Wnt-Notch Crosstalk Tunes Intestinal Crypt Spatial Patterning

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Short Abstract — The intestinal epithelium is the fastest regenerative tissue, yet it maintains a remarkably consistent structure. While Notch signaling is implicated in the formation of the crypt base checkerboard arrangement of stem and Paneth cells, recent works suggests that β-catenin can form a complex with Notch Intracellular Domain (NICD) and upregulate expression of Hes1 on its own or through this complex. Additionally, numerous questions exist about short-range Wnt secretion by Paneth cells at the crypt base. To address these questions, we perform bifurcation analysis on a dynamical model of this gene circuit, suggesting that the crosstalk may facilitate transition from the stem niche to transit amplifying region and that short range Wnt secretion may spatially constrain the size of the stem niche.

Keywords — Intestinal Stem Cell, Paneth Cell, Wnt Signaling, Notch Signaling, Hes1, Systems Biology

I. INTRODUCTION

The crypts of the small intestinal epithelium are the fastest regenerating cell population in the body, turning over almost all cells every 2–6 days [1]. However, precise control of the crypt structure is maintained by the Wnt and Notch pathways. They are integrated through the transcription factor Hes1 to control differentiation the stem or Paneth cell type and the rate of stem cell proliferation [2].

Wnt proteins, such as mesenchymal Wnt 2b and Paneth-produced Wnts 3 and 11, increase accumulation of β-catenin which upregulates Hes1 [3]. When a stem cell’s Notch receptor is activated by a Paneth cell’s Delta-like ligand, NICD translocates to the nucleus where it upregulates production of Notch receptors (positive feedback) and of Hes1 which inhibits the production of the cell’s own Delta like ligands (lateral inhibition). This combined PFLI mechanism drives the formation of the characteristic checkerboard pattern of stem cells and Paneth cells [4].

Recently, two intriguing observations have been made: First, NICD may form a complex with β-Catenin instead of directly upregulating Hes1 [2]. Second, the Paneth cells appear to only secrete Wnt to their immediate neighbors [5]. To understand the roles of crosstalk in Hes1 regulation and of short-range Paneth-mediated Wnt secretion, we modeled the integrated gene circuit considering these effects.

II. RESULTS

To compare competing models of the pathways, we employed tuning parameters that allowed us to vary the relative control of β-catenin and β-catenin-NICD complex control over the Hes1 promoter without altering the steady state [2]. Additionally, three Wnt secretion models were considered: mesenchymal (constant), paracrine, and juxtacrine.

In two cell simulations, bifurcation analysis of Wnt production rate and percent control of the Hes1 promoter by the β-cat/NICD complex was conducted. With greater than 80% control by the complex, the models exhibited bistability of cell fates at both low and supra-physiologic Wnt concentrations. Below 50%, the cells failed to differentiate. From 50 – 80%, the model exhibited desirable switching behavior. At high Wnt concentrations (crypt base), the model demonstrated bistability, while at lower concentrations (TA region) the model predicted a monostable population. Accordingly, the mesenchyme may provide a constant level of Wnt to drive proliferation in the stem niche and TA region, but short range Wnt secretion by Paneth cells may exist to drive differentiation at the crypt base by reinforcing Hes1-mediated lateral inhibition.

Last, the models were implemented in a multi-cell simulation. All three models exhibited formation of a characteristic checkerboard pattern. While the juxtacrine model produces stem and Paneth cells with less variance in the final protein concentrations, the concentrations are less polarized than in the constant and paracrine models, and it takes significantly longer to achieve steady state.

III. CONCLUSION

Via crosstalk, short range Wnt secretion by the Paneth cells defines the size of the stem niche since it reinforces the Hes1 mediated lateral inhibition necessary to promote differentiation in a spatially constrained region.

REFERENCES