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Metabolic teamwork in the stem cell niche

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Summary

Nearby cells can support stem cell differentiation, but the metabolic activities in stem cell niches are unknown. A recent study (Rodríguez-Colman et al., 2017) reveals a metabolic partnership in the intestinal stem cell niche: glycolysis in niche Paneth cells provides lactate to drive mitochondrial oxidative phosphorylation in intestinal stem cells.

Main Text

Many mammalian tissues are maintained by tissue-specific stem cells, which self-renew and differentiate into other cell types, and niche cells that support stem cell function. For example, endothelial and perivascular cells provide short-range signals such as Stem Cell Factor to maintain hematopoietic stem cell function, and hair follicle stem cells require cues from the dermal papilla to initiate growth and regeneration of the hair follicle (Mihaylova et al., 2014). In the intestine, stem cells are located at the bases of the crypts of Lieberkühn, and differentiate to form adjacent Paneth cells, transit amplifying cells or progenitor cells, Goblet cells, enteroendocrine cells, and absorptive enterocytes. Paneth cells support stem cell activity by secreting Wnt3a, epidermal growth factor, and the Notch ligand delta-like 1. In the mouse intestine, ISCs are marked by the receptor protein Lgr5 and can be isolated from Lg5 reporter mice using flow cytometry. In an *in vitro* assay of stem cell function, intestinal stem cells (ISCs) efficiently form “mini-intestines” in culture (also known as organoids) only when co-cultured with Paneth cells, and genetic depletion of Paneth cell function results in loss of ISCs (Sato et al., 2011).

ISCs and Paneth cells also demonstrate distinct responses to nutrient cues. Calorie restriction enhances ISC numbers and function by inhibiting mTORC1 activity in Paneth cells, but does not reduce mTORC1 in ISCs (Yilmaz et al., 2012). In contrast, a high fat diet fat boosts ISC activity through PPAR-δ signaling directly in ISCs and renders them less dependent on Paneth cells (Beyaz et al., 2016). Given the well-known roles for the mTOR and PPAR-δ signaling pathways in glycolysis and fatty acid oxidation, respectively, these studies and reports in other stem cell compartments suggest that metabolic differences between stem cells and their supporting cells may drive their distinct functions (Ochocki and Simon, 2013). However, the metabolic functions of stem cells in the context of their niche cells are currently not known.

Rodríguez-Colman et al. addressed this important topic by first analyzing the metabolomes of ISCs and Paneth cells sorted by flow cytometry from mice in which Lgr5+ ISCs are labelled with a GFP fluorescent marker. Principal component analysis of ISC and Paneth cell metabolic profiles revealed distinct clustering of each cell type. The pyruvate to lactate ratio was higher in ISCs versus Paneth cells, and ISCs displayed increased respiration compared to Paneth cells, which together suggest that ISCs exhibit greater mitochondrial respiration than Paneth cells. Next, the authors applied an established *in vitro* organoid model of intestinal crypt function to study the metabolic pathways involved in ISC differentiation. Removal of Wnt3a from growth media induces the formation of organoid "buds" that recapitulate crypt differentiation, with ISCs and Paneth cells located at the base of each budding structure. Using this approach, they found that galactose, which activates mitochondrial oxidative phosphorylation (i.e., OXPHOS), enhanced crypt formation and differentiation, while inhibition of OXPHOS reduced crypt formation. Additional experiments showed that mitochondrial OXPHOS generated reactive oxygen species during crypt differentiation, which then activated the p38 MAP kinase pathway. Furthermore, the authors demonstrated using small molecule inhibitors that p38 activity was required for crypt formation and differentiation.

The authors then utilized ISC and Paneth cell co-culture experiments to assay the role of metabolic pathways in stem and niche cell function. They treated ISCs and Paneth cells with inhibitors of OXPHOS and glycolysis, cultured the cells together, and then measured organoid formation, which is a proxy for stem cell regeneration and differentiation. They found that OXPHOS in ISCs and glycolysis in Paneth cells were required to support ISC function. Since lactate can be converted into pyruvate to fuel OXPHOS, the authors hypothesized that Paneth cells may provide lactate to support ISC function. Indeed, co-culture of ISCs with Wnt3a and lactate significantly augmented organoid reconstitution compared to Wnt3a and glucose. Thus, the authors conclude that Paneth cells undergo glycolysis to produce lactate, which is converted into pyruvate in ISCs to support mitochondrial OXPHOS. OXPHOS, in turn, activates reactive oxygen species and MAPK p38 signaling to induce crypt differentiation (Figure 1). Overall, these findings support a model in which metabolic functions are compartmentalized in the intestinal crypt base to support stem cell function.

The study by Rodríguez-Colman et al. adds to our understanding of how tissue-specific stem cells regulate energy metabolism to support their diverse functions, and raise the question of whether their findings are applicable to other stem cell compartments. Consistent with their findings, previous work in Drosophila ISCs suggests that OXPHOS enhances stem cell self-renewal and promotes longevity (Rera et al., 2011). Unlike ISCs, hematopoietic stem cells and mesenchymal stem cells reside in hypoxic niches, which may explain why they rely on glycolysis for their energy supply rather than mitochondrial OXPHOS (Chen et al., 2008; Simsek et al., 2010).

One limitation of the current study is that metabolic activities of stem and niche cells were examined using *in vitro* epithelial cultures only. Therefore, further research will be required to assess how intestinal stromal cells, immune cells, bacterial species, and other factors impact stem cell metabolism *in situ* in the living organism. In addition, it is unknown

whether the findings in this study are applicable to the colon (the site of intestinal tumorigenesis in patients), where most crypts contain Reg4+ niche cells rather than Paneth cells (Sasaki et al., 2016). Finally, stem cell hierarchies in some early cancers are thought to reflect the organization of normal tissue stem cell niches, particular in the intestine. Are there metabolic distinctions between cancer stem cells and differentiated cancer cells that can be therapeutically exploited? Colon cancer stem cells have been reported to exhibit mitochondrial metabolism, and it is now clear that a subset of cancer cells utilize mitochondrial OXPHOS. The findings of Rodríguez-Colman et al. raise the intriguing possibility that cancer stem cells could be therapeutically targeted with p38 MAPK inhibitors or mitochondrial complex I inhibitors such as metformin.

Selected Reading

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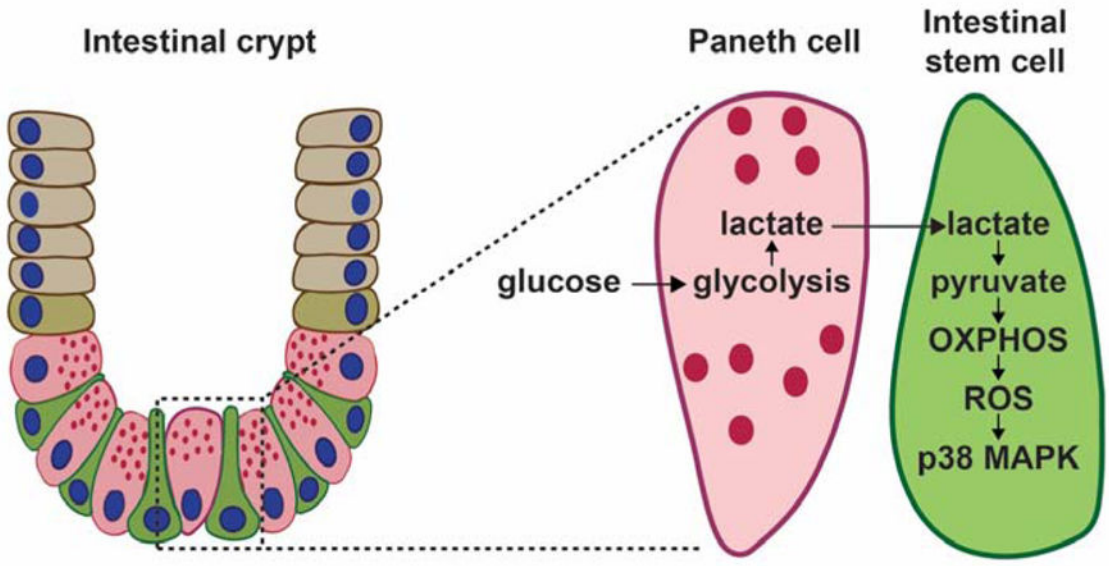

Figure 1. Metabolic regulation of intestinal stem cell niche homeostasis

Intestinal stem cells (ISCs) and niche Paneth cells (dotted box) reside in the bases of the crypts of Lieberkühn. ISCs differentiate to form all intestinal cell types. Paneth cells support ISC function by producing growth factors. Rodríguez-Colman et al. examined the metabolic activities of ISCs and Paneth cells. The authors used *in vitro* models of crypt differentiation and ISC function to identify distinct, yet complementary, metabolic programs in these cells. Paneth cells undergo glycolysis to produce lactate. Lactate is then back converted into pyruvate to fuel mitochondrial oxidative phosphorylation (OXPHOS) in ISCs. This process generates reactive oxygen species (ROS) that in turn activate p38 MAP kinase signaling. Together, these processes promote intestinal crypt differentiation.