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EDITORIAL

Intestinal GPCRs Control Paneth Cell Maturation and Susceptibility to Experimental Colitis

Typical G-protein–coupled receptors (GPCRs), upon specific ligand binding, initiate intracellular signaling by activating an immediately downstream trimeric G-protein complex consisting of α, β, and γ subunits. Dissociation of the guanosine triphosphate–bound α subunit from β and γ subunits triggers intracellular signaling. Intestinal epithelial GPCRs may respond to various gastrointestinal growth factors, hormonal ligands, or neurotransmitters to regulate multiple aspects of intestinal homeostasis. Well-studied intestinal GPCRs include Paneth cell–enriched Frizzled 5, which is crucial for Paneth cell maturation,[1] as well as the rhodopsin family leucine-rich repeat-containing GPCR 4/5/6, which function as R-spondin receptors to potentiate canonical Wnt signaling.[2] There are 4 types of G-protein α subunits: Gαs, Gαi/o, Gαq/11, and Gα12/13; the exact physiological significance of these particular G-protein subunits are poorly understood, especially in the gastrointestinal system.

In this issue, Watanabe et al[3] established mouse models with intestinal epithelial cell–specific deletion of genes that encode Gαq and Gα11, and characterized the intestinal phenotypes in single- and double-knockout mice. The investigators showed that at steady states, Gαq and Gα11 double-knockout mice (DKO), although appearing healthy in general, showed abnormal Paneth cell morphology, a distinct phenotype that the investigators described as an emergence of enlarged and mislocalized "intermediate" cell types with dual characters of Paneth and Goblet cells.[4] Aberrant Paneth cells with similar features have been reported elsewhere with a severely disrupted crypt cell organization.[5,6] Remarkably, although there was no detectable phenotype in the colons of these DKO mice, upon dextran sulfate sodium challenge these mice showed more severe colitis with higher mortality rates and disease penetrance. Further mechanistic explorations by the investigators identified a reduced Wnt/β-catenin activity in DKO mouse intestinal epithelia, exemplified by reductions of multiple Wnt targets, including Sex Determining Region Y Box 9 and T Cell-Specific Transcription Factor 1. The investigators did examine other key signaling pathways, but only detected minor changes in Notch activity in these mutant mice.

Overall, the study convincingly delineated a positive contribution of $G_{\alpha q/11}$ toward the crypt Wnt/β-catenin signaling, in particular with 2 major supportive pieces of evidence, as follows: the pronounced Paneth cell phenotype, which was indicative of defective maturation of this Wnt-dependent cell type,[1] and the enhanced colitis susceptibility in DKO mice upon dextran sulfate sodium challenge. Blocked Paneth cell maturation seen in this study is echoed by at least another recently reported knockout mouse model in which the crypt Wnt signaling activity was weakened because of a reduced Wnt ligand secretion.[7,8] The enhanced colitis susceptibility shown in $G_{\alpha q/11}$ DKO mice suggests that the mucosal regenerative program induced by the chemical injury probably increased the cellular demands for $G_{\alpha q/11}$-mediated signaling activities in the intestine. The observation that neither $G_{\alpha q}$ nor $G_{\alpha 11}$ single-knockout mice showed a discernible phenotype supports the idea that individual α subunits may compensate for each other at least at steady conditions. The fact that even the double knockouts appear healthy overall strongly suggests that loss of $G_{\alpha q/11}$ can be well tolerated in uninjured intestines.

Although the current study provided important implications to the field of GPCR physiology, how $G_{\alpha q/11}$ deficiency impairs the canonical Wnt signaling, as the investigators also pointed out, remains poorly understood. Given that EphB3 is one major downstream effector of Wnt/β-catenin signaling and is crucial for normal Paneth cell positioning,[9] future studies may be necessary to determine, in DKO intestines, the EphB3 protein expression and cellular localization, even though the investigators did not detect significant changes at the messenger RNA level. In addition, certain $G_{\alpha q/11}$-interacting GPCRs such as Ca^{2+} sensing receptors are known to inhibit Wnt/β-catenin activity in the colon.[10] Likewise, Frizzled/G-protein/Ca^{2+}/protein kinase C signaling is believed to antagonize the canonical Wnt signaling.[11] The level of pan-p–protein kinase C indeed was decreased in DKO tissues, which presumably would increase, rather than reduce, Wnt activity. Thus, it is necessary for future studies to interrogate specific pathway components described earlier and resolve these opposing observations. It also will be interesting to determine which $G_{\alpha q/11}$ downstream effectors mediate its regulatory role in Paneth cell differentiation.

Together, this study by Watanabe et al[3] opened many intriguing questions critical for our understanding of the complicated involvement of major epithelial GPCRs in intestinal stem cell regeneration, Paneth cell differentiation, and mucosal injury and adaptation.

XIAO ZHANG, MS
NAN GAO, PhD
Department of Biological Sciences
Rutgers Newark
Newark, New Jersey

References

1. van Es JH, Jay P, Gregorieff A, et al. Wnt signalling induces maturation of Paneth cells in intestinal crypts. Nat Cell Biol 2005;7:381–386.
2. de Lau W, Peng WC, Gros P, et al. The R-spondin/Lgr5/Rnf43 module: regulator of Wnt signal strength. Genes Dev 2014;28:305–316.

3. Watanabe N, Mashima H, Miura K, et al. Requirement of $G\alpha_q/G\alpha_{11}$ signaling in the preservation of mouse intestinal epithelial homeostasis. Cell Mol Gastroenterol Hepatol 2016;2:767–782.
4. Troughton WD, Trier JS. Paneth and goblet cell renewal in mouse duodenal crypts. J Cell Biol 1969;41:251–268.
5. Sakamori R, Das S, Yu S, et al. Cdc42 and Rab8a are critical for intestinal stem cell division, survival, and differentiation in mice. J Clin Invest 2012;122:1052–1065.
6. Sakamori R, Yu S, Zhang X, et al. CDC42 inhibition suppresses progression of incipient intestinal tumors. Cancer Res 2014;74:5480–5492.
7. Das S, Yu S, Sakamori R, et al. Rab8a vesicles regulate Wnt ligand delivery and Paneth cell maturation at the intestinal stem cell niche. Development 2015;142:2147–2162.
8. Zhang X, Gao N. RAB and RHO GTPases regulate intestinal crypt cell homeostasis and enterocyte function. Small GTPases 2016;7:59–64.
9. Batlle E, Henderson JT, Beghtel H, et al. Beta-catenin and TCF mediate cell positioning in the intestinal epithelium by controlling the expression of EphB/ephrinB. Cell 2002;111:251–263.
10. Rey O, Chang W, Bikle D, et al. Negative cross-talk between calcium-sensing receptor and beta-catenin signaling systems in colonic epithelium. J Biol Chem 2012;287:1158–1167.
11. Westfall TA, Brimeyer R, Twedt J, et al. Wnt-5/pipetail functions in vertebrate axis formation as a negative regulator of Wnt/beta-catenin activity. J Cell Biol 2003;162:889–898.

Correspondence
Address correspondence to: Nan Gao, PhD, Department of Biological Sciences, Rutgers University, 195 University Avenue, Boyden Hall, Suite 206, Newark, New Jersey 07102. e-mail: ngao@rutgers.edu.

Conflicts of interest
The authors disclose no conflicts.

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