

Chapter 5

Autophagy in Spinal Cord Injury: A Double-Edged Sword in Preclinical Studies of Synthetic and Natural Compounds

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ABSTRACT

Autophagy is a crucial cellular process involved in spinal cord injury (SCI) patho-

DOI: 10.4018/979-8-3693-5908-2.ch005

physiology. It can protect neural tissues by removing damaged cellular components, thereby promoting recovery. However, excessive autophagy may lead to neuronal apoptosis, inflammation, and disrupted cellular balance. This chapter explores the balance between autophagic activity and cellular health, emphasizing the need for precise regulation to harness autophagy's therapeutic potential. Recent studies highlight how autophagy interacts with mitochondrial dysfunction, reactive oxygen species, and inflammatory responses in SCI. Moreover, it discusses how natural compounds and nutraceuticals can modulate autophagy, offering promising strategies for managing consequences of SCI. Understanding autophagy is vital for advancing therapeutic interventions in SCI.

1. INTRODUCTION

Spinal cord injury (SCI) is a complex condition that results in sensory, motor, and autonomic dysfunction, often leading to long-term disabilities and significant healthcare burdens (Cunha et al., 2023). Traumatic SCI (tSCI) results from external physical forces, such as falls, sports injuries, and vehicular accidents (Grassner et al., 2016). Current treatment strategies include both surgical and conservative approaches. Recent studies suggest that targeting molecular pathways involved in SCI may offer therapeutic benefits by modulating cellular responses to injury (Ray, 2020; Luo & Tao, 2020). SCI progresses through two phases: the primary injury, caused by mechanical trauma leading to neural tissue compression and axonal disruption, and the secondary injury, characterized by oxidative stress, inflammation, and excitotoxicity, which exacerbate neuronal damage (Ghaffari et al., 2024; Ahuja et al., 2017). A key pathological feature of secondary injury is the activation of the NLRP3 inflammasome, contributing to immune responses and programmed cell death (Mokhtari & Uludag, 2023). Autophagy, a crucial cellular process, plays a dual role in SCI, with evidence suggesting both neuroprotective and detrimental effects (Vargova et al., 2021), serving as an evolutionarily conserved process where lysosomes degrade cellular components to maintain metabolic balance. It progresses through four stages: initiation, autophagosome formation, maturation, and degradation (Chen et al., 2024), ultimately preserving cellular homeostasis and preventing disease (Yu et al., 2018). While autophagy supports neuroprotection and functional recovery in SCI by reducing apoptosis and inflammation (Tang et al., 2014; Liao et al., 2021), excessive activation may contribute to cellular damage, highlighting the need for precise regulation (Wang et al., 2024; Wu et al., 2024).

Neurons, due to their postmitotic nature and specialized morphology, are particularly vulnerable to autophagy–lysosomal dysfunction. These dysfunctions intensify with age and are associated with neurodegenerative diseases, including

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