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Unveiling the Molecular Mechanism of Autophagosome-lysosome Fusion in Mammalian Cells

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Description

Autophagy, a highly conserved cellular process, plays a crucial role in maintaining cellular homeostasis by degrading damaged organelles, misfolded proteins, and pathogens. Central to autophagy is the fusion of autophagosomes with lysosomes, facilitating cargo degradation. This article delves into the intricate molecular mechanisms underlying autophagosome–lysosome fusion in mammalian cells, encompassing the key players and regulatory factors involved in orchestrating this essential cellular process [1]. Autophagy is a finely regulated process crucial for cellular health and survival. The fusion of autophagosomes with lysosomes represents a pivotal step in autophagic flux, ensuring the efficient degradation of engulfed cargo. Dysregulation of auto phagosome–lysosome fusion has been implicated in various pathological conditions, including neurodegenerative diseases, cancer, and metabolic disorders. Understanding the molecular intricacies of this fusion event is therefore paramount for elucidating disease mechanisms and developing targeted therapeutic interventions [2].

The process of autophagosomal biogenesis initiates with the formation of the Phagophore Assembly Site (PAS), where the Autophagy-related (Atg) proteins orchestrate membrane nucleation and expansion. Key players in this process include the ULK1 complex, comprising ULK1, FIP200, ATG13, and ATG101, which coordinates autophagy initiation in response to nutrient status and cellular stress. Subsequently, the class III Phosphatidylinositol 3-Kinase (PI3K) complex, composed of Beclin-1, VPS34, VPS15, and ATG14, generates Phosphatidylinositol 3-Phosphate (PI3P) to recruit other Atg proteins and facilitate membrane elongation [3].

Autophagy receptors, such as p62/SQSTM1, NBR1, NDP52, and optineurin, recognize ubiquitinated cargo and facilitate its encapsulation into auto phagosomes via interaction with Atg8 family proteins. This selective autophagy pathway ensures the specific targeting of damaged organelles, protein aggregates, and intracellular pathogens for degradation. Moreover, the cargo adaptors bridge the autophagosomal membrane with the dynein–dynactin motor complex, facilitating retrograde transport of cargo toward the Microtubule-Organizing Center (MTOC) for efficient autophagosome maturation. The fusion of auto phagosomes with lysosomes culminates in cargo degradation within the acidic lysosomal lumen. Several molecular players and regulatory factors govern this fusion process, including Rab GTPases, tethering factors, SNARE proteins, and lysosomal membrane proteins. Rab GTPases, such as Rab7 and Rab8a, regulate vesicle trafficking and maturation by recruiting effector proteins involved in membrane fusion. Tethering factors, such as HOPS and EPG5 facilitate the initial docking of auto phagosomes to lysosomes, priming them for fusion [4].

SNARE proteins mediate membrane fusion events by forming trans-SNARE complexes between the autophagosomal and lysosomal membranes. The core SNARE complex comprises the Qa-SNARE (syntaxin 17), Qb-SNARE (SNAP29), and two Qc-SNAREs. The assembly of these SNARE proteins orchestrates membrane fusion, allowing the content of auto phagosomes to be delivered into the lysosomal lumen for degradation. Moreover, lysosomal membrane proteins, such as LAMP1 and LAMP2, play crucial roles in stabilizing lysosomal membranes and regulating lysosome fusion events.

The fusion process is tightly regulated by various cellular signaling pathways, including mTORC1, AMPK, and calcium signaling. MTORC1 inhibition promotes autophagy induction and enhances autophagosome–lysosome fusion by dephosphorylating ULK1 and activating the autophagy machinery. Conversely, AMPK activation in response to energy stress stimulates autophagy and facilitates fusion by phosphorylating ULK1 and Beclin-1. Additionally, calcium signaling regulates lysosomal positioning and fusion by modulating the activity of calcium-regulated proteins, such as synaptotagmins and TRPML1. The fusion of autophagosomes with lysosomes represents a critical step in the autophagic process, essential for cellular homeostasis and the clearance of damaged components. Elucidating the molecular mechanisms governing autophagosome–lysosome fusion provides valuable insights into cellular physiology and disease pathogenesis. Further research into the regulation and dysregulation of this fusion event holds promise for the development of novel therapeutic strategies targeting autophagy-related disorders [5].

Acknowledgement

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Conflict of Interest

None.

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