cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

MTorc1 at the Crossroads of Facultative Intestinal Stem Cell Activation

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Bohin et al[1] identify insulin-like growth factor-1 (Igf1) as regulator of mTorc1-dependent facultative intestinal stem cell (FSC) activation and epithelial barrier regeneration in response to DNA damaging injury.

The columnar epithelium of the intestinal tract is not only the body's highest turnover tissue; it is also remarkably capable of regeneration in response to high doses of DNA damaging injury. Over the past 15 years, mouse studies using an array of lineage tracing strategies have led to a model of the intestinal stem cell compartment in which active crypt base columnar (CBC) stem cells driven by canonical Wnt-β-catenin signaling maintain homeostatic turnover, yet they are readily ablated by DNA damaging injury.[2] In the face of such injury, an extremely rare and poorly defined pool of FSCs, likely within the secretory lineage, can reenter the CBC state to drive rapid epithelial regeneration and barrier restoration.[3–5] The molecular mechanisms governing the resistance of FSCs to DNA damage-induced death and their subsequent reacquisition of CBC identity remain poorly understood.

Here, Bohin et al[1] identify dramatic increases in Igf1 levels in the subepithelial mesenchyme in response to DNA damaging injury (using a standard experimental paradigm of 12 Gy ionizing radiation). The peak of Igf1 expression is coincident with the earliest FSC divisions, about 48 hours after injury, and treatment with small molecule inhibitors of the Igf1 receptor (Igfr) abrogates the epithelial regenerative response. Interestingly, the subepithelial source of Igf acting on Igf1r-expressing epithelial cells may be the recently described Foxl1+ telocytes,[6,7] which are responsible for generating the Wnt^{High} niche for CBCs during normal homeostasis. Indeed, telocytes appear unique in their expression of Igf1 among cells of the mucosa,[8] yet how telocytes respond to insults and how their response shapes epithelial function remain unknown.

Igf/Igfr signaling acts upstream of both the Ras/ERK pathway and the PI3K/AKT/mTorc1 pathway. Using a combination of genetic and pharmacologic approaches, Bohin et al[1] go on to dissect the requirement for mTorc1 activity for FSC activation. They find that mTorc1 inhibition with rapamycin before, but not after, initial FSC activation abrogates regeneration and lineage tracing from *Bmi1C-reER*-marked FSCs.

These data add to a growing body of literature describing a requirement for mTorc1 during FSC activation and regeneration in response to DNA damaging injury. Recently, a related study[9] observed that mTorc1 activity in FSCs could be potently stimulated through dietary leucine; if leucine is given before DNA damaging injury, FSCs become prematurely activated, enter the cell cycle, and undergo DNA damage-induced apoptosis, resulting in compromised regeneration. Conversely, if mTorc1 is inhibited via caloric restriction before DNA damage, a larger pool of FSCs is available to enhance the regenerative response. In contrast, and consistent with the current study, inhibition of mTorc1 with rapamycin immediately before or after injury abrogates regeneration, despite protecting FSCs against apoptosis. We may interpret these findings as mTorc1 inhibition via caloric restriction being readily reversible in response to injury, in contrast to the effects of rapamycin.

In another related and consistent study, Richmond et al[10] observe that acute fasting increases the pool of FSCs (in this instance marked by mTert-CreER or -GFP reporters), that this pool of cells has increased Pten phosphatase protein activity (an upstream inhibitor of mTorc1), and that refeeding after fasting results in mTorc1 activation in FSCs. Furthermore, Pten phosphatase protein–deficient intestines have a compromised regenerative response to DNA damage, illustrating how the timing and balance of mTorc1 activity dictate the response to injury.

In aggregate, these studies support a model where a pool of FSCs is maintained in a highly DNA damage-resistant state with low mTorc1 activity. These FSCs must activate mTorc1 to enter the cell cycle and regenerate the epithelium in response to DNA damage that ablates cycling CBCs and progenitors. Importantly, the cues acutely inducing mTorc1 at the correct time after DNA damage are likely acting via signal transduction pathways (eg, the Igf/Igfr axis proposed by Bohin et al[1]). However nutrient-sensing inputs into mTorc1 are similarly able to control FSC activation and modulate the regenerative response to DNA damaging injury. Thus, although caloric restriction or fasting might better poise the epithelium to respond to a future injury, acute growth factor stimulation might enhance the regenerative process after injury.

Although these studies are beginning to provide insight into the molecular control of FSC activity, this remains a challenging area of research. FSCs are exceedingly rare on the basis of their functional definition: the ability to form a clonal regenerative crypt after injury, which ablates the cycling stem/progenitor compartment. They also remain poorly defined molecularly because they are present at greater or lesser frequency in populations marked by *Bmi1-CreER*, *mTert-CreER*, *Hopx-CreER*, and numerous other, more widely active CreER drivers. To date, no single CreER allele has been identified that marks a homogenous population of

functional FSCs required for epithelial regeneration, making the prospective identification and study of these powerful cells an ongoing challenge.

CHRISTOPHER J. LENGNER, PhD
Department of Biomedical Sciences
School of Veterinary Medicine
Institute for Regenerative Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

References

1. Bohin N, McGowan KP, Keeley TM, Carlson EA, Yan KS, Samuelson LC. Insulin-like growth factor-1 and mTORC1 signaling promote the intestinal regenerative response after irradiation injury. Cell Mol Gastroenterol Hepatol 2020;10:797–810.
2. Tao S, Tang D, Morita Y, Sperka T, Omrani O, Lechel A, Sakk V, Kraus J, Kestler HA, Kühl M, Rudolph KL. Wnt activity and basal niche position sensitize intestinal stem and progenitor cells to DNA damage. EMBO J 2017; 36:2920–2921.
3. Bankaitis ED, Ha A, Kuo CJ, Magness ST. Reserve stem cells in intestinal homeostasis and injury. Gastroenterology 2018;155:1348–1361.
4. Li L, Clevers H. Coexistence of quiescent and active adult stem cells in mammals. Science 2010; 327:542–545.
5. Yousefi M, Li L, Lengner CJ. Hierarchy and plasticity in the intestinal stem cell compartment. Trends Cell Biol 2017;27:753–764.
6. Aoki R, Shoshkes-Carmel M, Gao N, Shin S, May CL, Golson ML, Zahm AM, Ray M, Wiser CL, Wright CVE, Kaestner KH. Foxl1-expressing mesenchymal cells constitute the intestinal stem cell niche. Cell Mol Gastroenterol Hepatol 2016;2:175–188.
7. Kaestner KH. The intestinal stem cell niche: a central role for foxl1-expressing subepithelial telocytes. Cell Mol Gastroenterol Hepatol 2019;8:111–117.
8. Shoshkes-Carmel M, Wang YJ, Wangensteen KJ, Tóth B, Kondo A, Massasa EE, Itzkovitz S, Kaestner KH. Subepithelial telocytes are an important source of Wnts that supports intestinal crypts. Nature 2018;557:242–246.
9. Yousefi M, Nakauka-Ddamba A, Berry CT, Li N, Schoenberger J, Simeonov KP, Cedeno RJ, Yu Z, Lengner CJ. Calorie restriction governs intestinal epithelial regeneration through cell-autonomous regulation of mTORC1 in reserve stem cells. Stem Cell Rep 2018;10:703–711.
10. Richmond CA, Shah MS, Deary LT, Trotier DC, Thomas H, Ambruzs DM, Jiang L, Whiles BB, Rickner HD, Montgomery RK, Tovaglieri A, Carlone DL, Breault DT. Dormant intestinal stem cells are regulated by PTEN and nutritional status. Cell Rep 2015; 13:2403–2411.

Correspondence
Address correspondence to: Christopher J. Lengner, PhD, Department of Biomedical Sciences, School of Veterinary Medicine, Institute for Regenerative Medicine, University of Pennsylvania, 3800 Spruce Street, Room 309EA, Philadelphia, Pennsylvania 19104. e-mail: Lengner@upenn.edu; fax: (215) 573-6810.

Conflicts of interest
The author discloses no conflicts.


Most current article

2352-345X
https://doi.org/10.1016/j.jcmgh.2020.07.007