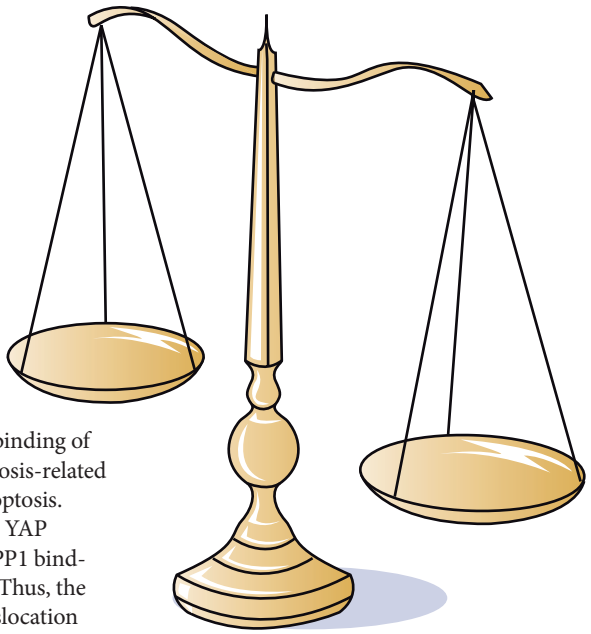
TUMOUR SUPPRESSION

YAP tips the balance



Yes-associated protein (YAP) is a transcriptional co-activator that shuttles between the cytoplasm and the nucleus. The role of YAP-mediated gene expression in tumorigenesis is unclear, as there are reports that YAP has both oncogenic and tumour suppressive roles. Such contradictory findings often reflect complex control networks, and three studies published in *Genes and Development* make further inroads into understanding the interactions and regulatory events that are centred around YAP.

Like YAP, apoptosis-stimulating protein of p53 1 (ASPP1) also shuttles between the nucleus, where it modulates the transactivation of p53, and the cytoplasm, where its function is unknown. Karen Vousden and colleagues have identified a role for cytoplasmic ASPP1 in regulating YAP-mediated gene expression. In the cytoplasm, the kinases large tumour suppressor 1 (LATS1) and LATS2 phosphorylate YAP, targeting it for sequestration and degradation. However, ASPP1 can bind to LATS1 and inhibit the interaction with YAP, preventing YAP phosphorylation and inactivation. This results in increased localization of YAP to the nucleus, increased YAP-dependent transcriptional regulation and inhibition of apoptosis.

Moshe Oren and co-workers showed that, conversely, YAP can interfere with the nuclear function of ASPP1. In response to HRAS activation, LATS2 phosphorylates cytoplasmic ASPP1 and mediates its translocation to the nucleus. There, LATS2 and phospho-ASPP1 cooperate to increase the binding of p53 to promoters of apoptosis-related genes and to stimulate apoptosis. High levels of cytoplasmic YAP interfere with LATS2–ASPP1 binding and inhibit cell death. Thus, the cytoplasmic–nuclear translocation of YAP and ASPP1 is dependent on complex regulatory interactions, the outcome of which determines cell fate.

In a complementary study, Duojia Pan's group studied the function of YAP in tissue development and regeneration. Knockout mice lacking *Yap1* in the epithelium of the small intestine and colon developed normally; however, intestinal regeneration following injury was impaired relative to wild-type mice. Deletion of *Sav1*, a gene encoding a regulatory protein that activates LATS, resulted in YAP-dependent enlargement of colonic crypts and development of sessile serrated polyps, precursors to colorectal neoplasia and invasive adenocarcinomas. This hyperplasia was accelerated after tissue injury and regeneration, and the authors conclude that the regenerative capacity of colonic cells must be kept in check by phosphorylation and downregulation of YAP to prevent excessive proliferation leading to oncogenesis.

The results of these studies reveal an interconnected regulatory network between ASPP1, LATS, YAP and SAV1 and highlight the need for tight regulation of both their levels and cellular localization in order to maintain the balance between controlled proliferation and apoptosis, and to prevent tumour progression.

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ORIGINAL RESEARCH PAPERS Vigneron, A. M. *et al.* Cytoplasmic ASPP1 inhibits apoptosis through the control of YAP. *Genes Dev.* **24**, 2420–2429 (2010) | Aylon, Y. *et al.* The Lats2 tumor suppressor augments p53-mediated apoptosis by promoting the nuclear proapoptotic function of ASPP1. *Genes Dev.* **24**, 2430–2439 (2010) | Cai, J. *et al.* The Hippo signalling pathway restricts the oncogenic potential of an intestinal regeneration program. *Genes Dev.* **24**, 2383–2388 (2010)