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Mechanisms of Cell Death in the Inherited Retinal Degenerations

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Genes Affected in Human Retinal Degenerations

Humans are afflicted with a large and heterogenous group of inherited blinding diseases. Most share the common histopathological feature of photoreceptor-cell death. The prototypical disease in this group is retinitis pigmentosa (RP), with the clinical phenotype of progressive night blindness and tunnel vision, advancing to complete visual loss in later life. As a group, human retinal degenerations are characterized by both allelic and nonallelic heterogeneity. For example, mutations in multiple unrelated genes may cause the RP phenotype, whereas different alleles of a single gene, such as *RDS,* may cause clinically disparate retinal diseases.

Many genes have been identified as responsible for human retinal degeneration. The genes for several proteins in the visual transduction pathway have been implicated, including those for rhodopsin (reviewed in Rao and Oprian 1996; Shastry 1997), transducin (Dryja et al. 1996), both α- and β-catalytic subunits of cGMP-phosphodiesterase (PDE) (Huang et al. 1995; McLaughlin et al. 1995), the cGMP-gated cation channel (Dryja et al. 1995), rhodopsin kinase (Yamamoto et al. 1997), arrestin (Fuchs et al. 1995), and guanylate cyclase (Perrault et al. 1996). Mutations in genes for other photoreceptor-specific proteins, including rds/peripherin (reviewed in Shastry 1997), rom1 (Kajiwara et al. 1994), rim protein (RmP) (Allikmets 1997; Allikmets et al. 1997; Azarian and Travis 1997), and crx, a newly discovered otx-like homeodomain protein (Freund et al. 1997), have been reported to cause retinal degeneration. Photoreceptor-cell death also may be caused by mutations in genes expressed in the overlying retinal pigment epithelium (RPE), including the genes for cellular retinaldehyde binding protein (CRALBP) (Maw et al. 1997) and RPE65 (Gu et al. 1997; Marlhens et al. 1997). Finally, retinal degeneration, which, in some cases, is a component of a more complex disease phenotype, may be caused by mutations in widely expressed genes, including those for myosin VIIA (Weil et al. 1995), rab geranylgeranyl transferase (Seabra et al. 1993), the cytosolic retinitis pigmentosa GTPase regulator (Meindl et al. 1996), and the tissue inhibitor of metalloproteinase-3 (TIMP3) (Weber et al. 1994). Despite the large number of identified loci, the molecular defect cannot be found in >50% of patients with RP only. Since commonly affected genes generally are discovered early, the total number of genes responsible for human inherited retinal degeneration may be several-fold greater than the number identified to date. No other mammalian-cell type is affected by this number of mutations.

Predisposing Characteristics of Photoreceptor Cells

What does this tremendous genetic heterogeneity suggest about the mechanisms of photoreceptor degeneration? Superficially, it implies that photoreceptors may be more vulnerable to random biochemical insults than are other cells. Can we identify any features of these cells that might confer exceptional vulnerability? In photoreceptors, light activation of an opsin receptor results in activation of the G-protein, transducin, which activates cGMP-PDE. The plasma membranes of rod and cone outer segments contain cGMP-gated cation channels permeable to Na^+ and Ca^{2+} ions. Activation of the visual transduction pathway lowers the concentration of cGMP and thus reduces the frequency of cation-channel opening, causing relative hyperpolarization of the photoreceptor and local depletion of intracellular Ca^{2+}. The "decision" by photoreceptors to use cGMP-PDE as an effector molecule in the transduction cascade may predispose to degeneration. This unusual arrangement affords a wide dynamic range in the photoresponse but also requires that photoreceptors sustain exceptional "resting" metabolic rates. In a nonstimulated photoreceptor, cGMP-gated cation channels have a relatively high open probability, demanding continuous activity of the Na^+/K^+-ATPase, to maintain membrane electrochemical gradients. This high metabolic activity is reflected by the large number of mitochondria in photo-

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receptor cells, their impressive oxygen consumption, and the steep gradient in oxygen partial pressure (pO_2) along their length (reviewed in Steinberg 1987). At the level of the outer segments, which are close to the supplying vessels of the choriocapillaris, very high pO_2 values (near 120 mm Hg) have been recorded. The pO_2 falls steeply, to ~30 mm Hg, at the photoreceptor cell bodies, owing to mitochondrial uptake. The diurnal shedding of distal outer segments permits photoreceptors to discard membrane that may have undergone irreversible modifications, such as lipid peroxidation. The distal shedding of outer-segment disks necessitates ongoing compensatory synthesis of new disk membrane and proteins, representing a further metabolic burden on the cell.

Photoreceptor Degeneration Is by the Apoptotic Pathway

Little is known about the mechanism of photoreceptor-cell death in humans, owing to the scarcity of surgical or autopsy specimens of retina from RP patients with defined genetic lesions. However, animals that carry spontaneous or engineered mutations in multiple genes implicated in human inherited retinal degeneration have been described. The mode of cell death in several of these animal systems has been studied, including in (1) the *retinal degeneration* (*rd*) mouse (Chang et al. 1993; Lolley et al. 1994; Portera-Cailliau et al. 1994); (2) the *retinal degeneration slow* (*rds*) mouse (Chang et al. 1993; Portera-Cailliau et al. 1994); (3) transgenic mice carrying the RP-associated mutations in the rhodopsin gene, P347S and Q344ter (Chang et al. 1993; Portera-Cailliau et al. 1994); (4) knockout mice deficient for the β2-subunit of Na^+/K^+-ATPase expressed in retinal Müller cells (Molthagen et al. 1996); (5) Royal College of Surgeons (RCS) rats (Tso et al. 1994); (6) albino rats undergoing light-induced photoreceptor degeneration (Abler et al. 1996); and (7) cats with experimental retinal detachments (Cook et al. 1995). In every case, photoreceptors were shown to die via the apoptotic pathway, as evidenced by the histological picture, by terminal deoxynucleotidyl transferase-mediated biotin-dUTP nick end-labeling assays, and/or by direct demonstration of retinal-DNA nucleosomal laddering by gel electrophoresis. On the basis of these studies, it is likely that, in most if not all forms of human retinal degeneration, photoreceptors similarly are dying by apoptosis. Unfortunately, this statement says little about what is actually killing the cells.

Possible Mechanisms of Photoreceptor Death

The rd *Mouse*

A null mutation in the gene for cGMP-PDE, which is responsible for the *rd* mutation in mice, is perhaps easiest to understand mechanistically as a cause of photoreceptor degeneration. The level of cGMP in *rd/rd* null mutants, before loss of photoreceptor cells, is >10-fold that in wild-type control retinas (Farber and Lolley 1977). This results in a several-fold increase of conductance through the cGMP-gated cation channels. Photoreceptors lacking cGMP-PDE endure massive influxes of Na^+ and Ca^{2+} ions, causing both metabolic overload and direct toxicity. In particular, an increase in free Ca^{2+} may directly activate the apoptotic pathway in *rd/rd* photoreceptors. Photoreceptor degeneration in *rd/rd* mutants is very rapid. Loss of cGMP-PDE catalytic activity results in an exaggeration of the conditions normally associated with dark-adaptation and may thus be thought of as the "super-dark" photoreceptor lesion.

Mutations That Result in Outer-Segment Shortening

Another potential cause of photoreceptor degeneration, which may be common to multiple genetic lesions, results from shortened or absent outer segments. This class of mutation is exemplified by the *rds* mouse. Phenotypically, the striking feature of *rds/rds* null mutants is complete nondevelopment of photoreceptor outer segments (Jansen and Sanyal 1984), owing to loss of a structural protein in the disk rim. This causes degeneration of rod and cone cells, which progresses more slowly than in *rd/rd* mutants. A possible mechanism for photoreceptor death in these animals is oxygen toxicity. According to this hypothesis, loss of outer segments is accompanied by loss of the cGMP-gated cation channels and, hence, by a dramatic reduction in cation influx. This unloads the Na^+/K^+-ATPase pumps, resulting in significantly reduced oxygen consumption by inner-segment mitochondria and in a much flatter pO_2 gradient across the distal retina. Also, with loss of outer segments, the photoreceptor cell bodies are physically closer to the oxygen-rich choriocapillaris. These two effects may conspire to produce toxic levels of oxygen in the microenvironment of photoreceptor cell bodies. The association between apoptotic cell death and the presence of reactive-oxygen species is well established. Significant dysplasia and shortening of photoreceptor outer segments have been shown in transgenic mouse models for heterozygous null and P216L alleles of *RDS,* both of which are associated with autosomal dominant RP (Kedzierski et al. 1997). Might this mechanism be responsible for the cell death associated with other forms of RP? Mutations in the rhodopsin gene are the most prevalent causes of autosomal dominant RP, collectively accounting for ~25% of cases. The ultrastructural effects of several RP-associated mutations in the rhodopsin gene—including the heterozygous null, P347S, P23H, V20G, and P27L alleles—have been studied in transgenic mice (Naash et al. 1993; Li et al. 1996; Humphries et al. 1997; Liu et al. 1997). Shortening and disorgan-

ization of outer segments was observed in all these animals, suggesting a mechanism of cell death similar to that observed in *rds* mutants.

Some years ago, the surprising observation was made that in *rd/rd, rds/rds* double-homozygous mutants the rate of photoreceptor-cell death is much slower than in *rd/rd* single homozygotes (Sanyal and Jansen 1989). This observation can be understood if we consider that the loss of outer segments is associated with a greatly reduced cationic influx, conferring a protective effect on cells lacking cGMP-PDE. The mode of cell death in these double mutants is probably identical to that of *rds/rds* single homozygotes, as proposed in the previous paragraph.

Constitutive Activation of the Transduction Cascade

Continuous exposure of experimental animals to light has been shown to result in photoreceptor degeneration that leads to blindness. Mutations in the genes for several components of the visual transduction machinery effectively result in continuous activation of the cascade and have been associated with retinal degeneration in humans. These include mutations affecting residues G90, E113, A292, and K296 in rhodopsin (Rim and Oprian 1995) and homozygous mutations in the cGMP-gated cation channel (Dryja et al. 1995). The proposed "equivalent-light hypothesis" states that the cause of photoreceptor-cell death in these constitutive transduction-activation mutants may be equivalent to continuous light exposure (Lisman and Fain 1995). However, the mechanism of cell death is not understood for either case. Here again, it may involve oxygen toxicity. For both continuous light exposure and constitutive activation of the cascade, we would predict unloading of the Na^+/K^+-ATPase, loss of the mitochondrial oxygen sink, and increased pO_2 values in the photoreceptor microenvironment.

Disturbed RPE-Photoreceptor Interactions

Apical processes of RPE cells interdigitate with photoreceptor outer segments (fig. 1) and participate in the shedding of distal outer-segment disks and the regeneration of bleached visual pigments. Mutations that disturb the RPE-photoreceptor relationship may represent still another mechanism of inherited retinal degeneration. An example is in the RCS rat. These animals undergo photoreceptor degeneration due to a cellular defect in the RPE, as has been demonstrated in experimental chimeras (Mullen and LaVail 1976). The accumulation of membranous debris in the subretinal space, before the onset of photoreceptor-cell death, suggests that the primary cellular defect may be impaired phagocytosis of shed outer segments by the RPE. The gene affected in the RCS rat has not been identified yet, but mutations in the RPE-specific genes for CRALBP and RPE65 have been implicated in human retinal degeneration. Furthermore, both recessive Stargardt macular dystrophy and a subset of age-related macular degeneration are caused by mutations in the photoreceptor-specific gene for RmP, a novel ATP-binding cassette transporter in disk rims (Azarian and Travis 1997; Illing et al. 1997). Both disorders are characterized by early lipofuscin accumulation in the RPE, suggesting impaired digestion of phagocytosed outer-segment fragments. These disorders may reflect indirect RPE defects, in which alterations in outer-segment composition due to loss of this transporter function may poison the RPE, resulting in secondary photoreceptor-cell death. Disturbances in the relationship between RPE and photoreceptor cells may play some role in all forms of retinal degeneration.

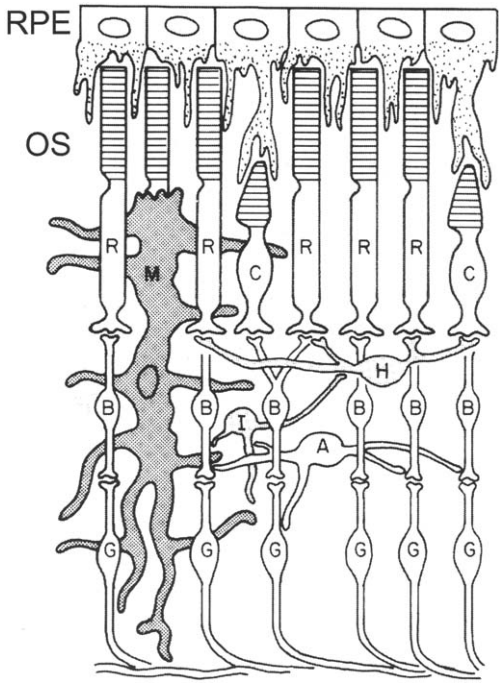

Figure 1 Schematic drawing of an adult-vertebrate retina, with the RPE. Note the intimate relationship between rod (R) and cone (C) outer segments (OS) and the apical processes of the RPE. B = bipolar cells; H = horizontal cells; A = amacrine cells; I = interplexiform cells; G = ganglion cells; and M = Müller cells. (Adapted from figure 2 in Farber and Adler 1986, p. 5.)

Non–Cell-Autonomous Mechanisms

A non–cell-autonomous mechanism for photoreceptor degeneration is supported by several lines of evidence. First, multiple genetic forms of RP are due to mutations in genes expressed specifically in rod but not in cone photoreceptor cells. The terminal RP phenotype of blindness, however, results from the loss of both rod and cone cells. Thus, in these forms of RP, the cones are

"being killed," rather than dying from an intrinsic defect. Furthermore, in aggregation chimeras generated between wild-type and transgenic mice carrying an RP-associated rhodopsin allele, uniform reductions in the number of photoreceptor nuclei across both transgenic and nontransgenic patches were observed (Huang et al. 1993). Interestingly, the rate of photoreceptor-cell loss correlated with the degree of transgenic chimerism. In another study, a transgene expressing wild-type rds/peripherin was shown to have integrated into the X chromosome. When this transgene was placed onto an *rds/rds* null background, a mosaic pattern of transgene expression was observed in hemizygous-female retinas. Again, photoreceptor cells degenerated uniformly, whether or not they expressed the transgene (Travis et al. 1996). These observations suggest that photoreceptor death may be induced by the death of neighboring cells, owing to either the release of diffusible pro-apoptotic factors or the withdrawal of trophic factors. In a cell-culture system, conditioned medium from immortalized retinal precursor cells undergoing apoptosis was shown to contain a heat-labile factor that induced apoptosis in healthy cells (Seigel and Liu 1997), which is consistent with the former model. In both the chimeric and X-chromosome mosaic transgenic systems, thinning of the photoreceptor-cell layer was uniform, even deep within "normal" patches (Huang et al. 1993; Travis et al. 1996), suggesting that the putative pro-apoptotic factor has a diffusion path of many cell diameters. Possible candidates for this diffusible factor are nitric oxide (NO) and tumor necrosis factor (TNF). NO synthase (NOS) is present in multiple retinal cells including photoreceptors, Müller glial cells, horizontal cells, and ganglion cells (Liepe et al. 1994). NOS activity is strongly induced by elevated free Ca^{2+} in photoreceptors (Koch et al. 1994). NO has been shown to decrease phagocytosis of bovine outer segments by RPE cells in vitro (Becquet et al. 1994). Both NO and TNF are released by retinal Müller cells from RCS rats but not from normal rats after stimulation with γ-interferon (de Kozak et al. 1997). Finally, an inhibitor of NOS has been shown to confer partial protection of rat photoreceptors from light-induced degeneration (Goureau et al. 1993). The short half-life of NO is a problem for the NO hypothesis, which cannot explain the conditioned-medium effect. It is very possible that multiple extrinsic factors contribute to non–cell-autonomous death of photoreceptors. The non–cell-autonomous effects suggested by these studies probably act in many if not all forms of inherited retinal degeneration.

Summary

The human retina possesses both extraordinary sensitivity and a huge adaptive range. A light flash containing only a few photons is sufficient to be consciously perceived in humans. We also can see over a range of nearly nine orders of magnitude in background illumination. The vertebrate visual system has been pushed, by evolutionary pressures, to approach its thermodynamic limitations. This exquisite tuning, however, comes at a cost. Photoreceptors are forced to carry large metabolic burdens, to renew continuously their light-sensitive outer segments and to exist under conditions of very high pO_2. Modest changes in the biochemical environment or cellular structure of photoreceptors, caused by genetic lesions or environmental insults, are sufficient to induce cell death through apoptosis. For the inherited retinal degenerations, understanding the impact of each molecular defect on the biology of photoreceptors is important, in addition to studying how these effects converge upon the apoptotic pathway. Collectively, these studies should lead to the development of rational therapies that may slow or even reverse the progression of this devastating disease process.

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