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REVIEW

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YAP and the Hippo pathway in pediatric cancer

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ABSTRACT

The Hippo pathway is an important signaling pathway that controls cell proliferation and apoptosis. It is evolutionarily conserved in mammals and is stimulated by cell–cell contact, inhibiting cell proliferation in response to increased cell density. During early embryonic development, the Hippo signaling pathway regulates organ development and size, and its functions result in the coordinated balance between proliferation, apoptosis, and differentiation. Its principal effectors, YAP and TAZ, regulate signaling by the embryonic stem cells and determine cell fate and histogenesis. Dysfunction of this pathway contributes to cancer development in adults and children. Emerging studies have shed light on the upregulation of Hippo pathway members in several pediatric cancers and may offer prognostic information on rhabdomyosarcoma, osteosarcoma, Wilms tumor, neuroblastoma, medulloblastoma, and other brain gliomas. We review the results of such published studies and highlight the potential clinical application of this pathway in pediatric oncologic and pathologic studies. These studies support targeting this pathway as a novel treatment strategy.

Introduction

The Hippo pathway is an important signaling pathway that controls cell proliferation and apoptosis. Dysfunction of this pathway often contributes to cancer development. It is stimulated in normal cells by cell–cell contact and inhibits cell proliferation in response to increased cell density. The pathway is evolutionarily conserved in mammals, and plays an important role in tissue homeostasis resulting in coordinated balance between proliferation, apoptosis, and differentiation.[1,2] Hippo signaling pathway is activated with the phosphorylation of the large tumor suppressor kinases 1 and 2 (LATS1/2) by the STE-20 protein kinases (MST1/2) leading to activation of downstream members. Protein salvador homolog 1 (Sav1) and Mob kinase activator 1A (Mob1) are regulatory proteins that coordinate the phosphorylation of MST1/2 and LATS1/2 protein kinases, respectively. A principal member and downstream effector, Yes-associated protein (YAP), is a transcriptional coactivator that is phosphorylated and inactivated by the Hippo signaling cascade. Another member, the transcriptional coactivator with PDZ-binding motif (TAZ), shares similar functions to YAP in transcriptional activation and regulation.[1-4] YAP and TAZ are phosphorylated by LATS1/2-Mob1 complex at specific amino acid residues. When Hippo signaling is attenuated, the phosphorylation of YAP and TAZ is reduced, leading to their nuclear localization. Inside the nucleus, they bind to one of the DNA-binding TEA domain (TEAD) family of transcription factors and activate target genes that are involved in cell proliferation, survival, and tissue growth (Fig. 1).

The Hippo pathway is regulated by several upstream pathways members. Merlin, a cytoskeletal protein and product of *NF2* gene, activates MST, eventually leading to YAP phosphorylation.

Another upstream Hippo member, the Kidney and Brain Protein (KIBRA), causes activation of LATS and YAP. Loss of KIBRA expression causes cells to display epithelial to mesenchymal transition features leading to tissue growth, which is concomitant with decreased LATS and YAP phosphorylation.[5] The Hippo pathway is also regulated through cross-talk interaction with other intracellular signaling pathways. For example, MST1/2 activity is regulated by RAF-1, a product of the MAPK/ERK pathway, and by the RAS-association domain (RASSF) family proteins, which are implicated as tumor suppressors in many cancers. The phosphoinositide 3-kinase (PI3K) pathway regulates Hippo core components directly or through Protein kinase B (AKT) activation. Both YAP and TAZ interact with and are components of the Wnt signaling where they play a role as transcriptional mediators, similar to Beta-catenin.[3,4]

The Hippo signaling pathway regulates cell proliferation and apoptosis during organ development and is essential for the accurate formation and maintenance of tissues and organs.[6] The nuclear/cytoplasmic distribution of YAP and TAZ is important in embryonic development through regulation of cell polarity and signaling by the embryonic stem cells.[7,8] Nuclear localization of YAP and TAZ promotes progenitor cell renewal, facilitates tissue regeneration, and increases proliferation of undifferentiated progenitor cells in the liver, skin, intestines, and heart. Aberrant activation of nuclear TAZ and YAP transcriptional activity results in stem cell proliferation. Shifting of YAP to the cytoplasm results in cellular differentiation and maturation.[8,9] Signals mediated by YAP and TAZ are also important in determining cell fate. Hippo pathway members influence mesenchymal stem cells and regulate their subsequent differentiation. Depletion of TAZ was found to promote

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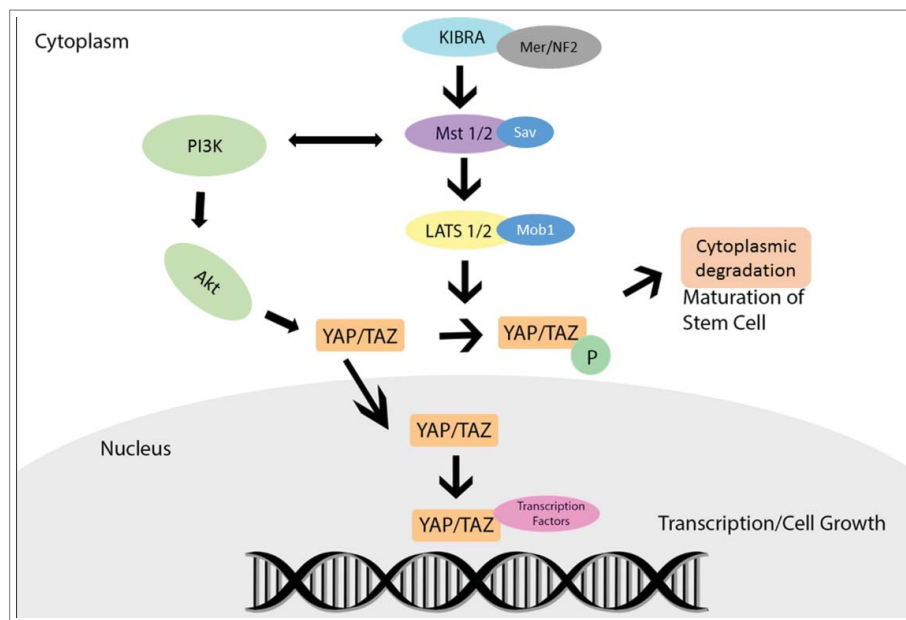
Figure 1. YAP protein interaction, activation, and inactivation within the canonical Hippo Pathway.

adipogenesis, and increased nuclear TAZ activity resulted in osteogenesis.[10,11] During further organ development and histogenesis, the Hippo pathway becomes essential in regulating final organ and cell size.[9,10]

The role of Hippo pathway in embryogenesis and organ development portends its importance in the development of many pediatric cancers. In this review, we discuss the role of Hippo pathway in pediatric malignancies with reference to the clinical applications of YAP as a diagnostic and prognostic biomarker in pathology and oncology.

Hippo pathway and cancer

Hippo signaling pathway in stem cells signifies an important role in cancer stem cells and tumor initiation. Dysregulation of Hippo pathway members evokes tumorigenesis in various human adult cancers, including breast, ovary, and liver. Hippo core kinases, MST1/2 and LATS1/2 are often described as tumor suppressors. Other Hippo pathway members, such as KIBRA, can also play a role in the development of cancers.[5] However, YAP and TAZ are the main culprits in cancer pathogenesis, mainly through their interaction with the TEAD family of transcription factors.[12] The exact mechanism of YAP in cancer development is still under investigation. Many previous studies have reported elevated YAP protein levels in various types of cancer, such as colorectal, gastric, and human hepatocellular carcinoma.[12,13] In this context, YAP is often described as an oncogene and its increased expression in cancers correlates with poor prognosis. For example, increased YAP expression is associated with high clinical stage and short overall survival in colorectal and ovarian cancer.[13,14] In other contexts, YAP functions as a tumor suppressor while inducing cell apoptosis. This alternate function of YAP has been noted in few morphologic studies of breast and prostate cancer, which have shown that YAP expression is lost in the tumor cells and retained in normal tissues.[15,16] YAP

has also been noted to induce apoptosis in several hematologic malignancies.[17] This dual role as an oncogene as well as tumor suppressor gene makes it similar to FAT atypical cadherin 1, and may be related to its phosphorylation status and nuclear versus cytoplasmic localization as shown in a subset of head and neck squamous cell carcinomas.[18,19]

Because of its role in embryologic organ development, the Hippo pathway is thought to play a more significant role in the development of pediatric cancer. Many pediatric cancers represent arrest of cellular differentiation at the embryonal level and childhood cancers are frequently associated with congenital malformations, consistent with the notion that disruption of normal embryologic development is linked to oncogenesis.

Rhabdomyosarcoma

Major components of the mammalian Hippo pathway are expressed in fully differentiated skeletal muscles, progenitor cells, myoblasts, and myotubes. Both TAZ and YAP can bind to and function as coactivators of the paired box protein PAX3, an important transcription factor in early muscle development. Unlike canonical Hippo signaling, PAX3-TAZ and PAX3-YAP complex does not require TEAD factors to mediate activity, and PAX3 acts as the DNA-binding moiety.[20] During normal muscle development and activation of Hippo kinases, YAP phosphorylation increases and translocates from the nucleus to the cytosol permitting myoblast differentiation.[21,22] Nuclear expression of TAZ also increases the expression of myogenic genes and hastens myofiber formation and muscle differentiation through a MYOD1-dependent manner. In pathologic conditions, phosphorylation of TAZ leads to its cytoplasmic retention and delays myogenic differentiation.[23] Similarly, YAP is retained in the nucleus, where it promotes satellite cells proliferation, and prevents their differentiation.

Rhabdomyosarcomas are tumors of skeletal muscle origin that exhibit overexpression of the myogenic regulatory proteins, MYOD1 and myogenin. Evidence of disruption of the Hippo pathway in rhabdomyosarcoma has emerged in few studies, principally through dysregulation of YAP. YAP is upregulated and both embryonal and alveolar rhabdomyosarcoma types show high expression of cytoplasmic and nuclear YAP protein. In alveolar rhabdomoyosarcoma (aRMS), *PAX3-FOXO1* fusion transcript supports tumor initiation by upregulation of RASSF4. Enhanced RASSF4 expression in *PAX3-FOXO1* fusion positive aRMS cell lines and tumors promotes tumorigenesis through inhibition of the Hippo pathway tumor suppressor MST1 and subsequent increased activity of YAP.[24,25] YAP overexpression was found in RAS-driven rhabdomyosarcoma, where it supports cell growth, proliferation, and survival *in vitro*.[24] YAP-deficient alveolar rhabdomyosarcoma cells were found to be significantly less proliferative than control cells.[26] Additional data have also suggested that TAZ may play a role, albeit less prominent than that of YAP, in the pathogenesis of aRMS.[23]

YAP overexpression is also implicated as a key factor in the development of embryonal rhabdomyosarcoma (eRMS). A recent study using multiple genetically engineered mice has demonstrated that YAP protein overexpression transforms activated satellite cells leading to the development of embryonal rhabdomyosarcoma-like tumors.[26] YAP combines with TEAD1 to upregulate pro-proliferative and oncogenic genes and maintain eRMS tumorigenesis by blocking MYOD1 activities. TAZ is also overexpressed in eRMS where it functions as an oncogene independent from YAP and activates the expression of other cancer-related genes. Knockdown of *TAZ* in human eRMS cell lines reduces their proliferation and anchorage-independent growth.[23]

Expression of YAP and TAZ in clinical cases of rhabdomyosarcoma signifies their potential applications as diagnostic and prognostic biomarkers. Both proteins show slightly more expression in eRMS than in aRMS. In immunohistochemical experiments of tissue microarray samples, YAP and TAZ are detected in 87% and 55% of eRMS and in 72% and 36% of aRMS respectively.[23,26] Activity of both proteins is related to poor patient prognosis and adverse clinical outcome. In eRMS, YAP protein expression correlates with advanced clinical stage and its gene expression correlates with reduced survival.[26] TAZ expression is also associated with short survival in eRMS.[23] In this aspect, blocking or modulating YAP or TAZ activity may be considered as potential therapy for rhabdomyosarcoma.[27]

Ewing's sarcoma

Sarcomas in general are hypothesized to develop from mesenchymal stem/progenitor cells, which are able to differentiate into many cell types and give rise to several adult human tumors.[28,29] Hippo pathways members are expressed in mesenchymal stem cells where they regulate their differentiation and fate.[30] Thus, it is understandable that dysregulations of the Hippo pathway occur in many bone and soft tissue sarcomas.[31,32] However, only a few oncogenic mutations are found in the Hippo pathway that result in its dysregulation. Instead, the most likely cause of perturbed Hippo signaling in sarcoma is the cross-talk with commonly mutated cancer genes such as *KRAS, PIK3CA, CTNNB1*, or *FBXW7*.[33] In tissue microarray samples of human sarcomas, both YAP and TAZ are expressed in variety of tumors, including Ewing's sarcoma.[31] YAP expression in Ewing's sarcoma is positively correlated with the expression of polycomb protein (BMI-1), which promotes the tumorigenicity of Ewing's sarcoma. YAP expressions levels are maintained and do not diminish in confluent Ewing's sarcoma tumor cells that express high levels of BMI-1. In contrast, YAP expression and nuclear localization are reduced in confluent *BMI-1* knockdown cells, suggesting that silencing of BMI-1 restores contact inhibition by resuming normal activation of the Hippo-YAP growth-suppressor pathway.[34] YAP nuclear expression is also documented in clinical human samples of Ewing's sarcoma, but this expression does not affect the patient's survival.[35] These facts suggest that YAP expression may not have a major diagnostic role in Ewing's sarcoma but may be useful in selecting cases for YAP-targeted therapy. Other canonical Hippo pathway members have not yet been studied. However, the promoter regions of *RASSF1A* and *RASSF2*, which are closely related to the Hippo pathway, are found in a hypermethylated state in Ewing's sarcoma in correlation with worse clinical outcome.

Osteosarcoma

The Hippo pathway and its downstream targets help regulate proliferation of immature osteoblasts and their maturation into nonproliferating mature osteoblasts. It also regulates chondrocyte differentiation.[36,37] Thus, aberrations in the Hippo signaling are proving to be important in the biology of osteosarcoma. These aberrations partly occur through the upregulation of Hedgehog (HH) signaling leading to increased expression of YAP and partly through upregulation of the sex-determining region Y-box 2 (Sox2) leading to inhibition of Mer/NF2 and KIBRA. Inhibition of HH signaling reduces YAP expression, and knockdown of *YAP* significantly inhibits osteosarcoma tumor progression and decreases cell proliferation and invasion.[36,37] Sox2 is highly expressed in osteosarcoma where it maintains cancer stem cells.[37,38] It disrupts the Hippo pathway in these cells through the inhibition of Mer/NF2 and KIBRA leading to increased YAP expression. Expression of Mer/NF2 in osteosarcoma cell lines leads to a more differentiated phenotype associated with the depletion of Sox2. Thus, in contrast to cancer stem cells, the more differentiated tumor cells are characterized by the expression of Mer/NF2 and decreased Sox2 and YAP expression. TAZ is also elevated in osteosarcoma cells, independent of Sox2, and stimulates osteogenic differentiation through Runx2 activation.[38]

Of the Hippo pathways members, only YAP and TAZ have been studied in human osteosarcoma tissues. A tissue microarray analysis has revealed high YAP protein expression in osteosarcoma when compared to the surrounding noncancerous

tissue, and the expression correlates with advanced clinical stage.[37] In another immunohistochemical study, both YAP and TAZ showed expression in up to 60% of osteosarcoma cases and that nuclear expression of these proteins served as independent prognostic factor.[39] These experiments hint to the potential role of YAP and TAZ as prognostic indicators in osteosarcoma.

Neuroblastoma

YAP is expressed in early neural crests and regulates their phenotype and migration. YAP expression subsequently decreases upon maturation and differentiation of neural crest cells. Neuroblastoma is a common pediatric malignancy that arises from neural crests, and thus it is reasonable to extrapolate that Hippo pathway members are overexpressed in this tumor.[40] YAP and TAZ activation has been described in neuroblastoma and shows a positive correlation with adverse prognostic features. Mutations of *PTPN14*, which encode a negative regulator of YAP, have been identified at neuroblastoma relapse.[41] Migratory and invasive properties of human neuroblastoma cells have been found to be associated with high expression levels of TAZ. There is evidence that TAZ promotes epithelial to mesenchymal transition and metastasis of neuroblastoma.[42] Although these experiments have suggested a potential role of YAP and TAZ as therapeutic targets, no experiments have been conducted so far on the immunohistochemical expression of these proteins in the different subtypes of clinical neuroblastoma cases.

Liver cancer

The mammalian Hippo pathway is thought to play an important role in the regulation of liver progenitor cells.[43] Ablation of this pathway in mice has induced YAP expression and its localization to the nucleus, thus permitting hepatic tumorigenesis. Several studies have documented dysregulation of various Hippo members liver cancer, particularly in hepatocellular carcinoma (HCC). In a recent study on human HCC tissue, increased expression of YAP and downregulation of LATS were observed. Inhibition of LATS or MST1/2 has attenuated YAP phosphorylation and significantly increased YAP nuclear accumulation.[43] In turn, the upregulation of the YAP inside the nucleus and its association with TEAD2 has led to transcriptional activation and cell invasion in HCC cells. Increase in YAP activity (nuclear localization and decreased phosphorylation) has also resulted in increased cell proliferation and HCC formation in mice.[44] YAP expression by immunohistochemistry has been noted in adult and pediatric HCC clinical cases.[45-48] Two recent studies have revealed YAP and TAZ are expressed in 60-70% of HCC cases and their expression has correlated with clinical stage and high serum alpha-fetoprotein levels.[45,46] In a study of seven pediatric HCC cases, increase of YAP expression is identified at the protein and mRNA transcript levels.[47] Increased YAP expression and activity is also noted in pediatric hepatoblastoma, where nuclear expression of the protein is noted in up to 73% of cases.[45] However, no prognostic studies have yet shed light on the significance of YAP expression in pediatric liver tumors.

Wilms tumors

Genome-wide analysis has unraveled a potential role of the Hippo signaling system in kidney development through the regulation of the transcription factor WT-1.[49,50] YAP expression in wild-type developing kidneys is found in the nephron progenitor cells, ureteric bud, and stroma. There is evidence to suggest that Fat4 from the stromal fibroblasts may drive phosphorylation of YAP in the progenitor cells. In the absence of this FAT4 signal, dephosphorylated YAP resides in the nucleus, which leads to increased proliferation and expansion of the progenitor cells.

Wilms tumor is an embryonic kidney tumor in young children that harbors WT-1 mutations in most cases. YAP is expressed in Wilms tumor cell lines and clinical tissue specimens in both the cytoplasm and the nucleus. Immunoblotting experiments have revealed that YAP and its phosphorylated counterpart (p-YAP) vary in content across 40 clinical Wilms tumor specimens. Tumors with unfavorable histology (i.e., anaplastic) have shown a 5.2-fold greater p-YAP content than those with favorable histology.[50] Supportive immunohistochemical studies on Wilms tumor tissue still have to be published.

Brain tumors

The role of Hippo pathway in brain development is unclear. Deletion of TAZ and YAP in pre-migratory neural crest has resulted in craniofacial defects suggesting a role of this pathway in normal brain development.[51] In normal brains, YAP was undetectable in neurons, but expressed in neural stem cells and astrocytes. At least in mice, there is evidence for YAP regulation of neocortical astrocytic differentiation and proliferation.[51] These facts attests to the importance of this pathway in pediatric brain tumors, particularly gliomas where they are widely expressed.

Medulloblastoma

Sonic Hedgehog (HH) interacts with the Hippo pathway in a subset of medulloblastomas, leading to an upregulation and nuclear localization of YAP.[52] Medulloblastoma falls into four distinct molecular subgroups, and YAP immunohistochemical nuclear staining is clinically validated and accepted as a surrogate marker for the classification of a medulloblastoma into the HH tumor subgroup. The HH subgroup tumors (YAP-positive) have a very good prognosis in infants and an intermediate prognosis in all other age groups.[53,54] Though YAP nuclear expression has been noted in all histological subtypes of medulloblastomas, desmoplastic nodular medulloblastomas have a particularly high proportion of cases with YAP immunopositivity. The staining in desmoplastic nodular medulloblastomas is also peculiar in that it is highly expressed in the internodular areas and to a much lesser extent in the intranodular regions (Fig. 2).
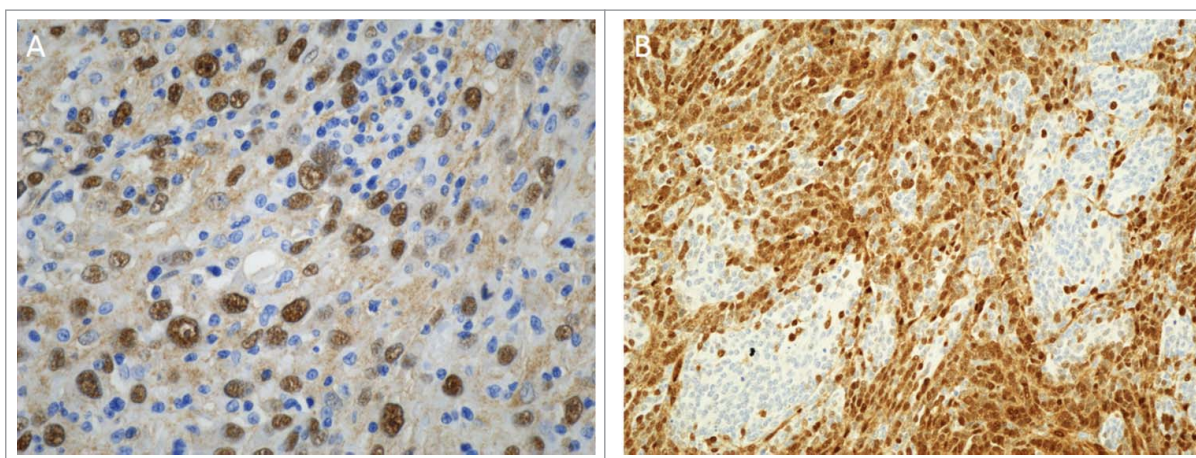
Figure 2. Potential applications of YAP immunohistochemistry in clinical practice as a diagnostic or a prognostic marker. Immunohistochemistry for YAP was performed at The Children's Mercy Hospital, Kansas City, Missouri on the Leica Bond instrument using an antibody against the nonphosphorylated protein (Santa Cruz, Dallas, Texas). A. Nuclear staining for YAP is identified in embryonal rhabdomyosarcoma cells, while the infiltrating lymphocytes are negative (x400). B. YAP immunoreactivity in nodular desmoplastic medulloblastoma. Nuclear staining is present in the internodular region (x200).

Astrocytomas

A recent study has determined that YAP is expressed in astrocytomas that span the entire World Health Organization (WHO) grading range.[53,54] It is frequently expressed in infiltrating astrocytoma and oligodendroglioma and less often in pilocytic astrocytoma. Pilocytic astrocytomas show variable staining in 30% of cases, and only 13% show a high level of nuclear staining. Other WHO II-WHO IV astrocytomas exhibit a higher degree of nuclear staining. As the WHO grade increases, from WHO II to WHO IV, YAP expression is increased. Additionally, pediatric glioblastoma cases are less likely to show a high degree of nuclear staining when compared to adult glioblastomas (40% vs. 66%). Furthermore, diffuse astrocytic tumors with high expression of YAP are associated with a reduction in overall survival when compared to similar tumors without high expression of YAP.[55,56] In vitro experiments have shown that YAP signaling enhances glioblastoma growth and invasiveness implying that targeting this protein may offer a potential therapeutic option.[57]

Other brain tumors

Recently, YAP immunoreactivity was reported in a study to have strong nuclear staining in atypical teratoid rhabdoid tumors, medulloepitheliomas, and primitive neurectodermal tumors. This study included only a small number of these tumor subtypes. Further investigation is needed to determine the prevalence of YAP immunostaining in these cases.[56]

A recent study has highlighted the expression of TAZ in retinoblastoma in 65% of clinical cases. High TAZ expression in this tumor was found to be prognostically significant, associated with shorter overall survival and disease-free survival rates.[58] Although no studies were done on clinical cases of germ cell tumors, there is a preliminary evidence suggesting that MST1/MST2 are required for teratoma formation, at least in mice.[59]

Hematologic malignancies

The role and significance of Hippo pathway in hematopoiesis are not well understood. A study using transgenic mouse model has shown that overexpression of YAP within the hematopoietic system has no effect on hematopoiesis or hematopoietic stem cell functions.[60,61] MST1 and MST2, the core components of Hippo pathway, seem to act as a switch between self-renewal and differentiation in primitive hematopoiesis in one study using *Xenopus* model.[62]

The deregulation of Hippo pathway and its role in the pathogenesis of hematopoietic malignancies have been studied by several groups, but their results were not consistent. One study has shown that YAP can trigger DNA damage and induce apoptosis in myeloma and other leukemia/lymphoma cells and that low YAP levels prevent nuclear ABL1–induced apoptosis.[17] Knockdown of *MST1* results in increased YAP expression and triggers cell death.[17] YAP has been found to be consistently downregulated in human hematologic cancers.[63] One study has shown that loss of MST1 in mice enhances lymphoma development, and that MST1 is frequently decreased in clinical specimens of lymphoma and leukemia.[64] In other studies, the expression levels of MST1/2 and YAP in hematologic malignancies are not significantly different from normal controls.[65,66] The discrepancy of the results may reflect the etiologic and pathologic heterogeneity of the hematologic malignancies. Further studies with larger sample size and more components of this pathway should be performed in this area.

Conclusions

Hippo pathway members are dysregulated in various pediatric tumors, attesting to the importance of this pathway in the development of these embryonal cancers. Of all Hippo members, YAP is the most commonly studied protein on clinical cases of pediatric tumors. Evidence indicates that YAP

expression affects patients' prognosis in rhabdomyosarcoma, osteosarcoma, HCC, Wilms tumor, and brain tumors. More useful clinical applications of YAP and other pathway members can be envisioned in the diagnosis and prognosis of pediatric tumors and await further research. Because of their wide expression, Hippo pathway members, particularly YAP, are potential novel treatment targets for those tumors that show overexpression.

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