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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

# DeMISTifying Paneth Cell Maturation

Paneth cells contribute to the maintenance of the enteric microbiome and the intestinal stem cell microenvironment by secreting numerous antimicrobial factors and growth factors. Their secretory function depends on induction and maintenance of subcellular secretory architecture via unknown mechanisms. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Dekaney et al[1] show that the basic helix-loop-helix Class A basic helix-loop-helix protien 15 (BHLHA15)/Muscle, Intestine, and Stomach expression 1 (MIST1) (BHLHA15) helps govern secretory function in Paneth cells.

Paneth cells play key roles in the small intestine. They shape the enteric microbiome by secreting antimicrobial peptides,[2] and they may collaborate with mesenchymal telocytes to support adjacent intestinal stem cells in the crypts during homeostasis and after regeneration.[3] The transcriptional regulators that dictate Paneth cell differentiation from stem cells have largely been characterized[4,5]; however, it has not been clear how the elaborate secretory machinery is induced and maintained throughout the relatively long lifespan of these cells. In addition, there is limited understanding of so-called *intermediate cells*, which may be precursors for Paneth and goblet cells and express markers of both those lineages.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Dekaney et al[1] make important steps toward increasing our understanding of Paneth and intermediate cells. Similar to pancreatic acinar and gastric chief cells, Paneth cells have long lifespans and elaborate exocrine secretory machinery. Dekaney et al[1] reasoned that Paneth cells also might share dependence on the basic loop helix transcription factor BHLHA15 (MIST1), which regulates maturation and secretory architecture in acinar and chief cells.[6–10] Accordingly, they showed that Paneth cells lacking MIST1 have altered secretory machinery with disorganized, swollen, rough endoplasmic reticulum (ER) cisternae and decreased diameter of secretory granules. Loss of MIST1 does not otherwise disrupt cell fate decisions of any other intestinal lineage besides Paneth cells, and upstream transcription factors that coordinate to specify differentiation of Paneth cells from stem cells, including *Spdef*, *Sox9*, and *Gfi3*, are similarly unaffected. However, failed maturation of Paneth cells causes an increase in cells harboring an intermediate phenotype (ie, cells in *Mist1*$^{-/-}$ crypts co-expressed goblet and Paneth markers), suggesting that MIST1-governed maturation of the secretory apparatus in Paneth cells is required for the cells to quench goblet cell gene expression.

Inhibition of Notch signaling, which disrupts lineage fate decisions, also causes intermediate cell increase.[11] However, Dekaney et al[1] found no alterations in Notch in the absence of MIST1, indicating that the increased intermediate cell phenotype in *Mist1* null mice likely is owing to defects in cell-autonomous terminal maturation and/or maintenance of Paneth cells, and again is not an effect of cell fate choice. Dekaney et al[1] also previously observed an increase in intermediate cells after doxorubicin-induced damage.[12] In the current article, Dekaney et al[1] found that organoids grown from *Mist1*$^{-/-}$ crypts have increased budding relative to wild-type. They interpreted this as showing that lack of MIST1 does not compromise Paneth cell ability to support stem cells in an ex vivo situation. Alternatively, but not mutually exclusively, disruption of the intestinal epithelium followed by culture ex vivo may induce Paneth cells to revert to a stem cell role,[13,14] consistent with an emerging role for plasticity of mature cells in regeneration.[15] Perhaps *Mist1*$^{-/-}$ Paneth cells, with their more intermediate cell phenotype, have more potential to revert to stem or progenitor cells after stress similar to doxorubicin or ex vivo culture in organoids.

Dekaney et al[1] stimulate a number of questions. First, many of the transcriptional targets of MIST1 that help coordinate the secretory phenotype in cells in diverse tissues have been identified (eg, RAB3D and RAB26),[8,16] which are required in Paneth cells? Second, MIST1 has been shown to be regulated by and also regulate the key ER maintaining gene *Xbp1*,[17,18] how much of the Paneth cell phenotype is caused by ER stress? Third, would *Mist1*$^{-/-}$ crypts be better at regenerating after stem cell injury (eg by doxorubicin)? Would any such phenotype occur because Paneth cells themselves are key sources of cells and/or because *Mist1*$^{-/-}$ Paneth cells support actual stem cells differentially? It seems relevant to note that it may not be a coincidence that many of the mature cells already described to be able to re-enter the cell cycle after injury express MIST1 and then rapidly scale it down as they scale down their mature cell architecture. It has been proposed that there may be universal mechanisms for recruiting mature cells back into the cell cycle (a process termed *paligenosis*).[19] MIST1-mediated downscaling may be a critical aspect of paligenosis of secretory cells.

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