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AMBRA1 Regulation: An Overview

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ABSTRACT

AMBRA1 (DCAF3) (Activating Molecule in Beclin-1-Regulated Autophagy) is a key regulator in the autophagy pathway, playing a critical role in cellular homeostasis and survival. This review provides a comprehensive overview of AMBRA1 regulation, focusing on its involvement in autophagy, its interaction with other proteins, and its implications in health and disease.

KEYWORDS: AMBRA1, health, regulation.

INTRODUCTION

Autophagy is a fundamental cellular process that involves the degradation and recycling of cellular components. Autophagy is a cellular degradation and recycling process that is highly conserved in all eukaryotes. In mammalian cells, there are three primary types of autophagy: microautophagy, macroautophagy, and chaperone-mediated autophagy (CMA). While each is morphologically distinct, all three culminate in the delivery of cargo to the lysosome for degradation and recycling(1). During microautophagy, invaginations or protrusions of the lysosomal membrane are used to capture cargo(2). Uptake occurs directly at the limiting membrane of the lysosome, and can include intact organelles. CMA differs from microautophagy in that it does not use membranous structures to sequester cargo, but instead uses chaperones to identify cargo proteins that contain a particular penta peptide motif; these substrates are then unfolded and translocated individually directly across the lysosomal membrane(3). In contrast to microautophagy and CMA, macroautophagy involves sequestration of the cargo away from the lysosome. In this case, *de novo* synthesis of double-membrane vesicles—auto phagosomes—is used to sequester cargo and subsequently transport it to the lysosome(4).

AMBRA1 Ambra1 is a 1,300-amino acid protein with a predicted molecular weight of 130 kDa. The *AMBRA1* gene is located on chromosome 11 and is composed of 18 exons.[4] Of the large number of alternative transcript variants predicted to exist (Ensembl Database), it will be interesting to determine which encode functional products and the significance of these proteins.

AMBRA1 is absent in lower eukaryotes but is highly conserved among vertebrates(5).The structure of the protein is characterized by WD40-domains in the N-terminal region. WD40 domains are highly abundant in eukaryotes and can participate in diverse cellular functions (including signal transduction, cell division, and RNA processing) by mediating protein–protein, protein–peptide, and protein–DNA interactions. These domains are probably the most pervasive interactors in the cell because they can provide platforms for the assembly of macromolecular complexes(6). Understanding the regulation of AMBRA1 is essential for elucidating the mechanisms of autophagy and its role in various diseases, including cancer, neurodegenerative disorders, and cardiovascular diseases.

1. AMBRA1 and Autophagy

1.1. Role in Autophagy:

AMBRA1 is essential for the initiation of autophagy. It interacts with Beclin-1, a key autophagy protein, to form the Beclin-1-Vps34 complex, which is necessary for the nucleation of autophagosomes(5). AMBRA1 also regulates the activity of ULK1, another critical autophagy protein, by promoting its dephosphorylation and activation(7)

1.2. Regulation by Post-Translational Modifications:

Post-translational modifications (PTMs) such as phosphorylation, ubiquitination, and acetylation play a significant role in the regulation of AMBRA1. For instance, AMBRA1 phosphorylation by ULK1 enhances its interaction with Beclin-1, facilitating autophagy initiation (8).Additionally, AMBRA1 can be ubiquitinated and degraded by the proteasome, which serves as a regulatory mechanism to control its levels and activity (Strappazzon et al., 2015).

1.3. Interaction with Other Proteins:

AMBRA1 interacts with various proteins involved in autophagy and other cellular processes(9). It binds to dynein, a motor protein, facilitating the transport of autophagosomes along microtubules(7) .AMBRA1 also interacts with BCL-2, an anti-apoptotic protein, to regulate the balance between autophagy and apoptosis(10).

2. AMBRA1 in Health and Disease

2.1. Cancer:

AMBRA1 plays a dual role in cancer, acting as both a tumor suppressor and a promoter depending on the context. Its ability to regulate autophagy can influence cancer cell survival and resistance to therapy. For example, AMBRA1-mediated autophagy has been shown to protect cancer cells from apoptosis induced by chemotherapy. On the other hand, loss of AMBRA1 function can lead to uncontrolled cell proliferation and tumorigenesis (10).

2.2. Neurodegenerative Disorders:

Dysregulation of autophagy is implicated in various neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and Huntington's disease. AMBRA1 plays a protective role in these conditions by promoting the clearance of damaged organelles and protein aggregates through autophagy(11). Enhancing AMBRA1 activity could be a potential therapeutic strategy for these diseases.

2.3. Cardiovascular Diseases:

Autophagy is crucial for maintaining cardiac homeostasis and function. AMBRA1 regulates autophagy in cardiac cells, protecting them from stress-induced damage. Studies have shown that AMBRA1 deficiency in the heart leads to increased susceptibility to ischemia/reperfusion injury and heart failure (12). Targeting AMBRA1 to modulate autophagy could provide new avenues for treating cardiovascular diseases.

CONCLUSION

AMBRA1 is a vital regulator of autophagy, influencing various cellular processes and disease states. Its regulation through PTMs and interactions with other proteins underscores the complexity of autophagy control mechanisms. Further research into AMBRA1 regulation could reveal new therapeutic targets for a range of diseases, from cancer to neurodegenerative and cardiovascular disorders.

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