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The WNT signalling pathway promotes regeneration and homeostatic self-renewal of the mammalian intestine; however, the mechanisms that oppose WNT activity to halt proliferation and maintain organ size are less clear. Camargo and colleagues now show that Yes-associated protein (YAP) restricts WNT signals during intestinal regeneration. This finding is unexpected given that YAP, which is a transcriptional activator in the Hippo signalling pathway, is known for its potent growth-promoting properties in both organs and tumours.

When expressing YAP specifically in the intestinal epithelium of mice, the authors were surprised to observe the progressive loss of proliferating crypts and the consequent degeneration of the colon and small intestine. This phenotype was associated with repression of WNT target genes and the gradual loss of intestinal stem cells at the crypt base and of Paneth cells (which are essential components of the intestinal stem cell niche). This suggests that, in contrast to other tissues where YAP promotes growth, epithelial-specific expression of YAP suppresses intestinal renewal by inhibiting the WNT pathway.

> “YAP restricts WNT signalling by blocking DVL nuclear translocation”

Previous studies had shown that loss of YAP does not affect normal intestinal homeostasis. However, Camargo and colleagues found that after injury by irradiation, *Yap*-knockout mice showed crypt overgrowth throughout the intestine and increased numbers of intestinal stem cells and Paneth cells. This was accompanied by upregulation of WNT target genes. As intestinal regeneration after irradiation is characterized by WNT hyperactivity, these data suggest that YAP counteracts increased WNT signalling *in vivo*. A hypersensitive response to WNT in the absence of YAP was confirmed upon administration of the WNT agonist R-spondin 1.

YAP is normally inactivated by Hippo-dependent phosphorylation, which prevents its translocation from the cytoplasm to the nucleus. However, this study shows that endogenous YAP is nuclear in cells at the crypt base, in which WNT signalling is active. Conversely, YAP is cytoplasmic in the remaining parts of the villi, where WNT is inactive, which suggests a role for cytoplasmic YAP in restricting WNT signalling.

The authors report that YAP interacts with the WNT effector Dishevelled 2 (DVL2), which is nuclear in cells at the base of crypts and has a more diffuse localization in cells of the adjacent transient-amplifying compartment. DVL proteins have previously been shown to be positive regulators of WNT signalling that act both in the cytoplasm and in the nucleus. Here, nuclear DVL2 was increased in *Yap*-knockout mice during irradiation-induced regeneration. Furthermore, YAP prevented DVL-induced WNT transcriptional responses. Together, these results indicate that YAP might restrict WNT signalling by blocking DVL nuclear translocation.

Thus, the role of YAP in growth control is context dependent. As suggested by the authors, this calls for careful consideration of current therapies that target YAP for the treatment of malignancies such as colorectal cancer, as such manipulations could potentially increase tumour growth.

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ORIGINAL RESEARCH PAPER Barry, E. R. *et al.* Restriction of intestinal stem cell expansion and the regenerative response by YAP. *Nature* 25 Nov 2012 (doi:10.1038/nature11693)