Neural and Müller glial adaptation of the retina to photoreceptor degeneration

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From the Contents

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 antiapoptotic 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. Electroretinography (ERG) precisely records the electrical activation of the retina, producing data with signals corresponding to specific cellular subtypes. The eye´s transparency allows unrestricted examination of retinal anatomy using optical coherence tomography and fundoscopy. The retina is also a very practical target tissue for molecular biology and neuroscience research techniques (**Figure 1**). These aspects contribute to the retina being one of the best characterized neuronal systems in our bodies. Deciphering how the retina adjusts to photoreceptor defects could enhance our understanding of sensory diseases in general. In this review, we focus on the current knowledge of the impacts of retinal plasticity on neuronal function. Literature was searched between March and June 2022 using keywords “Retinal AND degeneration AND vision AND remodeling OR plasticity” and “Müller AND glial AND reprogramming OR remodeling”, respectively.

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,

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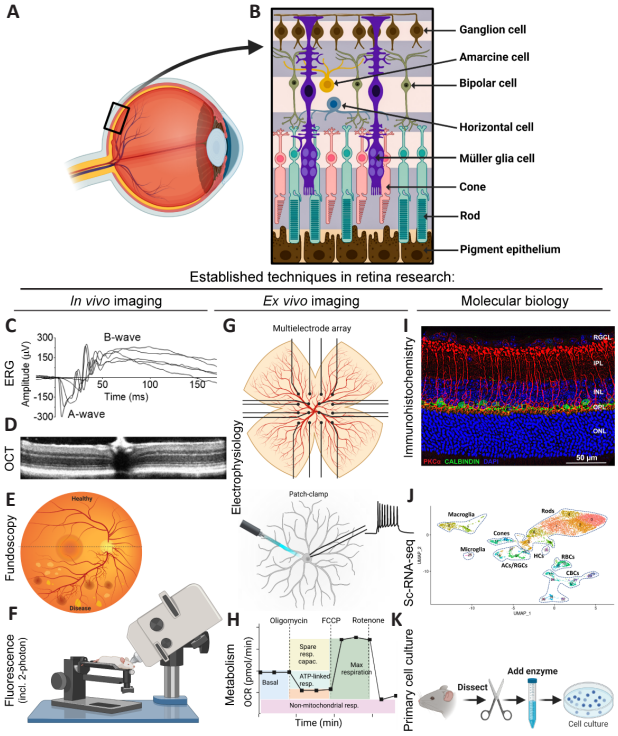

Figure 1 | **Schematics of retinal structure and established technologies for retina research.**

(A) The transparency of the eye allows direct visual access to the retina, which is the only neural tissue that is exposed to visual inspection noninvasively. (B) The layered and strictly hierarchical architecture of the retina is arguably the best characterized neural system in our bodies. (C) Electroretinogram (ERG) is a minimally invasive method to inspect sensory neuron (photoreceptor) activation (a-wave) and synaptic transmission to interneurons (b-wave). (D) Optical coherence tomography (OCT) allows segmentation of the retina noninvasively. (E) Scanning laser ophthalmoscopy (SLO) allows high-resolution images of vasculature. (F) Several advanced retina imaging methods using fluorescence, including 2-photon excitation, are established. (G) Dissected and perfused live retina is highly amenable to electrophysiology by e.g. multielectrode arrays (MEA) and patch-clamp, and (H) to assessment of metabolism. (I) Retina's distinctly layered anatomy renders histological inspection and immunohistochemistry very practical. RGCL: Retinal ganglion cell layer; IPL: inner plexiform layer; INL: inner nuclear layer; OPL: outer plexiform layer; ONL: outer nuclear layer. (J) Single-cell transcriptomics maps gene profile at specific cells. (K) Established methods exist for preparation of primary cell cultures of several main cell classes in the retina. Graphs A, B, E, F, G, H, and K were adapted/reprinted from "Eye and Retina schematics", "Diabetic Retinopathy Hallmarks", "Rodent Fundoscopy", "Retina MEA", "Retinal ganglion cell patch clamp", "Metabolic Assays-Using Seahorse Analyzers" and "Primary Cell Culture Preparation" with BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates (license #: ZR241JTGY4, BU241JTVMS, NW241JU576, AQ241JUC41, LR241JUJWJ, JB241JVDIA, RD241JUX5O). Graphs C, D, I, and J present unpublished data from the Leinonen Retina Laboratory.

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 global retinal cell death.

Unlike anatomical descriptions of remodeling, the functionality of the rewired retina, particularly in early disease stages, is less well understood. Emerging evidence suggests that early remodeling could be a manifestation of neuroplastic events (homeostatic plasticity) trying to retain normal light responses and visual function. Adaptational changes in retinal function in response to partial photoreceptor degeneration have been observed in multiple disease paradigms such as the light-induced retinal degeneration (LIRD) model (Richards et al., 2006; Montalban-Soler et al., 2012; Rubin et al., 2022), the photoreceptor ablation model (Care et al., 2019, 2020), and the progressive retinal degeneration model (Leinonen et al., 2020).

Retina can adapt to partial photoreceptor loss

Inner retina function recovers after partial light-induced retinal degeneration

Increasing evidence of inner neural retinal plasticity in mature retinas has been suggested in the past two decades. When C57BL/6J and Balb/C cross-bred mice are subjected to a continuous 20-day bright white light regimen (150–175 lux) to induce partial LIRD, there is a 50% loss in both the outer nuclear layer (ONL) thickness and scotopic ERG a-wave amplitude (Richards et al., 2006). Interestingly, the b-wave amplitude recovers to a higher 60% level. The negative polarity ERG a-wave represents the sum activation of photoreceptors, which is primarily rod-driven in scotopic conditions (Penn and Hagins, 1969). The positive b-wave occurs when the signal is transmitted from the photoreceptors to bipolar cells (Stockton and Slaughter, 1989). In theory, if diminished photoreceptor function directly propagates to inner retinal function, both ERG a- and b-wave amplitudes should decline by the same degree. Furthermore, the amplitude of fast frequency oscillatory potentials, which are believed to be mainly generated at the level of amacrine and ganglion cell interactions (Dong et al., 2004), initially drops significantly at 0–60 days post LIRD, but recovers to near normal levels by 90 days post LIRD (Richards et al., 2006). These observations indicate functional adaptation in the inner retinal circuitry during long-term LIRD. Similar observations are also reported in a 24-hour LIRD paradigm with a brighter light regimen (3000 lux) in Balb/C mice, in which a permanent 30% loss of a-wave amplitude is reported. However, these mice also display b-waves that gradually recovered to near normal levels by 7 days post LIRD (Montalban-Soler et al., 2012). The scotopic threshold responses representing ganglion cell function (Saszik et al., 2002) recovered completely (Montalban-Soler et al., 2012). In Sprague-Dawley albino rats subjected to partial LIRD, the ERG b-wave also recovered to over 80% of its original amplitude (Rubin et al., 2022). Moreover, inner neural retinal adaption may occur in large animals subjected to LIRD. In LIRD-induced *RHO*^{T4R} mutant dogs, there is a light-dose-dependent thinning of ONL (Iwabe et al., 2016). The visual behavior of these dogs at scotopic, mesopic, or photopic testing conditions (ranging from 0.003 to 65 lux) is normal as measured at 2 and 33 weeks post LIRD in an obstacle-avoidance behavioral vision testing. Taken together, following an acute phase of suppressed inner retina function after partial light damage, the downstream retinal circuitry seems to recover despite permanent sensory cell dysfunction.

Synaptic connectivity plasticity and cell migration restoration after controlled photoreceptor injury

In addition to LIRD, laser photocoagulation has also been used to injure the outer retina structures while leaving the inner retina without directly applied damage (Sher et al., 2013; Beier et al., 2017). In rabbit retinas with laser-induced injury specifically in RPE/photoreceptors, the lesion site heals as evidenced by the migration of adjacent photoreceptors to occupy the lesion site. The migrating photoreceptors establish new functional synaptic 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). Importantly, typical remodeling events include deafferentation of RBCs, followed by sprouting and formation of ectopic synapses in the ONL, which typically occur immediately following injury (Beier et al., 2017). However, as healthy photoreceptors continuously migrated into the lesion site, RBCs abandon aberrant connections to favor properly formed local synapses at the OPL. 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) connecting CBCs dendritic trees bypass the closely related medium-wavelength sensitive cones to selectivity synapse with their correct target, the S-cones. The adult retina's propensity for synaptic plasticity is further corroborated in the *Cngb1*$^{neo/neo}$ mouse RP model, which lacks a crucial CNGB1 protein for phototransduction (Wang et al., 2019). CNGB1 defects lead to diminished ERG a- and b-wave amplitudes, attenuated b-wave sensitivity, as well as severely mislocalized and malformed synaptic contacts between rods and RBCs. When CNGB1 expression is recovered in young adult *Cngb1*$^{neo/neo}$ mice, photoreceptor degeneration is halted, rod-RBC synapse organization 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 circuit leading to a matching defect in retinal output; (2) functional defects 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 circuitry so that retina 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 $A_{ON\text{-}S}$ RGCs to flashes of light is reduced by only 20%, although the average loss of rods in the experiment is 60%. Furthermore, $A_{ON\text{-}S}$ RGC sensitivity to dim light flashes appears to increase compared to the values of normal controls. Secondly, scotopic ERG b-wave amplitude is much less reduced than the a-wave amplitude (Care et al., 2020), similar to what has been shown after partial rod death due to LIRD (Richards et al., 2006; Montalban-Soler et al., 2012; Rubin et al., 2022). To elucidate the locus of the apparent functional compensation, Care et al. (2020) have also patched and recorded individual RBCs. Voltage 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 juvenile 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., 2020). 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 alongside 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 profile shifts 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-waves, i.e. increased amplitude ratio of b to 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 express only 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 *Rd10* retinas (Barhoum et al., 2008). This finding is remarkable as 2-month-old *Rd10* 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 when nearly all rods have died but most cones remain, RGC receptive field distortion is primarily linked with anatomic holes in cone mosaic and cone structural changes, rather than inner retina 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) function have suggested that RGC's 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 practically 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 *S334ter-3* rats at a disease stage when 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 C50 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

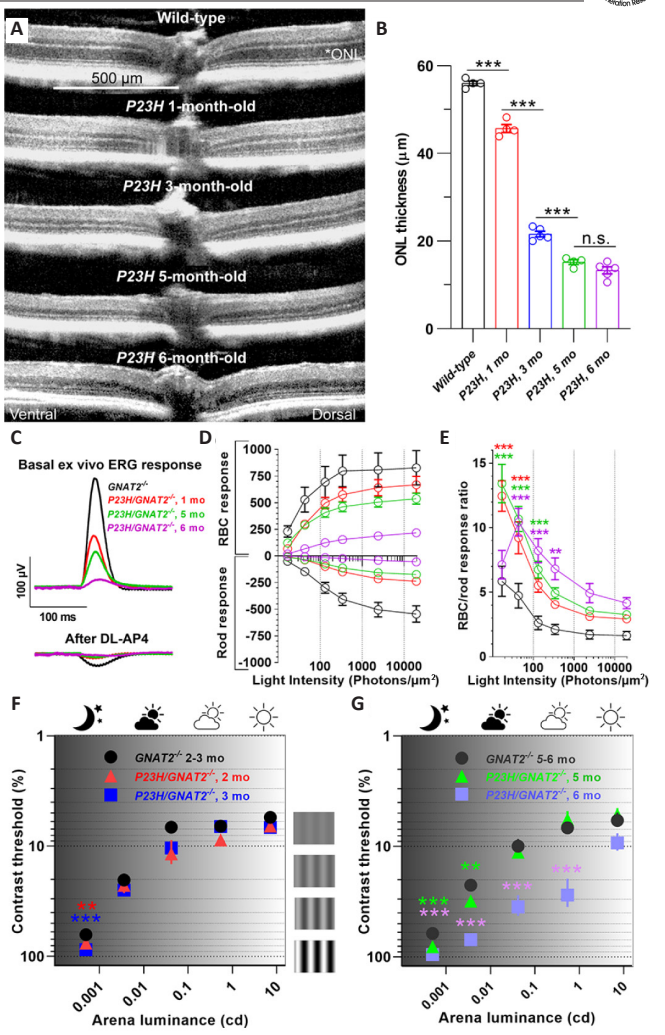

Figure 2 | **Near normal rod-dependent visual contrast sensitivity remains for several months in retinitis pigmentosa mice.**

(A) Representative optical coherence tomography (OCT) images showing degeneration progression in *P23H* mice. (B) Mean outer nuclear layer (ONL, photoreceptor nuclei layer) thickness as measured at 500 µm from the optic nerve head at dorsal, ventral, nasal, and temporal retinal quadrants. (C) Representative *ex vivo* ERG responses for dim flash (17 photons/µm^2) in *GNAT2*$^{-/-}$ control and *GNAT2*$^{-/-}$*/P23H* retinitis pigmentosa mice at baseline and after DL-AP4 perfusion to isolate rod-specific response. (D) Rod bipolar cells (RBC) and rod response amplitudes. RBC response was acquired offline by digitally subtracting the rod-specific response from the basal response. (E) RBC/rod response ratio. (F, G) Visual contrast thresholds as measured by optomotor responses (OMR) in 2–3-month-old (F) and 5–6-month-old (G) mice. Note the abrupt drop in ERGs and OMR performance between 5 and 6 months of age in *GNAT2*$^{-/-}$*/P23H* mice. Adapted from Leinonen et al. (2020).

(Lunghi et al., 2019; Castaldi et al., 2020). Still, many aspects of visual function remain unexpectedly stable, with contrast sensitivity particularly remaining strikingly resistant to retinal degeneration in animal models.

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, dominant frequencies. The less characterized are slow, sub-3 Hz oscillations that are believed to originate from spontaneous Ca^{2+} transients 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 (Toychiev 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 (Drager and Hubel, 1978; Leinonen 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 (Telias et al., 2019). The light responses at RGCs are normal before degeneration onset in P14 *Rd10* mice, but at P28, RGC's spontaneous activity 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 retinoic 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 (Telias et al., 2019) and after laser-induced local photoreceptor ablation (Denlinger et al., 2020). Suppression of retinoic acid signaling remarkably improves luminance-detection and pattern vision in *Rd10* mice (Telias et al., 2019, 2022), revealing a novel drug target to improve vision in RP.

An intriguing hypothesis is that increased retinal electrical activity upon retinal 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-RBC 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 glial cells span 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., 2009). However, prolonged gliosis 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 synapse formation and energy production (Fu et al., 2021a). In healthy retinas, Müller glia have a very homogenous metabolic signature, which becomes highly variable in the levels of glutamine, glutamate, taurine, and glutamine synthetase among neighboring Müller glia in the region of the degenerating retina (Pfeiffer et al., 2016).

Recent single-cell transcriptomics shows decreased expression of genes involved in metabolism in both rods and cones in *P23H* mice during early photoreceptor loss. These analyses also show increased expression of genes involved in mitochondrial localization and microtubule-based transfer in Müller glia (Tomita et al., 2021), suggesting possible transfer of mitochondria from Müller glia to photoreceptors or increased energy production in Müller glia. Although the mechanisms of mitochondrial release are unclear, brain astrocytes shuttle mitochondria to injured neurons after stroke (Hayakawa et al., 2016). Decreased photoreceptor metabolism accelerates photoreceptor loss; therefore, improving glucose supply and uptake could promote the photoreceptor survival in degenerating mouse retinas (Punzo et al., 2009; Ait-Ali et al., 2015). Therefore, the question arises of whether Müller glia can compensate for photoreceptor energy shortage during early retinal degeneration.

Our current knowledge of Müller glia metabolic fuel sources is still quite limited. Most of the current literature relies on *in vitro* studies, making it difficult to fully characterize Müller glial metabolic properties, as the normal cell interactions between Müller glia with their connecting cells is lost. Furthermore, Müller glial cells *in vitro* are positive for GFAP, which reflects gliosis and fails to capture their diverse pathophysiology in the retina (Fu et al., 2021a). A recent report has shown that loss of hexokinase 2 (catalyzes the first step in glycolysis) and phosphoglycerate dehydrogenase (an endogenous serine synthetic gene), but not pyruvate dehydrogenase E1 alpha 1 (catalyzes the conversion of pyruvate into acetyl-CoA) and lactate dehydrogenase A (catalyzes the interconversion of pyruvate and L-lactate) in Müller glia leads to photoreceptor degeneration and reduced retinal neuronal function (Shen et al., 2021), suggesting that Müller glia may use glucose to produce serine to supply photoreceptors. Consequently, photoreceptors convert glucose to lactate to fuel Müller glia (Kanow et al., 2017). The contribution of cellular metabolic changes to cell fate decisions warrants extensive investigation. Illustrating the importance of this concept, targeting metabolic modulation via nutrient supplementation is a feasible approach to treat retinal degeneration (Rowe et al., 2021).

Remodeling

Müller glial activation facilitates the adaptive retinal remodeling as the hypertrophied glial cell processes may guide neuronal migration and aberrant neuronal cell process sprouting to maintain visual function (Bringmann et al., 2009; Fu et al., 2021b). Following the loss of photoreceptors, glial scars are formed between the remnant neural retina and RPE/choroid to fill the retinal breaks. The initial purpose of glial scars is to protect the neuroretina from further damage. However, glial scars also account for the failure of tissue repair and therapeutic intervention.

In fibroblast growth factor 21 (FGF21)-treated *P23H* mice, not only is there improved retinal neural function, but there is also a notable increase in the expression of genes involved in axon and synapse development in Müller glia and amacrine cells identified with single-cell transcriptomics (Fu et al., 2021b), suggesting glial remodeling may preserve retinal function during photoreceptor degeneration. However, the preservation of retinal neuronal responses lasts for six weeks and diminishes at nine weeks of treatment. This could be due to the inhibitory impacts of FGF21 on RPE fatty acid oxidation, 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 loss.

In addition, Müller glia produce photoreceptor components such as 11-*cis*-retinol in the chicken retina and rhodopsin protein in mouse retina (Goel and Dhingra, 2012; Kaylor et al., 2014). In *P23H* mouse retinas, there is co-expression of rod markers (*Rho* and *Pde6b*), cone markers (*Opn1mw* and *Opn1sw*), and Müller glial cell markers (*Rlbp1* 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 cilium, and photoreceptor development are found in both rods and cones 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 undergo neurogenesis to replace degenerated photoreceptors. Further 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 possess the ability to regenerate a damaged retina and restore vision (Goldman, 2014; Lahne et al., 2020). In response to retinal injury, multiple extrinsic signaling pathways could trigger Müller glial cell cycle-reentry (**Figure 3A**). Growth factors and cytokines such as insulin, FGF2 (Wan et al., 2014), heparin-binding epidermal-like growth factor (HBEGF) (Wan et al., 2012), midkine-a (Nagashima 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/β-catenin, Mapk/Erk, PI3K/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 (Fausett 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-cdk inhibitor $p57^{kip2}$ and suppresses cell-cycle genes (such as *ccna2*, *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 Nr2e3 (a photoreceptor-specific nuclear receptor responsible for rod photoreceptor specification), is required for photoreceptor differentiation in the developing zebrafish retinas (Forbes-Osborne et al., 2013). Meanwhile, suppression of the Notch signaling (Campbell et al., 2021) and transforming growth factor β (TGFβ) signaling (Lenkowski et al., 2013), which drive Müller glial differentiation and quiescence, promotes progenitor proliferation and retinal regeneration. 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 proliferate and instead return towards 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 progenitor cell generation in mammalian retinas. In isolated mouse retinal explants, EGF treatment via activation of Erk1/2 and PI3K/Akt pathways induces Müller glial proliferation (Ueki and Reh, 2013). HBEGF pretreatment also stimulates Müller glial-derived progenitor cell formation in N-methyl-D-aspartate-damaged mouse retinas (Todd et al., 2015). TGFβ inhibitors further potentiate EGF-stimulated Müller glial proliferation in rat retinas *in vivo* (Close et al., 2005). A combination of factors including FGF2, insulin-like growth factor 1, taurine, retinoid acid induces photoreceptor differentiation of human Müller stem cells *in vitro*; however, TGFβ suppresses the process (Angbohang et al., 2016). Moreover, insulin treatment via increasing glucose use prolongs cone photoreceptor survival in mice with inherited retinal degeneration (Punzo et al., 2009). Intravitreal injection of both insulin and basic fibroblast growth factor induces Müller glial migration from the inner nuclear layer to photoreceptor layer in degenerating mouse retinas (Goel and Dhingra, 2021). However, migrated Müller glial cells in photoreceptor layer express stem cell marker Chx10 but do not further

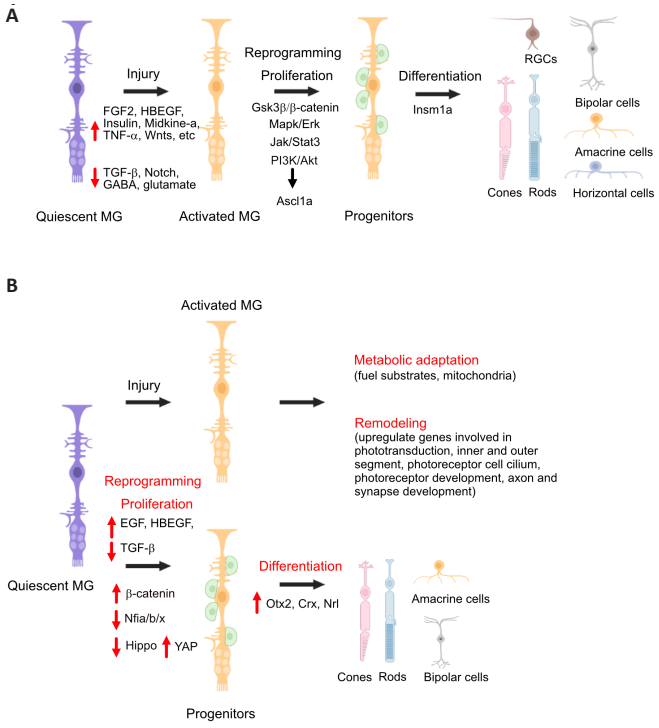

Figure 3 | **Müller glial responses in retinal degeneration.**
(A) Müller glial regeneration in zebrafish. Upon injury, Müller glia undergo reprogramming and enter the cell cycle for proliferation, stimulated by β-catenin, Mapk/Erk, Jak/signal transducer and activator of transcription 3 (Stat3), PI3K/Akt. These signaling pathways further induce *Ascl* expression to generate Müller glial progenitor cells, which regenerate the injured retina. Growth factors and cytokines (such as FGF2, HBEGF, insulin, Midkine-a, TNFα) as well as Wnts positively stimulate the process. TGF-β, Notch, and neurotransmitter (GABA, glutamate) signaling negatively regulates the process. Adapted and updated from Salman et al. (2021). (B) In mammalian retina, the regeneration potential of Müller glia is limited. The activated Müller glial 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 *Otx2*, *Crx*, and *Nrl* following the stimulation of the Wnt pathway by targeting *β-catenin*. The graph was adapted/reprinted from "retinal cell (Müller glia)", "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 #:HT240EKBMT). Ascl: Achaete-scute complex-like 1; Crx: cone-rod homeobox; EGF: epidermal-like growth factor; FGF2: fibroblast growth factor 2; GABA: gamma-aminobutyric acid; HBEGF: heparin-binding epidermal-like growth factor; Insm1a: insulinoma-associated 1a; Jak/Stat3: 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: neural retina leucine zipper; Otx2: orthodenticle homeobox 2; PI3K/Akt: phosphatidylinositol-3-kinase/protein kinase B; TGF-β: transforming growth factor-β; TNFα: 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, Otx2, 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 (Nifa/b/x), which maintains glial quiescent status, leads to *Ascl1* up-regulation, Müller glial reprogramming, 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.

Interestingly, a recent report shows that the hybrid resulting from fusion of Müller glia with adult stem cells can integrate within human retinal organoid and differentiate towards a neural fate (Bonilla-Pons et al., 2022). Treatment of a combo of small molecules (dbcAMP, Forskolin, ISX9, CHIR99021, I-BET151, and Y-27632) in Müller glia *in vitro* drives the direct reprogramming into bipolar-like cells (Yang et al., 2022). Further tests *in vivo* are needed to confirm these findings. Taken together, these findings suggest that the stimulation of retinal regeneration in mammals is possible. However, the efficiency needs to be further improved in developed retinas. The long-term impacts also need to be carefully evaluated, because the balance between the differentiative state and proliferative state is interfered with, which could compromise the supportive role of Müller glia in retinal neural and vascular function.

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 signals are 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 transcriptomics that map the cell gene 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 therapeutics that tackle the unmet medical need caused by retinal degeneration.

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References

Ait-Ali N, Fridlich R, Millet-Puel G, Clerin E, Delalande F, Jaillard C, Blond F, Perrocheau L, Reichman S, Byrne LC, Olivier-Bandini A, Bellalou J, Moyse E, Bouillaud F, Nicol X, Dalkara D, van Dorsselaer A, Sahel JA, Leveillard T (2015) Rod-derived cone viability factor promotes cone survival by stimulating aerobic glycolysis. Cell 161:817-832.

Aleman TS, LaVail MM, Montemayor R, Ying G, Maguire MM, Laties AM, Jacobson SG, Cideciyan AV (2001) Augmented rod bipolar cell function in partial receptor loss: an ERG study in P23H rhodopsin transgenic and aging normal rats. Vision Res 41:2779-2797.

Angbohang A, Wu N, Charalambous T, Eastlake K, Lei Y, Kim YS, Sun XH, Limb GA (2016) Downregulation of the canonical WNT signaling pathway by TGFbeta1 inhibits photoreceptor differentiation of adult human Muller glia with stem cell characteristics. Stem Cells Dev 25:1-12.

Barhoum R, Martinez-Navarrete G, Corrochano S, Germain F, Fernandez-Sanchez L, de la Rosa EJ, de la Villa P, Cuenca N (2008) Functional and structural modifications during retinal degeneration in the rd10 mouse. Neuroscience 155:698-713.

Barrett JM, Degenaar P, Sernagor E (2015) Blockade of pathological retinal ganglion cell hyperactivity improves optogenetically evoked light responses in rd1 mice. Front Cell Neurosci 9:330.

Beier C, Palanker D, Sher A (2018) Stereotyped synaptic connectivity is restored during circuit repair in the adult mammalian retina. Curr Biol 28:1818-1824.

Beier C, Hovhannisyan A, Weiser S, Kung J, Lee S, Lee DY, Huie P, Dalal R, Palanker D, Sher A (2017) Deafferented adult rod bipolar cells create new synapses with photoreceptors to restore vision. J Neurosci 37:4635-4644.

Bonilla-Pons SA, Nakagawa S, Bahima EG, Fernandez-Blanco A, Pesaresi M, D'Antin JC, Sebastian-Perez R, Greco D, Dominguez-Sala E, Gomez-Riera R, Compte RIB, Dierssen M, Pulido NM, Cosma MP (2022) Muller glia fused with adult stem cells undergo neural differentiation in human retinal models. EBioMedicine 77:103914.

Borowska J, Trenholm S, Awatramani GB (2011) An intrinsic neural oscillator in the degenerating mouse retina. J Neurosci 31:5000-5012.

Bringmann A, Iandiev I, Pannicke T, Wurm A, Hollborn M, Wiedemann P, Osborne NN, Reichenbach A (2009) Cellular signaling and factors involved in Muller cell gliosis: neuroprotective and detrimental effects. Prog Retin Eye Res 28:423-451.

Campbell LJ, Hobgood JS, Jia M, Boyd P, Hipp RI, Hyde DR (2021) Notch3 and DeltaB maintain Muller glia quiescence and act as negative regulators of regeneration in the light-damaged zebrafish retina. Glia 69:546-566.

Care RA, Kastner DB, De la Huerta I, Pan S, Khoche A, Della Santina L, Gamlin C, Santo Tomas C, Ngo J, Chen A, Kuo YM, Ou Y, Dunn FA (2019) Partial cone loss triggers synapse-specific remodeling and spatial receptive field rearrangements in a mature retinal circuit. Cell Rep 27:2171-2183.

Care RA, Anastassov IA, Kastner DB, Kuo YM, Della Santina L, Dunn FA (2020) Mature retina compensates functionally for partial loss of rod photoreceptors. Cell Rep 31:107730.

Castaldi E, Lunghi C, Morrone MC (2020) Neuroplasticity in adult human visual cortex. Neurosci Biobehav Rev 112:542-552.

Chen K, Hou B, Zhao Y, Yuan P, Yao D, Chan LLH (2020) Residual contrast response in primary visual cortex of rats with inherited retinal degeneration. Vision Res 177:6-11.

Close JL, Gumuscu B, Reh TA (2005) Retinal neurons regulate proliferation of postnatal progenitors and Muller glia in the rat retina via TGF beta signaling. Development 132:3015-3026.

Corredor RG, Goldberg JL (2009) Electrical activity enhances neuronal survival and regeneration. J Neural Eng 6:055001.

Cuenca N, Fernandez-Sanchez L, Campello L, Maneu V, De la Villa P, Lax P, Pinilla I (2014) Cellular responses following retinal injuries and therapeutic approaches for neurodegenerative diseases. Prog Retin Eye Res 43:17-75.

D'Orazi FD, Suzuki SC, Wong RO (2014) Neuronal remodeling in retinal circuit assembly, disassembly, and reassembly. Trends Neurosci 37:594-603.

Denlinger B, Helft Z, Telias M, Lorach H, Palanker D, Kramer RH (2020) Local photoreceptor degeneration causes local pathophysiological remodeling of retinal neurons. JCI Insight 5:e132114.

Di Marco S, Nguyen VA, Bisti S, Protti DA (2009) Permanent functional reorganization of retinal circuits induced by early long-term visual deprivation. J Neurosci 29:13691-13701.

Dong CJ, Agey P, Hare WA (2004) Origins of the electroretinogram oscillatory potentials in the rabbit retina. Vis Neurosci 21:533-543.

Drager UC, Hubel DH (1978) Studies of visual function and its decay in mice with hereditary retinal degeneration. J Comp Neurol 180:85-114.

Fausett BV, Gumerson JD, Goldman D (2008) The proneural basic helix-loop-helix gene ascl1a is required for retina regeneration. J Neurosci 28:1109-1117.

Forbes-Osborne MA, Wilson SG, Morris AC (2013) Insulinoma-associated 1a (Insm1a) is required for photoreceptor differentiation in the zebrafish retina. Dev Biol 380:157-171.

Fransen JW, Pangeni G, Pyle IS, McCall MA (2015) Functional changes in Tg P23H-1 rat retinal responses: differences between ON and OFF pathway transmission to the superior colliculus. J Neurophysiol 114:2368-2375.

Fu Z, Kern TS, Hellstrom A, Smith LEH (2021a) Fatty acid oxidation and photoreceptor metabolic needs. J Lipid Res 62:100035.

Fu Z, Qiu C, Cagnone G, Tomita Y, Huang S, Cakir B, Kotoda Y, Allen W, Bull E, Akula JD, Joyal JS, Hellstrom A, Talukdar S, Smith LEH (2021b) Retinal glial remodeling by FGF21 preserves retinal function during photoreceptor degeneration. iScience 24:102376.

Gargini C, Terzibasi E, Mazzoni F, Strettoi E (2007) Retinal organization in the retinal degeneration 10 (rd10) mutant mouse: a morphological and ERG study. J Comp Neurol 500:222-238.

Gehlen J, Esser S, Schaffrath K, Johnen S, Walter P, Muller F (2020) Blockade of retinal oscillations by benzodiazepines improves efficiency of electrical stimulation in the mouse model of RP, rd10. Invest Ophthalmol Vis Sci 61:37.

Goel M, Dhingra NK (2012) Muller glia express rhodopsin in a mouse model of inherited retinal degeneration. Neuroscience 225:152-161.

Goel M, Dhingra 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, Ail D, Bitard J, Chesneau A, Dalkara 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, Lahne M, Todd LJ, Jia M, Saez C, Keuthan C, Palazzo I, Squires N, Campbell WA, Rajaii F, Parayil T, Trinh V, Kim DW, Wang G, et al. (2020) Gene regulatory networks controlling vertebrate retinal regeneration. Science 370:eabb8598.

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

Iwabe S, Ying GS, Aguirre GD, Beltran WA (2016) Assessment of visual function and retinal structure following acute light exposure in the light sensitive T4R rhodopsin mutant dog. Exp Eye Res 146:341-353.

Johnson RE, Tien NW, Shen N, Pearson JT, Soto 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 degeneration. J Comp Neurol 519:2713-2733.

Kanow MA, Giarmarco MM, Jankowski CS, Tsantilas K, Engel AL, Du J, Linton JD, Farnsworth CC, Sloat SR, Rountree A, Sweet IR, Lindsay KJ, Parker ED, Brockerhoff 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.

Kaylor JJ, 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 multifunctional O-acyltransferase (MFAT). Proc Natl Acad Sci U S A 111:7302-7307.

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

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

Lee JY, Care RA, Kastner DB, Della Santina L, Dunn FA (2022) Inhibition, but not excitation, recovers from partial cone loss with greater spatiotemporal integration, synapse density, and frequency. Cell Rep 38:110317.

Leinonen H, Pham 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.

Leinonen H, Lyon DC, Palczewski K, Foik AT (2022) Visual system hyperexcitability and compromised V1 receptive field properties in early-stage retinitis pigmentosa in mice. eNeuro 9:ENEURO.0107-22.2022.

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, Binda P, Cicchini GM, Placidi G, Falsini B, Morrone MC (2019) Visual cortical plasticity in retinitis pigmentosa. Invest Ophthalmol Vis Sci 60:2753-2763.

Machida S, Kondo M, Jamison JA, Khan NW, Kononen LT, Sugawara T, Bush RA, Sieving PA (2000) P23H rhodopsin transgenic rat: correlation of retinal function with histopathology. Invest Ophthalmol Vis Sci 41:3200-3209.

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

Montalban-Soler L, Alarcon-Martinez L, Jimenez-Lopez M, Salinas-Navarro M, Galindo-Romero C, Bezerra de Sa F, Garcia-Ayuso D, Aviles-Trigueros M, Vidal-Sanz M, Agudo-Barriuso M, Villegas-Perez MP (2012) Retinal compensatory changes after light damage in albino mice. Mol Vis 18:675-693.

Nagashima M, D'Cruz TS, Danku AE, Hesse D, Sifuentes C, Raymond PA, Hitchcock PF (2020) Midkine-a is required for cell cycle progression of Muller glia during neuronal regeneration in the vertebrate retina. J Neurosci 40:1232-1247.

Nelson CM, Ackerman KM, O'Hayer P, Bailey TJ, Gorsuch RA, Hyde DR (2013) Tumor necrosis factor-alpha is produced by dying retinal neurons and is required for Muller glia proliferation during zebrafish retinal regeneration. J Neurosci 33:6524-6539.

Newton F, Megaw R (2020) Mechanisms of photoreceptor death in retinitis pigmentosa. Genes (Basel) 11:1120.

Ortega JT, Parmar T, Carmena-Bargueno M, Perez-Sanchez H, Jastrzebska B (2022) Flavonoids improve the stability and function of P23H rhodopsin slowing down the progression of retinitis pigmentosa in mice. J Neurosci Res 100:1063-1083.

Penn RD, Hagins WA (1969) Signal transmission along retinal rods and the origin of the electroretinographic a-wave. Nature 223:201-204.

Pfeiffer RL, Marc RE, Jones BW (2020) Persistent remodeling and neurodegeneration in late-stage retinal degeneration. Prog Retin Eye Res 74:100771.

Pfeiffer RL, Marc RE, Kondo M, Terasaki H, Jones BW (2016) Muller cell metabolic chaos during retinal degeneration. Exp Eye Res 150:62-70.

Procyk CA, Allen AE, Martial FP, Lucas RJ (2019) Visual responses in the dorsal lateral geniculate nucleus at early stages of retinal degeneration in rd(1) PDE6beta mice. J Neurophysiol 122:1753-1764.

Punzo C, Kornacker K, Cepko CL (2009) Stimulation of the insulin/mTOR pathway delays cone death in a mouse model of retinitis pigmentosa. Nat Neurosci 12:44-52.

Ramachandran R, Fausett BV, Goldman D (2010) Ascl1a regulates Muller glia dedifferentiation and retinal regeneration through a Lin-28-dependent, let-7 microRNA signalling pathway. Nat Cell Biol 12:1101-1107.

Ramachandran R, Zhao XF, Goldman D (2011) Ascl1a/Dkk/beta-catenin signaling pathway is necessary and glycogen synthase kinase-3beta inhibition is sufficient for zebrafish retina regeneration. Proc Natl Acad Sci U S A 108:15858-15863.

Ramachandran R, Zhao XF, Goldman D (2012) Insm1a-mediated gene repression is essential for the formation and differentiation of Muller glia-derived progenitors in the injured retina. Nat Cell Biol 14:1013-1023.

Rao MB, Didiano D, Patton JG (2017) Neurotransmitter-regulated regeneration in the zebrafish retina. Stem Cell Reports 8:831-842.

Richards A, Emondi AA, Rohrer B (2006) Long-term ERG analysis in the partially light-damaged mouse retina reveals regressive and compensatory changes. Vis Neurosci 23:91-97.

Rowe AA, Patel PD, Gordillo R, Wert KJ (2021) Replenishment of TCA cycle intermediates provides photoreceptor resilience against neurodegeneration during progression of retinitis pigmentosa. JCI Insight 6:e150898.

Rubin GR, Wen Y, Loop MS, Kraft TW (2022) ERG and behavioral CFF in light-damaged albino rats. Int J Mol Sci 23:4127.

Rueda EM, Hall BM, Hill MC, Swinton PG, Tong X, Martin JF, Poche RA (2019) The Hippo pathway blocks mammalian retinal Muller glial cell reprogramming. Cell Rep 27:1637-1649.

Salman A, McClements ME, MacLaren RE (2021) Insights on the regeneration potential of Muller glia in the mammalian retina. Cells 10:1957.

Saszik SM, Robson JG, Frishman LJ (2002) The scotopic threshold response of the dark-adapted electroretinogram of the mouse. J Physiol 543:899-916.

Sekirnjak C, Jepson LH, Hottowy P, Sher A, Dabrowski W, Litke AM, Chichilnisky EJ (2011) Changes in physiological properties of rat ganglion cells during retinal degeneration. J Neurophysiol 105:2560-2571.

Sekirnjak C, Hulse C, Jepson LH, Hottowy P, Sher A, Dabrowski W, Litke AM, Chichilnisky EJ (2009) Loss of responses to visual but not electrical stimulation in ganglion cells of rats with severe photoreceptor degeneration. J Neurophysiol 102:3260-3269.

Shen N, Wang B, Soto F, Kerschensteiner D (2020) Homeostatic plasticity shapes the retinal response to photoreceptor degeneration. Curr Biol 30:1916-1926.

Shen W, Lee SR, Mathai AE, Zhang R, Du J, Yam MX, Pye V, Barnett NL, Rayner CL, Zhu L, Hurley JB, Seth P, Hirabayashi Y, Furuya S, Gillies MC (2021) Effect of selectively knocking down key metabolic genes in Muller glia on photoreceptor health. Glia 69:1966-1986.

Sher A, Jones BW, Huie P, Paulus YM, Lavinsky D, Leung LS, Nomoto H, Beier C, Marc RE, Palanker D (2013) Restoration of retinal structure and function after selective photocoagulation. J Neurosci 33:6800-6808.

Stockton RA, Slaughter MM (1989) B-wave of the electroretinogram. A reflection of ON bipolar cell activity. J Gen Physiol 93:101-122.

Strettoi E, Pignatelli V (2000) Modifications of retinal neurons in a mouse model of retinitis pigmentosa. Proc Natl Acad Sci U S A 97:11020-11025.

Strettoi E, Volpini M (2002) Retinal organization in the bcl-2-overexpressing transgenic mouse. J Comp Neurol 446:1-10.

Strettoi E, Mears AJ, Swaroop A (2004) Recruitment of the rod pathway by cones in the absence of rods. J Neurosci 24:7576-7582.

Strettoi E, Di Marco B, Orsini N, Napoli D (2022) Retinal plasticity. Int J Mol Sci 23:1138.

Strettoi E, Porciatti V, Falsini B, Pignatelli V, Rossi C (2002) Morphological and functional abnormalities in the inner retina of the rd/rd mouse. J Neurosci 22:5492-5504.

Telias M, Denlinger B, Helft Z, Thornton C, Beckwith-Cohen B, Kramer RH (2019) Retinoic acid induces hyperactivity, and blocking its receptor unmasks light responses and augments vision in retinal degeneration. Neuron 102:574-586.

Telias M, Sit KK, Frozenfar D, Smith B, Misra A, Goard MJ, Kramer RH (2022) Retinoic acid inhibitors mitigate vision loss in a mouse model of retinal degeneration. Sci Adv 8:eabm4643.

Thompson S, Blodi FR, Lee S, Welder CR, Mullins RF, Tucker BA, Stasheff SF, Stone EM (2014) Photoreceptor cells with profound structural deficits can support useful vision in mice. Invest Ophthalmol Vis Sci 55:1859-1866.

Tian N, Copenhagen DR (2001) Visual deprivation alters development of synaptic function in inner retina after eye opening. Neuron 32:439-449.

Tian N, Copenhagen DR (2003) Visual stimulation is required for refinement of ON and OFF pathways in postnatal retina. Neuron 39:85-96.

Tien NW, Soto F, Kerschensteiner D (2017) Homeostatic plasticity shapes cell-type-specific wiring in the retina. Neuron 94:656-665.

Todd L, Volkov LI, Zelinka C, Squires N, Fischer AJ (2015) Heparin-binding EGF-like growth factor (HB-EGF) stimulates the proliferation of Muller glia-derived progenitor cells in avian and murine retinas. Mol Cell Neurosci 69:54-64.

Tomita Y, Qiu C, Bull E, Allen W, Kotoda Y, Talukdar S, Smith LEH, Fu Z (2021) Muller glial responses compensate for degenerating photoreceptors in retinitis pigmentosa. Exp Mol Med 53:1748-1758.

Toychiev AH, Ivanova E, Yee CW, Sagdullaev BT (2013) Block of gap junctions eliminates aberrant activity and restores light responses during retinal degeneration. J Neurosci 33:13972-13977.

Trenholm S, Borowska J, Zhang J, Hoggarth A, Johnson K, Barnes S, Lewis TJ, Awatramani GB (2012) Intrinsic oscillatory activity arising within the electrically coupled AII amacrine-ON cone bipolar cell network is driven by voltage-gated Na+ channels. J Physiol 590:2501-2517.

Ueki Y, Reh TA (2013) EGF stimulates Muller glial proliferation via a BMP-dependent mechanism. Glia 61:778-789.

Ueki Y, Wilken MS, Cox KE, Chipman L, Jorstad N, Sternhagen K, Simic M, Ullom K, Nakafuku M, Reh TA (2015) Transgenic expression of the proneural transcription factor Ascl1 in Muller glia stimulates retinal regeneration in young mice. Proc Natl Acad Sci U S A 112:13717-13722.

Vecino E, Rodriguez FD, Ruzafa N, Pereiro X, Sharma SC (2016) Glia-neuron interactions in the mammalian retina. Prog Retin Eye Res 51:1-40.

Wan J, Ramachandran R, Goldman D (2012) HB-EGF is necessary and sufficient for Muller glia dedifferentiation and retina regeneration. Dev Cell 22:334-347.

Wan J, Zhao XF, Vojtek A, Goldman D (2014) Retinal injury, growth factors, and cytokines converge on beta-catenin and pStat3 signaling to stimulate retina regeneration. Cell Rep 9:285-297.

Wang T, Pahlberg J, Cafaro J, Frederiksen R, Cooper AJ, Sampath AP, Field GD, Chen J (2019) Activation of rod input in a model of retinal degeneration reverses retinal remodeling and induces formation of functional synapses and recovery of visual signaling in the adult retina. J Neurosci 39:6798-6810.

Yang P, Cao Q, Liu Y, Wang K, Zhu W (2022) Small-molecule-driven direct reprogramming of Muller cells into bipolar-like cells. Cell Prolif 55:e13184.

Yao K, Qiu S, Wang YV, Park SJH, Mohns EJ, Mehta B, Liu X, Chang B, Zenisek D, Crair MC, Demb JB, Chen B (2018) Restoration of vision after de novo genesis of rod photoreceptors in mammalian retinas. Nature 560:484-488.

Yu WQ, Grzywacz NM, Lee EJ, Field GD (2017) Cell type-specific changes in retinal ganglion cell function induced by rod death and cone reorganization in rats. J Neurophysiol 118:434-454.

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