

REVIEW ARTICLE

The Hippo Tumor Suppressor Pathway (YAP/TAZ/TEAD/MST/LATS) and EGFR-RAS-RAF-MEK in cancer metastasis

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Abstract Hippo Tumor Suppressor Pathway is the main pathway for cell growth that regulates tissue enlargement and organ size by limiting cell growth. This pathway is activated in response to cell cycle arrest signals (cell polarity, transduction, and DNA damage) and limited by growth factors or mitogens associated with EGF and LPA. The major pathway consists of the central kinase of Ste20 MAPK (*Saccharomyces cerevisiae*), Hpo (*Drosophila melanogaster*) or MST kinases (mammalian) that activates the mammalian AGC kinase *dmWts* or LATS effector (MST and LATS). YAP in the nucleus work as a cofactor for a wide range of transcription factors involved in proliferation (TEA domain family, TEAD1-4), stem cells (Oct4 mononuclear factor and SMAD-related TGFβ effector), differentiation (RUNX1), and Cell cycle/apoptosis control (p53, p63, and p73 family members). This is due to the diverse roles of YAP and may limit tumor progression and establishment. TEAD also coordinates various signal transduction pathways

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such as Hippo, WNT, TGF β and EGFR, and effects on lack of regulation of TEAD cancerous genes, such as KRAS, BRAF, LKB1, NF2 and MYC, which play essential roles in tumor progression, metastasis, cancer metabolism, immunity, and drug resistance. However, RAS signaling is a pivotal factor in the inactivation of Hippo, which controls EGFR-RAS-RAF-MEK-ERK-mediated interaction of Hippo signaling. Thus, the loss of the Hippo pathway may have significant consequences on the targets of RAS-RAF mutations in cancer.

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Introduction

The most common oncogenic pathway in different types of tumor is the RAS transduction pathway and also the active mutations responsible for the direct growth and survival signals.^{1,92,93} Mutation in all RAS isoforms (K-RAS, H-RAS, and N-RAS) enhances the active form of the protein. In addition, the normal signal for wild-type RAS is membrane tyrosine kinase receptors that can be activated by mutation, gene replication, or high levels of receptor-ligand (EGF).² Mitogen and other chemicals (such as lysophosphatidic acid and sphingosine-1-phosphate) increase growth and can also send a signal directly to RAS via G-protein-coupled receptors. This has led to the activation of heterotrimeric G-proteins and G α_i ,³ that are capable of targeting RAS activity by activating G-protein-independent, β -arrestin, and SRC.⁴ Also, activation or mutation of G-protein-coupled receptors in cancer can increase cell proliferation activity and survival pathways.⁹² Undoubtedly, wild-type RAS increases by changing endogenous control mechanisms. It is important that by increasing the expression of GTPase exchange factors or by decreasing the expression of GTPase activating proteins (hydrolysis of GTP to GDP), RAS changes, eventually resulting in the elimination of neurofibromatosis protein 1.^{5,92} Indeed, after activation, RAS signaling is mediated through interaction with RAS-binding domains (RAF kinases, A-RAF, B-RAF, or C-RAF (RAF-1), PI3K, Tiam1, and RGS12/14) or through the domain RAS association (RA), such as RalGDS, Afadin-6, Rin1, phospholipase C epsilon, and RASSF proteins (RASSF1-10) transmitted to downstream effectors.^{6,7} Notably, many downstream effectors are oncogenes or tumor suppressor genes that are mutated or silenced in cancers independently of RAS (B-RAF, PI3K, RalGDS, and RASSF1).⁹² In fact, mitogen-activated protein kinase (MAPK), PI3K-AKT, and RASSF1-MST (Hippo) are downstream pathways that activated in these cases. These pathways also mediate the interaction between EGFR-RAS signaling and the Hippo tumor suppressor pathway. Thus, the mitogen-activated protein kinase cascade comprises several related parallel pathways that activate a set of extracellular regulated kinase 1/2, JNK1/2, p38 $\alpha/\beta/\gamma/\delta$ or extracellular regulated kinase 5.⁸ Although growth and inflammation can activate different amounts of these events, however, RAS is highly correlated with JNK activation as well as p38 with extracellular regulated kinase 1/2 activation. Activation of RAF kinases by RAS stimulates MEK1/2 activation, which in turn MEK1/2 activates kinases of extracellular regulated kinase

1/2 and increases proliferation by stimulating cell entry into the cell cycle.⁹ Remarkably, this process supported by a number of scaffolding proteins and places the cascade forming units adjacent to the cell, which also enhances the control of the output signal. Beside, Scaffold proteins may be essential to increase signal diffusion. These proteins are also capable of directing the mechanical position of a signal in a cell and stimulating the output domain of the signal to create the proper cellular response. Many scaffold proteins disrupt cancer cells and cause inappropriate levels of RAS signaling (RAS-RAF scaffolds, CNK, RAF-MEK scaffolds KSR and IQGAP).^{10,11} In principle, MP1 supports MEK-ERK, and the RASSF1 scaffold also restricts MEK activation (Fig. 1).^{12,13}

Certainly, RAS is a potent oncogene and the occurrence of additional mutations (N-RAS and B-RAF mutations in melanoma) in its pathway causes the development of a neoplasm.¹⁴ However, mutations (K-RAS, B-RAF, or PI3K) can occur in normal human or mouse tissues without tumorigenesis, that indicate mutations in the RAS pathway limit tumor suppressor pathways.^{15–18} Importantly, p53 responds to RAS activation by stimulating the cell cycle, that in most cancers p53 is mutated; accordingly, although germline mutations or loss of TP53 induce tumorigenesis independently of RAS, however, somatic changes are a late event in tumor progression that is often related to metastatic expansion.^{19–21} This fact indicates that family members associated with TP53 (p63 and p73) or other tumor suppressor pathways play an important role in the early stages of tumorigenesis, which will certainly help to identify the RAS pathway of cancer.

Hippo pathway

Hippo Tumor Suppressor Pathway

A major pathway for cell growth is the Hippo tumor suppressor pathway that regulates tissue and organ growth by limiting cell growth.²² This pathway is also activated in response to cell cycle arrest signals (cellular polarity, transduction, and DNA damage) and blocked by growth factors or mitogens associated with EGF and LPA.^{23,24} It should be noted that the main pathway consists of the central kinase Ste 20 MAPK (*Saccharomyces cerevisiae*), Hpo (*Drosophila melanogaster*) or MST kinases (mammalian) that activate the mammalian AGC kinase dmWts or LATS effector (MST and LATS).²⁵ The major output of LATS-mediated

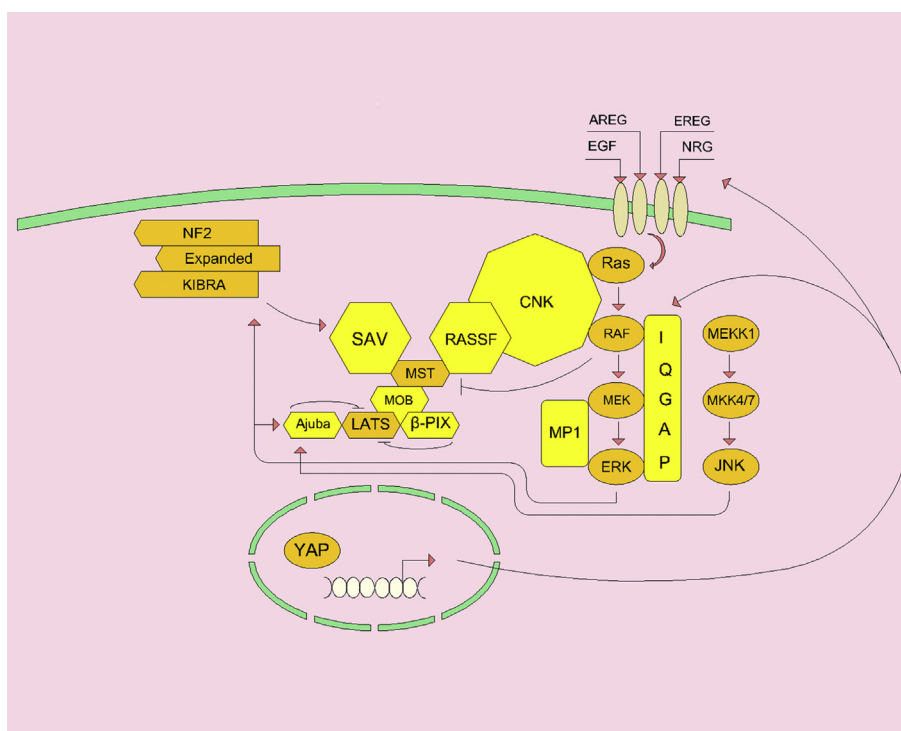


Figure 1 MOB, RASSF, SAV scaffolding proteins play an essential role in activating the Hippo pathway. β -PIX and Ajuba scaffolds inhibit LATS's ability to phosphorylate YAP and trigger a positive response to JNK or ERK phosphorylation. ERK can phosphorylate KIBRA (upstream activator of SAV) and increase growth. RAS-MAPK scaffolds enhance MAPK signaling and help to suppress Hippo signaling. Activation of YAP transcription increases IQGAP, EGFR, and growth factors.

phosphorylation pathway is the co-factor yes-associated protein (YAP) (dmYki) that participates in various activities (biological responses associated with different transcription factors).²⁶ The number of inputs of cell polarity regulators (Crumbs, Fat, Par 6/aPkc) and FERM domains upstream signal inducer proteins are very limited, as well as direct binding modulators regulate Hippo kinase activity including scaffolds Sav1 (hWW45, dmSalvador), RASSF1-6 (dmRASSF) and MOB1 (dmMats), which actually these regulators support LATS dimerization.^{27–29} Importantly, developmental studies indicate that this pathway limits the proliferation of cancer cells in model organisms and human tumors.²³ However, genetic alterations in the components of the path increase the risk of tumors that somatic mutations play a central role.^{30–32} In fact, activation of the pathway may depend on the type of tumor selected, due to the diverse roles of YAP (proliferation, differentiation, apoptosis and cell cycle arrest) that may limit tumor progression and establishment.^{33–35} Studies show that in cancer, Hippo-pathway signaling is deactivated epigenetically by YAP proliferation, deletion (MST2), or gene silencing (MST, LATS, and RASSF1).^{26,36–40} Other evidence suggests that in breast cancer, bladder and brain tumors, methylation-associated gene silencing of the RAS and Hippo pathway scaffold (RASSF1) increase by activation of YAP.⁴¹ Other studies have shown that the loss of Hippo activator correlates with clinical outcomes in mice.^{42–44} However, RAS signaling is an essential factor in Hippo deactivation, with reports suggesting that EGFR-RAS-RAF-MEK-ERK-mediated interaction controls Hippo signaling.^{45–48} Accordingly, loss of the Hippo

pathway may have important consequences on the targets of RAS-RAF mutations in cancer.⁴⁸ That is why we intend to discuss the details of this route.

LATS and MST

The mammalian pathway consists of two central kinases: 1- MST, Ste20-like kinases 1 and 2 (MST1 and MST2), homologs of *Saccharomyces cerevisiae* Ste 20 kinase. 2- LATS; Tumor Suppressors LATS1 and LATS2, homologs of the mitotic yeast Dbf2 kinase.⁴⁹ Activation of MST1/2 occurs by homo-dimerization or hetero-dimerization and trans-phosphorylation of the remaining T183/T180 in the ATP-binding pocket. This activation (MST1/2) is essential for the coordination of ATP in hydrolysis.²⁵ Dimerization of MST kinases also occurs via the leucine zipper motif at the C-terminal,²² which found as the SARAH domain in the SAV, RASSF1-6, and Hippo kinases. The domains of MST1 and MST2 kinases are located at the N-terminal and are released by apoptosis via caspase cleavage, indicating that the C-terminal sequences restrict kinase activity. Thus, between the kinase domain and the SARAH domains is the auto-inhibitory α -helix that limits the activity of the monomer kinase.²⁵

The SAV and RASSF proteins can bind to the monomeric MST and eliminate the kinase activity of LATS or eliminate its inhibitory activity through dimerization of the RASSF-MST heterodimer.²² RASSF1-MST:MST-RASSF1 complex cause the auto-transphosphorylation of T183/T180.^{28,50} Evidence

suggests that RASSF1, RASSF2, and RASSF5 (NORE1/RAPL) maintain MST kinases in the inhibitory state until induces dimerization, whereas RASSF3, RASSF4, and RASSF6 resemble dRASSF and suppress its activity.^{51,52} RASSF1 and RASSF5, however, may affect dimerization capacity or activation of MST.⁵³ Interestingly, wild-type RAS activation may play an inhibitory role in activating the Hippo pathway.³⁷ It is important to note that RAF is a RAS effector that binds directly to the MST1/2 SARAH domain and prevents dimerization and association with RASSF1, which limits the activity of the Hippo pathway in mice and *Drosophila melanogaster*.^{50,54}

The evidence suggests that RAF induces hypertrophy in the heart by stimulating YAP activity, which leads to inhibition of RAF-mediated MST kinase. SAV1 is also involved in inhibiting tissue growth during development and RASSF1A in response to injury.^{55,43} It appears that the regulation between RAF and MST is reciprocal since activation of MST kinase enhances RAF communication and limits RAF's ability to activate MEK (Fig. 2).¹³ A mechanism that helps the inhibitor bind to RAF or MEK molecules enhances B-RAF/RAF-1 dimerization, which inhibits MST and facilitates YAP transcription by inactivating RAF-MST.⁵⁶

Upon activation, MST kinase phosphorylates Scaffold MOB1 and causes deformation and ultimately LATS kinase activation.⁵⁷ Responsible for directing the LATS-MOB1 heterodimer to the spindle apparatus is the RAS-GTPases involved in cell division and mitosis. LATS activation also

induces transcriptional activator phosphorylation and YAP. Since MST and LATS have significant effects on the living organism, they are only epistatically associated with YAP.^{58–64} One of the conserved proteins in the Hippo pathway is the Ajuba Scaffold protein, which interacts with LATS kinases and SAV, limiting centromere signaling and decreasing inhibition of YAP phosphorylation.⁶⁵ EGFR-RAS signaling activates MAPKs (ERK and JNK), both of which MAPKs phosphorylate Ajuba proteins, increase LATS binding, and YAP transcriptional activation.^{66,67} Mammalian MST kinases are involved in JNK activation (with the help of MKK7 and MEKK1); therefore, MST cannot activate JNK in cells lacking MKK7.^{68–70} Also, MST kinases respond to actin stress disorder and stimulatory activity of JNK, indicating that there is a physiological pathway downstream of the GTPase RHO-like RAS.⁷¹ Recent studies suggest that this pathway regulates Ajuba by JNK (Lim protein domain), increased actin f, increased MST1/2, decreased activation of the Hippo pathway and YAP transduction from the nucleus.⁷² JNK also inhibits YAP activity, whereby, YAP directly phosphorylated by JNK and leads to apoptosis by p73.^{73,74}

The tumor suppressor of neurofibromatosis 2 is the false Expanded/KIBRA/NF2 (dmMerlin) complex located in the Hippo cassette upstream and contributes to activation of SAV1 and MST.⁷⁵ Also, one of the MAPK signaling events is KIBRA phosphorylation by ERK, which is essential for cell proliferation. It is worth noting that KIBRA itself can play an

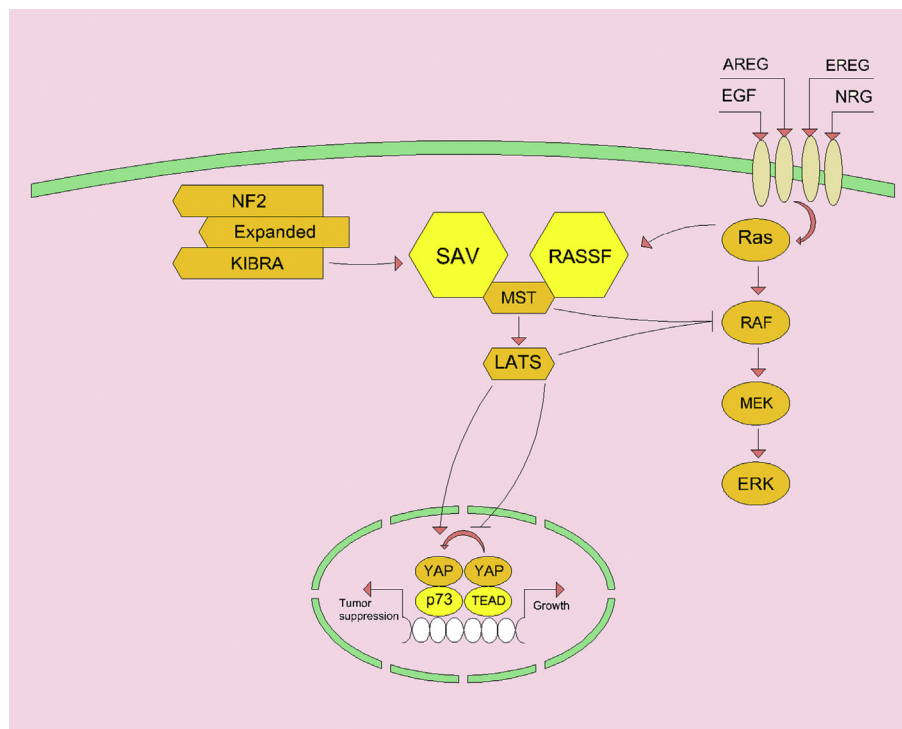


Figure 2 The MST activation center is the Hippo path. This pathway is stimulated through signals from the NF2/Expanded/KIBRA complex to SA or through the interaction of RAS with RASSF. Activation of MST results in activation of LATS kinase and phosphorylation of YAP, which prevents association with oncogenic TEAD growth-promoting transcription factors. In addition to increasing cytoplasmic levels, YAP phosphorylation decreases the transcription factor association under tumor suppression and differentiation conditions. Increased MST activity inhibits MEK activation and also, LATS inhibits RAF activity through S259 phosphorylation and silencing of RAF.

important role in collagen-induced ERK signaling,⁷⁶ indicating another level of regulatory activity between pathways. Another Hippo pathway scaffold is ARFGEF7 (or beta-Pix) that not required for GEF activity.⁷⁷ ARFGEF7 also stimulates LATS in combination with YAP and TAZ, limiting the output of the Hippo pathway and YAP/TAZ transcription. In general, this scaffold mainly binds to RAS-like GTPases (Rac 1 and Cdc 42) that are active in cancer under different conditions of RAS, RHO, RAC, or CD42.⁷⁸

In general, increased KRAS activity in RAF-MST, ERK-KIBRA, or ERK-Ajuba and JNK-Ajuba can have inhibitory effects on YAP and TAZ transcriptional activity (Fig. 1). Importantly, Hippo pathway scaffolding proteins and KRAS pathway scaffolds (IQGAP) increase RAS-RAF-MEK-ERK signaling (Fig. 1), which is required to suppress the Hippo pathway and some similar inhibitory events.⁷⁹ Upstream receptor-driven activation of RAS results in inhibition of the output of the Hippo pathway. In mammals, activators of the ERBB family of EGF, EGF, epiregulin (EREG), amphiregulin (AREG), hairpin-binding EGF (hbEGF) and neuregulin 1 and 2 (NRG1 and NRG2) associated receptors lead to inactivation of the Hippo pathways (Fig. 3).^{42,54,80} LPA can inhibit the Hippo pathway by activating G heterodimer proteins (this activation mediated by RHO/Rock and directly suppressed by LATS). Also, the effects of LPA on RAS, PKA on RAS/RAF-1, and RHO/Rock on MST can be ambiguous factors that are not considered (Fig. 3).^{81–84} All ligands that regulated by EGF were deleted and G α activation by LPA occurs in the

presence of RAS-independent Hippo pathway inhibition signal.⁸¹ Accordingly, EGF ligands are different or LPA plays an independent role could be important. Despite specific mechanisms, there are several distinct levels by which RAS-activated cancers are inhibited, including direct inhibition of RAF-MST and suppression of LATS through Ajuba phosphorylation by ERK.

YAP signaling and regulation

YAP is a regulatory protein found in the cytoplasm (in cellular junctions) as well as in the nucleus as a cofactor for a range of transcription factors involved in proliferation (TEA domain family, TEAD1-4), stem cells (Oct 4 mononuclear factor and TGF β effector related SMAD), differentiation (RUNX1), and cell cycle/apoptosis control (p53, p63 and p73 family members).⁸⁵ Mostly, proliferative activity occurs in growing tissues during development as well as in cancer cells that have transcription factors containing TEA domain (TEAD1-4). Responsible for nuclear loci and transcriptional activity of SMADs in response to TGF β , is Yap and its homolog WWTR1 (TAZ).⁸⁵ YAP and TAZ influence differentiation by regulating RUNX and PPAR γ (differentiating into osteoclasts and adipocytes, respectively).⁸⁵ Also, YAP participates in tumor suppression by p73, which suggests that YAP transcriptional activity synchronized with the switch between proliferation, cell cycle arrest, and

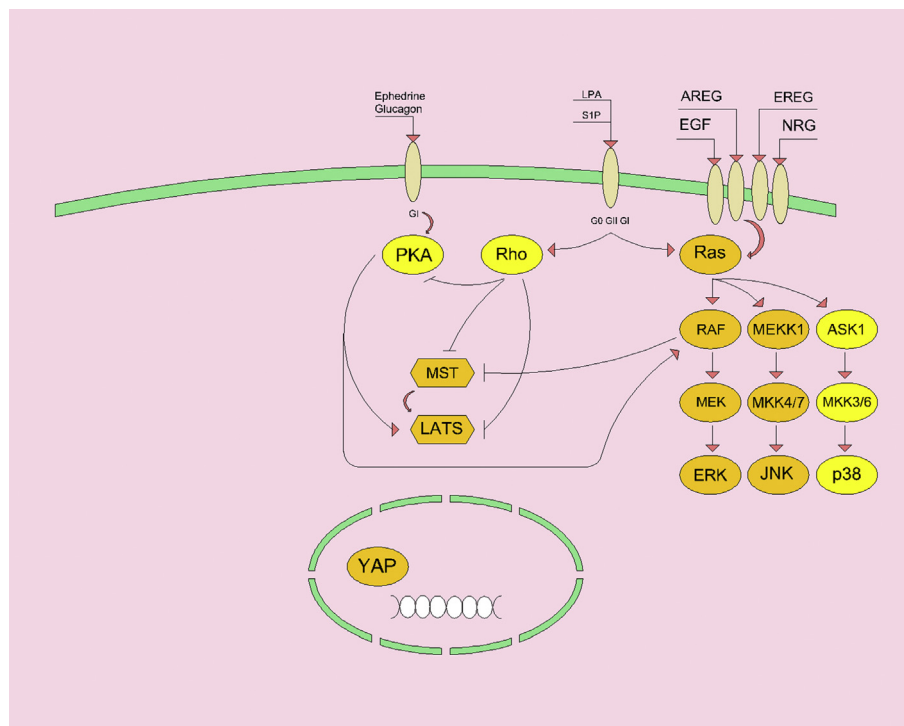


Figure 3 Activation of ERBB family receptors by growth factors can activate RAS MAPK signaling. The RAF effector deactivates MST1 and MST2 by preventing dimerization. RAS can also be activated by G-protein coupled receptors. Activation of G heterodimer proteins (G α , G11, and Gq) by GPCR could stimulate RHO activity. RHO activity inhibits MST and LATS by regulating actin dynamics. In addition, RHO inhibits cAMP-dependent protein kinase A. In contrast, GPCR activation activates protein kinase A and suppresses LATS, thereby facilitating YAP nuclear localization. It should be noted that protein kinase A has different effects across a range of substrates (for example, RAF is associated with MST repression and LATS also facilitates YAP activity).

differentiation. Indeed, studies have shown that direct phosphorylation by LATS is a pre-p73 communicative signal, whereas the same signal disrupts TEAD and ultimately results in rapid alteration of tumor proliferation and suppression.^{24,35,86} However, with activation of Hippo, YAP binds to p73, which accumulates in the cytoplasm through association with the catenin complex. Free cytoplasmic YAP is degraded by the ubiquitin ligase β TrCP-SCF complex, which in the presence of RAS, decreases the ligase targeting compounds and thereby increases YAP stability.⁸⁷ Thus, active RAS can increase YAP levels independently of Hippo, which required for RAS-induced tumorigenesis.

Disruption of the Hippo pathway activity disrupted tumor suppressor activity in p73, which supports tumor growth through TEAD transcription. Evidence suggests that in mice models, the activation of TEAD causes tumorigenesis, with several somatic alterations leading to YAP-TEAD activity in common cancers.³⁶

Studies show that the RAS-RAF-MEK-ERK cascade interacts with the Hippo tumor suppressor pathway to facilitate tumorigenesis. Further studies show the inter-relationship between RAS signaling and the Hippo pathway through the feedback loop. Consequently, inactivation of Hippo signaling resulted in increased YAP/TEAD

transcription of target genes and increased RAS activation. Importantly, YAP is one of the most important activators of transcriptional stimulation of EGF and AREG ligands. In fact, MAPK signaling reflects a response that further inhibits Hippo activity. With enhancing survival signals (AKT) in response to stimulation of the EGFR family and increasing level of insulin-like growth factor (IGF), the PI3K-AKT signaling increased.^{37,88} High levels of YAP are maintained by E6 viral oncoprotein through proteasome inhibition.⁸⁹ Most importantly, deactivation of the NF2 tumor suppressor (dmMerlin) stimulates neurofibromatosis (which is associated with RAS activation by inactivating RAS-GAP). Loss of NF2 is associated with decreased activation of the Hippo and YAP pathways, which in general, K-RAS, H-RAS, and N-RAS transcription factors increase mRNA replication and K-RAS pre-oncogenic activity.⁹⁰ Certainly, YAP activation directly enhances transcription of the EFGR, EFGR, and RAS family receptor ligands, increases mRNA levels in the TEAD-dependent manner, and generates a positive feedback loop to stabilize Hippo-suppression and enhances MAPK activity (Fig. 1). The most important method of activating the RAS pathway in tumors is enhancement of EGFR, via gene amplification or transcription.⁹¹

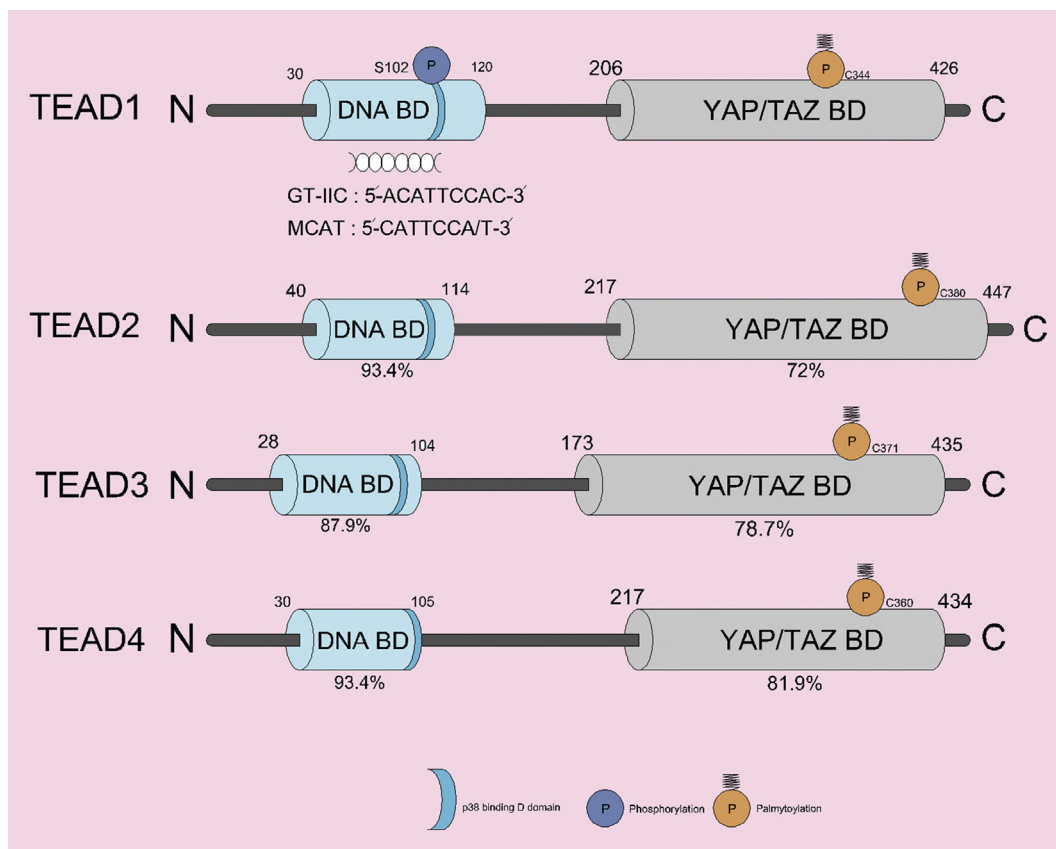


Figure 4 Domain structure of human TEADs. The N-terminal DNA binding domain and the C-terminal YAP/TAZ binding domain of TEAD1-4 have high similarity in four different patterns. It shows the similarity of each TEAD domain to the percentage (%) of TEAD1. TEAD post-translational modifications include palmitoylation and PKC-mediated phosphorylation (occurring in YAP/TAZ-BD and DNA-BD, respectively). Palmitoylation is essential for TEAD functions. TEAD cytoplasmic translocation occurs through a protein-protein interaction with p38 MAPK, which binds to the p38-binding motif in the DNA binding domain (all TEADs).

Transcriptional enhanced associate domain (TEAD)

Since its inception, TEAD has been best studied in the Hippo-YAP/TAZ signaling pathway and in tumorigenesis. There has been extensive evidence on TEAD activity that is limited to its function in the Hippo-YAP/TAZ pathway.⁹⁴ Recent studies suggest that the determinants of TEAD activity in vitro and in vivo are nucleocytoplasmic silencing, post-translational modifications, and interactions between oncogenic signaling pathways.⁹⁴ TEAD produced as an important drug candidate for the treatment of human diseases (cancer, cardiovascular disease, and neurological disorders).⁹⁴ The oncogenic role of TEADs in tumorigenesis and development of TEAD anticancer drugs discussed below.

TEAD family transcription factors

TEAD transcription factor (all four transcription factors) are conserved in most human body tissues,^{95,96} and are widely expressed as each family member has several names: TEAD1 (TEF1/NTEF), TEAD2 (TEF-4/ETF), TEAD3 (TEF-5/ETFR-1) and TEAD4 (TEF-3/ETFR-2/FR-19). In animal model experiments, despite the high homology and pattern of expression between TEAD1-4, each TEAD plays different roles in specific tissues (heart, neurodevelopment, tropoderm characterization, and fetal growth)^{97–102} Their most important role in cell biology is the regulation of cell proliferation and contact inhibition.^{103,104} TEADs are very similar in domain architectures (Fig. 4). The N-terminal of TEAD contains a TEA/ATTS DNA-binding domain containing 68 conserved amino acids that bind to the MCAT element (5'-CATTCCA/T-3') and serve as a GT-IIC motif (5'-ACATTCCAC-3') Simian virus 40 (SV40) amplifiers are defined.^{105–107} These sequences, are an 8xGTIIC luciferase plasmid reporter synthetic TEAC luciferase containing 8 GT-IIC motifs used to measure YAP/TAZ and TEAD activity.¹⁰⁸ Other transcription factors of TEAD, are more attached to DNA (barely showing transcriptional activity themselves) and are found in the chromatin segment.^{109,110} Thus, TEAD activity predominantly linked to the C terminal, in which all TEADs share their trans-activation domain to recruit YAP/TAZ transcription coactivators, VGLL1-4 corepressor, NuRD chromatin remodeling factors, and mediators.^{111–122} TEAD, in addition to interacts with final transcription factors of the Hippo-YAP/TAZ pathway, also interacts with other transcription factors (SMAD, TCF, OCT4, AP-1, and MRTF).^{123–127} TEAD transcription involves established genes that are involved in cell growth, proliferation, and tissue homeostasis. In recent studies, in addition to classical target TEAD genes (CTGF and CYT61), there has been focused on WNT5A/B, DKK1, TGFB2, BMP4, AREG, EGFR, PD-L1, MYC, LATS2, SLC38A1/SLC7A5 amino acid carriers and glucose transporter GLUT3 as the TEAD direct target genes.^{112,128–144} These signaling inputs illustrate protein-protein interactions and the role of TEAD in direct control of WNT, TGFB, RTK, mTOR and Hippo signaling that is involved in tumorigenesis, cancer immunity, stem cell amplification, metabolism, and development.

TEAD in cancer

Expression and role of TEAD in human cancers and metastasis

Many studies have highlighted the importance of TEAD in cancer progression, with overexpression of TEAD and its high activity in several stages of cancer progression. TEAD may be involved in the reduction of some cancers (breast and kidney or bladder tumors), but the high-level expression of TEAD is associated with poor clinical outcomes as a prognostic marker for various tumors (prostate cancers, colon cancers, gastric cancers, breast cancers, embryonic cell tumors, squamous cell carcinoma of the head and neck, kidney cell carcinoma, and medulloblastomas).^{145–157} In addition, loss of function of TEAD1 (Y421H) causes Sveinson's chorioretinal atrophy, resulting in genetic disorder and impaired TEAD1-YAP interaction.^{158,159} According to a recent meta-analysis, nuclear YAP and TAZ expression are associated with overall survival and disease-free survival of various cancers, indicating the prognostic role of TEADs and YAP/TAZ expression in patients with various malignancies.^{160,161} TEAD has also been shown to be an important drug target in YAP-induced tumorigenesis. In hepatocellular carcinoma, TEAD negative domain can regulate YAP-induced hepatomegaly reversely. In addition, VGLL4-mimicking peptide (bind to YBD) and verteporfin (YAP-binding small chemical) have therapeutic effects against YAP-induced tumorigenesis through impaired TEAD-YAP interaction.^{162–164,190}

Most cancer-related death are due to metastasis (the spread of cancer cells from the primary tumor site to the secondary organs). In metastasis, cancer cells must prevent anoikis (apoptosis induced by detachment) and enter the blood vessels and should get out of it (intravasation and extravasation), thereby demonstrating complete metastatic colonization and drug resistance. These are critical features of cancer stem cells that after interacting with platelets, metastatic cancer cells induce TEAD activation through the RHOA-MYPT1-PP1-YAP pathway. Platelet-activated TEAD transcription program in cancer cells results in resistance to anoikis and stimulation of cell viability and metastasis.¹⁶⁵ In this way, YAP enhances the resistance of anoikis to the separation of cancer cells.¹⁶⁶ Also, exposure of cancer cells to the cut through ROCK-LIMK-cofilin signaling activates TEAD and stimulates cancer cell and metastasis.¹⁶⁷ On the other hand, activation of the target TEAD gene, CTGF, and metastatic colonization of breast cancer occurs through leukemia inhibitory factor receptor suppression.¹⁶⁸ In colon cancer, RAR via the Hippo pathway stimulates TEAD activation and induces EMT, invasion, and metastasis.¹⁶⁹ However, overexpression of TEAD and its nuclear localization in colorectal cancer cells via Hippo-independent mechanism induce EMT and metastasis.¹⁴⁸ Activation of TEAD results in induction of osteoclast differentiation by ROR1-HER3 and through Hippo-YAP pathway cause cancer cells metastasis.¹⁷⁰ In addition, TEAD activated by MRTF stimulates breast cancer cell metastasis to the lung.¹²³ In breast and melanoma cancer cells, induced cell adhesion to ECM by SRC tyrosine kinase activates TEAD

and stimulates tumor growth and enhances metastasis.¹⁷¹ TGF β -induced TEAD transcriptional activity is required to induce metastatic phenotypes in breast cancer cells. The target gene for TEAD is ARHGAP29, which upregulates actin and metastasis by regulating actin in cancer cells.¹⁷² Also, TEADs are involved in metastatic diffusion of cancer cells. For metastatic colonization, tumor cell expansion through TEAD activation by L1CAM-ILK-YAP signaling is important.¹⁷³ However, these studies indicate that activation of TEAD enhances metastatic tumor formation and inhibition of TEAD can prevent tumor cell survival and proliferation.

EGFR-RAS-RAF-MAPK pathway

TEADs are intermediates of the EGFR-RAS-RAF-MAPK pathway, one of the most important uncontrolled molecular pathways in cancers. TEAD plays a vital role in tumor progression and drug resistance downstream of EGFR, KRAS, or BRAF overactive mutations. In NSCLC patients, TEAD activity is associated with EGFR mutation. EGFR mutations in lung cancer tissues and cell lines indicate that increased YAP expression results in increased TEAD activity.¹⁷⁴ EGFR through T790M mutation induces drug resistance to TKI, but inhibition of TEAD decreases the viability of TKI-resistant lung adenocarcinoma cells.^{175,176} TEAD also contributes to the safety of NSCLC cells by direct transcription of PD-L1 and in turn, causes CD8 + T cell senescence.^{137,177} In addition, TEAD enhances EGFR expression through direct binding to the EGFR promoter and induces tumorigenesis and drug resistance in esophageal cancer.¹³³ One of the most common proteins in human cancer is the KRAS oncogene located downstream of EGFR. The KRAS activation mutation in Pancreatic Ductal Adenocarcinoma is quite clear. BRAF (unlike EGFR and KRAS) is not considered an appropriate therapeutic target. This is due to downstream effects in the treatment of Pancreatic Ductal Adenocarcinoma. Activation of TEAD-induced target genes (COX2 and MMP7), promotes pancreatic Ductal Adenocarcinoma by KRASG12D in vitro and in vivo. Celebrex (COX2 inhibitor) and marimastat (clinical MMP inhibitor) are used as potential drug agents for the treatment of pancreatic Ductal Adenocarcinoma.¹⁷⁸ Besides, several TEAD target genes have been associated with poor prognosis for Pancreatic Ductal Adenocarcinoma.¹⁷⁹ TEAD2 cooperates with the E2F transcription factor to stimulate cell-cycle gene expression, which enables the activation of pancreatic Ductal Adenocarcinoma by oncogenic KRAS through a KRAS-independent tumor.¹⁸⁰ Approximately, in half of the patients with metastatic melanoma, the BRAFV600E mutation occurs that the most common mutation is the BRAF^{V600E}.¹⁸¹ Although vemurafenib (PLX4032) and dabrafenib have developed for the treatment of BRAF^{V600E}-mutant metastatic melanoma, the patients eventually show resistance.¹⁸² Numerous studies have shown that TEAD activity contributes to BRAF inhibitor-resistance in melanoma cells. TEAD activity in drug resistant-melanoma cells results in cancer resistance and invasion.^{183,184} BRAF inhibitor-resistant cells can reduce the immune system by activating TEAD. TEAD-mediated direct transcription of PD-L1 is responsible for PD-1-dependent CD8 + T cell senescence, which enables immune responses by BRAF inhibitor-

resistant cells.^{135,136} In addition, IL-6 and TEAD-induced CSF1-3 cytokines in PDAC mutant cells in KRAS can induce myeloid-derived suppressor cells (MDSCs) and induce immunosuppressive activity.¹⁸⁵ Overall, TEAD transcriptional output plays an important role in the pathogenesis of the EGFR-RAS-RAF-MAPK pathway and induces tumor progression through mutation.

Conclusion

Given all the evidence, it is clear that there is a need for an understanding of how the Hippo pathway deactivates in cancer. Although we observe RAS-MAPK suppression of the Hippo pathway at the signaling level, the fact is that the Hippo pathway enhances RAS-MAPK activity. When Hippo eliminate, EGFR-RAS-MAPK is activated and, conversely, when EGFR-RAS-MAPK inhibited, the Hippo signaling pathway is activated.^{30–32} Therefore, in the early stages of tumorigenesis, especially in the absence of mutation, the RAS pathway is active. Genetic polymorphisms weaken the Hippo pathway. This type of weakening has been observed in cancers such as soft-tissue sarcomas, lung cancer, and breast cancer. In addition, somatic changes (these changes are very rare) have been observed in cancers such as melanoma.^{186,187} Recent advances indicate that in endocrine pancreatic β cells, RASSF1 responds to KRAS and prevents MAPK activation.¹⁸⁸ In these cells, the Hippo pathway is activated. This has also been observed in colorectal cancer, where activation of K-RAS causes the inhibition of the Hippo tumor by RASSF1, but not in the case of loss of RASSF1 and MST kinases. Expression of RASSF1 disappears in colorectal cancer. Not only mutations, genomic deletion of ch3p21 and epigenetic silencing of RASSF1A have also been linked to the incidence of lung, breast, and ovarian cancers.^{37,40,189} This condition not only occurs frequently but is a clinical prognosis to tumor onset. Thus, activation of YAP in the pancreas and gastrointestinal tumors may be the result of the loss of the RASSF1-mediated Hippo pathway.^{45–47} In this regard, RASSF1 methylation also associated with pre-cancerous colon dysplasia.⁴³ This suggests that inactivation of RASSF1 is likely associated with a reduction of the Hippo pathway and activation of YAP in chronic diseases.⁴¹ Overall, this condition suggests that epigenetic inactivation of MST and LAST may be a key sign of Hippo pathway loss and that EGFR-RAS-RAF-MEK genetic disorders should be considered in susceptible patients.

Conflict of Interests

The authors declare no conflict of interests.

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