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Interaction of GCN5L1 with WHAMM and KIF5B Regulates Autolysosome Tubulation

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Abstract : Lysosome-dependent autophagy is a nutrient-deprivation-induced evolutionarily conserved intracellular recycling program that sequestrates intracellular cargo into autophagosomes (AP), which then fuse with lysosomes to form autolysosomes (ALs) for cargo digestion. To restore free lysosomes, autophagic lysosome reformation (ALR) is initiated by extrusion of tubular structures from autolysosomes at the final stage of autophagy, in a process called lysosomal tubulation (LT). This project aimed to investigate the molecular mechanism of GCN5L1 in LT and the following lysosomal signaling. GCN5L1 belongs to the BORC multiprotein complexes and is involved in controlling lysosomal trafficking; however, the effect of GCN5L1 on lysosome tubulation remains largely unknown. Genetic ablation of GCN5L1 in the mouse primary hepatocytes showed dramatically increased autolysosomes (ALs), decreased lysosome regeneration and absence of lysosomal tubulation. This phenotype suggests the possibility of disruption in lysosome tubulation, which results in the disturbance of the overall lysosome homeostasis. The formation of tubulars from ALs requires kinesin motor protein KIF5B. Immunoprecipitation was employed and confirmed the interaction of GCN5L1 with the ARL8B-KIF5B complex, which recruited KIF5B to ALs. At the same time, GCN5L1 interacted with WHAMM, which promotes the actin nucleation factor, which brings actin cytoskeleton to ALs and initiates LT. Furthermore, impaired LT in GCN5L1 deficient hepatocytes was restored by overexpression of GCN5L1, and this rescue effect was attenuated by knockdown of KIF5B. Additionally, lysosomal mTORC1 activity was upregulated in GCN5L1-/- hepatocytes, while inhibition of mTORC1 abrogated the GCN5L1 mediated rescue of LT in knockout hepatocytes. Altogether these findings revealed a novel mechanism of ALR, in which a simultaneous interaction of GCN5L1 with KIF5B and WHAMM is required for LT and downstream mTORC1 signaling.

Keywords : autophagy, autolysosome, GCN5L1, lysosome
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