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Dual states of Bmi1-expressing intestinal stem cells drive epithelial development

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Bmi1, intestinal stem cell, development

Abstract

Tight regulation of the proliferative status of intestinal stem cells is critical for establishing a functional epithelial layer during development, a homeostatic state in adulthood, and the ability to rapidly repair injury to maintain the barrier to the outside environment. We identified Bmi1-expressing intestinal stem cells (ISCs) to be highly proliferative during the intestinal growth phase, but dormant or slow-cycling during homeostasis. The pathways that regulate Bmi1+ ISC proliferative state transition and the extent of their contribution to downstream differentiated progeny have not been identified. To investigate this, we employed single cell RNA-seq (scRNA-seq) to analyze FACS-isolated Bmi1+ intestinal epithelial cells and EpCAM- mesenchymal cells across distinct developmental time points. After pre-processing and data normalization, we performed dimension reduction, cluster identification, differential gene expression analyses, CytoTRACE (Cellular Trajectory Reconstruction Analysis using gene Counts and Expression) and cellular trajectory inference across the different time points. We found that the E12.5, E15.5, and E17.5 stem cell clusters were distinct based upon their expression of pioneer transcription factors (e.g., Pou5f1 (or Oct4)), and pathways involved in differentiation (e.g., dietary lipid metabolism and digestion). Additionally, genes highly expressed in mature absorptive and secretory cells were present almost exclusively in the E17.5 dataset. Furthermore, critical canonical and non-canonical Wnt signaling pathway genes were differentially expressed across development stages. A role for reciprocal canonical/non-canonical Wnt signaling was further substantiated by analyses of receptor-ligand interactions between cells from the mesenchyme with ISC populations. Our data reveal functional differences in the Bmi1+ ISC across development, with evidence that late stage Bmi1+ ISCs give rise to differentiated cell lineages. Importantly, our data provide the foundation for exploring an underlying mechanism that regulates proliferative state of a stem cell population in the intestine, with important implications on development, injury repair and diseases such as cancer.