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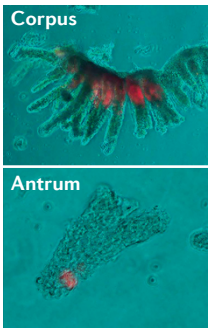
STEM CELLS

Settling the stomach — tracing gastric stem cells



Stem cells in the stomach. Red colour indicates the position of eR1$^+$ stem cells. Top: partially dissociated corpus gland, stem cells are clustered at the isthmus. Bottom: isolated antral gland, stem cells localized at the isthmus. Image courtesy of Y. Ito.

Stem cells have been identified in the epithelium of the corpus and antrum of the stomach in mice. These stem cells could be traced after induction of oncogenic mutations, providing a new model for studying gastric carcinogenesis.

"For many years, researchers in the gastric cancer field have been trying to identify stem cells," explains author Yoshiaki Ito. However, these efforts have been hampered by the existing models, and the origin, position and expression markers of gastric stem cells has been much debated.

Ito and colleagues examined the expression of RUNX1 (a key regulator of haematopoiesis) and the activity of a RUNX1 enhancer element (eR1) as a marker of haematopoietic stem cells; interestingly, eR1 was also a marker for stem cells in the stomach. A variety of techniques were used to track these eR1$^+$ stem cells including *in situ* hybridization, immunofluorescence and lineage tracing.

Immunofluorescence staining revealed that RUNX1 was expressed in epithelial cells in the upper region of the mouse stomach corpus and also in epithelial cells near the bottom of the pyloric gland. In eR1-EGFP mice, 83% of eR1$^+$ cells were located in the isthmus–pit region.

Crucially, eR1$^+$ cells were found to have a major role in tissue regeneration. Lineage tracing studies revealed that eR1$^+$ stem cells in the isthmus and antrum continuously differentiate and mature, regenerating and maintaining the gastric units. Moreover, organoids could be generated *in vitro* from eR1$^+$ cells from gastric units isolated from eR1-CreERT2 mice. After 7 days incubation, the cells in the organoids differentiated into at least three different lineages, mainly neck cells, pit cells and chief cells.

Finally, the investigators used the eR1-CreERT2 system to track the effects of expression of an oncogenic KRAS mutation in gastric stem cells as a means to study stepwise gastric carcinogenesis. MUC5AC$^+$ cells rapidly differentiated from stem cells in the isthmus into abnormal metaplastic lesions typically seen in human gastric atrophy and metaplasia.

The researchers plan further work tracing stem cells from pre-neoplasia to malignancy, in the hope of elucidating the pathophysiology of gastric cancer, as well as further studies of gastric stem cells using different markers. "A key question is whether there is more than one origin of stem cells in each tissue," notes Ito.

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ORIGINAL ARTICLE Matsuo, J. *et al.* Identification of stem cells in the epithelium of the stomach corpus and antrum of mice. *Gastroenterology* http://dx.doi.org/10.1053/j.gastro.2016.09.018 (2016)