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,4 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 al3 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 than in uninjured intestines.

Further mechanistic explorations by 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 than in uninjured intestines.

Overall, the study convincingly delineated a positive contribution of Gαq/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 Gαq/11 DKO mice suggests that the mucosal regenerative program induced by the chemical injury probably increased the cellular demands for Gαq/11–mediated signaling activities in the intestine. The observation that neither Gαq nor Gα11 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 Gαq/11 can be well tolerated in uninjured intestines.

Although the current study provided important implications to the field of GPCR physiology, how Gαq/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 Gαq/11-interacting GPCRs such as Ca2+ sensing receptors are known to inhibit Wnt/β-catenin activity in the colon.10 Likewise, Frizzled/G-protein/Ca2+/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 Gαq/11 downstream effectors mediate its regulatory role in Paneth cell differentiation.

Together, this study by Watanabe et al3 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.

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Conflicts of interest
The authors disclose no conflicts.

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