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EDITORIAL

Intestine, Heal Thyself! Regulating the Intestinal Epithelial Response to Injury

The inflammatory bowel diseases (IBDs) are chronic, relapsing-remitting intestinal ulcerating diseases with a global prevalence, through rapidly rising incidence in newly industrialized countries.[1] Therapeutics for IBD, a market worth US$9.5 billion,[2] focus on reduction of the provoking inflammation through targeting prostaglandin production (aminosalicylates), suppressing the immune system (corticosteroids and immunomodulators), or antagonizing specific cyto- or chemokines (biologic agents). The therapeutic goal of symptom reduction through mucosal restitution, relies on epithelial healing through secondary intention, and is dependent on the regenerative capacity of the intestinal mucosa. Intestinal regeneration is a complex, dynamic, and multicompartmental process, with barrier breach provoking a localized immune response, activating stromal cells, promoting angiogenesis, and inducing a profound change in neighboring intact epithelium, characterized phenotypically by crypt budding, fission, and the generation of lateral wound channels.[3] At a cellular level, epithelial adaptive cell reprogramming impacts almost all cells along the crypt-villus axis of the gut; inducing dedifferentiation and stem cell plasticity in a range of progenitor and differentiated cell types,[4] promoting transit-amplifying cell proliferation and inhibiting postmitotic cell differentiation and apoptosis. The complexity of this spatiotemporal response, mediated by profound changes in secreted cell signalling,[3] and extracellular matrix remodelling[5] are poorly understood.

In this edition of *Cellular and Molecular Gastroenterology and Hepatology,* Meijer et al[6] explore the role of activating transcription factor 2 (ATF2) and ATF7 in regulating the intestinal epithelial response to damage. ATF2 and ATF7 belong to the large AP1 family of transcription factors known to be downstream of a number of key intestinal morphogens, including Wnt, bone morphogenetic protein, and transforming growth factor β pathways, and are capable of forming hetero and homodimers with other family members such as *c-Jun.* It is this dimerization capacity, together with considerable transcriptional, posttranscriptional, and posttranslational regulatory control, that generates a powerful mechanism for conferring diverse cellular function in a context-dependent manner.[7] Thus, the role of ATFs in mediating intestinal epithelial cell homeostatic and regenerative function is hitherto unexplored. Using a combination of floxed and null alleles, Meijer et al successfully knocked out epithelial *Atf2* and *Atf7* and used mouse phenotype and organoid culture to assess the impact of deletion on epithelial homeostatic and regenerative response. Interestingly, the homeostatic consequences were minimal, indicating dispensability or functional redundancy in steady state, but there was a pronounced impact on the regenerative capacity of the epithelium resulting in exaggerated ulceration and impaired intestinal healing following both Dextran sodium sulfate and irradiation-induced injury. At a cellular level, *Atf2* and *Atf7* loss increased the rate of apoptosis, abrogated a proportionate increase in proliferation, reduced expression of some key stem cell markers including *Lgr5* and *Ascl2*, and decreased the number of functioning goblet cells, with concomitant downregulation of *Muc2* and the enteroendocrine cell marker *CgA*. In vitro work was consistent with mouse models, as intestinal organoids generated from knockout epithelium showed impaired growth in the regenerative organoid culture milieu, and increased sensitivity to both mechanical damage and tumor necrosis factor α challenge, with the latter inducing apoptotic and inflammatory pathways. Mechanistically, it is not determinable whether this multifaceted effect of *Atf2/7* loss—simultaneously impacting stem cell marker expression, transit-amplifying cell proliferation, secretory cell fate, and apoptosis—is the consequence of abrogation of the numerous cell signaling pathways that converge on the ATF transcription factors, or the demonstration of a key role for *Atf2* and *Atf7* in regulating regeneration-induced adaptive cell reprogramming. However, this work clearly shows that although these transcription factors are functionally redundant in murine epithelial cell homeostasis, they are rapidly called into action following epithelial cell damage and are absolutely required for effective mucosal healing.

This interesting paper sheds some light on the role of these particular transcription factors in mediating intestinal epithelial cell repair but perhaps also highlights how much there is to learn about the regulation of the intestinal mucosal response to injury. Although recent work has demonstrated the capacity for injury induced dedifferentiation of a panoply of cell types,[4] we understand comparatively little about how changes in intercompartmental signaling and the extracellular matrix induce such profound and rapid responses in epithelial cell fate. Furthermore, the demonstrated uncoupling of homeostatic and regenerative roles for the ATF transcription factors may illustrate an important point. Therapies directed at enhancing the epithelial cell regenerative response may not necessarily impact homeostatic cell function elsewhere, so there may be a number of key therapeutic opportunities, or indeed an entirely new treatment paradigm, that await our understanding and harnessing of the regenerative capacity of the intestinal epithelium in IBD.

SIMON J. LEEDHAM, PhD, FRCP
Intestinal Stem Cell Biology Laboratory
Wellcome Trust Centre for Human Genetics
University of Oxford
Oxford, United Kingdom

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Correspondence
Address correspondence to Simon J. Leedham, PhD, Intestinal Stem Cell Biology Laboratory, Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, United Kingdom. e-mail: simon.leedham@well.ox.ac.uk; fax: +44 1865 287664.

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