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Mechanism of Hippo Signalling Pathway in Anti-Cancer Treatment- An Overview

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Abstract:

Chemotherapy represents one of the maximum efficacious strategies to deal with cancer sufferers, bringing effective changes at least quickly even to those sufferers with incurable malignancies. However, maximum patients respond poorly after a sure quantity of cycles of treatment due to the development of drug resistance. Resistance to drugs administrated to cancer sufferers significantly limits the advantages that patients can reap and is still a severe scientific problem. Among the mechanisms that have been uncovered to mediate anti-cancer drug resistance, the Hippo signaling pathway is gaining growing interest due to the brilliant oncogenic sports of its additives (as an instance, YAP and TAZ) and their druggable residences. Hippo pathway changed into to start with recognized via genetic displays for genes regulating organ size in fruitflies. Recent studies have highlighted the role of Hippo signaling as a key regulator of homeostasis, and in tumorigenesis. Hippo pathway is constructed from genes that act as tumor suppressor genes like hippo (hpo) and warts (wts), and oncogenes like yorkie (yki). YAP and TAZ are associated mammalian homologs of Drosophila Yki that act as effectors of the Hippo pathway. Hippo signaling deficiency can cause YAP- or TAZ-established oncogene dependency for cancer cells. YAP and TAZ are frequently activated in human malignant cancers. These transcriptional regulators may provoke tumorigenic changes in stable tumors by using inducing most cancers stem cells and proliferation, culminating in metastasis and chemo-resistance. Given

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the complicated mechanisms (e.G., of the most cancers microenvironment, and the extrinsic and intrinsic cues) that overpower YAP/TAZ inhibition, the molecular roles of the Hippo pathway in tumor boom and progression stay poorly described. This overview will spotlight cutting-edge expertise of how the Hippo signaling pathway regulates anti-most cancers drug resistance in tumor cells, and presently available pharmacological interventions focused on the Hippo pathway to remove malignant cells and potentially deal with cancer sufferers.

Keywords: YAP, HAZ, Yorkie, Growth, Tumor, TAZ

Introduction

Hippo pathway become to begin with identified through genetic screens for genes regulating organ size in fruitflies. Recent research has highlighted the position of Hippo signaling as a key regulator of homeostasis, and in tumorigenesis. Hippo pathway is constructed from genes that act as tumor suppressor genes like hippo (hpo) and warts (wts), and oncogenes like yorkie (yki). YAP and TAZ are associated mammalian homologs of Drosophila Yki that act as effectors of the Hippo pathway. Hippo signaling deficiency can cause YAP- or TAZ-dependent oncogene dependency for most cancers' cells. YAP and TAZ are regularly activated in human malignant cancers. These transcriptional regulators may provoke tumorigenic modifications in solid tumors by inducing cancer stem cells and proliferation, culminating in metastasis and chemo-resistance. Given the complex mechanisms (e.G., of the most cancers microenvironment, and the extrinsic and intrinsic cues) that overpower YAP/TAZ inhibition, the molecular roles of the Hippo pathway in tumor boom and development remain poorly described.

Cancer is a complex genetic ailment where cells divide uncontrollably and infiltrate everyday cells causing debilitating effects often leading to death. Cancer cells spark off mechanisms that dispose of the ordinary exams on increase and sell tumor growth and survival. The present day general of care is surgical procedure, often observed via radiation- or chemo-therapy for treating cancer. However, cancer cells display exquisite capabilities to steer clear of immune-surveillance mechanisms and are regularly proof against these treatments. A key question is what are the key mobile occasions that arise in early levels of cancer? Further, what are the environmental or inner cues that cause these adjustments? Although those questions remain unresolved, the sizeable body of labor has revealed the function of mobile indicators brought on through oncogenic pathways in most cancers boom and progression. In addition, the focal point of such studies is to expand targeted therapies which can be more powerful and benefit the patients. Specifically, oncogene activation induces signaling outputs which are specific, and purpose activation of effectors that promote out of control proliferation of cancer cells. One such key effector is the YAP/Yki transcriptional co-activator that acts downstream of the Hippo pathway.

As a effective weapon to kill aberrantly rapid-growing tumor cells, chemotherapy represents one of the most efficacious treatment techniques for the general public of cancer sufferers,

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immensely prolonging development-free survival and improving great of lifestyles. However, most cancers remain in large part incurable, because of their early asymptomatic nature and overdue prognosis, nearby and distant metastasis, and the development of healing resistance. Although combinations of multiple healing retailers have become the paradigm for cancer remedy as preliminary answers to the resistance towards single-agent treatment, drug resistance is still a huge impediment (1). Till now, although a variety of mechanisms through which tumor cells increase resistance against anti-cancer agents had been described, the precise organic methods stay incompletely understood. Improved therapeutic final results and survival may be achieved from decoding the biological determinants of drug resistance in tumors, a good way to manual the design of novel techniques to defeat drug resistance. Numerous research has unraveled how the disorder or dysregulation of the Hippo signaling pathway in human most cancers cells contribute to anti-cancer drug resistance and the way these mechanisms might be exploited to clinically advantage most cancer patients. In addition to how the activation or inactivation of these molecules (no longer handiest YAP/TAZ, however also different components within the Hippo pathway) results in drug resistance. We additionally summarize the pharmacological marketers that allow the intensive anti-most cancers performance by targeting the Hippo pathway.

Mechanism of Hippo Signalling

According to a traditional theory, the mammalian Ste20-like kinases 1/2 (MST1/2; homologs of Drosophila Hippo [Hpo]) phosphorylate and activate large tumour suppressor 1/2 (LATS1/2; homologs of Drosophila Warts [Wts]) in the centre of the Hippo pathway (Fig. 1A). Two transcriptional coactivators, Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif, are inhibited by this kinase cascade in a normal manner (TAZ; two homologs of Drosophila Yorkie [Yki]). When YAP and TAZ are active, they go into the nucleus to bind the TEAD transcription factor family (homologs of Drosophila Scalloped [Sd]) and trigger the activation of a variety of genes that are essential for cell survival, migration, and proliferation.

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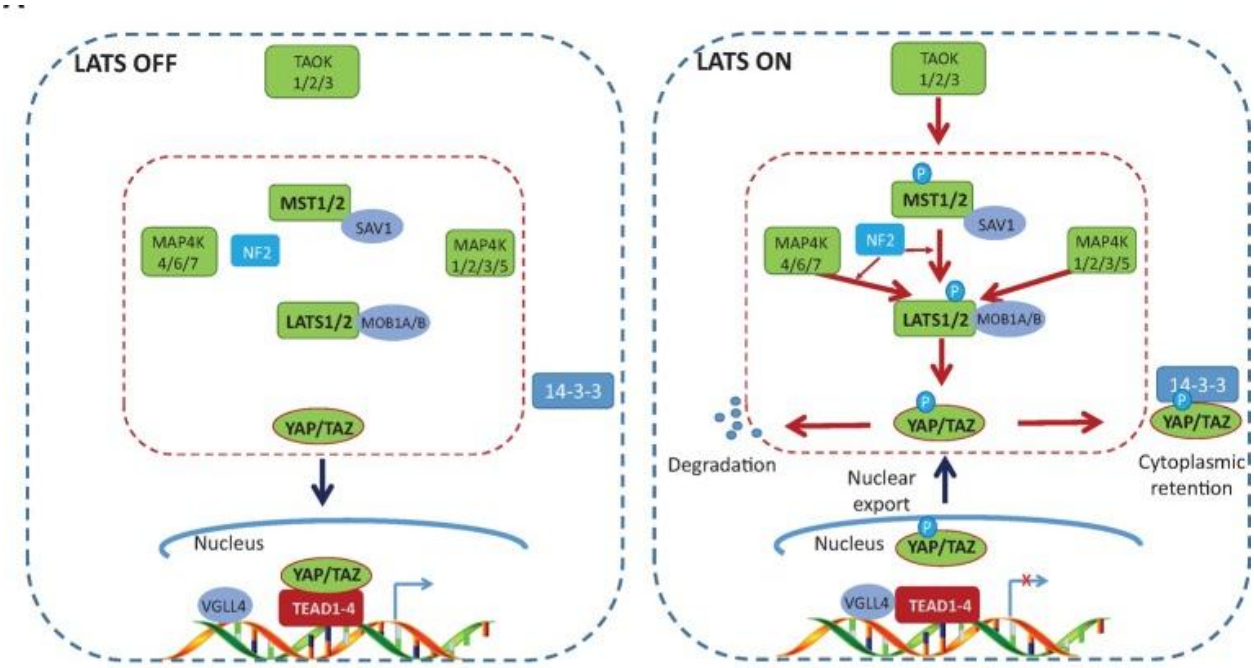

Fig 1: ZhipengMeng, Toshiro Moroishi and Kun-Liang Guan. Mechanism of Hippo Regulation. Genes Dev 2016 Jan. doi: 10.1101/gad 274027.115

TAO kinases (TAOK1/2/3), which phosphorylate MST1/2's activation loop (Thr183 for MST1 and Thr180 for MST2; from here on, all residues belong to human proteins), can start the Hippo kinase cascade mechanically (4,5). Additionally, there is proof that MST1/2 autophosphorylation can lead to the activation loop phosphorylation (6). According to this concept, MST1/2 dimerization increases the activation loop phosphorylation (7). Therefore, it is possible that dimerization can start MST1/2 activation and that upstream kinases are not always necessary. In addition to MST1/2, MAP4K1/2/3/5 (homologs of Drosophila Happyhour [Hppy]) and MAP4K4/6/7 (homologs of Drosophila Misshapen [Msn]) can also directly phosphorylate LATS1/2 at its hydrophobic regions, activating LATS1/2 (8,9). Under serum deprivation, triple MAP4K4/6/7 knockout in HEK293A cells significantly lowers YAP/TAZ phosphorylation compared to double MST1/2 knockout, suggesting that MAP4Ks may regulate the Hippo pathway more prominently than MST in some circumstances (8). However, in order to prevent YAP phosphorylation in response to LATS-activating cues, such as contact inhibition, energy stress, serum deprivation, and F-actin disintegration, both MST1/2 and MAP4Ks must be deleted (8). As a result, MST1/2 and MAP4Ks play somewhat complementary roles in the control of LATS1/2. YAP and TAZ are phosphorylated to make them bind to 14-3-3, and this interaction causes cytoplasmic sequestration of YAP/TAZ (10). Degradation of YAP/TAZ occurs as a result of ubiquitination and degradation of LATS-induced phosphorylation of YAP/TAZ by Casein kinase 1 and engagement of the SCF E3 ubiquitin ligase (11,12). Additionally, autophagy has the ability to break down YAP protein (13).

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YAP and TAZ lack DNA-binding domains because they are transcriptional coactivators. Instead, they interact with TEAD1-4, sequence-specific transcription factors that in mammalian cells drive the primary transcriptional output of the Hippo pathway, to control gene expression when they translocate into the nucleus (10). TEAD1-4 can act as transcriptional repressors by binding to VGLL4 in the nucleus. By separating VGLL4 from TEAD1-4 through their connection, YAP/TAZ and TEAD1-4 activate TEAD-mediated gene transcription, which encourages tissue development and prevents apoptosis (14). The functional roles of these genes in the Hippo pathway have been supported by mouse models with deletion of MST1/2, SAV1, MOB1A/B, NF2, LATS1/2, or YAP overexpression. These mouse models also show up-regulated expression of TEAD target genes, increased expansion of progenitor cells, and tissue overgrowth (15,16,10,17,12).

Signals that control the Hippo pathway upstream

The Hippo pathway controls the phosphorylation-induced cytoplasmic retention and protein degradation of YAP and TAZ in response to a variety of internal and extrinsic cues, and studies over the past ten years have established YAP and TAZ as its main effectors. In most cases, these signals act on peripheral Hippo pathway components to modify phosphorylation activities of the core kinase cascade. In addition, a number of proteins directly control the location or transactivation of YAP without influencing the activity of LATS kinase (18). Furthermore, because these signals also influence the actions of YAP and TAZ, the Hippo pathway interacts with Wingless/Ints (Wnt), bone morphogenetic proteins (BMPs), Notch, and Hedgehog (Hh) (19). Here, we list the upstream signals and parts of the peripheral Hippo pathway that communicate with the core kinase cascade (Fig. 2).

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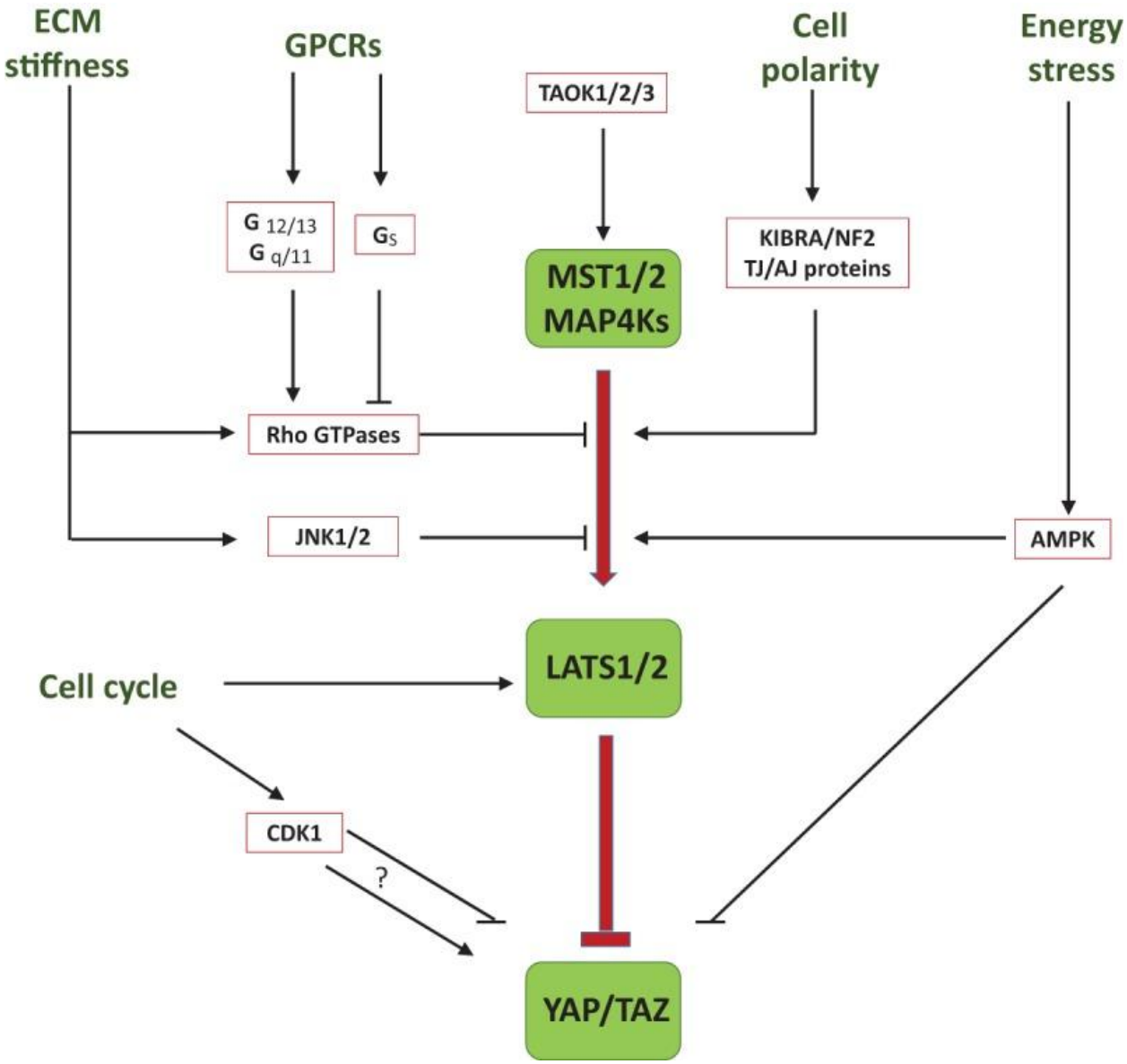

Mechanisms that activate the Hippo kinase cascade

LATS1/2 are members of the protein kinase A/G/C (AGC) family's subgroup known as the NDR (nuclear Dbf2-related) family of kinases (20). NDR1 (STK38) and NDR2 are the NDR family's other two members (STK38L). NDR1/2 is consistently included in the Hippo pathway network in a number of recent proteomic analyses of the Hippo pathway interactome (21,22,23). To prevent YAP-driven carcinogenesis in the intestinal epithelium, NDR1/2 may act as a YAP kinase (24). It is important to note that the phosphorylation motifs of LATS1/2 and NDR1/2 are identical. The precise function of NDR1/2 in the control of the Hippo pathway has to be

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clarified, nevertheless, as loss of LATS1/2 is sufficient to stop YAP phosphorylation and result in constitutive YAP nuclear localization in the majority of the conditions tested (8).

The hydrophobic motif regulatory site and a conserved Ser/Thr residue within the activation loop must be phosphorylated for the NDR family kinases to be activated. Upstream Ste20-like kinases MST1/2 for LATS1/2 and NDR1/2, (24,25,26,27), and MST3 for NDR1/2, phosphorylate the hydrophobic motif (28). Recent research has demonstrated that the Ste20 family member MAP4Ks can phosphorylate the LATS1/2 hydrophobic motif (8,24). The hydrophobic motif is phosphorylated by a Ste20-like kinase, which encourages LATS autophosphorylation in the activation loop and raises kinase activity (29,28). It's interesting to note that although LATS1/2 and NDR1/2 appear to utilise different subsets of MOB proteins, the N-terminal regulatory domain of the kinases interacts with MOB proteins (the human genome encodes six MOBs: MOB1A/B, MOB2, and MOB3A/B/C). While MOB2 mediates an inhibitory connection with NDR1/2 but not LATS1/2, MOB1A/B associate with both LATS1/2 and NDR1/2 (30,31,32,33).

New molecular understanding of MOB1's functions in LATS1/2 phosphorylation and activation by MST1/2 is provided by a recent crystal structure research, and a sequential phosphorylation model is presented (Fig. 3; 34). MST2 creates a phosphor-docking motif by autophosphorylating the lengthy linker between the kinase domain and the SARA domain, which can attract MOB1. The MOB1-phosphoMST2 complex's structure demonstrates how MOB1 is released from its autoinhibitory conformation and made available to LATS1 by attaching to the phosphorylated MST2. The MST2-MOB1-LATS1 ternary complex is then formed when LATS1 attaches to the MOB1-phosphoMST2 complex, boosting the phosphorylation of LATS1 at its hydrophobic motif (T1079) and MOB1 at its N-terminal tail (T35 and T12) by MST2. While phosphorylation of MOB1 really causes the separation of phosphorylated LATS1 and MOB1 from MST2, phosphorylation of T1079 in LATS1 by MST2 directly leads to LATS1 activation. The phosphorylated MOB1 also allosterically promotes LATS1 autophosphorylation at its activation loop (S909), which is necessary for LATS1 activation after its hydrophobic motif, T1079, has been phosphorylated by MST2. This information is further revealed by the structure of the phosphoMOB1 and LATS1 complex. The molecular mechanism by which LATS1/2 is activated by MST1/2 and the crucial function of MOB1 in this process are structurally revealed by this study.

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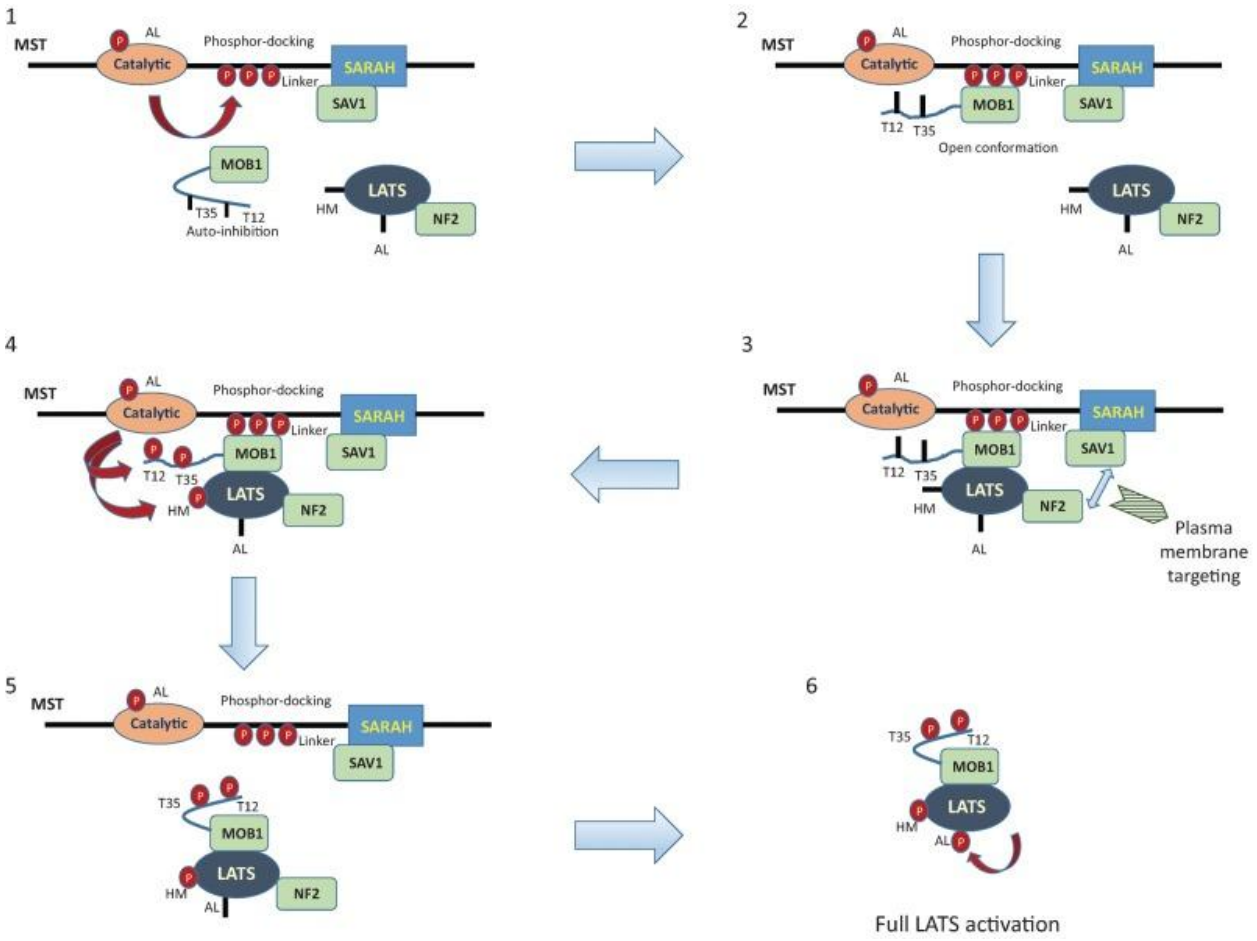

Fig 3: Fig 1: ZhipengMeng, Toshiro Moroishi and Kun-Liang Guan. Mechanism of Hippo Regulation. Genes Dev 2016 Jan. doi: 10.1101/gad 274027.115

In addition, a recent work employing the crystal structures of the NDR and MOB homologs in budding yeast, Cbk1 and Mob2, demonstrates that Mob2 binding to Cbk1 not only enhances Cbk1's enzymatic activity but also generates a docking motif for Cbk1 substrates (35). Given that Cbk1 is the only AGC family kinase with robustness and substrate selectivity, this docking is essential. This suggests that MOB has a function in both kinase activation and substrate specificity. One could hypothesise that a comparable process is involved in the activation of the MOB and NDR/LATS kinases in mammals.

Conclusion

Tumor cell resistance to anti-cancer treatment medications can be mediated by hyperactivation of YAP/TAZ or loss-of-function of tumour suppressors in the Hippo pathway. Drug sensitivity can be restored by pharmacologically depleting or inhibiting YAP/TAZ, or by re-expressing

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tumoursuppressors in the Hippo pathway, indicating that YAP/TAZ activity intervention is a potential method for overcoming drug resistance in cancer cells.

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