cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

A Little Disorder Can Be Healthy: PRAP1 as a Protective Factor in the Intestine

Tight control of cell survival and death in the intestinal epithelium is critical for maintaining a healthy barrier in this rapidly renewing tissue. Excessive necrosis, apoptosis, and necroptosis in the epithelium are hallmarks of a number of diseases, including necrotizing enterocolitis and inflammatory bowel disease. Furthermore, intestinal cell death is a limiting side effect of a number of anticancer chemotherapeutic regimens. Thus, potential therapeutic bolstering of epithelial survival is a perennial hot topic of gastrointestinal research.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology,* a new study from Wolfarth et al[1] describes a novel antiapoptotic role in the intestinal epithelium for a little-studied molecule called proline-rich acidic protein 1 (PRAP1). A previous report from the same lab had identified *Prap1* in a screen for genes induced by the probiotic bacterium *Lactobacillus rhamnosus* GG.[2] PRAP1 has also been defined as a p53 effector mediating survival of human colon cancer cells.[3] However, a function in nontransformed intestinal cells or the intestine in vivo had not yet been tested.

Using a *Prap1* null mouse and newly generated antibodies, Wolfarth et al show here that PRAP1 is robustly expressed in the human and mouse small intestinal epithelium, and that its deletion sensitizes to irradiation induced apoptosis. While *Prap1* null mice also had a baseline mild inflammation and dysbiosis in the gut, they showed no frank disease in the absence of additional challenge, and heightened apoptosis sensitivity appears to be epithelial-intrinsic as it was robustly replicated in enteroid cultures.

The authors also show *Prap1* expression is itself induced by irradiation. Previous studies noted probiotic induction of the gene in mice,[2] stimulation by p53 activation in human colon cancer cells,[3] and elevated transcript levels during adaptation to massive small bowel resection in mice.[4] Together, these results suggest that PRAP1 may be a target of multiple injury response, cell stress, or repair-oriented pathways in the intestine, though whether these are all p53 dependent or converging on PRAP1 through multiple mechanisms remains unknown.

Considering mechanism(s) of the epithelial protection, at this point there are more questions than there are answers, but they are interesting questions. The authors provide evidence that PRAP1 is an intrinsically disordered protein (ie, while it may have defined secondary structures, it has little to no fixed 3-dimensional tertiary structure). This characteristic is shared by a number of proteins important for intracellular signaling, and may suggest an ability to flexibly bind different effector proteins and bring them together in a transient, scaffold-like manner. On the other hand, there is evidence that PRAP1 is secreted from cells,[5] which opens up additional potential functions (and therapeutic uses, if the secreted protein is antiapoptotic). A more detailed exploration of intracellular versus extracellular actions will be a necessary step forward in understanding the activity and functions of this molecule.

Wolfarth et al show that Prap1 influences messenger RNA levels of a number of key genes regulating cell survival and death, including Bcl-2 family mediators and $p21^{waf1/cip1}$. The authors hypothesize that inhibition of p21 expression is the mechanism of protection by Prap1, though this will require further testing. On the one hand, the bulk of available data support a default role for p21 in suppressing cell death rather than inducing it; as noted by the authors, under some circumstances p21 can partner with p53 to release proapoptotic Bcl-2 family proteins (eg, Bax) and cause cell death. Because both p21 and Prap1 are p53 targets, it is tempting to speculate that under extreme cell stress conditions an excess of p21 can flip to a proapoptotic profile unless repressed by Prap1. The means by which Prap1 might block p21 expression will be an important future question as well.

In summary, this intriguing report identifies the small intrinsically disordered protein PRAP1 as a new mediator of cell survival in the intestinal epithelium both in vivo and in vitro. Mechanistic questions remain, and any potential effects of PRAP1 activity beyond epithelial protection need to be defined (though a casual search of online datasets such as TCGA colon cancer does not raise any obvious red flags vis-à-vis tumorigenesis, at least). However, it is exciting to see a new mediator of cell survival emerge that might develop into a target that can be exploited to protect the intestinal lining.

MARK R. FREY, PhD
Saban Research Institute
Children's Hospital Los Angeles
Los Angeles, California
Department of Pediatrics
University of Southern California Keck School of Medicine
Los Angeles, California
Department of Biochemistry and Molecular Biology
University of Southern California Keck School of Medicine
Los Angeles, California

References

1. Wolfarth AA, Liu X, Darby TM, Boyer DJ, Spizman JB, Owens JA, Chandrasekharan B, Naudin CR, Hanley KZ, Robinson BS, Ortlund EA, Jones RM, Neish AS.

Proline-rich acidic protein-1 (PRAP1) protects the gastrointestinal epithelium from irradiation-induced apoptosis. Cell Mol Gastroenterol Hepatol 2020; 10:713–727.

2. Jones RM, Desai C, Darby TM, Luo L, Wolfarth AA, Scharer CD, Ardita CS, Reedy AR, Keebaugh ES, Neish AS. Lactobacilli modulate epithelial cytoprotection through the Nrf2 pathway. Cell Rep 2015;12: 1217–1225.
3. Huang BH, Zhuo JL, Leung CHW, Lu GD, Liu JJ, Yap CT, Hooi SC. PRAP1 is a novel executor of p53-dependent mechanisms in cell survival after DNA damage. Cell Death Dis 2012;3:e442.
4. Seiler KM, Waye SE, Kong W, Kamimoto K, Bajinting A, Goo WH, Onufer EJ, Courtney C, Guo J, Warner BW, Morris SA. Single-cell analysis reveals regional reprogramming during adaptation to massive small bowel resection in mice. Cell Mol Gastroenterol Hepatol 2019; 8:407–426.
5. Zhang J, Wong H, Ramanan S, Cheong D, Leong A, Hooi SC. The proline-rich acidic protein is epigenetically regulated and inhibits growth of cancer cell lines. Cancer Res 2003;63:6658–6665.

Correspondence
Address correspondence to: Mark R. Frey, PhD, University of Southern California Keck School of Medicine, Departments of Pediatrics, Biochemistry and Molecular Biology, 4650 Sunset Boulevard, MS #137, Angeles, CA 90089. e-mail: mfrey@usc.edu.

Conflicts of interest
The author discloses no conflicts.

Most current article

2352-345X
https://doi.org/10.1016/j.jcmgh.2020.08.001