Researchers uncover drivers of healthy gut maintenance

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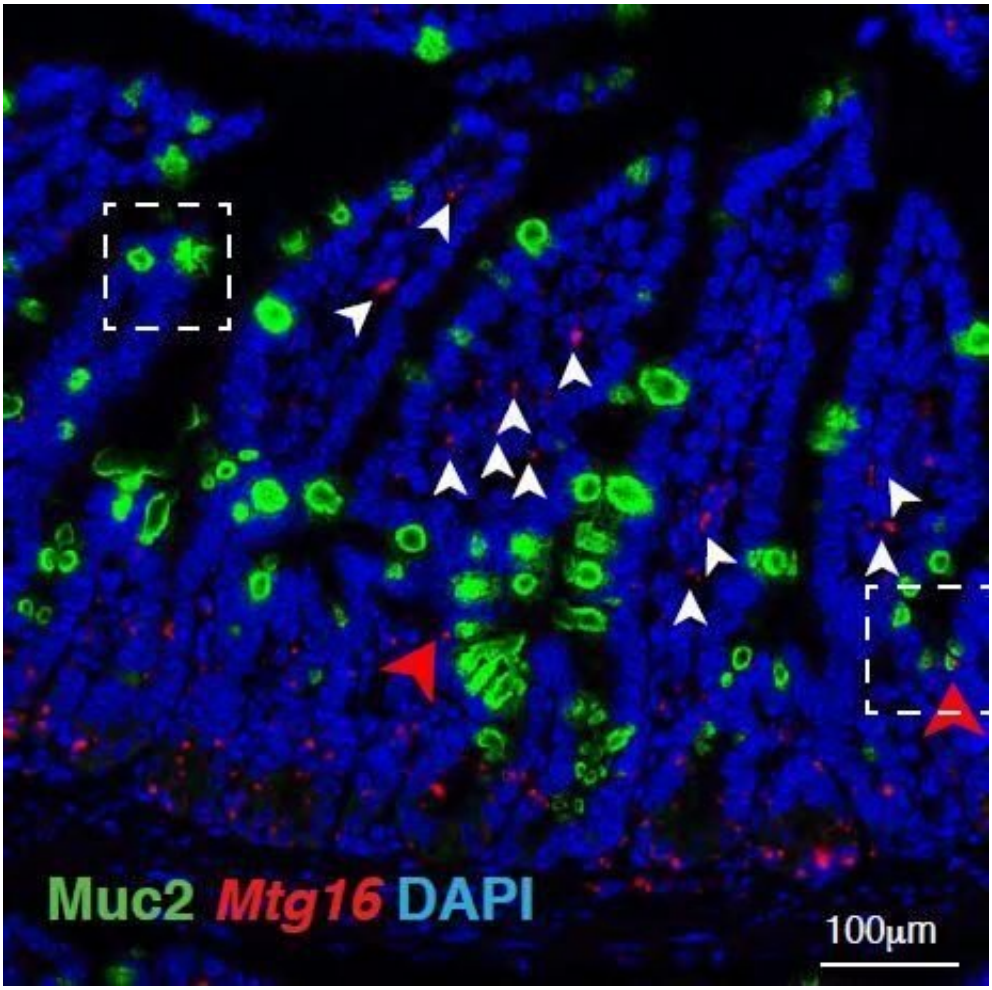

Image of crypts and villi in the small intestine with red marking MTG16 RNAscope and green labelling a type of differentiated intestinal cell, Goblet cells. Credit: The Francis Crick Institute

Researchers at the Francis Crick Institute have found two genes that regulate the differentiation of stem cells in the small intestine, offering valuable insight into how the body develops and maintains a healthy gut.

Cells in the lining of the small intestine are replaced around every five days, the quickest rate for any organ in the body. This fast replacement helps the lining cope with the damage it suffers as a result of breaking down food and absorbing nutrients.

This process, which is important for the healthy functioning of the small intestine, is supported by the stem cells in a part of the small intestine called the crypt.

In their study, published in *Gastroenterology*, the researchers found two genes, MTG8 and MTG16, which are highly expressed in cells that have just left the stem cell zone. These genes 'switch off' signals that keep these cells in a multipotent or 'immature' state, leading them to start to differentiate.

When the team analyzed intestinal tissue and small intestine organoids grown from mice lacking these genes, they found there were many more stem cells, indicating that the process of differentiation was impeded.

Anna Baulies, lead author and postdoctoral training fellow in the Stem Cell and Cancer Biology lab at the Crick says: "These genes maintain the flow of cells which are needed for the healthy functioning of the small intestine, starting the stem cells on the road to become enterocyte cells which are needed to absorb nutrients."

Importantly, by working with human small intestine organoids, the researchers also found that while the stem cells are still in the crypt, these genes are repressed by a key developmental pathway, Notch signaling. This ensures the stem cells do not differentiate too early.

Vivian Li, senior author and group leader of the Stem Cell and Cancer Biology lab at the Crick says, "Understanding the role these genes play in healthy tissue will also help us to understand how the intestine regularly regenerates and also if these genes are a helpful or harmful force in the presence of disease."

"For example, loss of these genes may increase the number of stem cells and contribute to colorectal cancer progression. Further study on the underlying mechanism might be helpful to limit the number of stem cells in the cancer."

The signal that these genes repress, Wnt signaling, also keeps stem cells in a multipotent state in many other tissues, including the skin, stomach, liver and brain. These findings could therefore help other research into stem cell differentiation outside of the small intestine.

The researchers will continue this work, looking to understand more about the mechanism these two genes use to regulate stem cell differentiation and regeneration.

More information: Anna Baulies et al, The Transcription co-Repressors MTG8 and MTG16 Regulate Exit of Intestinal Stem Cells From Their Niche and Differentiation into Enterocyte vs Secretory Lineages, *Gastroenterology* (2020). DOI: 10.1053/j.gastro.2020.06.012

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