The Dark Side of Light: 
Rhodopsin and the Silent Death of Vision
The Proctor Lecture

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In the following a surprising effect of light upon the retina of albino and pigmented rats will be described. It was discovered when "normal" unanesthetized and unrestrained rats were maintained continuously for 24 hours in an environment illuminated by ordinary fluorescent light bulbs.—Noell et al., 1966

Paracelsus, the medieval alchemist and physician, noted that it is the dose of a substance that renders it a poison or a remedy. This is also true of light, which obviously is essential for most life on earth, but in an overdose, can threaten the health of vision.

Such an overdose was observed in the seminal studies of Noell et al. on damage caused by "normal" laboratory lights in the rat, a nocturnal species. The human visual system can adapt to an illuminance range of 10 to 11 log units. Why then should the human retina be endangered by light? However, epidemiologic studies and numerous case reports demonstrate that light can indeed injure the human retina (for a review, see Ref. 2).

Light damage and retinal degenerative diseases in humans and in animal models have an important feature in common: cell loss by apoptosis of photoreceptors and pigment epithelium (PE). This crucial feature may render light damage a suitable model system to investigate cellular and molecular mechanisms of apoptosis with the aim of understanding and eventually treating or preventing, if only in part, retinal degenerative diseases in humans.

There are several model systems suitable for the investigation of cellular and molecular mechanisms of light-induced damage to the retina:

- Chronic, low-level exposure in the range of weeks to white fluorescent light in unrestrained animals.
- Acute high-level exposure in the range of 30 minutes to several hours to white fluorescent light in unrestrained animals.
- Spectral exposures in the range of 1 to 30 minutes to light of defined wavelengths, in unrestrained or restrained animals.

In our laboratory, we use acute, short-term exposure of unrestrained mice and rats to high levels of white fluorescent light and acute exposure of anesthetized mice and rats to defined wavelengths (blue and green).

IS RHODOPSIN AN ESSENTIAL MEDIATOR OF WHITE LIGHT–INDUCED APOPTOSIS?

In our model, we create a dose–response from threshold lesions to cell death. Threshold lesions are confined to photoreceptor outer segments and consist of dilations and disruptions of disc membranes. Disc dilations and disruptions increase from the tip toward the base, with increasing doses of light. Damage confined to outer segments is removed in the course of physiological renewal and can thus be considered reversible. Shedding of injured membranes bearing oxidized proteins and lipids imposes a metabolic burden on the digestive apparatus including lysosomal function in PE cells. Undigestible remnants accumulate throughout life in PE-lipofuscin, such as the well-known retinoid fluorophore A2E and perhaps its precursors A2PE and A2-Rh, which are initially formed in photoreceptors. Above threshold, light exposure induces apoptotic death of photoreceptors and, in rats, of PE cells. Dying cells then evoke conspicuous phagocytic activity by PE cells and mobile invading phagocytes (Fig. 1).

Even though there are several pigments in retina and PE that absorb visible light, rhodopsin and cone pigments have been proposed to represent the death-mediating chromophores since the work of Noell et al. in rats. By using a mouse model lacking measurable amounts of functional rhodopsin, the Rpe–/– mouse, we showed that no light-induced apoptotic cell loss and no PE lesions occur after exposure to damaging light. Therefore, rhodopsin constitutes the major mediator of light-induced apoptosis in the mouse and presumably other species.

Earlier work in our laboratory has shown that rat retinas devoid of the polyunsaturated fatty acid docosahexaenoic acid (22:6 n-3; DHA) were protected against light-induced damage. Notably, retinas of those rats contained higher rhodopsin levels than did those of untreated control rats, but the regeneration of rhodopsin after light exposure was slowed. When levels of unsaturated fatty acids were increased by means of a fish oil diet, light-induced lesions were not increased, indicating that oxidative stress promoted by those higher levels of polyunsaturated fatty acids was not a crucial damage determinant.

In the mouse, significant strain differences in susceptibility to damage have been described earlier; however, the underlying molecular mechanism was unclear. The PE protein RPE65 was discovered to bear two genetic variants coding for leucine or methionine at position 450. Depending on the genetic variant, RPE65 levels were found to be low (methionine variant, M/M) or high (leucine variant, L/L), perhaps because of instability or reduced activity of the M/M-bearing protein. Retinyl esters in the PE bind to soluble RPE65 protein which promotes the flow of retinyl esters to the isomerohydrolase for conversion into 11-cis retinal. By correlating levels of RPE65 with rhodopsin regeneration rates and damage thresholds, a
clear correlation appeared: mice with low levels of RPE65 and a slow regeneration rate showed high damage thresholds, whereas a fast regeneration conferred a low damage threshold. Thus, any light damage study performed in mice should carefully investigate the genetic background with respect to the RPE65 variant. A recent study shows that this can also apply to animal models of inherited degenerations, especially those that are accelerated by light.

In contrast to the mouse, susceptibility to damage in rats is not primarily determined by the levels of RPE65, and RPE65 levels may not be a limiting factor for rhodopsin regeneration. It is important to identify determinants of susceptibility in rats, apart from those that already have been described, such as the modification of phospholipid fatty acid composition, rhodopsin content, antioxidant levels, and time of day.

If a slow rhodopsin regeneration rate increases the threshold for light-induced apoptosis, could inhibition of rhodopsin regeneration confer protection against light-induced cell death in mice? The volatile anesthetic halothane is known to compete for the chromophore binding site in the opsins molecule. Thus, rhodopsin regeneration is blocked at the step of 11-cis retinal insertion into the opsins molecule. When dark-adapted mouse retinas are bleached and animals are placed into darkness for rhodopsin regeneration under halothane anesthesia, no regeneration occurs. Accordingly, when dark-adapted mice are exposed to damaging light under halothane, their retinas are completely protected against light-induced apoptosis.

These data show that one strong bleaching of rhodopsin without its regeneration, as was applied under halothane anesthesia, is insufficient to induce damage by light. We made similar observations by exposing mice to green light of 550 nm. Rhodopsin, of course, was rapidly bleached, but no detectable lesions occurred (Remé CE, et al. IOVS 2003;43:ARVO E-Abstract 5132). We conclude that continuous absorptions by rhodopsin molecules or, in other words, availability of unbleached rhodopsin during light exposure are needed to inflict damage and cell death.

Blocking the regeneration of 11-cis retinal by pharmacological means also confers protection. Application of 13-cis retinoic acid in vivo is likely to inhibit the PE-retinol dehydrogenase and RPE65, so that 11-cis retinal cannot be regenerated.

THE ROLE OF PHOTOTRANSDUCTION AND SHUT OFF IN WHITE LIGHT–INDUCED APOPTOSIS

Because rhodopsin is crucial in mediating light-induced apoptosis, the investigation of steps downstream of the initial bleaching event is essential. Activated rhodopsin (Rho* or metarhodopsin II [M II]) combines with the α subunit of the G-protein transducin with an exchange of GDP for GTP. This complex activates the αβ subunit of the phosphodiesterase so that on hydrolysis of cGMP, a fraction of the light-sensitive channel closes. The hyperpolarized photoreceptor cell then initiates a visual signal. Deactivation of Rho* (M II) or down-
regulation of its capacity to bind transducin occurs through phosphorylation by rhodopsin kinase (RhoK) and subsequent "capping" by arrestin (Arr). To investigate the role of phototransduction in our light-damage system we used mice without functional transducin (Gnat 1/H9251/H11002/H11002). In these mice, rhodopsin can absorb photons, but no binding to transducin/H9251/H11002/H11002 retinas were damaged indistinguishably from those of control mice; therefore, in damage induced by acute exposure to bright light, phototransduction is not involved. By contrast, when low-level, continuous light is applied, Gnat 1/H9251/H11002/H11002 mice are protected, thus essentially distinguishing mechanisms of short-term bright light and long-term low-level light exposures.

Studying the role of rhodopsin inactivation in light damage produced puzzling data. We used mice without RhoK and Arr (Rhok/H11002/Sag/H11002) and exposed them for different periods to acute bright light. As little as 2 minutes of light exposure had devastating effects on the retina, with abundant cell death and increased activity of the proapoptotic transcription factor activator protein (AP)-1 (described later). Rhodopsin regeneration was completed within 1 hour (Fig. 2), which corresponds to the effect in wild-type mice of the L/L genotype for the RPE65 protein.18

**REGULATIVE MECHANISMS IN BRIGHT LIGHT–INDUCED APOPTOSIS**

The immediate early gene c-fos responds rapidly to a variety of stress situations in many organs and tissues. The c-Fos protein is a component of the transcription AP-1, which is involved in a multitude of cellular processes, such as proliferation, differentiation, cell death, and tumor cell growth. Furthermore, AP-1 is proapoptotic in many tissues. It is induced by a vast number of stimuli, including cytokines and UV irradiation, and couples such signals to cellular responses by regulating target genes. In the retina, c-fos activity follows a diurnal rhythm and also responds to light pulses. Similarly, c-fos activity in the suprachiasmatic nuclei, the circadian master clock, responds to retinal light exposure. In the rd1 mouse, a model of human retinitis pigmentosa, abnormal c-fos expression occurs during the period of apoptotic cell death of photoreceptors.
Activation of AP-1 during light-induced apoptosis

**FIGURE 3.** Time course of activation of the proapoptotic transcription factor AP-1. (A) After light exposures leading to photoreceptor apoptosis, AP-1 activity increases for up to 6 hours after the end of light exposure. The increase begins at approximately 30 minutes and gradually declines at 12 hours. (B) In mice without a functional c-fos gene, no increase in AP-1 activity is seen (M/M genotype for RPE65 protein, but see section Regulative Mechanisms in Bright Light-Induced Apoptosis). Reprinted, with permission, from Wenzel A, Grimm C, Marti A, et al. c-fos controls the “private pathway” of light-induced apoptosis of retinal photoreceptors. *J Neurosci.* 2000;20:841-88. © Society for Neuroscience.

Considering the known effects of light exposure on c-fos expression, could c-fos be a mediator of bright light-induced apoptosis in the retina? We used c-fos<sup>−/−</sup> mice and exposed them and corresponding wild-type control animals to acute bright light. The knockout animals were completely protected against cell death: the morphology of the degenerative apoptosis from c-fos<sup>−/−</sup> was observed in double-mutant mice, indicating an independent apoptosis pathway in the retina not primarily regulated by AP-1.

**BLU LIGHT–INDUCED LESIONS: ANOTHER PATHWAY OF LIGHT-INDUCED APOTOPSIS?**

Lesions induced by high-energy blue light have been observed in primate cones (e.g., Ref. 46), in rodent photoreceptors (e.g., Ref. 47), and in several studies of the PE in vivo and in vitro (reviewed in Ref. 2). Furthermore, there is ongoing discussion of whether life-long blue-light exposure, for example, as an important component of sunlight or of bright artificial light sources, may contribute to pathogenic steps in age-related macular degeneration (AMD). There are several chromophores in the retina and PE that absorb in the blue range and thus could mediate such lesions.

We investigated whether rhodopsin and its bleaching products may play a role in blue light–induced lesions. To achieve fast and strong bleaching of rhodopsin in anesthetized rats, notably by a light source that does not emit any blue components, we used exposure to green light of 550 ± 10 nm. We observed the distinct death of photoreceptor cells and PE, and spectrophotometry indicated that blue light induced a molecule maximally absorbing at 500 nm. Other studies have shown the formation of such a molecule in
vitro. We also observed that blue light alone can inflict apoptotic death of visual cells, indicating to us, not only that rhodopsin readily absorbs blue light and is bleached, but also that this same blue light is absorbed by a photochemically active bleaching product that inflicts cellular damage (Remé CE, et al. IOVS 2003;43:ARVO E-Abstract 5132).  

When anesthetized mice were exposed to blue light of 408±10 nm (in previous studies in rats a 403±10-nm blue light was used), distinct photoreceptor apoptosis occurred (Fig. 4). In notable contrast, exposure to green light of 550±10 nm did not induce any structural lesions in the retina and PE, similar to our observations in rats (Remé CE, et al. IOVS 2003;43:ARVO E-Abstract 5132). These findings further support the notion that one strong bleaching event of rhodopsin is not sufficient to induce apoptosis but rather, a further molecular mechanism is required. During exposure to white, green, or blue light, bleaching of rhodopsin is supposed to generate a molecule that, by itself, is a strong absorber of blue light and thus a potential mediator of cell death. Inhibition of metabolic rhodopsin regeneration by halothane (as described earlier) did not prevent blue light–induced cell death, suggesting the rapid formation of such a detrimental molecule by blue light independent of metabolic regeneration.

AP-1, which is a crucial mediator of white light–induced apoptosis, was upregulated after blue but also after green light exposure. Dexamethasone, which inhibits AP-1 expression and completely protects against white light–induced lesions, did not prevent cell death after blue-light exposure (Remé CE, et al. IOVS 2003;43:ARVO E-Abstract 5132). Rpe65 knockout mice crucially demonstrated the role of rhodopsin also for blue light lesions. There was no apoptotic cell death in knockout mice but distinct apoptosis in wild-type control mice. Thus, all lesions described so far in our light-damage studies appear to depend on rhodopsin. However, consecutive steps in the death cascade may differ. Current studies in our laboratory in knockout mouse models lacking phototransduction (Gnat1−/−) or rhodopsin inactivation (Rhok−/−/Sag−/−) or lacking a functional c-fos gene (c-fos−/−) in both genotypes for RPE65 indicate that none of these conditions can prevent blue light–induced lesions (Remé CE, unpublished observations, 2004).

PE chromophores may also absorb blue light and generate photo-oxidative lesions in PE cells and photoreceptors. An important molecule has been demonstrated as a strong PE photosensitizer: the lipofuscin fluorophore A2E, a pyridinium bis-retinoid generated from bleached rhodopsin (two molecules of all-trans retinal) and disc membrane phospholipid (1 molecule of phosphatidylethanolamine). Apart from its light-independent toxic effect on PE functions, A2E induces free radicals by photo-oxidation in lipofuscin and apoptosis when PE cells are irradiated with blue light.

In summary, we have shown that the threshold for white light–induced apoptosis critically depends on the rate of metabolic rhodopsin regeneration in mice. The regeneration rate, in turn, depends on the level of the PE protein RPE65. The genetic variants leucine or methionine determine availability of RPE65. In rats, by contrast, damage susceptibility and rhodopsin regeneration rate do not critically depend on RPE65. Other determinants, such as time of day, photoreceptor outer segment lipid and protein composition, antioxidant state, and, to date, unknown factors, contribute to the damage threshold. In mice, the proapoptotic transcription factor AP-1 is essential in white light–mediated cell death. To date, it is...
unclear, which signals transduce the light–induced message to transcriptional activity of AP-1, and further, whether AP-1 transactivates death genes or transsuppresses protective ones or whether there may be any other more indirect effect of AP-1. Phenomenologically, we have observed that apoptotic bodies are removed by abundant invading phagocytic cells and by the PE. Signaling and execution of phagocytic activity remain to be elucidated.

Concerning blue light–induced apoptosis, we have shown that, similar to white light, the photon absorption by rhodopsin plays a critical role. A special feature of blue light, however, comes into play by the fact that rhodopsin bleaching product(s) strongly absorb in the blue (and near UV) range and possibly induce detrimental photochemical lesions in photoreceptors. Theoretically, apoptosis at aspartate residues. At present, evidence is accumulating that caspase-independent proteolysis may play an important role in apoptosis, either in concert with or without caspases. Proteolytic enzymes include cathepsins, serine proteases, calpains, and granzymes A and B.

Apoptosis further includes internucleosomal cleavage of DNA and externalization of membrane phosphatidylserine as a signal for phagocytosis of dead cells. Finally, the formerly strict distinction between apoptosis and necrosis no longer applies, because morphologic features of both types of cell death are observed in dying cells and the same proteolytic machinery may be used by both apoptosis and necrosis. Further intracellular degradative pathways comprise different cytoplasmic functional units: autophagosomes, lysosomes, and proteosomes. These pathways may operate independently or in concert with caspases to initiate and execute apoptosis. These proteolytic units may interact at different points in the hierarchy of death pathways, with or without involvement of caspases. Neither autophagy nor lysosomal or proteasomal degradation kills the cells; rather, they subserve physiologic functions, such as those resulting from rhodopsin gene mutations in retinal degenerations and how abnormal proteins resulting from different gene mutations in retinal degenerations and how abnormal proteins convey the message for apoptotic cell death. In such cases, an efficient rescue strategy would include the removal of aggregated and undigestible proteins.

We have extensively studied autophagy in photoreceptors and PE under various conditions, including different light regimens (e.g. Ref. 75). In early stages of light–induced photoreceptor apoptosis, there are abundant autophagic vacuoles in rod inner segments, suggesting possible links between autophagy and apoptosis (Fig. 5). Of interest, rather scarce autophagy was seen in photoreceptors from animals protected against light-induced apoptosis, such as the c-fos−/− mouse with the genetic variant methionine in the RPE65 protein and the Rpe65+/- mouse (Fig. 6; Remé CE, unpublished observations, 2004). In an earlier study we interpreted a significant increase of autophagy after acutely changing illumination levels from low to bright as an adaptive measure to prevent induction of cell death. Adaptation was construed to consist of removal of rhodopsin in rod inner segments to reduce visual pigment content and, with that, sensitivity to light. In view of potential apoptotic signaling by autophagy, there may be a point of no return beyond which autophagy confers a death message.

Ubiquitin-dependent proteolysis by proteasomes also has been observed in the retina. Light exposure induces ubiquitin conjugation, and degradative activity in the rat retina, the βγ subunits of the G-protein transducin, and rhodopsin, have been shown to be a substrate of ubiquitin-mediated degradation, and ubiquitin was observed in rod inner and outer segments in the rat retina after illumination levels were acutely changed from low to high. It is important to note that oxidized proteins in the retina are removed by proteasomes. In other tissues, misfolded or mutated proteins have been shown to be targets of proteasomes and, in some instances, also of autophagy.

Some of the lysosomal proteases can also function at neutral pH, that is, in the cytosol, and lysosomal proteases can trigger apoptosis by multiple molecular pathways including caspase activation and the Bcl-2 family. In the retinal PE, lysosome-triggered apoptosis has been amply documented, assigning an important role to the lipofuscin fluorophore A2E (N-retinylidene-N-retinylethanolamine). Lysosomal dysfunction may be induced by A2E, which is a lysosomotropic compound or by photodamage. Alternatively, A2E may be released from lysosomes and taken up into mitochondria, leading to mitochondrial damage and release of proapoptotic factors.

**Deficient Degradation in Retinal Degenerations: A Pathway to Cell Death?**

A multitude of mutations are known (www.sph.uth.tmc.edu/Retnet/) provided in the public domain by the University of Texas Houston Health Science Center, Houston, TX) that lead to retinal degenerations with the endpoint of apoptotic cell death. However, much less data exist on the signaling and molecular pathways that comprise the road to cell death. Increasing evidence indicates that insufficient intracellular degradation may be an important contributory factor. Altered gene products, such as those resulting from rhodopsin gene mutations, can lead to misfolded proteins that cannot be degraded by the proteolytic machinery and thus accumulate. Those “aggresomes” may eventually lead to cell death by inhibiting vital metabolic functions. Comparable mechanisms have been described for several neurodegenerative diseases of the central nervous system. It is unclear to date how visual cells deal with the abnormal proteins resulting from different gene mutations in retinal degenerations and how abnormal proteins convey the message for apoptotic cell death. In such cases, an efficient rescue strategy would include the removal of aggregated and undigestible proteins.

An important role in retinal degenerations is ascribed to molecular chaperones, which cannot properly handle mis-
Autophagy segregates and degrades cytoplasmic organelles and recycles important molecules

folded or otherwise altered molecules that therefore accumulate and disturb cellular function.86 Another level of complexity is reached when proteasome systems or molecular chaperones themselves bear mutations alone or in addition to a mutation leading to an abnormal protein of important cellular function.87

Proteasomes are known to remove oxidized proteins. In view of light-induced apoptosis it is important to note that impaired proteasome activity can potentiate the effects of oxidative stress.87,88 Oxidative stress is readily encountered after damaging light exposure (for review, see Refs. 2, 89). Thus, the severity of light-induced degeneration may be

Abundant autophagy in rod inner segments in early stages of light-induced apoptosis in wildtype but not in c-fos −/− and Rpe −/− mice

FIGURE 5. Autophagic vacuoles in photoreceptor inner segments. (A) Schematic drawing depicting the process of autophagic vacuole formation and degradation. Cytoplasmic organelles (e.g., mitochondria, are surrounded by double membranes, forming autophagic vacuoles which then fuse with primary lysosomes and thus constitute secondary lysosomes or phagolysosomes). (B) Electron micrograph of a newly formed autophagic vacuole containing mitochondria (arrow) in a frog ellipsoid. (C) Electron micrograph of degraded contents of an autophagic vacuole (arrow) in a frog myoid, with acid phosphatase staining for secondary lysosomes.

FIGURE 6. Electron micrographs of mouse rod inner segments. (A) Light-induced early apoptotic stages in wild-type mice show condensed cytoplasm of inner segments with abundant autophagic vacuoles (arrow). Note the relatively well-preserved mitochondria in apoptotic and nonapoptotic inner segments. Arrowhead: outer limiting membrane. (B) Mice that are protected against light-induced apoptotic cell death such as the Rpe65 −/− mice and c-fos −/− mice of the methionine-450 genotype for the RPE65 protein reveal only few autophagic vacuoles after exposure to damaging light doses.
modulated by the functional capacity of the proteasome system.

The role of autophagic degradation in retinal degenerations remains to be investigated. Activation of autophagy has been observed in those neurodegenerative diseases that are characterized by aggregations of abnormal proteins.74 Autophagy was suggested to be increased as a compensatory mechanism for a deficient proteasome pathway.90 One may envision that failing proteasome and autophagy function eventually constitutes a death signal in those degenerative diseases associated with abnormal protein (and lipid) aggregation.

**LIGHT AND AMD: THE DISCUSSION CONTINUES**

Recent studies have been focused on a role of inflammation and immune responses in the pathogenesis of AMD. A key role is ascribed to injured PE cells, which may activate microglia-derived dendritic cells that in turn constitute a core for drusen formation. Recent analyses of drusen indicate the likely origin of many of their components in PE cells. The necrotic and apoptotic cells that are not rapidly removed by phagocytes are known to generate stimuli for autoimmune responses.91 In contrast, clearance of apoptotic cells can also induce immune responses and inflammation—for example, by triggering caspase-1-mediated release of IL-1β from dying cells.92 Drusen proteome analysis has revealed, among several other elements, protein and lipid oxidation products, which also arise after bright light exposure and may represent molecules damaging the PE (Reganathan K, et al. IOVS 2004;45:ARVO E-Abstract 1795).93 Thus, numerous pathogenic stimuli emerge that eventually lead to drusen formation and AMD.94-98 However, it has been known for a long time by clinicians that not all eyes that accumulate lipofuscin and develop drusen will have AMD. A potential missing link was recently described by using mice deficient for monocyte chemoattractant protein-1 (Ccl-2/MCP-1) or its chemokine receptor.97 Those mice exhibited several features similar to those observed in human AMD. Thus, a macrophage dysfunction leading to the accumulation of cellular debris and drusen formation was implicated as an important factor in the pathogenesis of AMD.

In an earlier review, we have summarized our observations on light exposure eliciting inflammatory responses on a cellular and molecular level.2 Macrophages removing apoptotic photoreceptor cells are distinct in our models. In some species such as the rabbit, PE cells appear to proliferate, besides removing cellular debris. We have also observed light-evoked release of eicosanoid mediators derived from retinal phospholipids, which in turn may activate cytokine responses. Those effects were suggested to be contributory to the pathogenesis of AMD.2

Light can also release polyunsaturated fatty acids in the retina, such as arachidonic acid (AA) and DHA.99,100 Dietary deprivation of DHA, by contrast, protects against light-induced apoptosis.15 The carboxyethyl pyrrole adducts demonstrated in drusen are exclusively formed from the oxidation of docosahexaenoate-containing lipids,93 suggesting exposure to light as a possible factor in drusen formation.

**LIGHT-INDUCED APOPTOSIS: A GOOD OR A BAD MODEL FOR LEARNING ABOUT HUMAN DISEASE?**

Many models are born with the “genetic defect” of limited applicability to human disease. An obvious but unavoidable obstacle is the fact that hardly any animal model reaches the lifespan of humans. Thus, this very simple condition enables many more environmental stress factors to interact with different genes or affect directly the human eye than can ever be simulated in the long term in animal models. Animal models, therefore, often have to be manipulated in a time-lapse fashion. This manipulation is essentially what our laboratory has developed with short-term high illuminance levels to induce apoptosis. This model has the advantage of synchronized cell death and, therefore, an easier way to interact with apoptosis. Furthermore, short-term exposures to light reduce the probability of masking by secondary phenomena after the initial event of cell death. The knowledge from this artificial situation does help in the study of how the apoptotic machinery works in the retina and which rescue strategies are effective. With this gain, we can then move to animal models of retinal degenerations and analyze differences and commonalities of both conditions.

An essential difference between light- and mutation-induced apoptosis needs consideration in the context of cell rescue. Light evokes apoptosis in an otherwise healthy cell, and rescue would restore this health. This is in contrast to mutation-induced apoptosis, in which abnormal proteins are synthesized from birth, and rescue may prevent cell death, but in most cases does not repair the metabolic defect resulting from the mutation. Nevertheless, there are several animal models in which rescue works in both light-damage–and mutation-induced apoptosis, perhaps indicating similar mechanisms of apoptosis.

Apart from representing a model system, light-induced apoptosis is directly linked to human life. Light-induced retinopathies are observed in the clinic and the laboratory, and findings in epidemiologic studies have suggested that exposure to light can contribute to AMD. Therefore, the development of preventive measures is important, as is the elucidation of pathogenic mechanisms through which light promotes retinal degenerations.

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