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EDITORIAL

KLF5 Governs Stemness in the Adult Intestinal Stem Cell Niche

The inherent self-renewal capability of mammalian intestinal epithelium relies on crypt base columnar intestinal stem cells (ISCs) expressing high levels of leucine-rich repeat-containing G-protein-coupled receptor 5 (Lgr5).[1] Through proliferation and differentiation, these ISCs replenish the epithelium on a daily basis. However, ablating Lgr5 ISCs, such as by total body irradiation, was found to activate the function of stemness in slow-cycling progenitors or even differentiated epithelial cells, most notably secretory lineages.[2] By restoring the lost Lgr5 ISCs via dedifferentiation, these reserve cells were believed to contribute to epithelial regeneration after injury-induced ISC loss. Much has been learned regarding major signaling pathways, in particular the canonical Wnt and Notch signaling pathway, which are required for ISCs to maintain stemness. However, the epithelial cell–intrinsic regulators that maintain stemness as well as pathways governing injury-induced stemness acquisition by reserve epithelial cells have not been fully explored.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Kim et al[3] reported that Krüppel-like zinc-finger transcription factor 5 (KLF5) can be such an ISC intrinsic factor with the earlier-described important features. They collected a substantial amount of evidence to support that KLF5, by exerting epigenetic and transcriptional control over Wnt and Notch pathway genes, is critical for stemness maintenance in ISCs and for dedifferentiation to take place after injury. They first compared the clonogenicity of isolated Lgr5 ISCs carrying *Klf5* wild-type and knockout genetic setups ex vivo. They found that ISCs lacking *Klf5* underwent rapid proliferation, premature enterocyte differentiation, and loss of self-renewal. By examining the lineage tracing activities of Lgr5 ISCs in mice after irradiation, they documented that KLF5 was essential for epithelial regeneration after injury-induced ISC attrition. Furthermore, by a synthesized analysis of transcriptome, Assay for Transposase- Accessible Chromatin sequecing, and H3K27ac chromatin immunoprecipitation sequencing, they gained remarkable insights into the mechanism by which KLF5 prevents premature enterocyte differentiation while supporting ISC functions. Specifically, KLF5 regulates histone modification and chromatin accessibility at a distinct set of Wnt and Notch signaling targets in ISCs. As a consequence, KLF5 deficiency diminished expression of these ISC factors known to regulate self-renewal and homeostasis. Most notably, the KLF5's control over the regulatory element of *Ascl2* established a critical regulatory mechanism in ISCs, placing KLF5 above this Wnt-regulated ISC determinant factor within a transcriptional cascade. Likewise, the illustration of KLF5-mediated control over several Notch pathway genes, including Hes5 and Dll4, further supported Notch's involvement in ISC renewal as well as in injury-activated dedifferentiation of mature epithelial cells.[4,5]

Kim et al[3] noted that *Klf5*-null ISCs failed to produce secretory cell lineages, an observation that may warrant future investigation. If the dominant role of KLF5 in ISCs was to maintain stemness, it would be tempting to learn why loss of *Klf5* in ISCs selectively favored enterocyte differentiation at the expense of a secretory program. In other words, is KLF5 a prerequisite for normal secretory cell lineage commitment? Because the secretory signature genes analyzed in the study represented mature cell markers, it is plausible that loss of *Klf5* in secretory cell precursors might prevent them from terminal differentiation. It also was unclear whether the observed Atoh1 reduction was owing to a direct KLF5-mediated regulation, and whether KLF5 activation or overexpression, as exemplified in the samples of radiation colitis patients, would favor a secretory lineage differentiation in addition to stemness maintenance. Although the exact mechanism is not clear at this time, the diminished secretory cell program was interesting and might contribute in part to the reduced epithelial dedifferentiation in KLF5-deficient epithelium.

KLF5 regulates self-renewal and pluripotency in embryonic stem cells (ESCs).[6] Constitutively expressing KLF5 prevented ESC differentiation, in part through its direct control of *Nanog* and *Oct3/4* transcription.[7] In line with these earlier studies in ESCs and previous work of KLF5 in intestinal epithelium,[8–10] the epigenetic findings by Kim et al[3] shed new light on KLF5 being a stemness controller in an adult stem cell niche in addition to ESCs. The knowledge is useful for KLF5-targeting therapeutics for mitigating gastrointestinal epithelial damages after injury or infection.

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