RESEARCH HIGHLIGHT

# A gut feeling: diet-sensing mesenchymal cells regulate intestinal stem cell function

Julia Messina-Pacheco[1,2,3] and Alex Gregorieff[1,2,3]✉

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**Due to its remarkable regenerative capacity, the intestine and particularly intestinal stem cells (ISCs), have become a popular model for studying homeostasis, regeneration, and oncogenic transformation of adult mammalian tissues. In a recent paper published in *Cell Research*, Deng et al. report that Leptin receptor-positive mesenchymal cells surrounding intestinal crypts sense diet alterations and modulate ISC function via a stromal IGF1–epithelial IGF1R axis.**

Maintenance of the physiological functions of the gut epithelium, including preservation of barrier integrity, nutrient absorption, and hormonal regulation, is highly dependent on the self-renewal capacity of intestinal stem cells (ISCs). Residing at the base of the crypts of Lieberkühn, ISCs proliferate throughout life and are sustained by a handful of niche factors derived from adjacent Paneth cells and the underlying lamina propria, an elaborate network of mesenchymal, vascular, immune and neuronal cell types. Recently, single-cell RNA sequencing (scRNA-seq) and functional studies have shown how distinct fibroblast populations positioned along the crypt–villus axis and expressing varying amounts of Wnt and BMP regulators control ISC renewal and differentiation. Although the importance of mesenchymal cells (MCs) in gut homeostasis is now unquestioned, it remains uncertain how the mesenchymal niche itself is regulated by environmental factors. A recent study by Deng et al.[1] addresses this question by revealing the effects of diet on pericryptal fibroblasts and the regulation of ISC function (Fig. 1).

How much and what we eat is a critical determinant of human health and longevity. Indeed, obesity and high-fat diet (HFD) promote cardiovascular disease, neurodegeneration, metabolic disorders, inflammation, and cancer, while caloric restriction extends lifespan in many organisms. Part of these systemic effects can be attributed to the impact of diet on adult stem cell function. In the gut, stem cell numbers and regenerative capacity are enhanced in response to caloric restriction or intermittent fasting (reviewed elsewhere[2]). Mechanistically, these effects depend on the nutrient-sensing capacity of the ISC microenvironment. For example, in response to caloric restriction, Paneth cells secrete cyclic ADP-ribose (cADPR) which, in turn, drives SIRT1 activity and proliferation of ISCs in an mTORC1-dependent manner.[2] Fasting also promotes ISC self-renewal via a peroxisome proliferator-activated receptor δ (PPARδ) program, triggered by oxidation of free fatty acids released from adipose stores.[2] Interestingly, similar outcomes can be achieved with HFD, which drives ISC expansion through an increase in free fatty acids.[2] In contrast, mice on Western-style diets rich in carbohydrates and with diminished Vitamin D intake display impaired ISC self-renewal activity.[3]

The delicate balance between food intake and energy expenditure is regulated by leptin, which exerts its effects by binding to its receptor, Lepr, in the hypothalamus and peripheral tissues, including the intestine. In the digestive system, leptin has been shown to play a role in modulating immune responses, supporting cell growth and tissue repair, and regulating glucose and lipid metabolism.[4] Using scRNA-seq and in situ hybridization, Deng et al.[1] found that *Lepr* is highly enriched in pericryptal fibroblasts but largely absent from Acta2- and FoxL1-expressing telocytes, a prominent ISC niche component.[5] Importantly, Lepr was significantly upregulated in irradiated mice, as well as patients undergoing radiation therapy. Genetic ablation of Lepr$^+$ cells by diphtheria toxin treatment revealed a key role for these cells in ISC maintenance. Indeed, depletion of Lepr$^+$ cells resulted in thinning of the intestinal mucosa, villus atrophy, reduced crypt proliferation and defective regenerative capacity following irradiation. Loss of Lepr$^+$ cells also reduced the proliferative capacity of Lgr5$^+$ ISCs both in vivo and in organoid cultures. Co-culture experiments demonstrated that Lepr-expressing MCs enhanced intestinal organoid growth and colony-forming capacity. Given the transcriptional profile, spatial localization, and functional attributes of Lepr$^+$ cells, one may speculate that these cells correspond, at least partially, to CD81$^+$ trophocytes, a fibroblast population enriched in BMP antagonists localized at the crypt base and previously shown to be essential for crypt viability.[6] Further analyses will be required to determine the extent of overlap between these two populations.

A previous report showed that germline deletion of *Lepr* causes impaired Wnt2b expression and crypt regeneration following DSS-induced colitis.[7] To gain further insight into the molecular mechanisms by which Lepr$^+$ cells control ISC homeostasis and regeneration, the authors performed scRNA-seq on sorted Lepr$^+$ cells derived from untreated and irradiated *Lepr-Cre* transgenic mice harboring a GFP reporter. This analysis revealed *Igf1* as a highly expressed gene in Lepr-expressing fibroblasts following irradiation. Consistent with previous studies showing the positive effects of IGF1 overexpression or ectopic addition on crypt proliferation,[8, 9] the authors found that deleting *Igf1* in Lepr$^+$ cells led to a significant reduction in crypt proliferation, particularly following irradiation.

[1]Department of Pathology, McGill University, Montreal, QC, Canada. [2]Cancer Research Program, Research Institute of the McGill University Health Centre, Montreal, QC, Canada. [3]McGill Regenerative Medicine Network, McGill University, Montreal, QC, Canada. ✉email: alex.gregorieff@mcgill.ca

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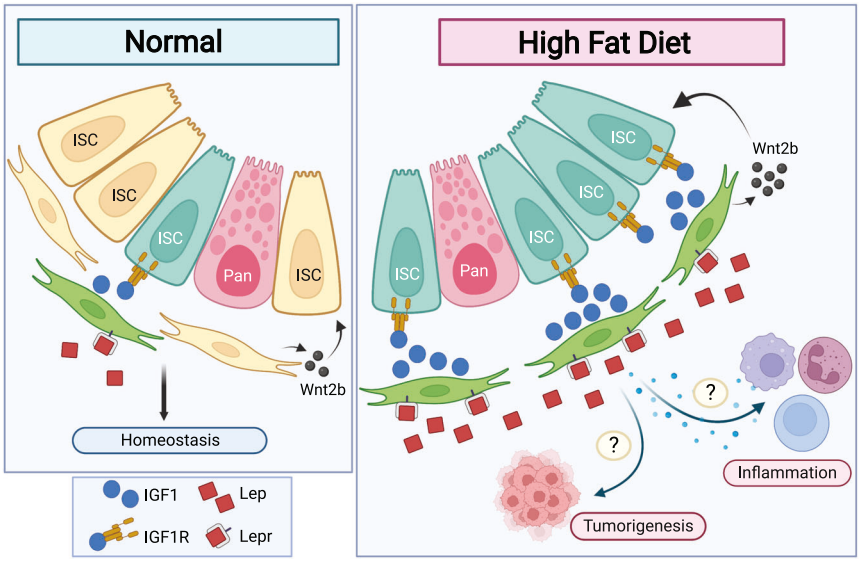


**Fig. 1 The effects of diet on pericryptal fibroblasts and the regulation of ISC function.** Deng et al. showed that Lepr$^+$ fibroblasts (green) respond to diet-induced alterations in Leptin by modulating the ISC niche. When HFD is consumed, Lepr$^+$ fibroblasts surrounding the intestinal crypt increase and secrete high levels of IGF1, which, in turn, induces proliferation of IGF1R-expressing ISCs (mint). These findings raise further questions about the impact of diet on the regulation of the Lepr-IGF1 axis and its role in driving inflammation and colorectal cancer progression. ISC, intestinal stem cell; Pan, Paneth cell; IGF1, insulin-like growth factor 1; IGF1R, insulin-like growth factor 1 receptor; Lep, leptin; Lepr, leptin receptor. Created with BioRender.com.

Moreover, supplementation with recombinant IGF1 rescued these growth defects, as well as homeostatic and regenerative defects associated with Lepr$^+$ cell ablation.

Finally, Deng et al. investigated the impact of diet on the regulation of the Lepr-IGF1 axis. Both the overall abundance of Lepr$^+$ MCs and *Igf1* expression were increased with HFD but drastically decreased upon fasting, which correlated with ISC marker expression. Inversely, HFD or administration of recombinant Leptin promoted *Igf1* expression and correlated with enhanced ISC and progenitor cell proliferation. Furthermore, genetic ablation of *Igf1* abrogated the HFD-induced increase in ISC and progenitor cells, suggesting that Lepr$^+$ MC-derived IGF1 is an important effector in modulating ISCs in response to diet-induced Leptin alterations.

Overall, this study solidifies the notion that diet is a critical environmental factor regulating adult stem cell behavior. The importance of an intrinsic fatty acid oxidation program in ISCs that mediates the pro-proliferative and tumorigenic effects of HFD has previously been highlighted.[2] The discovery of the non-cell autonomous effects of Leptin on the pericryptal mesenchyme reveals an additional mechanism underlying ISC self-renewal and may explain the pro-tumorigenic effects of Leptin signaling on colorectal cancer progression.[10] This is further supported by previous reports describing HFD and IGF1 as risk factors in colorectal cancer. Finally, given the role of HFD in driving inflammatory bowel disease, Lepr$^+$ MCs may also be important actors in promoting inflammation. In light of this, it will be interesting to determine whether and how Lepr$^+$ cells crosstalk with immune cells to exacerbate inflammation.

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## ADDITIONAL INFORMATION

**Correspondence** and requests for materials should be addressed to Alex Gregorieff.

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