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Apoptosis in Retinal Degeneration—Recent Developments

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Dear Readers,

Irreversible degeneration of photoreceptors and RPE cells affects millions of patients in diseases such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP) and is a major cause of disability. Thus, many researchers investigate the causes of photoreceptor degeneration and how to prevent it. Rod and cone photoreceptors are one of the most physiologically active cells in the body. There are different experimental models of photoreceptor degeneration: hereditary models, retinal detachment and environmentally induced retinal degeneration, such as exposure to bright or continuous light or chemical injury. Almost hundred papers are published in this subject every year. This short review wants to concen- trate on just a few publications.

Using a light damage model of exposure to low continuous light which results in a 50% reduction of the outer nuclear layer after 7 d, Contin *et al*. showed rod photoreceptor cell death is independent of caspase 3 (as has been shown by others). Rhodopsin expression did not decrease before rod death, but rhodopsin became more phosphorylated at the Ser334 residue after light damage [1]. Abnormal rhodopsin phosphorylation has also been reported in rhodopsin mutants [2].

One of the most severe and sudden developing retinal diseases is neovascular ("wet") AMD (age-related macular degeneration) where leaky blood vessels grow into the subretinal space detaching the photoreceptors from their supportive retinal pigment epithelium (RPE). Notomi and colleagues [3] recently demonstrated that a significant increase in extracellular ATP occurs in neovascular AMD with subretinal hemorrhage (bleeding). This initiates neurodegenerative processes that are specifically tied to the ligand-gated ion channel 7 of the Purinergic receptor P2X (P2RX7; P2X7 receptor). Photoreceptor cell apoptosis is accompanied with activation of caspase-9 and translocation of apoptosis-inducing factor (AIF) from mitochondria to nuclei, as well as TUNEL-detectable DNA fragmentation. In mouse models (cell culture of retinal cells exposed to blood and an *in vivo* model of subretinal hemorrhage), photoreceptor cell apoptosis was prevented by a selective P2RX7 antagonist, brilliant blue G (BBG), which is an approved adjuvant in ocular surgery [3].

In a retinal detachment model of retinal degeneration, Zhu *et al*. showed that photoreceptor apoptosis can be reduced by RNAi (inhibitor RNA) for GADD153 (growth arrest DNA damage-inducible gene 153, also known as C/EBP homologous protein) with is involved in endoplasmatic reticulum stress during apoptosis and upregulated after retinal detachment [4]. Lentivirus with GADD153 siRNA was injected 2 weeks before retinal detachment, and retinas analyzed 1 - 7 days after detachment. GADD153 siRNA prevented loss of photoreceptors and preserved the outer nuclear layer. The authors suggested the gene therapy with GADD153 siRNA may be effective in retinal diseases. However, it needs to be emphasized that the treatment was done 2 weeks before the injury, similar to the effect of various growth factors that prevent retinal degeneration after light damage.

In retinitis pigmentosa, mutations in rod proteins lead to apoptosis of rod photoreceptors which then triggers later "non-autonomous" cone death. This has the greatest impact on human vision because cones provide daylight, high acuity color vision. If cone death could be prevented in retinitis pigmentosa, the patients would still have useful daylight vision.

Cone death after rod apoptosis (as is common in retinitis pigmentosa) can be delayed by insulin treatment and the Insulin receptor (IR)-phosphoinositide 3-kinase (PI3K) signaling pathway, indicating that cones surviving after rod death are starving [5]. Conditional deletion of the p85α subunit of the phosphoinositide 3-kinase (PI3K, a downstream effector of the insulin receptor) specifically in cone photoreceptors in transgenic mice

(using Cre-Lox technology) results in age-related cone degeneration [6]. These studies suggest that cones may have their own endogenous PI3K/Insulin-mediated neuroprotective pathway in addition to the cone viability survival signals derived from rods [6].

p53, a tumor suppressor protein involved in apoptosis during development, does not seem to be involved in photoreceptor apoptosis in the rd mouse, a model of retinitis pigmentosa, as rd mice that have p53 knocked out show the same rate of degeneration as rd mice with p53 [7]. However, p53 is upregulated when retinal pigment epithelium (RPE) cells are exposed to bright light and undergo apoptosis [7]. Thus, cell death mechanisms differ between photoreceptors and RPE. In a follow up paper [8], the same authors demonstrate that p53 is involved in developmental cell death, as a transgenic mouse over-expressing p53 ("super p53" mice) showed loss of rods and inner retinal cells combined with reduction of function of both rods and cones, but no age-dependent progression of photoreceptor death due to increased apoptosis during retinal development. In contrast, transgenic mice that specifically expressed p53 specifically in photoreceptors ("HIP mice") showed progressive cells death of both rods and cones.

Partial reprogramming of adult rods to cones by knockout of Nrl (neural retinal leucine zipper gene, essential for rod photoreceptors) results in protection of cone function and retinal integrity in two RP models, rd1 and rho−/− mice that have mutations in rod phototransduction proteins [9]. The investigators achieved this reprogramming by creating transgenic mice with an Nrl flowed allele (that developed a normal retina), and then crossing the Nrl floxed mouse to a transgenic line carrying a tamoxifen-inducible Cre recombinase, so they could induce Nrl knockout by taxominofen treatment in adult mice. However, in adult mice, rods could only partially be reprogrammed to cones but this was sufficient to prevent cone death and to maintain cone function.

On the other hand, mutations in cone phototransduction proteins only lead to apoptosis of cones without affecting rods. However, Cho *et al*. [10] showed recently cone-dependent rod death after conditional ablation of Ran-binding protein-2 (Ranbp2) in cone photoreceptors in mice. (Ranbp2 is essential for viability and energy metabolism, and plays a critical role cell-type dependent role in mediating gene-environment interactions. Mutations or deficits in Ranbp2 have been implicated in a variety of diseases, such as Parkinson, light toxicity, and the effects of carcinogens.) Cone-specific ablation of Ranbp2 causes non-apoptotic cone death, followed by death of rods. Dying rod populations were mixed apoptotic (TUNEL, Caspase 3) and necrotic (cell plasma permeability by EthD-III). These data support the existence of complex, unique and atypical cell death mechanisms between rod and cone photoreceptors which are likely determined by the cell-type dependent activities of Ranbp2.

In summary, photoreceptor apoptosis often does not follow the classical apoptotic pathways.

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