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Photoreceptor cell death and rescue in retinal detachment and degenerations

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ABSTRACT

Photoreceptor cell death is the ultimate cause of vision loss in various retinal disorders, including retinal detachment (RD). Photoreceptor cell death has been thought to occur mainly through apoptosis, which is the most characterized form of programmed cell death. The caspase family of cysteine proteases plays a central role for inducing apoptosis, and in experimental models of RD, dying photoreceptor cells exhibit caspase activation; however, there is a paradox that caspase inhibition alone does not provide a sufficient protection against photoreceptor cell loss, suggesting that other mechanisms of cell death are involved. Recent accumulating evidence demonstrates that non-apoptotic forms of cell death, such as autophagy and necrosis, are also regulated by specific molecular machinery, such as those mediated by autophagy-related proteins and receptor-interacting protein kinases, respectively. Here we summarize the current knowledge of cell death signaling and its roles in photoreceptor cell death after RD and other retinal degenerative diseases. A body of studies indicate that not only apoptotic but also autophagic and necrotic signaling are involved in photoreceptor cell death, and that combined targeting of these pathways may be an effective neuroprotective strategy for retinal diseases associated with photoreceptor cell loss.

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1. Introduction

Photoreceptor cells die when they are physically separated from the underlying retinal pigment epithelium (RPE) and choroidal vessels, which provide metabolic support to the outer layers of the retina. Retinal detachment occurs in various retinal disorders, including age-related macular degeneration (AMD) (Dunaief et al., 2002), diabetic retinopathy (Barber et al., 1998), as well as rhegmatogenous, tractional, and exudative retinal detachment (RD) (Cook et al., 1995). Although surgery is carried out to reattach the retina, only two-fifths of patients with rhegmatogenous RD involving the macula recover 20/40 or better vision (Campo et al., 1999). In other conditions mentioned, sustained serous RD causes progressive visual decline. Although various pathological changes occur in detached retina (Anderson et al., 1981; Lewis et al., 1994; Jablonski et al., 2000), studies on experimental models and human patient samples have shown that photoreceptor cell death is immediately induced as early as 12 h and peaks at around 2–3 days after RD (Cook et al., 1995; Hisatomi et al., 2001; Arroyo et al., 2005). Retinal imaging by optical coherence tomography have demonstrated that the microstructure of foveal photoreceptor cells is a critical factor predicting better visual function in patients who received successful RD repair (Schocket et al., 2006; Wakabayashi et al., 2009). These findings suggest that loss of photoreceptor cells may be an important cause of vision loss after RD. Photoreceptor cell death also underlies the pathology of other retinal disorders such as retinitis pigmentosa (RP) and AMD, and is the basis for visual decline. Although the causes and clinical characteristic of each retinal disorder differ, accumulating evidence suggests that some molecular pathways leading to photoreceptor cell death appear to be shared by these diseases at least in part. Therefore, identification of the mechanisms involved in photoreceptor cell death will be critical to developing new treatment strategies for these retinal diseases associated with photoreceptor cell loss. In the present review, we summarize the current knowledge of cell death mechanisms and their roles in RD and other retinal disorders.

2. Classification of cell death: apoptosis, autophagic cell death, and necrosis

2.1. Morphological features

Apoptosis, autophagy, and necrosis are three major forms of cell death defined by morphological appearance (Kroemer et al., 2009; Galluzzi et al., 2012). Schweichel and Merker (1973) proposed this classification in an ultrastructural study of physiological cell death in prenatal tissues. The morphological characteristics of each form