Injury and Repair: Retinal Remodeling

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Glossary

reprogramming - a major change in the gene expression profile of a cell, typically the expression of genes not characteristic of homeostasis

neuritogenesis - the activation of new dendrites and axons from neurons; typically associated with developing cells, it is vigorously demonstrated by mature neurons in remodeling retinas.

migration - the ability of a cell to relocate to a new position in a tissue. It is often thought that mature neurons cannot migrate without “de-differentiating”, but mature retinal neurons can migrate both intra- and extra-retinally without losing their characteristic molecular profiles.

microneuromas - New, anomalous complexes of synapses by mature neurons

glial seal - a compaction of the distal microvillar processes of mature Müller cells and their stabilization by intermediate junctions to form a barrier to diffusion and cellular movement.

self-signaling - the ability of retinal networks to generate their own excitatory activity in the absence of photoreceptor drive.

Synopsis

Retinal remodeling is a collection of molecular and cellular revisions triggered by retinitis pigmentosa (RP), Usher syndrome and age-related macular degeneration (AMD). These revisions include neuronal rewiring and reprogramming; neuritogenesis and synaptogenesis; self-signaling; neuronal migration; neuronal death; glial hypertrophy; altered glial gene expression; vascular remodeling; retinal pigmented epithelium (RPE) invasion and hyperpigmentation. Some revisions begin as soon as photoreceptor stress is initiated, while others are manifest only upon complete local photoreceptor loss. Remodeling impacts the timing and potential outcomes of gene therapy, survival factor treatments, stem or progenitor cell implantation, retinal transplantation, and bionic implants.

Body

Overview

Retinal remodeling is a collection of molecular and cellular revisions triggered by primary inherited degenerative diseases such as retinitis pigmentosa (RP), Usher syndrome; secondary degenerative diseases with mixed environmental / genetic risks, such as AMD; and acquired retinal defects such as prolonged retinal detachment and light-induced retinal damage. These revisions include anomalous neuronal rewiring (targeting canonically inappropriate cells) and reprogramming (expressing canonically inappropriate genes or repressing characteristic genes); *de novo* neuritogenesis and synaptogenesis; spontaneous and corruptive self-signaling; bipolar cell (BC) dendrite truncation; supernumerary axon generation; neuronal migration along hypertrophic Müller cell (MC) columns; neuronal death; altered glial molecular profiles; vascular remodeling; and retinal pigmented epithelium (RPE) invasion, vascular occlusion and hyperpigmentation. Some revisions (e.g. reprogramming) begin as soon as photoreceptor stress is initiated, while others (e.g. synaptogenesis) are manifest only after complete local photoreceptor loss. Importantly, local survival of even heavily altered cones can prevent much late-stage remodeling, apparently by stabilizing the dendritic compartment of BCs. Remodeling impacts the timing and potential outcomes of gene therapy, survival factor treatments, stem or progenitor cell implantation, retinal transplantation, and bionic implants.

It was not until the detailed imaging studies of Ann Milam (U Penn) in the mid-1990s that the nature and scope of remodeling in human RP became evident. More recently, Enrica Strettoi (CNRS Pisa Italy) and Bryan W. Jones (U Utah) independently demonstrated that remodeling was also characteristic of animal models of human inherited retinal degenerations. Though remodeling was not initially given much credence despite strong homology to central nervous system (CNS) degenerative disorders, it is now gaining understanding as a serious denouement of retinal disease.

Progression

Remodeling kinetics are largely independent of the source of photoreceptor deafferentation and occurs in distinct phases (Fig. 1). In phase 1, neuronal and glial cells react to photoreceptor stress signals prior to photoreceptor death. In phase 2, neurons, glia and microglia interact in the processes of photoreceptor death, outer nuclear layer decimation and formation of the glial seal, encapsulating the remnant retina. In phase 3, neural cells respond to deafferentation and non-neural cells form new cytoarchitectures in the remnant retina. The speed of these phases depends on the nature of the degeneration (Fig. 2). Aggressive primary rod, cone-rod or cone dystrophies, as well as RPE phagocytosis defects can rapidly transit phases 1 and 2 to extensive phase 3 remodeling. Slower photoreceptor degenerations (e.g. autosomal dominant RP models of rhodopsin mutations) can lead to extended periods of cone survival, delaying the onset of phase 3. In rodent models, the faster overall kinetics are partly due to the small eye and the likely constancy of cell-cell interaction areas. Greater loss of peripheral retina is tolerated in humans as long as the macula is spared.

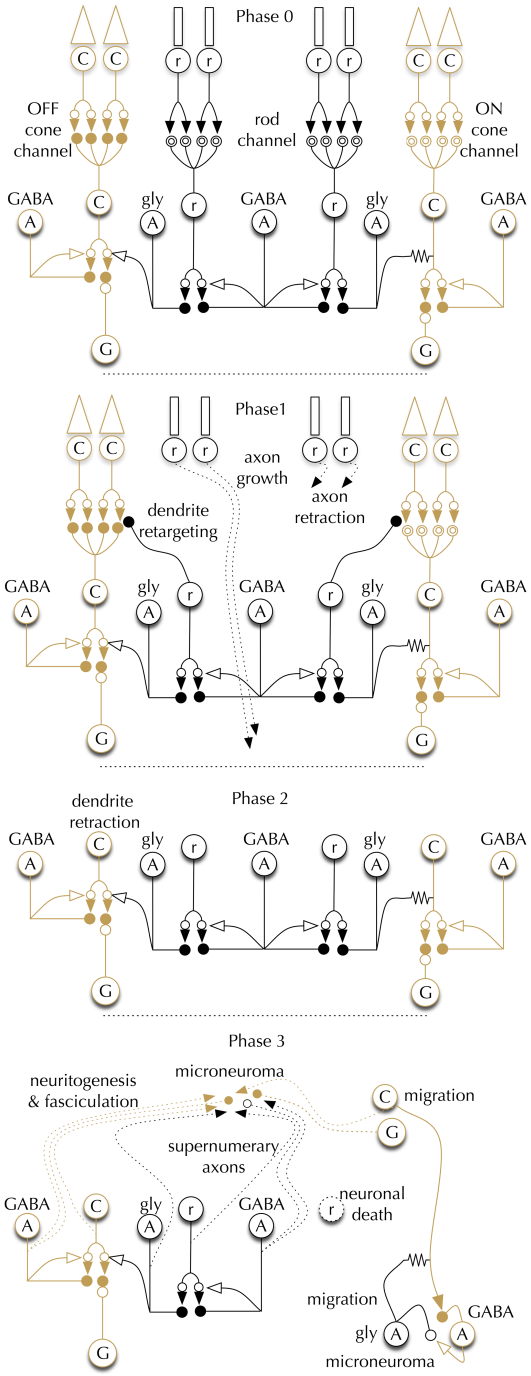

Figure 1. Remodeling phases in the mammalian retina. Phase 0 is the normal retina prior to the onset of acquired or inherited defect stress. The mammalian retina uses separate cone (C) and (r) channels prior to converging on retinal GCs (G). Cone BC receive cone input with either ionotropic sign-conserving glutamate receptors (solid circle) or metabotropic sign-inverting glutamate receptors (double circle), and drive ACs (A) and GCs which decode signals with sign-conserving glutamate receptors. Rod BCs receive rod input with metabotropic sign-inverting glutamate receptors and then drive glycinergic rod ACs, which fan their signals out to ON cone channels via gap junctions (resistor symbol) and OFF cone channels via glycine release decoded by inhibitory receptors (open circles).In phase 1, rod photoreceptors reprogram to either bypass rod BCs with new axons or retract their synapses. Rod BCs both retract dendrites and retarget some to adjacent cone pedicles. In phase 2, photoreceptors are lost and all BCs lose their dendrites. In phase 3 extensive rewiring, neuritogenesis, microneuroma formation, cell migration and neuronal death occur.

Phase 1

The first evidence that remodeling precedes photoreceptor death was the demonstration that human rods harboring a rhodopsin defect were able to form new fascicles of axons, bypass their normal BC targets and project into the ganglion cell (GC) layer prior to apoptotic stress and death. Some rodent model degenerations show the same ability. Furthermore, rodents with autosomal recessive RP, such as the *Pdeb6*^{rd1} mouse (the rd1 mouse) show truncated BC dendritic arbors and horizontal cell (HC) axonal fields long before photoreceptor death. MC stress signals and protective alterations in neuronal glutamate receptor expression in light-induced retinal degeneration (LIRD) albino rodents are activated within hours of light-stress onset and long before pho-

toreceptor death. Please spell out abbreviated words when using them for the first time in the text ie. Light-indiced Retinal Degeneration (LIRD).

Phase 2

Degenerations transition to extensive cell-autonomous and/or bystander photoreceptor death. The nuclear layer (ONL) is dismantled with the involvement of activated microglia and hypertrophic MCs. The details are poorly understood and may vary according to gene defect. For example, dominant mutations that impair rhodopsin trafficking may activate endoplasmic reticulum (ER) stress in several ways: anomalous protein multimerization, inhibition of proteasome cycling, and activation of the unfolded protein response. This results in a slow dismantling of the ONL by sporadic apoptosis. Conversely, mutations of transduction pathways that trigger death calcium-dependent apoptosis are faster and more coherent. In either case photoreceptor apoptosis and migroglial-initiated bystander cytolysis may create debris zones that must be cleared. The mechanisms of such clearance are unknown. Phase 2 ends with the entombment of the remnant neural retina by a thick seal of distal Müller cell processes similar to the normal outer limiting membrane, with extensive adherens junctions (are more modern usage for intermediate junctions is adherens junctions. Please consider using this term instead: done) between the processes. Though often termed a glial scar, there is no evidence that the seal involves astrocyte proliferation as in CNS glial scars. There are occasional breaks in the seal that are associated with phase 3 RPE and choroidal vascular invasion of the neural retina and neuronal escape into the choroid.

Phase 2+

In some degenerations, the death of rods is slow and seems to trigger variable bystander killing, leaving clusters of deconstructed cones with apparently functional synaptic contacts. This results in patches of retina suspended in late phase 2 (phase 2+) in a sea of phase 3 retina. The extent to which these preserve vision is unknown, but they definitely provide evidence that even marginal rescue of cones is a critical step if late phase therapies are to be viable.

Phase 3

After loss of all photoreceptors, the stability of neuronal connectivity in the retina becomes progressively compromised via at least nine distinct processes (see below) including molecular reprogramming, individual cell rewiring, large-scale neuritogenesis, synaptogenesis and microneuroma formation, spontaneous self-signaling, neuronal migration to ectopic foci, progressive neuronal death, MC remodeling and altered gene expression, as well as RPE and vascular remodeling and migration. In severe degenerations, including human late stage RP and geographic atrophy, the revision of the retina can be so severe that no visual function could ever be restored. In other cases, the neural retina survives but is likely to be so altered that upstream strategies such as subretinal implants, stem/progenitor cell transplants, or even fetal retinal transplants will likely not successfully deliver form vision. Further, there is increasing evidence that bionic implants and transplants do not stabililze phase 3 remodeling and may accelerate it.

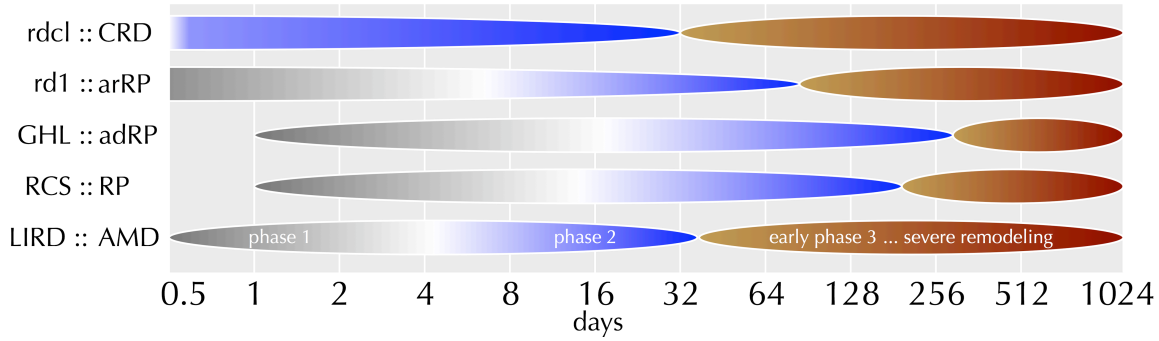

Figure 2. Different forms of retinal degeneration express different kinetics. The abscissa is exponential time in either postnatal or post-light exposure days. Light-induced retinal degeneration (LIRD) is fast with phase 1 stress appearing almost immediately and phase 2 photoreceptor death extending for a couple of weeks before patches of phase 3 remodeling begin. In the RCS rat, photoreceptor debris build up in the subretinal space causes stress, but photoreceptor death is not complete for 3 months or more. after which extensive remodeling occurs. The GHL mouse model of autosomal dominant RP (adRP) does not begin to show photoreceptor stress until opsin synthesis begins and slowly traverses phase 2 for nearly a year before phase 3 remodeling begins. In contrast, the rd1 model of autosomal recessive RP (arRP) is already stressed at birth with phase 2 photoreceptor death reaching completion around 90 days. Similarly the rodless-coneless (rdcl) mouse is a model of cone-rod dystrophy (CRD) and cell death actually begins pre-natally. This model spends most of its life in phase 3.

Remodeling events

Reprogramming

Reprogramming is a shift, possibly reversible, in the gene expression of cells to anomalous molecular and anatomic states. This is best known for MCs in retinal stress where intermediate filament expression is elevated, but is also becoming evident for retinal neurons as well, especially in terms of glutamate receptor expression. Receptor reprogramming can begin in phase 1-2 when rods lose the ability to directly signal rod BCs. In the *Pde6b*^{rd1} mouse, expression, localization and function of the mGluR6 receptor essential for proper ON pathway encoding decreases. In both mouse and human RP models, rod ON BCs appear to transiently up-regulate expression of ionotropic glutamate receptors (iGluRs). In the LIRD mouse model, rapid upregulation of protective GluR2 subunits occurs with 24h after initiation of photoreceptor stress. There is also evidence of GABA receptor redistribution in ON BCs of the *Pdeb6*^{rd1} mouse. Further the expression of dendrites in all BCs appears to be completely suppressed after rod and cone loss and supernumerary axons are formed. While the mechanisms initiating these changes are not yet known, they demonstrate that mature retinal neurons can change their architectures and receptor expressions, while glia can change their architectures and metabolic profiles. More reprogramming events are certain to be found.

Rewiring

Rewiring is the switching of dendritic or axonal targeting. The first known instance of this was the escape of rod synaptic terminals from BC dendrites to form long axonal fascicles (Fig. 1), but with no established targets; cones behave similarly in some cases. In other forms of retinal degeneration, photoreceptors retract their synaptic terminals, which may associated with alterations in the balance of cyclic adenosine and guanosine monophosphate production. The numerous reports of BC sprouting in many model degenerations, as well as aging mice likely reflect simple extension of the dendrites still attached to retracting rod synaptic terminals and not true plasticity. More concretely, BCs bereft of rod input transiently retarget dendrites to cone terminals and, though they do not make structurally appropriate ribbon-associated synapses, they do express anomalous iGluRs. This is is consistent with the disappearance of the electroretinogram b-wave despite the fact that no rod BCs die early in phase 2, and with observations that ON center GC responses disappear long before those of OFF center GCs.

Neuritogenesis

Neuritogenesis is the large scale evolution of new processes by ACs, BCs and GCs in phase 3. The mechanism of activation is unknown, but it encompasses all cell classes, suggesting a global signaling process and a pan-neural response. Many new fascicles course just distal to the glial seal and contain mixed neurites in patterns never observed in normal retina. In other regions, especially near invading RPE processes, large tracts of tiny new neurites with only one or two microtubules form homogeneous fascicles. The tracts can traverse several hundred microns, suggesting significant alteration in the spatial patterning of circuits.

Synaptogenesis and microneuromas

A logical extension of neuritogenesis is synaptogenesis. The extent to which new synapses are made in the inner plexiform layer (IPL) of phase 3 remodeling retina is not clear, but in regions of MC hypertrophy, surrounding migration columns (see below), in the GC layer and especially in the remnant distal retina, numerous new AC, BC and GC connections are made. The most distinctive zones are microneuromas, which range from 10-100 μm in width and contain abundant conventional and ribbon synapses. The mechanisms that stimulate new synapse formation are also unknown but seem closely associated with RPE processes. As RPE cells are known to release several growth factors, it is plausible that they are the activators of synaptogenesis. The wiring within microneuromas seems chaotic and, by serial section reconstruction and modeling, such networks appear to be resonant, which is incompatible with visual processing.

Self-Signaling

A number of observations suggest that retinal degenerations lead to spontaneous self-signaling in phase 3 retina. Photopsias (scintillating illusions common in RP) are initiated in the retina and the generator mechanisms can remain quiescent for decades in the absence of vision, only to be reactivated by experimental transocular currents. Spontaneous, erratic retinal waves of depolarization occur in rodent models of RP after light-driven responses are lost. Physiological measures show that rodent ACs and GCs are glutamate-activated in phase 3. GC activation in the phase 3 *Pdeb6*^{rd1} mouse is clearly glutamatergic

and not intrinsic. This means that BCs must be voltage modulated in some way. However, most remodeled BCs lack functional glutamate receptors and they must be depolarized by another mechanism. One plausible mechanism is periodic AC membrane potential fluctuations, leading to modulation of BC anion currents and modulation in BC glutamate release. Some isolated ACs have shown endogenous oscillations in K^+ channel conductance, alternately hyperpolarizing and depolarizing them, presumably modulating GABA (or glycine) release. The isolation of ACs from normal visual drive in retinal degenerations may unmask this intrinsic capacity. Once self-signaling is initiated, resonant networks created by rewiring or microneuroma formation can rapidly generate periodic activity. Such networks may be inimical to restoration.

Migration

Neuronal migration is a large-scale remodeling event. In most instances migration is closely associated with both hypertrophy of Müller cells and anomalous vascular tangles (see below). All forms of cell mixing occur: collections of ACs and BCs can become displaced to the ganglion cell layer. Conversely, ACs and even GCs can migrate to the distal margin of the remnant retina. One fundamental question is whether these cells remain functional. Ultrastructurally, cells in migration columns such as GCs seem to have processes extending both distally and proximally much like neuroepithelial cells in development. But after migration, the original orthotopic processes seem to be retracted. Migrated cells seem heavily connected to microneuromas. A more serious form of migration (emigration) occurs in when RPE cells and the basement membrane are focally ablated and the distal seal can surge into the choroid. Large tracts of MCs and neurons can emigrate, decimating the remaining neural structures. This is especially evident in LIRD and suggests that it may play a role in loss of vision in severe non-vascular forms of AMD such as geographic atrophy.

Cell Death

There is little evidence of glial death in remodeling, but the proportions and numbers of survivor neurons change significantly. BCs form the largest cohort of neurons (other than photoreceptors) in normal retina, but ACs always predominate in phase 3 suggesting that BC death is far more common than AC or GC death. This may be due to the fact that BCs are the only retinal cells that lose all of their glutamatergic input. Neurons require a basal level of Ca influx to maintain homeostatic gene expression and, via self-signaling, ACs and GCs clearly possess the critical glutamatergic input required to provide both transmitter-gated Ca flux and voltage-gated Ca channel activation. BCs clearly lack that input. As subjects age, ACs and GCs also decrease in number. In any event, loss of neurons has strong implications for all therapeutic interventions, including epiretinal implants.

Müller cell remodeling

MCs make up nearly 50% of the mass of the peripheral primate retina and are one of the major drivers of remodeling. While there has been little analysis of phase 1 MC function in inherited retinal degenerations, there is abundant evidence that they respond to rapid, coherent photoreceptor stress initiated by LIRD within hours by increasing intermediate filament expression, displaying distal process hypertrophy in the outer nuclear layer, and increasing arginine expression (a marker of increased protein synthesis). In phase 2, MCs

play a lead role in forming a seal between the remnant RPE and / or choroid. The transport characteristics of that seal are unknown, but its formation is paralleled by a massive increase in MC glutamine levels. MCs normally export glutamine from MCs to surrounding neurons. This transport is voltage-sensitive and, like many Na-coupled transporters, allows increasing export with depolarization. Depolarization of MCs is closely coupled to light-activated events and the loss of photoreceptors may play some role in progressive hyperpolarization of MCs and retention of gluamine. But as the increase in MC glutamine is temporally linked to the formation of the distal seal, the mechanism of glutamine retention appears more complex than just constraining MC voltage.

RPE remodeling

In classical RP, invading RPE cells are one of the hallmarks of advanced disease. After formation of the MC seal, certain RPE cells and sometimes choriocapillaris endothelia are able to penetrate into the neural retina, forming large complexes of hypertrophic MCs, RPE with altered melanosomes encapsulating invading and remnant retinal capillaries, clusters of new neurites and columns of migrating neurons. RPE cells seem to be the foci of large-scale morphologic derangements in the survivor retina, but whether they are an intiator or responder is not clear. The RPE remains partially intact for long periods in many retinal degenerations, including the Royal College of Surgeons (RCS) rat *mertk*$^{-/-}$ defect, but the RPE layer can become broken by patches of invading RPE cells and apical processes. In the RCS rat, apical REP processes can extend to the ganglion cell layer.

Vascular remodeling

New capillaries invade the neural retina in phase 3, emanating from both vitreal and choroidal sources. Little is known of either the fundamental transport properties of these new vessels (e.g. whether they are fenestrated or not) but both molecular and genetic profiling shows that neural retina in RP is metabolically deprived. New imaging data as well as electron microscopy suggest that the new vessels are too attenuated and too heavily invested by hypertrophic MCs and RPE to allow proper perfusion of the retina. These anomalous foci may trigger neuronal migration. The stimuli for vascular remodeling remain unknown, but VEGF secretion by invading RPE cells is one plausible source.

Impact of remodeling on therapeutics

The potential reversibility of remodeling events varies. For example, phase 1 and 2 changes in reprogramming of gene expression and neurite switching are reminiscent of normal plastic behavior and might respond to the appropriate therapeutic signals. However, phase 3 changes such as rewiring, neuritogenesis and microneuroma formation, migration, and neuronal cell death are not reversible by any known means. Intermediate phenomena such as MC, RPE and vascular remodeling are similarly challenging. Human RP patients show the full spectrum of remodeling defects, so most therapies are impacted by a narrowing therapeutic window.

Primary gene therapy

All prospective primary gene therapies (those targeting known gene defects) depend on photoreceptor survival. However, it is clear that photoreceptor deconstruction starts long before photoreceptor death. The recent successes with gene therapy for replacing deficient

RPE65 in that variant of Leber Congenital Amurosis (LCA) is not likely relevant to primary rod or cone gene defects, nor to defects associated with the accumulation of genotoxic and cytotoxic debris in the subretinal space (e.g. MERTK defects). In human rod dystrophies, it is clear that mutations impacting rhodopsin trafficking also lead to changes in inner segment function and photoreceptor architecture. Rod photoreceptor rewiring in human RP is unlikely to be reversible regardless of the success in replacing defective phototransduction genes. So far, gene therapy successes in animal models are largely restricted to prenatal or early postnatal genetic interventions. With the exception of "soft" diseases such as LCA and stationary night blindnesses that don't trigger photoreceptor deconstruction, most retinal degenerations clearly have only a tiny window for gene therapy. Primary gene therapies are currently restricted to phase 1.

Survival factor therapy

One strategy to retard retinal degeneration involves the use of survival factors such as neurotrophins (e.g. ciliary neurotrophic factor, CNTF) that slow photoreceptor apoptosis. These strategies were validated for slower models of adRP (the rat P23H and S344ter rhodopsin transgenic models). Some argue that the structural preservation afforded by CNTF in these models does not reflect a parallel functional rescue. There is evidence that early postnatal CNTF infusion in other rodent models of RP negatively alters photoreceptor gene expression profiles, activates MC stress signaling and alters inner retinal organization. Simple survival factor therapy without a known cellular and molecular target is not likely to generalize well across human RP types. At present, survival factors offer little prospect of reversing or retarding remodeling. Survival factor therapies are restricted to phase 1 and early phase 2.

Stem / neuroprogenitor cell therapy

Several groups have shown that isolated stem / progenitor cells, particularly murine postnatal day 5 rod neuroprogenitor cells, have the potential to intercalate in the outer nuclear layer and possibly repopulate the retina. The efficiency of such intercalation is low and it is not likely these cells will survive in phase 3 retinas. Penetration of the MC seal is unlikely and several groups have failed to get significant numbers of exogenous photoreceptors to extend synapses through it. Direct injection into the retina is likely to activate microglial killing and, in any event, isolates any surviving photoreceptors from the remnant RPE. For photoreceptor progenitor cells to be successful in rescuing vision they must also lead to cone survival and reconnect with existing neurons before morphologic remodeling begins. This excludes most current RP patients. Stem / neuroprogenitor cell therapies are current restricted to phase 1 and early phase 2.

Retinal transplantation

The team of Seiler and Aramant pioneered the effort to insert sheets of fetal retina into the subretinal space of degenerating retina. They have successfully demonstrated long-term photoreceptor survival and some visual driving in rats. Remodeling remains a major barrier in several ways. The extent of transplant-to-host neurite intermingling is small and the glial seal predominates. Further, the transplanted retina begins to remodel and appears even more susceptible to alteration than the host. This suggests that remodeling signals emanate from the survivor retina. Certainly after phase 3 BC dendrite truncation in the

host retina, a semi-intact fetal retina cannot recapitulate normal circuitry by tandem connections. It is likely that most transplant-to-host connectivity is AC → AC driven and probably functionally random. Even so, such networks can generate light driven behavior. Though lacking the spatiotemporal precision normal GCs, transplants have the potential for much higher sensitivity, range and resolution than bionic mechanisms. Retinal transplantation therapies are largely restricted to phases 1-2, but may function if connection can traverse the glial seal in phase 3 retinas.

Secondary gene therapies: photosensitive proteins

A recent development of import is the ability to induce expression of photosensitive proteins in survivor neurons by viral or molecular transfection, generating light responses directly in neurons. Several groups have shown that it is possible to express channelrhodopsin 2 (ChR2) in retinal BCs, and elicit ChR2-BC-driven photoresponses in GCs and light-dark preferences in behavioral search. This is an important advance and represents the potential to convert blind retinas into navigational systems without surgical intervention and ancillary equipment. The challenge is to demonstrate that this is possible in phase 3 profoundly blind patients, as these are the most obvious candidates for therapy. This technique has, once again, only been established in phase 2 or earlier models. Further, as with transplantation, there is no evidence that such secondary therapies will be resistant to remodeling, prevent cell death, or overcome signal corruption. A significant amount of basic research remains to be done, but despite promise, secondary gene therapies still seem limited to phases 1-2 although they may function in phase 3, even if randomly targeted.

Bionic implants

The most successful schemes to restore vision to the profoundly blind from aggressive phase 3 retinal degenerations are epiretinal bionic implants. Surgically placed near the GC layer, epiretinal implants provide direct current stimulation of retinal GCs or nearby circuitry to activate patches of visual sensation. The argument that such stimulation conflates ON and OFF responses seems irrelevant as several implanted patients can now successfully navigate with such devices. It is clear that the severe remodeling, especially neuronal death, limits candidacy. All implants, be they epiretinal, intraretinal or subretinal seem to induce further glial and neuronal remodeling. Severe remodeling, BC death and microneuroma formation will more severely impact subretinal models.

The importance of cone rescue

In every model, the survival of cones seems to delay the onset of phase 3, holding the retina in a phase 2+ state indefinitely. The effect is local and small patches of cones preserve connected BC dendrite structure even when surrounding BCs have lost all dendrites and glutamate receptors. The preservation persists even when cones are severely deconstructed, lacking outer segments and visual pigment expression, and significantly reduced in size. This suggests that cone contact alone, perhaps through synaptic integrins, may be sufficient to preserve BC function. Expression array studies suggest that cone deconstruction may be accelerated by metabolic deprivation. While preserving cones will not rescue vision, it will permit holding the survivor retina in suspended animation, making an array of interventions such as stem/progenitor cell transplantation, fetal retinal sheet transplantation and secondary gene therapy viable for adults suffering from advanced retinal degen-

erations. Revisiting survival factor research with a focus on cones may be the critical advance needed for all intervention methods.

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Cross-referencing

210. Primary photoreceptor degenerations: retinitis pigmentosa
Weleber, Richard G

211. Secondary photoreceptor degenerations: age-related macular degeneration
Johnson, L

212. Secondary photoreceptor degenerations: other diseases
Bok, Dean

217. Injury and repair: light damage
Anderson, Robert

219. Injury and repair: glial responses
Fisher, Steven & Lewis, Geoffrey

221. Injury and repair: stem cells and transplantation
Young, Michael

222. Injury and repair: prostheses
Humayun, Mark

223. Unique specializations - anatomical: separate rod and cone pathways
Nusinowitz, Steven

Figure Captions

Figure 1. Remodeling phases in the mammalian retina. Phase 0 is the normal retina prior to the onset of acquired or inherited defect stress. The mammalian retina uses separate cone (C) and rod (r) channels prior to converging on retinal GCs (G). Cone BC receive cone input with either ionotropic sign-conserving glutamate receptors (solid circle) or metabotropic sign-inverting glutamate receptors (double circle), and drive ACs (A) and GCs which decode signals with sign-conserving glutamate receptors. Rod BCs receive rod input with metabotropic sign-inverting glutamate receptors and then drive glycinergic rod ACs, which fan their signals out to ON cone channels via gap junctions (resistor symbol) and OFF cone channels via glycine release decoded by inhibitory receptors (open circles). In phase 1, rod photoreceptors reprogram to either bypass rod BCs with new axons or retract their synapses. Rod BCs both retract dendrites and retarget some to adjacent cone pedicles. In phase 2, photoreceptors are lost and all BCs lose their dendrites. In phase 3 extensive rewiring, neuritogenesis, microneuroma formation, cell migration and neuronal death occur.

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Please spell out all abbreviations when using them for the first time.
Examples:
GHL
RCS etc. done