# Natural Selection, Crypt Fitness, and Pol III Dependency in the Intestine

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The intestinal epithelium is a rapidly self-renewing tissue. The enormous replicative burden is borne by stem cells, which in mice divide approximately once a day, and by the transit-amplifying compartment, where cells replicate 2–3 times more frequently. Because the continual production of many new cells creates substantial demands, the intestine of conditional mutant mice is an ideal organ to examine tissue-specific functions of pervasive housekeeping factors.

Beyond the sheer pace of self-renewal, the intestine offers other advantages. Arguably no other site shows the relationship of mother and daughter cells—to each other and to the surrounding niche—as clearly. In addition, lineage tracing through cell-restricted expression of Cre recombinase allows monitoring of cells’ immediate and distant progeny, an approach that has contributed much to the current understanding of stem and progenitor cells. Finally, the intestinal epithelium is exceptionally adaptive. Intact crypts compensate rapidly for defective ones, first by increasing the rate of cell proliferation and then by undergoing fission to produce new crypts; this fission resembles the process of intestinal growth in fetuses and children. The gut mucosa is thus a Darwinian terrain: as a population, crypts continually express a fitness that is necessary to maintain vital barrier and absorptive functions. In this issue of [Cellular and Molecular Gastroenterology and Hepatology](https://www.cell.com/cmhg), Kieckhaefer et al exploit tissue-specific gene disruption and the experimental assets of the mouse intestine to identify the cells most vulnerable to the absence of a “housekeeping” factor.

The DNA-dependent enzyme RNA polymerase III (Pol III) synthesizes noncoding transfer RNAs (tRNAs) and other transcripts associated with RNA splicing and protein synthesis. Its highest activity occurs during cell division and organogenesis, and the enzyme is essential for organismal viability. Pol III subunit B (Polr3B), the second largest protein in the complex, is important for enzyme structure and function, and human POLR3B mutations cause neurologic defects and leukodystrophy rooted in hypomyelination. In mice, loss of the Polr3b gene disrupts villus formation and results in embryonic lethality. The villus, the structure of the small intestine that is responsible for nutrient absorption, is the functional unit of the small intestine. The villus is comprised of a columnar absorptive epithelium and crypts. Crypts are regions of proliferation and differentiation, where the epithelial cells are generated. The villus allows for nutrient absorption, and crypts are responsible for cell renewal.

Kieckhaefer et al also observed many crypts that contained an abundance of proliferating cells, showed ongoing Wnt pathway activity, lacked dying cells, and produced normal villi. Cells in these intact crypts had escaped Cre-mediated recombination of one or both Polr3b gene copies, and over time they occupied larger fractions of the mucosa. This process of natural selection recapitulates many other instances of loss of genes linked to vital cellular processes, such as mitosis and modulation of chromatin. The presence and expansion of these adaptive crypts enables intestinal function in surviving animals.

The findings reported by Kieckhaefer et al thus highlight the acute need for protein synthesis to sustain perinatal intestinal growth and function, as well as the tissue’s remarkable versatility in the face of crypt attrition. The strain of Polr3b mutant mice reported in this study will help determine how other tissues respond, at various developmental stages and under stressful conditions, to reduced levels of Pol III–dependent tRNAs and other transcripts. With regard to the intestine, 2 questions come to mind. The demand for protein synthesis and cell replication seems, on the surface, at least as high in the fetal as in the neonatal gut. One now wonders if this is indeed true, and, if so, how the fetal intestine withstands the paucity of vital RNAs. More generally, it is important to understand how intact crypts sense and respond to defects in their neighbors, because that understanding holds one key to improved treatments for inflammatory and other bowel disorders.

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