Chapter 1
Autophagy and Its Role in Neurodegenerative Diseases

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ABSTRACT

Autophagy is an intrinsic cellular process whereby cells degrade their own constituents, enabling them to acquire vital components during periods of nutrient deprivation and to eliminate damaged organelles and misfolded proteins. Neurodegenerative diseases are predominantly characterized by the accumulation of protein aggregates and tend to be more common with advancing age. Given that autophagy becomes less effective with age and is crucial for maintaining cellular homeostasis, its potential link to neurodegenerative disorders raises significant questions. Moreover, since neurons are post-mitotic and possess limited regenerative capacity, they are particularly reliant on autophagic mechanisms to sustain

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their viability. Understanding the role of autophagy in neurodegenerative diseases is critical not only for elucidating the pathogenesis of these diseases but also for developing effective therapeutic interventions. This chapter elucidates the mechanisms underlying autophagy in the context of recent findings and underscores its role in the progression of neurodegenerative diseases.

AUTOPHAGY

Autophagy is a process in which cells break down their organelles and proteins for recycling (J. Liu et al., 2024; S. Liu et al., 2023). Autophagy is a physiological mechanism aimed at maintaining homeostasis in cells (Gómez-Virgilio et al., 2022; Pavlinov et al., 2020). Autophagy provides crucial contributions to cells by balancing energy sources in response to nutrient stress, removing misfolded or aggregated proteins, clearing damaged organelles, and eliminating intracellular pathogens (Bai et al., 2020; Morimoto et al., 2023). During periods of starvation, autophagy is triggered to support cell survival by supplying essential nutrients through non-selective autophagy (Almannai et al., 2022; Iriondo et al., 2023; Yu et al., 2023). Additionally, it serves a critical housekeeping function by selectively degrading misfolded or aggregated proteins, damaged or unnecessary organelles, and intracellular pathogens through selective autophagy (Almannai et al., 2022; Iriondo et al., 2023). However, disruption of autophagy or excessive autophagic activity can lead to impaired cellular functions, which may be associated with diseases (Gómez-Virgilio et al., 2022; S. Liu et al., 2023). Additionally, the agents targeting the control and regulation of autophagy may contribute to the treatment of diseases (S. Liu et al., 2023).

AUTOPHAGY TYPES

There are three types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) (L. Chen et al., 2024; Morimoto et al., 2023) (Figure 1). Macroautophagy is the predominant mechanism of autophagy (Tutas et al., 2025). In macroautophagy, the phagophore, an isolation membrane, engulfs and sequesters cellular material (i.e. misfolded and aggregated proteins, damaged or unnecessary organelles, or microorganisms), leading to the formation of a double-membrane autophagosome (Demeter et al., 2020; Gómez-Virgilio et al., 2022). The autophagosome fuses with a lysosome, forming a single-membrane autolysosome, where the outer membrane merges with the lysosomal membrane, allowing the degradation of the inner membrane and its enclosed cargo (Holzer