Secondary Photoreceptor Degenerations*

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Glossary

Epigenetic – The heritable modifications of gene expression that are not the result of changes in the DNA sequence. This can include methylation of DNA that results in inactivation of gene transcription or factors that modify how RNA transcripts are spliced to form the final transcripts that are translated into peptide sequences.

Extrinsic factor – An agent external to the organism that contributes to or is causative of a disease state. This can include drugs, foods, normal nutrients (excess or deficiency), toxins, inhaled chemicals, infectious agents, and exposures to radiation such as light, sound, and high-energy particles.

Intrinsic factor – An agent that is inherent to the organism that contributes to or is causative of a disease state. While commonly these factors are genetic variants in the organism's DNA that may predispose (or be protective) of specific conditions, other intrinsic factors include epigenetic changes, aging changes, and the effects of the biology of symbiotic bacteria in the skin or gut. Another intrinsic agent is an organism's immunologic response behavior and memory (though obviously the immunologic memory is heavily affected by the exposure to extrinsic agents, such as viral infections).

Microbiomics – The genetic information expressed by the microbes that are indigenous to a host organism (e.g., bacteria colonized to the skin or intestinal tract).

Introduction

Secondary retinal degeneration occurs when cells in the retina die by a process triggered by factors not inherent to retina. Secondary retinal degeneration can be caused by trauma, infection, inflammation, toxins, anti-retinal antibodies, or as an adverse effect of medications.

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* All of the genes that are mentioned in this article are described in Table 2 of Chapter 210 (for the retinal degenerations), RetNet (www.sph.uth.tmc.edu/retnet/), and/or Online Mendelian Inheritance of Man (OMIM) (www.ncbi.nlm.nih.gov/Omim/).

In the past, clinicians have tended to view genetic and nongenetic etiologies of retinal degeneration as easily separated categories. The molecular studies of hereditary retinal degenerations have shown that, while some retinal conditions are caused by mutations in genes with photoreceptor-specific expression, many retinal conditions are the results of mutations in genes that are widely expressed in the body as well as from the secondary effects of metabolic changes caused by the expression of mutated genes in ocular cell types other than photoreceptors as well as from other organs and tissues distant from the eye. Based on our understanding of complex genetic disorders, we now realize that there can be interplay of genetic and nongenetic factors that run the entire spectrum of possibilities. For example, rhegmatogenous retinal detachments, which can lead to secondary photoreceptor degeneration, may be influenced or caused by genetic variants (e.g., COL11A1, VCAN, COL9A1, and COL2A1) that are expressed in nonretinal cells, and whose expression may be limited to a particular period in ocular development. Thus, we have to consider this continuum of causality as we attempt to make useful classifications that can guide diagnostics and therapy. In light of these complexities, we offer the following operational distinctions among primary and secondary photoreceptor and retinal degenerations that may be relevant to therapeutic approaches.

- If the genetic defect is such that it would require actual alteration of the gene expression in the photoreceptors to correct the abnormality and arrest the degeneration, then this can be considered a primary photoreceptor degeneration. The genetic alteration is necessary and sufficient to cause photoreceptor degeneration. The gene that is mutated may (e.g., opsin, peripherin/rds, cone transducin, AIPL1, and GUCY2D) or may not (e.g., splicing factors PRPF8, PRPF3, and PRPF31, IMPDH1, and CA4) be photoreceptor specific. For a primary photoreceptor degeneration, one would expect that the correction of the genetic alteration outside of the photoreceptors would not be sufficient to prevent photoreceptor degeneration. However, a secondary photoreceptor degeneration that results from loss of expression or expression of a mutated protein in either other retinal cells or the retinal pigment epithelium (RPE) (e.g., RPE-65, RGR, and LRAT) might be corrected by gene therapy to the key nonphotoreceptor cells in the retina or RPE.

- If one reviews the genes attributed to primary photoreceptor degenerations, it is clear that many of these causative genes are not limited to photoreceptor-specific

expression. Mutations in these genes have been attributed to nonsyndromic primary photoreceptor degenerations (such as retinitis pigmentosa (RP), Leber congenital amaurosis (LCA), cone dystrophy, and cone–rod dystrophy) as well as syndromic forms (e.g., Usher syndrome, Bardet–Biedl syndrome, Alstrom disease, and Cohen syndrome). Most of these conditions are further described and discussed elsewhere in the encyclopedia. In some instances, the mechanisms of action of these genes may not be solely mediated through their direct effects on the photoreceptors, thus raising the possibility that, in some cases, the photoreceptor degeneration is mediated through a mixed primary and secondary photoreceptor degeneration model (see below). Two unique examples of this potential ambiguity are the ABCA4 (Stargardt disease, cone–rod dystrophy) and RS1 (X-linked retinoschisis) genes. Both genes are specifically expressed in the photoreceptors, but their mechanism of action appears to be mediated through other retinal/RPE cells that lead to a secondary photoreceptor degeneration (see below).

- If the photoreceptors degenerate as the result of an alteration in a gene whose expression is primarily in other retinal or RPE cells, then this would be a primary retinal degeneration with secondary photoreceptor degeneration. Correction of the genetic defect would require modification of the effects of those retinal/RPE cells. A primary retinal degeneration without photoreceptor degeneration can occur such as with optic neuropathies that lead to retinal ganglion cell loss without significant loss of photoreceptors (Table 1).

- A mixed model of primary and secondary photoreceptor degeneration can be considered in two different modes. One is when a genetic alteration within the photoreceptors themselves would not be sufficient to

cause photoreceptor degeneration by itself but would predispose to degeneration in the presence of an extrinsic or intrinsic agent. The genetic alteration within the photoreceptors could be necessary, conditional, or probabilistic but not sufficient. An intrinsic agent could be a genetic alteration in nonphotoreceptor retinal cells or due to expression elsewhere in the body. As noted above, a number of genes that are expressed in photoreceptors and for whom there are mutations that are known to be responsible for photoreceptor degeneration also have expression in other retinal cells as well as in other tissues. In some of these cases, it is not always clear if the expression in the photoreceptors alone is sufficient to cause cell death or whether or not there is a component of photoreceptor degeneration that is secondary to the effects on other cells and tissues. The only way to distinguish a secondary effect from a primary one would be to create animal models in which the genetic alteration is limited to specific cell populations and to determine if the photoreceptors are spared when their gene expression is normal. This is especially true for the forms of RP that are associated with mutations in genes that affect metabolic processes throughout the body. Examples of these conditions include gyrate atrophy, Bietti crystalline retinopathy, abetalipoproteinemia, and Refsum disease. At this time, we simply cannot establish if the effects of these genetic mutations are mediated by a primary effect on the photoreceptors or by secondary mechanisms. In the case of gyrate atrophy and Refsum disease, there is evidence that nutritional therapy can ameliorate the progression of the condition, which suggests an interplay of a person's intrinsic genetic makeup and diet (an extrinsic agent), but we still do not know if the effect is due to the systemic reduction of toxic metabolites or a photoreceptor-specific mechanism is also involved. Similarly, with Bietti crystalline retinopathy, the defect in CYP4V2 has multitissue consequences but it is not known if a systemic correction of the metabolic defect would be sufficient to overcome the enzyme deficiency in photoreceptor cells. Only future studies will be sufficient to distinguish if these conditions are representative of a mixed model of photoreceptor degeneration or secondary photoreceptor degenerations of an intrinsic type (see below).

An extrinsic agent can be a drug or environmental exposure (including something in the diet). There are relatively few established human examples of this model for retinal degenerations, though retinal degeneration-B (rdgB) mutants in *Drosophila* show light-dependent photoreceptor degeneration. This mixed model could possibly account for some of the cases of photoreceptor degenerations with incomplete penetrance (individuals who have the disease-causing mutation but show no clinical evidence of retinal degeneration).

Table 1   Secondary photoreceptor degenerations associated with primary retinal/RPE degeneration/dystrophy

Gene involved, site of cell/tissue expression related to retinal degeneration (RPE-retinal pigment epithelium, RVE-retinal vascular endothelium, RVP-retinal vascular pericytes, MGC-Muller glial cells), and phenotype (LCA-Leber congenital amaurosis, RP-retinitis pigmentosa) (from RetNet)

RPE65	RPE	LCA and RP
MERTK	RPE	RP
CRALBP	RPE, MGC	Bothnian dystrophy
LRAT	RPE, liver	RP
RGR	RPE	RP and dominant choroidal sclerosis
TIMP3	RPE, RVP	Macular dystrophy
C1QTNF5	RPE	Macular dystrophy
ABCC6	REV	Macular dystrophy
AMD-related genes	RPE, liver	Macular dystrophy
BEST1	RPE	Macular dystrophy

- If one could prevent the photoreceptor degeneration by preventing an individual's exposure to an extrinsic agent or condition (e.g., toxin, drug, infectious agent, light, and trauma), then this is secondary photoreceptor degeneration of the extrinsic type (even if the body converts that agent to a toxic form as part of a normal metabolic pathway – such as methanol to formaldehyde). Clearly, the primary method of management is to avoid exposure to the extrinsic conditions that would induce the degeneration. This form of degeneration can be due to exposure to an external agent as well as deprivation of a mandatory nutrient (such as vitamin A). The deficiency can be the result of a lack of intake or synthesis of the key nutrient (vitamin-A- or zinc-deficient diet) or due to the inability to process or use such a metabolite/nutrient. Examples would be malabsorption of vitamin A and zinc due to intestinal disorders or drugs which block utilization, such as fenretinide or accutane (Table 2).

- A second mode of a combined primary and secondary photoreceptor degeneration is when one group of photoreceptors, such as the rod photoreceptors, undergoes a primary degenerative process due to a mutation in a gene that is expressed in those photoreceptors that precipitates apoptosis. At the same time, there is a second group of photoreceptors, the cone photoreceptors, which undergoes a secondary degenerative process due to alterations in the cellular environment induced by the death of neighboring cells. This situation is actually very common among patients with retinal dystrophies such as rod–cone (e.g., RP) or cone–rod forms. Recent studies of several mouse models of RP due to rod-photoreceptor specific genes have showed that the nonautonomous death of the cone photoreceptors is influenced by activation of the rapamycin pathway that can be modified by exogenous insulin, suggesting a possible intrinsic mechanism that could be influenced by a systemic therapeutic approach. The importance of this mechanism cannot be overemphasized since preservation of cone photoreceptor cells and function in a patient with RP would have a dramatic impact on maintaining useful visual function and it does not necessarily require the correction of the primary photoreceptor degeneration mechanism in the rod photoreceptors.

- If one can prevent photoreceptor degeneration by correcting or reversing a systemic or ocular metabolic or immune process, then it is a secondary photoreceptor degeneration of the intrinsic type. A number of these conditions are driven or influenced by genetic etiologies (necessary and sufficient in the case of metabolic syndromes, but often conditional or probabilistic in immune-related conditions), but the retinal degeneration is still secondary. Intrinsic causes are not exclusively genetic, one may have to consider epigenetic factors as well as immunologic memory and the microbiomics of the natural flora. Clearly, one would primarily direct therapy to correcting the primary metabolic or immune disturbance rather than focusing on modifying the behavior of the photoreceptors. Therapy might be directed specifically to the affected eye(s), (such as periocular or intraocular steroid therapy) rather than systemically, but it would be intended to primarily modify effector cells in the tissue, rather than the photoreceptors themselves (Table 3).

Table 2 Retinotoxic drugs and agents, nutrient deficiencies, infectious agents, light injury, and trauma

Drugs
Ethambutol, aminoglycosides, epinephrine, desferroximine, antimalarials (hydroxychloroquine, chloroquine, quinine), vigabatrin, phenothiazines (e.g., fluphenazine, mellaril, and stellazine).
Nutrient deficiencies
Zinc, vitamin A, omega-3 fatty acids.
Infectious
Toxoplasmosis, cytomegalovirus, herpes simplex, varicella zoster, HIV, DUSN (nematode), rubella, syphilis, prion, corona virus, others.
Toxins
Cadmium, iron (siderosis), lead, mercury (suspected), copper (intraocular chalcosis), cobalt, iodoacetic acid (IAA), methanol.
Light
Solar, laser chronic exposure.
Trauma
Commotio, retinal detachment.
Vascular
Occlusive disease, embolic, inflammatory, retinopathy of prematurity (ROP), Coats disease.

Table 3 Intrinsic factors: genes, phenotypes (e.g., RP nonsyndromic, RP syndromic, and macular degeneration), mechanism (e.g. metabolic, immune, inflammatory (inflamm))

OAT	Gyrate atrophy	Metabolic
CYP4V2	Bietti crystalline retinopathy	Metabolic
PEX1, PEX2	Zellweger Syndrome	Metabolic
PEX7, PHYH	Refsum disease (adult)	Metabolic
MTP	Abetalipoproteinemia	Metabolic
PANK2	Hypoprebetalipoproteinemia	Metabolic
	Niemann–Pick	Metabolic
	neuronal ceroid lipofuscinosis	Metabolic
CTNS	Cystinosis	Metabolic
CA4 (carbonic anyhydrase 4)	RP	Metabolic
LRP5	FEVR	Metabolic
HLA-B27, A29, B7	Ankylosing spondylitis	Immune
	Birdshot choroidopathy	Immune
	Bechet's disease	Immune
Unknown, retinal antigens, cancer	Cancer-assoc. retinopathy	Immune
	Autoimmune retinopathy	Immune
CFH	Hemolytic uremia – mac deg	Inflamm

- A mixed intrinsic and extrinsic etiology for a secondary photoreceptor degeneration would be when a person has a genetic variant that creates a toxic metabolite in the presence of an extrinsic molecule that would normally not be encountered. A normal person would not experience a retinal degeneration under the same exposure conditions. This set of conditions has overlap with the purely extrinsic and intrinsic etiologies if the genetic variation simply shifts the dose–response characteristics of the host. For example, a person is genetically predisposed to react to an extrinsic molecule at levels in the normal environment, while another person would experience similar photoreceptor degeneration only when the exposure is at levels that would exceed normal exposures. Reduction of the extrinsic exposure below the normal levels could be beneficial for these individuals (such as Refsum disease or gyrate atrophy). Alternatively, correction of the genetic variant would allow the person to cope with normal exposure levels. An animal model of the mixed intrinsic and extrinsic secondary photoreceptor degeneration would be the RPE65-MET450 mutants (intrinsic) that have varying reduced sensitivity to light-induced (extrinsic) photoreceptor degeneration as compared to animals that have the LEU450 variant in the RP65 gene.

- We are only beginning to understand these types of situations, although it is likely that many of the idiosyncratic reactions that some patients experience to certain situations or medications are the result of genetic variations that affect drug bioavailability, mechanism of action, and elimination. One such example would be the patient who develops cystoid macular edema (CME) after uncomplicated surgery. The surgical intervention would be considered an extrinsic agent. While CME is common in cases of complicated surgery and postsurgical inflammation, it is relatively uncommon (but not rare) in individuals whose surgery and postoperative care are uneventful and have no predisposing clinical conditions. Yet, this is most likely due to intrinsic (nonphotoreceptor-specific) genetic factors that govern inflammation. Persistent CME can lead to secondary photoreceptor degeneration.

If the extrinsic exposure cannot be manipulated, then essentially, one is forced to treat the mixed etiology as a purely intrinsic issue. For example, if a person had a genetic condition from an intrinsic metabolic defect that is light sensitizing such that normal ambient light would trigger photoreceptor degeneration, the distinction between an intrinsic etiology and a mixed intrinsic/extrinsic etiology becomes almost meaningless, since having a person avoid all light exposure to prevent photoreceptor degeneration is neither feasible nor desirable. However, reduction of the light exposure might alter the rate of disease progression, but therapy directed toward the intrinsic factor(s) would be essential to preserve vision under normal exposure circumstances. This situation is comparable to the mixed primary and secondary photoreceptor degeneration category (such as a mutation in an photoreceptor-specific gene that is responsible for light-dependent degeneration) except that, instead of the intrinsic etiology being disconnected from the photoreceptors themselves, the photoreceptors are directly affected by a genetic variant that renders the photoreceptors vulnerable to the extrinsic factor (e.g., light). While the reduction of the extrinsic exposure would be desirable, it may not be realistic and thus therapy would also have to be directed to the photoreceptors themselves.

The combination of extrinsic and intrinsic factors that affect photoreceptor degeneration is comparable to the genetic and environmental interactions that are often discussed in the context of complex genetic diseases such as age-related macular degeneration. At this time, our understanding of these interactions is very limited, but there are some examples for simpler retinal conditions. Mice that are heterozygous for a deletion in the PDE6B subunit (the rd mouse), a dose of sildenafil citrate (Viagra) that would normally have no effect in the normal mouse, will show a major change in the electroretinogram. It is likely that some of the individuals who experience visual side effects from this medication may have a genetic variant that reduces the overall level of phosphodiesterase activity in their retinas, thus conferring sensitivity. Another mixed etiology of secondary photoreceptor dysfunction (which can ultimately lead to degeneration) can be seen in an individual with a normally adequate intake of vitamin A, who becomes vitamin A deficient due to an acquired or hereditary malabsorption syndrome (including postsurgical bowel resection or remodeling). The etiology may be intrinsic or iatrogenic, but the treatment is directed toward the extrinsic agent by increasing the dose or mode of absorption of the vitamin A.

Mechanisms of Secondary Photoreceptor Death

Photoreceptors can die from several mechanisms, including physical lysis, destruction by thermal denaturation (such as by laser), or by triggering the apoptotic pathways. Apoptosis can be triggered by a number of disruptions, including loss of key trophic factors such as vascular endothelial growth factor (VEGF), energy depletion through mitochondrial failure, oxidative damage of proteins and lipids, release of calcium by shifts in membrane permeability, which can be caused by deregulation of ionic channels, or from the fixation of complement to the membrane

surface. Light levels below those that cause thermal denaturation can lead to direct activation of caspases, calpain 2, and cathepsin D. In addition, mitochondrial-dependent apoptotic pathways also appear to be activated.

In a number of cases, signaling of the apoptotic pathway appears to be governed by at least two pathways: the Wnt pathway and the Jak–STAT pathway. A number of research groups are attempting to identify nonspecific therapies that can block or inhibit the pathways that result in photoreceptor death. The use of ciliary neurotrophic factor (CNTF) as a trophic factor to inhibit activation of the apoptosis pathway is currently in clinical trials to treat primary and secondary photoreceptor degenerations.

As one considers these multiple mechanisms of photoreceptor death, it becomes clear that a major value of experimental animal models for these conditions is to specifically determine the extent to which photoreceptor death is a primary event and if genetic defects within the photoreceptors themselves are necessary and sufficient to initiate apoptosis. At the same time, this does not negate the importance of understanding the intrinsic (both genetic and nongenetic) factors and extrinsic factors that either trigger or modify cell death that may be amenable to therapeutic intervention at a systemic level. Finally, even in the presence of a combination of factors that lead to photoreceptor death, there is the possibility of interrupting or inhibiting the common apoptosis signaling pathways within the photoreceptor cells and other retinal neurons in order to preserve function and vision.

See also: Primary Photoreceptor Degenerations: Retinitis Pigmentosa; Primary Photoreceptor Degenerations: Terminology; Retinal Ganglion Cell Apoptosis and Neuroprotection.

Further Reading

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Relevant Website

http://www.sph.uth.tmc.edu – Retinal information network.