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MAP4K2 connects the Hippo pathway to autophagy in response to energy stress

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ABSTRACT

As a key regulator of development, organ size, tissue homeostasis and cancer, the Hippo pathway is tightly regulated by various growth-related signaling events. Among them, energy stress activates the Hippo pathway to inhibit its downstream effector YAP1. Our recent work reported a YAP1-independent role of the Hippo pathway in promoting macroautophagy/autophagy and cell survival in response to energy stress, a process mediated by Hippo kinase MAP4K2. MAP4K2 interacts with and phosphorylates MAP1LC3A/LC3A at S87, which in turn drives autophagosome-lysosome fusion via the RAB3GAP-RAB18 axis. Energy stress activates MAP4K2 by reducing its association with the Hippo phosphatase complex STRIPAK component STRN4. Moreover, MAP4K2 is highly expressed in head and neck cancer, while MAP4K2 and its mediated autophagy are required for head and neck cancer development. Taken together, our study not only reveals a noncanonical role of the Hippo pathway in energy stress response, but also suggests Hippo kinase MAP4K2 as a potential therapeutic target for head and neck cancer treatment.

Abbreviation: AMPK: 5′-AMP-activated protein kinase; Atg8: autophagy related 8; LATS1: large tumor suppressor 1; LIR: microtubule-associated protein 1 light chain 3-interacting region; MAP1LC3A/LC3A: microtubule-associated protein 1 light chain 3 alpha; MAP4K2: mitogen-activated protein kinase kinase kinase kinase 2; PPP2/PP2A: protein phosphatase 2; RAB3GAP: RAB3 GTPase activating protein; RAB18: RAB18, member RAS oncogene family; SLMAP: sarcolemma associated protein; STK3/MST2: serine/threonine kinase 3; STK4/MST1: serine/threonine kinase 4; STRIPAK: striatin-interacting phosphatase and kinase; STRN4: striatin, calmodulin binding protein 4; SQSTM1/p62: sequestosome 1; TEAD: TEA domain family member; ULK1: unc-51 like kinase 1; WWTR1/TAZ: WW domain containing transcription regulator 1; YAP1: yes-associated protein 1.

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Autophagy; Energy stress; Hippo pathway; LC3; MAP4K2; STRIPAK

Main text

The Hippo pathway is an evolutionarily conserved signaling pathway known for its crucial roles in development, regeneration, organ size control, and tissue homeostasis. In the mammalian Hippo pathway, STK3/MST2, STK4/MST1 and MAP4Ks function in parallel to phosphorylate and activate LATS1 and LATS2, which in turn phosphorylate transcriptional co-activators YAP1 and WWTR1/TAZ, resulting in their cytoplasmic retention and degradation. As a PPP2/PP2A-family member, the STRIPAK complex suppresses STK3/STK4 and MAP4Ks via its adaptors SLMAP and STRN4, respectively. When the Hippo pathway is inactivated, unphosphorylated YAP1 and WWTR1/TAZ are translocated into the nucleus, where they bind TEAD transcription factors to promote the transcription of growth-related genes including those involved in glucose metabolism. Energy stress activates the Hippo pathway and AMPK to phosphorylate YAP1 at different sites and respectively target its nuclear localization and TEADs association (Figure 1). Interestingly, our recent work uncovers a YAP1-independent role of the Hippo pathway in driving autophagy under energy stress conditions, a process mediated by Hippo components STRIPAK and MAP4K-family member MAP4K2 [1].

Through a Hippo pathway interactome analysis, we uncovered Atg8-family proteins as putative binding proteins for MAP4K2. A LIR motif was identified in MAP4K2 and required for its interaction and colocalization with LC3. Although LC3 binding does not affect MAP4K2 kinase activity, MAP4K2 plays a critical role in autophagy. Specifically, targeting MAP4K2 induces the accumulation of LC3 and SQSTM1/p62 proteins, LC3 puncta, and vesicle-like structures in cells and lipid droplets in fasted mouse livers. Interestingly, the viability of the MAP4K2-deficient cells is dramatically reduced under energy stress conditions, while this is not the case for other tested stress conditions (e.g., serum starvation, amino acids starvation), suggesting a unique role of MAP4K2-mediated autophagy in energy stress response.

Based on these findings, we further discovered that MAP4K2 is required for the autophagosome-lysosome fusion in autophagic flux but is not involved in early signaling events of autophagy, such as ULK1 activation and LC3 lipidation. Moreover, MAP4K2 phosphorylates LC3A at multiple sites, among which S87 phosphorylation is required for the MAP4K2-mediated autophagosome-lysosome fusion and cell survival under energy stress conditions. Upon S87 phosphorylation, LC3A binds and recruits RAB3GAP1 to an autophagosome, which in turn activates RAB18 to drive autophagosome-lysosome fusion. These data suggest the MAP4K2-LC3A-RAB3GAP-RAB18 signaling axis as a key regulator of autophagic flux and cell survival in response to energy stress.

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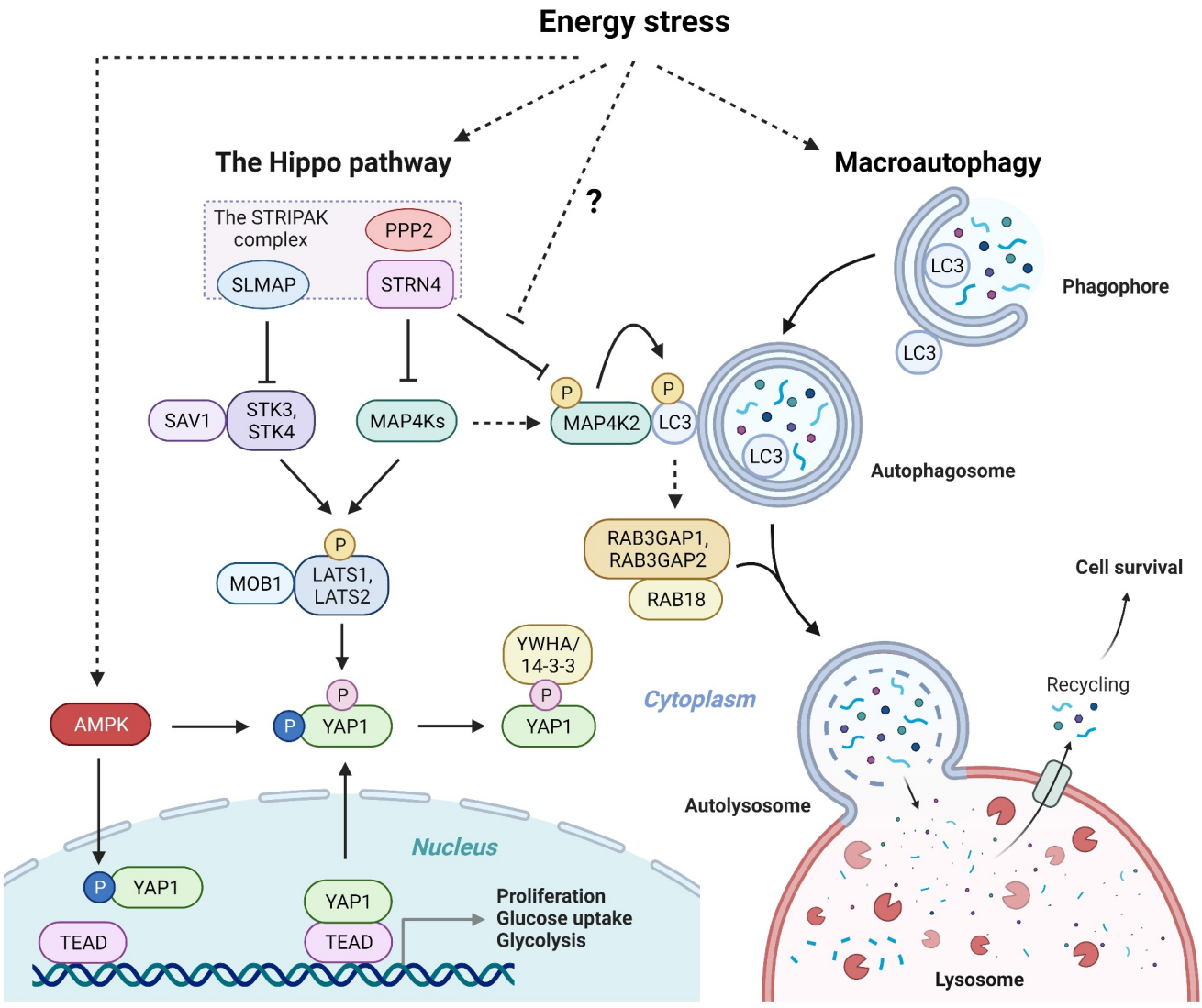

Figure 1. The Hippo pathway facilitates autophagy in response to energy stress. Upon energy stress, the Hippo pathway and AMPK phosphorylate YAP1 to respectively target its nuclear localization and TEAD association, resulting in the loss of the transcription of genes involved in cell proliferation, glucose uptake and glycolysis. Our recent work reveals a YAP1-independent role of the Hippo pathway in promoting autophagy in response to energy stress, a process mediated by its components STRIPAK and MAP4K2. Energy stress activates MAP4K2 by attenuating its association with the STRIPAK complex component STRN4, which in turn phosphorylates autophagy protein LC3 to drive autophagosome-lysosome fusion and cell survival via the RAB3GAP-RAB18 axis.

Regarding the upstream regulation of MAP4K2, we showed that energy stress, but not other tested stress conditions, promotes MAP4K2 activation and LC3A S87 phosphorylation. This process is mediated by the STRIPAK complex in the Hippo pathway, which binds and inhibits MAP4Ks via its component STRN4. Although energy stress does not affect STRIPAK complex formation, it abolishes the interaction between STRN4 and MAP4K2, unleashing MAP4K2 for activation. Again, this regulation is specific to energy stress because other tested stress conditions do not affect STRN4-MAP4K2 complex formation. These data suggest that energy stress feeds to the Hippo component STRIPAK to activate MAP4K2 and its dependent autophagy.

Given the roles of the Hippo pathway and autophagy in cancer development, we examined the cancer relevance of this newly discovered signaling axis centered on MAP4K2. Interestingly, MAP4K2 is highly expressed in head and neck cancer correlating with the poor survival rate of head and neck cancer patients. Furthermore, MAP4K2 and its mediated LC3A S87 phosphorylation are required for head and neck tumor growth in both the orthotopic and patient-derived xenograft models. These findings indicate the oncogenic roles of MAP4K2 and autophagy as well as therapeutic potential of the MAP4K2 inhibitors for head and neck cancer.

Although our work uncovers a noncanonical role of the Hippo pathway in promoting autophagy and cell survival in energy stress response, key questions remain to be answered. First, it is unclear how energy stress is transduced to STRIPAK to inhibit the interaction of STRN4 with MAP4K2. Notably, our recent interactome data reveal the subunits of AMPK, the master kinase in energy stress response, as potential binding proteins for STRN4. This finding suggests that AMPK can act upstream of STRIPAK to affect STRN4-MAP4K2 complex formation upon energy stress and deserves to be further characterized. Second,

because the Hippo pathway and autophagy are both highly conserved signaling events, how such MAP4K2-mediated autophagy evolved in evolution is interesting and warrants examination. Third, upon energy stress, AMPK-induced YAP1 phosphorylation targets YAP1-TEADs complex formation and completely abolishes YAP1 transcriptional activity (Figure 1), making the Hippo-induced YAP1 cytoplasmic translocation dispensable. Here, our study provides novel insights into the Hippo pathway in energy stress response, highlighting the possibility that the Hippo pathway may exert additional functions in this process through other Hippo pathway components, such as MAP4Ks, LATS1 and LATS2, and cytoplasm-localized phospho-YAP1, which deserves further investigation.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Reference

[1] Seo G, Yu C, Han H, et al. The Hippo pathway noncanonically drives autophagy and cell survival in response to energy stress. Mol Cell. 2023 Sep 7;83(17):3155–3170 e8. doi: 10.1016/j.molcel.2023.07.019