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Review

# Control of YAP/TAZ Activity by Metabolic and Nutrient-Sensing Pathways

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**Metabolism is a fundamental cellular function that can be reprogrammed by signaling pathways and oncogenes to meet cellular requirements. An emerging paradigm is that signaling and transcriptional networks can be in turn regulated by metabolism, allowing cells to coordinate their metabolism and behavior in an integrated manner. The activity of the YAP/TAZ transcriptional coactivators, downstream transducers of the Hippo cascade and powerful pro-oncogenic factors, was recently found to be regulated by metabolic pathways, such as aerobic glycolysis and mevalonate synthesis, and by the nutrient-sensing LKB1–AMPK and TSC–mTOR pathways. We discuss here current data linking YAP/TAZ to metabolism and suggest how this coupling might coordinate nutrient availability with genetic programs that sustain tissue growth, neoplastic cell proliferation, and tumor malignancy.**

## YAP/TAZ: Transcriptional Integrators of Multiple Cellular Cues

Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) are two orthologous mammalian transcriptional coactivators that shuttle between the cytoplasm and the nucleus, where they interact with the TEAD (TEA domain) family of transcription factors, and possibly other transcription factors, to regulate transcription [1,2]. YAP/TAZ are powerful regulators of cell proliferation and survival, and play important roles in stem cells, organ growth, and adult tissue homeostasis; as such, their activity is frequently subverted in cancer, where YAP/TAZ are hyperactivated to sustain tumor growth and to acquire malignant traits, including self-renewing and metastatic abilities [1,3,4]. A surge of publications in the past decade identified YAP/TAZ as downstream effectors of multiple inputs, including the Hippo pathway – a key conserved regulator of organ size (Box 1) – as well as cell polarity and the epithelial-to-mesenchymal transition (EMT), mechanical and cytoskeletal cues, and WNT and other growth factor signaling cascades [5–7]. Thus, rather than being dedicated downstream transducers of a single signaling pathway, YAP/TAZ act as integrators of a series of converging cellular and tissue-embedded cues to determine cell behavior in a coherent and coordinated manner.

Recent findings have also implicated metabolic pathways as regulators of YAP/TAZ activity. Indeed, glycolysis, energy stress, and mevalonate biosynthesis have been shown to modulate YAP/TAZ activity, suggesting a role for YAP/TAZ in coordinating nutrient availability, or cell metabolic traits, with transcription and cell proliferation. We examine here the biochemical and functional data supporting the proposed molecular mechanisms underlying metabolic regulation of YAP/TAZ, in the hope of providing a framework for future work that deepens the physiological relevance of these fascinating connections.

### Trends

Recent findings indicate that YAP/TAZ transcriptional coactivators, downstream transducers of the Hippo cascade, can be regulated by key metabolic pathways and nutrient-sensing mechanisms.

Mevalonate metabolism, by providing essential precursors for protein prenylation, sustains RHO membrane localization and activity, and in turn, YAP/TAZ nuclear localization.

Glucose metabolism and aerobic glycolysis promote binding of YAP/TAZ to TEAD factors, thus sustaining YAP/TAZ transcriptional activity and protumorigenic functions.

Energy status and LKB1/AMPK kinases regulate YAP phosphorylation, providing an alternative mechanism to Hippo for regulation of Yorkie in *Drosophila* tissues.

Inactivation of the TSC tumor-suppressor in perivascular epithelioid cell tumors inhibits autophagy, which leads to increased YAP protein levels and tumor growth.

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### Box 1. The Core Hippo Pathway

The Hippo tumor-suppressor pathway was discovered and characterized in *Drosophila* [86]. Homologs of the key components of the pathway are also found in mammals, where the Hippo pathway is centered on the activity of two kinase families, MST1/2 and LATS1/2, and on their cofactors, SAV/WW45, which act as a scaffold for the interaction between MST1/2 and LATS1/2, and Mob1A/B, which facilitate LATS1/2 activity (Figure I). MST1/2 phosphorylates and activates LATS1/2, which in turn phosphorylates YAP and TAZ at several serine residues (five in YAP, four in TAZ). YAP/TAZ phosphorylation leads to functional inhibition through multiple mechanisms, including nuclear exclusion, binding to 14-3-3 proteins, and, mainly in the case of TAZ, proteasomal degradation mediated by the ubiquitin ligase β-TRCP [1]. α-Catenin can bind to phosphorylated YAP together with 14-3-3 proteins, and this prevents YAP dephosphorylation [87,88]. Functional data indicate that two of the LATS phosphorylation sites (S127/381 in YAP, S89/311 in TAZ) are mainly responsible for phosphorylation-mediated inhibition. Phosphorylation of YAP/TAZ is also regulated by phosphatases of the PP1 family [89,90]. It is currently unknown where in the cell LATS1/2 phosphorylates YAP and TAZ, also because multiple LATS- and YAP- containing protein complexes have been described [91,92].

The activity of LATS1/2 can be regulated by several inputs. NF2/Merlin activates LATS1/2 in parallel to MST1/2, but it is not clear whether this occurs in the nucleus, where NF2 can prevent the ubiquitin ligase DCAF1 from inhibiting LATS1/2, or at the cell membrane [93,94]. SCRIBBLE acts at the basolateral cortex, and promotes the assembly of an MST–LATS–TAZ inhibitory complex [16]. CRUMBS is localized at the apical membrane, where it interacts with multiple cell junction-associated proteins such as LIN7C, MPDZ, PALS1/MPP5, and INADL/PATJ, and where it is thought to facilitate YAP phosphorylation [95,96]. MAP4Ks can directly phosphorylate and activate LATS1/2, acting in parallel to MST1/2 [97–99]. LATS1/2 kinase activity can be also indirectly regulated by GPCRs and by the F-actin cytoskeleton through as yet unknown mechanisms [1]. NF2, LATS1/2, and YAP/TAZ can all bind to proteins of the angiomotin family (Amot, AMOTL1, and AMOTL2), but discordant functional roles have been proposed *in vitro*; *in vivo*, the available genetic evidence indicates a pro-YAP/TAZ function for Amot in the liver [100].

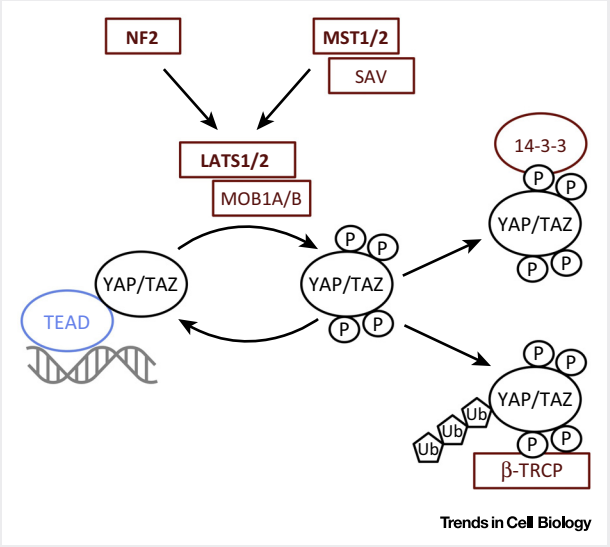


Figure I. A Simple Scheme for the Hippo Kinase Signaling Cascade. Only core components of the mammalian Hippo pathway are shown, for which extensive genetic and/or biochemical data are available. (Bottom left) TEAD transcription factors bind to nuclear DNA and recruit YAP/TAZ to regulate transcription. (Bottom right) Phosphorylation (P) of YAP/TAZ by LATS1/2 kinases causes their inhibition through multiple mechanisms, including nuclear exclusion, binding to 14-3-3 proteins, and ubiquitin-mediated degradation (Ub). Other regulators and interacting proteins are discussed in Box 1 and the main text.

## Mevalonate and RHO Signaling

The first connection between YAP/TAZ activity and cell metabolism emerged from the identification of the mevalonate pathway as a required input for YAP/TAZ activity *in vitro* [8,9]. The mevalonate pathway is responsible for the conversion of acetyl-coenzyme A into the biochemical precursors of isoprenoids, which include cholesterol, bile acids, steroid hormones, and heme. In addition, some of the intermediates such as farnesyl-pyrophosphate and geranylgeranyl-pyrophosphate are directly involved in protein prenylation, in other words the covalent linkage of a hydrophobic molecule to cysteine residues, thereby facilitating protein attachment to cell