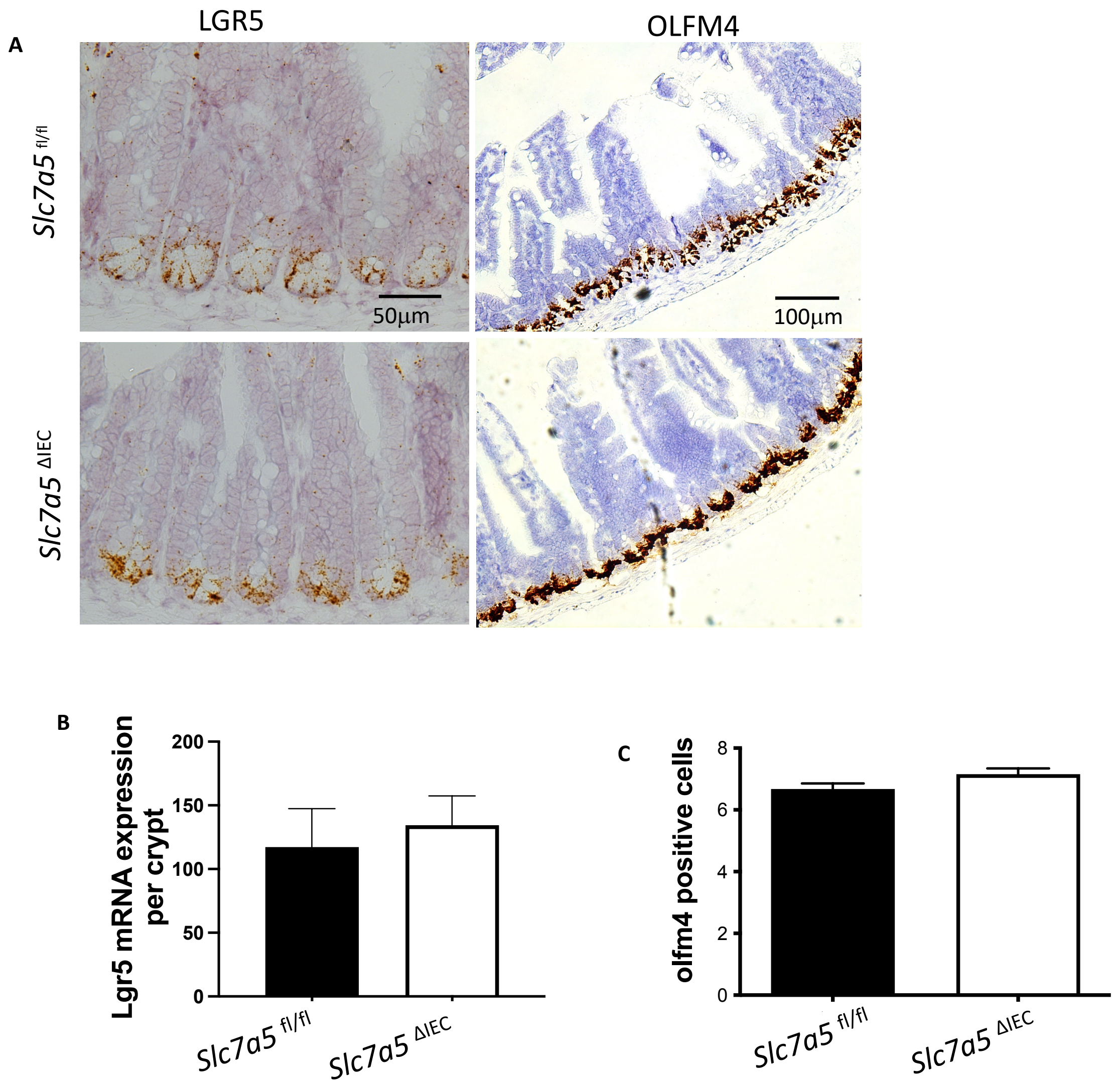


Supplementary Figure 1



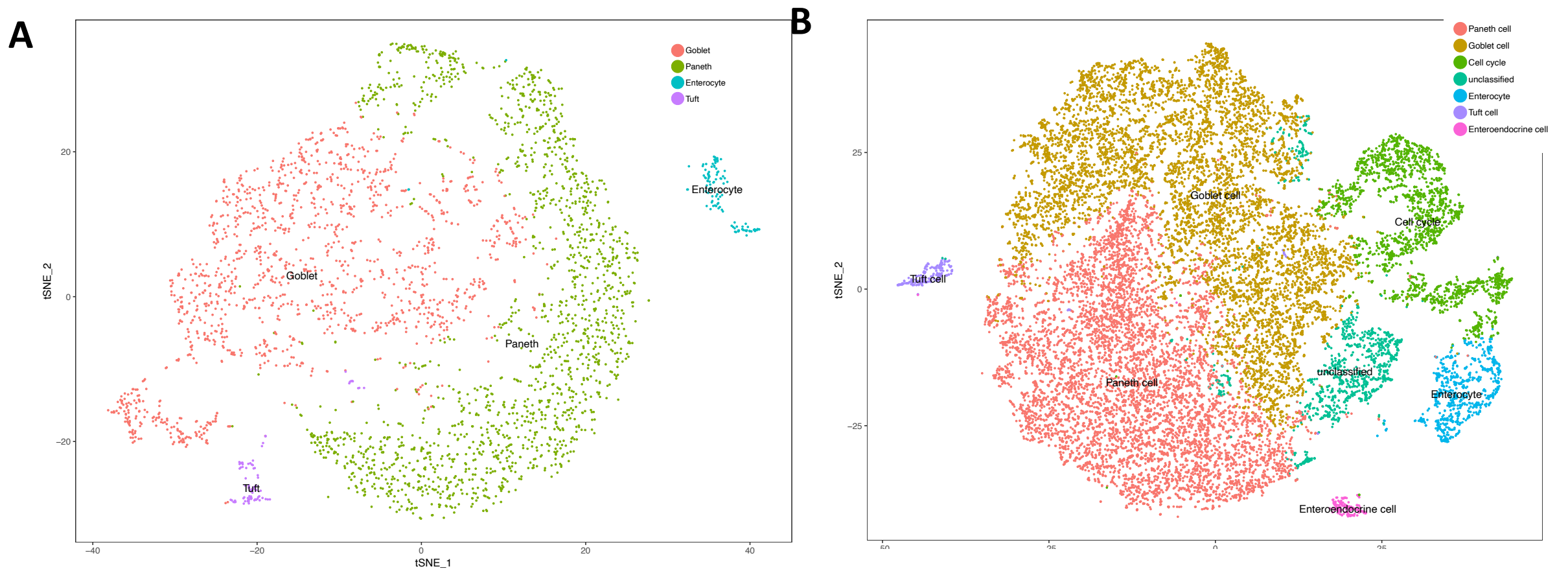
**Supplementary Figure 1. *Slc7a5*<sup>ΔIEC</sup> does not affect stem cell marker gene expression in the crypt.**

**A.** Representative pictures of LGR5 and OLFM4 single molecule in situ hybridization.

**B-C.** Quantification of the in situ hybridization data showed that *lgr5* mRNA level (**B**) and OLFM4+stem cell numbers (**C**) were similar between *Slc7a5*<sup>fl/fl</sup> and *Slc7a5*<sup>ΔIEC</sup> crypts.

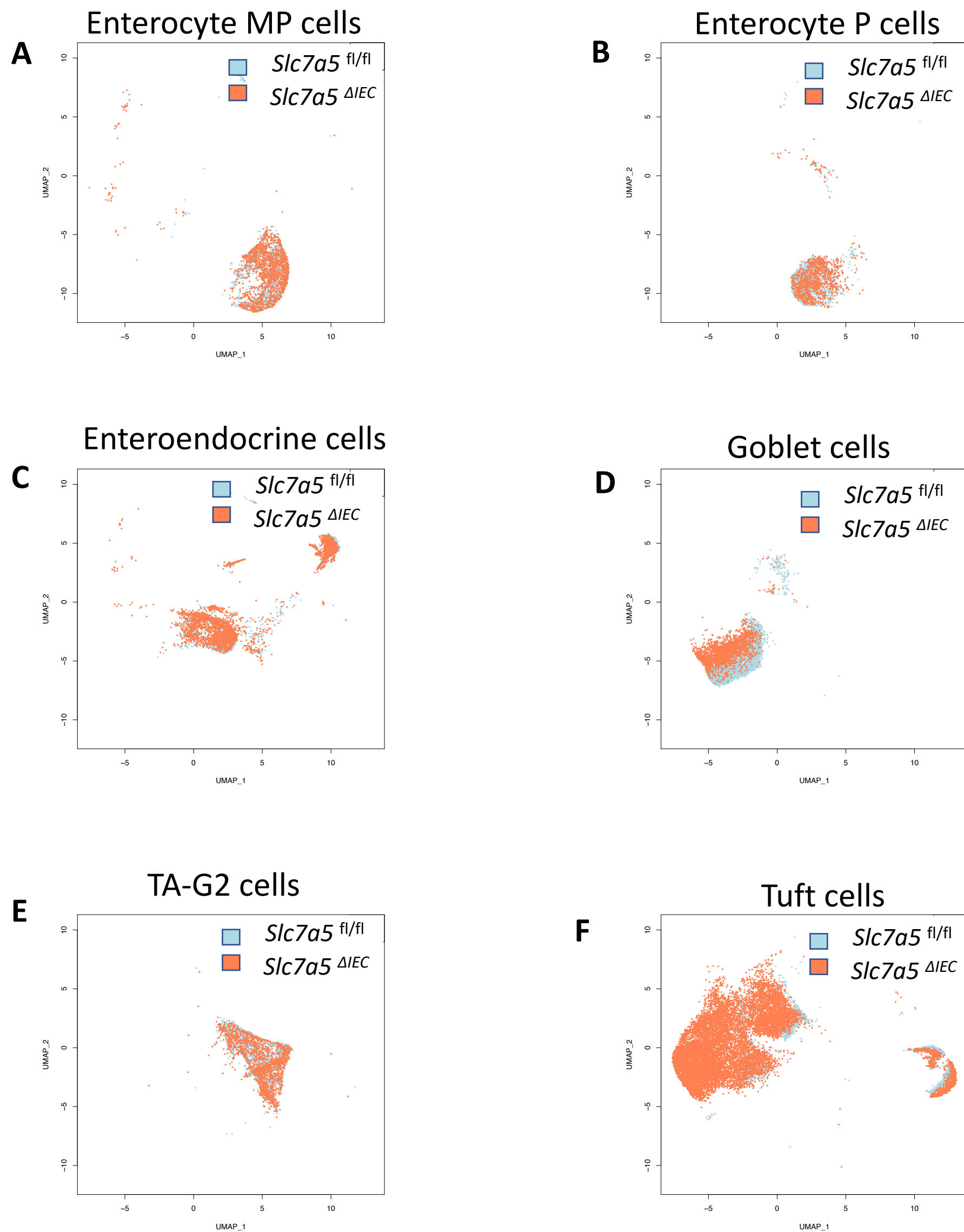


## Supplementary Figure 2



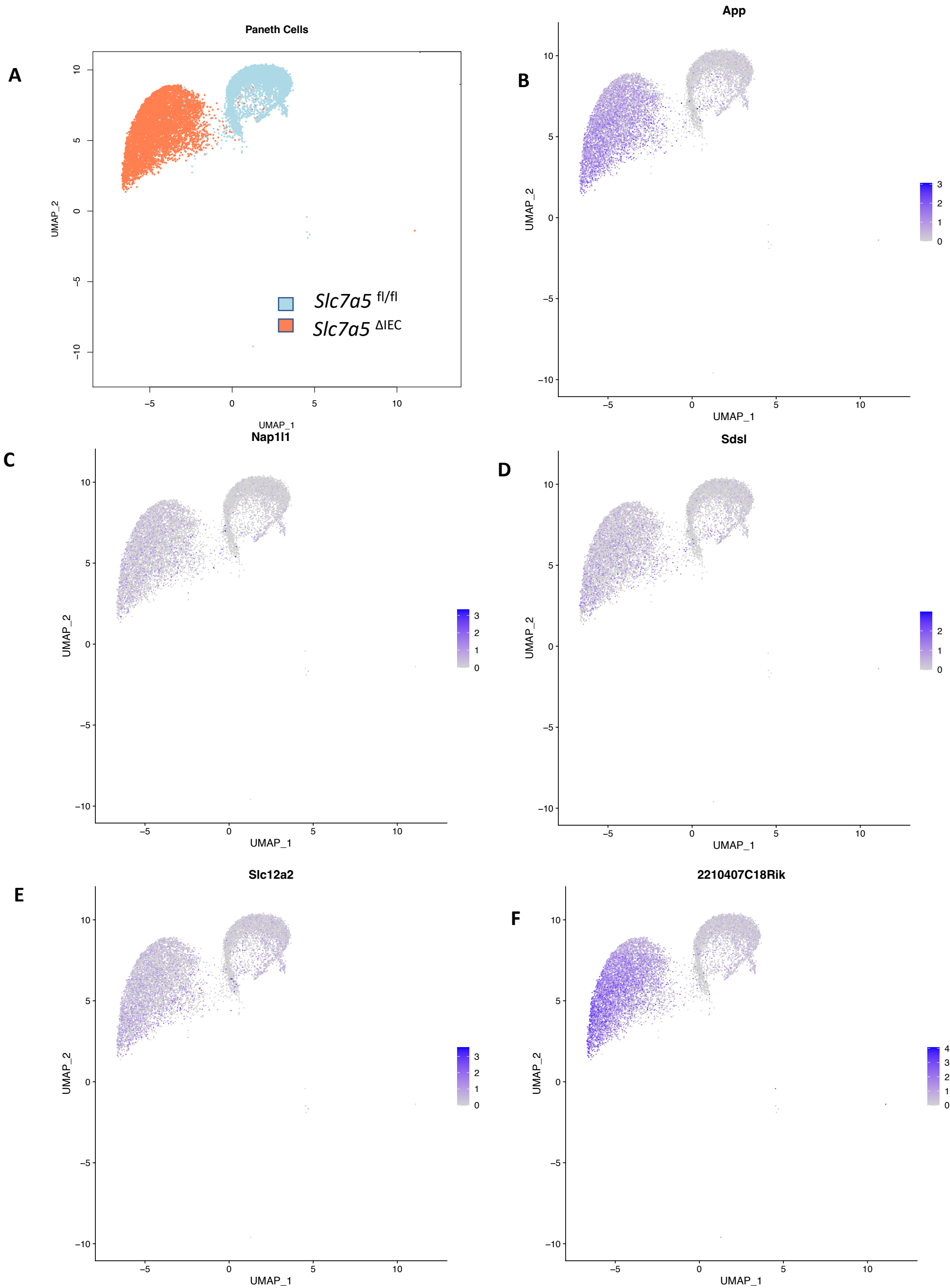
**Supplementary Figure 2. ScRNA-seq analysis.** Epithelial cells from intestinal crypts of *slc7a5*<sup>fl/fl</sup> (A) and *slc7a5*<sup>ΔIEC</sup> (B) mice, respectively, were used for scRNA-seq and the cells for each animal type were clustered based on t-SNE plot of the scRNA-seq data with different cell types shown in different colors (note that the cells in cluster labeled as cell cycle were transit amplifying cells or TA cells).





**Figure s3. Focused views of the regions of the UMAP (Fig. 5C) for the indicated individual epithelial cell types from *slc7a5*<sup>fl/fl</sup> mice (blue dots) and *slc7a5*<sup>ΔIEC</sup> (orange dots) mice. Note that the co-locations of the cells from the *slc7a5*<sup>fl/fl</sup> mice and *slc7a5*<sup>ΔIEC</sup> mice for these cell types suggest little or few changes in gene expression between *slc7a5*<sup>fl/fl</sup> mice and *slc7a5*<sup>ΔIEC</sup> mice.**





**Supplementary Figure 4. UMAP views of increased expression of several stem cell feature genes in the Paneth cells from *Slc7a5*<sup>ΔIEC</sup> mice compared to that in *Slc7a5*<sup>fl/fl</sup> mice.**

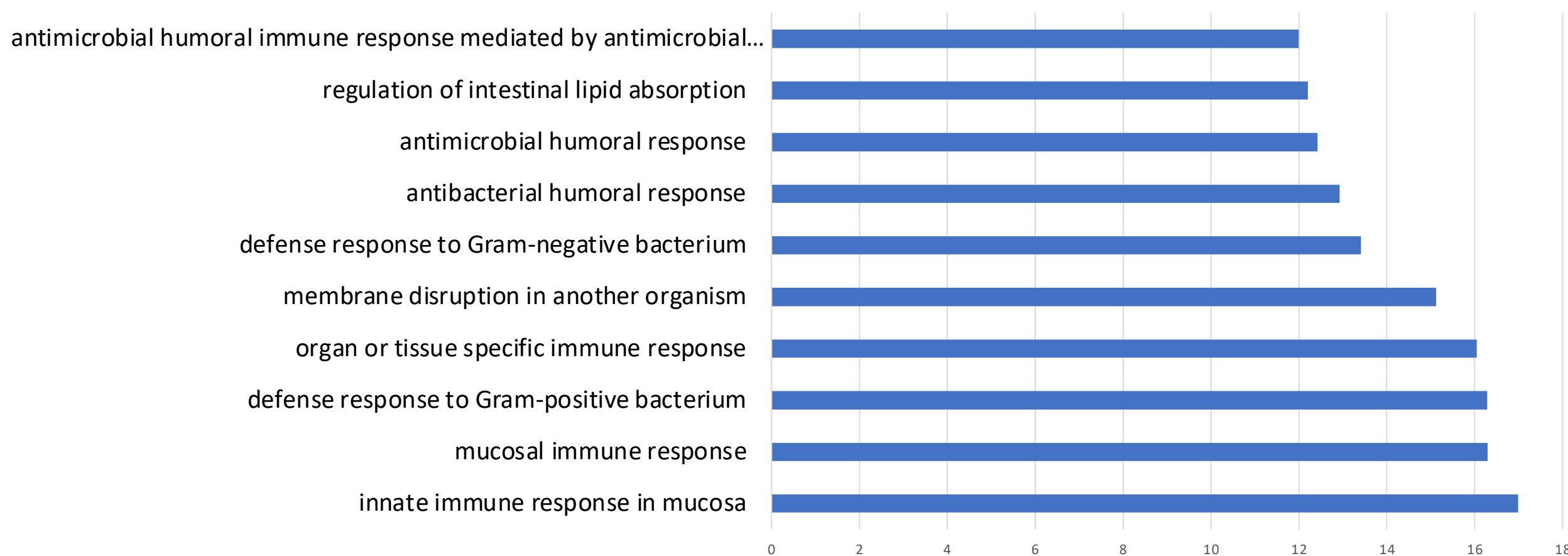
**A.** Same image as in figure 5D to show UMAP regions for Paneth cells from *Slc7a5*<sup>fl/fl</sup> mice (blue dots) and *Slc7a5*<sup>IEC-KO</sup> (orange dots) mice.

**B to F:** The expression levels of 5 stem cell feature genes, App, Nap11, Sdsl, slc12a2 and 2210407C18Rik, in Paneth cells as obtained from scRNA-seq were mapped on to the UMAP, showing higher levels in *Slc7a5*<sup>ΔIEC</sup> mice than those in *Slc7a5*<sup>fl/fl</sup> mice.

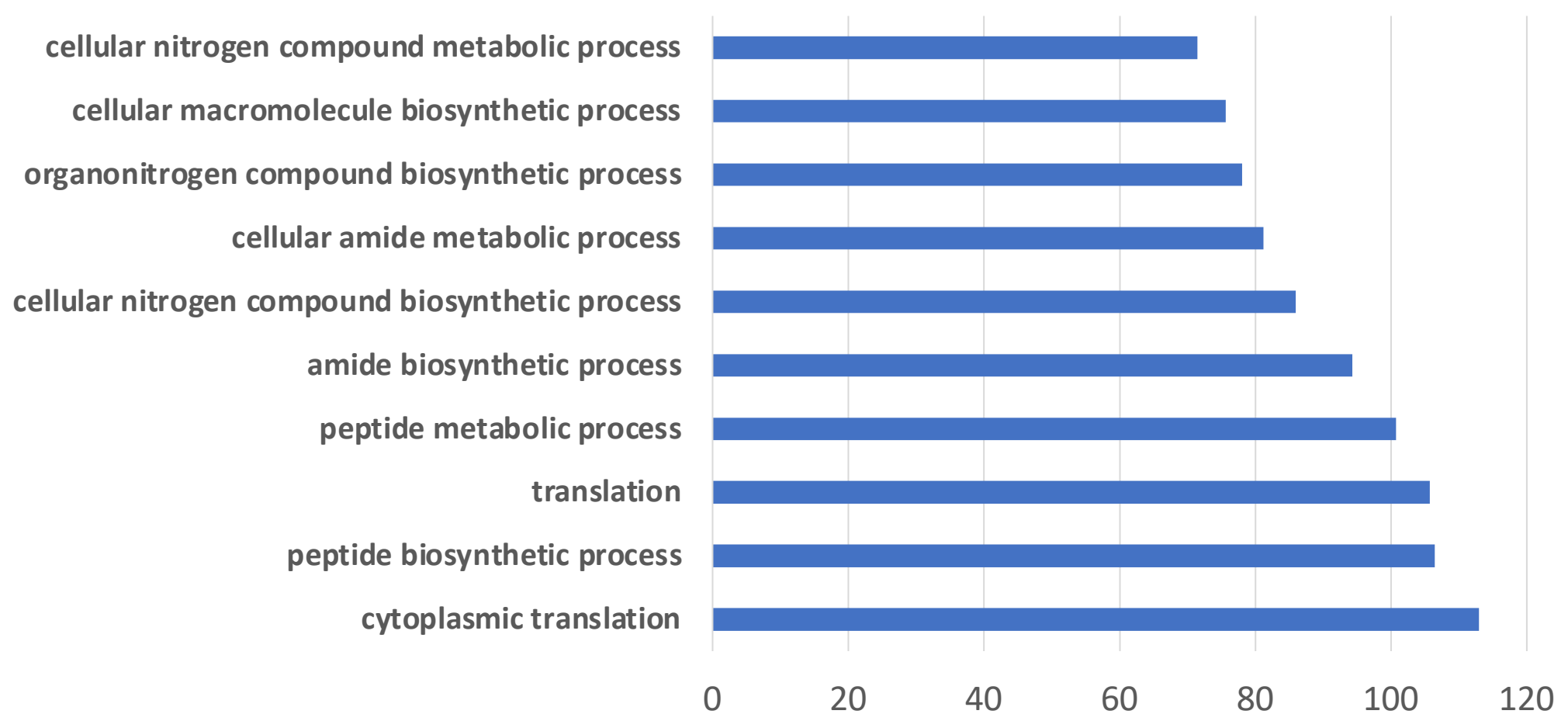
**Supplementary Figure 4**



*Slc7a5*<sup>fl/fl</sup>



*Slc7a5*<sup>ΔIEC</sup>



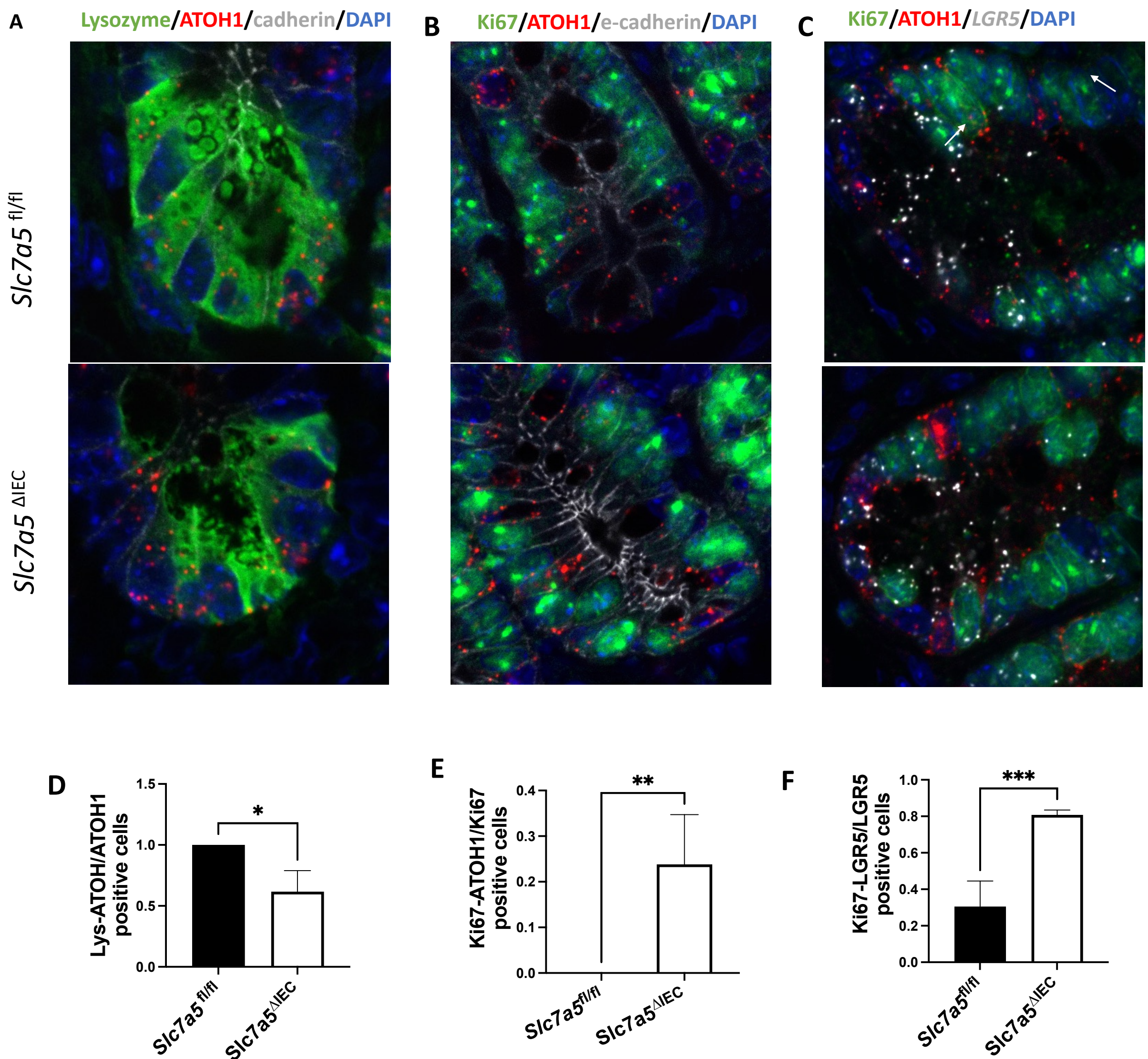
**Supplementary Figure 5. GO analysis of DEGs between *Slc7a5*<sup>fl/fl</sup> mice and *Slc7a5*<sup>ΔIEC</sup> mice's Paneth cell.**

**A.** GO terms related to anti-microbial and immune responses were most significantly enriched among the genes expressed at higher levels in the wild type Paneth cells than those in knockout Paneth cells.

**B.** GO terms related to metabolism and biosynthetic processes were most significantly enriched among the genes expressed at higher levels in the knockout Paneth cells than those in wild type Paneth cells.



## Supplementary Figure 6



### Supplementary Figure 6. Single RNA in situ hybridization and/or immunohistochemical (for lysozyme) analyses of small intestinal crypt base.

**A.** Representative pictures of lysozyme and atoh1 expression at crypt base in *Slc7a5*<sup>fl/fl</sup> and *Slc7a5*<sup>ΔIEC</sup> mice.

**B.** Representative pictures of Ki67 and atoh1 expression at crypt base in *Slc7a5*<sup>fl/fl</sup> and *Slc7a5*<sup>ΔIEC</sup> mice.

**C.** Representative pictures of Ki67, ATOH1, and LGR5 expression at crypt base in *Slc7a5*<sup>fl/fl</sup> and *Slc7a5*<sup>ΔIEC</sup> mice.

**D.** Quantitative analysis of panel A showing that all ATOH1+ cells were lysozyme-positive in *Slc7a5*<sup>fl/fl</sup> mice, while only about 60% ATOH1+ cells were lysozyme positive in *Slc7a5*<sup>ΔIEC</sup> mice.

**E.** Quantitative analysis of panel B showing that Atoh1 were expressed in some proliferating cells in the crypt base of *Slc7a5*<sup>ΔIEC</sup> but not *Slc7a5*<sup>fl/fl</sup> mice.

**F.** Quantitative analysis of panel C showing increased fraction of LGR5+ cells were proliferating in *Slc7a5*<sup>ΔIEC</sup> mice crypt base.