YAP1 grabs the spotlight in oncogenic Ras addiction

YAP1 and the Hippo pathway

The Hippo signal transduction pathway plays a critical role in the regulation of organ size through the coordinated modulation of cell fate. The core pathway members include two sets of serine/threonine kinases (MST1/2 and LATS1/2) that act in succession to shut down pro-growth signaling through the phosphorylation and "inactivation" of the transcriptional co-activators YAP and TAZ (Fig. 1). YAP and TAZ are paralogous proteins that have overlapping, but not identical, functions in regulating cell growth, differentiation, and apoptosis. For simplicity, this newsletter will focus specifically on YAP1; however most of what will be discussed has been shown to be true for TAZ. The MST1/2 → LATS1/2 → YAP1 signaling axis is activated as a result of a cell's response to physical changes in the extracellular environment, including cell adhesion, cell-cell contacts, and extracellular matrix stiffness, etc. (Fig. 1). Notably, several signaling pathways intersect with the Hippo pathway to ultimately control YAP1 activity. As a result of Hippo pathway activation, YAP1 is phosphorylated by LATS1/2 on multiple serine residues (S61, S109, S127, S164, S381), which subsequently leads to the binding of 14-3-3 proteins, leading to further serine phosphorylations (S384, S387) that promote the interaction of YAP1 with the SCF ubiquitin ligase complex. This chain of events results in YAP1 ubiquitination and subsequent proteosome-dependent degradation. In the absence of Hippo pathway signaling, YAP1 is shuttled into the nucleus where its primary nuclear partners are the TEAD transcription factors. Importantly, there are several other transcription factors that have been shown to partner with YAP1 in a context-dependent manner (e.g., SMADs, β-catenin, Fox, E2F, etc.) (Fig. 1).

The role of YAP1 in cancer is complex

The overexpression of YAP1 in non-transformed cells leads to its nuclear accumulation, resulting in adhesion-independent cell growth, epithelial-to-mesenchymal transition (EMT), suppression of apoptosis, and growth factor-independent proliferation, all hallmarks of neoplastic cells. While a direct cause and effect relationship has not been firmly established for YAP1 and the development of cancer, it is clear that in many contexts elevated YAP1 activity would support neoplastic behavior. Consistent with the in vitro YAP1 overexpression studies, several cancers have been shown to exhibit elevated YAP1 expression. Moreover, elevated YAP1 activity has been correlated to a poor prognosis in several cancers. The etiology of YAP1 activation in cancer is varied and often results from the dysregulation of the Hippo pathway and/or the amplification of the 11q22 genomic locus that encompasses the YAP1 gene. In contrast to its association with cancer progression, there are cases where YAP1 appears to act as a tumor suppressor (e.g., breast cancer and some colon cancers).
YAP can overcome oncogenic Ras addiction

Recent evidence has shed light on the importance of YAP1 in Ras-dependent cancers4,8,9,21,22. Gain of function mutations in Ras (H-, K-, or N-Ras) have been observed in 33% of all human cancers23,24. These mutant Ras isoforms are dominant drivers of oncogenesis and the resultant cancers are highly dependent, or “addicted”, to mutant Ras signaling for their survival25,26. YAP1 has been identified as a critical factor in oncogenic Ras signaling that allows cells to overcome their Ras addiction4,8,9,22. Ras signaling modulates YAP1 activity at multiple levels, including the inactivation of LAT5 kinases27, and through the regulation of YAP1 turnover by a ubiquitin ligase complex that is distinct from the SCFTRC complex employed by the Hippo signaling pathway28 (Fig. 1). In the latter case, Ras signaling downregulates the expression of SOCS6, which is the YAP1 substrate recognition component of the Elongin B/C ubiquitin ligase complex27. This ultimately leads to increased levels of YAP1, its nuclear accumulation, and the activation of pro-oncogenic transcription that is mediated through its binding partners Fos and TEAD2/E2F8,9,22 (Fig. 1).

Conclusion

The finding that YAP1 can overcome oncogenic Ras addiction, and that its activity is elevated in several cancers, implies that therapeutics targeting Ras alone will likely meet with resistance that is mediated in part by YAP1. Moreover, YAP1 can act in a cell context dependent manner in either a pro-oncogenic or tumor suppressive capacity, suggesting that there may be therapeutic opportunities to promote its tumor suppressive behavior when developing drugs to target oncogenic Ras. Importantly, the activity of YAP1 is significantly modulated by several post-translational modifications (PTMs) (i.e., serine and tyrosine phosphorylation and ubiquitination). At Cytoskeleton, we have several products to further research in this area, including Ras activation assays, PTM antibodies, and GEF assays.

PTMtrue™ Antibodies

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References

22. X. Hong et al. 2014. Opposing activities of the Ras and Hippo pathways con-verge on regulation of YAP protein turnover. EMBO J. 33, 2447-2457.