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Suppressing Retinal Remodeling to Mitigate Vision Loss in Photoreceptor Degenerative Disorders

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Abstract

Rod and cone photoreceptors degenerate in retinitis pigmentosa and age-related macular degeneration, robbing the visual system of light-triggered signals necessary for sight. However, changes in the retina do not stop with the photoreceptors. A stereotypical set of morphological and physiological changes, known as remodeling, occur in downstream retinal neurons. Some aspects of remodeling are homeostatic, with structural or functional changes compensating for partial loss of visual inputs. However, other aspects are nonhomeostatic, corrupting retinal information processing to obscure vision mediated naturally by surviving photoreceptors or artificially by vision-restoration technologies. In this review, I consider the mechanism of remodeling and its consequences for residual and restored visual function; discuss the role of retinoic acid, a critical molecular trigger of detrimental remodeling; and discuss strategies for suppressing retinoic acid biosynthesis or signaling as therapeutic possibilities for mitigating vision loss.

INTRODUCTION

Sight is our most precious sense, and vision loss has enormous physical, psychological, and economic consequences for millions of people around the world. The most common cause of vision loss in developed countries is the degeneration of rods and cones, the photoreceptor cells that transduce light into a visible neural signal. The remaining neurons in the retina can survive for a lifetime after the rods and cones have degenerated. Critically, retinal ganglion cells (RGCs), the output neurons of the retina, can remain connected to the brain (Mazzoni et al. 2008, Medeiros & Curcio 2001). This gives us hope that vision might be restored by regenerating the lost photoreceptors from stem cells or by artificially installing light responses in surviving downstream retinal neurons—for example, with optoelectronic (Humayun et al. 2012), optogenetic (Bi et al. 2006, Sahel et al. 2021), or optopharmacological strategies (Polosukhina et al. 2012, Tochitsky et al. 2014). As long as the signal can make its way to RGCs, it should be transmitted to the brain. Recent studies, however, show that physiological and morphological remodeling occurs after the photoreceptors die and suggest that these changes limit the effectiveness of vision-restoring technologies (Caravaca-Rodriguez et al. 2022, Lindner et al. 2022). Moreover, functional remodeling can begin even before photoreceptor degeneration is complete, impairing proper neural processing of visual information triggered by residual photoreceptors (Telias et al. 2019, 2020). This review considers the types of remodeling triggered by photoreceptor loss, what consequences they have for residual vision, and what limitations they may impose on restored vision. I also review the molecular and cellular events that lead to remodeling and consider potential therapies that might improve vision by removing the aspects of retinal remodeling that corrupt visual information processing.

PHOTORECEPTOR DEGENERATIVE DISORDERS AND POTENTIAL TREATMENTS

Retinitis Pigmentosa

In retinitis pigmentosa (RP), retinal photoreceptor cells degenerate, reducing visual acuity; constricting the visual field; impairing light and dark adaptation; and, in advanced cases, causing complete loss of light perception. RP is an inherited disease; thus, the underlying cause is present from birth. Inherited retinal degenerations occur when a mutation in one or more genes affects the survival of photoreceptors. RP afflicts 1 in 4,000 people (Verbakel et al. 2018) and is therefore considered a rare disease (fewer than 100,000 patients in the United States). It is also categorized as an orphan disease, defined as any neglected condition whose treatment is not considered profitable to develop because of the limited patient population. Mutations in more than 100 distinct gene loci can lead to RP, with some mutations exhibited by only a handful of patients, sometimes limited to members of an individual family. Gene therapy–based treatments can address the underlying mutation causing RP, but each mutation will require its own therapeutic gene and its own delivery vehicle, slowing the development of effective treatments.

Depending on the nature of the mutation, inheritance of RP may be autosomal dominant, autosomal recessive, or X linked. The locus of the RP mutation can be a gene for a phototransduction protein, such as rhodopsin or cyclic GMP photosphodiesterase, or for a retinal pigment epithelial (RPE) protein involved in retinoid metabolism, as in Leber's congenital amaurosis (Gu et al. 1997), sometimes categorized as a distinct disorder from RP. However, in many forms of RP, the connection between the mutation and photoreceptor death is tenuous, and in some cases, the causative mutation is difficult to identify. Some mutations that result in RP also lead to nonocular deficits in other organ systems and are therefore considered syndromic. For example, RP is a

consequence of some types of Usher's syndrome (Tsang et al. 2018b), also associated with deafness and vestibular deficits, and Bardet–Biedl syndrome (Tsang et al. 2018a), also associated with pleiotropic developmental defects.

RP symptoms can vary widely, first presenting anytime from early childhood to late adulthood. The average age of RP diagnosis is approximately 35 years, and it usually progresses slowly over subsequent years to decades, resulting in a gradual but relentless degradation of vision. Why photoreceptor function and survival can remain nearly normal for years or decades and then start to decline with age remains a mystery. RP presents initially as night blindness and loss of the peripheral visual field, consistent with loss of rods. Later, loss of central vision can occur owing to secondary cone degeneration. In many cases, RP is caused by a rod-specific mutation, leaving open the question of why cones also eventually die. Deleterious effects of oxidative stress seem to contribute to cone death, but there is compelling evidence that the loss of a trophic factor named rod-derived cone viability factor (RdCVF) also plays a role (Sahel & Léveillard 2018). Much less prevalent than rod-cone dystrophies are cone-rod dystrophies (affecting 1 in 40,000 people), in which cones deteriorate first, impairing central vision, followed eventually by loss of rods and peripheral vision (Hamel 2007).

Gene Therapy for Retinitis Pigmentosa

The advent of gene therapy has for the first time presented opportunities for arresting or even reversing some types of RP. At present, the gene delivery vehicles of choice are adeno-associated viruses (AAVs). AAVs elicit a very mild immune response and are not associated with known diseases. Even so, for safety's sake, replication-incompetent versions are used therapeutically. AAVs can be tuned to deliver genes into selected retinal cell types, either by using a serotype that favors infection of a particular cell or by incorporating a gene regulatory element for cell-type-selective expression of the introduced gene. The tuning of AAV vectors is becoming ever more refined. However, there are still problems delivering AAVs because of barriers such as the inner limiting membrane (ILM), which hinders access of virus injected into the vitreous cavity (Dalkara et al. 2009, Leclercq et al. 2022). Subretinal injection is an alternative, but the resulting local retinal detachment is cause for concern. Nonviral genetic treatments may circumvent these problems, especially for gene suppression therapy. Antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) are alternatives for suppressing expression of specific genes, and these tools may have broader access to retinal neurons than AAVs introduced either in front of or behind the retina.

Depending on the type of RP, different gene therapy strategies may be more or less appropriate for preventing further deterioration. Gene addition therapy is most appropriate for disorders in which a mutation renders missing or inactive an essential gene product, and introduction of the normal gene is sufficient for restoring function. These include autosomal recessive RP and recessive types of X-linked RP, where patients lack a gene product critical for photoreceptor function or survival. Clinical trials employing AAV-mediated gene addition therapy are underway for both syndromes. Gene replacement therapy is necessary for dominant autosomal RP, where the mutant gene product impairs function or causes the degeneration, even if another nonmutated copy of the gene is present. Gene replacement therapy lends itself particularly well to monogenic diseases, such as sickle cell disease, cystic fibrosis, and spinal muscular atrophy. In these disorders, the phenotype is driven by the mutation or deletion of a single gene, and replacement is the only thing that provides any hope of improved vision. Gene editing therapy employs new molecular genetic tools that allow correction of deleterious mutations in the genome. In particular, the development of CRISPR/Cas9-mediated gene therapy holds tremendous promise for preventing retinal degeneration in patients with inherited retinal diseases, but this approach has not yet been implemented therapeutically in humans.

Age-Related Macular Degeneration: Disease and Treatment

Age-related macular degeneration (AMD) represents a distinct disorder in which degeneration is restricted to the macula, the small, cone-rich region in the center of the retina responsible for high-acuity vision. Approximately 8 million people in the United States have symptoms of early or intermediate AMD, and approximately 1 million will develop late AMD within the next 5 years, making it the leading cause of vision loss in people age 55 or older. The causes of AMD are complex, with genetic factors predisposing individuals to the disease. However, environmental factors, including cigarette smoking and high body mass index (Wang et al. 2016), are also major risk factors. Roughly 80% of AMD patients exhibit dry AMD, often involving minor vision loss that progresses slowly. However, in 10–15% of AMD patients, the degeneration progresses more rapidly, causing geographic atrophy characterized by complete loss of photoreceptors and the underlying RPE and choriocapillaris in patches within the macula, leading to central vision impairment.

Dry AMD can also progress into wet, or neovascular, AMD, which is the most serious form of the disorder, often exhibiting rapid progression. Wet AMD is characterized by the growth of abnormal blood vessels beneath the retina that leak blood and fluid, triggering inflammatory responses and scarring that further exacerbate vision loss. There is currently no treatment for dry AMD, but the neovascularization underlying wet AMD can be suppressed with monthly injections of US Food and Drug Administration (FDA)-approved drugs that block the action of vascular endothelial growth factor, including bevocizumab, brolucizumab, ranibizumab, and aflibercept.

The Hope of Vision Restoration

Once photoreceptor degeneration is nearly complete, other strategies are needed to bring light sensitivity back to the blind visual system. Fortunately, most RGCs maintain synaptic connectivity with the brain long after the rod and cone photoreceptors die (Mazzoni et al. 2008, Medeiros & Curcio 2001); thus, the RGCs and upstream retinal neurons are both potential substrates for vision restoration. Light-elicited signals can be imposed on these neurons with optogenetics (Bi et al. 2006) or optopharmacology (Fortin et al. 2008). To date, light sensitivity has been conferred onto remnant cone cell bodies (Busskamp et al. 2010), bipolar cells (Lagali et al. 2008), amacrine cells (Polosukhina et al. 2012), and RGCs (Bi et al. 2006, Polosukhina et al. 2012, Tochitsky et al. 2014).

Light responses can also be indirectly transmitted to retinal neurons with a subretinal optoelectronic implant (Palanker 2023) or an epiretinal retinal chip that electrically stimulates RGC firing (Humayun et al. 2012). The Argus II system received FDA approval in 2013 and since then has been implanted into hundreds of patients worldwide. While it can restore perception of light and recognition of large objects and shapes, visual acuity among recipients has been lower than hoped, owing in part to unintended electrical stimulation of axons of passage located between the implant and targeted RGCs (Beyeler et al. 2019).

Most ambitious of all is the hope that fully functioning rod and cone photoreceptors might be regenerated from stem cell precursors, replacing the ones that were lost. Efforts to make this a reality are still in their infancy, but experiments have shown promising results for restoring light responses in a mouse model of RP (Ribeiro et al. 2021).

Installing light sensitivity by any of these means might, in principle, restore near-normal visual perception as long as the neural circuitry encoding and transmitting the information through RGCs to the brain remains intact and uncorrupted. However, there is abundant evidence that the physiology and morphology of downstream neurons in the retina undergo dramatic changes as the photoreceptors are lost, and these changes do indeed corrupt visual information processing. The following sections discuss these changes, what causes them, and how they might be prevented or reversed to improve residual and restored vision.

STRUCTURAL REMODELING OF THE RETINA

Remodeling in Retinitis Pigmentosa

Observations of morphological remodeling of the human retina in RP depend on retrospective studies of retinal tissue obtained postmortem. Despite the heterogeneity of genes causing RP, many general features can be observed in the progression of degeneration and in changes in the microstructure, apparent synaptic connectivity, and position of downstream neurons and glial cells in the retina. The sequence of downstream morphological changes triggered by photoreceptor degeneration is stereotypical across a wide range of mammalian models of RP, including mice, rats, rabbits, pigs, and dogs, and notable in human subjects with RP (Anderson et al. 2016, Jones et al. 2016, O'Brien et al. 2014, Phillips et al. 2010). Thus, animal models have been tremendously useful for correlating photoreceptor loss, morphological remodeling of the retina, and visual degradation in a manner that would be difficult or impossible in humans.

Some of the most widely used animal models have mutations identical to those occurring in human cases of RP. Perhaps the best-studied models of the degeneration process itself and subsequent events in remodeling are mouse strains with mutations in the β-subunit of rod-specific cGMP phosphodiesterase (PDE6) (Kalloniatis et al. 2016, Wang et al. 2018), which causes photoreceptor cell death by promoting excessive cGMP-dependent ion influx. The rd1 strain is very aggressive, with almost complete rod loss occurring within 14 days of birth, mostly before eye opening. In the rd10 strain, which has a different PDE6 mutation, rods degenerate more slowly, starting at approximately 28 days after birth and remaining incomplete until 2–3 months. Other commonly used animal models of RP include the Royal College of Surgeons (RCS) rat (García-Ayuso et al. 2014, Villegas-Pérez et al. 1998), mice or rats with a mutation causing a truncation of rhodopsin (S332-ter), and large mammals including dogs and pigs (Winkler et al. 2020). Finally, long-sought nonhuman primate models of RP are now becoming available (Peterson et al. 2019, Seah et al. 2022).

The first morphological change in RP is in the photoreceptors themselves. In rd10 mice, rod outer segments disintegrate, and layers of rod cell bodies disappear, thinning the outer retina. Cones undergo a similar sequence of degenerative changes, but later than rods. Changes in glial cells begin at the same time as rod loss. Resident microglia are activated and move to superficial layers of the retina to engulf dying photoreceptors. Müller glial cells become hypertrophic, ultimately forming a scar that fills the subretinal space (Cuenca et al. 2014).

The immediate postsynaptic partners of photoreceptors, horizontal and glial cells, are the next to show morphological changes. As the photoreceptor terminals degrade, the dendrites of bipolar and horizontal cells that formerly contacted them begin to retract, shrinking the overall thickness of the outer plexiform layer. However, shortly thereafter, horizontal cells (Michalakis et al. 2013) and some bipolar cells (Lin et al. 2012) sprout new dendrites, which can form ectopic contacts on other retinal cell types. Interestingly, bipolar cell dendritic sprouting also occurs as a normal consequence of aging in both mice (Liets et al. 2006) and humans (Eliasieh et al. 2007).

Morphological changes in the inner retina happen even later (Strettoi et al. 2002). In fact, at up to 3 months of age, long after photoreceptors have completely disappeared in rd1 and rd10 mice, there is little change in the appearance of various amacrine cells, including starburst cells, dopaminergic cells, and AII amacrines. Likewise, the dendritic field size of RGCs remains normal in rd1 at 6 months of age, with the first significant changes noted at 11 months (O'Brien et al. 2014). However, with age, more substantial changes begin to occur even in these cells. In very aged RP mice (>1 year), changes occur throughout the retina. Neurons begin to migrate from their usual locations, and the beautiful stratification of the retina breaks down. A fraction of RGCs themselves degenerate. A study on retinas from aged human RP donors (Santos et al. 1997) showed loss of

inner nuclear layer and RGC layer cells, also attributable to a decrease in the number of RGCs (Stone et al. 1992). The loss of RGCs with age sets a time limit on how long we might expect any vision restoration technology working at the level of the retina to remain effective.

Retinal Remodeling in Age-Related Macular Degeneration

Animal models are unavailable for studying possible morphological remodeling in AMD, but there is a wealth of information from postmortem studies on human retinal tissue. AMD results in loss of macular photoreceptors, which are almost exclusively cones, but remodeling occurs in many other cell types. Müller glial cells show dramatic enlargement, termed reactive gliosis. The RPE undergoes many changes, including atrophy of microvilli, loss of melanin granules, accumulation of lipofuscin, and accumulation of drusen between the RPE and the inner collagenous layer of Bruch's membrane (Falsini et al. 1994). In addition to all of these changes, AMD is associated with subretinal neovascularization and immune activation leading to inflammation. Whereas overt tissue damage in RP is largely restricted to the photoreceptors, AMD involves many more cell types than can impact vision in many ways.

Further studies showed dramatic metabolic reprogramming of the tissue (Jones et al. 2016) revealed by immunolabeling of glutamate, GABA, and glycine, the main neurotransmitters of the adult retina, as well as taurine and glutathione, markers of metabolic stress. AMD retinas have heightened taurine in remaining cone outer segments and glutathione in the RPE, as well as very high levels of glutamate in Müller cells, all restricted to areas overlying dry AMD lesions. These morphological findings show that human AMD retinas exhibit many of the same remodeling events observed in RP retinas. In contrast, functional evidence for downstream remodeling is indirect. For example, AMD patients exhibit alterations of the fundamental and second harmonic components of the focal electroretinogram, suggestive of changes in synaptic information transfer in the downstream retinal circuitry (Falsini et al. 1994).

Difficulties Studying Retinal Remodeling

Studying retinal remodeling presents several challenges. Experiments require a long-term commitment, as photoreceptor degeneration and subsequent remodeling are usually slow processes taking months in mice and a year or more in larger mammals such as dogs. Rapid degeneration models, such as the rd1 mouse, are available, but in these models, photoreceptor cells die before they even reach maturity, raising concerns that downstream alterations may be a consequence of altered development rather than postdevelopment plasticity. This has led many labs to adopt slower-degenerating rd10 mice (Gargini et al. 2007), but this slows experimental progress. RP model mice can be difficult to breed. Both rd1 and rd10 are autosomal recessive. Therefore, the mice must be homozygous to exhibit the degeneration phenotype. There are many other RP models, but whether remodeling phenomena observed for one mutation are universal for other mutations remains to be determined. Human RP can be caused by mutations in many different genes, each progressing with a different time course, making it difficult to generalize what sequence and severity of remodeling effects to expect from animal models. While a nonhuman primate model for RP might soon be widely available, at present there is no practical way to carry out functional studies on living retinal tissue with pathological changes that accurately resemble AMD, although aged macaques do develop drusen deposits (Yiu et al. 2020). Highly localized laser ablation of photoreceptors, which is geographically restricted in the same manner as AMD, has been achieved in macaques (Dhakal et al. 2020). Mice and rats do not have a macula, but rods and cones can be cut off from the RPE by subretinal implantation of a metallic chip, also leading to

highly localized photoreceptor degeneration (Lorach et al. 2015), which might simulate some of the effects of AMD; a better model would certainly be welcome.

Studies on humans are made difficult by the limited number of patients with specific RP mutations, the varying ages of human subjects, and the wide variability of other risk factors. Despite all of these hindrances, descriptions of how the retina progressively remodels over time are becoming more accurate and complete. The most recent work on morphological remodeling is employing semiautomated serial section electron microscopy to reveal a complete connectivity map of the degenerated retina (i.e., the patho-connectome) (Pfeiffer et al. 2020), which can then be compared to the normal connectome to elucidate precise changes in wiring. This information may be of great importance for future attempts to improve or restore vision with therapies acting at different stages of the visual pathway.

FUNCTIONAL REMODELING OF THE RETINA

Characterizing morphological remodeling has been relatively straightforward, with light and electron microscopic analyses paving the way. Slower to emerge are findings about functional remodeling of the retina, some of which occur long before any morphological remodeling is evident. These findings have come largely from electrophysiological recordings, either intracellular measurements from individual patch-clamped cells or extracellular multi-electrode array recordings from populations of spiking cells, thus limited to RGCs.

Bipolar Cells

Apart from losses of neurotransmitter release from the degenerating photoreceptors themselves, the first physiological changes to emerge in postsynaptic bipolar and horizontal cells are changes in their response to glutamate, the photoreceptor neurotransmitter. Experimental ablation of cone photoreceptors causes disappearance of postsynaptic mGluR6 receptors in ON-bipolar cells within just a few hours (Dunn 2015, Strettoi & Pignatelli 2000). This coincides with altered localization in rd10 mouse retinas of the TRPM1 ion channels that are normally the downstream targets of mGluR6 signaling (Gayet-Primo & Puthussery 2015). TRM1 channels normally colocalize with mGluR6 in dendrites that invaginate the cone terminal, but this entire structure, including the postsynaptic signaling proteins, dissipates when cones degrade, presumably impairing glutamate responsiveness. In contrast, glutamate responses of OFF-bipolar cells appear to be preserved for months (Puthussery et al. 2009). Why ON- and OFF-bipolar cells respond differently is unknown. Perhaps a signal derived from photoreceptor degeneration more effectively reaches the ON-bipolar cells, or perhaps they are more susceptible to the putative signal.

Very recently, we have discovered another remarkable example of functional remodeling, at the output synaptic terminals at the other end of the bipolar cell (Kramer lab, unpublished results). Whole-cell patch-clamp studies reveal that certain bipolar cells in rd1 and rd10 retinas have much smaller voltage-gated Ca^{2+} currents than in wild-type mice, where Ca^{2+} channels are localized to output terminals in the inner plexiform layer (IPL). Optogenetically depolarizing ON-bipolar cells elicited much smaller excitatory postsynaptic currents in RGCs, consistent with the smaller Ca^{2+} current evoking less Ca^{2+}-dependent transmitter release from the bipolar cell. These effects were observed in rod bipolar cells and type 6 cone bipolar cells, both ON-type. Whether similar changes also occur in OFF-bipolar cells or other ON-bipolar cells remains unknown, but the results have important implications for how information is transmitted to RGCs, regardless of whether it is driven by residual photoreceptors or by vision-restoration devices acting on or upstream of bipolar terminals.

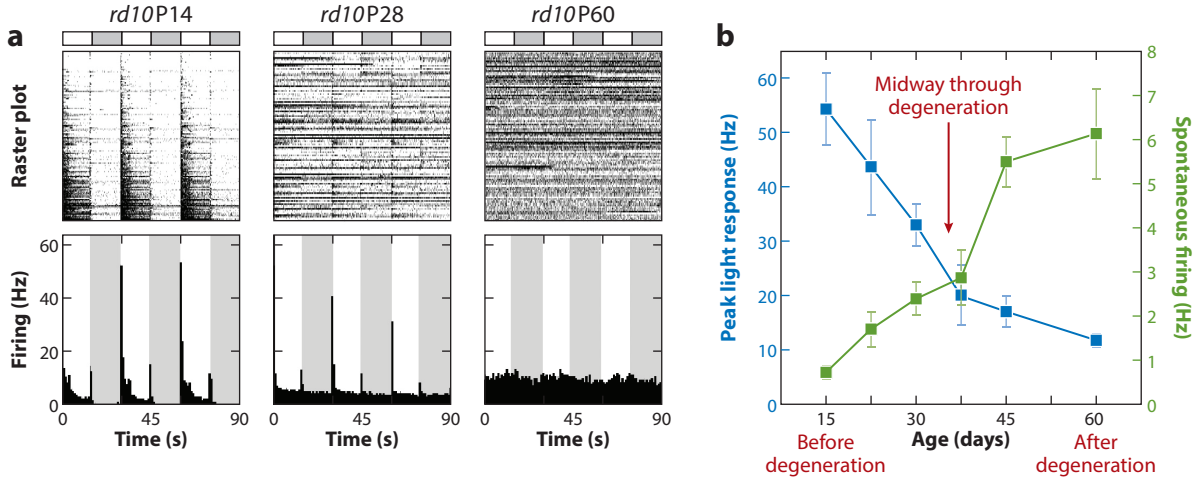

Figure 1

Photoreceptor degeneration leads to retinal ganglion cell (RGC) hyperactivity. (*a*) Multi-electrode array (MEA) recordings of RGC firing in slowly degenerating rd10 retina. The bar above the raster shows periods of light and dark. (*b*) Loss of the RGC light response correlates with hyperactive firing. Figure adapted with permission from Telias et al. (2019).

Retinal Ganglion Cells

The spontaneous firing rate of RGCs in darkness tends to be higher in retinas whose photoreceptors have degenerated than in healthy retinas (Sekirnjak et al. 2011, Stasheff 2008, Telias et al. 2019), and hyperactivity emerges in parallel with the loss of light responses (**Figure 1**). RGCs are a heterogenous population of neurons, with at least 40 distinct types in mice (Baden et al. 2016) and 18 in nonhuman primates (Masri et al. 2019), identified by their morphology, spatial-temporal receptive field properties, and gene transcriptional profiles. It is not known exactly which of these types account for the net hyperactivity of RGCs. However, RGCs can be broadly grouped into ON-RGCs, OFF-RGCs, and ON/OFF-RGCs, and the evidence for hyperactivity is strongest for the OFF-RGCs (Sekirnjak et al. 2011; Tochitsky et al. 2014, 2016).

At first, RGC hyperactivity was attributed to increased excitatory synaptic drive from bipolar cells (Margolis et al. 2008, Stasheff 2008), but hyperactive firing remains after pharmacological blockade of all chemical synaptic transmission onto RGCs (Borowska et al. 2011, Sekirnjak et al. 2011, Trenholm et al. 2012, Yee et al. 2012). Patch-clamp recordings from synaptically isolated RGCs show upregulation of voltage-gated ion channels known to promote spontaneous firing in other excitable cells, namely hyperpolarization and cyclic nucleotide-activated (HCN) channels and voltage-gated K^+ channels. Gene transcriptional studies confirm upregulation of HCN channel messenger RNA (mRNA) in degenerated retina (Tochitsky et al. 2014, 2016). Taken together, these results establish that altered intrinsic properties contribute to RGC hyperactivity. Upregulated ion channels might be localized to the dendritic tree of RGCs, where somatic current injections may fail to activate them. This might explain why a change in intrinsic RGC excitability was discounted in earlier studies (Margolis et al. 2008). RGCs also exhibit increased electrical coupling to amacrine cells in rd mouse models. Consequently, amacrine cells in these models can transmit oscillatory voltage changes to RGCs in the absence of chemical synaptic transmission (Choi et al. 2014, Ivanova et al. 2016, Toychiev et al. 2013). The emergence of oscillatory activity in the inner retina is discussed more thoroughly below.

Other physiological changes also occur in RGCs upon photoreceptor degeneration. We discovered that the plasma membrane of certain RGCs becomes permeable to large cation molecules that would ordinarily be membrane impermeant (Tochitsky et al. 2016). Membrane hyperpermeability can be seen by staining with cationic DNA-binding fluorescent dyes such as Yo-Pro-1. In rd1 and rd10 retinas, the nuclei of approximately 30% of RGCs label with Yo-Pro-1, compared to <5% in wild-type retinas (Tochitsky et al. 2016). The source of the membrane hyperpermeability is a large-pore cation channel named the P2X receptor. P2X receptors are ligand-gated ion channels activated by extracellular ATP. ATP is released from cells upon hypoxia, inflammatory stress, and tissue damage and might be released from photoreceptors as they degenerate. In addition, transcriptional studies show upregulation of mRNA for certain P2X receptor isoforms, and immunolabeling shows increased P2X protein in the membrane of RGCs (Tochitsky et al. 2016). Among RGCs, membrane hyperpermeability occurs nearly exclusively in OFF-RGCs, with little Yo-Pro-1 labeling in ON-RGCs or ON/OFF-RGCs.

The hyperpermeability of RGCs explains another difference between healthy and photoreceptor-degenerated retinas. Polosukhina et al. (2012) and Tochitsky et al. (2014) found that synthetic photoswitch molecules such as AAQ and DENAQ can restore light sensitivity to degenerated retinas of rd1 and rd10 mice and improve light-evoked behaviors in these mice. These molecules possess a photoisomerizable azobenzene group and a quaternary ammonium group that blocks many voltage-gated ion channels. Remarkably, light sensitivity is only restored in RGCs of degenerated retinas; the compounds have little or no effect on RGCs in healthy retinas from wild-type mice. The explanation for the degeneration dependence of photoswitches resides in the upregulation and chronic activation of P2X receptors. Photoswitches simply cannot enter RGCs in wild-type retina, precluding any action on cellular excitability.

The Emergence of Retinal Oscillations

Studies on rodents show that, in addition to changes intrinsic to individual retinal neurons, photoreceptor degeneration also leads to spontaneous oscillatory activity that involves interactions between multiple cell types (Euler & Schubert 2015, Menzler & Zeck 2011). In the outer retina, Ca^{2+} imaging studies on rd1 retina show spontaneous Ca^{2+} transients that are synchronous between remnant cones and horizontal cells and between cones and rod bipolar cells, to which they become aberrantly connected (Haq et al. 2014). The synchronous activity occurs in clusters of approximately 10 cells each, with a frequency of 1–3 Hz.

Even more dramatic is the emergence of oscillatory activity in the inner retina. Bipolar cells, AII amacrine cells, and RGCs all show large spontaneous fluctuations in membrane potential, with a frequency ranging from 3 to 10 Hz (Borowska et al. 2011, Margolis et al. 2014, Yee et al. 2012), depending on the preparation and the temperature. The intrinsic properties of AII amacrine cells promote oscillations that are transmitted to RGCs to evoke rhythmic burst firing (Choi et al. 2014). However, the inner retina oscillation and RGC bursting remain even after excitatory and inhibitory synaptic transmission among bipolar cells, amacrine cells, and RGCs is blocked (Borowska et al. 2011, Margolis et al. 2014, Yee et al. 2012). The oscillation can be suppressed by agents that uncouple gap junctions, and increased gap-junctional coupling between inner retinal neurons has been observed in degenerated retina (Ivanova et al. 2016, Tu & Chiao 2016).

Photobleaching of the isolated retina, which can occur within minutes of exposure to bright light, induces similar oscillations (Menzler et al. 2014). This suggests that remodeling, involving slower changes in gene expression or post-translational modifications such as protein phosphorylation, is not required to induce the oscillation (Trenholm & Awatramani 2015). RGC oscillations with similar characteristics are generated in a strain of mice whose glutamate release from photoreceptors is normal, but whose ON-type bipolar cells have defective signal transduction, making

them unable to respond to the glutamate (*nob* mouse) (Demas et al. 2006, Winkelman et al. 2019). Taken together, these findings suggest that the emergence of oscillations in RP models may not be a consequence of an enduring remodeling mechanism, such as a change in gene transcription, but instead may reflect intrinsic properties of the retinal circuit that are unleashed by the loss of photoreceptor drive onto the ON-bipolar cell pathway.

WHAT IS THE MOLECULAR TRIGGER OF REMODELING?

Morphological and physiological analyses have given us a detailed picture of the changes that occur in retinal neurons downstream of photoreceptor loss. However, identifying the signals that trigger remodeling has received much less attention. How do downstream neurons know that the photoreceptors are dead or dying? There are two broad possibilities. The loss of a signal from photoreceptors might trigger changes in downstream cells. Alternatively, photoreceptor degeneration might lead to a gain of signal that normally fails to reach downstream cells. Evidence suggests that both of these mechanisms may be at play, triggering different aspects of retinal remodeling.

The most obvious signal that is lost when photoreceptors degenerate is glutamate, the photoreceptor neurotransmitter. Rods and cones tonically release glutamate at their ribbon synapses, at a much higher rate than at conventional excitatory synapses. The loss of this signal might lead to compensatory changes in downstream neurons. However, other signaling molecules are also lost when photoreceptors die. This includes diffusible growth factors such as RdCVF, which has been implicated as the critical factor whose absence leads to cone death in RP models caused by rod-specific mutations (Léveillard et al. 2004, 2014). However, there is no evidence that the RdCVF receptor is expressed in downstream retinal neurons, ruling out a role for it as a trigger for remodeling. Other components that are lost include trans-synaptic adhesion proteins necessary for forming stabilizing synaptic connections between photoreceptors and bipolar cells (Burger et al. 2021, Orlandi et al. 2018). The possible downstream consequences of losing these molecular contacts have not been studied.

Homeostatic Plasticity Due to Loss of Photoreceptor Glutamate Release

Homeostatic plasticity broadly refers to any pre- or postsynaptic compensatory change that restores the set point of neuronal activity following a maladaptive perturbation (Davis 2013, Turrigiano & Nelson 2004). The loss of rods and cones in RP and AMD qualifies, as it eliminates glutamatergic synaptic transmission in the outer retina, perhaps triggering compensatory changes in the immediate downstream retinal neurons, namely, horizontal cells and bipolar cells. However, homeostatic plasticity can project through multiple stages of a neural circuit, with photoreceptor loss evoking changes in the activity of second-order neurons, which in turn might elicit changes in third-order neurons and so on. In principle, such a butterfly effect of homeostatic changes might apply throughout the retinal circuit into the brain. Homeostatic plasticity can apply during development, regulating the wiring of upstream to downstream neurons to compensate for changes in activity. Homeostatic plasticity can also apply to mature neural circuits, maintaining a given set point of activity in the face of diminishing input strength.

Homeostatic plasticity can involve changes in the intrinsic excitability of neurons, for example, up- or downregulation of voltage-gated ion channels (Debanne et al. 2019). One classic example of this is in developing *Xenopus* retinotectal circuits. As excitatory inputs become established, the number of voltage-gated Na^+ currents decreases, reducing intrinsic excitability (Pratt & Aizenman 2007). Experimentally silencing the synaptic inputs results in the opposite change—an increase in Na^+ current and augmented excitability. In another example, prolonged exposure to tetrodotoxin (TTX) causes hippocampal neurons to upregulate HCN and T-type calcium channels, leading to

hyperactivity when the TTX is removed (Rátkai et al. 2021). It is interesting that photoreceptor degeneration leads to upregulation of HCN channels in OFF-RGCs of rd1 and rd10 mouse retinas (Tochitsky et al. 2016), and it seems possible that this might be a pathological consequence of homeostatic plasticity in the retinal circuit.

Homeostatic plasticity can also manifest as changes in synaptic efficacy. In the developing hippocampus, quantal synaptic amplitude increases when spiking is suppressed in presynaptic neurons, consistent with an increase in postsynaptic glutamate receptors (Wierenga et al. 2006). After development is complete, blocking spikes also results in an increase in the frequency of quantal events, consistent with changes in presynaptic vesicular release (Burrone et al. 2002).

In the visual cortex, homeostatic plasticity can be evoked simply by depriving an animal of visual stimulation during development (Lee & Kirkwood 2019). For studies on the retina, various perturbations have been used to remove specific types of neurons and to then examine downstream consequences in the remainder of the retinal circuit. Photoreceptors can be ablated with exogenous chemicals, light damage, or laser photocoagulation (Lee et al. 2021). However, the most precise method involves genetic expression of diphtheria toxin receptors to enable selective rod- or cone-targeted ablation upon treatment with the toxin. For example, ablating half of the rods in the mouse retina leads to rebalancing of the strength of excitatory and inhibitory inputs to bipolar cells, resulting in partial recovery of RGC responses to compensate for the lost rod input (Care et al. 2019). Ablating most cones leads to changes in the receptive field properties of at least one type of RGC (the α-ON sustained RGC), slowing and prolonging responses and widening the receptive field surround (Care et al. 2020). These changes enhance the spatial and temporal integration properties of the RGC, partially compensating for cone loss. Other studies suggest that homeostatic plasticity is more widespread in the retinas of young mice than in mature mice (Shen et al. 2020). In young mice, eliminating half of the cones leads to expansion of synaptic inputs from remaining cones to several types of bipolar cell. In mature mice, homeostatic rewiring still occurs, but only in one type of bipolar cell.

These studies highlight the remarkable resilience of the retinal circuit to partial loss of photoreceptor input, but they do not address the molecular trigger of the compensatory changes. However, work on other systems suggests a strong candidate associated with homeostatic plasticity: Ca^{2+}. Depolarization that occurs during sustained activity almost always leads to elevated intracellular Ca^{2+}, which enters cells through voltage-gated Ca^{2+} channels, Ca^{2+}-permeant glutamate receptors, or both. Loss of photoreceptors may cause the opposite response—a fall in intracellular Ca^{2+}. Studies in other systems, including the cerebral cortex, indicate that Ca^{2+}-dependent sensors regulate the transcription, trafficking, and membrane insertion of postsynaptic receptors, leading to compensatory synaptic changes (Fitzpatrick & Kerschensteiner 2023). It is plausible that, in the same manner, Ca^{2+}-dependent mechanisms also trigger compensatory changes in retinal neurons.

Retinoic Acid

Recent studies point to a different signal as the trigger for remodeling in the degenerating retina: retinoic acid (RA). RA is a metabolite of vitamin A, which is of great importance for rod and cone phototransduction. However, during early development, RA plays a critical signaling role as a morphogen, establishing the anterior and posterior patterning in the early embryo (Duester 2008). Later in development, RA triggers differentiation of cells in the central nervous system; heart; pancreas; pituitary; and sensory organs, including the eye (Niederreither & Dollé 2008), where it has been implicated in excessive growth in myopia (Brown et al. 2022). However, the functional role of RA in the mature eye has been unclear. The canonical RA signaling pathway (**Figure 2**) begins with retinol, which accesses the RPE from the bloodstream. Retinol is converted into 11-*cis* retinaldehyde (i.e., 11-*cis* retinal), the critical chromophore that combines with opsins to form

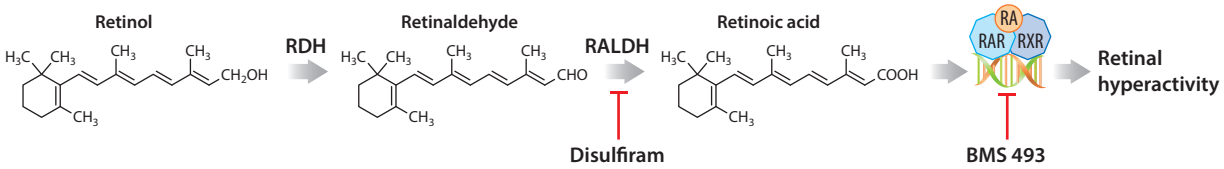

Figure 2

Retinoic acid (RA) signaling pathway and sites of action of anti-RA drugs. Figure adapted with permission from Telias et al. (2019).

light-sensitive rhodopsin or cone opsins. Once photoisomerized in the rod outer segments (ROSs), the all-*trans* photoisomer of retinaldehyde shuttles back to the RPE as part of the visual cycle. Rods, and to lesser extent cones, sequester an enormous amount of 11-*cis* retinal, as each human ROS harbors approximately 100 million copies of rhodopsin. The biosynthesis of retinaldehyde is tightly regulated (Palczewski & Kiser 2020), but many cells in the eye, including RPE and choroid cells, Müller glia, and retinal neurons, express one or more forms of retinaldehyde dehydrogenase (RALDH) (Amamoto et al. 2022, Harper et al. 2015), which converts excessive retinaldehyde into RA. The canonical signaling pathway activated by RA involves a nuclear RA receptor (RARα), which heterodimerizes with RXR and then binds to DNA at a specific sequence named the retinoic acid response element to enhance transcription of downstream genes.

The first hint that RA might be involved in retinal remodeling came from studies on bipolar cell dendritic sprouting in mice with a light-induced form of retinal degeneration (Lin et al. 2012). Exogenous RA triggered growth of neurites from bipolar cells cultured from these retinas, and inhibitors of RARα reduced dendritic sprouting in vivo. These findings led us to ask whether RA might also initiate physiological remodeling of RGCs (Telias et al. 2019, 2020), specifically in the case of membrane hyperpermeability due to P2X receptor upregulation and electrophysiological hyperactivity due to HCN channel upregulation. We found that the incidence of both phenomena was reduced in rd1 and rd10 mice when the RA signaling pathway was blocked. This was done either by inhibiting RALDH, the enzyme that synthesizes RA, or by inhibiting RARα, the receptor necessary for RA signal transduction. Injecting exogenous all-*trans* RA into a healthy wild-type mouse eye was sufficient to elicit some aspects of physiological remodeling. Finally, a GFP-based reporter gene assay demonstrated elevated RA-induced gene transcription in rd1 mice. Taken together, results from blocking, mimicking, and visualizing experiments all point to RA as the critical trigger for physiological remodeling, at least in RGCs.

Local atrophy of photoreceptors, induced by subretinal implantation of a metallic chip, also caused elevation of RA-induced gene expression in nearby RGCs, leading to local hyperactivity (Denlinger et al. 2020). This suggests that RA-induced hyperactivity might be a common sequel to photoreceptor loss, whether the underlying cause is hereditary, as in RP, or environmental, as in local retinal disorders such as AMD, which affects only the 2% of the retinal surface area that constitutes the macula.

It should be noted that RA has been implicated as a critical signal in homeostatic synaptic plasticity in hippocampal and cortical neurons (Chen et al. 2014). In contrast to its role as a regulator of gene transcription in retinal remodeling, RA regulates local protein translation in dendrites of brain neurons, a quite different mechanism.

IMPACT OF RETINOIC ACID–INDUCED REMODELING ON RETINAL INFORMATION PROCESSING AND VISION

The functional consequences of remodeling for retinal information processing and visual perception are only recently becoming clear. Heightened spontaneous RGC firing masks responses

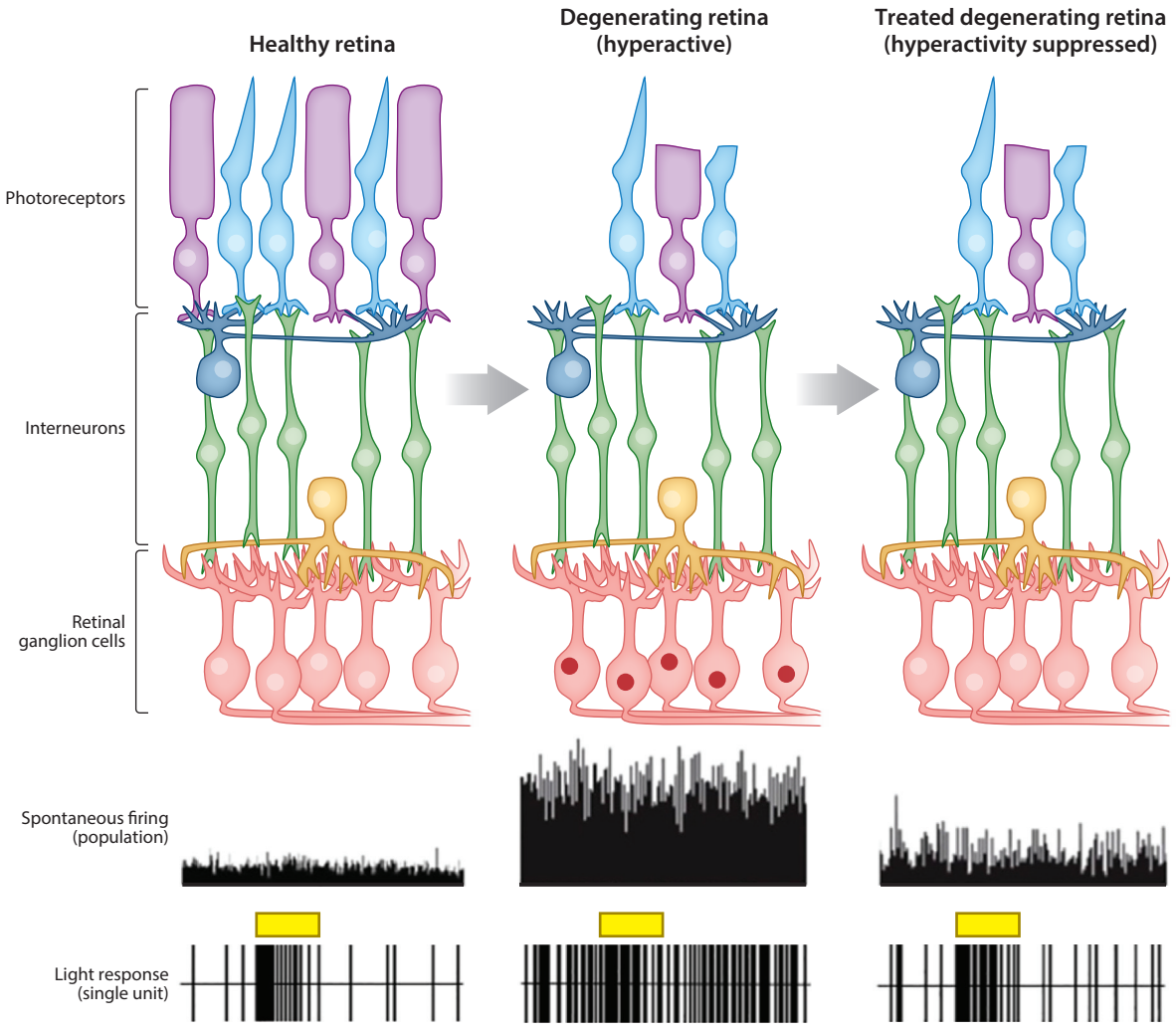

Figure 3

Illustrations showing how hyperactive firing may obscure encoding of light responses by retinal ganglion cells.

triggered by residual photoreceptors in rd10 mice (Telias et al. 2019, Toychiev et al. 2013) (**Figure 3**). Hence RALDH or RARα inhibitors reduce spontaneous firing in RGCs and unmask light responses, particularly those to low-intensity flashes (Telias et al. 2019).

It is not yet clear whether RA also induces changes in upstream retinal cell types such as the many different types of bipolar and amacrine cells. Preliminary evidence suggests that photoreceptor degeneration leads to reduced voltage-gated Ca^{2+} current in certain ON-bipolar cells, and this effect is also abrogated by inhibiting RA signaling (Kramer lab, unpublished observations). Increased gap junctions among amacrine cells and with bipolar cells is thought to contribute to the inner retinal oscillation that emerges after photoreceptor degeneration, but whether RA is the trigger for these events or whether a distinct mechanism is at play is unknown. Resolving this issue is particularly relevant as chemical uncouplers of gap junctions also unveil masked light responses in RGCs (Toychiev et al. 2013), correlated with eliminating the inner retinal oscillation. It will

be important to determine which is more important for corrupting the visual signal in rd10 mice, the enhanced intrinsic hyperactivity of RGCs or the emergence of oscillating synaptic inputs that drive burst firing in RGCs.

The corrupted light responses of RGCs are reflected in the response properties of neurons in the brain. Ca^{2+} imaging from the visual cortex of rd10 mice shows that neurons have much weaker orientation tuning than in wild-type mice with intact photoreceptors (Telias et al. 2022). However, inhibitors of RALDH or RARα sharpen orientation tuning in rd10 mice. RA inhibitors also increase the reliability of responses of cortical neurons to complex naturalistic scenes. These results indicate that RA-induced remodeling not only masks retinal responses to light, but also corrupts higher-order processing, consistent with it impairing visual perception.

To more directly test the effect of RA-induced remodeling on vision, Telias et al. (2022) performed visual behavioral experiments in which young rd10 mice were trained to respond to a high-contrast grating before photoreceptor degeneration was severe. Once mice learned the task, the contrast of the image was randomly altered during each presentation, generating an initial contrast-sensitivity curve. One month later when photoreceptor degeneration was severe, the images were presented once again. The contrast-sensitivity curve declined substantially in mice who had not received treatment with RALDH or RARα inhibitors. However, mice that had received the inhibitors had contrast-sensitivity relationships almost the same as those of wild-type mice (**Figure 4**). The observation that contrast sensitivity can be improved dramatically by RA inhibitors implies that RA-induced remodeling is a major contributor to impaired vision, at least at this stage of photoreceptor degeneration.

DOES FUNCTIONAL REMODELING APPLY TO HUMANS?

The evidence that RA triggers retinal hyperactivity and impairs vision in mouse models of RP is strong. However, while advanced RP in humans is associated with morphological remodeling (Jones et al. 2016), there is only circumstantial evidence for earlier physiological remodeling in the human retina, and whether RA might underlie any functional changes has not been explored. To directly test for RGC hyperactivity, electrophysiological recording from living human retinal tissue would be needed, specifically from donors with RP or AMD. Noninvasive methods appropriate for the intact human visual system include field potential recordings from the eye (electroretinogram) or brain (electroencephalogram) and radiological methods such as functional magnetic resonance imaging. However, these methods are designed to report stimulus-evoked responses, not spontaneous activity.

Nonetheless, there is indirect evidence for retinal hyperactivity in RP. Human subjects with RP experience shimmering photopsias (Bittner et al. 2009), suggestive of spontaneous RGC firing. They also have a heightened threshold for electrically induced phosphenes, consistent with interference by spontaneous retinal activity (Delbeke et al. 2001). RGC hyperactivity is a common feature of RP model retinas from the mouse, rat, rabbit, and dog (Nikonov et al. 2022), making it likely that the phenomenon occurs in humans with RP. RA is a highly labile molecule, so direct measurement from extracted retinal tissue or vitreous fluid is impractical, but analysis suggests an increase in RA-responsive gene transcription in RP (Telias et al. 2019). Nonetheless, the lack of direct evidence makes a potential human clinical trial with disulfiram particularly compelling (see below).

THERAPEUTIC OPPORTUNITIES TO IMPROVE VISION BY SUPPRESSING REMODELING

Despite RP being a progressive disorder, few patients reach complete loss of light perception. Most patients retain some functional photoreceptors throughout their lifetime, yet their vision

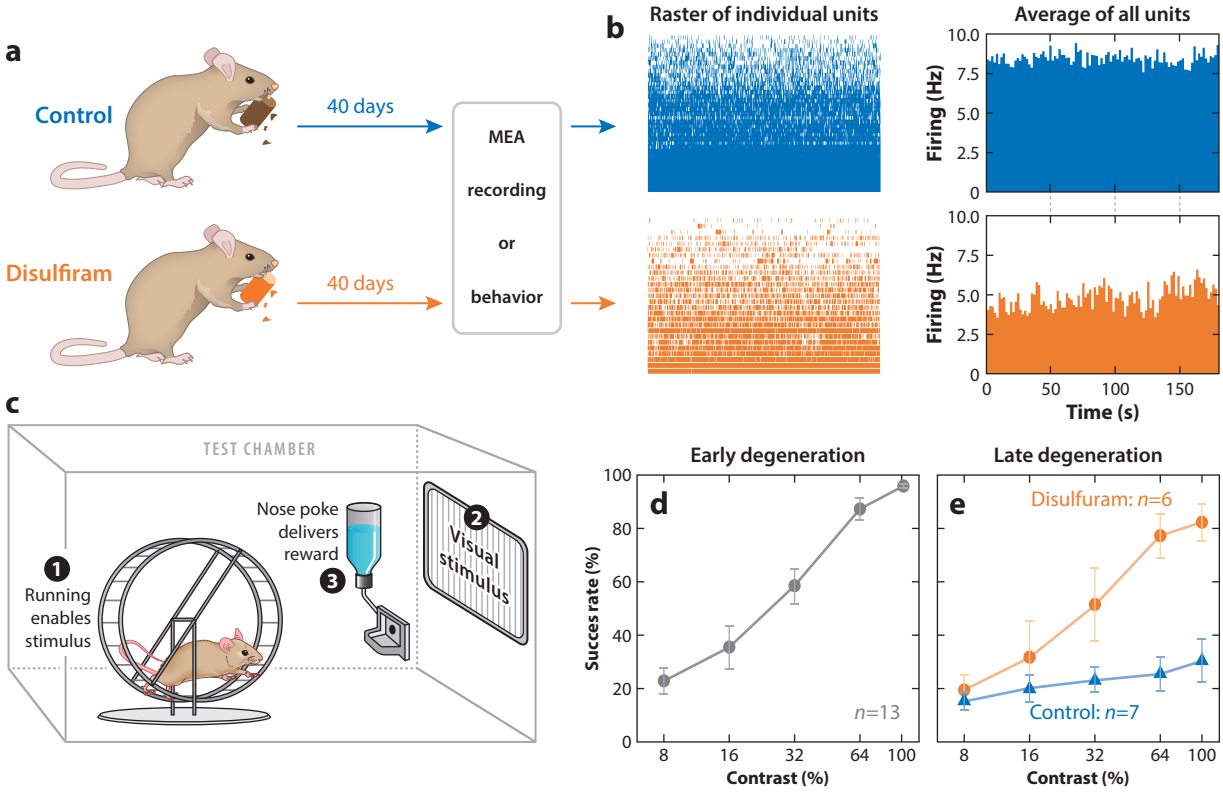

Figure 4

Suppression of hyperactivity and mitigation of vision loss in rd10 mice treated with disulfiram. (*a*) Treatment paradigm. (*b*) Multi-electrode array (MEA) recordings from rd10 retinas showing that disulfiram reduced spontaneous activity. Records show the raster of activity from approximately 50 retinal ganglion cells (RGCs) (*top*) and average firing (*bottom*). (*c*) Visual behavioral test chamber, based on operant conditioning to a visual cue paired with reward. (*d*) Contrast sensitivity of the mice early in degeneration [postnatal day (P) 40] and later in degeneration (P70). Note the reduced contrast sensitivity in control mice and the dramatic mitigation of vision loss with disulfiram treatment. Figure adapted with permission from Telias et al. (2022).

loss may be severe enough to qualify the patient as legally blind. However, if some of the visual deficit is caused by elevated RA, then inhibitors of RA synthesis or signaling might be therapeutic for improving vision in these patients.

Several agents are known to inhibit RALDH, but disulfiram is of particular interest because it is already an FDA-approved drug. Disulfiram (Antabuse®) is a nonspecific inhibitor of aldehyde dehydrogenases (ALDHs), including RALDH (Kragh 2008). For decades, the drug has been prescribed for chronic alcoholism. Ethanol is converted in the bloodstream into acetaldehyde, which is normally broken down by ALDHs. By preventing this reaction, disulfiram allows buildup of acetaldehyde, discouraging alcohol consumption by causing unpleasant hangover symptoms. In the absence of alcohol use, disulfiram has few side effects. Disulfiram crosses the blood–brain barrier, so it should have access to the retina. Because disulfiram is FDA approved, with safety established over decades, clinical trials on RP patients would face low regulatory hurdles. If disulfiram showed efficacy, then it could be administered orally, but local ocular delivery involving a new drug formulation might ultimately be more appropriate for avoiding any undesired systemic consequences associated with alcohol consumption. Disulfiram nonselectively inhibits all ALDH isozymes, but

new drug candidates that selectively target RALDH isoforms in the retina (Harper et al. 2015) might also help alleviate concerns about side effects.

While therapeutic inhibition of RALDH has immediate practical advantages because of the availability of disulfiram, these are offset by possible long-term detrimental consequences of suppressing aldehyde degradation. Furthermore, RA can promote survival of peripheral cones in the outer retina (Amamoto et al. 2022), and retinoid precursors can improve visual function in disorders involving impaired production of the visual chromophore (Koenekoop et al. 2014). The complex actions of RA on different cells and tissues in the eye ultimately may make RARα a better drug target for mitigating vision impairment.

RARα is important during eye development, but in the inner retina of adult wild-type mice with normal vision, it is largely inactive (Telias et al. 2019). This implies that local inhibition of RARα in the inner retina would produce few if any side effects on healthy retinal regions. BMS-493 inhibits RARα signaling with high affinity (100 nM range) (Germain et al. 2006), but it has not been tested therapeutically in humans. There are libraries of related RAR inhibitors developed by various pharmaceutical companies, many with high affinity and aqueous solubility and, therefore, potentially suitable for development as drug candidates.

As an alternative to pharmacological inhibition of RARα, molecular genetic tools can disrupt its function or prevent its expression. RA signaling can be inhibited with a dominant-negative version of RARα (RAR_{DN}), delivered with an AAV vector targeted to a selected retinal cell type. Viral expression of RAR_{DN} dramatically increased light sensitivity of learned visual behavioral responses in rd10 mice in vivo (Telias et al. 2019). Other strategies for suppressing RARα expression include CRISPR interference (CRISPRi) (Qi et al. 2013), antisense oligonucleotides, or siRNAs. siRNAs have generated considerable excitement as therapeutics in the eye (Dhiman et al. 2021, Gupta et al. 2021), as interference can persist for >6 months after a single intraocular injection.

Rescue of visual function by RAR might extend useful vision, but there is no evidence that it will slow photoreceptor degeneration itself. The strategy of rescuing vision with RA inhibitors is distinct from the strategy of restoring vision with retinal prosthetics, optogenetic or optopharmacological tools, or cell-based therapies. Most vision-restoration therapies are aimed, at least for now, at the small fraction of patients with end-stage photoreceptor degeneration, but treatments targeting the RA pathway may be relevant to the much larger patient population with low vision. Moreover, reducing RGC hyperactivity with RA inhibitors might be beneficial even after all of the photoreceptors have degenerated and light perception is absent (Barrett et al. 2015). Responses evoked by opto-electric (Dagnelie et al. 2017, Stronks & Dagnelie 2014), optogenetic (Bi et al. 2006), or optopharmacological stimulation of the degenerated retina (Tochitsky et al. 2018) are superimposed on the heightened background and oscillatory activity of RGCs, interfering with the proper encoding of visual images. The combination of a light-sensitive actuator with an RARα inhibitor could have a synergistic effect, boosting neural signals to more effectively restore visual function to patients with no light perception.

SUMMARY POINTS

1. Rod and cone photoreceptors degenerate in retinitis pigmentosa (RP) and age-related macular degeneration (AMD), gradually leading to loss of visual function.
2. Even though most downstream retinal neurons survive, they undergo changes known as remodeling. Physiological remodeling begins as photoreceptors are degenerating; morphological remodeling generally occurs later.

3. Early physiological changes include reduced synaptic transmission from ON-bipolar cells to retinal ganglion cells (RGCs), hyperactive firing of OFF-RGCs, and the emergence of oscillatory activity in the outer and inner retinal network.
4. Physiological remodeling corrupts the proper processing and encoding of information that is initiated by photoresponses in surviving rod and cone photoreceptors.
5. Experimental ablation of retinal neurons in mice results in electrophysiological changes in downstream retinal neurons that partially compensate for lost inputs, demonstrating the resilience of the retina.
6. However, in mouse models of RP, physiological remodeling of downstream neurons is largely maladaptive, with hyperactivity obscuring remaining light responses. Retinoic acid (RA) is the key signal that triggers hyperactive firing of RGCs.
7. Drugs that inhibit biosynthesis of RA by retinaldehyde dehydrogenase (RALDH) or signal transduction by the RA receptor (RAR) suppress retinal hyperactivity. These drugs also unmask neural responses to features of visual scenes, as revealed by electrophysiological recordings from the isolated retina and calcium imaging of the visual cortex in vivo.
8. Behavioral studies show that inhibitors of RALDH or RAR mitigate visual loss in a mouse model of progressive RP. How long vision is improved remains to be seen, but photoreceptor degeneration continues unabated after treating with RA inhibitors, suggesting that the vision-reviving effects may be temporary.

FUTURE ISSUES

1. Disulfiram, a small-molecule inhibitor of RALDH, is a Food and Drug Administration–approved drug used for decades as a treatment for chronic alcoholism. Future clinical trials in RP and AMD patients should reveal whether disulfiram can be repurposed for sustaining or reviving vision.
2. Gene therapy for inhibiting RALDH or RAR may offer longer-lasting solutions for sustaining or reviving vision corrupted by physiological remodeling. Options include adeno-associated virus–mediated delivery of a dominant-negative gene for RAR or RNA interference for suppressing expression of genes encoding RALDH or RAR subtypes.
3. Photoreceptor degeneration is often incomplete, with a single layer of cone photoreceptor somata remaining present in the retinas of animal models of RP and humans with RP. These remnant cones might be capable of generating small light responses, but signals transmitted to downstream neurons might be obscured by physiological remodeling, providing a ray of hope for reviving some vision even in advanced RP.
4. The molecular triggers for compensatory changes in the degenerating retina remain to be determined, but identification of these may offer additional therapeutic targets for mitigating vision loss.
5. Whether physiological or morphological remodeling triggered by photoreceptor loss is exhibited downstream in the lateral geniculate nucleus or superior colliculus remains to be determined. If changes do occur, it will be important to elucidate the molecular

mechanism of these changes, and it will be interesting to determine what effect these changes have on residual vision.

6. Physiological remodeling may also corrupt signals generated by new technological tools intended to restore vision to the blind, including retinal implants, optogenetic and optopharmacological agents, and stem cell–derived regenerated photoreceptors. The same treatments that unmask neural responses initiated by residual rods and cones may unmask responses triggered artificially by these tools, enhancing their effectiveness.

DISCLOSURE STATEMENT

R.H.K. is a founder and board member of Photoswitch Therapeutics, Inc., a company that aims to commercialize therapies for treating degenerative eye disorders, including photoswitch molecules and inhibitors of the RA signaling system.

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