Nature Reviews Gastroenterology & Hepatology | Published online 23 Dec 2015; doi:10.1038/nrgastro.2015.221

STEM CELLS

IL-22 activates ISCs for intestinal regeneration

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The immune system is able to regulate intestinal regeneration by acting directly on intestinal stem cells (ISC), according to new research published in *Nature*. The findings demonstrate that IL-22 promotes ISC-mediated intestinal epithelial regeneration in organoid models.

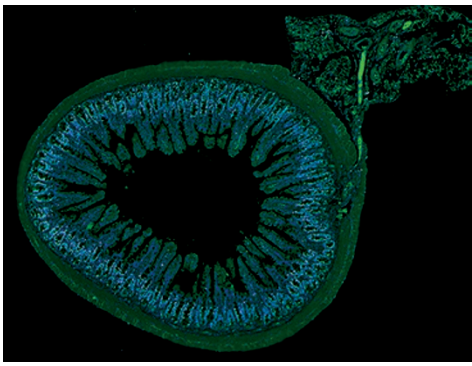
"There has been an explosion of information related to stem cells and ISCs in particular; however, most of what we have learned relates to the normal development and function of ISCs and their niche, and there is not as much understanding related to how ISCs are regulated after tissue injury," says author Alan Hanash. A loss of ISCs and epithelial cells contributing to the stem cell niche has been observed in gastrointestinal graft versus host disease (GVHD, a major complication of haematopoietic transplantation) and so Hanash and colleagues took advantage of models of experimental GVHD and intestinal organoid culture to explore how immune function is involved in intestinal tissue injury and regeneration.

Using *ex vivo* mouse small intestinal organoid cultures, the investigators found that group 3 innate lymphoid cells (potent producers of IL-22) increased the growth of mouse small intestinal organoids, which was dependent on IL-22. The addition of recombinant mouse IL-22 (rmIL-22) to both mouse and human small intestinal organoid cultures yielded substantially larger organoids than without rmIL-22, increasing proliferation and expansion of ISCs directly. Further experiments revealed that IL-22 induced STAT3 phosphorylation in $Lgr5^+$ ISCs, and STAT3 was essential for organoid formation and IL-22-mediated regeneration (which was independent of Paneth cells).

Finally, in experimental GVHD *in vivo*, treatment with IL-22 after mouse allogeneic bone marrow transplantation reduced intestinal pathology (such as reduced apoptosis within intestinal crypt epithelium) and mortality. Moreover, IL-22 treatment enhanced ISC recovery and increased epithelial regeneration after tissue injury.

The new findings confirm that the immune system can directly regulate ISCs after tissue damage as part of the restoration process of the intestinal barrier. "Under normal conditions, it seems that ISCs along with the epithelial and stromal components of their niche are adequate to maintain tissue homeostasis; after damage, production of IL-22 is increased and expression of the IL-22 receptor is increased within intestinal crypts as well," explains Hanash, adding that IL-22 seems to be an immune-derived component of the stem cell niche in response to injury.

"There is still a lot more for us to learn about the specific genes in ISCs that are being regulated by IL-22 and the different contributions to regeneration provided by stem cells and progenitors," says Hanash, "IL-22 is most certainly not the only molecule derived from the immune system to regulate the stem cell compartment". The researchers plan to translate their findings to the clinic and conduct a clinical trial in which recombinant human IL-22 will be tested with corticosteroids (the current standard of care) as treatment for patients with newly diagnosed gastrointestinal GVHD.



Regenerating $Ki67^+$ (white) crypts in a mouse treated with recombinant IL-22 after allogeneic bone marrow transplantation. Courtesy of A. M. Hanash.

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ORIGINAL ARTICLE Lindemans, C. A. *et al.* Interleukin-22 promotes intestinal-stem-cell-mediated epithelial regeneration. *Nature* http://dx.doi.org/10.1038/nature16460