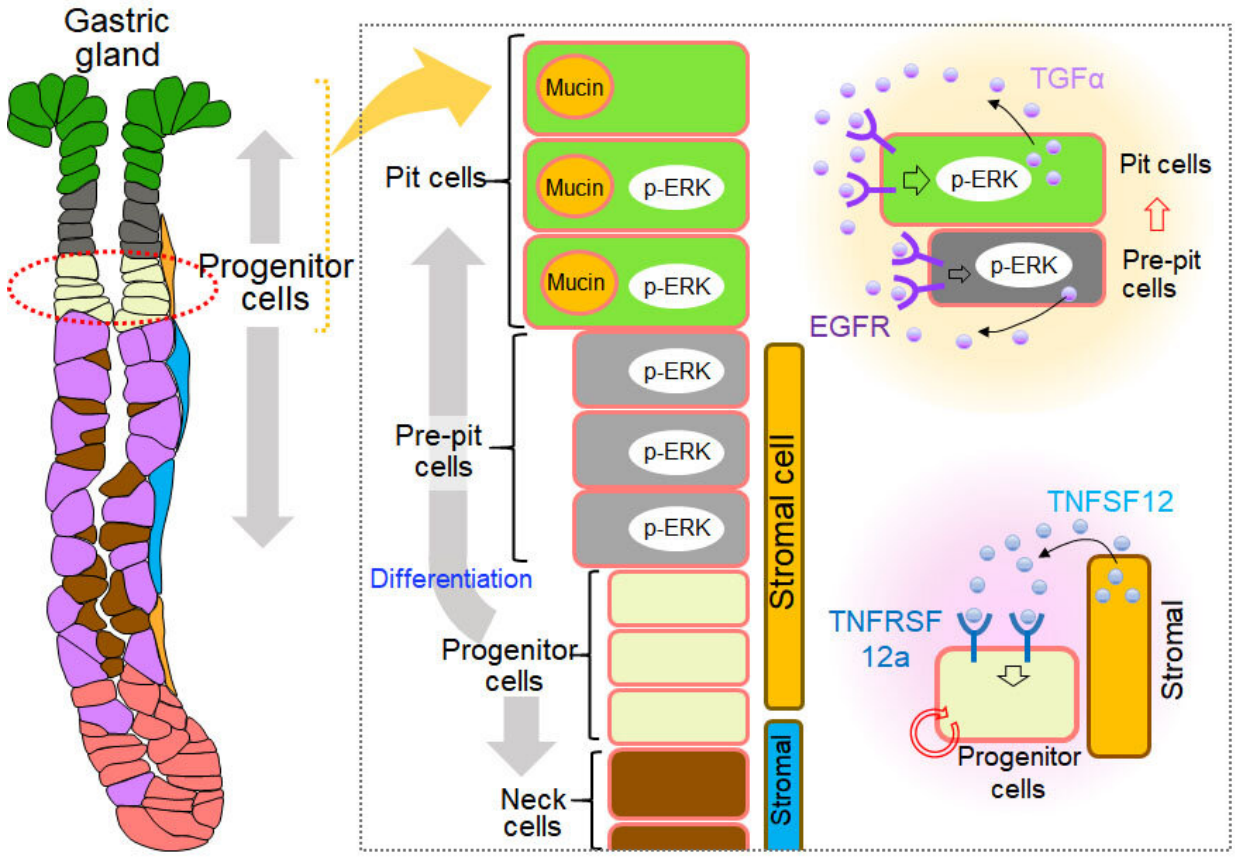
Researchers discover secret of stem cells protecting the gastric mucosa

June 29 2023



Model for the mechanisms of gastric stem cell differentiation and maintenance. Credit: Hitomi Takada

The gastric corpus, which is a major component of the glandular stomach, is composed of parietal, chief, pit, and neck cells. Each of these specialized epithelial cells play an important role in digestion, and they are continuously replenished by new ones which are formed via the differentiation of stem cells. Defects in this process lead to gastric diseases such as intestinal metaplasia and gastric cancer. However, the underlying mechanisms responsible for the renewal and differentiation of stem cells, and thus the maintenance of gastric homeostasis, have yet to be explained.

Aiming to bridge this gap, a group of researchers led by Hitomi Takada and Akira Kurisaki of the Nara Institute of Science and Technology (NAIST), Japan has recently proposed two signaling pathways which play a role in the regulation of stem cell differentiation. Their findings have been published in *Nature Communications*.

"The signaling pathways that induce the differentiation of stem cells into a particular gastric cell type are yet to be confirmed. To address this gap, we employed Quartz-Seq2—the most precise single-cell RNA sequencing technology developed by RIKEN—along with in vitro gastric assays using cells isolated from gastric glands, and in vivo experiments using mouse models," says Takada, lead author of the study. The team's combinatorial approach allowed them to profile the gene expression dynamics of stem cell differentiation into pit, neck, and parietal cell lineages, and identify the signaling pathways that regulated pit cell differentiation.

Using pseudo-time-dependent gene analysis (which provides information on gene expression as the cells pass through various stages during differentiation) along with the in vitro and in vivo assays, the team identified that the transforming growth factor alpha-epidermal growth factor receptor-extracellular signal-regulated kinase (TGFα-EGFR-ERK) signaling pathway was responsible for stem cells' differentiation into

mucus-secreting pit cells.

The team also noted that fewer pit cells were produced when EGFR was pharmacologically inhibited, suggesting that this pathway is needed for the gastric stem cell differentiation toward pit cells in mice. Further, the team also identified the tumor necrosis factor ligand superfamily member 12-nuclear factor kappa light chain enhancer of activated B cell (TNFSF12-NF-κB) signaling pathway and noted that it helped maintain gastric epithelial cells in an undifferentiated state.

Setting some context to their findings, "We knew that EGFR signaling is intricately involved in gastric cancers and several EGF receptors are overexpressed in various cancers. However, it was a pleasant surprise to find through our single-cell analysis that EGFR signaling has a differentiation-promoting role rather than a mitogenic role in healthy gastric homeostasis," explains Kurisaki, senior author of the study.

This study is the first step towards understanding the mechanisms which are involved in maintaining cellular homeostasis in a healthy stomach.

So, where does the group go from here? They are buoyed by the prospects moving forward. "We've shown that TGFα-EGFR-ERK and TNFSF12-NF-κB form a fine-tuned regulatory framework for healthy stomach epithelial homeostasis. This has laid the foundation to investigate the mechanisms of other gastrointestinal diseases," concludes Takada.

More information: Single-cell transcriptomics uncovers EGFR signaling-mediated gastric progenitor cell differentiation in stomach homeostasis, *Nature Communications* (2023). DOI: 10.1038/s41467-023-39113-0