STEM CELLS

T_H cells tune intestinal stem cell fate

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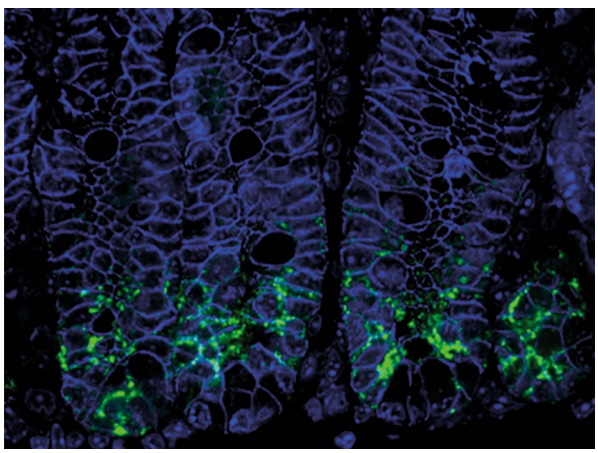
New findings reported in *Cell* show that intestinal stem cells (ISCs) interact with T helper (T_H) cells, modulating ISC fate and epithelial remodelling. Distinct inflammatory or regulatory T_H cell subsets and their cytokines can stimulate ISC differentiation and renewal, respectively.

ISC fate has previously been shown to be modulated by signalling from resident innate immune cells and other accessory cells, but a possible role of adaptive immune cells in this process has been unclear. The new research originated from studies using single-cell RNA sequencing (scRNA-seq) to characterize epithelial cells of the small intestine in mice. The researchers queried their data for gene expression indicating interaction with immune cells. Focusing on ISCs (selected by *Lgr5* positivity), they found three subsets with distinct characteristics: ISC-I cells were most stem-like and low-cycling, whereas ISC-II and ISC-III were more proliferative and differentiated. Further analysis showed enriched expression of components of the major histocompatibility complex (MHC) class II machinery, including *Cd74*, which encodes the invariant chain of the MHC class II complex and was particularly highly expressed in ISC-II and ISC-III.



Increased intestinal stem cell pool in Villin-positive intestinal crypts of mice with conditional MHC class II-knockout. In situ stain of *Olfm4* mRNA (green), nuclei and E-cadherin (blue). Image courtesy of Moshe Biton, Broad Institute of MIT and Harvard, USA.

Interaction of intestinal epithelial cells (IECs) with T_H cells via MHC class II had previously been observed. Hence, the team investigated whether this interaction occurred via ISCs and, using intravital imaging, observed T_H cells in close proximity to ISCs in the crypts of the mouse small intestine. Ex vivo studies with IECs demonstrated that ISCs were the IEC subset with the greatest antigen-processing ability. Furthermore, T_H cell interaction with these cells in an antigen-dependent manner caused substantially higher levels of T_H cell activation and expansion compared with IECs lacking the ISC subset.

The team further characterized the relationship between T_H cells and ISCs in an organoid model in which different T_H cell subsets or respective key cytokines were added to observe effects on ISCs. Supplementation with regulatory T (T_{reg}) cells or IL-10 resulted in expansion of the ISC population, whereas T_H1, T_H2 or T_H17 cells, as well as IL-13 or IL-17, resulted in depletion of the ISC pool and expansion of cells with differentiated features. This finding was corroborated by the observation that formation of further organoids was reduced after treatment with IL-13 but increased after treatment with IL-10. For in vivo validation, the researchers created a mouse model of conditional MHC class II-knockout in IECs. These mice had more ISCs in intestinal crypts and fewer $CD4^+$ T cells in the crypt lamina propria, whereas the number of $CD4^+$ T cells in the villus lamina propria remained unchanged.

Next, the team explored the effect of the interaction between T_H cells and ISCs on intestinal epithelial remodelling in vivo. In a mouse model of helminth (*Heligmosomoides polygyrus*) or *Salmonella enterica* infection, expression levels of a stem cell signature decreased, whereas those of an MHC class II signature increased. Furthermore, relative to each other, ISC-I proportions decreased and ISC-II and ISC-III proportions increased.

The researchers then assessed the role of T cells in ISC fate using T cell-deficient mice. In their models, ISCs and transit-amplifying cell populations were substantially expanded, whereas the population of enterocyte progenitors was decreased compared with controls. Expanding on findings of the organoid studies, in mice in which T_{reg} cells were conditionally depleted, ISC populations were reduced, whereas enterocyte progenitor, tuft cell and goblet cell numbers were substantially increased. In the ISC pool, proliferation and MHC class II expression were increased, matching increased relative proportions of ISC-II and ISC-III.

"The most significant result from this paper is that T_H cells are actively involved in specific epithelial cell differentiation processes by interacting with ISCs," Moshe Biton, first author of the study tells *Nature Reviews Gastroenterology & Hepatology*. "In addition, ISCs can sense and activate T_H cells via MHC class II interactions, which may lead to T cell activation or tolerance. We still need to understand this axis in gut T cell education and its effect on local and systemic immunity."

Clemens Thoma

ORIGINAL ARTICLE Biton, M. et al. T helper cell cytokines modulate intestinal stem cell renewal and differentiation. *Cell* **175**, 1307–1320 (2018)
FURTHER READING Gehart, H. & Clevers, H. Tales from the crypt: new insights into intestinal stem cells. *Nat. Rev. Gastroenterol. Hepatol.* https://doi.org/10.1038/s41575-018-0081-y (2018)