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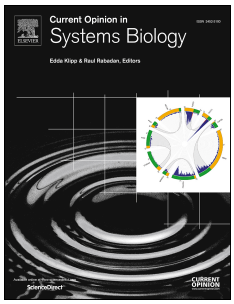

Cancer Systems Biology: Live imaging of intestinal tissue in health and disease

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Cancer Systems Biology:
Live imaging of intestinal tissue in health and disease

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Abstract
Our understanding of the epithelial stem cell compartment of the intestine has seen tremendous progress over recent years. As a result, the crypt is progressively transforming into the primary model system to address fundamental questions about epithelial homeostasis, lineage differentiation and cancer development. Instrumental for these developments were genetic mouse models to identify and manipulate intestinal stem cells *in vivo,* as well as *ex vivo* organoid systems of mouse and human intestinal tissue. This review discusses the emergence of live cell imaging of intestinal biology and briefly touches on the potential of such studies to reveal cell biological phenomena that take place within an epithelium, such as heterotypic cell-cell interactions, cellular development and cell type-specific responses to tumorigenesis or infections.

The intestinal epithelium; simple architecture allows quantitative measurements
Intestinal physiology has always attracted the interest of researchers due to its relation to common human diseases, such as colon cancer, inflammatory bowel disease (IBD) and infections. During the last decade, however, intestinal biology has also attracted researchers whose primary interest is not gut physiology but merely the fundamental principles of stem cell biology and epithelial homeostasis. Indeed, these researchers take advantage of the rapidly advancing knowledge about the intestinal stem cell compartment, transforming the intestine into a prototype model system for stem cell research [1].

On the basal level, the intestinal epithelium has a simple, highly repetitive architecture that consists of tubular-like invaginations (crypts) and finger-like protrusions (villi) (Figure 1). The epithelium is rapidly self-renewing through stem cells that divide approximately once per day. Despite the stochastic processes that underlie stem cell self-renewal and progenitor cell fate decisions, there is surprisingly little variation between different crypts in cellular composition, cell numbers and the relative location of different cell types along the crypt-villus axis. The stem cell niche resides at the entire crypt base and is highly accessible for confocal microscopy when scanning through the intestinal wall. As a result, thousands of crypts can easily be analyzed to obtain sufficiently high numbers for quantitative experiments. In addition, most intestinal cell types have macroscopically morphological characteristics that allow straightforward identification without the strict need of sophisticated markers, while their relative location along the crypt-villus axis is a proxy for their maturation status and age.
Currently, it is widely accepted that crypt base columbar (CBC) cells represent the adult stem cells in the intestine. CBC cells, commonly referred to as $Lgr5^{+}$ intestinal stem cells, are easily recognizable by their specific location in between the post-mitotic and granule-rich Paneth cells at the base of the crypt [2]. Instrumental for the boost in knowledge about intestinal stem cell biology were *state-of-the-art* genetic mouse models that allowed their visualization and manipulation within their natural surroundings (e.g. genetic lineage tracing, cell type depletion and/or tumor initiation) [3-6].