Chapter 6
Autophagy and Inflammation in Neuropsychological Disorders:
Autophagy in the Neurological-Visual Disease – Mechanisms and Therapeutic Potential

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ABSTRACT

Vision is a highly complex neural process that begins in the retina and is transmitted to the brain through the optic nerve, relying on the precise function of highly specialized neural and glial cells. It is of great importance for the integrity of vision to maintain the health of these cells. Autophagy, a lysosome-dependent degradation pathway, plays a crucial role in maintaining cellular homeostasis by eliminating misfolded proteins and damaged organelles. Dysregulation of autophagy has been recognized as a pivotal factor in the pathogenesis of multiple neurological-visual diseases, such as glaucoma, age-related macular degeneration (AMD), and inherited retinal dystrophies (IRDs). This chapter studies how autophagy is essentially governed at the molecular level during physiological/pathophysiological processes, particularly in the retina and optic nerve. Finally, emerging therapeutic approaches that aim to regulate autophagy are discussed to offer potential avenues to slow disease progression and preserve vision in neurodegenerative eye disorders.

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INTRODUCTION

Neurological-Visual Diseases: Definition and Scope

Neurological-visual diseases including both the central nervous system (CNS) and visual system are a category of eye disorders, particularly affecting the optic nerve, retina, and visual cortex. These include glaucoma, age-related macular degeneration (AMD), and inherited retinal dystrophies (IRDs), which lead to causes of irreversible vision loss worldwide (Ahmad et al., 2020; Jindal, 2015), commonly defined by the gradual decline in retinal ganglion cells (RGCs), retinal pigment epithelium (RPE), and optic nerve axons, via mechanisms involving apoptosis and autophagy dysfunction (Golestaneh et al., 2018; Rodríguez-Muela et al., 2012).

The retina and the CNS are composed mainly of post-mitotic neurons, which have a limited regenerative capacity and are long-lived. These neurons are particularly dependent on autophagy, a lysosome-dependent mechanism of cellular digestion, to clear damaged organelles and accumulated proteins (Gao et al., 2018; Scrivo et al., 2018). Dysregulation of autophagy has been increasingly recognized as a contributing factor in the pathogenesis of neurological-visual disorders (Jiménez-Loygorri et al., 2023).

Autophagy: A Critical Cellular Mechanism

Autophagy is a highly conserved intracellular process essential for maintaining neural and retinal homeostasis. This process of decomposition and recycling of damaged organelles, misfolded protein complexes, and proteins is particularly applied to differentiated cells such as RGCs and photoreceptors that cannot dilute toxic substances through cell division (Jiménez-Loygorri et al., 2023).

In eye tissues, degradation and quality control mechanisms operate through autophagy-dependent pathways, such as macroautophagy (De Duve & Wattiaux, 1966; Yang & Klionsky, 2010). Key molecular players like LC3, Beclin-1 (BECN1), autophagy-related 5/7 (ATG5/7) factors, and PINK1 (PTEN-induced kinase 1) / Parkin regulate mitophagy in RPE and photoreceptors, protecting against AMD and glaucoma (Chen et al., 2013; Greene et al., 2012; Nishida et al., 2009; Park et al., 2016; Sinha et al., 2017) Autophagy-independent degradation pathways are also vital for ocular physiology (Morishita, 2022). In contrast, autophagy-independent pathways, especially the UPS (ubiquitin-proteasome system) (Ross & Pickart, 2004) and PLAAT (phospholipase A and acyltransferase)-mediated organelle degradation contribute to lens transparency and protein quality control without involving canonical autophagy machinery (Morishita et al., 2021) (Table 1).