



## Intestinal Stem Cells

### *New concepts and methods*

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#### **Paneth cells, the guardian of the intestinal stem cell niche: A controversy about the involvement of an old suspect**

Intestinal epithelium has the capacity to self-renew and generate differentiated cells through the existence of at least two types of epithelial stem cells: active crypt base columnar (CBC) and quiescent +4 cells. The behaviors of these cells are regulated both by intrinsic programs and by extrinsic signals sent by neighboring cells, which define the niche. The specific markers for +4 cells are still controverted and the nature of their niche remains unknown. In contrast, remarkable progress has been made in identifying and characterizing CBC cells. It is clear that the Wnt pathway and Notch pathways acts as essential intrinsic signals for their maintenance and their proliferation. Interestingly, Wnt also drives differentiation of Paneth cells that are in direct contact with CBC stem cells. In contrast to previous studies which produced evidences that Paneth cell ablation yielded normal crypt proliferation, recent work indicates that Paneth cells provide a crucial niche by secreting Wnt ligands. We then re-examined the Paneth cell role as intestinal stem cell niche by analyzing *Math1*<sup>-/-</sup> mice which lack Paneth cells entirely. *Math1* is a transcription factor required for secretory cell differentiation which has a direct role in mediating intestinal Notch functions. We found that complete loss of Paneth cells due to *Math1* deficiency did not perturb the crypt architecture and allowed the maintenance and proliferation of CBCs. Indeed, *Math1*-deficient crypt cells tolerated *in vivo* Paneth cell loss and maintained active  $\beta$ -catenin signaling but could not grow *ex vivo* without exogenous Wnt, implying that *in vivo* underlying mucosal cells act as potential niche. Upon irradiation, *Math1*-deficient crypt cells regenerated and CBC cells continued cycling. Finally, CBC stem cells deficient in *Apc* and *Math1* were able to promote intestinal tumorigenesis. Thus, depending on genetic context, redundant Wnt ligands derived from mesenchymal component can overcome Paneth cell ablation and maintain CBC function.