A constant pool of Lgr5+ intestinal stem cells is required for intestinal homeostasis

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Abstract

Lgr5+ crypt base columnar cells, the operational intestinal stem cells (ISCs), are thought to be dispensable for small intestinal (SI) homeostasis. Using a Lgr5-2A-DTR (Diphtheria Toxin Receptor) model which ablates Lgr5+ cells with near-complete efficiency and retains endogenous levels of Lgr5 expression, we show that persistent depletion of Lgr5+ ISCs in fact compromises SI epithelial integrity and reduces epithelial turnover *in vivo*. *In vitro,* Lgr5-2A-DTR SI organoids are unable to establish or survive when Lgr5+ ISCs are continuously eliminated by adding DT to the media. However, transient exposure to DT at the start of culture allows organoids to form, and the rate of outgrowth reduces with increasing length of DT presence. Our results indicate that intestinal homeostasis requires a constant pool of Lgr5+ ISCs, which is supplied by rapidly reprogrammed non-Lgr5+ crypt populations when pre-existing Lgr5+ ISCs are ablated.

Figure

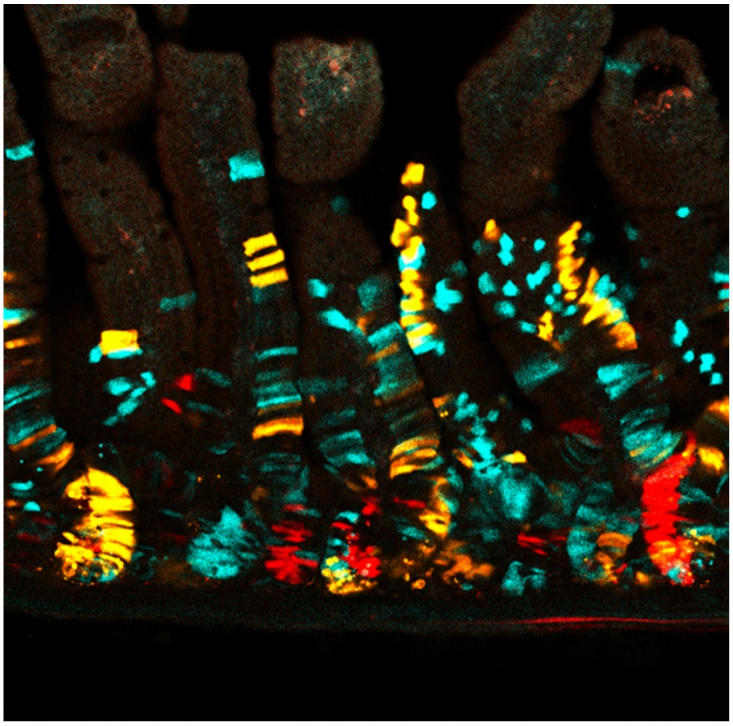

Figure legend: Multicolour lineage tracing shows Lgr5+ stem cells to be essential for epithelial homeostasis in the intestine.