STEM CELLS

Self-sufficient

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The highly organized small intestinal crypt has proved to be an ideal tissue in which to study stem cells — we knew where they were in the crypt long before we knew precisely which cells they were. Now, Toshiro Sato, Hans Clevers and colleagues have identified the cells that maintain these stem cells in a self-renewing state: the Paneth cells.

Paneth cells are specialized, terminally differentiated cells that secrete bactericidal proteins and reside at the bottom crypt where the stem cells hang out. Previous work from Clevers and colleagues identified leucine rich-repeat-containing G protein-coupled receptor 5-positive (LGR5$^+$) cells as crypt stem cells and showed that with the right ingredients (epidermal growth factor (EGF), the Wnt agonist R-spondin 1 and the bone morphogenetic protein inhibitor noggin) and Matrigel, single LGR5$^+$ cells can give rise to crypt–villus structures *in vitro* that contain stem cells, Paneth cells and all other epithelial cell types. The idea that Paneth cells might constitute a stem cell niche had previously been dismissed by others; however, Sato and colleagues decided to take a second look. Although single LGR5$^+$ stem cells can produce crypt–villus organoids *in vitro*, this process is relatively inefficient and was substantially enhanced by the addition of Paneth cells. In such cultures, LGR5$^+$ stem cells were always in close proximity to Paneth cells.

Gene expression profiling of Paneth cells showed that they express genes known to be important for stem cell function, such as Wnt, EGF and the Notch ligand δ-like 4. Further experiments in mice suggested that the Wnt signal produced by Paneth cells is increased by R-spondin 1, and that only the cells closest to the Paneth cells, the LGR5$^+$ stem cells, receive a strong Wnt signal. So, are Paneth cells essential for LGR5$^+$ cell survival *in vivo*? Expression of *Sox9* in the small intestine is required for Paneth cell differentiation. A floxed *Sox9* and Cre recombinase, which was expressed using a promoter that is not active in mature Paneth cells but is active in other cells of the crypt, were used to examine the effect of Paneth cell loss over time in the mouse small intestine. Paneth cells are renewed every 8 weeks or so, and a profound reduction in Paneth cell numbers was evident 7–8 weeks after activation of Cre. LGR5$^+$ stem cell numbers also declined in concert with Paneth cell loss. However, there remained a few crypts with SOX9$^+$ Paneth cells around which LGR5$^+$ stem cells were crowded, and these crypts gradually replaced those without Paneth cells by crypt fission. These findings suggest Paneth cells are essential for the maintenance of stem cells and crypts.

As LGR5$^+$ stem cells can spawn Paneth cells, these findings suggest that stem cells in the small intestine can generate their own supporting niche cells, similar to findings in *Drosophila melanogaster*. These findings pose the interesting idea that a cancer stem cell might be capable of similar acts of self-sufficiency.

Nicola McCarthy

ORIGINAL RESEARCH PAPER Sato, T. *et al.* Paneth cells constitute the niche for Lgr5 stem cells in intestinal crypts. *Nature* 28 Nov 2010 (doi:10.1038/nature09637)

DIGITAL VISION