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EDITORIAL

Ptpn2: A Critical Regulator of Paneth Cell Homeostasis

Paneth cells are terminally differentiated secretory intestinal epithelial cells that provide many important functions for the small intestine, such that they have been called "maestros of the small intestinal crypts."[1] Paneth cells play a critical role in mucosal innate immunity through synthesis and secretion of antimicrobial peptides (AMPs), such as lysozyme, α-defensins (cryptdins in mice), and secretory phospholipase A_2 that shape the gut microbiota composition and, in turn, modulate host/microbiota interaction. Residing at the base of the crypts interspersed between Lgr5+ stem cells, Paneth cells also secrete factors necessary for homeostasis of neighboring intestinal stem cells, such as epidermal growth factor, Notch ligands, WNT3, and lactate.[2] Some 20%–50% of patients with Crohn's disease manifest Paneth cell defects, which correlate with worse clinical outcomes and gut microbiota dysbiosis.[3,4] Several Crohn's disease susceptibility genes integrate into cellular processes that converge on Paneth cell homeostasis including autophagy, endoplasmic reticulum (ER) stress, and bacterial sensing.[5]

Several single-nucleotide polymorphisms in the protein tyrosine phosphatase nonreceptor type 2 (*PTPN2*) gene locus are associated with inflammatory bowel disease, including Crohn's disease.[6] *PTPN2* encodes T-cell protein tyrosine phosphatase (TCPTP), which inactivates many targets via dephosphorylation, including epidermal growth factor receptor, Src family kinases, and JAK-STATs. Previous studies have provided insight on the crucial role of *PTPN2* in intestinal homeostasis including regulation of proinflammatory cytokine secretion, autophagy, intestinal epithelial barrier function, and gut microbiota homeostasis.[7,8] In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Canale et al[9] defined the role of *PTPN2* in Paneth cell homeostasis.

Using *Ptpn2* knockout (KO) mice, the investigators demonstrate Paneth cell dysfunction with decreased Paneth cell numbers, decreased AMPs produced by Paneth cells (lysozyme, cryptdin-1), inability to form cytosolic secretory granules, and increased Muc2 expression suggesting an immature Paneth cell phenotype in *Ptpn2*-KO ileum. Paneth cells of *Ptpn2*-KO mice harbored ER stress, which when persistent, has been shown to drive Paneth cell dysfunction.[10] This was accompanied with an increase of proliferative ileal epithelial cells but no indication of epithelial cell apoptosis, autophagy impairment, nor alteration to intestinal stem cell function/marker expression. Expression of fibroblast growth factor receptor 3 (*Fgfr3*), involved in the commitment of Paneth cell differentiation, was decreased in *Ptpn2*-KO mice. Importantly, numerous immune cells that supply stimulatory factors required for Paneth cell maturation and AMP secretion were present in *Ptpn2*-KO ileum and AMPs not specific to Paneth cells (*Reg3b* and *Reg3g*) were unchanged, suggesting a selective effect of *Ptpn2*-KO on Paneth cell function.

To further test epithelial-intrinsic responses during *Ptpn2* deletion, the investigators assessed Paneth cells in mice with inducible deletion of *Ptpn2* specifically in intestinal epithelial cells ($Ptpn2^{\Delta IEC}$). Unlike whole-body *Ptpn2*-KO mice, Paneth cell numbers, cytosolic secretory granules, Muc2 staining, and ER stress markers were unchanged in $Ptpn2^{\Delta IEC}$ mice. However, similar to *Ptpn2*-KO mice, lysozyme expression was decreased in $Ptpn2^{\Delta IEC}$ mice. These results suggest that epithelial *Ptpn2* is critical for lysozyme expression but is not necessary for homeostasis of Paneth cell numbers. The depletion of Paneth cells in *Ptpn2*-KO mice is likely driven by nonepithelial cells, such as immune cells, and is not epithelial-induced based on homeostatic Paneth cell numbers in $Ptpn2^{\Delta IEC}$ mice. Additionally, given no alteration of intestinal stem cell function nor stem cell marker expression, the Paneth cell depletion during *Ptpn2*-KO is likely not the result of Paneth cell dedifferentiation to a more stem-like phenotype and instead because of a dampening of their maturation. These immature Paneth cells exhibited ER stress and dysfunction. Many other mouse models manifesting Paneth cell dysfunction also noted an immature Paneth phenotype.[11-13]

At the transcriptional level, the regulators of Paneth cell differentiation from stem cells have been largely defined.[2] Canale et al[9] demonstrate an important role of post-transcriptional regulation via dephosphorylation by TCPTP in Paneth cell health and maturation. It remains unknown whether this action of TCPTP is direct on known regulators of Paneth cell differentiation; indirect via other TCPTP substrates; or via dampening stress pathways Paneth cells are highly susceptible to, such as ER stress. An important next step is to assess Paneth cells for defects in patients with inflammatory bowel disease with *PTPN2* single-nucleotide polymorphisms to corroborate their findings in *Ptpn2* deficient mice. This study by Canale et al[9] suggests targeting underlying Paneth cell defects (restoration of AMPs, dampening of ER stress) could provide a potential therapy in patients with inflammatory bowel disease carrying *PTPN2* variants.

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