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Hippo signalling in intestinal regeneration and cancer

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The Hippo pathway is a unique signalling module that regulates cell-specific transcriptional responses and responds to a wide range of intrinsic and extrinsic cues. Besides its classical role in restricting tissue size during development, Hippo signalling is now recognized to control numerous processes including cell proliferation, survival, cell fate determination, epithelial-to-mesenchymal transitions and cell migration. Because of its highly dynamic nature, the intestinal epithelium has served as an exceptional model to study the complex roles of Hippo signalling. In this review, we shall present an overview of Hippo function in the mammalian intestine and discuss the various mechanisms regulating Hippo signalling and how they contribute to intestinal regeneration and cancer.

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Introduction

A primary function of the gut epithelium is nutrient uptake and forming a protective barrier against the external milieu. To maintain barrier function the epithelium is continuously renewed by intestinal stem cells (ISCs), or crypt base columnar cells (CBCs), located in the crypts of Lieberkühn (Figure 1). Over the last decade significant progress has been made in our understanding how ISCs function during homeostasis [1], but less is known about gut epithelial regeneration upon damage and how chronic injury is linked to cancer initiation and progression. In models of gut injury, such as whole body irradiation or dextran sodium sulfate (DSS)-induced colitis, surviving cells of the crypts undergo a rapid, transient proliferative boost that replenishes non-functional cells. Increased Wnt, Egfr and Jak/Stat signalling are important in this response [2–6], while the recent discovery of the Hippo pathway has revealed an additional layer of complexity [7]. The core Hippo pathway in mammals includes the Mst and Lats kinase cassette (see Box 1 for details), which inactivates the transcriptional regulators, Yap and Taz that in turn regulate transcription of genes typically associated with proliferation, cell survival and cell fate.

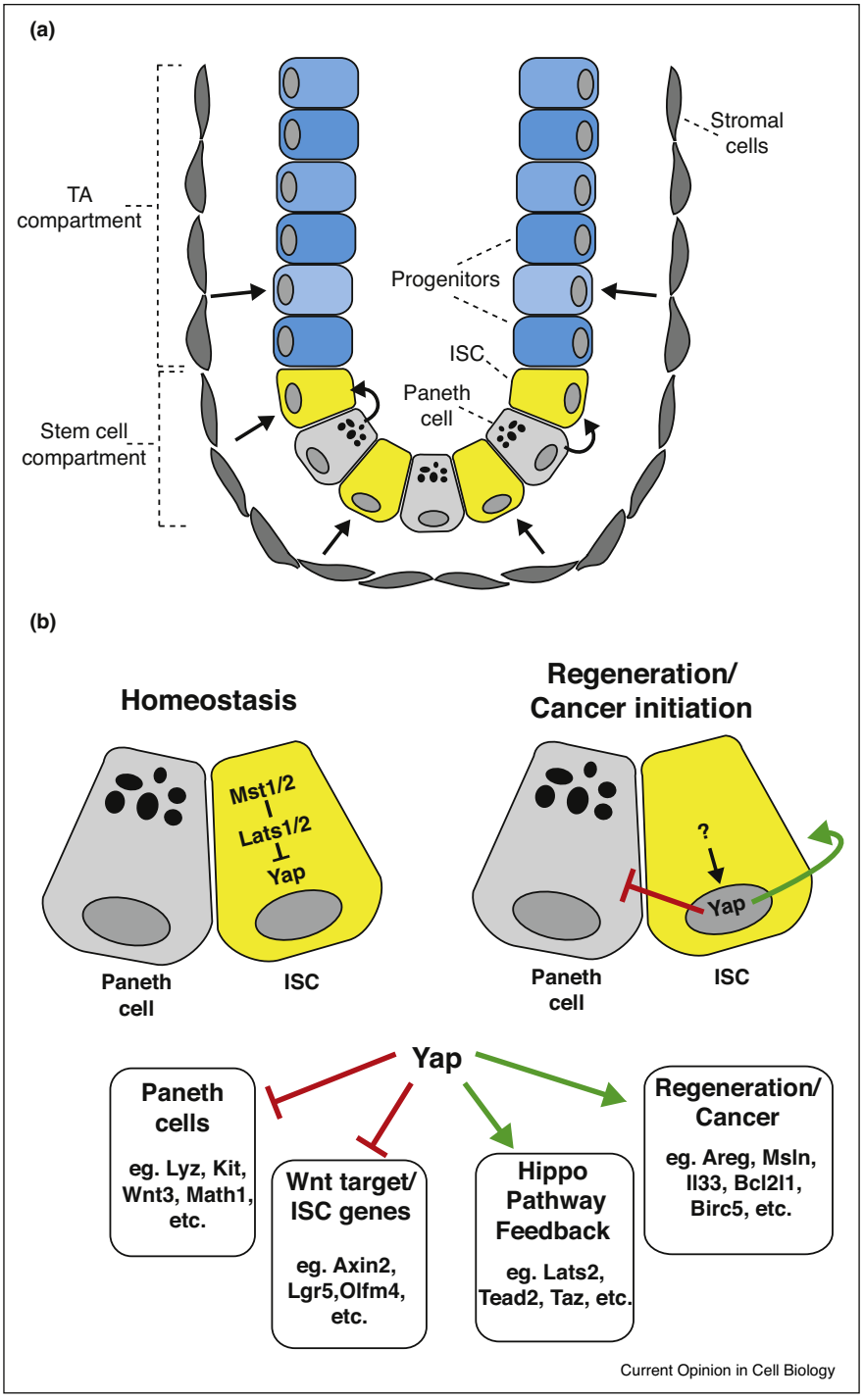
Loss of function studies *in vivo* have shown that Yap and Taz are dispensable for gut homeostasis, but following chemical injury or gamma irradiation, Yap is required to regenerate the Lgr5+ ISC pool and crypt regeneration [8,9,10••]. One exception is the work of Imajo *et al.*, who used a novel intestinal RNAi delivery system [11•] and suggested Yap/Taz promote ISC proliferation and differentiation into goblet cells without prior injury. However, the Yap/Taz dependent effects observed in their system might reflect induction of tissue injury responses from the surgical interventions required for virus-mediated gene transfer. Collectively, the studies on Hippo signalling in the gut indicate that under normal circumstances Yap/Taz are tightly controlled by the inhibitory upstream kinases Mst and Lats that is released during regenerative responses.

The initial hyperproliferation phase during crypt regeneration is reminiscent of the effects of Apc loss during tumour initiation and genetic studies show Yap and Taz are also required for adenoma formation in Apc^{min} mice [10••,12•,13]. Furthermore, Yap activation by Mst1/2 or Sav deletion increases crypt proliferation and tumorigenicity [9,14], with Yap/Taz potentially regulated by additional Lats-related NDR kinases [15]. Studies in human colorectal cancer cell lines similarly show that reducing Yap/Taz levels leads to impaired proliferation, survival and tumourigenicity [14,16] and a number of clinical reports link high Yap/Taz activity to colorectal cancer progression and overall poor prognosis [17].

Hippo transcriptional program

In the crypt epithelium loss and gain of function approaches show that Yap promotes expression of numerous genes implicated in cancer and regenerative signalling (*i.e.* Egfr ligands, Ctgf, Cyr61, Msln, Il33, *etc.*) (Figure 1b) [8,10••]. Studies in intestinal organoids and tumour initiating cells *in vivo*, suggest that Yap drives Egfr signalling during crypt regeneration and adenoma formation [10••]. Indeed impaired crypt formation in Yap mutant organoids is rescued by the exogenous Egfr ligand, Epiregulin [10••]. In human colorectal cancer cells, Yap also promotes anti-apoptotic gene expression (*e.g.* Bcl2l1 and Birc5) through a transcriptional complex

Figure 1



Hippo function in the crypt epithelium.
(a) The crypt epithelium is subdivided into two functional units: the ISC and transit amplifying (TA) compartments. ISCs reside at the base of the crypts and are intermingled between post-mitotic Paneth cells. The TA compartment is composed of mitotic progenitor cells for the various cell lineages of the gut epithelium (*i.e.* enterocytes, goblet cells, Paneth cells, enteroendocrine cells, *etc.*) [86]. The Wnt, Notch, Egfr and Bmp signalling pathways represent the major stimuli regulating ISC/progenitor proliferation, as well as determining cell lineage commitment and differentiation during homeostasis. Receptor activation of these signalling cascades in ISCs is largely dependent on the expression of their specific ligands in the stem cell niche, that is Paneth cells and underlying stromal cells (see arrows) [87–89]. **(b)** During homeostasis the Mst-Lats kinase cassette, as well as other kinases (*i.e.* NDR1/2 and Pkcζ) maintain Yap in the cytoplasm and transcriptionally inactive. Following tissue injury or an oncogenic event Yap translocates to the nucleus and induces a genetic program that suppresses Paneth cell differentiation and maintenance of ISCs. Representative Yap responsive genes identified so far are highlighted below. The precise mechanism(s) leading to activation of Yap remains unclear (see below).