Nature Reviews Gastroenterology & Hepatology | Published online 30 Mar 2017; doi:10.1038/nrgastro.2017.41

STEM CELLS

A case of metabolic identity in the intestinal crypt

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How does metabolism contribute to epithelial renewal in the intestinal crypt? According to a new study published in *Nature*, LGR5$^+$ crypt base columnar cells (CBCs) and Paneth cells — key constituents of the intestinal stem cell niche — have different metabolic identities. Furthermore, this study reveals novel mechanisms supporting intestinal stem cell function that could have important implications for targeting cancer stem cells.

The intestinal epithelium is a rapidly self-renewing tissue in which apoptosis at the tips of villi is balanced by cell production in the crypts of Lieberkühn. Here, at the base of the crypt, stem cells (LGR5$^+$ CBCs) generate transit-amplifying cells capable of differentiating towards all intestinal epithelial cell lineages, alongside niche cells (Paneth cells) that support the stem cell function of LGR5$^+$ CBCs by supplying essential factors. The importance of cell metabolism in stem cell fate has been highlighted in some stem cell populations, but the role of metabolism in intestinal stem cells and epithelial homeostasis was previously unknown.

In the latest study, Maria Rodríguez-Colman and colleagues first analysed the metabolomes of LGR5$^+$ CBCs and Paneth cells from the small intestine of mice using fluorescence-activated cell sorting. Principal component analysis of the data showed distinct clustering of the metabolic profiles conforming to the different cell identities. Measurement of pyruvate:lactate ratio, used to ascertain the contribution of mitochondrial respiration versus glycolysis, revealed significantly higher mitochondrial activity in LRG5$^+$ CBCs than Paneth cells.

To more closely analyse mitochondrial activity, as well as the activity of p38 MAP kinase, which responds to cellular redox changes, the investigators then performed experiments using mouse intestinal organoids. "Small intestinal organoids closely recapitulate the properties and cell dynamics of the tissue *in vivo* and this includes the interaction between stem cells and Paneth cells," explains Rodríguez-Colman.

By establishing an organoid model for studying differentiation preceding crypt formation, the researchers showed that high oxidative phosphorylation (OXPHOS) activity in LGR5$^+$ CBCs, indicative of mitochondrial metabolism, was driving differentiation and crypt formation by a mechanism involving p38 MAP kinase. Conversely, Paneth cells were found to have reduced OXPHOS activity and instead relied on the glycolysis metabolic pathway, which strongly affected organoid formation when impaired.

To examine stem and niche cell function, the investigators used an organoid reconstitution assay to model the effects of OXPHOS or glycolysis inhibitors on the ability of LRG5$^+$ CBCs and Paneth cells to form self-renewing organoids. They found that the metabolic compartmentalization seen during differentiation also had a major contribution to stem cell function. "The end product of glycolysis in the Paneth cells becomes a substrate for mitochondrial oxidative phosphorylation in the stem cells," reports Rodríguez-Colman. "In addition to the well-characterized growth factor secretory function, Paneth cells secrete lactate and 'feed' stem cell oxidative metabolism."

Looking forward, the investigators now plan to investigate the existence of different metabolic profiles and dependencies in other systems, particularly in cancer stem cells. "Cancer stem cells have been reported to display increased resistance to conventional cancer treatments. Application of metabolic targeting compounds could potentially enhance the sensitivity of cancer stem cells to current treatments," concludes Rodríguez-Colman.

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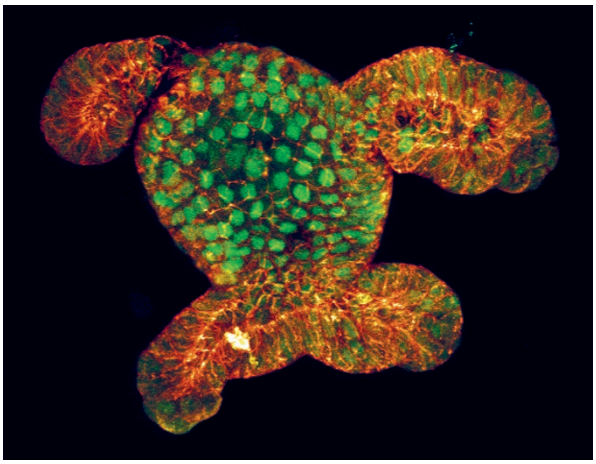

3D confocal microscopy image of a mouse intestinal organoid. Green staining shows p38 MAPK activity (p38 KTRClover), E-cadherin is stained orange. The image shows inactive p38 (nulcear signal) in the villi domain and active p38 (decreased nuclear signal) in the crypt domain. Image courtesy of M. J. Rodríguez-Colman.

ORIGINAL ARTICLE Rodríguez-Colman, M. J. *et al.* Interplay between metabolic identities in the intestinal crypt supports stem cell function. *Nature* **543**, 424–427 (2017)