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Hippo - hungry, hungry for melanoma invasion

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Summary

The acquisition of invasive properties in melanoma is associated with a high proclivity for metastasis, but the underlying pathways are poorly characterized. The Hippo pathway plays an important role in organ size control and is dysregulated in some types of tumors. The present study, “Pro-invasive activity of the Hippo pathway effectors YAP and TAZ in cutaneous melanoma” by Nallet-Staub *et al.*, provides the first in-depth analysis of expression of the Hippo pathway effectors YAP (yes-associated protein) and TAZ (Tafazzin) in human melanocytic lesions. Importantly, results from this study demonstrate a causal relationship between YAP/TAZ levels and melanoma cell tumorigenicity and invasiveness.

The Salvador/Warts/Hippo signaling pathway, here simply referred to as the Hippo pathway, is an evolutionarily conserved regulator of organ size and tumorigenesis (Harvey *et al.*, 2013). The *hpo* gene was originally identified in *Drosophila melanogaster*. Its loss resulted in mutant fruit fly heads bearing overgrown cuticles with dark folds (Udan *et al.*, 2003). It was this hippopotamus head-like appearance for which the gene and the pathway were named (Udan *et al.*, 2003). Activation of the pathway induces the interaction of a core cassette of serine/threonine kinases and adaptors that cascade to result in the phosphorylation of effector molecules, YAP and TAZ (Harvey et al., 2013) (Figure 1). These core components include the serine/threonine kinases MST1/2 (*hpo* homologs) and LATS 1/2 and the adaptor proteins MOB1 and SAV1. (Harvey *et al.*, 2013). The loss of other pathway components phenocopies the overgrowth seen in *hpo* mutants through effects on both cell proliferation and apoptosis (Jia *et al.*, 2003; Justice *et al.*, 1995; Udan *et al.*, 2003). The pathway terminal kinases, LATS1/2, phosphorylate transcriptional co-activator YAP to regulate transcription of proliferative and apoptotic factors (Harvey *et al.*, 2013). Whereas unphosphorylated YAP translocates to the nucleus and interacts with TEAD family transcription factors, LATS 1/2-phosphorylated YAP is rendered inactive via cytoplasmic sequestration by 14-3-3 proteins (Zhao *et al.*, 2007). TAZ, a YAP paralog, shares 50% sequence identity with YAP, and also interacts with the TEAD family transcription factors (Lei *et al.*, 2008). This interaction is prevented by phosphorylation and sequestration in a similar manner to YAP (Lei 2008). Thus, YAP/TAZ phosphorylation and localization can be used as markers for Hippo signaling. Due to its aforementioned role in cell growth, the Hippo pathway has been investigated in tumorigenesis, using various cancer types (Harvey *et al.*, 2013). YAP expression is amplified in colonic adenocarcinoma, lung adenocarcinoma, ovarian serous cystadenocarcinoma, and ductal carcinoma of the breast (Steinhardt *et al.*, 2008). Cutaneous melanoma is well-known for its invasive and metastatic

behavior; however, the role of Hippo signaling in this disease remains poorly characterized. In this highlighted article, Nallet-Staub *et al.* show a link between Hippo pathway effectors and melanoma invasion and colony formation *in vitro* and *in vivo*.

Nallet-Staub *et al.* analyzed YAP and TAZ expression in melanoma cell lines and melanocytic lesions. While TAZ expression was elevated in melanoma cell lines compared to normal human melanocytes, these levels were variable, and no differences in YAP1/2 expression were noted. Furthermore, immunohistochemical analyses showed no differences in YAP and TAZ staining between benign nevi and superficial spreading melanoma. Thus, YAP and TAZ do not represent biomarker candidates for melanoma invasion. However, the data does support a causal relationship between Hippo signaling and melanoma invasive properties. YAP and TAZ knockdown in melanoma lines with high basal YAP/TAZ levels inhibited *in vitro* tumorigenicity, Matrigel invasion, and lung colonization *in vivo*. Furthermore, these effects were associated with TAZ and YAP regulation of CCN2, the gene that encodes connective tissue growth factor, which was previously found to promote melanoma metastasis (Mohammad *et al.*, 2011).

The data from Nallet-Staub *et al.* corroborate the findings of Lamar *et al*., who reported that overexpression of active YAP enhanced the frequency and size of melanoma colonies in the lung after tail vein injection, in a TEAD binding dependent manner (Lamar *et al.*, 2012). Nallet-Staub *et al.* extended these findings to link endogenous YAP and co-activator TAZ directly to melanoma growth and metastasis. YAP and TAZ now join the list of regulators of invasion and metastasis that includes TWIST1, a mutant BRAF-regulated E-box transcription factor that promotes melanoma invasion (Weiss *et al.*, 2012), RhoC, a GTPase involved in actin cytoskeleton regulation, adaptor protein NEDD9, and matrix metalloproteinase-1/MMP1 (Orgaz and Sanz-Moreno, 2013). Some of these previously identified invasion and metastasis regulators in melanoma are linked to ERK 1/2 pathway activation. Importantly, the findings from Nallet-Shaub *et al.* demonstrate that alternate signaling molecules, particularly Hippo pathway components, may have major implications for melanoma dissemination as well.

Prognosis for melanoma sufferers has improved greatly using ERK pathwaytargeting BRAF inhibitors, but these drugs are limited in use for mutant BRAF melanoma populations (50% of melanoma patients), and they are FDA-approved only for advanced stage disease. While much focus on targeted therapies has centered on ERK 1/2 signaling, targeting Hippo pathway effectors may provide a new avenue for treatment. Verteporfin is a small molecule that inhibits YAP-TEAD association and YAP-induced liver overgrowth (Liu-Chittenden *et al.*, 2012). It will be interesting to examine the ability of verteporfin to inhibit Hippo effector interactions and its effect on melanoma invasion and metastasis in both the mutant BRAF and wild-type BRAF settings.

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Clinical implications

1. Aberrant Hippo signaling may promote invasion irrespective of mutant BRAF status of melanomas.
2. A small molecule, verteporfin, inhibits YAP-TEAD transcription factor interaction and should be tested for its effects on melanoma growth and invasiveness.
3. There is no evidence to date that YAP and TAZ expression will serve as biomarkers for invasive/metastatic potential.

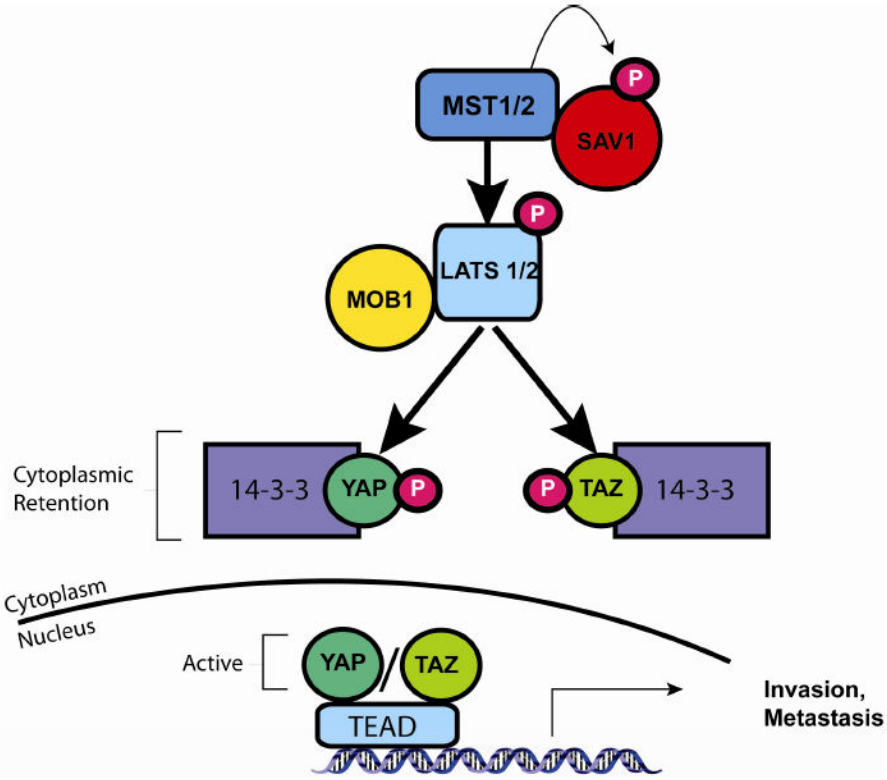

Figure 1.

The Hippo pathway signaling cascade results in the phosphorylation and cytoplasmic retention of effector molecules YAP and TAZ. Un-phosphorylated YAP and TAZ can translocate to the nucleus to interact with TEAD transcription factors and regulate transcriptional events that promote melanoma invasion and metastasis.