

# Chapter 11

## Photoreceptor Degeneration: Molecular Mechanisms of Photoreceptor Degeneration

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**Abstract** Rod and cone photoreceptors initiate the visual process by capturing photons and transducing the information into chemical and electrical signals. These functionally specialized neurons have high metabolic activity and oxygen consumption, making them vulnerable to genetic insults and changes in microenvironment. Inherited retinal degenerative diseases are clinically and genetically heterogeneous, with more than 200 genes identified so far. In a majority of retinal degenerations, the genetic defects affect diverse functions in photoreceptors, such as phototransduction, gene regulation, splicing, or intracellular transport. To develop efficient therapies, it is critical to elucidate how genetic defects affect cellular functions and activate death pathways. Caspase-dependent and -independent apoptosis appear to be the major route for photoreceptor cell death in retinal diseases, although the importance of necrosis and autophagy has been demonstrated. Distinct molecules associated with oxidative or endoplasmic reticulum stress can activate these interconnected cell death pathways. Notably, in most inherited diseases, the first signs of photoreceptor dysfunction or loss are observed years after birth and late in life, indicating adaptive mechanisms that protect the cells and suggesting their breakdown may lead to cell death. Mitochondria are predicted to play a critical role in integrating cellular homeostasis to stress and initiation of death pathways. Investigations of adaptive behavior and pre-death molecules that modulate the response to genetic factors should provide attractive targets for the development of better therapeutic approaches.

**Keywords** Cell death • Dystrophy • Retina • Neuro degeneration

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## 11.1 Introduction

Vision is probably the most important of all senses in humans, allowing us to integrate the information from the surrounding world. From a functional perspective, the eye is sometimes compared to a camera with the ability to focus images with an optimal amount of light on the retina, which acts as the film. However, the light-sensitive retina is much more complicated and versatile than a camera, functioning as an extension of the central nervous system to detect, integrate, and process visual information before sending it to the cortex. Retinal photoreceptors capture light photons and initiate visual transduction cascade. The vertebrate retina contains two types of photoreceptors for light detection: rods optimally function under dim light conditions, whereas cones mediate color vision and high resolution in daylight conditions. The rod and cone photoreceptors are specialized neurons with distinct compartments to carry out distinct functions, as elaborated here.

- *The outer segment* is made of membranous discs containing the phototransduction machinery (Hubbell and Bownds 1979), including visual pigment proteins, called opsins, which vary between rod and different types of cone photoreceptors. The outer segment discs are in contact with the retinal pigment epithelium (RPE), which serves as a selective barrier for transport of macromolecules between choroidal capillaries and photoreceptors and participates in the retinoid cycle necessary for phototransduction.
- *The inner segment* encloses the metabolic machinery, including mitochondria, ribosomes, and other organelles associated with protein synthesis and transport to the outer segment and synaptic region. Massive amounts of protein are transported from the inner to the outer segment through a microtubule-based connecting cilium.
- *The nucleus* is the control center localized in the outer nuclear layer, with discrete chromatin architecture depending on the type of the photoreceptor (Carter-Dawson and LaVail 1979; Solovei et al. 2009).
- *The synaptic terminal*, called the “spherule” for rods and the “pedicle” for cone cells, is located in the outer plexiform layer and is connected to different types of interneurons, called bipolar cells, for signal transmission. Photoreceptors also make synapses with horizontal cells.

The photoreceptors have a high metabolic rate and carry out a complex phototransduction process (Fain et al. 2010; Hubbell and Bownds 1979; McBee et al. 2001). The unique characteristics of photoreceptors contribute to their high vulnerability to genetic defects and to changes in metabolism or microenvironment. Thus, photoreceptor dysfunction or death is commonly observed in many blinding diseases, including retinal and macular degeneration. Retinal degenerative diseases constitute a genetically and clinically heterogeneous group with almost 250 human genetic loci associated with Mendelian forms (such as retinitis pigmentosa and cone dystrophies) and more than 200 genes identified so far (*Retnet*; <https://sph.uth.edu/retnet/sym-dis.htm>) (Ratnapriya and Swaroop 2013). In addition, dysfunction and

death of retinal photoreceptors are observed in complex multifactorial diseases including age-related macular degeneration (AMD) (Jackson et al. 2002; Swaroop et al. 2009).

Genetic defects associated with photoreceptor degeneration can lead to different outcomes in terms of visual dysfunction:

- Functional abnormalities, consequent to developmental defects or death of some/all of the photoreceptors.
- Functional abnormalities associated with early cell death.
- No or minimal functional abnormalities in early to mid-life, but late disease onset (including cell death).

Rod and cone photoreceptor function and survival can be differentially impacted in retinal diseases. Consequently, a clearer understanding of molecular mechanisms underlying photoreceptor cell death is crucial for developing effective treatments or cure to prevent vision loss or to preserve/restore vision. However, the clinical and genetic diversity associated with distinct forms of photoreceptor degeneration has complicated the elucidation of molecular mechanisms and hampered disease management (Goetz et al. 2012; Swaroop et al. 2007). Recent advances in gene therapy of Leber congenital amaurosis (LCA) caused by *RPE65* mutations demonstrate the invaluable contribution of understanding fundamental cellular processes in designing therapies for blinding retinal diseases and other neurodegenerative disorders (Jacobson et al. 2012). Several excellent reviews have discussed the clinical and genetic aspects of retinal and macular degeneration (Ambati and Fowler 2012; Bramall et al. 2010; Fletcher 2010; Lim and Wong 2012; Ratnapriya and Swaroop 2013; Wright et al. 2010). In this chapter, we therefore focus on the discussion of cell death mechanisms involved in photoreceptor death. We also examine how the knowledge of affected cellular pathways can contribute to the development of therapeutics.

## 11.2 Retinal Diseases and Photoreceptor Degeneration

### 11.2.1 *Retinitis Pigmentosa (RP)*

RP is a genetically heterogeneous form of inherited blindness with prevalence ranging from 1 in 3,000 to 1 in 5,000 individuals worldwide. More than 50 genes have been identified for RP with autosomal dominant, autosomal recessive, or X-linked modes of inheritance. In almost half the patients it is difficult to assign the inheritance; these are called simplex RP cases. One can observe characteristic abnormal pigmentary deposits predominantly in the peripheral retina of RP patients. In some instances, nonocular phenotypes can be associated with RP in syndromic diseases.

In one form of RP, referred to as rod-cone dystrophy, patients initially exhibit progressive loss of night and peripheral vision because of the dysfunction or death of rod photoreceptors. Eventually, at later stages of the disease cone photoreceptors also die, resulting in loss of central vision and a severe restriction of the visual field.

Cone-rod dystrophy (CRD) has a prevalence of 1 in 40,000, with more than 15 genes identified so far. Even though CRD and RP overlap genetically and clinically, CRD often exhibits an initial loss of cone photoreceptors with subsequent or concomitant loss of rods.

### ***11.2.2 Macular Degeneration (MD)***

Macular degeneration initially affects the central part of the retina, called the macula, associated with high visual acuity. MD can be inherited in a Mendelian manner or manifest as a complex late-onset disease; the latter is termed age-related macular degeneration (AMD).

Mutations in several genes are associated with MD (Stone 2007). Among the monogenic disorders affecting the macula, Stargardt disease is the most common form of inherited juvenile MD with a prevalence of 1 in 8,000 to 1 in 10,000. In most cases, the disease is caused by mutations in the *ABCA4* gene (Allikmets 1997), but *ELOVL4* mutations have also been associated (Zhang et al. 2001). Stargardt patients display accumulation of yellowish-white deposits in the macular region and eventually exhibit photoreceptor and RPE cell death. Histological examination of donor eyes demonstrates the presence of oxidized cholesterol and insoluble aggregates in these deposits from incomplete degradation of shed photoreceptor outer segments (Molday and Zhang 2010). Another inherited MD, called Best disease or vitelliform macular dystrophy, is caused by mutations in the *VDM2* gene that encodes the RPE protein Bestrophin. Best disease is also characterized by the accumulation of yellow, insoluble deposits within the subretinal space and in the RPE (Sun et al. 2002). Mutations in *RDS*, *TIMP-3*, and *EFEMP1* (also known as *Fibulin-3*) genes also cause different forms of MD (Stone 2007).

In contrast to monogenic disease, AMD is a late-onset multifactorial disorder caused by interaction of environmental and genetic components (Priya et al. 2012; Swaroop et al. 2007; Chamberlain et al. 2006). In developed countries, AMD is a leading cause of blindness in the elderly. In the United States, almost 2 million people past the age of 50 years have some form of AMD, and the prevalence is more than 13% for people older than 85 years (Smith et al. 2001; Friedman et al. 2004; <http://www.visionproblemsus.org/index.html>). AMD is characterized by decreased central vision because of the loss of photoreceptors and RPE in the macular region of the retina. The Age-Related Eye Diseases Study (AREDS) classified AMD into four categories based on clinical features (Davis et al. 2005). Geographic atrophy is the major advanced form, characterized by the accumulation of large deposits, termed drusen, between the RPE and the Bruch's membrane, and scattered areas of RPE atrophy and photoreceptor degeneration in the macula (Davis et al. 2005).

Drusen are composed of numerous proteins and lipids, but their origin is still unclear (Rudolf et al. 2008). A more severe form of late AMD, called choroidal neovascularization (CNV), accounts for only about 10 % of cases and is characterized by the presence of new blood vessels in the macula. The nascent expanding blood vessels are leaky and lead to photoreceptor cell death. The patients usually experience sudden loss of central vision with distortion of straight lines and/or a dark spot in their central visual field (Lim et al. 2012).

Genome-wide association studies (GWAS) have identified a number of genetic risk variants linked to advanced stages of AMD (Priya et al. 2012). More recently, meta-analysis of GWAS from a large consortium of investigators has established as many as 19 AMD risk loci (Fritsche et al. 2013).

### 11.2.3 Cone Dystrophy

Cone dystrophies include a group of rare disorders that affect the function and survival of cone photoreceptors, resulting in high sensitivity to bright light, poor color vision, and low visual acuity (Simunovic and Moore 1998). Most cone dystrophy patients have better vision at dusk. Achromatopsia are usually autosomal recessive and represent a majority of stationary cone dystrophy. Individuals have impaired color discrimination, caused by mutations in one of the following five genes: *CNGB3*, *CNGA3*, *GNAT2*, *PDE6C*, *PDE6H* (Hamel 2007). In contrast, progressive cone dystrophy is inherited as autosomal dominant and overlaps with cone-rod dystrophy. For instance, mutations in *GUCAIA* encoding Guanylate Cyclase Activating Protein 1 (GUCAP1) are associated with autosomal dominant cone dystrophy, CRD or MD (Michaelides et al. 2005). Cone opsin gene mutations lead to X-linked cone dystrophy with varying severity from color blindness to progressive cone dystrophy (Gardner et al. 2010).

### 11.2.4 Leber Congenital Amaurosis (LCA)

LCA is a clinically and genetically heterogeneous congenital or early onset retinal disease (den Hollander et al. 2008) that is characterized by vision loss associated with other clinical symptoms including nystagmus and nonrecordable rod and cone electroretinogram (ERG) (Traboulsi 2010). LCA accounts for as much as 5% of all inherited retinopathies but 20% of the children attending schools for the blind and visually impaired (Koenekoop 2004). Seventeen genes have so far been associated with autosomal recessive LCA, and two, *CRX* and *IMPDH1*, can cause autosomal dominant disease (den Hollander et al. 2008; Freund et al. 1998; Bowne et al. 2002). LCA is the first neurodegenerative disease with effective gene-replacement therapy for patients with *RPE65* mutations (Cideciyan et al. 2008).

### 11.3 Interdependence of Rod and Cone Photoreceptors for Survival

An interesting feature of retinal degeneration is that rod-specific mutations do not lead only to rod cell death. One would expect that mutations in genes exclusively expressed in rods would affect only night vision and have no major effect on daylight vision. However, patients with mutations in rod-specific genes also experience loss of cone photoreceptors. The kinetics of cone death is variable, depending on the affected gene (LaVail 1981; Punzo et al. 2009; Wright et al. 2004). Thus, in addition to cell-autonomous mechanisms mediating death pathways in rods, non-cell-autonomous factors appear to contribute to the death of normal and otherwise healthy cones. Chimera generated from a mixture of wild-type cells and those expressing mutant rhodopsin show homogenous retinal degeneration independent of the patch of normal or mutant cells (Huang et al. 1993). Similarly, female hemizygous-transgenic *rd*s mutant mice also show uniform cell death in the outer nuclear layer, including those of genetically normal photoreceptors (Kedzierski et al. 1998). These studies reveal that photoreceptor death involves not only genetic defects but also cell interactions.

Even mutations that affect other cell types, such as those in RPE-specific genes, can cause non-cell-autonomous photoreceptor death. For instance, in mutant mice as well as human patients, mutations in *RPE65*, an enzyme expressed specifically in RPE, lead to absence of visual response and slow degeneration of rods (Redmond et al. 1998; Gu et al. 1997; Marlhens et al. 1997). Interestingly, rod photoreceptors are generally unaffected in cone dystrophies caused by cone-specific gene mutations.

### 11.4 Pathways of Photoreceptor Cell Death

Cell death is a part of normal development and can occur in different modes, such as apoptosis, necrosis and autophagy. Multiple interdependent pathways may participate sequentially or overlap to mediate photoreceptor cell death (Kunchithapautham and Rohrer 2007a, b; Metrailler et al. 2012; Lo et al. 2011; Lohr et al. 2006; Doonan et al. 2003).

#### 11.4.1 Apoptosis

Apoptosis is the major cell death pathway (Portera-Cailliau et al. 1994), at times referred as programmed cell death (PCD). Apoptosis is a complex process leading to DNA fragmentation and generation of apoptotic bodies that can be phagocytized and quickly removed to prevent the surrounding cells from further damage by extrusion of cellular contents. Prompt removal of cellular debris avoids

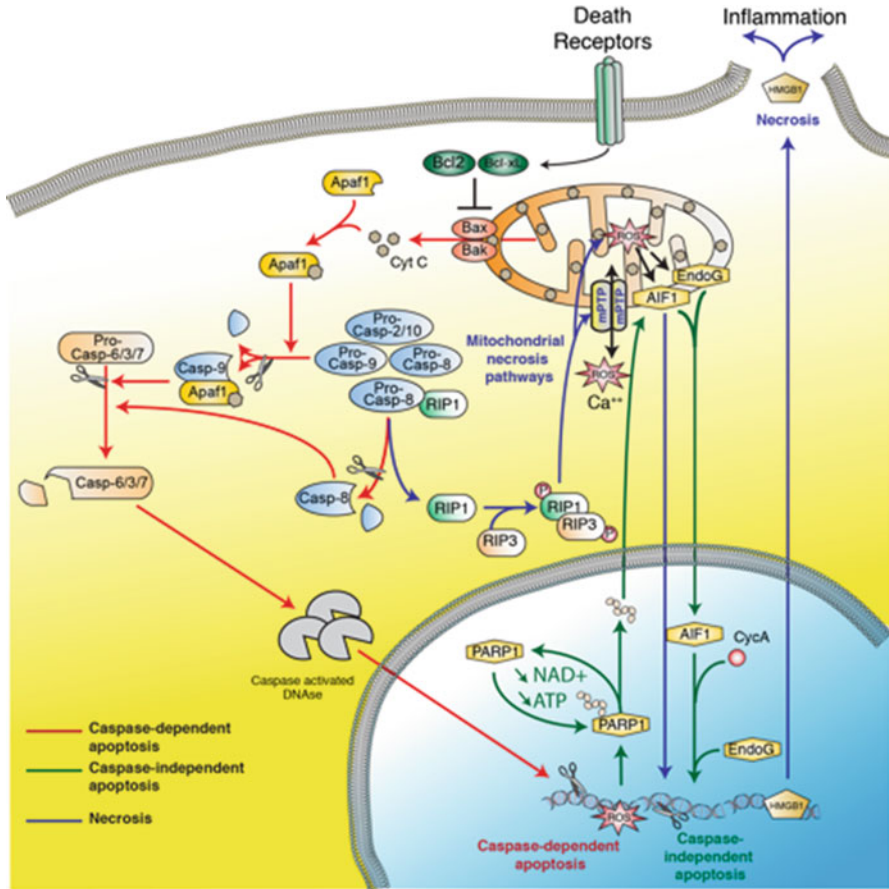
inflammation. The TUNEL assay that labels the fragmented DNA is extensively used to detect apoptosis, but other cell death pathways, such as necrosis and autolysis of the cells, can also exhibit DNA fragmentation (Grasl-Kraupp et al. 1995).

Apoptosis is a critical part of normal retinal development especially for photoreceptors that may be produced in excess (Vecino et al. 2004). In addition, apoptosis is a major cause of cell death under disease conditions, such as RP, retinal detachment, or light-induced apoptosis (Portera-Cailliau et al. 1994; Gregory and Bird 1995; Hafezi et al. 1997; Chang et al. 1995; Cook et al. 1995). Apoptosis is an active process involving several steps controlled by the cell itself (Fig. 11.1). The first step, called induction phase, triggers apoptosis by a wide variety of stimuli such as tumor necrosis factor (TNF), Fas-ligand, and other extracellular factors. During this phase, production of necessary effectors, called pro-apoptotic factors, is increased. Among them, c-Fos and c-Jun form a heterodimer complex, termed activator protein complex 1 (AP1) (Hafezi et al. 1997; Rich et al. 1997; Vuong et al. 2013; Wenzel et al. 2000). The subsequent executive phase leads to morphological changes including chromatin condensation, DNA fragmentation, cell shrinkage, and ultimately cell fragmentation into apoptotic bodies, in which organelles remain intact to prevent inflammation and damages to the surrounding cells. During the degradation phase, cleavage of proteins, further DNA fragmentation, and cellular shrinkage allow apoptotic bodies to be removed without inflammation by macrophages and activated microglia (Langmann 2007; Ng and Streilein 2001; Joly et al. 2009). Apoptosis can occur in a caspase-dependent or -independent manner.

#### 11.4.1.1 Caspase-Dependent Apoptosis

Caspases, a family of highly conserved cysteine proteases, play a central role in the executive phase. The initiator caspases (2, 9, 8, 10) activate the effector caspases (3, 6, 7) by cleavage. The role of activated caspases is to conduct proteolytic degradation of intracellular targets leading to the cell death program. During this phase, mitochondria play a critical role by releasing cytochrome c by permeabilization of the mitochondrial outer membrane (Green and Kroemer 2004). B-cell lymphoma 2 (Bcl-2) family members participate in the release of cytochrome c; some of these members are pro-apoptotic [e.g., Bcl-2 homologous antagonist/killer (Bak) and Bcl-2-associated X protein (Bax)], whereas others are anti-apoptotic (such as Bcl-2 and Bcl-xL). Cytochrome c activates the caspase cascade by binding to apoptotic peptidase activating factor 1 (Apaf1) and triggering the cleavage of initiator caspases, such as caspase-9, in an ATP-dependent manner (Brenner and Mak 2009; Liu et al. 1996). The cleavage of procaspase-9 to caspase-9 allows the cleavage and activation of the downstream effector caspases, such as caspase-3, which initiate the degradation phase by activating DNase. Caspase-dependent apoptosis has been demonstrated in *rdl* (calcium overload) and *rds* (structural defects) mutant mice and in a light damage model (oxidative stress) (Jomary et al. 2001; Lohr et al. 2006; Perche et al. 2007).





**Fig. 11.1** Crosstalk between apoptotic cell death pathway and necrosis. Upon activation of death receptors, caspase-dependent apoptosis involves mitochondria and the release of cytochrome c, which activates APAF1 to cleave procaspases (2, 10, 9,8). The complex APAF1 and Caspase-9 then activate effector caspases such as caspase-3, -6, and -7, allowing the activation of caspase-activated DNases that cleave genomic DNA and participate at the formation of apoptotic bodies. Caspase-independent apoptosis is also dependent on mitochondria and induced by cell death effectors such as AIF1, EndoG, and PARP1. AIF1 and EndoG are released from mitochondria under oxidative stress condition and translocate into the nucleus. PARP detects DNA strand breaks and transfers polymers of ADP-ribose to a wide range of nuclear proteins. High PARP activity leads to a high ATP consumption and accumulation of poly(ADP-ribosyl) polymers, which leads to the release of AIF1 from the mitochondria to trigger caspase-independent apoptosis. Caspase-dependent apoptosis and necrosis activation can overlap after cleavage of procaspase-8 by the release of RIP1 protein, the key protein to trigger necrosis. Phosphorylation of RIP1 and RIP3 leads to the formation of a pronecrotic complex initiating necrosis. This complex opens the mitochondrial permeability transition pores (mPTP) leading to an increase of intracellular  $\text{Ca}^{2+}$ , reactive oxygen species (ROS), and the translocation of AIF1 into the nucleus. Necrosis activation ultimately causes the disruption of the plasma membrane and the release of HMGB1 into the extracellular environment to mediate inflammation



### 11.4.1.2 Caspase-Independent Apoptosis

Although caspase-dependent apoptosis occurs in several retinal degenerative diseases, increasing evidence using a wide range of caspase inhibitors indicates that apoptosis can occur in a caspase-independent manner (Borner and Monney 1999; Bouchier-Hayes et al. 2005) in both in vitro and in vivo models of photoreceptor cell death (Carmody and Cotter 2000; Donovan and Cotter 2002) (Fig. 11.1). Caspase-independent apoptosis is also dependent on mitochondria and induced by cell death effectors, such as apoptosis-inducing factor 1 (AIF1), endonuclease G (EndoG), or poly(ADP-ribose) polymerase I (PARP1).

AIF1 is an oxido-reductase normally localized in the mitochondrial intermembrane space (Cande et al. 2002), and its activity is directly correlated to oxidative stress (Klein et al. 2002). After induction by appropriate apoptotic stimuli, AIF1 translocates to the nucleus and induces chromatin condensation and DNA fragmentation in cooperation with cyclophilin A to elicit apoptosis (Susin et al. 1999). In purified mitochondria, AIF1 triggers cytochrome C and caspase-9 release. AIF1 is involved in apoptosis triggered by retinal detachment in rodent models (Hisatomi et al. 2001), and its inhibition has a protective effect on photoreceptor degeneration (Hisatomi et al. 2008).

EndoG, similar to AIF1, is confined to the mitochondria under normal conditions but translocates to the nucleus upon apoptotic stimulation (Lemarie et al. 2004). In a mouse model of achromatopsia, these two factors are shown to participate in cone cell death caused by endoplasmic reticulum stress (Thapa et al. 2012).

PARP proteins also play a key role in mediating caspase-independent apoptosis. These factors detect DNA strand breaks and are involved in DNA repair (Barth et al. 2006). After activation, PARP enzymes use NAD<sup>+</sup> as a substrate to transfer polymers of ADP-ribose onto itself as well as to many nuclear protein targets. Excessive DNA damage leads to enhanced activation of PARP1, with consequent accumulation of poly(ADP-ribosyl) polymers, which play a critical role in the release of AIF from mitochondria to trigger caspase-independent pathways (Yu et al. 2002; Yu et al. 2006). PARP activation has been shown in several models of retinal degeneration (Kaur et al. 2011; Paquet-Durand et al. 2007). Notably, the lack of PARP1 in the mouse retina does not alter retinal function and protects photoreceptors from cell death (Sahaboglu et al. 2010). Several studies suggest a possible clinical relevance of the pharmacological inhibition of PARP proteins (Jagtap and Szabo 2005; Paquet-Durand et al. 2007).

Photoreceptor cell death is shown to be caspase independent in a number of models of retinal degeneration, such as in *rd* mouse, *N*-methyl-*N*-nitrosourea (MNU)-treated mice, or in light-induced apoptosis (Donovan and Cotter 2002; Doonan et al. 2003; Donovan et al. 2001; Chahory et al. 2010). In these models, cytochrome c release from the mitochondria or activation of the caspase cascade could not be detected (Doonan et al. 2003).

It is widely accepted that caspase-dependent and -independent mechanisms often act in cooperation during apoptosis (Lohr et al. 2006; Kroemer et al. 2009). Hence, the success of therapeutics based on apoptosis inhibition would depend on targeting both caspase-dependent and caspase-independent mechanisms.

### 11.4.2 Autophagy

Autophagy is an alternative and equally critical death pathway that plays an important role during development and homeostasis of mature tissues. Growing evidence demonstrates that autophagy might be even more important under disease conditions (Kim et al. 2013; Mizushima et al. 2008). The primary function of this catabolic process is to maintain cellular integrity by targeting proteins (e.g., aggregates) and dysfunctional organelles (e.g., mitochondria) to the lysosome for degradation (Marino et al. 2011). A stringent regulation of autophagy is critical for cell homeostasis under normal conditions, and loss of control of degradation can be lethal. During starvation, the degradation of cellular components by autophagy provides resources for survival. Autophagy is an adaptive response under stress and disease conditions to promote cell survival; however, under other scenarios, it may promote cell death. The main autophagy pathway, called macroautophagy, involves organelle and protein degradation by engulfment in a double membrane and formation of an autophagosome, which is then targeted to and fuses with the lysosome for degradation of the enclosed material by lysosomal proteases. In contrast, microautophagy is characterized by direct invagination of the lysosomal membrane to completely enclose the cytoplasmic material. Chaperone-mediated autophagy (CMA) is a more complex and specific pathway in which cytosolic soluble proteins containing a recognition motif for chaperones are selectively transported to the lysosome. The translocation to the lysosome is triggered after binding of the chaperone to a lysosomal receptor, named lysosome-associated membrane protein type 2A (LAMP2A) (Cuervo 2010).

Macroautophagy is a nonspecific process often activated in response to nutrient deprivation and stress conditions. In contrast, CMA is usually activated after long periods of starvation leading to an increase of LAMP2A synthesis (Cuervo and Dice 2000; Marino et al. 2011; Massey et al. 2004). Crosstalk among different autophagic pathways can compensate for each other (Kaushik et al. 2008; Massey et al. 2008). Recent work on photoreceptor aging indicates that dysfunction of macroautophagy is correlated with significant increase of CMA markers in aged animals (Rodriguez-Muela et al. 2013). Such compensatory mechanisms can explain the delay between the start of expression of macroautophagy markers and apparent cell death occurring much later. Interestingly, inhibition of CMA in the retina does not lead to an increase in macroautophagy; instead, cells become more sensitive to stress.

In aging, AMD, and a majority of retinal dystrophies, rod photoreceptors die first, followed later by cones, which have a much slower rate of cell death (Kolesnikov et al. 2010; Punzo et al. 2009). Interestingly, macroautophagy is not activated in dying cones. On the contrary, it is inhibited with a concomitant increase of LAMP2A expression specifically in the lysosomal membrane of cones, potentially reflecting starvation of these cells. Microarray analysis of dying cone photoreceptors in mouse models of RP has identified several genes associated with insulin metabolism, suggesting that the level of intracellular glucose in cones may

be altered (Punzo et al. 2009). Recently, glucose starvation of cones *in vitro* has also been shown to trigger autophagy (Balmer et al. 2013).

It is often difficult to determine whether autophagy is the cause or the consequence of photoreceptor stress and death. For instance, RPE accumulates proteins, lipofuscin, and damaged mitochondria during aging and in AMD (Kaarniranta et al. 2010; Kaarniranta et al. 2013; Krohne et al. 2010; Wang et al. 2009a, b). Accumulation of lipofuscin in the RPE can alter the fusion between the autophagosome and the lysosome. In addition, accumulation of A2E, the major lipofuscin fluorophore reportedly inhibits ATP-driven proton pump in the RPE cells, leading to increase of lysosomal pH. Increase in the autophagy flux and accumulation of toxic products may thus contribute to drusen formation, which are hallmarks of AMD (Bergmann et al. 2004). Autophagy is an important pathway for photoreceptor maintenance and homeostasis, especially during disc outer segment shedding (Kim et al. 2013; Long et al. 1986). Autophagy may also regulate opsin protein levels to adjust to lighting environment (Reme et al. 1999).

The ubiquitin proteasome system (UPS) is a major protein degradation pathway. Several lines of evidence indicate a crosstalk between autophagy and proteasomal degradation, especially in selective autophagy (Kraft et al. 2010). The UPS controls protein stability and degradation of the target proteins by posttranslational modifications, including covalent addition of several monomers of a small protein ubiquitin, transferred by sequential action of E1-, E2-, and E3-ligases. The proteasome complex then degrades poly-ubiquitinated proteins. This complex regulates a number of intracellular proteins associated with cell signaling, cell-cycle regulation, and synaptic plasticity. UPS also plays a critical role in regulating cell death (Tai and Schuman 2008; Vucic et al. 2011). Protein aggregation is a characteristic feature of a wide variety of neurological diseases. Parkinson's disease, Alzheimer's disease, and prion disease are among the most common neurodegenerative diseases, which reveal protein aggregation and dysfunction of the UPS-triggered apoptosis (Bence et al. 2001; Sherman and Goldberg 2001; Snyder et al. 2003). Several mutations associated with inherited retinal degeneration, such as those in rhodopsin, cause protein misfolding, mistargeting, or aggregation (Comitato et al. 2007; Surgucheva et al. 2005; Illing et al. 2002). In the case of formation of the transducin  $\beta\gamma$ -subunit complex, critical for phototransduction, lack of transducin  $\gamma$ -subunit (G $\gamma$ 1) in mice leads to increase in production of its partner, transducin  $\beta$ 1 (G $\beta$ 1), which in the absence of G $\gamma$ 1 cannot be folded properly and is targeted to the proteasome (Lobanova et al. 2013). Consequently, large increases in G $\beta$ 1 overload the UPS, causing cellular stress and photoreceptor cell death. Defects in degrading misfolded proteins have also been observed in rodent models, including *rd*s (PRPH2), *Rho*<sup>-/-</sup>, and *Rho*<sup>P23H</sup>. Such mechanisms are also described for extended polyglutamine proteins, such as SCA7 and Huntingtin, leading to neuronal cell death (Lobanova et al. 2013; Yvert et al. 2000; Abe et al. 2000; Helmlinger et al. 2002; Schipper-Krom et al. 2012). Mutations in components of the UPS have also been identified in autosomal dominant RP patients (Friedman et al. 2009).

### 11.4.3 Necrosis

Necrosis, also called necroptosis, is characterized by an increase in cell volume, swelling of the organelles, and rupture of the plasma membrane causing the release of intracellular components in the surrounding microenvironment and initiating an inflammatory response (Vandenabeele et al. 2010). If apoptosis is a regulated cellular process that can be beneficial and necessary for the organism, necrosis almost always has a negative impact. At first, necrosis was thought to be a nonspecific, uncontrolled cell death mechanism, but recent evidence indicates some level of regulation of this pathway (McCall 2010). Several regulators of necrosis have now been identified, including receptor-interacting protein (RIP) kinases. RIP1 is essential to trigger necrosis in response to tumor necrosis factor (TNF)- $\alpha$ , and FasL stimulation and promotes activation of nuclear factor  $\kappa$ B (NF- $\kappa$ B) (Ea et al. 2006; Moquin and Chan 2010; Christofferson and Yuan 2010). In case of failure to activate caspase-dependant apoptosis, RIP1 interacts with RIP3 to form a pronecrotic complex, stabilized by phosphorylation that leads to necrosis pathway activation. Often, apoptosis and necrosis pathways overlap and crosstalk (Fig. 11.1) (Brenner and Mak 2009; Zhang et al. 2009). In necrosis, high-mobility group box 1 (HMGB1), a non-histone chromatin-binding protein, is usually released into the extracellular matrix and acts as a pro-inflammatory factor (Fang et al. 2012). However, little is known about the downstream effectors of necrosis, and additional studies are required.

The importance of RIP and necrotic pathway activation in the secondary death of cone photoreceptors has recently been demonstrated in models of rod-cone dystrophy (Murakami et al. 2012). In the *rd10* mouse, a model of rod-cone dystrophy caused by a mutation in the rod-specific gene, cGMP phosphodiesterase  $\beta$ -subunit (Pde6 $\beta$ ), an increase in RIP proteins has been observed in the late phase of retinal degeneration during the period of cone death but not in earlier stages, when most of the rods die. A detailed morphological analysis of dying photoreceptors shows that necrosis is an important cell death pathway for cones in contrast to rods, where apoptosis appears to be the preferred cell death pathway. In concordance, lack of RIP3 expression does not prevent rod cell death but leads to preservation of cones. The importance of RIP proteins in mediating necrosis is also shown recently in a mouse model of retinal degeneration induced by subretinal injection of dsRNA, a component of the drusen, causing RPE cell death and inflammation in AMD patients (Murakami et al. 2013). In such a model, lack of RIP3 expression has a protective effect by preventing necrosis and inflammation and suppressing the release of HMGB1 (Fang et al. 2012; Murakami et al. 2013). Recent studies have highlighted the contribution of necrosis in several models of photoreceptor degeneration, such as retinal detachment, light damage, and retinal ischemia (Shahinfar et al. 1991; Trichonas et al. 2010; Rosenbaum et al. 2010).

## 11.5 Mediators of Cell Death Pathways

### 11.5.1 Calcium Signaling and Photoreceptor Cell Death

Under dark conditions, rod photoreceptors are depolarized because of an inward flow of sodium and calcium through cyclic nucleotide-gated channels (cGMP-dependent) located in the outer segment. Upon light stimulation, 11-*cis*-retinal bound to rhodopsin is isomerized into all-*trans*-retinal, triggering the release of  $\alpha$ -subunit of the G-protein transducin, which in turn activates a photoreceptor-specific cyclic nucleotide phosphodiesterase (PDE). Activated PDE hydrolyzes cGMP to GMP, reducing its intracellular concentration, and thereby closing cyclic nucleotide-gated channels and triggering an outward flux of potassium leading to hyperpolarization of the photoreceptor membrane. Channel closure also leads to a decrease in calcium influx and a decrease of glutamate release at the synaptic terminal. cGMP concentration is restored by activation of guanylate cyclase upon reduction in intracellular calcium. Enzyme dysregulation, altered energy utilization, and changes in signaling molecule concentration are predicted to cause photoreceptor cell death when the visual transduction cascade is continuously active. Thus, calcium may play a crucial role in cell death.

Overload of intracellular calcium is a major contributor to cell death, including in photoreceptors (Wenzel et al. 2005; Zhivotovsky and Orrenius 2011; Fox et al. 1999; Takano et al. 2004; Read et al. 2002; Fox et al. 2003; Sharma and Rohrer 2004). However, it is still unclear whether the additional  $\text{Ca}^{2+}$  enters from the extracellular space or is released from intracellular storage in mitochondria or endoplasmic reticulum (Orrenius et al. 2003). The importance of  $\text{Ca}^{2+}$  in photoreceptor cell death has been investigated in the *rdl* mouse retina, where a strong activation of  $\text{Ca}^{2+}$ -dependent enzymes occurs (Paquet-Durand et al. 2006; Hauck et al. 2006). Here, photoreceptors go under severe and rapid degeneration caused by a mutation in PDE- $\beta$ , which, when mutated, also causes photoreceptor death in humans (Bowes et al. 1990; McLaughlin et al. 1993). The mutated PDE6 $\beta$  is not functional, potentially leading to cGMP accumulation and constitutive opening of cGMP-gated channels, resulting in an influx of  $\text{Ca}^{2+}$  into the cells. The deleterious effect of  $\text{Ca}^{2+}$  has been further demonstrated using *rdl* mice that also lack a major L-type voltage-dependent  $\text{Ca}^{2+}$  channel at the photoreceptor synapse. In the double mutant mice, photoreceptor cell death is slower compared to the *rdl* mice (Read et al. 2002). Calpains are a group of 15  $\text{Ca}^{2+}$ -activated cysteine proteases that have been implicated in degeneration of neuronal tissues (Paquet-Durand et al. 2006; Smith and Schnellmann 2012; Nakazawa 2011). Association of calpains with calpastatins in the endoplasmic reticulum specifically inhibits their activity, and overexpression of calpastatins has neuroprotective effects (Suzuki et al. 2004; Schoch et al. 2013; Wingrave et al. 2004; Cao et al. 2007). In the retina, calpains also play a critical role in photoreceptor cell death, and their inhibition can delay photoreceptor demise (Paquet-Durand et al. 2010; Mahajan et al. 2012; Ozaki et al. 2013). In the *rdl* mutant, calpains are strongly activated during photoreceptor

cell death with a concomitant downregulation of calpastatin and cyclic AMP response element-binding protein (CREB)-1 (Paquet-Durand et al. 2006). CREB1, a transcription factor critical for neuronal survival (Finkbeiner 2000; Mantamadiotis et al. 2002), is critical for integrating  $\text{Ca}^{2+}$  and cAMP signals. It can be activated by the AC/cAMP/PKA pathway, triggered by high intracellular  $\text{Ca}^{2+}$ , or by  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinases (CAMK).

### ***11.5.2 Oxidative Stress and Photoreceptor Cell Death***

Oxidative stress is closely linked to a number of neurodegenerative diseases (Andersen 2004; Komeima et al. 2006; Shen et al. 2005; Anderson et al. 1999) and is produced by increase in free radicals that cause damage to proteins, lipids, and DNA. Reactive oxygen species (ROS) are highly reactive molecules produced by normal oxygen metabolism from the mitochondria or by exogenous sources such as ionizing radiation. Varying rates of ROS production have been proposed to underlie differential rates of cell death in neurodegenerative diseases sharing the same mutation (Wright et al. 2004). Neuronal cells have very high metabolism and their membranes are rich in lipids and unsaturated fatty acids, which are ideal targets of lipid peroxidation, thus making them highly susceptible to damage by ROS.

During aging, the scavenging activities of endogenous antioxidants decrease and trigger oxidative stress (Klein and Ackerman 2003). However, it is still difficult to discriminate whether oxidative stress is the cause or the consequence of neuronal cell death (Andersen 2004). Additional investigations are required to identify signaling pathways activated by ROS and to define their role in death pathways.

Similar to other neuronal cells, photoreceptors are under constant environmental and intrinsic stress. Their function and location in the retina and the presence of high concentration of lipids in the outer segments make photoreceptors specially vulnerable as they are exposed to light, and ultraviolet radiations in particular, which can lead to the production of free radicals (Kagan et al. 1973; Oguni et al. 1996; Yang et al. 2003). These deleterious effects are amplified by high oxygen tension caused by proximity of the choroidal blood vessels that also participate in the production of ROS (Nickla and Wallman 2010). Interestingly, impairment of choroidal blood circulation in light-exposed albino rats is shown to delay photoreceptor cell death (Tanito et al. 2007b).

Mitochondrial metabolism is a major source of ROS. In photoreceptors, mitochondria are located in the inner segments. Mouse cone photoreceptors contain twofold more mitochondria than rods, and the ratio reaches tenfold in humans and primates (Hoang et al. 2002; Perkins et al. 2003). If rod and cone mitochondrial membranes have the same width, the total membrane surface is greater in cones compared to rods, suggesting high-energy demand and higher cytochrome c oxidase activity in cones (Hoang et al. 2002; Perkins et al. 2003). Oxidative stress and photoreceptor degeneration are tightly linked (Costa et al. 2008;

Shen et al. 2005), as has been described in models of retinal degeneration (Cao and Phillis 1995; Costa et al. 2008; Komeima et al. 2006; Kowluru and Odenbach 2004). As a by-product of energy production, mitochondria produce free radicals, including superoxide ( $O_2^-$ ) radicals. Mitochondria are also equipped with antioxidant mechanisms to preserve cell homeostasis. Among them are superoxide dismutase (SOD), in charge of converting  $O_2^-$  to hydrogen peroxide ( $H_2O_2$ ), and glutathione peroxidase and related enzymes, which convert  $H_2O_2$  to  $H_2O$ , making glutathione an important cellular antioxidant. Transgenic mice with gain-of-function mutation in *SOD1*, associated with familial amyotrophic lateral sclerosis in human, show specific light-induced photoreceptor cell death (Mittag et al. 1999). In addition, decreased expression of *SOD2* leads to photoreceptor cell death (Justilien et al. 2007). Such alterations in antioxidant properties of mitochondria may also be linked to AMD (Khandhadia and Lotery 2010). Because rod photoreceptors outnumber cones, it has been proposed that rod death leads to a great increase of oxygen tension on the remaining cone photoreceptors, thereby increasing their oxidative stress (Yu et al. 2000). Such mechanisms might participate in the non-cell-autonomous death occurring in rod-specific inherited retinal degeneration and explain the initially slow death rate in cones. Oxidative damage is reported in a transgenic pig model with rhodopsin mutation, in which cone photoreceptors progressively accumulate oxidative damage over time in parallel to their death (Shen et al. 2005). A similar pattern of oxidative damage and cell death is observed in *rdl* mice (Komeima et al. 2006). In contrast, reduction of superoxide radical production can reduce cone cell death (Komeima et al. 2008). Thus, loss of rod photoreceptors in RP may lead to hyperoxia in the outer nuclear layer, causing oxidative damage and slow death of cone photoreceptors.

The presence of free radicals in photoreceptor outer segments can also result in peroxidation of lipids, which account for about 15% of the total weight of photoreceptors compared to about 1% in most other cells (Bramall et al. 2010). Photoreceptors have a high amount of docosahexaenoic acid (DHA), a very long chain polyunsaturated fatty acid, which can be oxidized to highly reactive molecules such as malondialdehyde (MDA) and 4-hydroxy-2-neoal (4-HNE), two by-products that indicate the level of oxidative stress in cells (Moreira et al. 2010). Furthermore, oxidized phosphatidylcholine increases in human photoreceptors and RPE located in the macula during aging and at even higher levels in AMD patients (Suzuki et al. 2007). Oxidative stress is also shown to damage mitochondrial DNA in human RPE (Liang and Godley 2003). The decreased antioxidant capacity during aging, together with a concomitant damage to mitochondrial DNA, can contribute to AMD pathophysiology. Our recent studies in cone-only *Nrl*<sup>-/-</sup> mouse retina have shown an association between rapid and transient death of cones and transient increase of oxidative stress that are followed by long-term preservation of the remaining cone photoreceptors after lipid peroxidation suppresses (Roger et al. 2012).

Daily shedding and renewal of photoreceptor outer segments by the RPE can also be considered an antioxidant mechanism, designed to remove oxidized lipids and their by-products (Winkler 2008). Additional antioxidant mechanisms can



protect photoreceptors; for example, thioredoxins are small proteins playing an important role in the redox signaling cascade (Tanaka et al. 2000). Their expression is upregulated in response to oxidative stress and shown to have neuroprotective effects, especially in the retina (Tanito et al. 2002a, b, 2005, 2007a; Wang et al. 2008; Kong et al. 2010). Thioredoxin-like protein rod-derived cone survival factor (RdCVF) has been identified based on its property to sustain the viability of cone photoreceptors (Leveillard et al. 2004). RdCVF proteins are localized in the cone extracellular matrix, and lack of their expression in mice affects photoreceptor function and increases oxidative stress, suggesting a relationship between RdCVF and redox signaling (Cronin et al. 2010).

### ***11.5.3 Purine and Photoreceptor Death***

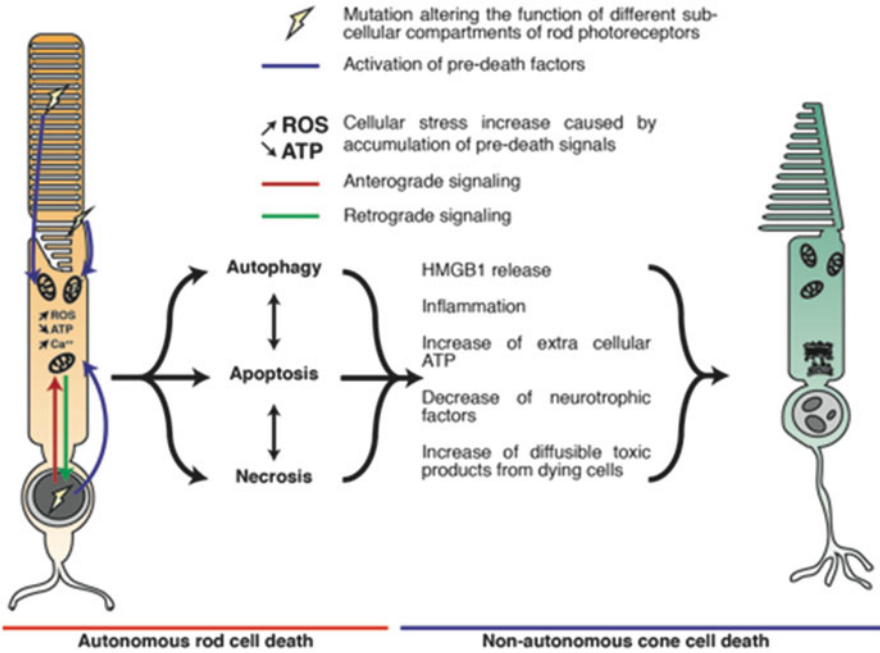
Intracellular ATP is a major source of cellular energy. When released into the extracellular space, it can also be used as a purinergic neurotransmitter in the central and peripheral nervous system. If the intracellular concentration of ATP is in the millimolar range, the extracellular concentration ranging from nanomolar to micromolar must result from the balance between release and degradation (Schwiebert 2000). Enzymes located at the cellular membrane, called ectonucleotidases, which produce ADP or AMP, control ATP concentration in the extracellular space. ATP can be released by damaged membranes of dying cells, by ATP transporters, channels, or osmotic transporters, or by exocytosis from synaptic vesicles. Two families of receptors, called P2X (seven subtypes) and P2Y receptors (eight subtypes), mediate ATP signaling. P2X receptors assemble into ATP-activated cation channels, selectively permeable to sodium and calcium ions, leading to an increase of intracellular calcium concentration and depolarization of the cell membrane (Abbracchio et al. 2009). P2X receptors have low affinity for ATP and have a fast response because they do not require the diffusion of a second messenger (Volonte et al. 2003). In contrast, P2Y receptors are metabotropic receptors belonging to the family of seven-transmembrane domain G protein-coupled receptors that generate a slower response because they have a higher affinity for their ligand and are coupled to potassium or calcium channels (Weisman et al. 2012).

ATP is demonstrated to regulate retinal function, especially as a neuromodulator released by Müller glia cells (Ward et al. 2010; Neal and Cunningham 1994; Newman 2003). P2X<sub>7</sub> and P2Y<sub>6</sub> receptors are expressed in the plexiform layers of rodent retinas, especially in the photoreceptor synaptic terminals (Puthussery and Fletcher 2004; Puthussery et al. 2006; Zhang et al. 2012). In addition to their role in modulating neurotransmission, P2 receptors are shown to be involved in cell homeostasis in the central nervous system (Franke and Illes 2006). The release of ATP into the extracellular environment can also participate in apoptosis-induced cell death after injury (Wang et al. 2004). In the retina, intravitreal injections of ATP, but not its breakdown products (i.e., ADP or AMP), induce extensive and

selective photoreceptor apoptosis through activation of P2 purinoreceptors in a dose-dependent manner and lead to severe photoreceptor degeneration and impaired ERG (Puthussery and Fletcher 2009). Notably, injection of the purinergic antagonist pyridoxal-phosphate-6-azophenyl-2',4'-disulfonic acid (PPADS) prevents ATP-induced apoptosis and reduces photoreceptor cell death in *rd1* mouse retina. The critical role of P2RX<sub>7</sub> in ATP-mediated apoptosis has been reported in cells under physiological stress such as nutrient starvation (Notomi et al. 2011). Injection of a P2RX<sub>7</sub> agonist triggered photoreceptor cell death in wild-type animals but has no effect in mice lacking P2X<sub>7</sub> receptor. Apoptosis can be mediated by activation of caspase-8 and -9, leading to the translocation of AIF1 from mitochondria to the nuclei (Notomi et al. 2011). Such a mechanism has also been identified in AMD patients with subretinal hemorrhage caused by choroidal neovascularization (CNV), in which increased levels of ATP are observed (Notomi et al. 2013). In vitro, extravascular blood initiates apoptotic pathways after binding to P2X<sub>7</sub> receptors, suggesting an important role for ATP in exacerbating photoreceptor cell apoptosis in AMD patients with CNV. The preceding discussion suggests that dying photoreceptors may release ATP into the extracellular space, and released ATP can bind to P2 receptors on neighboring photoreceptors and contribute to cell death by excessive stimulation.

## 11.6 Complexities Associated with Photoreceptor Degeneration

In addition to the large number of genes associated with photoreceptor degeneration, different mutations in the same gene can have diverse outcomes in terms of disease type, progression, and severity. For instance, mutations in *CRX*, a critical transcription factor for photoreceptor development, can cause dominant LCA, cone-rod dystrophy, or RP (Huang et al. 2012). In addition to allelic differences, environmental factors and genetic modifiers can also cause phenotypic variability. Modifier genes can protect or have additional deleterious effects, as described for *RPGR/RPGRIP1L*, *RPE65*, or *CEP290* (Cideciyan et al. 2013; Coppieters et al. 2010; Fahim et al. 2011; Khanna et al. 2009). Furthermore, clear heterogeneity exists in disease progression and cell death location within the retina. Nonuniform photoreceptor cell death illustrates the importance and differential sensitivity of photoreceptors expressing the exact same mutation (Jacobson et al. 2000). In mice, photoreceptor degeneration can follow in either way around a central/peripheral axis, suggesting that a gradient of molecules makes the photoreceptor cells more or less sensitive to cellular stress. One can also hypothesize the existence of distinct rod subtypes in the retina with differential sensitivity to cell death. Consequently, gene-profiling analysis from macula versus peripheral retina may reveal factors influencing photoreceptor homeostasis (Sharon et al. 2002). The heterogeneity of retinal photoreceptors is illustrated with different distribution of cones among



**Fig. 11.2** Convergence of cell death signals to trigger autonomous and nonautonomous cell death during photoreceptor degeneration. The large number of mutations in genes causing photoreceptor degeneration can alter any subcellular compartments of the photoreceptor cells. Mitochondria play an important role in the integration of pre-death factors generated by the cellular stress caused by mutated genes over time. Exchange of signals from the nucleus to the mitochondria (anterograde signaling) and vice versa (retrograde signaling) is an important part of this integration of life and death signal by the mitochondria to maintain cell homeostasis. Accumulation above a certain threshold of pre-death signal and cellular stress, such as ROS, activates photoreceptor cell death. In rod-cone dystrophies, rod photoreceptor cell death by apoptosis, necrosis, or autophagy leads to nonautonomous cone cell death by the release of toxic signals or a decrease of neurotrophic factors produced

vertebrates and especially by a dorsal–ventral gradient of short and medium/long wavelength opsins in the mouse retina (Applebury et al. 2000; Ng et al. 2001). However, very few molecules displaying gradient have so far been identified in the retina. Alternatively, a gradient of neurotrophic factors may create variability in the neuroprotective effects, generating resistance of photoreceptors to cellular stress (Cornish et al. 2005).

A large number of mutations leading to photoreceptor cell death converge to common death pathways such as apoptosis, necrosis, and autophagy (Fig. 11.2). Consequently, all these mutations must share common death effectors (Swaroop et al. 2010). Many genes associated with photoreceptor degeneration are ubiquitously expressed and exhibit extensive functional diversity. In addition, mutations in disease-causing genes do not always lead directly to nonfunctional photoreceptors. Slow progression of disease in many mutations supports a model involving the

accumulation of toxic molecules and damage before cell death (Clarke et al. 2001). LCA and AMD represent two extremes, with LCA-causing genes leading to early childhood blindness, whereas in AMD the first signs of the disease appear after many decades.

It is critical to identify pre-cell death molecules shared by different types of mutations because it is unlikely that each mutated gene triggers its own pre-apoptotic pathway (Swaroop et al. 2010). In such a model, the pre-death signal must reach a certain level to trigger cell death. The pre-death signal may also participate in death of neighboring photoreceptors because of the accumulation of toxic products extruded by dying cells into the microenvironment or the depletion of pro-survival factors [such as rod-derived cone viability factor (Rdcvf) and ciliary neurotrophic factor (Cntf)] (Fig. 11.2). The presence of diffusible toxic factors released by dying photoreceptors is supported by studies using chimeric animals in which the retina contains both normal and mutant photoreceptors and the cell death rate is proportional to the number of mutant cells (Burns et al. 2002; Huang et al. 1993). In such a model, the pre-death signal may converge and be integrated by an organelle in the cell to trigger cell death. One organelle where such integration takes place is the mitochondria, as the production of ROS appears to be correlated with the rate of photoreceptor cell death (Perez-Campo et al. 1998; Sastre et al. 2000; Wright et al. 2004). Overexpression of antioxidant defenses, such as SOD, which has neuroprotective effects, can extend cellular lifespan (Sampayo et al. 2003). However, the correlation between oxidative stress and neurodegeneration is still unclear, because most genes do not alter or directly induce ROS production. Mitochondrial DNA is more vulnerable to mutations compared to nuclear DNA, and such accumulation of genomic abnormalities would occur independently in each photoreceptor (Wright et al. 2009). The consequence could be altered mitochondrial bioenergetic functions, which then act as redox damage sensors. Mitochondria and the nucleus are suggested to have anterograde (nucleus to mitochondria) and retrograde signaling to maintain homeostasis and prevent the triggering of cell death pathways (Galganska et al. 2010). Oversaturation of ROS can modify proteins involved in cell death pathways and damage key mitochondrial proteins (Luce et al. 2010). The other consequence of ROS would be the modification of lipids in the mitochondria, which may influence the release of cytochrome c (Ott et al. 2002). In the retina, P53 and HDAC4 are two important components regulating photoreceptor cell death partly because of their sensitivity to oxidative stress (Ali et al. 1998; Chen and Cepko 2009).

## 11.7 Concluding Remarks and Therapeutic Perspective

Photoreceptor degeneration has often been associated with classical caspase-dependent apoptotic pathways. However, as discussed here, caspase-independent apoptosis and nonapoptotic pathways, such as necrosis or autophagy, can also play important roles. In addition, crosstalk among different death pathways would make

therapeutic approaches for photoreceptor degeneration challenging (Doonan et al. 2005; Lohr et al. 2006). One target can be mitochondria, which are one of the main hubs to integrate cellular stress signal and activate downstream cell death pathways (Lezi and Swerdlow 2012; Newmeyer and Ferguson-Miller 2003).

Retinal dystrophies offer great therapeutic potential because of easy anatomical access of the eye, an immunologically confined environment, and availability of noninvasive tools for assessing treatment outcomes in clinical trials. Such tools include direct vision assessment, the electroretinogram to test retinal function, and optical coherence tomography, which provides live imaging of the retina.

To prevent loss of vision in individuals with predisposing mutations, several approaches must be attempted concurrently: gene therapy, cell therapy, prosthesis implantation, and more recently optogenetic methods. Neuroprotection can also be used to preserve photoreceptors by blocking cell death or to strengthen endogenous pro-survival pathways. Such methods present the advantage of being mutation independent. However, studies using neurotrophic factors to delay degeneration showed significant variation in efficiency depending on the type of animal model studied, reflecting the complexity of cell death pathways (Trifunovic et al. 2012). The heterogeneous effects observed with neurotrophic factors suggest that multiple and combined pharmacological approaches may be required to thwart photoreceptor cell death.

Neurotrophic factors (i.e., bFGF, NGF, BDNF, PEDF, CNTF) have shown different degrees of neuroprotection in mouse models. Among these neurotrophic factors, ciliary neurotrophic factor (CNTF) has shown efficiency in more than ten different animal models (Wen et al. 2012; MacDonald et al. 2007). The use of encapsulated CNTF-expressing cells implanted in the eye of RP patients has shown promising results, especially for cone preservation, although the protective mechanism is still unclear (Sieving et al. 2006; Talcott et al. 2011). However, sustained CNTF expression leads to morphological and functional alterations (Bok et al. 2002; Rhee et al. 2007). It is still unclear if CNTF directly protects photoreceptors or indirectly by activating secretion from Müller glia cells of extrinsic factors having neuroprotective effects on photoreceptors.

As discussed here, oxidative stress and photoreceptor cell death are linked, and endogenous antioxidants play critical roles in redox homeostasis and photoreceptor survival (i.e., RdCVF, glutathione-S-transferase), which have been tested for different type of retinal dystrophies. For instance, in a clinical trial involving patients with RP, the combination of vitamin E, diltiazem, and taurin showed protective effects by delaying the progressive visual field reduction (Pasantes-Morales et al. 2002). Still, therapeutic success appears to be dependent on the genetic background and the nature of the mutation, as described for neurotrophic factors. In regard to the great variety of genetic modifications leading to photoreceptor cell death, it is critical to identify downstream death effectors commonly used in most mutant photoreceptors. The identification of a drug inhibiting such common death effectors will be of interest for further pharmaceutical development as it could have broader neuroprotective effects in a large number of retinal diseases. All these approaches require a detailed understanding of death pathways

activated during photoreceptor degeneration and of the intracellular effectors mediating neuroprotection. The technological advances made during the past few years in high-throughput genomic sequencing and in proteomics will certainly further our understanding of cellular mechanisms mediating photoreceptor homeostasis and assist in the development of therapeutics.

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