



Intestinal Stem Cell Regulation via Glycolytic Activity of Neighboring Paneth Cells

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Keywords

Paneth Cell; Intestinal Stem Cell; Crypt Based Columnar cells

Short Communication

The epithelial lining of the small intestine (SI) is regenerated in its entirety at a rapid pace of every three to five days [1,2]. In order to perpetuate normal physiological functions of digestion and absorption provided by the SI epithelium, regeneration of this magnitude is required and must be properly maintained [3]. In tissues of high turnover such as the intestinal epithelium, stem cells are crucial regulators of tissue homeostasis. In the gastrointestinal tract, crypt base columnar (CBC) stem cells, a population of rapidly dividing cells at the crypt base expressing leucine-rich-repeat-containing G-protein coupled receptor 5 (Lgr5⁺), give rise to all terminally differentiated intestinal epithelial cell types (enterocytes, Paneth, goblet, enteroendocrine, tuft, and M cells) [4]. Local conditions in which the Lgr5⁺ CBCs reside, called the stem cell niche, regulate cell proliferation, differentiation, and stem cell self-renewal [1]. Paneth cells are long-lived secretory cells that migrate into the crypt base and reside between Lgr5⁺ CBCs where they produce and secrete antimicrobial peptides and stem cell factors such as epidermal growth factor, Wnt3, and Notch ligand D114 that sustain the stem cell niche [3,5-7]. Maintenance of crypt homeostasis is well documented in the literature; however, Rodriguez-Colman et al. [2] have recently highlighted the role of mitochondrial activity in Lgr5⁺ CBC maintenance. Compared to other differentiated intestinal epithelial cells and relatively quiescent stem cell populations in the adult, such as hematopoietic stem cells [8] and neural stem cells [9,10], Lgr5⁺ CBCs show higher mitochondrial oxidative phosphorylation activity [7,11]. Rodriguez-Colman et al. [2] revealed that in support of increased demand for mitochondrial oxidative phosphorylation for Lgr5⁺ CBCs to maintain the immense amount of cell turn over in the small intestine, lactate from Paneth cells is fed into neighboring Lgr5⁺ CBCs fueling their oxidative phosphorylation processes. Inhibition of glycolysis, and subsequently lactate production, in Paneth cells affects Lgr5⁺ CBC function and hinders crypt maturation [2]. Therefore, the glycolytic phenotype in Paneth cells is crucial for lactate production, which drives increased oxidative phosphorylation in Lgr5⁺ CBCs. Mechanistically, Rodriguez-Colman et al. [2] demonstrated that mitochondrial-derived reactive oxygen species produced in Lgr5⁺ CBCs during oxidative phosphorylation stimulate activation of p38 MAP kinase, which in turn regulates Lgr5⁺ CBC self-renewal and differentiation. These results show that the glycolytic phenotype in Paneth cells and increased OXPHOS in Lgr5⁺ CBCs are required in supporting both stem cell niche and function. Provision of lactate from Paneth cells is therefore another critical aspect of the interdependent relationship between Lgr5⁺ CBCs and Paneth cells, essential to the maintenance and differentiation of SI epithelium.

Alteration of crypt homeostasis affects Lgr5⁺ CBC and Paneth cell function leading to ramifications for the small intestine as a whole. Inflammation, intestinal dysbiosis, radiation, spontaneous genetic mutations and consumption of a diet composed of 45% to 60% fat are all documented examples of such alterations [7,12-14]. Aside from impending weight gain, high fat diets (HFD) cause changes in both Paneth and Lgr5⁺ CBCs. Gou et al. [13] recently demonstrated that Paneth cell-derived immune health regulation is impaired following prolonged implementation of a HFD as the mRNA expression of antimicrobial peptides significantly decreased in these cells. Decreased antimicrobial peptide secretion from Paneth cells leads to less pathogen defense and detrimental changes in microbiome composition [1]. In addition, chronic HFD exposure reduces Paneth cell numbers themselves not only decreasing immune defense but also Lgr5⁺ CBC support [12]. In the face of decreased Paneth cell support, Beyaz et al. [12] reports that proliferating Lgr5⁺ CBCs exposed to HFD lack differentiation of progenitor cells resulting in diminished villi

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length. Adverse effects induced by prolonged HFD intake upsets the epithelial regeneration and innate immunity sustained by efficiently functioning symbiotic relationship between Paneth cells and Lgr5⁺ CBCs. Without this Paneth/Lgr5⁺ CBC relationship, a decline in effective absorptive digestive function is observed.

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