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Control of ATG14 solubility and autophagy by MARCHF7/MARCH7-mediated ubiquitination

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ABSTRACT

Emerging research has unequivocally demonstrated the significance of post-translational modifications (PTMs) of proteins in orchestrating macroautophagy/autophagy regulation. Ubiquitination is a common PTM of proteins that regulates their stability, activity, and localization, thus playing a crucial role in various cellular processes, including autophagy. In recent work, a ubiquitination-related study revealed that MARCHF7/MARCH7 promotes the mixed polyubiquitination of ATG14 at multiple sites, mainly through the linkages of K6, K11, and K63 ubiquitin chains. Consequently, mixed ubiquitination leads to substantial insoluble aggregation of ATG14/ATG14L/Barkor, reducing its interaction with STX17, and ultimately causing a decrease in autophagy flux. It is noteworthy that we have observed that this regulation may hold significant potential value for the autophagic degradation of protein aggregates, as the number of aggresome-like induced structures (ALISs) is markedly reduced in *MARCHF7* knockout cells. This may have important potential implications for neurodegenerative diseases characterized by protein aggregation and impaired degradation.

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ATG14 plays a vital role in the regulation of autophagy and cellular homeostasis. Understanding its interactions with other proteins can provide valuable insight into not only the investigation of the regulatory mechanisms underlying autophagy, but also the development of potential therapeutic strategies for autophagy-related diseases. In a recent article, we identified a key role of MARCHF7, an E3 ubiquitin ligase of ATG14, in controlling autophagy through mass-spectrometry based interactomics of ATG14 [1]. The presence of MARCHF7 functions as a switch, turning autophagy off or on in autolysosome formation step (Figure 1).

One of the primary and most well-known functions of ATG14 is to serve as a core component of the class III phosphatidylinositol 3-kinase (PtdIns3K) complex I. This complex is involved in regulating autophagy initiation and the formation of the autophagosome. Further research has revealed that ATG14 plays a key role in promoting the fusion of autophagosomes and lysosomes through its interaction with the STX17-SNAP29. In our experimental investigations, we found that MARCHF7 specifically ubiquitinates ATG14 that interacts with STX17-SNAP29, while it has no significant effect on ATG14 within the PtdIns3K complex I. This indicates that the impact of MARCHF7 on autophagic flux is likely primarily concentrated on the fusion of autophagosomes with lysosomes. However, it is perplexing why MARCHF7 only exhibits catalytic activity on ATG14 in one complex while having no catalytic effect on ATG14 in the other complex. This discrepancy can be attributed to unknown protein-protein interactions or spatial conformation differences influenced by the formation of different complexes. Further experimental validation is needed to determine the specific reasons.

Ubiquitination is an important cellular quality control mechanism used to regulate the stability and functionality of proteins. As an E3 ligase, MARCHF7 catalyzes the mixed polyubiquitination of ATG14, thereby influencing autophagy. Additionally, MARCHF7-WI, a mutant variant with impaired E3 activity, was found to mainly localize in the nucleus of the cell. This localization discrepancy suggests a close relationship between the initiation of MARCHF7 catalysis and its cellular localization. It is now well-acknowledged that protein-protein interaction (PPI) or PTMs are important for protein shuttling between the nucleus and cytoplasm. Therefore, it is interesting to investigate whether MARCHF7-WI has a different interactome compared to wild-type MARCHF7, which may regulate MARCHF7 cellular localization. Furthermore, physiological and/or pathological stimuli that regulate the localization or activity of MARCHF7 need to be discovered.

Another significant observation that warrants attention is the formation of insoluble ATG14 aggregates after ubiquitination by MARCHF7. How do K6, K11, and K63 mixed ubiquitin chains induce the insoluble aggregation of ATG14? We speculated that the assembly order, abundance ratios, and spatial conformations of these chains may significantly contribute to this process. Additionally, why does ubiquitinated-ATG14 form insoluble aggregates in cells that are not degraded by the proteasome or lysosome? Does the formation of these insoluble aggregates serve the purpose of rapidly restoring ATG14 functionality

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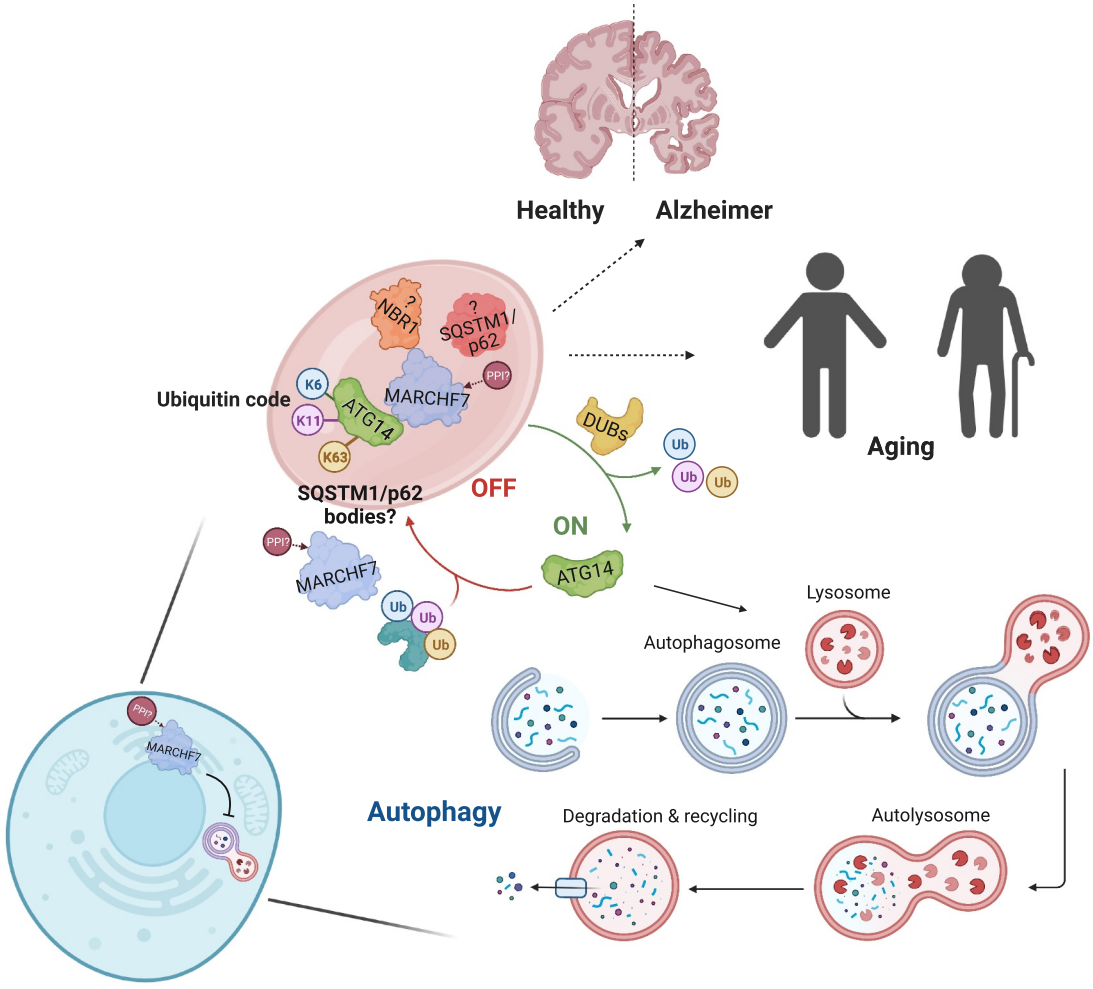

Figure 1. MARCHF7 mediates the ubiquitination and insoluble aggregation of ATG14, thereby acting as a switch for autophagic flux. The initiation of this regulation may be controlled by PPI of MARCHF7, which in turn affects neurodegenerative diseases or aging. Dashed arrows indicate hypothetical effects. Created with BioRender.com.

through deubiquitination under different stress conditions? Furthermore, whether the insoluble ATG14 aggregates have a relationship and/or colocalization with SQSTM1/p62 bodies and NBR1 is yet to be determined. These uncertainties highlight the importance of further clarifying the components of the AT14 aggregates and SQSTM1/p62 bodies.

In conclusion, comprehending the mechanism of ATG14 regulation through ubiquitination may offer potential strategies for restoring autophagic flux and advancing research on neurodegenerative disorders or aging. Future investigations might also involve fully characterizing additional regulatory factors that participate in the interaction between MARCHF7 and ATG14. This includes studying whether the modulation of the insoluble aggregates represents a more general mechanism, and if PPIs or PTMs play a role in multi-level switch in autophagy regulation.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Abbreviations

ALIS: aggresome-like induced structure; PPI: protein-protein interaction; PtdIns3K: phosphatidylinositol 3-kinase; PTM: post-translational modification

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Reference

[1] Shi X, Wu W, Feng Z, et al. MARCH7-mediated ubiquitination decreases the solubility of ATG14 to inhibit autophagy. Cell Rep. 2023;42(9):113045. doi: 10.1016/j.celrep.2023.113045