

Parasitic helminths induce fetal-like reversion in the intestinal stem cell niche.

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Public Summary:

Scientific Abstract:

Epithelial surfaces form critical barriers to the outside world and are continuously renewed by adult stem cells(1). Whereas dynamics of epithelial stem cells during homeostasis are increasingly well understood, how stem cells are redirected from a tissue-maintenance program to initiate repair after injury remains unclear. Here we examined infection by *Heligmosomoides polygyrus*, a co-evolved pathosymbiont of mice, to assess the epithelial response to disruption of the mucosal barrier. *H. polygyrus* disrupts tissue integrity by penetrating the duodenal mucosa, where it develops while surrounded by a multicellular granulomatous infiltrate(2). Crypts overlying larvae-associated granulomas did not express intestinal stem cell markers, including *Lgr5*(3), in spite of continued epithelial proliferation. Granuloma-associated *Lgr5*(-) crypt epithelium activated an interferon-gamma (IFN-gamma)-dependent transcriptional program, highlighted by *Sca-1* expression, and IFN-gamma-producing immune cells were found in granulomas. A similar epithelial response accompanied systemic activation of immune cells, intestinal irradiation, or ablation of *Lgr5*(+) intestinal stem cells. When cultured in vitro, granuloma-associated crypt cells formed spheroids similar to those formed by fetal epithelium, and a sub-population of *H. polygyrus*-induced cells activated a fetal-like transcriptional program, demonstrating that adult intestinal tissues can repurpose aspects of fetal development. Therefore, re-initiation of the developmental program represents a fundamental mechanism by which the intestinal crypt can remodel itself to sustain function after injury.

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