The Hippo pathway target, YAP, promotes metastasis through its TEAD-interaction domain

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AUTHOR SUMMARY

Cancer is the second leading cause of death worldwide, and more than 90% of these deaths are caused by metastasis. Therefore understanding the cellular mechanisms that regulate metastasis is vital to the development of effective cancer therapies. Of particular interest are transcription factors, because they are able to regulate the expression of multiple genes in response to extracellular cues and therefore can influence multiple prometastatic processes simultaneously. Here, we showed that Yes-associated protein (YAP), a transcription cofactor regulated by the Hippo pathway, promotes cancer progression and metastasis.

In normal cells, the Hippo pathway, a kinase cascade that is activated in response to changes in cell density, cell shape, and cell adhesion, controls proliferation and maintains normal organ size. It does so by repressing the activity of two closely related proteins, YAP and TAZ, both of which, when active, promote proliferation and cell survival (1, 2). This repression occurs via phosphorylation of YAP/TAZ, which results in cytoplasmic sequestration, proteasomal degradation, or both. Given the importance of YAP and the Hippo pathway in regulating proliferation, it is not surprising that aberrantly increased YAP activity or inhibition of the Hippo pathway can play a causal role in cancer. Indeed, many human cancers have increased YAP protein levels or increased nuclear localization as compared with normal tissues. Furthermore, several mutations in Hippo pathway proteins are known to be present in human tumors (1, 2). Experimental overexpression of YAP or inhibition of the Hippo pathway results in tumor formation and increased tumor growth (1, 2). Despite these clearly established oncogenic properties of YAP, roles for this protein or the Hippo pathway in tumor progression and metastasis are, to the best of our knowledge, unknown.

To explore the consequences of aberrant YAP activity on metastasis, we expressed mutant forms of YAP that are insensitive to repression by the Hippo pathway. We found that this aberrant increase in YAP activity not only enhanced mammmary carcinoma and melanoma growth but also rendered cells highly metastatic. The YAP protein contains several protein–protein interaction domains that mediate binding of YAP to numerous downstream proteins, including several transcription factors. We tested the importance of these domains by using mutant forms of YAP and a Luminex-based approach to multiplex in vivo tumor independent processes, any of which, if augmented, could result in enhanced metastatic potential. Our data suggest that, in addition to promoting primary tumor growth, increased YAP activity enhances growth and survival of tumor cells at the metastatic site. Although this effect contributes significantly to the increased metastatic burden, YAP also can promote metastasis through additional mechanisms. YAP enhanced migration and invasion, two processes known to play an important role in promoting the spread of cancerous cells from the primary tumor. Consistently, YAP rendered nonmetastatic primary tumor cells highly metastatic. Thus, increased YAP activity can promote metastasis by enhancing prometastatic processes that occur both in the primary tumor and at the metastatic site (Fig. P1). Using mutant forms of YAP, we further demonstrated that the Hippo growth and metastasis assays. These multiplexed in vivo experiments revealed that the TEAD-interaction domain of YAP, but not the WW domains or PDZ-binding motif, is essential for YAP-mediated tumor growth and metastasis. Because mutation of the TEAD-interaction domain prevents the interaction of YAP with the four TEF/TEAD transcription factors and impairs TEAD-mediated transcriptional activity (3), we hypothesized that YAP promotes metastasis by promoting TEAD-dependent gene expression. Indeed, we found a strong correlation between TEAD transcriptional activity and metastatic potential in human and mouse cancer cells. In addition, mutant forms of YAP that enhanced metastasis dramatically increased TEAD transcriptional activity.

Metastasis involves multiple independent processes, any of which, if augmented, could result in enhanced metastatic potential. Our data suggest that, in addition to promoting primary tumor growth, increased YAP activity enhances growth and survival of tumor cells at the metastatic site. Although this effect contributes significantly to the increased metastatic burden, YAP also can promote metastasis through additional mechanisms. YAP enhanced migration and invasion, two processes known to play an important role in promoting the spread of cancerous cells from the primary tumor. Consistently, YAP rendered nonmetastatic primary tumor cells highly metastatic. Thus, increased YAP activity can promote metastasis by enhancing prometastatic processes that occur both in the primary tumor and at the metastatic site (Fig. P1). Using mutant forms of YAP, we further demonstrated that the Hippo


The authors declare no conflict of interest.

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pathway is able to repress YAP-mediated tumor growth and metastasis by promoting cytoplasmic sequestration and proteasomal degradation of YAP (Fig. P1).

Our present study suggests that increased YAP/TEAD activity plays a causal role in cancer progression and metastasis. Although to our knowledge mutant forms of YAP have not been described in human cancers, the yap1 locus is amplified in several human cancers, and increased nuclear YAP staining in human tumors is associated with poor prognosis (1, 2). Mutations in the Hippo pathway, which would result in increased YAP activity, also are present in human cancers (1, 2). Evidence indicates that YAP participates in the cellular response to DNA damage as well as in promoting resistance to chemotherapeutics. Thus disrupting YAP function in tumor cells might decrease primary and metastatic tumor burden, block further metastatic spread, and make disseminated tumor cells more susceptible to chemotherapy. Interestingly, a recent study demonstrated that verteporfin, a small molecule that inhibits TEAD–YAP interaction, suppresses the oncogenic effects of YAP (4). In summary, our results suggest that increased YAP activity can contribute functionally to metastatic disease, making YAP and the Hippo pathway potential therapeutic targets.