of Utah, USA) for recording and providing the ex vivo ERG data shown in Figure 2C.

Author contributions: HOL and ZF contributed to the writing and editing of the manuscript. EB contributed to the editing of the manuscript. All authors approved the final version of the manuscript.

Conflicts of interest: The authors declare no conflicts of interest.

Availability of data and materials: All data generated or analyzed during this study are included in this published article and its supplementary information files.

Open access statement: This is an open access journal, and articles are distributed under the terms of the Creative Commons AttributionNonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Open peer review: Open peer review report 1.

We thank Mr. Umair Seemab (University of Eastern Finland, Finland) for generating the UMAP graph in Figure 1J. We thank Ms. Nguyen Pham and Dr. Frans Vinberg (University of Utah, USA) for recording and providing the ex vivo ERG data shown in Figure 2C.

Open access statement: This is an open access journal, and articles are distributed under the terms of the Creative Commons AttributionNonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Open peer review: Open peer review report 1.

We thank Mr. Umair Seemab (University of Eastern Finland, Finland) for generating the UMAP graph in Figure 1J. We thank Ms. Nguyen Pham and Dr. Frans Vinberg (University of Utah, USA) for recording and providing the ex vivo ERG data shown in Figure 2C.

Open access statement: This is an open access journal, and articles are distributed under the terms of the Creative Commons AttributionNonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Open peer review: Open peer review report 1.

We thank Mr. Umair Seemab (University of Eastern Finland, Finland) for generating the UMAP graph in Figure 1J. We thank Ms. Nguyen Pham and Dr. Frans Vinberg (University of Utah, USA) for recording and providing the ex vivo ERG data shown in Figure 2C.

Open access statement: This is an open access journal, and articles are distributed under the terms of the Creative Commons AttributionNonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Open peer review: Open peer review report 1.

We thank Mr. Umair Seemab (University of Eastern Finland, Finland) for generating the UMAP graph in Figure 1J. We thank Ms. Nguyen Pham and Dr. Frans Vinberg (University of Utah, USA) for recording and providing the ex vivo ERG data shown in Figure 2C.

Open access statement: This is an open access journal, and articles are distributed under the terms of the Creative Commons AttributionNonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Open peer review: Open peer review report 1.

We thank Mr. Umair Seemab (University of Eastern Finland, Finland) for generating the UMAP graph in Figure 1J. We thank Ms. Nguyen Pham and Dr. Frans Vinberg (University of Utah, USA) for recording and providing the ex vivo ERG data shown in Figure 2C.

Open access statement: This is an open access journal, and articles are distributed under the terms of the Creative Commons AttributionNonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Open peer review: Open peer review report 1.

We thank Mr. Umair Seemab (University of Eastern Finland, Finland) for generating the UMAP graph in Figure 1J. We thank Ms. Nguyen Pham and Dr. Frans Vinberg (University of Utah, USA) for recording and providing the ex vivo ERG data shown in Figure 2C.

Open access statement: This is an open access journal, and articles are distributed under the terms of the Creative Commons AttributionNonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Open peer review: Open peer review report 1.
Goel M, Dhangra NK (2012) Muller glia express rhodopsin in a mouse model of inherited retinal degeneration. Neuroscience 225:152-161.

Goel M, Dhangra NK (2021) bFGF and insulin lead to migration of Muller glia to photoreceptor layer in rd1 mouse retina. Neurosci Lett 755:135936.

Goldman D (2014) Muller glial cell reprogramming and retina regeneration. Nat Rev Neurosci 15:431-442.

Hamon A, Garcia-Garcia D, Ali D, Bitard J, Chesneau A, Dalkaia D, Locker M, Roger JE, Perron M (2019) Linking YAP to Muller glia quiescence exit in the degenerative retina. Cell Rep 27:1712-1725.

Haq W, Arango-Gonzalez B, Zrenner E, Euler T, Schubert T (2014) Synaptic remodeling generates synchronous oscillations in the degenerated outer mouse retina. Front Neural Circuits 8:108.

Hartong DT, Berson EL, Dryja TP (2006) Retinitis pigmentosa. Lancet 368:1795-1809.

Hayakawa K, Esposito E, Wang X, Terasaki Y, Liu Y, Xing C, Ji X, Lo EH (2016) Transfer of mitochondria from astrocytes to neurons after stroke. Nature 535:551-555.

Hoang T, Wang J, Boyd P, Wang F, Santiago C, Jiang L, Yoo S, Lahme M, Todd LJ, Jia M, Saetz C, Keuthan C, Palazzo J, Squires N, Campbell WA, Rajaii F, Parayil T, Trinh V, Kim DW, Wang G, et al. (2020) Gene regulatory networks controlling vertebral retinal regeneration. Science 370:eaab5598.

Ibarra M, Hyde DR, Masai I (2019) TNF-alpha induces Muller glia to transition from non-proliferative glia to a regenerative response in mutant zebrashark presenting chronic photoreceptor degeneration. Front Cell Dev Biol 7:296.

Iwase S, Ying GS, Aguirre GD, Beltman WA (2016) Assessment of visual function and retinal structure following acute light exposure in the light sensitive TR rhodopsin mutant dog. Exp Eye Res 146:341-353.

Johnson RE, Tien NW, Shen N, Pearson JT, Sato F, Kerschensteiner D (2017) Homeostatic plasticity shapes the visual system's first synapse. Nat Commun 8:1220.

Jones BW, Watt CB, Frederick JM, Baehr W, Chen CK, Levine EM, Milam AH, Lavail MM, Marc RE (2003) Retinal remodeling triggered by photoreceptor degenerations. J Comp Neurol 464:1-16.

Jones BW, Kondo M, Terasaki H, Watt CB, Rapp K, Anderson J, Lin Y, Shaw MV, Yang JH, Marc RE (2011) Retinal remodeling in the Tg P347L rabbit, a large-eye model of retinal degenerative disease. Elife 9:e59422.

Kang DW, Wang G, et al. (2020) Gene regulatory networks controlling vertebrate retinal regeneration. Science 370:eabb8598.

Kawaguchi T, Nakashima Y, Kudoh I, Inoue K, Hori M, Hirose M, Ogawa S, Kuroda M, Horiike K, Tamaoki N, et al. (2020) Retinal proliferation and gliosis in the degenerative retina. eNeuro 9:ENEURO.0107-22.2022.

Kawano MA, Giamarco MM, Jankowski CS, Tantillas K, Engel AL, Du J, Linton JD, Farnsworth CC, Sloat SR, Rountree A, Sweet IR, Lindsay KJ, Parker ED, BROCHERKOFF SE, Sadilek M, Chao JR, Hurley JB (2017) Biochemical adaptations of the retina and retinal pigment epithelium support a metabolic ecosystem in the vertebrate eye. Elife 6:e28899.

Kiley JI, Cook JD, Makshanoff J, Bischoff N, Yong J, Travis GH (2014) Identification of the 11-cis-specific retinyl-ester synthase in retinal Muller cells as a multifunctional O-acetyltransferase (MFAT). Proc Natl Acad Sci U S A 111:7302-7307.

Kern MR, Kara N, Patton JG (2021) Inhibition of GABAA-rho receptors induces retina regeneration in zebras. Neural Regen Res 16:367-374.

Lahme N, Nagashima M, Hyde DR, Hitchcock PF (2020) Reprogramming Muller glia to regenerate retinal neurons. Annu Rev Vis Sci 6:171-193.

Lee JT, Care RA, Kastner DB, Della Santina L, Dunn FA (2022) Inhibition, but not excitation, required for photoreceptor differentiation in the zebrafish retina. Dev Biol 380:157-171.

Lee JY, Care RA, Kastner DB, Della Santina L, Dunn FA (2022) Inhibition, but not excitation, required for photoreceptor differentiation in the zebrafish retina. Dev Biol 380:157-171.

Levinson H, Fhmc NC, Boyd T, Santoso J, Palczewski K, Vinberg F (2020) Homeostatic plasticity in the retina is associated with maintenance of night vision during retinal degenerative disease. Elife 9:e59422.

Levinson H, Lyon DC, Palczewski K, Foik AT (2022) Visual system hyperpolarization and compromised V1 receptive field properties in early-stage retinitis pigmentosa in mice. eNeuro 9:E0017-22.2022.

Lenkowski JR, Qin Z, Sifuentes CJ, Thummel R, Soto CM, Moens CB, Raymond PA (2013) Retinal regeneration in adult zebrafish requires regulation of TGFbeta signaling. Glia 61:1687-1697.

Lunghi C, Galli-Resta L, Bindu P, Cicchini GM, Placidi G, Falsini B, Morrone MC (2019) Visual cortical plasticity in retinitis pigmentosa. Invest Ophthal Vis Sci 6:2753-2763.

Machida S, Kondo M, Jamison JA, Khan NW, Kononen LT, Sugawara T, Bush RA, Sieving PA (2000) P347L rhodopsin transgenic rat: correlation of retinal function with histopathology. Invest Ophthal Vis Sci 41:3200-3209.

Marc RE, Jones BW, Anderson JR, Kinard K, Marshall DW, Wilson JH, Wensel T, Lucas RJ (2007) Neural reprogramming in retinal degeneration. Invest Ophthal Vis Sci 48:3364-3371.
