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EDITORIAL

Gastrointestinal Tract Homeostasis: The Role of the Inositol Polyphosphate Multikinase

The gastrointestinal (GI) tract manages a multitude of physiological functions. The primary function is to absorb nutrients, but it also plays an important defense role by responding to infectious stimuli. Moreover, the GI tract regulates full organismal physiology by secreting neurotransmitters and hormones. The intestinal epithelial cells (IECs) of the GI tract are a highly functional barrier subject to constant mechanical and chemical stresses going through a constant and rapid renewal process. Alteration of the GI tract's fine-tuned physiology could lead to chronic inflammatory disorders such as Crohn's disease and ulcerative colitis, more generally known as inflammatory bowel disease. The etiology of Crohn's disease still mostly is unknown because it is a multifactorial and genetically complex disorder in which both genetic and environmental risk factors contribute to its insurgence. Over the past 2 decades, Mendelian genetic family studies and high-throughput genome-wide association studies have identified many genes as potential Crohn's disease risk factors.

Three independent genetic studies have identified 2 inositol phosphate kinases responsible for the synthesis of high-phosphorylated inositol phosphates as risk factors for Crohn's disease. The 2 identified genes are *IPMK*,[1,2] which primarily converts the phospholipase C–generated and calcium release factor inositol trisphosphate to inositol pentakisphosphate (IP_5), and *IP6K1*,[3] which generates inositol pyrophosphate (IP_7) from inositol hexakisphosphate. These genetic studies originally hinted and underlined the likely importance of the inositol phosphate signaling network to regulate GI tract physiology. Genetic studies often lack functional analysis. For IPMK, this lacuna is being filled by the work of Park et al[4] published in this issue of *Cellular and Molecular Gastroenterology and Hepatology*. The investigators generated IEC-specific IPMK knockout mice and characterized the functionality of the GI tract. They found that the GI tract of $IPMK^{\Delta IEC}$ mice develops normally, with the intestinal epithelium possessing regular permeability to fluorescent dextran and normal barrier function. However, after challenging the GI tract with the widely used chemical colitogen dextran sodium sulfate (DSS), a molecule that induces acute colitis, thus mimicking human inflammatory bowel disease, $IPMK^{\Delta IEC}$ deficiency results in exacerbated colitis and delayed recovery. Transcriptome analysis as well as flow cytometry studies of DSS-challenged colon showed a substantial down-regulation of tuft cell number in $IPMK^{\Delta IEC}$ mice. The analysis of DSS-unchallenged intestine indicated that depletion of IPMK in colonic epithelium impaired tuft cell development and resulted in a smaller number of tuft cells in healthy $IPMK^{\Delta IEC}$ colon. Therefore, although the developmental defects of tuft cells in $IPMK^{\Delta IEC}$ mice do not result in any notable phenotype in homeostatic conditions, it increases the vulnerability to colitis upon DSS administration.

Tuft cells are a minor, if not rare, and functionally distinct population of cells of the intestinal epithelium.[5] They are considered sentinel chemosensory epithelial cells with a key role in regulating the intestinal immune response and therefore are highly involved in GI tract diseases. Although tuft cells represent the least-studied IECs, over the past 10 years the interest in this cell type has grown exponentially. The article by Park et al[4] offers new insights into tuft cell biology. Using single-cell RNA sequencing transcriptional profiling, the investigators showed an unexpected heterogeneity and the existence of 3 subtypes of colonic tuft cells instead of 4 as previously believed.[6] This discovery challenges the current knowledge and will be instrumental to fully appreciate tuft cell biology.

The important work of Park et al[4] did not mechanistically address how IPMK regulates tuft cell development, their number, and the differentiation in the 3 subtypes. It is reasonable to postulate that tuft cell development is controlled transcriptionally. This hypothesis is consistent with the transcriptional roles attributed to IPMK in both yeast and mammalian cells.[7] Therefore, the characterization of the role(s) of IPMK in transcriptional control in tuft cells becomes instrumental to appreciate the function in health and diseases of this minor but utterly important intestinal cell type. These studies should take into account the multifaceted nature of IPMK, an enzyme that is able to synthesize water-soluble inositol phosphates such as IP_5, but that also converts the lipid phosphatidylinositol(4,5)-bisphosphate to PIP3. Furthermore, IPMK could transduce the signal independently from its catalytic activity and work as a signaling hub by physically interacting with protein effectors. However, in light of the fact that genetic studies also highlighted IP6K1 as a Crohn's disease risk factor,[1–3] it is conceivable that the inositol pyrophosphate IP_7 plays a fundamental role in regulating GI tract physiology. Indeed, IPMK synthesized IP_5 as an intermediate to IP6K1 production of IP_7. These considerations point to the importance of measuring the GI tract metabolism of these important signaling molecules. The recent development of new analytical technologies[8,9] now permit the measurement of inositol phosphates extracted from mammalian tissues. There is no doubt that these biochemical analyses will shed light on the role of these important signaling metabolites in regulating GI tract functions, and might lead to unforeseen discoveries and new therapeutic approaches.

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