

Review

Retinal remodeling during retinal degeneration

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Abstract

Retinal degenerations, regardless of the initiating event or gene defect, often result in a loss of photoreceptors. This formal deafferentation of the neural retina eliminates the intrinsic glutamatergic drive of the *sensory retina* and, perhaps more importantly, removes coordinated Ca^{++} -coupled signaling to the *neural retina*. As in other central nervous system degenerations, deafferentation activates remodeling. Neuronal remodeling is the common fate of all photoreceptor degenerations.

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Keywords: plasticity; computational molecular phenotyping; retina; remodeling; amacrine cell; photoreceptor; ganglion cell; bipolar cell; horizontal cell; retinitis pigmentosa; RCS; *rd1*; *rd2*; *or^l*; *pcd*; *nr^l*; GHL; *rhoΔCTA*; TG9N; *rdcl*; P23H; S334ter; *or^l + P27Kip1^{-/-}*; *rho^{-/-}*; *elovl4^{-/-}*; hrhoG; hrhoG(H); hrhoG + *rd1*; light damage

1. Introduction

Many forms of blindness, particularly those arising from photoreceptor degenerations, have no satisfactory resolution, which has inspired prosthetic and biological schemes to rescue or reconstruct retinal tissues. But does the neural retina remain receptive to such intervention? Though the neural retina grossly *appears* to survive the loss of its photoreceptors in retinitis pigmentosa and age-related macular degeneration, most brain pathways are clearly not so forgiving. Is the retina really different? The answer is: no.

Of the retinal degenerative diseases, retinitis pigmentosa (RP) is the best characterized (Bird, 1995) with an incidence of approximately 1 in 3500–4000 (Bunker et al., 1984) and involves more than 40 known genes, with many mutations in the rhodopsin gene (<http://www.sph.uth.tmc.edu/RetNet/>). Over 160 gene loci have been associated with retinal degenerations (Farrar et al., 2002). RP and its allied diseases (e.g. the cone and cone/rod dystrophies), age-related macular degeneration and

environmental challenges to the retina, all stress and kill photoreceptors. Roughly speaking, most retinal degenerations fall into three forms: rod-degenerative forms, the mixed rod/cone-degenerative forms or debris-associated forms (e.g. *merlk* defects and light damage). Though these forms have differing specific mechanisms and dependencies, and may trigger diverse modalities of cell death, all share a common outcome: photoreceptor loss and neuronal remodeling.

Our laboratory employs a fusion of molecular and computational technologies (Computational Molecular Phenotyping: CMP) to concurrently visualize sets of small molecules with subcellular resolution, allowing a multi-dimensional segmentation of cell classes in normal retinal tissues with the aim of cataloging cell classes and elucidating their circuitries. We have used CMP to screen samples of human RP (Fig. 1), as well as natural and engineered rodent models of retinal disease, examining all cell types in 18 human cases of RP and greater than 200 cases of rodent retinal degenerations encompassing 18 different models. We concurrently visualized glial transformations, neuronal translocations, neuronal loss and the emergence of ectopic neurite complexes. The fusion of phenotyping and ultra-structure also enabled the visualization of novel synaptic assemblies, illustrating that the degenerating retina produces new synapses with vigor. Though these seeming plasticities might be exploited to rescue vision, the new circuitry is more likely corruptive of visual processing and reflects, we believe, attempts by neurons to find synaptic excitation.

Abbreviations RP, retinitis pigmentosa; CMP, computational molecular phenotyping; RCS, Royal College of Surgeons; RPE, retinal pigment epithelium; CORD, cone/rod dystrophies; LD, light damage; AMD, age related macular degeneration.

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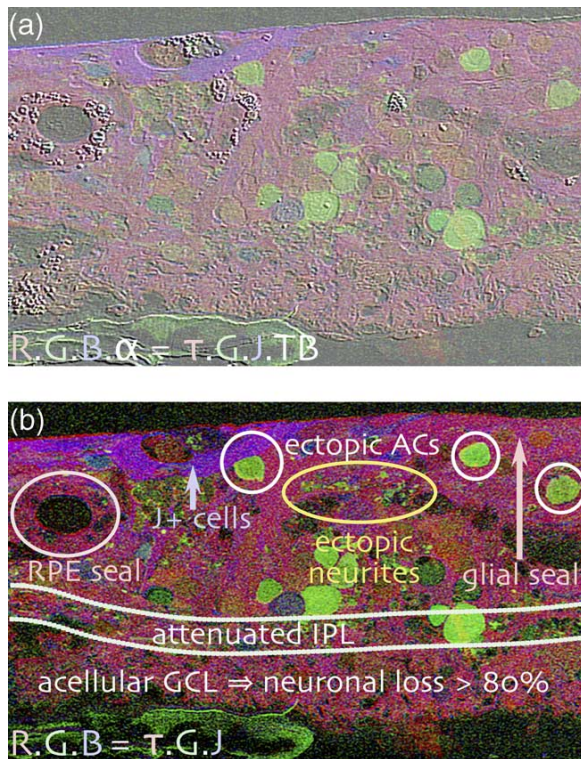


Fig. 1. Molecular imaging of late stage remodeling in human retinitis pigmentosa. (1a) A CMP map of $\tau\text{GJ:phase} \rightarrow \text{rgb}:\alpha$ signals. This notation indicated that taurine (τ) signals are mapped to the red (r) channel, glycine (G) to the green (g) channel, glutathione (J) to the blue (b) channel, and phase contrast signals to a grey-scale alpha (α) overlay channel. The phase overlay shows the presence of phase-bright melanosomes from migratory RPE cells throughout the retina. (1b) CMP map of $\tau\text{GJ} \rightarrow \text{rgb}$ signals highlighting specific cell classes with image annotations indicating major defects. Remnant Müller cells have a strong τ signal and are red. Isolated glycinergic amacrine cells (ACs) are bright green and novel, unidentified glutathione-rich (J+) cells are blue. Image width = 183 μm . Modified from Jones et al. (2003a,b).

Even minor rewiring may corrupt signal processing in retinal pathways, leaving many current approaches to bionic and biological retinal rescue unsustainable. The ultimate conclusion is that the sequelae of retinal degenerative disease are far more complex than previously believed, and schemes to rescue vision via bionic implants or stem/engineered cells are based on presumed preservation of normal wiring and cell population patterning after photoreceptor death. Those beliefs are incorrect: retinal neurons die, migrate, and create new circuitries. Vision rescue strategies need to be refined.

2. History of retinal remodeling

2.1. Why was retinal remodeling overlooked despite years of work in retinal degenerations?

Certainly, the impetus to analyze remnant tissues held little motivation after photoreceptor death, but

the progression of strategies to rescue vision in these retinas has brought issues related to the status of the neural retina into the forefront. Most papers concerned with the survival of the neural retina after photoreceptor loss have focused on simple cell counts to document numbers of cells surviving as opposed to documenting specific changes occurring in the surviving cohorts. Another major issue has been the availability of aged animals. Most researchers have been interested in models that have rapid photoreceptor degeneration times because of cost and convenience. Once the photoreceptors degenerated, there was little reason to maintain the animals, and animals aged two or more years were rare. However, it should be noted that a mouse retina is about 1% the area of a human retina and, assuming the same *spatial rate of progression* from initial disease foci, a 2-year-old *rd1* mouse may have experienced the equal of decades of human RP progression. The third and perhaps most important reason preventing the recognition of these fundamental changes in retina historically has been a lack of appropriate tools which can visualize all of the changes occurring in retina. Clinical observations observed in fundoscopic examinations of the retina of patients with retinal degeneration commonly reveal an ischemic appearance with a waxy, pale optic nerve head with brown or black pigmented 'bone spicules' observed in the periphery. However, this level of examination, and common histologic stains like Toluidine blue are impoverished methods for phenotyping tissues, particularly early events. The development of CMP has allowed us to data-mine every sample, revealing normal and abnormal circuitry, neuronal phenotype revision, and cellular translocation events invisible to standard histological approaches.

Neuronal remodeling is not a new concept and has been extensively documented by the epilepsy (Represa and Ben-Ari, 1992; Pollard et al., 1994; Sutula, 2002; Koyama et al., 2004) and learning/memory communities (Van Reempts et al., 1992; Doubell and Stewart, 1993; Gao et al., 1998). Moreover, indications of altered circuitry in retinal degenerations were noted by Kolb and Gouras (1974). The concept of remodeling in the retina did not really take hold until later studies of abnormal changes in the inner retina following photoreceptor degeneration, including sprouting of photoreceptors and horizontal cells. Machida et al. (2000) implied that photoreceptor synaptic remodeling may occur during photoreceptor degeneration and Strettoi and Pignatelli demonstrated specific changes occurring in the bipolar and horizontal cell populations in the *rd1* mouse after photoreceptor loss (Strettoi and Pignatelli, 2000; Strettoi et al., 2002). Milam et al. (1998) noted that pathological features in human RP correlate with those in the Royal College of Surgeons (RCS) rat, and demonstrated sprouting in horizontal cells and rod neurites in human tissue samples from patients with RP (Fariss et al., 2000). Other studies examining specifically early changes in the circuitry of the neural retina in photoreceptor degenerative events document a progressive event having

strong implications for therapeutic intervention (Banin et al., 1999; Peng et al., 2000; Strettoi and Pignatelli, 2000; Aleman et al., 2001; Strettoi et al., 2003). Taken together, these studies provide significant evidence that the retina, like CNS, exhibits remodeling in response to loss of afferent input. Despite these earlier studies, the perception that photoreceptor degeneration spares the neural retina from *consequential* changes persisted (Scarlati, 2000; Chow et al., 2002; Margalit et al., 2002; Zrenner, 2002; Chow et al., 2004). In retrospect, it is clear that a compelling case for linkage among the processes of retinal degeneration in humans or animal models and CNS neuropathologies had not been achieved. But it is also clear that many of these phenomena superficially resembled neural plasticity and likely affirmed strongly held views of retinal resilience in disease.

While this apparent *negative* plasticity might complicate or preclude the use of biological implants, it might prove advantageous to retinal rescue. But we do not yet know the practical intervention windows, and RP arising from different primary defects appears to progress at different rates (Jones et al., 2003a,b). Several studies attempted to document survivor neuron cohorts by examining the preservation of the ganglion cells in retinas from patients with RP including those diagnosed with moderate and severe forms of the disease (Stone et al., 1992; Santos et al., 1997; Humayun et al., 1999). Of these studies, one found approximately 20% of inner nuclear layer cells are lost in the macula of late stage RP patients (Santos et al., 1997) and another documented 20% survival in regions peripheral to the macula (Humayun et al., 1999). Losses are far more severe in peripheral retina and even these apparently small losses can be devastating (Marc and Jones, 2003). Anatomical surveys of the macula in human RP (Stone et al., 1992; Santos et al., 1997; Humayun et al., 1999) show variable ganglion cell loss, from mild to severe, but well-preserved regions of the neural retina invariably possess surviving sensory retina harboring cones, suggesting that cone loss and subsequent neuronal loss are related.

However, overt remodeling and perhaps even more cryptic molecular changes clearly start as soon as photoreceptors become stressed. Analyses of acquired (de Raad et al., 1996) and inherited (Fletcher and Kalloniatis, 1996) rodent degeneration models reveal subtle changes in cellular molecular phenotypes in the neural retina, some even preceding rod degeneration (Fletcher and Kalloniatis, 1996). Subtle remodeling of rod pathways emerges rapidly in the *rd1* mouse (Strettoi and Pignatelli, 2000; Strettoi et al., 2002), where a phototransduction defect evokes death of rods by postnatal day (pnd) 21. Rod driven bipolar cells and horizontal cell axon terminals retract their fine dendrites, and rod bipolar cell axon terminals assume immature synaptic structures. Defects extend to cone circuits with both cones (Fei, 2002) and cone horizontal cells (Strettoi et al., 2002) in the young *rd1* mouse sprouting new neurites. During human rod degeneration, surviving

rods, horizontal and amacrine cells similarly extend anomalous neurites throughout the retina (Fariss et al., 2000). But many human and rodent retinal degenerations progress slowly, and no consensus on the fate of the inner retina emerged as aged rodent retinal degeneration specimens are rare and studies rarely extend beyond pnd 90. But continuing work from our laboratory and several others have begun to fill this gap and we now understand the retinal remodeling is the *norm*.

3. Retinal remodeling: phases and patterns of expression

We began our work in retinal degeneration after CMP-profiling samples of aged human retina from patients with RP, which revealed confusing and profound alterations in neural retinal structure (Fig. 1). Did animal models of retinal degeneration maintain their neural structure and circuitry, as implied in the literature? Was human remodeling a spurious conflation of disease and long-life? The answers were: no and no. CMP-profiling of numerous retinal disease models now show that all known retinal degenerations trigger remodeling and that animal models accurately reflect the phenomena underlying human disease. From animal models we have been able to reconstruct the three basic phases of remodeling.

Retinal remodeling of the neural retina becomes obvious only after cone input to the neural retina has been eliminated, but actually starts long before the first rod dies. Retinal remodeling proceeds through three distinct phases: 1, photoreceptor stress; 2, photoreceptor death and 3, complex neural remodeling, (Fig. 2). Ultimately, photoreceptor cell death is followed by progressive neural degeneration and remodeling, radically transforming the retina. In brief, after retinal photoreceptor loss, Phase 3 encompasses a set of stereotyped events including, but are not limited to, Müller cell hypertrophy, and focal migration of survivor neurons of all classes to ectopic sites, and migration of retinal pigment epithelium (RPE) into the neural retina (Figs. 1 and 2). Additionally, survivor neurons display unexpected plasticity, rewiring the remnant inner plexiform layer and forming thousands of novel ectopic microneuromas per square millimeter in the remnant inner nuclear layer, with bipolar, amacrine and ganglion cells engaging in new circuit topologies, and often displaying novel presynaptic architectures (Jones et al., 2003a,b; Marc and Jones, 2003; Marc et al., 2003). This review focuses on Phase 3 remodeling, but we will briefly mention Phase 1 and 2.

3.1. Phase 1: photoreceptor stress

Retinal degenerations trigger the process of photoreceptor phenotype deconstruction, often manifested as the shortening of rods (Fig. 2b). In the RPE-mediated retinal degenerations, early indications of disorder are shown through alterations in the molecular signatures of

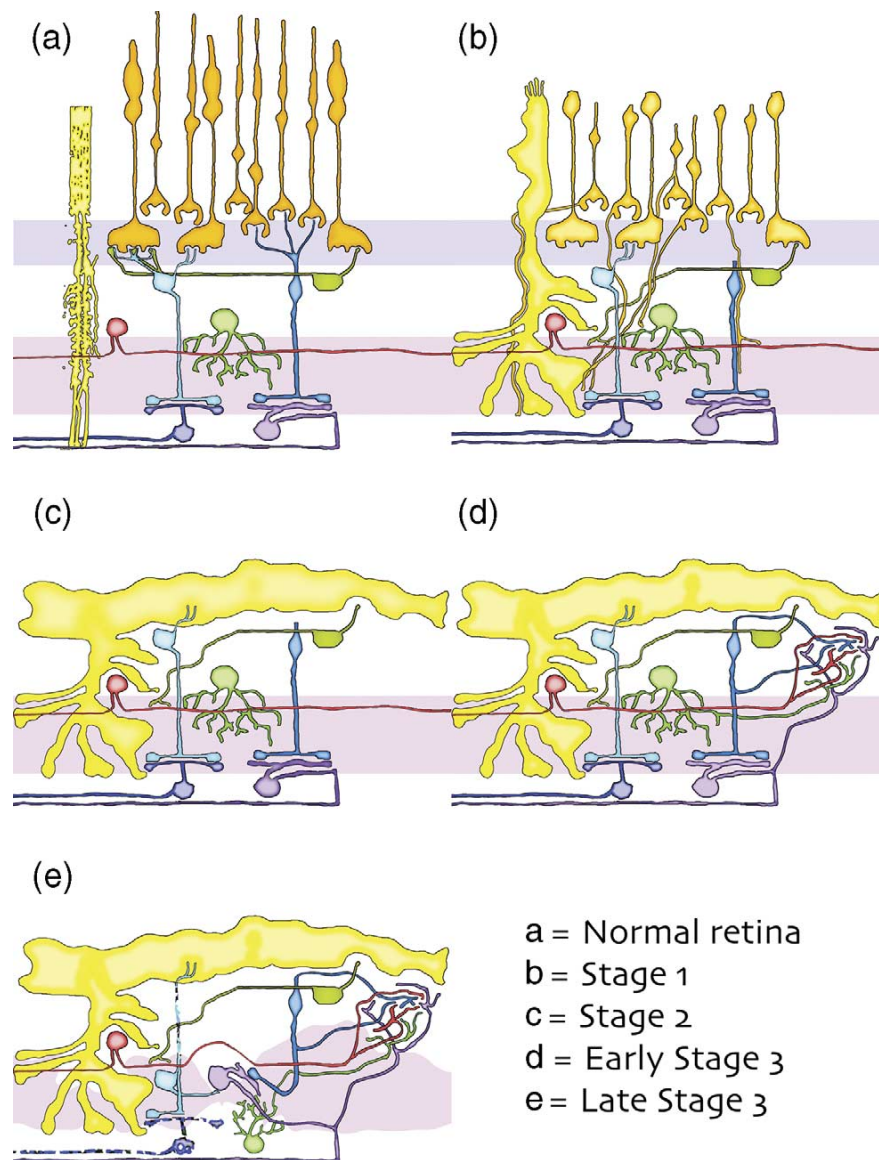


Fig. 2. A schematic representation of the three stages of retinal degeneration showing both rod and cone photoreceptors in orange, rod and cone bipolar cells in light and dark blue, ganglion cells in light and dark purple, a horizontal cell in olive, GABAergic amacrine cells in red and glycinergic amacrine cells in green. A Müller cell is shown in yellow with the two plexiform layers as horizontal bands. (a) Shows normal lamination and connectivity of cell classes in the retina. (b) Reveals early photoreceptor stress (pale orange in photoreceptors) and outer segment shortening along with rod and cone neurite extensions projecting down into inner nuclear layer and ganglion cell layer. Horizontal cells are also seen contributing to the neurite projections along with rod and cone bipolar cells undergoing dendrite retraction. Müller cells may also begin to hypertrophy in this stage. Stage 2 shown in (c) demonstrates a complete loss of photoreceptors and elaboration of a Müller cell seal over the entire neural retina, sealing it-off away from the remnant choroid. Early stage 3 events ensue in (d) with the elaboration of neurite extensions from glycinergic and GABAergic amacrine cells along with contributions from bipolar cells and ganglion cells into complex tangles of processes called microneuromas that form outside the normal lamination of the inner plexiform layer, sometimes merging with the inner plexiform layer. These microneuromas possess active synaptic elements corruptive of normal signaling. (e) Demonstrates the final phase of retinal degeneration with degeneration and cell death of many cell classes. Cellular translocation events also occur in this stage with bi-directional movements of cells from the inner nuclear layer and ganglion cell layer. Specifically, amacrine cells are commonly observed migrating into the ganglion cell layer and ganglion cells can be observed migrating into the inner nuclear layer. Also major alterations in the normal lamination of the inner plexiform layer can be observed.

RPE cells and their uncoupling (Jones et al., 2003a,b). Regardless of initial insult, stressed photoreceptors begin to deconstruct their synaptic terminals, sprouting neurites that bypass their normal targets (bipolar and horizontal cells)

and extend as far as the ganglion cell layer (Fig. 2b). Often these processes are marked by delocalized rhodopsin (Milam et al., 1996). Before cell death, rods may retract their processes, but we have also found that rare rod cells in

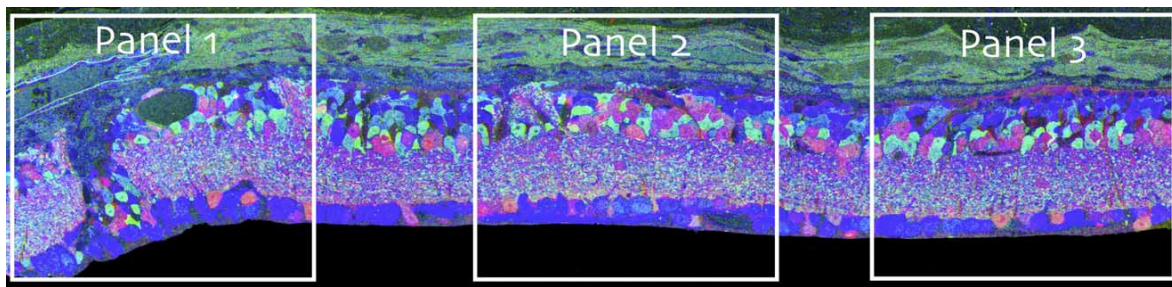


Fig. 3. A $\gamma\text{GE} \rightarrow \text{rgb}$ map (γ GABA, G glycine, E glutamate, see caption 1 for details) of late stage remodeling in a rodent model with a human rhodopsin-GFP fusion protein gene knockin expressed at low (16%) efficiency (see Doubell and Stewart, 1993). Three panels indicate regions manifesting key features of remodeling. Panel 1 includes a large migration column, a fluid channel and a large microneuroma eruption. Panel 2 illustrates the diversity and density of microneuromas. Panel 3 demonstrates that cone survival is associated with inhibition of remodeling. Image width=641 μm .

human RP might migrate into the inner nuclear layer and survive. This sprouting resembles that seen in early rod and cone photoreceptor development in the ferret: photoreceptor neurites project to the inner plexiform layer and retract as the outer plexiform layer matures (Johnson et al., 1999). However, during development and in retinal reattachment (Fisher and Lewis, 2003) retraction of neurites does not necessarily presage cell death as in retinal degenerations. This failure of synaptic signaling also triggers a range of rewiring events, including retraction of bipolar cell dendrites, switching of synaptic targets by bipolar cells, and anomalous extension of horizontal cell processes into the inner plexiform layer.

3.2. Phase 2: photoreceptor death

Though relatively brief, Phase 2 is complex, entailing a significant amount of debris removal by microglia, and bystander or trophic effects that ultimately lead to the death of most photoreceptors. Though small clusters of cones may survive in some systems (Figs. 3 and 6), the signature

event of Phase 2 is the formation a distal fibrotic glial seal composed of Müller cell distal processes (Figs. 2c and 6). This seal almost completely walls-off the neural retina from the remnant subretinal space, the remnant RPE and choriocapillaris (Fig. 2c). There are occasional gaps in the seal and these are sites of later RPE invasion, and perhaps more troubling, neuronal escape from the retina. For reasons yet unknown, seal-associated Müller cells express abnormally high glutamine levels (Fig. 1b). Unlike their aberrant behavior in retinal detachment though (Marc et al., 1998), any abnormal glutamate release due to photoreceptor cell death seems fully buffered by the Müller cells and glutamine synthetase expression appear unaltered. Even so, the metabolic regime and profile of these cells has apparently altered irreversibly. Neuronal death may also begin in phase two (Marc and Jones, 2003). After completion of the glial seal, Phase 3 remodeling of the neural retina begins with vigor (Fig. 2d) and involves all populations in the retina including horizontal cells, bipolar cells, amacrine cell and ganglion cells (Jones et al., 2003a,b).

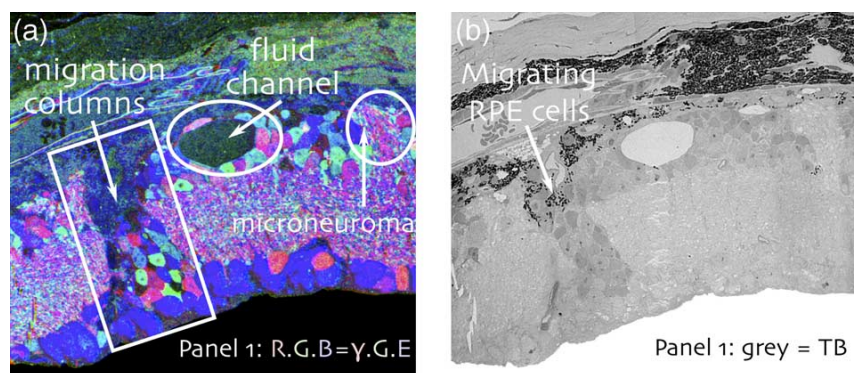


Fig. 4. (a) A $\gamma\text{GE} \rightarrow \text{rgb}$ map (γ GABA, G glycine, E glutamate, see caption 1 for details) of Panel 1 from Fig. 1, displaying a large migration column containing a mixture of GABAergic amacrine cells (red), glycinergic amacrine cells (green) and bipolar cells (blue and cyan). All of these cells are displaced from their normal loci and are closely associated with a large trunk of Müller cells (black spaces in the column). The void, labeled fluid channel is common in human and rodent retinal degenerations and may represent the inability of Müller cells to complete transretinal water transport after formation of the distal seal. The microneuroma in this panel is an eruption of processes from the inner plexiform layer that reach all the way to the remnant retinal pigmented epithelium. (b) A greyscale toluidine blue brightfield image of Panel 1 from Fig. 1, showing that RPE cells invade the neural retina in artificially induced retinal degeneration in a manner resembling normal human retinitis pigmentosa. Image width = 183 μm .

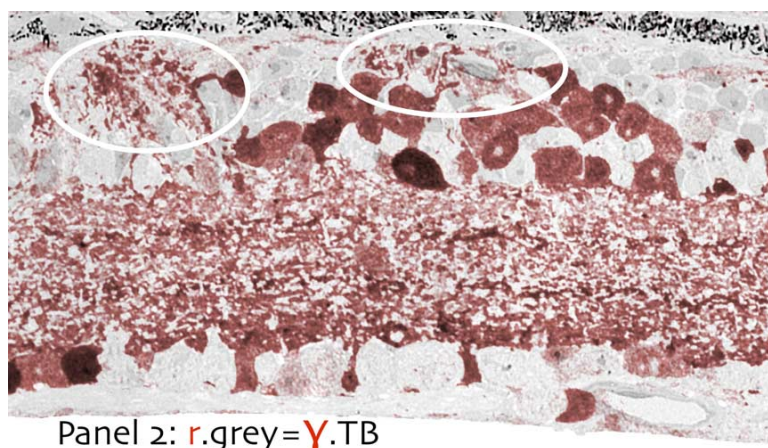


Fig. 5. An alternate image mapping of Panel 2 in Fig. 2, a greyscale image with $+ \gamma \rightarrow r$ density mapping of GABAergic amacrine cells forming multiple, focal microneuromas (circled). Note that each microneuroma receives processes from nearby amacrine cells that appear to have migrated distally in the retina, rather than proximally as in Fig. 3a. Image width = 167 μm .

3.3. Phase 3: neuronal remodeling

As neurons are increasingly isolated from excitatory synaptic contacts (in part due to reactive bipolar cell dendritic loss in Phase 1 and loss of bipolar cell drive in the inner plexiform layer) and the large Ca^{++} currents that they modulate, all surviving cell classes in the retina become vulnerable to cell death. As neurons die, the retina begins to thin leaving the Müller cells to partially fill vacated space. These new glial surfaces clearly serve as preferred pathways for neuronal migration and process extension. As Müller cells themselves hypertrophy and migrate, they may distort lamination of the inner and outer plexiform layers (Fig. 2e). Additionally, RPE cells migrate into the retina often with accompanying choroidal vessels, through gaps in the glial seal, displacing inner nuclear layer cells (Fig. 1a). Amacrine cells begin to migrate along glial columns down into the ganglion cell layer and microneuromas are formed (Figs. 2(e)–4). Microneuromas are tangles of GABAergic, amacrine cell, glycinergic amacrine cell, glutamatergic bipolar cell and ganglion cell processes, ranging from 20 to over 100 μm in diameter and exceeding 30 000/retina in some models (GHL, TG9N, RCS and most notably, hrhoG; see below). Many microneuromas merge with the existing inner and outer plexiform layers (Fig. 5) and contain numerous synapses formed de novo. We are able to fuse CMP datasets with conventional electron microscopy (Marc and Liu, 2000), enabling classification of participating elements in microneuromas. Both conventional and ribbon synapses are abundant and display all common synaptic arrangements (amacrine $\rightarrow$ amacrine, amacrine $\rightarrow$ bipolar, amacrine $\rightarrow$ ganglion cell, bipolar $\rightarrow$ amacrine, bipolar $\rightarrow$ ganglion cell) as well as a clear, though infrequent instances of bipolar $\rightarrow$ bipolar contacts (Jones et al., 2003a,b; Marc et al., 2003). Additionally, large

fascicles of mixed neurites course long distances through the retina, especially beneath the glial seal. With these fascicles, processes from ganglion cells, GABAergic amacrine cells, glycinergic amacrine cells and bipolar cells, apparently segregate and run together as sub-fascicles (Jones et al., 2003a,b). This massive reorganization is best summarized in the simple term ‘rewiring’, and we have been able to show that many instances of rewiring lead to anomalous circuitry (see sections on Corrupt visual circuitry and Self-signaling).

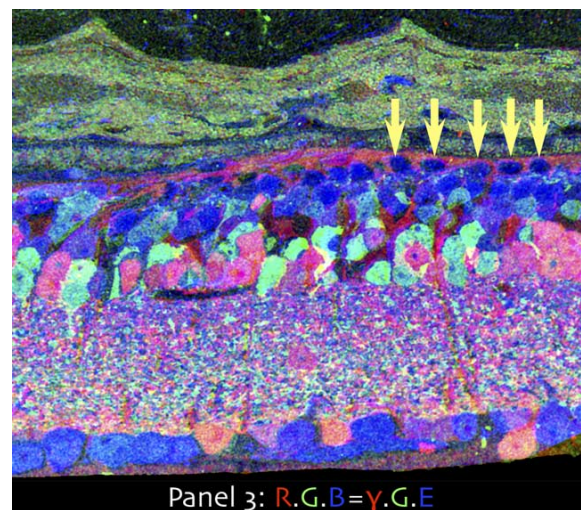


Fig. 6. A $\gamma\text{GE} \rightarrow \text{rgb}$ map (γ GABA, G glycine, E glutamate, see caption 1 for details) from Fig. 3, Panel 3 displaying the maintenance of normal lamination and neurite patterning in the presence of cones (arrows) albeit highly transformed and trapped beneath the glial seal (red band beneath arrows). This normal zone is, nevertheless, within 200 μm of highly remodeled retina on either side, suggesting that preservation of normal structure depends on spatially constrained signals such as synaptic contact. Image width = 145 μm .

4. Specific models and their defects

Remodeling is a general phenomenon but displays variations in speed and coherence that likely derive from the nature and duration of photoreceptor stress and death. Over twenty specific models of retinal degeneration have been analyzed (Table 1) in addition to tissues from RP human patients. Specific systems include natural (RCS rat, *rd1* mouse, *rd2* mouse, *or^f* mouse, *pcd* mouse, and *nr^f* mouse), transgenic (Tg GHL mouse, Tg rhoΔCTA mouse, Tg TG9N mouse, Tg *rdcl* mouse, Tg P23H rat [3 lines], Tg S334ter rat [4 lines], knockout (*or^f* + *P27Kip1*^{−/−} mouse, *rho*^{−/−} mouse, *elovl4*^{−/−} mouse), knockin (GFP-human rhodopsin fusion hrhoG, hrhoG(H), hrhoG + *rd1*) and the induced light damage (LD rat) rodent models (Table 1).

4.1. RCS rat

The RCS rat possesses a naturally occurring deletion mutation in the receptor tyrosine kinase gene, *merlk* that impairs the ability of the RPE to phagocytose shed photoreceptor outer segments (D' Cruz et al., 2000), resulting in a buildup of debris in the subretinal space that potentially generates cytotoxic and genotoxic lipid-derived aldehydes and free radicals. Onset of retinal remodeling in

the RCS rat is not as rapid as in highly coherent photoreceptor degeneration models (e.g. TG9N mouse), but is clearly advanced by pnd 270. RCS remodeling demonstrates dramatic reorganization of the neural retina including the inner nuclear layer and ganglion cell layers. Previous work has indicated there may be anomalous, unexplained Müller cell glutamate/glutamine processing in Phase 1, before photoreceptor death can be detected (Fletcher and Kalloniatis, 1996) as well as changes in NMDA receptor expression (Grunder et al., 2001). However, RCS rats exhibit all of the sequelae of remodeling including Müller cell hypertrophy, seals and columns. Displaced RPE cells embedded within the neural retina are common, as are columns of apical RPE processes that span the retina. Large avascular, aqueous channels form within the neural retina perhaps due to sealing the neural retina from the RPE-choriocapillaris transport system, eliminating a major pathway for retinal water export. Inner nuclear layer neurons aggressively migrate to the ganglion cell layer and some ganglion cells move towards the distal retina, along with massive focal loss of ganglion cells, bipolar cell and amacrine cells even in central retina (Jones et al., 2002, 2003a,b; Marc et al., 2003). Neurons of all classes, including horizontal (Chu et al., 1993), bipolar, amacrine and ganglion elaborate processes that form random fascicles

Table 1

Model	Genes	Cellular defect	Human phenotype	Reference
N RCS Rat	<i>merlk</i>	Tyrosine kinase signaling errors, debris stress	arRP	LaVail et al. (1975), D' Cruz et al. (2000)
N <i>rd1</i> Mouse	<i>PDE6B</i> ^{<i>rd1</i>}	Cytotoxic rod cGMP elevation in development	arRP	Keeler (1966), Pittler et al. (1993)
N <i>rd2</i> Mouse	<i>prph2</i>	Outer segment developmental failure	adRP	van Nie et al. (1978)
N <i>or^f</i> Mouse	<i>Chx10</i>	Developmental hypocellularity	Microphthalmia	Robb et al. (1978), Burmeister et al. (1996)
N <i>pcd</i> Mouse	<i>agtpbp1</i>	Purkinje cell degeneration	Spinal Muscular Atrophy	Blanks et al. (1982), LaVail et al. (1982)
N <i>nr^f</i> Mouse	?	Unknown, Chromosome 8	Tremors	Landis (1975), LaVail et al. (1993), Campbell and Hess (1996)
Tg GHL mouse	<i>Rho</i>	Protein aggregation/proteasome stress	adRP	Frederick et al. (2001)
Tg rhoΔCTA mouse	<i>Rho</i>	Rho phosphorylation sites lost, inactivation defect	adRP	Jones et al. (2003a,b)
Tg TG9N mouse	<i>RGS9</i>	Unknown, disruption of GAP complex formation?	CORD	Chen et al. (1993)
Tg <i>rdcl</i> mouse	<i>PDE6B</i> , <i>LCR</i>	Rod cGMP elevation, cone LCR-driven toxin expression	CORD	Freedman et al. (1999)
Tg P23H rat	<i>Rho</i>	Protein aggregation/proteasome stress	adRP	Steinberg et al. (1996), Machida et al. (2000)
Tg S334ter rat	<i>Rho</i>	Rho phosphorylation sites lost, inactivation defect	adRP	Steinberg et al. (1996)
<i>or^f</i> + <i>P27Kip1</i> ^{−/−} knockout mouse	<i>or^f</i> , <i>P27Kip1</i> ^{−/−}	Partial hypocellularity rescue	Microphthalmia	Green et al. (2003)
<i>rho</i> ^{−/−}	<i>Rho</i>	Outer segment developmental failure	arRP	Humphries et al. (1997)
<i>elovl4</i> ^{−/−}	<i>elovl4</i>	Stargardt like macular dystrophy	adMacular Dystrophy	Zhang et al. (2001)
HrhoG knockin mouse	<i>Rho</i> + <i>GFP</i>	Insertion of GFP at Rho C-terminal	?	Chan et al. (2004)
LD Albino Rat	<i>Tyr</i> , <i>RPE65</i>	Albinism, retinoid processing stress	AMD	Gorn and Kuwabara (1967)

outside the normal lamination of the plexiform layers (Jones et al., 2003a,b; Marc and Jones, 2003; Marc et al., 2003). Vascular invasion has also been well documented (Villegas-Perez et al., 1998), leading to compression of retinal structures, constrictions of IPL (Jones et al., 2003a,b; Marc et al., 2003) and compromise of ganglion cell viability (Wang et al., 2003). Additionally, myelinated processes have been observed in the RCS rats (Jones et al., 2003a,b; Sullivan et al., 2003) raising the possibility that ganglion cells generate intraretinal axonal fields that likely contribute to corruptive circuitry within the retina (Jones et al., 2003a,b; Marc and Jones, 2003; Marc et al., 2003; Peng et al., 2003).

4.2. *rd1* mouse

The *rd1* mouse contains a nonsense mutation in the PDE6 β subunit gene, which prematurely truncates the PDE6 β protein (Bowes et al., 1990) and renders the animal unable to form functional PDE $\alpha\beta$ heteromers, leading to elevated cGMP throughout development, which is ultimately lethal to rods (Lolley, 1994). Retinal remodeling in this system, despite the speed of rod death, is also rather slow, but is severely advanced by pnd 610. All remodeling phenomena of the RCS model are present in the *rd1* mouse. It is possible that the delay of phase 3 remodeling is associated with persistent islands of cone photoreceptors the *rd1* mouse (Jimenez et al., 1996; Ogilvie et al., 1997), providing focal input to the neural retina and preventing global remodeling as early as in other models. Early in the degenerative process in the *rd1* mouse, mGluR6 expression is compromised as early as pnd 10 with mGluR6 signals delocalized into the axons (Strettoi and Pignatelli, 2000; Strettoi et al., 2002, 2003). Varela et al. (2003) report that ON bipolar cells lack responsivity to glutamate and have anomalously elevated GABA sensitivity by pnd 28. Rods in the *rd1* mouse retina never form complete functional contacts with rod bipolar cells (Blanks et al., 1974), while cone photoreceptors display neurite sprouting (Fei, 2002). This suggests that the elevated cGMP signal in *rd1* rods impairs cytoskeletal and other structural processes associated with synapse formation. Complete loss of rod photoreceptors in the *rd1* mouse occurs relatively quickly with greater than 97% by pnd 17 (Carter-Dawson et al., 1978; Jimenez et al., 1996), with half of cone photoreceptors lost by pnd 26 and 98% by pnd 110 (Carter-Dawson et al., 1978; Jimenez et al., 1996). Rod death during the period of normal synaptic maturation deprives rod bipolar cells of targets, perhaps hampering their elaboration and development (Strettoi et al., 2002), although one report (Peng et al., 2000) documents rod bipolar cell neurites making synapses with cones at pnd 18. Even so, there are hardly enough cones to supply all rod bipolar cells and by pnd 90, as 30% of rod bipolar cells are lost as assayed by PKC α labeling (Strettoi and Pignatelli, 2000). Additionally, both ON and OFF center cone bipolar cells also show dendritic retraction (Strettoi et al., 2002). Horizontal cells show phase 1 remodeling in the *rd1* mouse: rod-specific axon terminals retract while dendritic arbors appear to hypertrophy

(Strettoi et al., 2002), as do their somas (Marc et al., 2003). By pnd 90, approximately 20% of horizontal cells die (Strettoi et al., 2000). No cell death is detectable in the Müller cell population, though GFAP expression rises as rod death progresses (Strettoi et al., 2002, 2003).

4.3. *rd2* mouse

The *rd2* mouse, formerly known as rd 'slow', possesses a *prph2* gene defect encoding for peripherin 2, a rod photoreceptor specific protein involved in maintaining the formation and structure of the outer segment disks (Connell and Molday, 1990). We were able to obtain only one *rd2* mouse at pnd 151 for our analysis (Jones et al., 2003a,b). At this age, lamination within the neural retina appeared normal with no overt evidence for remodeling at the light microscopy level. However, while there was rod photoreceptor cell loss along with formation of the Müller cell seal, cones were still abundant along with some isolated rod nuclei. We anticipate that because there was still glutamatergic input to the bipolar cell layer from remnant cones, phase 3 remodeling of the neural retina has yet to ensue.

4.4. *or^J Chx10* mouse

The *or^J Chx10* mouse is a hypocellularity defect. A null mutation in the Chx10 homeobox gene and subsequent failure to express the Chx 10 transcription factor results in microphthalmia (Robb et al., 1978; Burmeister et al., 1996). Reduced proliferation of neurons in the inner nuclear layer, especially among bipolar cell precursors (Burmeister et al., 1996), leads to loss of most retinal neurons, perhaps secondarily. Adult animals exhibit only isolated patches of less than a dozen neurons each, mostly amacrine cells. Most of the characteristics of remodeling are evident in this extreme model: in addition to massive cell death, only tiny fragments of neuropil exist, none of which resembles the plexiform layers. Müller cells appear to make up most of the remnant retina and RPE cells are distributed throughout the remnant neural retina. This apparent loss of neural structure and cell populations suggests that maintenance of a normal retinal structure may require a nearly complete cohort of neurons (Jones et al., 2003a,b; Marc et al., 2003).

4.5. *pcd* mouse

The *pcd* mouse is thought to contain a mutation in the regulatory region of *Agtpbp1* resulting in reduced levels of expression for the ATP/GTP binding protein 1 (Harris et al., 2000). This model was initially identified for its rapid degeneration of cerebellar Purkinje cells, but was later identified as a model of retinal degeneration as it loses approximately 50% of retinal photoreceptors. We were able to acquire two *pcd* mice for analysis where remodeling began to reveal itself at pnd 321 through the appearance of glial columns and a glial seal covering the retina.

Though lamination of the neural retina appeared normal and there were no microneuromas visible, there were abundant cones trapped beneath the seal, implying some intact signaling. Though the *pcd* mouse is nominally similar to the *nr^f* mouse in its CNS attributes (see below), the defect clearly is not particularly lethal for cones. This also suggests that the concepts of bystander effects or rod → cone survival factor dependencies in various models are not general (Jones et al., 2003a,b). However, those patches of retina lacking cones in the *pcd* mouse reveal strong deformations in the borders of the inner plexiform layer, implying incipient remodeling (Jones et al., 2003a,b).

4.6. *nr^f* mouse

The *nr^f* mouse possesses an autosomal recessive mutation in an as yet unknown gene on chromosome 8 producing a progressive degeneration in both the Purkinje cells of the cerebellum and rod photoreceptors of the retina (Landis, 1975; LaVail et al., 1993; Campbell and Hess, 1996). While this model does not begin retinal remodeling until pnd 300, the remodeling is nevertheless very aggressive, with numerous neuronal migration foci at pnd 450 and retina-wide remodeling by pnd 730.

4.7. *GHL* mouse

The transgenic *GHL* mouse was originally engineered to be a model of human autosomal dominant RP (adRP) and contains a triple V20G, P23H, P27L mutation in the rhodopsin gene (Naash et al., 1993). The mechanism for cell death is likely a proteasome processing defect as in the single P23H mutant (Illing et al., 2002). Mutant rhodopsin likely is not properly trafficked through the endoplasmic reticulum (Frederick et al., 2001). This was the first animal model of remodeling we studied, and it demonstrated all of the features of retinal remodeling observed in human tissues (Jones et al., 2001, 2002, 2003a,b). The *GHL* mouse is a slow model, and phase 2 photoreceptor death encompasses a full year, though neurite retraction might be occurring as in the *rd1* mouse (Strettoi and Pignatelli, 2000; Strettoi et al., 2002). Delocalization of rhodopsin in the *GHL* model has not been observed unlike the human tissues (Milam et al., 1998), though it may happen briefly just before cell death. Remodeling is advanced by pnd 555 and severe by pnd 746, with massive neuronal loss, including hypertrophy of amacrine cell somas common in human RP, a remarkable proliferation of glycinergic amacrine cell dendrites, Müller cell hyperplasia, abundant microneuroma formation and bipolar, amacrine and ganglion cells migration. Interestingly, the small molecular signatures of neurons and Müller glia remain unchanged throughout early remodeling while Müller cells in late stages of remodeling begin to exhibit higher concentrations of glutamate (Jones et al., 2001). This has not been a common feature of remodeling in other systems. The oldest retinas displayed profound loss of

bipolar cells with hypertrophy of survivor amacrine cells, ganglion cells and Müller cells, the latter often encapsulating blood vessels. An animation of retinal degeneration in the *GHL* mouse model can be seen at <http://prometheus.med.utah.edu/~marclab/supplemental.html>.

4.8. *rhoΔCTA* mouse

The transgenic *rhoΔCTA* mouse contains a premature truncation of rhodopsin at Ser334 essentially mimicking the transgenic S334ter rat and mechanistically undergoes photoreceptor cell death due to an inactivation defect (Jones et al., 2003a,b). Even though photoreceptor cell loss in this model appears rapid, remodeling is more gentle than in the S334ter rat model. Remodeling onset in this animal model does not begin until approximately pnd 541, evidenced as small microneuromas in the outer plexiform layer, distal glial seal formation and considerable disorder in the inner nuclear layer, perhaps as a precursor to migration. Amacrine cells were often seen in an everted position, resting against the remnant subretinal space, along with bipolar cells displaced to amacrine cell layer. In normal rodents, the bipolar and amacrine cell layers are quite distinct; never mixed (Jones et al., 2002, 2003a,b; Marc et al., 2003).

4.9. *TG9N* mouse

This is the race-horse of retinal degenerations. The *TG9N* mouse expresses an N-terminal fragment of the GTPase accelerator protein RGS9, which is normally required for rapid transduction inactivation in both rods and cones (Chen et al., 1993). This model exhibits fast, coherent photoreceptor death. Remodeling ensues by pnd 160 and is the most aggressive model so far described. Amacrine cells concurrently migrate distally to the glial seal and proximally into the ganglion cell layer. Ganglion cells can be seen migrating into the amacrine cell layer. Boundaries of the inner plexiform layer are profoundly altered, with both microneuroma formation and large complexes of inner plexiform layer-like processes spanning the entire retina, displacing all adjacent neuronal and glial somas (Jones et al., 2002, 2003a,b; Marc et al., 2003).

4.10. *rdcl* mouse

The dual transgenic *rdcl* mouse was engineered (Freedman et al., 1999) to provide a model that involves both cone and rod loss. These models possess an engineered defect in *PDE6b* leading to a constitutive increase in rod cGMP levels and LCR-driven toxin expression in developing cones. Initially intended for use in circadian rhythm studies, the *rdcl* model has proved a valuable model for cone/rod dystrophies (CORD) disorders. Indeed, CORD models appear to have the most coherent photoreceptor loss and also have the most aggressive remodeling.

Photoreceptors are lost almost completely in this animal model by pnd 40, with a strong phase 3 remodeling onset by pnd 180.

4.11. P23H rat

The transgenic P23H rat was designed to mimic adRP disorders and, like the P23H mouse, rhodopsin trafficking through the endoplasmic reticulum to the rod outer segment is compromised (Sung et al., 1994; Frederick et al., 2001). This model exhibits all of the attributes of phase 3 remodeling, is fairly aggressive and extensive at pnd 372 with numerous glial columns traversing the neural retina providing pathways for neuronal migration. Different lines of this model have been maintained, with clear variation in speed and coherence of degeneration. In line 1, dramatic cell loss can occur, with long stretches of retina devoid of ganglion cells (very much like advanced human RP) and over 90% neuronal loss integrated over the retina. This variability might be explained by different transgene integration, although human versions of this disease also exhibit marked variability that also involve environmental factors and stresses such as phototoxicity (Heckenlively et al., 1991).

4.12. S334ter rat

The S334ter rat possesses the same genetic defect as the transgenic rho Δ CTA mouse with a premature truncation of the rhodopsin gene at Ser334 (Steinberg et al., 1996). This model is also quite aggressive with remodeling onset at approximately pnd 340. Like the P23H rat, different lines of the S334ter rat model exhibit differing rates of degeneration and remodeling. Regardless, all four lines exhibited strong remodeling with notable plexiform layer thinning and dramatic restructuring of the retina. And like the P23H rat, there are stretches of retina with a complete absence of ganglion cells (Jones et al., 2003a,b).

4.13. *or^J+P27Kip1^{-/-}* knockout mouse

The *or^J+P27Kip1^{-/-}* knockout mouse is a genetic rescue of the *or^J Chx10* mouse model (Green et al., 2003). This double null mutation rescues amacrine cell numbers in the inner nuclear layer, some minor bipolar cell populations and weakly preserves lamination in the neural retina. Though cell number appears to be somewhat rescued in this model, these animals still exhibit severe retinal remodeling *without complete loss of photoreceptors*. This is a very interesting development, because it suggests that correct synaptic connections likely depend on both the correct timing and numbers of source and target neurons. Though total numbers are more normal, excess amacrine cells seem formed and few bipolar cells: the sole excitatory drive for the inner plexiform layer. Early in life, these animals demonstrate roughly normal lamination, but there

are regions with few bipolar cells and dramatically reduced numbers of photoreceptors. Glial seals, vascular abnormalities and invasion of RPE were not seen in the first year of life, but all other aspects of retinal remodeling are found. Microneuromas develop, and both isolated neurons and columns of migrating glycinergic and GABAergic amacrine cells are found throughout the inner plexiform layer and in the ganglion cell layer.

4.14. *rho^{-/-}* knockout mouse

The *rho^{-/-}* knockout mouse (Humphries et al., 1997) possesses a targeted disruption of the rhodopsin gene, which results in a failure to develop rod photoreceptors. These animals exhibit ‘gentle’ remodeling, with numerous cones persisting beneath the glial seal. Clearly this model has little bystander effect. Phase 3 remodeling does not begin until approximately pnd 365 (the oldest model we have evaluated), but is not advanced. Glial seals are evident, as well as formation of microneuromas, but migration has not begun (Jones et al., 2003a,b).

4.15. *elovl4^{-/-}* mouse

The *elovl4^{-/-}* mouse was developed as a model for Stargardt’s macular dystrophy through a single 5-bp deletion within the ELOVL4 protein-coding region (Zhang et al., 2001). We were able to study only three of these animals at relatively young ages with the oldest being 180-days-old. At pnd 180, these animals do not demonstrate any evidence of remodeling other than the formation of a glial seal along with early vascular invasion of the neural retina.

4.16. *hrhoG* knockin mouse

In the *hrhoG* and *hrhoG[H]* knockin models, the murine rhodopsin gene is replaced with a human rhodopsin-GFP fusion protein gene expressed at 80% (*hrhoG*) and 16% (*hrhoG[H]*) of normal rhodopsin levels (Chan et al., 2004). The protein is expressed in outer segments, rods are not photoresponsive and rapidly die. While this does not mimic a disease gene defect, it does provide a clear example of graded photoreceptor stress that triggers photoreceptor death and remodeling. We could not obtain young animals to pinpoint onset, extensive remodeling is present by pnd 500. Microneuroma expression is more extensive than any model yet seen and is often confluent across large retinal spans.

4.17. *LD albino* rat

The LD albino rat model may be a good model for AMD including the loss of photoreceptors, RPE and choriocapillaris (Jones et al., 2003a,b; Sullivan et al., 2003). The LD model clearly removes development as a

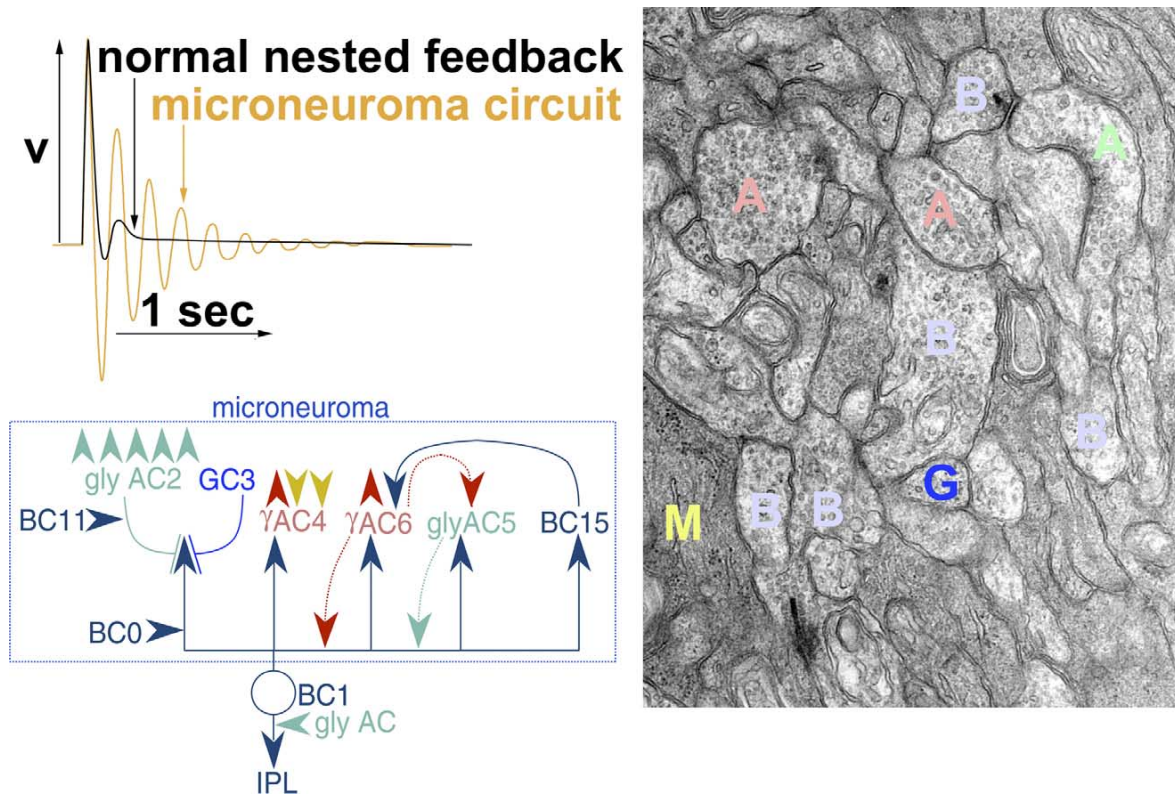


Fig. 7. Rewiring patterns within a microneuroma. A microneuroma from an RCS rat retina was completely reconstructed by serial section electron microscopy. Although the synaptic architecture of a single section superficially resembles the normal inner plexiform layer with bipolar cell profiles (B) displaying their distinctive ribbon synapses and GABAergic (red A) and glycinergic (green A) engaged in conventional synapses, along with ganglion cell (G) and surrounding Müller cell (M) processes, the reconstructed microneuroma shows circuitry unlike any described in normal retina (circuit diagram at left containing processes from 4 bipolar cells (BC1, BC11, BC0, BC15), two GABAergic amacrine cells (γ AC4 and γ AC6), three glycinergic amacrine cells (glyAC, glyAC5, glyAC5), and a single ganglion cell process (GC3). While it is still impossible to record from such complexes, we can model their behaviors with reasonable assumptions. A normal BC>GC circuit using nested AC feedback described by Marc and Liu (2000), will yield a small-signal GC voltage response to a brief impulse of depolarizing current in BC1 shown the black trace (top). This is a characteristic impulse response truncated by feedback with over damping blocked by nested feedback. Such signals are ideal for information processing. Conversely, the microneuroma produces a resonant 'ringing' response, suggesting that any persistent input would yield a persistent oscillatory behavior. While this is inconsistent with visual processing, it is ideal for self-activation in the absence of afferent input.

confounding factor. The LD model is complex, as phase 1 involves stress of the RPE and photoreceptors, while phase 2 includes the death of the choriocapillaris along with rod, cone and RPE ablation. Thus it is a very serious lesion and, not surprisingly, remodeling is correspondingly severe and advanced by pnd 240. LD triggers all of the basic modalities of remodeling plus a feature first noted in LD rats: regions where Müller, bipolar, amacrine and ganglion cells migrate out of the neural retina into the choroid (Jones et al., 2003a,b; Sullivan et al., 2003). Myelinated processes characteristic of ganglion cell axons can be found both within the retina and in the choroid (Sullivan et al., 2003). The time course of the LD model reveals photoreceptor loss within 14 days of even a brief 3 hr LD scotophase treatment. Focal photoreceptor stress and loss is accompanied by irregular 2–4-fold increases in RPE glutamine and rod aspartate levels, perhaps presaging cell death. The onset of Müller cell remodeling and formation of the glial seal is

accompanied by a dramatic >10-fold increase in Müller cell glutamine. The neural retina in this model remains stable until about 120–240 days post-LD, when neuronal migration on hypertrophic Müller cell columns and microneuroma formation are initiated. By 240 days post-LD there is extensive emigration of Müller cells and neurons into the remnant choroid, similar to that described by Sullivan et al. (2003) for the aged ambient-LD rat. This latter phenomenon is a severe blow to any rescue strategy, for it implies that the retina can be depleted of functional cells and that it is somehow deemed unsatisfactory by these surviving neurons. Moreover, we have recently observed neuronal escape in advanced human RP.

5. Corrupt visual circuitry

The RCS rat retina shows panretinal defects at a density of about 790 major defects/mm², equivalent to

40 000/eye, a quarter of which are microneuromas that include bipolar, amacrine and ganglion cell processes with abundant synapses. Is microneuroma circuitry normal? To explore the nature and scope of anomalous rewiring in microneuromas formed during retinal remodeling in late-stage retinal degenerations, we used serial section ultrastructural CMP (Jones et al., 2003a,b) in the RCS rat model to examine retinal microneuromas in PND 200–900 animals (Watt et al., 2003). All types of neurons can contribute terminal processes to a microneuroma, but it is now clear that the synaptic assemblies they form are clearly unlike those of the normal retina. By linear, small-signal lumped parameter models, such circuits show high instability and resonant activity (Fig. 7). It is unlikely that non-linear, saturation models with distributed parameters would improve performance. Further, we discovered that microneuromas are connected to the inner plexiform layer, so the corrupt behavior of a microneuroma is not confined. This anomalous circuitry is beyond the scope of this review, but demonstrates that retinal neurons do not intrinsically ‘know’ how to rewire into visually meaningful circuits (Marc et al., 2003, 2004; Watt et al., 2003).

6. Self signaling

The technology of excitation mapping can be used to ‘ask’ blind retinas about their excitatory environment. While electrophysiology is hampered by the lack of a simple stimulus and difficult sampling conditions, the glutamate-gated channel permeant probe AGB (1-amino-4-guanidobutane) enables concurrent sampling of the integrated excitation histories of all retinal neurons in vitro (Marc, 1999; Marc and Jones, 2002) and can be used in vivo by intravitreal injection, followed by CMP profiling. We attempted this activity mapping within the *rdcl* mouse retina and discovered remarkable deviations from normal response patterns. For example, in early phase 3, rod bipolar cells and all rod pathway neurons seem inactive. From a purely mechanistic perspective, in the absence of a rod glutamate signal, all cation channels gated by the rod bipolar cell mGluR6 pathway should be open. They are clearly not, consistent with loss of the channel activation path (Strettoi et al., 2003; Varela et al. 2003). Some OFF cone bipolar cells are moderately active, implying re-entrant signaling. A number of ON cone bipolar cells are extremely active, as are their target amacrine and ganglion cells. The mechanism of high ON cone bipolar cell activity is unknown. Even so, in early remodeling, most cone-pathway amacrine and ganglion cells are active, without any corresponding bipolar cell activity, implying a cryptic source of glutamate receptor activation. This source could be periodic disinhibition of bipolar cell terminals by spontaneously active GABAergic amacrine cells (Harris et al., 2002; Firth and Feller, 2004).

7. Discussion of implications for rescue

Much previous literature argued that retinal degenerations such as RP affect only the sensory retina. Many approaches to retinal rescue are based on this clearly incorrect assumption. What does this mean for the current state of vision rescue research? At first it may appear to be discouraging and even insurmountable given that the field of vision rescue has been laboring for 20 years to overcome the loss of photoreceptors alone, only recently recognizing the scope of neural remodeling in the retina. However, we would like to persuade readers that this reactivity is encouraging, by showing us that the retina is no different than the central nervous system in its response to deafferentation. Furthermore, this plasticity (albeit negative) and continued neural signaling reveals possible mechanisms for exploitation, and emphasizing the need for early diagnosis and intervention to retard remodeling.

The fact of remodeling influences all rescue strategies, especially since phase 1 remodeling begins before any cells die. Multi-scale and multi-modal approaches will be required to retard or, eventually, repair the complex damage associated with all retinal degenerations. Some retinal degenerative diseases may be more approachable than others in the immediate future, given the success reported in 2001 of vision rescue of an animal model of Leber’s Congenital Amaurosis (Acland et al., 2001).

There are two late-stage schemes for retinal rescue: Retinal transplant strategies and retinal prosthesis implant strategies. Transplant methods attempt replace or repair the RPE; transplant photoreceptors to replace diseased or degenerate photoreceptors; or transplant embryonic tissue or neuroprogenitors/stem cells to rebuild either photoreceptor or even neuronal cohorts. Implant strategies aim to replace photoreceptors with electronics and drive the remnant retina or optic nerve.

A number of approaches to a visual prosthesis have been proposed (Humayun et al., 1996; Chow and Chow, 1997; Zrenner, 2002) along with tissue based approaches (Li and Turner, 1988; Lund et al., 1997; Wang et al., 2004), but both strategies depend explicitly upon preservation of the neural retinal architecture. For example, attempts to preserve RPE function through surgical transplants (Sauve et al., 2002; Wang et al., 2004), must be made prior to photoreceptor loss. But it is unlikely that phase 1 remodeling can be completely prevented, though phases 2 and 3 may be delayed. Other therapies in development, including photoreceptor, fetal retina and stem cell transplants, depend upon the preservation of the neural retina, which is unlikely. It is probable that remodeling retinas will eventually co-opt any new cells. However, some strategies may exploit the reactivity of retinal neurons (especially neurite extension and migration) and may prove effective by controlling the proximities of electrodes and target cells, allowing a higher efficacy of

stimulation (Palanker et al., 2004), which may bridge transplant and implant schemes.

Bionic implants fall into two categories, using extra- or intraretinal photosensitive devices to transduce photons into currents to stimulate the surviving retina (Brindley and Lewin, 1968a,b; Dobbelle and Mladejovsky, 1974; Humayun et al., 1996; Chow and Chow, 1997). Subretinal implants are engineered with the goal of replacing the photoreceptors and stimulating surviving neural circuits. Epi-retinal implants placed on the vitreal surface of the retina would theoretically drive the ganglion cell populations, bypassing much retinal circuitry. These approaches depend explicitly upon the preservation of the neural retina; an assumption that is false for most forms of retinal degeneration. Future rescue methods will depend on strategies that prevent or exploit remodeling.

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