STEM CELLS

Origins of intestinal stem cells — all in it together?

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The intestinal epithelium is constantly replenished by a population of adult intestinal stem cells expressing markers such as LGR5 located at the bottom of the intestinal crypts. Now, new research published in *Nature* demonstrates that all cells of the fetal mouse intestinal epithelium contribute to the adult intestinal stem cell pool, irrespective of their location and pattern of LGR5 expression.

“All cells are born equal and cells are randomly selected to become adult stem cells following a last wave of morphogenesis (villus formation via remodelling of existing villi),” says author Kim Jensen. “This indicates that stemness is an induced rather than a hardwired property,” he adds.

The researchers used a number of different approaches, including lineage tracing, 3D imaging, biophysical modelling and intestinal transplantation to investigate whether fetal LGR5-expressing cells represent unique intestinal

stem-cell precursors. “This project actually started out as a control experiment aimed at showing in a quantitative manner that LGR5-expressing cells in the fetus were specialized precursors for the adult stem cells in the intestine,” explains Jensen, which was an assumption based on existing evidence. “Prior work from our team had demonstrated that specialized precursors precede the adult stem cells and that these can be maintained in vitro as spheres rather than as adult branching organoids, and that adult epithelial cells transition into this fetal state during tissue regeneration,” he adds.

The investigators first focused on the proximal part of the small intestine, tracking fetal LGR5-positive cells from embryonic day 16.5. They determined that, as expected, fetal LGR5-expressing progeny contributed to the adult intestinal stem-cell compartment. However, these cells were insufficient in numbers to explain intestinal tissue growth during development.

Further experiments, including fate mapping, demonstrated that fetal epithelial cells, irrespective of their location, could add to the pool of intestinal stem cells and had long-term self-renewal potential. Essentially, all fetal cells had a similar capacity to contribute to the growth of the intestinal epithelium during development and give rise to adult intestinal stem cells.

3D imaging revealed that the intestinal villus undergoes major remodelling (including pronounced reorganisation of the epithelial cell layer) and fission during fetal development. These structural

changes relocated intestinal epithelial cells from the non-proliferative villus into the proliferative intervillus region, which enabled them to contribute to the adult stem-cell niche. Crucially, predictions of biophysical modelling of this process were in agreement with the experimental data.

Finally, in vitro experiments using 3D cultures to generate spheroids demonstrated that fetal villus cells and intervillus cells had similar growth and regenerative potential. Importantly, this trend was also observed in vivo with mouse-derived spheroids transplanted into conditioned mice. Spheroids from both villus and intervillus regions engrafted with similar efficiencies, established adult intestinal stem-cell niches at the base of the crypt and gave rise to differentiated lineages of intestinal cells, including Paneth cells, goblet cells and enterocytes.

The results demonstrate a close link between large-scale remodelling of the intestinal epithelium and cell-fate specification. “We are currently trying to address in a quantitative and molecular manner how stem cells and differentiated cells are reprogrammed to a fetal-like state during regeneration,” says Jensen. “This will hopefully provide us with potential mechanisms for fuelling more efficient tissue repair,” he concludes.

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Fetal villus-derived cells engraft in adult colon (red) and produce differentiated lineages (blue, Paneth cell marker), thus demonstrating their regenerative potential. Tissue is counterstained with DAPI (green). Image courtesy of J. Guiu, University of Copenhagen, Denmark.

ORIGINAL ARTICLE Guiu, J. et al. Tracing the origin of adult intestinal stem cells. *Nature*. <https://doi.org/10.1038/s41586-019-1212-5> (2019)

FURTHER READING Gehart, H. & Clevers, H. Tales from the crypt: new insights into intestinal stem cells. *Nat. Rev. Gastroenterol. Hepatol.* **16**, 19–34 (2019)