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EDITORIAL

Intracellular Control of β-Catenin and Intestinal Cell Fate by SIRT2

Tight coordination of cell proliferation and differentiation is critical for the health of the intestinal epithelium, which accomplishes rapid and continuous turnover while maintaining a complex morphology and a regulated balance of stem, absorptive, and secretory cell populations. Disruption of this equilibrium can contribute to disorders such as inflammatory bowel disease (IBD) or colon cancer. At the same time, the epithelium needs to be able to dynamically alter its self-renewal and differentiation programs to protect against infection, injury, or chronic inflammation. Despite the importance of these processes, mechanisms that drive the context-dependent balance between proliferation and differentiation remain poorly understood.

In a new study published in this issue of *Cellular and Molecular Gastroenterology and Hepatology,* Li et al[1] shed light on an important aspect of intestinal renewal—regional and positional Wnt signaling—by exploring the function of the sirtuin protein SIRT2. Li et al demonstrate that, unlike other sirtuins (especially SIRT1, which is expressed primarily in the lower crypt), SIRT2 is restricted to the postmitotic compartment in the intestinal and colonic epithelia of humans and mice, and is induced by differentiation signals. Using a *Sirt2* knockout mouse, they show elongated intestines, greater villus height and crypt depth, and increased proliferation and stem cell markers in ileal crypts, accompanied by lineage-specific disruption in the balance of differentiated cells (more Paneth cells but fewer absorptive enterocytes and goblet cells).

Hunting for the mechanism behind these effects, Li et al note that most sirtuins have NAD^+-dependent deacetylase activity. β-Catenin can be stabilized by acetylation, and indeed *Sirt2*-null intestinal epithelia display elevated levels of acetyl-β-catenin and total β-catenin, consistent with increased expression of a number of Wnt signaling targets. In cell free assays, SIRT2 was able to deacetylate β-catenin directly, supporting a proposed mechanism in which SIRT2 in differentiating cells mediates destabilization of β-catenin, contributing to loss of proliferation and acquisition of functional differentiation. The observation that SIRT2 expression is reduced in IBD patient biopsies or in culture models exposed to tumor necrosis factor suggests that this mechanism is regulated by inflammation and thus could have functional consequences in both homeostasis and disease.

These results provide insight into an important question regarding control of renewal and differentiation in the epithelium. While numerous studies have defined the Wnt/β-catenin pathway as a central regulator of stemness,[2] current models of ligand-driven Wnt activation do not fully explain how the pathway's activity is precisely restricted to the specific cell populations that require it. Recognizing that intracellular regulators like SIRT2 directly modulate β-catenin stability and activity is a substantial advance in this regard.

Of course, important follow-up questions remain. For example, it is not clear how broadly SIRT2 targets regulators of stemness and differentiation. Does it also directly influence Notch, EGFR/ErbB signaling, or other key pathways? Furthermore, what in turn controls SIRT2's regional expression, and does its regulation interact with that of SIRT1, which seems to have opposite expression patterns and function?

Another interesting question touched on by Li et al is subspecification among the secretory lineages. Canonically, differentiating progeny of $Lgr5^+$ stem cells can commit to absorptive or secretory lineages, with additional fate decisions made after that branch point (especially among secretory cells). However, *Sirt2* knockout reduced both goblet cell and absorptive enterocyte numbers, while in contrast increasing the number of Paneth cells. This could potentially be a simple acute effect of increased intestinal stem cells numbers, or it might indicate that SIRT2 controls additional pathways, such that it influences both the overall differentiation state of the tissue and the downstream fate choice of a secretory progenitor. In this regard, it would be interesting to know whether SIRT2 is involved in cellular plasticity or activation of facultative stem cells after an injury[3] to repopulate the $Lgr5^+$ niche.

The responsiveness of SIRT2 to inflammatory signals suggests a possible role in injury response or IBD. On the one hand, the effects of *Sirt2* knockout suggest that this role might be complex—increased stem cell number or activity seems likely to support more rapid repair of epithelial damage; however, on the other hand, loss of goblet cell function can predispose to inflammation.[4] As noted by Li et al, scattered data in the literature on sirtuins in intestinal inflammation certainly support a possible link; however, they also underscore the need for more study of this interesting regulatory mechanism.

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