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ISSN: 0974-8369
Biology and Medicine

Perspective

Autophagy and its Crucial Role in Cellular Homeostasis and Human Disease

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DESCRIPTION

Autophagy, a highly conserved catabolic process, has emerged as a fundamental mechanism by which cells maintain homeostasis and adapt to stress. Derived from the Greek words "auto" (self) and "phagy" (eating), autophagy literally means self-digestion, reflecting its role in recycling damaged organelles, misfolded proteins, and other intracellular components. While initially studied as a response to nutrient deprivation, research over the past two decades has expanded our understanding of autophagy, revealing its involvement in development, immunity, metabolism, and disease. This intricate process balances cellular survival and death, acting as a double-edged sword in various physiological and pathological contexts.

At the molecular level, autophagy is orchestrated through a series of tightly regulated steps: initiation, nucleation, elongation, maturation, and degradation. Autophagosomes, double-membrane vesicles, form around cellular cargo and subsequently fuse with lysosomes, enabling enzymatic degradation of contents. Key regulatory pathways include the mammalian Target Of Rapamycin (mTOR), AMP-Activated Protein Kinase (AMPK), and the Autophagy-Related (ATG) proteins, which coordinate cellular responses to nutrient availability, energy status, and stress signals. Dysregulation of autophagy can disrupt homeostasis, leading to accumulation of damaged proteins and organelles, inflammation, and disease progression.

One of the most significant roles of autophagy is in neurobiology. Neurons, highly specialized and long-lived cells, are particularly dependent on efficient autophagic clearance to prevent accumulation of toxic protein aggregates. Defective autophagy is implicated in neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. In Alzheimer's disease, impaired autophagic flux contributes to the buildup of amyloid-beta and tau proteins, exacerbating neuronal dysfunction and cognitive decline. Experimental studies demonstrate that enhancing autophagy, either pharmacologically or genetically, can reduce aggregate accumulation and improve neuronal survival, highlighting its therapeutic potential.

Beyond neurodegeneration, autophagy plays critical roles in cancer biology. It exhibits a dual nature: on one hand, autophagy can suppress tumor initiation by eliminating damaged organelles and reducing genomic instability; on the other, established tumors can exploit autophagy to survive nutrient deprivation and hypoxia, promoting growth and metastasis. Cancer cells often display upregulated autophagic pathways, which contribute to resistance against chemotherapy and targeted therapies. Current research focuses on selectively modulating autophagy to impair tumor survival without compromising normal tissue homeostasis. Pharmacological inhibitors of autophagy, such as chloroquine derivatives, are being evaluated in clinical trials, often in combination with other anticancer agents.

Metabolic regulation is another area where autophagy is pivotal. In the liver, autophagy contributes to lipid metabolism by degrading lipid droplets through a process termed lipophagy. Dysregulation of lipophagy is associated with non-alcoholic fatty liver disease, obesity, and insulin resistance. In skeletal muscle, autophagy maintains mitochondrial quality, supporting energy homeostasis and preventing muscle atrophy. During starvation, autophagy provides essential substrates for gluconeogenesis and energy production, demonstrating its role in adaptive responses. Pharmacological activation of autophagy has been explored to improve metabolic function and protect against diet-induced obesity and type 2 diabetes in preclinical models.

The immune system relies on autophagy to regulate host defense and inflammation. Autophagy mediates the degradation of intracellular pathogens, a process termed xenophagy, contributing to innate immunity against bacteria, viruses, and parasites. It also shapes adaptive immunity by influencing antigen presentation, lymphocyte development, and cytokine production. Dysregulated autophagy can lead to immune deficiencies, hyperinflammation, and autoimmune diseases. For example, impaired autophagy is implicated in systemic lupus erythematosus and Crohn's disease, where defects in microbial clearance or immune tolerance exacerbate pathology. Therapeutic strategies targeting autophagy may thus offer novel

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Received: 04-Aug-2025, Manuscript No. BLM-25-30104; **Editor assigned:** 06-Aug-2025, Pre QC No. BLM-25-30104 (PQ); **Reviewed:** 20-Aug-2025, QC No. BLM-25-30104; **Revised:** 27-Aug-2025, Manuscript No. BLM-25-30104 (R); **Published:** 03-Sep-2025, DOI: 10.35248/0974-8369.25.17.787

Citation: Schultz H (2025). Autophagy and its Crucial Role in Cellular Homeostasis and Human Disease. Bio Med. 17:787.

approaches to modulate immune responses in infection and autoimmunity.

Aging is closely linked to autophagy, with evidence indicating a decline in autophagic efficiency over time. Reduced autophagy contributes to the accumulation of damaged proteins and organelles, chronic inflammation, and cellular senescence, all hallmarks of aging. Studies in model organisms demonstrate that interventions enhancing autophagy, such as caloric restriction, intermittent fasting, or pharmacological agents like rapamycin, can extend lifespan and improve healthspan. These findings suggest that modulating autophagy may represent a general strategy to combat age-related diseases and promote longevity.

Autophagy also intersects with cardiovascular health. Cardiomyocytes utilize autophagy to maintain mitochondrial quality and remove damaged proteins, particularly under stress conditions such as ischemia-reperfusion injury. Impaired autophagy in the heart contributes to myocardial dysfunction, hypertrophy, and heart failure. Conversely, enhanced autophagic activity has cardioprotective effects, mitigating tissue damage and preserving contractile function. Similarly, vascular smooth muscle cells and endothelial cells rely on autophagy to maintain vascular integrity and respond to oxidative stress, highlighting its systemic importance in cardiovascular physiology.