Towards Gut Epithelial Repair: Vitamin D’s Role in Intestinal Stem Cell Differentiation

Benjamin E. Mead¹²³*, Lin Lu³*, Xiaolei Yin¹²³, Robert Langer²³, Jeffrey M. Karp¹²#

¹Brigham & Women’s Hospital, Harvard Medical School, Boston, MA 02115
²Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA 02139
³Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA 02139

*Co-first authors
#Correspondence directed to: jmkarp@partners.org

Background: Clinicians have established correlations between inflammatory bowel disease (IBD) and vitamin D deficiency. Vitamin D is known to indirectly regulate gut epithelial turnover via electrolyte balance and immune modulation. We propose that vitamin D has a direct impact on gut epithelial turnover by influencing intestinal stem cell (ISC) differentiation.

Methods: We have developed an in vitro system for the culture of homogeneous ISC enteroids (Yin, et. al., Nature Methods 2014), allowing direct and isolated interrogation of gut stem cell function. Using this system we probed the role of vitamin D, and its active metabolites, in ISC self-renewal and differentiation, measured by mRNA expression, cell number, and viability. This was followed by in vivo dietary restriction and supplementation of vitamin D in mice, with measurements of serum vitamin D and H&E histology of the intestinal epithelium to assess vitamin D mediated epithelial turnover.

Results: The primary active metabolite of vitamin D, calcitriol, showed the greatest effect. As calcitriol concentration increased in vitro, ISC enteroid proliferation decreased. Calcitriol induced a shift in epithelial and cell cycle markers towards terminal gut epithelial cell types and a departure from ISC self-renewal in a dose-dependent manner. In vivo experiments revealed decreased serum vitamin D and reduced small intestine villi density in mice with restricted vitamin D intake, as compared to a vitamin D supplemented diet.

Conclusions: These data demonstrate that vitamin D promotes ISC differentiation to intestinal epithelial cell lineages by altering cell cycle and may drive increased turnover in vivo. Vitamin D supplementation could be a route to restore epithelial barrier integrity in IBD.