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Clinical and biological implications of Hippo pathway dysregulation in sarcomas

Research Article

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Abstract: Sarcomas are mesenchymal malignant tumors with poor prognosis and limited treatment options. Hippo pathway is a recently discovered pathway normally involved in organ development and wound healing. Hippo signaling is often altered in solid tumors. The molecular elements of Hippo signaling include MST1/2 and LATS1/2 kinases which phosphorylate and regulate the activity of YAP and TAZ co-transcriptional activators. Hippo pathway cross-talks with several molecular pathways with known oncogenic function. In sarcomas Hippo signaling plays a pivotal role in tumorigenesis, evolution and resistance in chemotherapy regimens. Targeting Hippo pathway could potentially improve prognosis and outcome of sarcoma patients.

Keywords: *Sarcomas • Hippo pathway • Yap • Taz*

1. Introduction

Sarcomas are a heterogeneous group of mesenchymal tumors. The recent WHO (World Health Organization) classification of tumors categorizes sarcomas in more than 50 entities based on their histopathological and genetic data (1). Sarcomas are malignant tumors that occur in both sexes and in almost every age of life, affecting people mainly of the 2nd to the 6th decade of life (2, 3). Treatment of sarcomas is still based on surgery and total resection of the tumor (4). Systemic treatment and/ or radiotherapy are mostly used in metastatic or high stage disease. However, to date no sarcoma-targeted therapies have been approved and traditional chemotherapy, namely doxorubicin and ifosfamide remain the most effective drugs available in our armamentarium (5). The benefit from systematic chemotherapy remains poor with PFS (progression-free survival) of 5-7 months and overall survival for metastatic sarcomas of about 11-13 months (6-8). The recent publication of a clinical trial phase Ib-II showed that the combination of Doxorubicin with Olaratumab - a PDGFRa inhibitor - has offered a benefit of 11.8 months in the median overall survival to the patients who received the doublet compared to those who received Doxorubicin monotherapy (9). NCCN (National Comprehensive Cancer Network) and ESMO (European Society of Medical Oncology) guidelines included this combination in their recent versions, with the ESMO experts commenting on the unknown mechanism of action of Olaratumab and the fact that the doublet was compared to Doxorubicin monotherapy and not to Doxorubicin plus Ifosfamide which is the standard of treatment in Europe (10, 11).

2. Hippo Pathway elements and regulation

Hippo signaling pathway is a developmental pathway discovered recently in *Drosophila melanogaster*. Hippo pathway controls organ size, tissue regeneration, wound healing and maintenance of tissue specific stem cells in mammals' development (12, 13). Hippo signaling pathway modulates mesenchymal stem cell fate like normal bone (osteogenic differentiation), adipocyte (adipogenic differentiation) and muscle (myogenic differentiation), which are the origins of the most common sarcomas (14).

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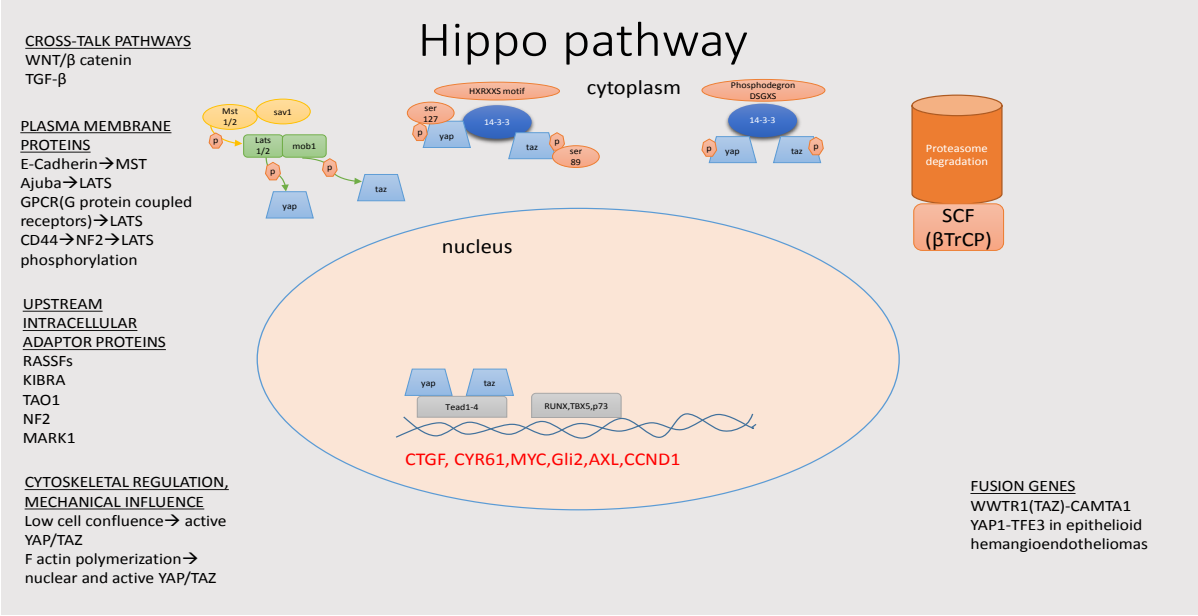

Figure 1: Hippo pathway proteins' localization and regulation.

Hippo signaling cascade includes MST1/2 and LATS1/2, two kinases which phosphorylate YAP and TAZ co-transcription factors. The phosphorylated forms of YAP and TAZ shuttle from the nucleus to the cytoplasm via their binding to 14-3-3 proteins. Ultimately, the cytoplasmic faith of pYAP and pTAZ is proteasomal degradation. The unphosphorylated forms of YAP and TAZ are rescued from 14-3-3 binding and cytoplasmic shuttling and remain in the nucleus. Thus, nuclear YAP and TAZ regulate their function through TEAD transcription factors (15, 16) (Figure 1).

Hippo signaling pathway is regulated through several mechanisms. Plasma membrane proteins like G protein coupled receptor ligands (GPCRs) have been identified as regulators of Hippo signaling (17). Upstream intracellular adaptor proteins such as NF2, RASSFs and KIBRA interact with MST1/2 and LATS1/2 alter their function and subsequently YAP and TAZ localization (18-20). Cytoskeletal remodeling is caused by mechanical changes which facilitate YAP and TAZ to emerge as important factors linking extracellular matrix signals to transcriptional outputs that regulate cell behavior (21, 22). Furthermore, there are many publications reporting cross-talk of Hippo with other pathways like Wnt/ b-Catenin, TGFb, PI3K, MAPK and Jak/Stat (23-26). Activation of Wnt/ b-Catenin pathway decreases Hippo pathway activity. YAP and TAZ dissociate from the proteasomal degradation complex resulting to dysregulation of Hippo signaling (23). JNK (Janus kinase pathway) cross-talks with Hippo pathway, through colocalization of AP1 (dimmer of JUN and FOS proteins) with YAP and TAZ in TEAD transcription factors (24, 27). Furthermore, Ajuba proteins inhibit LATS1/2 function and activate Hippo pathway (28). PI3K activation leads to Hippo pathway inhibition conferring antagonism between contact inhibition and growth promotion (29).

3. Hippo pathway in cancer

Recent data have shown that Hippo signaling pathway is frequently altered in several solid tumors, indicating a possible implication in their pathogenesis (12, 13). In details, comprehensive genomic analysis of Mesotheliomas has shown the presence of chromosomal translocations involving genes of the Hippo pathway as well as frequent mutations of these genes (30, 31). Of importance, fusion transcripts of Hippo pathway lead to inactivation of their tumor suppressor function promoting carcinogenesis (30). Also in Mesotheliomas strong dysregulation of Hippo pathway increases the transcription levels of cell cycle promoting genes like CyclinD1 (32). YAP and TAZ in Hepatocellular carcinoma contribute to disease progression by conferring stem cell-like properties (33). In Gastric cancer the downregulation of MST1/2 and LATS1/2 result to YAP,TAZ nuclear localization and Hippo pathway activation (34). YAP overexpression is related to shorter overall survival and TNM stage

in human Colorectal cancer patients (34). In Oral Squamus cell carcinoma YAP and TAZ are shown to drive protumorigenic signals (35). Hippo pathway is also engaged in Breast cancer, promoting several functions such as epithelial to mesenchymal transition, stem cell generation and therapeutic resistance (36).

4. Hippo pathway in sarcomas

Deregulation of Hippo pathway is also implicated in pathogenesis of sarcomas. This was initially demonstrated in preclinical models. Transgenic Hippo mouse models frequently develop sarcomas (37-39). Mouse models developing Rhabdomyosarcomas reveal the importance of YAP in this fatal sarcoma type (40).

In clinical samples, translocations with Hippo pathway genes have been detected in various sarcomas. In epithelioid hemangioendotheliomas YAP and TAZ create fusion genes resulting in YAP-TFE3 and TAZ-CAMTA1 respectively (41, 42). Clear cell sarcoma of the kidney and endometrial stromal sarcomas are characterized by the presence of the fusion gene YWHAE-FAM22. This fusion gene creates a nuclear fusion protein with a 14-3-3 element which interacts with YAP and TAZ (43, 44). Copy number alterations of YAP and TAZ have been reported in sarcomas, though mutations of these genes are not very common (45-47). Epigenetic regulation of Hippo elements have been shown in Ewing sarcomas and Osteosarcomas (48-50). FOXM1 interacts with YAP and promotes cell proliferation and tumorigenesis in a subset of soft tissue sarcomas (47). Despite all this descriptive evidence, a mechanistic biological understanding of Hippo pathway involvement in sarcomas is remarkably lacking.

In Rhabdomyosarcoma the characteristic PAX-FOXO1 fusion oncogene interacts with Hippo pathway to drive tumor development (40). Embryonal Rhabdomyosarcomas (eRMS) present with Ras activating mutations, while YAP is upregulated in eRMS. In Ras mutated RMS cell lines and in murine xenografts YAP promotes cell proliferation, decreases apoptosis and disrupts myogenic differentiation. Pharmacologic depletion of YAP with verteporfin decreased cell growth, showing that this molecular lesion is an early step in RMS tumorigenesis (51). TAZ, the second effector of Hippo pathway acts as an oncogene in eRMS. Its expression is correlated to Myf5 upregulation, an eRMS stem cell factor. TAZ is associated with poor survival in eRMS (52).

YAP is stabilized in Ewing sarcoma through the interaction of BMI-1 (53). In this sarcoma type YAP is expressed in tumor samples tested, however there is not a clear connection of survival and YAP expression. On the other hand, Akt expression in the same tumor samples was statistically related to survival, conferring a possible interaction of Hippo with Akt signaling (54).

In Osteosarcoma (OS) tumor samples YAP/TAZ and b-integrin were associated with prognosis. YAP and TAZ were independent prognostic factors for PFS (progression free survival) (55). Experiments looking for the molecular targets of Hippo signaling in Osteosarcoma revealed TEAD1 transcription factor to be the main Hippo effector. Cyr61 and PTGS2 were the downstream targets overexpressed in osteosarcoma cell lines (56). TAZ overexpression is accompanied by miR-224 overexpression, a TAZ phenocopy which inhibits tumor suppressor SMAD4, thus facilitating proliferation and migration of OS cells (57).

5. Hippo pathway and Drugs

Hippo pathway deregulation has been implicated in resistance to chemotherapeutic drugs (58). Overexpression of YAP and TAZ in BRAF V600E mutant melanoma cells confers resistance to BRAF inhibitors (59). In BRAF V600E mutant lung cells YAP expression correlates with resistance to MEK and RAF inhibitors (60). TAZ is shown to mediate resistance to taxol in Breast cancer cells (61).

Hippo pathway can be used as a target for therapeutic intervention. Small molecules like Verteporfin, statins and biphosphonates are being evaluated as putative treatment options (62, 63). There are few published reports of drug studies targeting Hippo pathway in sarcoma cells (64). Clinical trials of Phase I, II and III with drugs inhibiting Hippo pathway are still on-going (65-67).

In osteosarcoma cell lines YAP was reported to participate in chemoresistance. MG63 cells overexpressing YAP showed accelerated proliferation compared to YAP knocked out cells and presented resistance to high concentrates of chemotherapeutic drugs such as methotrexate and doxorubicin (68).

6. Conclusions and future challenges

Since Hippo signaling pathway constitutes a recently identified pathway, there are yet many critical aspects understudied. The oncogenic function of Hippo pathway is a “hot spot” of current cancer research efforts. Hippo pathway plays a crucial role in sarcoma stem cell formation, proliferation and resistance to chemotherapy regimens. Hippo pathway cross-talks with several other

molecular pathways and confers new insights in the complexity of the molecular cascades of sarcomas' tumorigenesis and evolution. Targeting Hippo pathway in sarcomas, where there is a great need of targeted therapies, could potentially improve prognosis and outcome in patients suffering from these lethal tumors.

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