Lrig1: a new master regulator of epithelial stem cells

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The intestine represents the most vigorously renewing, adult epithelial tissue that makes maintenance of its homeostasis a delicate balance between proliferation, cell cycle arrest, migration, differentiation, and cell death. These processes are precisely controlled by a network of developmental signalling cascades, which include Wnt, Notch, BMP/TGFβ, and Hedgehog pathways. A new, elegant study by Wong et al (2012) now adds Lrig1 as a key player in the control of intestinal homeostasis. As for epidermal stem cells, Lrig1 limits the size of the intestinal progenitor compartment by dampening EGF/ ErbB-triggered stem cell expansion.

The epithelium of the small intestine is separated into two distinct compartments: a proliferative crypt, containing tissue-specific stem cells, and a villus with differentiated, short-lived cells, which are replenished by a constant stream of cell migration from the underlying crypt (Scoville et al, 2008). In particular, the canonical Wnt pathway in combination with Notch signals control stem cell maintenance and proliferation in the crypt. In addition, both pathways direct differentiation into the Paneth and the absorptive cell lineage, respectively. Intensive cross-talk between the epithelium and the underlying mesenchyme helps to define the crypt–villus boundary. This relies on epithelial-derived Hedgehog and Wnt ligands that trigger stromal BMP production, which in turn signals back to the epithelium to restrict proliferation to the crypt. A gradient of BMP antagonists produced by mesenchymal cells at the bottom of the crypt supports compartmentalization. In addition, a Wnt gradient in the crypt defines EphB expression and establishes repulsion-mediated separation into Paneth cell, proliferative, and differentiation zones along the crypt–villus axis (Figure 1A).

In the small intestine, two stem cell (SC) populations coexist: Lgr5+/crypt base columnar cells (CBCs) that cycle every 24 h and are interspersed between Paneth cells, and slower dividing SCs concentrated above (around position +4 relative to the crypt bottom) the Lgr5+ position (Takeda et al, 2011). The localization of these Hopx+ mT+ ErbB+ slowly cycling SCs partly overlaps with that of quiescent cells, which show long-term label retention upon irradiation damage and pulse labelling with BrdU. Lgr5+/CBCs are, however, dispensable (Tian et al, 2008) and can be replaced by the second stem cell population, which also shows greater activity during damage repair. The relationship between these two stem cell populations, which can reciprocally generate each other, and the mechanisms that govern quiescence are being elucidated. Importantly, leucine-rich repeats and Ig-like domains 1 (Lrig1), a transmembrane protein that interacts with ErbBs and promotes its degradation, has now been found to be enriched at the crypt base and in the progenitor compartment of the small intestine and colon (Wong et al, 2012). Lrig1 is highly expressed in Lgr5+, Musashi1+, Ascl2+, and Olfm4+ CBCs, and shows an inverse relation to the pattern of activated, phosphorylated EGFR above the crypt base (Figure 1A). In line with these patterns, deletion of Lrig1 in the mouse causes a dramatic crypt expansion and increased numbers of CBCs, transit-amplifying and Paneth cells. Whether the increase of Paneth cells, which actually do not express Lrig1, is a secondary effect due to the progenitor expansion remains open. Importantly, reduction of EGFR...
BMP antagonists

Notch

EphB

Lrig1

BMP signalling

Proliferation

Differentiated cells

Transit-amplifying progenitors

Crypt base columnar cells (CBCs)

Mesenchymal cells

Paneth cells

Slow-cycling stem cells

A

Wnt

Notch

EphB

EGF

Lrig1

BMP

Hh

EphrinB1

EphrinB2

Adhesion

Eph/ephrin

Proliferation

Differentiation

Crypt base columnar cells (CBCs)

Slow-cycling stem cells

Wnt signalling

ErbB signalling

BMP signalling

GSK3β

PTEN

PI3K

AKT

Myc

Adhesion

Eph/ephrin

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signalling by pharmacological (Gefitinib) and genetic modulation (Egfrwa-2 mice) is able to partially normalize all Lrig1 phenotypes. These data establish EGF/ErbB signalling as an important regulator of the crypt compartment, and suggest Lrig1 as a central control that dampens the expansion of stem cells during normal intestinal homeostasis.

Lrig1 was initially identified in the skin and proposed to maintain epidermal stem cells in a quiescent state (Watt and Jensen, 2009). Lrig1 marks human interfollicular epidermal stem cells, which can give rise to all epithelial lineages including hair follicle cells in skin reconstitution assays. However, during normal homeostasis, these cells are only bipotent, contributing to the sebaceous gland and the interfollicular epidermis. In contrast to quiescent Lrig1−SCs in the skin, Lrig1+ intestinal SCs are rapidly dividing and Lrig1 appears to only reduce their proliferative capacity. However, similar to the situation in the skin, Lrig1 and EGF signalling may play an important role during damage repair. Earlier experiments analysed the phenotype of mice lacking major EGF family members (Egger et al., 1997; Troyer et al., 2001). While these mice display some duodenal lesions during normal homeostasis, further experiments established EGF signalling as a key protective component that ameliorates mucosal damage. It remains to be seen whether activation of intestinal SCs during damage repair involves mitigation of Lrig1 damping.

Lrig1 is known to repress ErbB signalling by mediating ubiquitinylination and degradation of activated receptors, thereby limiting the amplitude of EGF signalling (Watt and Jensen, 2009). Consequently, Lrig1 deletion in the intestine induced upregulation of EGFR, ErbB2, and ErbB3, promoting downstream activation of c-Myc within intestinal stem and progenitor cells (Wong et al., 2012). Importantly, Lrig1 is a direct Myc target gene, and thereby part of a negative feedback loop that helps to fine-tune the population size and proliferative activity of intestinal progenitor cells (Figure 1B).

Since the rescue of the Lrig1−/− phenotype by EGFR deficiency was only partial (Wong et al., 2012), other mechanisms may contribute. Intriguingly, Lrig1 has been shown to promote BMP signalling by direct binding to Type I (ALK6) and Type II (ALK1, ALK2, ALK3, and ActRIB) BMP receptors (Gumienny et al., 2010). BMPRIA inactivation, deficiency of its downstream effector PTEN, and transgenic overexpression of the BMP inhibitor Noggin display crypt expansion and increased SC numbers. Inhibition of BMP signalling in these genetic models enhanced Akt activation and increased Wnt signalling, promoting proliferation and adenoma formation (Figure 1B; Scoville et al., 2008). Future work will reveal a potential involvement of BMP and Wnt signalling in the Lrig1 knockout phenotype.

The ErbB pathway has been linked to inflammatory bowel disease, and progression and metastatic potential of colorectal cancer. EGFR inhibition blocks adenoma formation in preclinical models, and ErbB pathway inhibition is currently being evaluated in clinical trials with colorectal cancer patients, where promising results have been reported (Cunningham et al., 2004). In contrast, Lrig1 is expressed at low levels in several cancer types but is overexpressed in some prostate and colorectal tumours (Hedman and Henriksson, 2007). Given this heterogeneity, the Lrig1 function in tumours appears to be cell- and context-dependent. Due to early postnatal lethality of Lrig1 knockout mice, the exciting possibility that Lrig1 may act as an intestinal tumour suppressor could not be answered by the current study but clearly deserves further attention.

Conflict of interest
The authors declare that they have no conflict of interest.

References