HIPPO Stampede in Nerve Sheath Tumors

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Current therapies for malignant peripheral nerve sheath tumors (MPNSTs) are ineffective. The study by Wu et al. in this issue of Cancer Cell provides evidence that the HIPPO pathway is overactive in human MPNSTs and that combined modulation of LATS1/2-YAP/TAZ and PDGFR signaling in Schwann cells reduces MPNST arowth.

The evolutionarily conserved HIPPO pathway controls multiple cellular functions, including proliferation and tissue growth. The core of the HIPPO pathway is a kinase cascade wherein MST1/2 kinases activate LATS1/2 kinases, which in turn phosphorylate and inhibit the nuclear translocation of YAP and TAZ, two co-transcriptional regulators (Figure 1). Dysregulation of the HIPPO pathway is central to tumorigenesis and correlates with poor prognosis and reduced patient survival (Zanconato et al., 2016). Although the HIPPO pathway is activated in many tumor types, genetic mutations of HIPPO core components are rarely found. Peculiarly, loss-of-function mutations in both LATS1 and LATS2 are found in patients with Schwann cell associated tumors (Kim et al., 2014; Oh et al., 2015). Therapy aiming to restore HIPPO signaling in these Schwann cell associated cancers presents a challenge, because LATS1/2 loss of function causes persistent activation of YAP and TAZ, endowing tumor cells with resistance to chemotherapeutic and DNA-damaging agents (Zanconato et al., 2016). In the current issue of Cancer Cell, Wu et al. report on a major role for LATS1/2 kinases in suppressing tumorigenesis and malignant progression of Schwann cell tumors. The authors also demonstrate that combined pharmacological inhibition of LATS1/2 downstream effectors, namely YAP/TAZ and PDGFR pathway components, suppresses tumor growth. This allows for a novel therapeutic strategy for malignant peripheral nerve sheath tumors (MPNSTs).

Benign tumors of Schwann cells include Schwannomas and neurofibromas. Neurofibromas are the hallmark of neurofibromatosis (NF1). In NF1 patients with monoallelic NF1 mutations, neurofibromas are driven by somatic loss of NF1 heterozygosity in Schwann cells and activation of fibroblasts, mast cells, and macrophages. Schwannoma are the hallmark of NF2 in patients with biallelic-null mutations in merlin, an upstream regulator of the HIPPO pathway (Figure 1). MPNSTs appear in only 0.001% of the population, but their frequency is much higher in patients affected by NF1. They are very aggressive, with a 65% chance of recurrence and 40% chance of metastasis.

In this issue of Cancer Cell, the Lu laboratory members (Wu et al., 2018) first demonstrate that human and genetically engineered mice (GEM)-MPNSTs have reduced LATS1/2 and increased YAP/ TAZ signatures. Importantly, the YAP signature is present in MPNSTs regardless of their NF1 genetic status, suggesting that activation of the HIPPO-YAP/ TAZ pathway is common to both genetic and sporadic MPNSTs. The authors further show that downregulation of HIP-PO signaling characterizes Schwann cell transformation to MPNST. As such, it is possible that the dysregulation of the HIP-PO pathway can be used as a prognostic tool for Schwann cell tumors.

To investigate whether the activation of YAP and TAZ is necessary for the development of MPNSTs, Wu and colleagues used genetic mouse models to ablate both LATS kinases in Schwann cells. In these animals, the deficiency of LATS1/2 abolished the regulation of YAP and TAZ, which thus remain persistently active in the nucleus. Remarkably, animals deficient for LATS1/2 in Schwann cells rapidly develop 100% penetrant, aggressive nerve-associated tumors similar to human MPNSTs in their highly cellular, invasive characteristics and YAP

signature. Allografts of as few as 250 cells isolated from these GEM-MPNSTs propagate tumors in a notably short time. Data in the literature support the idea that Schwannoma and neurofibroma cells originate from Schwann cells, and probably from Schwann cell precursors. Tumors in LATS1/2-deficient mice develop after 20 days of age and could also be induced after deletion of LATS in adult Schwann cells. This suggests that hyperactivation of YAP and TAZ becomes oncogenic in Schwann cells after differentiation, consistent with reports that YAP and TAZ are required for Schwann cell myelination (Belin et al., 2017; Tricaud, 2018). Importantly, this also clearly shows that adult Schwann cells can give rise to tumors and is in line with the idea that differentiated Schwann cells are remarkably plastic and can be "reprogrammed" after injury and infection (Arthur-Farraj et al., 2012; Rambukkana et al., 2002).

Wu and colleagues further identify the molecular signature of LATS1/2 associated with malignant tumors. YAP and TAZ regulate gene expression by interacting with transcription factors such as TEADs. Genome-wide analysis of transcription and TEAD1 occupancy showed hyperactivation of YAP and TAZ transcriptional targets, including PDGFR and other oncogenic signals, with a concomitant decrease of tumor-suppressive pathways. Taking advantage of their LATS1/2 MPNST model, Wu et al. went on to elegantly demonstrate that genetically decreasing YAP and TAZ expression in animals deficient for LATS1/2 in Schwann cells impaired tumor progression. Although in vivo pharmacological inhibition of YAP/TAZ/TEAD1 was largely ineffective for reducing malignant tumor growth, combined targeting of

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YAP/TAZ/TEAD1, PDGFR, and RAF1 signaling reduces tumor cell proliferation in LATS1/ 2-deficient animals and human MPNST cell lines (Figure 1). These results bring new hopes for the treatment of MPNSTs. Inhibitors of PDGFR and RAF1 signaling (i.e., imatinib or sorafenib) used as single agents in phase II clinical trials showed minimal effect on MPNSTs. However, the data from the Lu laboratory (Wu et al., 2018) show that combined attenuation of both YAP/TAZ/TEAD1 and PGFDR/RAF1 signaling might now be considered as a potential treatment for MPNSTs.

This remarkable paper poses new questions for cancer, the HIPPO pathway, and Schwann cell biology. (1) Given that merlin/NF2 is a known inhibitor of the HIPPO pathway, why does loss of NF2 in Schwannoma not predispose to MPNSTs? It will be important to identify all the other inhibitors that keep YAP and TAZ in check in the absence of merlin. (2) YAP and TAZ are also regulated by mechanical stimuli (Dupont et al., 2011). Does the multicellular composition of neurofi-

bromas, with excessive matrix deposiincrease tissue stiffness to tion. contribute to YAP and TAZ activation and to malignant transformation? (3) Numerous GEM models of MPNSTs have been developed by deleting NF1, p53, and PTEN or by overexpressing neuregulin 1 in Schwann cells (Carroll, 2016); is a YAP activation signature also a feature of these models? (4) Loss of three, but not two, alleles encoding LATS1/2 is required for highly penetrant and rapid malignant transformation. Thus, is it the general level of YAP and TAZ dosage that determines the outcome between cell proliferation and differentiation? Or rather, do YAP and TAZ have specific and unique functions? (5) Finally, are there major targets downstream of LATS1/2



Figure 1. Schematic Representation of MPNST Tumorigenesis

The core of the HIPPO pathway is a kinase cascade wherein MST1/2 kinases activate LATS1/2 kinases, which in turn phosphorylate and inhibit the nuclear translocation of YAP and TAZ, two co-transcriptional regulators. YAP and TAZ are hyperactivated in MPNSTs and promote oncogenic pathways. Combined targeting of YAP/TAZ/TEAD1 (with verteporfin) and PDGFR and RAF1 signaling (with imatinib and sorafenib) reduces tumor growth.

that prevent MPNST, besides YAP and TAZ? Wu et al. could not remove more than two *Yap1* and *Taz* alleles *in vivo* due to their developmental requirements, so their complete necessity will have to be tested in an inducible system. In turn, YAP and TAZ necessity by genetic activation *in vivo* remains to be determined.

In summary, the targeting of YAP and TAZ has become a major interest for cancer research and clinical application (Zanconato et al., 2016). This comprehensive study by Wu et al. provides exciting insights into the role of the HIPPO pathway in MPNSTs and provides key elements for the development of novel diagnostic tools and a unifying pharmacological therapeutic strategy. The rapid, fully penetrant, and full-scale GEM-MPNST model developed by Lu and colleagues will surely prove useful to identify and test new therapies.

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