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 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 (IP5), and IP6K1,3 which generates inositol pyrophosphate (IP7) from inositol hexakisphosphate. These genetic studies originally hinted and underlined the importance of the inositol phosphate signaling network 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 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.

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 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 al4 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 2 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 al4 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 IP7, but that also converts the lipid phosphatidylinositol(4,5)-bisphosphate (PI(4,5)P2) to phosphatidylinositol (3,4,5)-trisphosphate PI(3,4,5)P3. 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,1,5 it is conceivable that the inositol pyrophosphate IP7 plays a fundamental role in regulating GI tract physiology. Indeed, IPMK synthesized IP5 as an intermediate to IP6K1 production of IP7. These considerations point to the importance of measuring the GI tract metabolism of these important signaling molecules. The recent development of new analytical technologies6,10 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.

**ADOLFO SAIARDI, PhD**
Medical Research Council, Laboratory for Molecular Cell Biology
University College London
London, United Kingdom

**References**

1. O’Donnell S, Borowski K, Espin-Garcia O, Milgrom R, Kabakchiev B, Stempak J, Panikkath D, Eksteen B, Xu W, Steinhart AH, Kaplan GG, McGovern DPB, Silverberg MS. The Unsolved Link of Genetic Markers and Crohn’s Disease Progression: A North American Cohort Experience. Inflamm Bowel Dis 2019; 25(9):1541–1549.

2. Yokoyama JS, Wang Y, Schork AJ, Thompson WK, Karch CM, Cruchaga C, McEvoy LK, Witoelar A, Chen CH, Holland D, Brewer JB, Franke A, Dillon WP, Wilson DM, Mukherjee P, Hess CP, Miller Z, Bonham LW, Shen J, Rabinovici GD, Rosen HJ, Miller BL, Hyman BT, Schellenberg GD, Karlsen TH, Andreassen OA, Dale AM, Desikan RS. Alzheimer’s Disease Neuroimaging I. Association Between Genetic Traits for Immune-Mediated Diseases and Alzheimer Disease. JAMA Neurol 2016;73(6):691–697.

3. Morgan AR, Han DY, Lam WJ, Fraser AG, Ferguson LR. Association analysis of 3p21 with Crohn’s disease in a New Zealand population. Hum Immunol 2010; 71(6):602–609.

4. Park SE, Lee D, Jeong JW, Lee S-H, Park SJ, Ryu J, Oh SK, Yang H, Fang S, Kim S. Gut epithelial inositol polyphosphate multikinase alleviates experimental colitis via governing tuft cell homeostasis. Cell Mol Gastroenterol Hepatol 2022;14:1235–1256.

5. Hendel SK, Kellermann L, Hausmann A, Bindslev N, Jensen KB, Nielsen OH. Tuft Cells and Their Role in Intestinal Diseases. Front Immunol 2022;13: 822867.

6. Haber AL, Biton M, Rogel N, Herbst RH, Shekhar K, Smillie C, Burgin G, Delorey TM, Howitt MR, Katz Y, Tirosi I, Beyaz S, Dionne D, Zhang M, Raychowdhury R, Garrett WS, Rozenblatt-Rosen O, Shi HN, Yilmaz O, Xavier RJ, Regev A. A single-cell survey of the small intestinal epithelium. Nature 2017;551(7680):333–339.

7. Hatch AJ, Odom AR, York JD. Inositol phosphate multikinase dependent transcriptional control. Adv Biol Regul 2017;64:9–19.

8. Ito M, Fujii N, Wittwer C, Sasaki A, Tanaka M, Bittner T, Jessen HJ, Saiardi A, Takizawa S, Nagata E. Hydrophilic interaction liquid chromatography-tandem mass spectrometry for the quantitative analysis of mammalian-derived inositol poly/phosphates. J Chromatogr A 2018;1573:87–97.

9. Qiu D, Wilson MS, Eisenbeis VB, Harmel RK, Riener E, Haas TM, Wittwer C, Jork N, Gu C, Shears SB, Schaff G, Kammerer B, Fiedler D, Saiardi A, Jessen HJ. Analysis of inositol phosphate metabolism by capillary electrophoresis electrospray ionization mass spectrometry. Nat Commun 2020;11(1):6035.

**Correspondence**
Address correspondence to: Adolfo Saiardi, PhD, Medical Research Council, Laboratory for Molecular Cell Biology, University College London, Gower Street, London, WC1E 6BT United Kingdom. e-mail: a.saiardi@ucl.ac.uk.

**Conflicts of interest**
The author discloses no conflicts.

**Funding**
Adolfo Saiardi’s laboratory is supported by Medical Research Council grant MR/T028904/1.

**Most current article**
© 2022 The Author. Published by Elsevier Inc. on behalf of the AGA Institute. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). 2352-345X
https://doi.org/10.1016/j.jcmgh.2022.09.001