Regulation of intestinal crypt homoeostasis: A balance between Wnt mediated expansion and proliferation inhibition

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***Short Abstract* — A hybrid stochastic model is used to investigate how exogenous niche signaling (Wnt and BMP) and auto-regulation promote homeostasis. This model uses sub-cellular element method to account for three-dimensional structure of the crypt, external regulation by Wnt and BMP, internal regulation by Notch, as well as regulation by internally generated diffusible signals. Results provide an alternative view of crypt homeostasis where the niche is in a constant state of expansion and the spatial structure of the crypt arises as a balance between this expansion and the action of various sources of negative regulation that hold it in check.**

I. Introduction

THE epithelium of the intestinal crypt is an incredibly dynamic tissue, constantly replenishing itself every 4-5 days, which is fueled by approximately 15 CBCs [1], dividing roughly once per day even in healthy tissue [2]. Numerous investigations have shown the canonical Wnt / b-catenin pathway to be critical in maintaining homeostasis [3]. There are two sources of Wnt signaling in the crypt [3]. The mesenchyme that surrounds it produces graded expression of Wnts; Paneth cells also produce Wnt3a. Genetic deletion of this "local", Paneth cell derived Wnt source does not impair stem cell populations in the *in vivo* crypt [4], suggesting the global Wnt gradient is sufficient for homeostasis. However, i*n vitro* studies of "mini-guts" grown from CBCs have shown that Paneth derived Wnt3a alone is also sufficient to maintain crypt structure in the absence of the other exogenous Wnt sources [5]. Additionally, Eph / ephrin signaling interactions generate repulsive forces that drive Paneth cells to migrate down the crypt wall while all other cells passively migrate upward from the base, driven by proliferative pressure [6]. Bone morphogenic proteins (BMPs) are also known to influence crypt homeostasis by suppressing proliferation of stem cells [7].

How do these signaling components contribute to maintaining the spatial structure of the crypt and how do they interact? Extensive computational modeling has been employed to address this and related questions.

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II. Results

Paneth derived Wnt promotes uncontrolled expansion of the stem cell niche. Simulations results show that stem and Paneth cells together create a mutually sustaining feedback that drives expansion of both populations. Thus, Paneth cell derived Wnt signaling alone cannot both fully sustain the niche and promote homeostasis at the same time.

Regulation of proliferation by BMP constrains niche expansion. Simulation results suggest that there is a balance between expansion and repression that is required to maintain homeostasis. Wnt, which influences differentiation, promotes niche expansion while BMP, which influences proliferation, constrains that expansion.

Eph/Ephrin mediated Paneth cell motion is required to constrain niche expansion. These results suggests that rather than being required to maintain the niche, Paneth cell migration is instead required to maintain proper structure in the upper walls of the crypt, and in particular to constrain niche expansion. Also the rate of cellular proliferation and the drag between cells and the crypt wall induced by adhesion are also observed to investigate the role of cell motions.

III. Conclusion

We find that there are redundant signals created by both the epithelium itself and surrounding tissues that act in parallel to maintain epithelial structure. However, this redundancy introduces the possibility of explosive stem cell population growth. Additional results suggest that other signals along with choreographed motion of cells are responsible for repressing this expansion. Taken together, our results provide a novel hypothesis for how robust but fast renewal of the crypt is achieved: as a balance between expansion, which drives fast renewal and repression, which holds that expansion in check to maintain the crypt's structure.

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