Supplementary Data

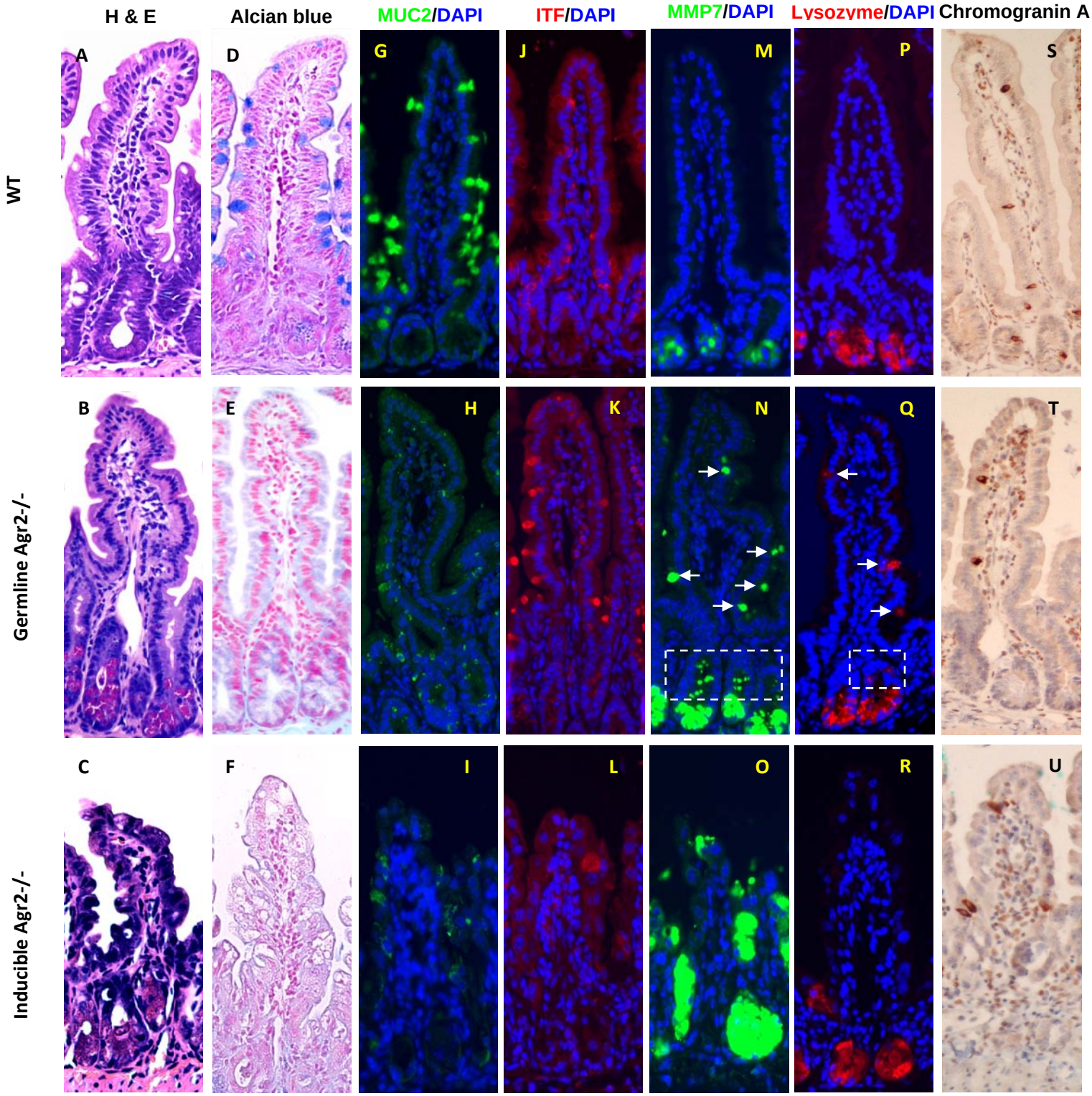


Figure 1. Histology of germline and inducible *Agr2-/-* mice. (A,B,C) Hematoxylin and Eosin staining of small intestine from WT (A), germline (B) and inducible (day5) (C) *Agr2-/-* mice. (A) WT Small intestine epithelium shows normal villous morphology, goblet cell number and distribution; morphologically normal goblet cells are absent in (B) germline *Agr2-/-* and (C) inducible *Agr2-/-* epithelium. There is marked villus atrophy and ileitis in the inducible Agr2-/- mice. **(D,E,F)** Alcian Blue staining for the small intestine from mice. Wild-type mice (D) had numerous Alcian Blue-positive cells, but no Alcian Blue-positive cells are seen in either germline (E) or inducible (F) *Agr2-/-* epithelium. Germline Agr2-/- epithelium is intentionally overstained. **(G,H,I,J,K,L)** Immunofluorescence for MUC2 and ITF in small intestine from mice, both of which are markers for mature goblet cells. MUC2 protein was abundant in WT (G) small intestine and dramatically decreased in both germline (H) and inducible (I) *Agr2-/-* epithelia. ITF protein was detected in WT (J) small intestine, increased in germline (K) *Agr2-/-* epithelium and detected in inducible(L) *Agr2-/-* epithelium. **(M,N,O,P,Q,R)** Immunofluorescence for MMP7 and Lysozyme in small intestine from mice, both of which are markers for mature Paneth cells. MMP7-positive cells were detected in WT (M) small intestine and limited to the bottom of crypts, and its expression was increased in both germline (N) and inducible (O) *Agr2-/-* epithelia. Also, MMP7-positive cells were migrated to the upper of crypts (white dash rectangle) and villi (white arrows) in germline *Agr2-/-* epithelia. Lysozyme-positive cells were detected in WT (P) small intestine and limited to the bottom of crypts, and its expression was increased in both germline (Q) and inducible (R) *Agr2-/-* epithelia. Also, Lysozyme-positive cells were migrated to the upper of crypts (white dash rectangle) and villi (white arrows) in germline *Agr2-/-* epithelia. **(S,T,U)** Immunohistochemistry for Chromogranin A in small intestine from mice. There is no significant difference in expression of Chromogranin A , which is one of the markers for endocrine enterocyte, among the wild type(S), germline Agr2-/-(T) and inducible Agr2-/-(U).

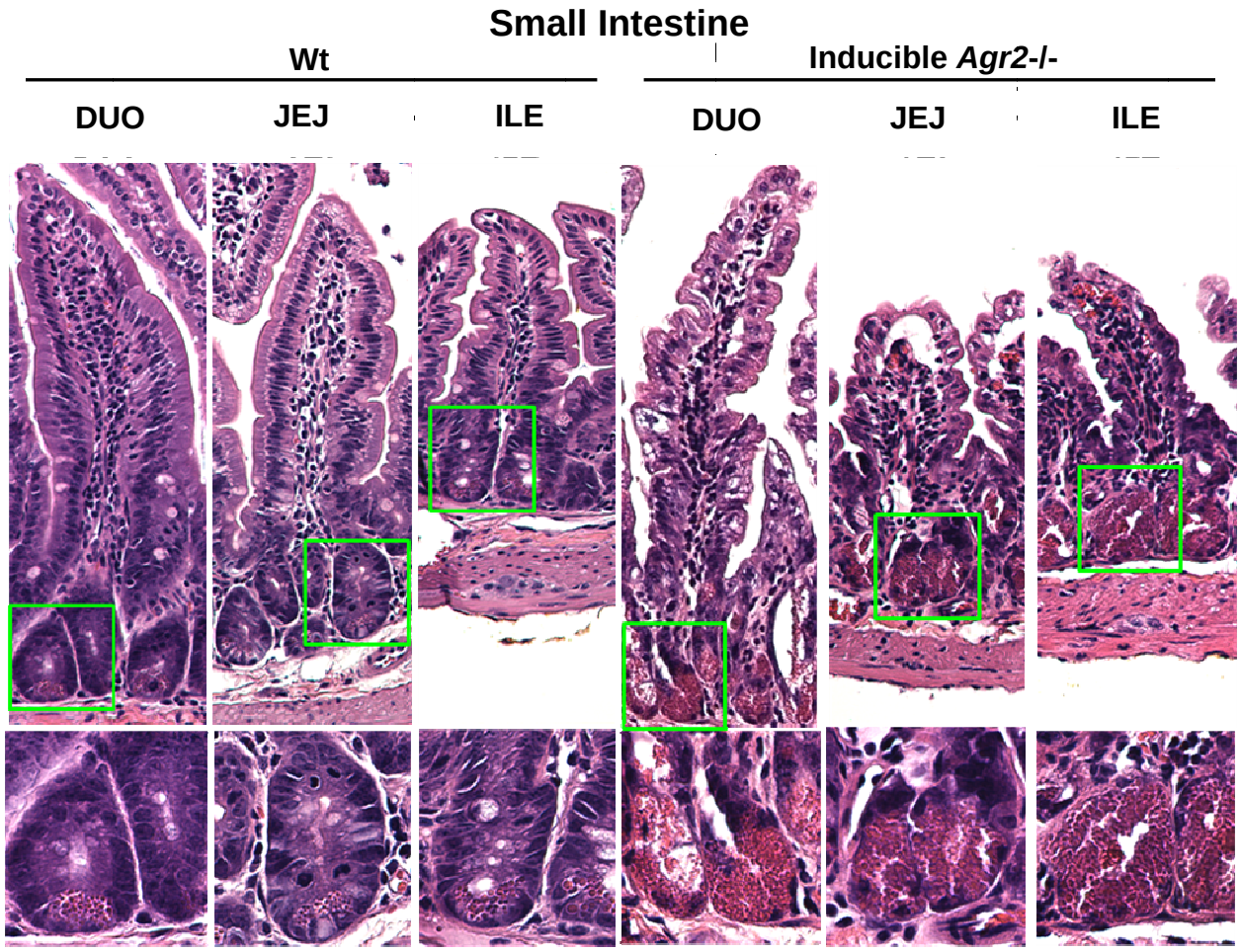


Figure 2. Paneth cells hypertrophy in the duodenum, jejunum and ileum of *Agr2-/-* mice. H+E histochemistry showing increased number of Paneth cells. Paneth cells are morphologically distinguished by eosinophilic granules. An inset is denoted by the green box and is shown at increased magnification in the very bottom panel.

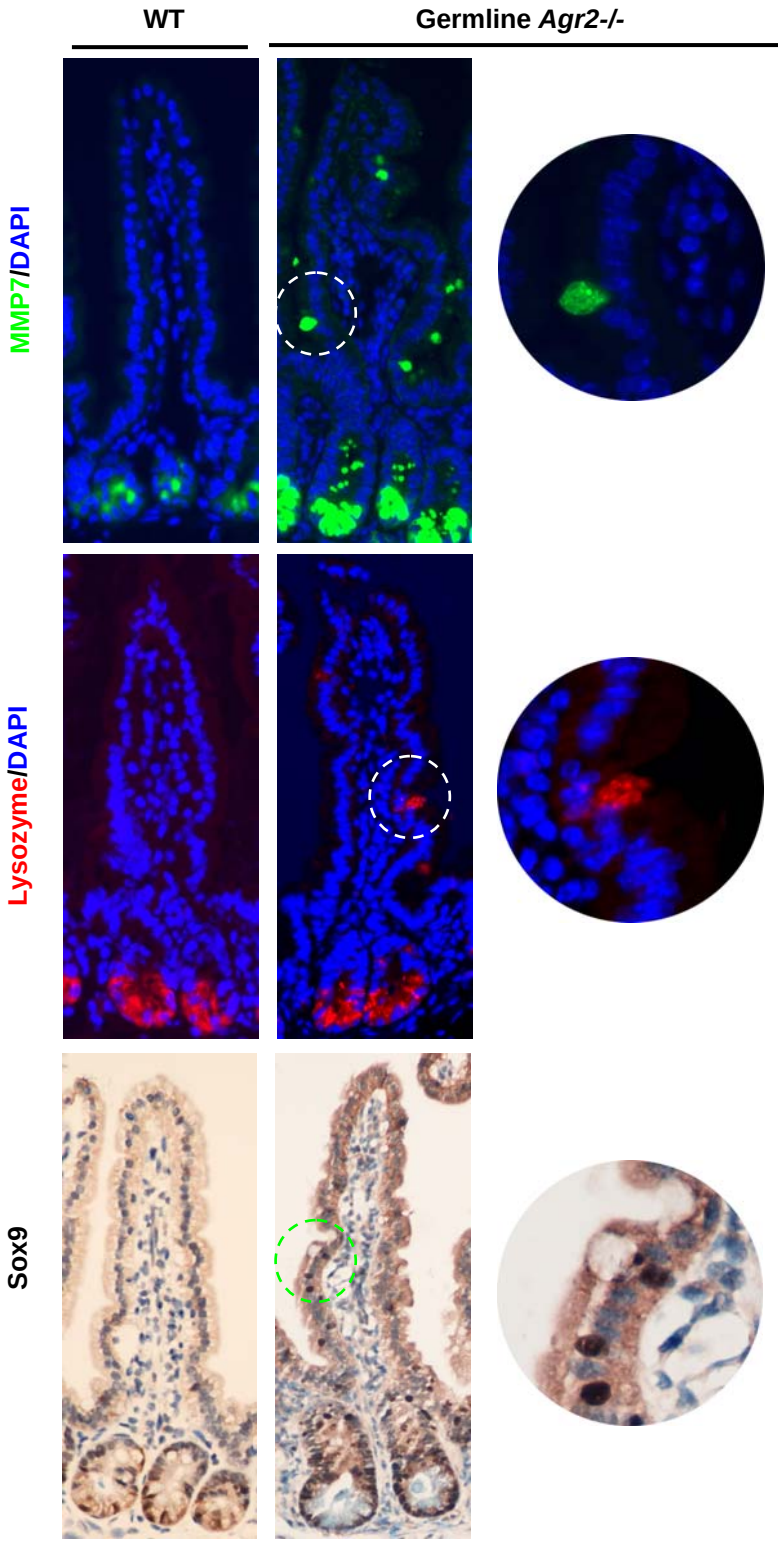
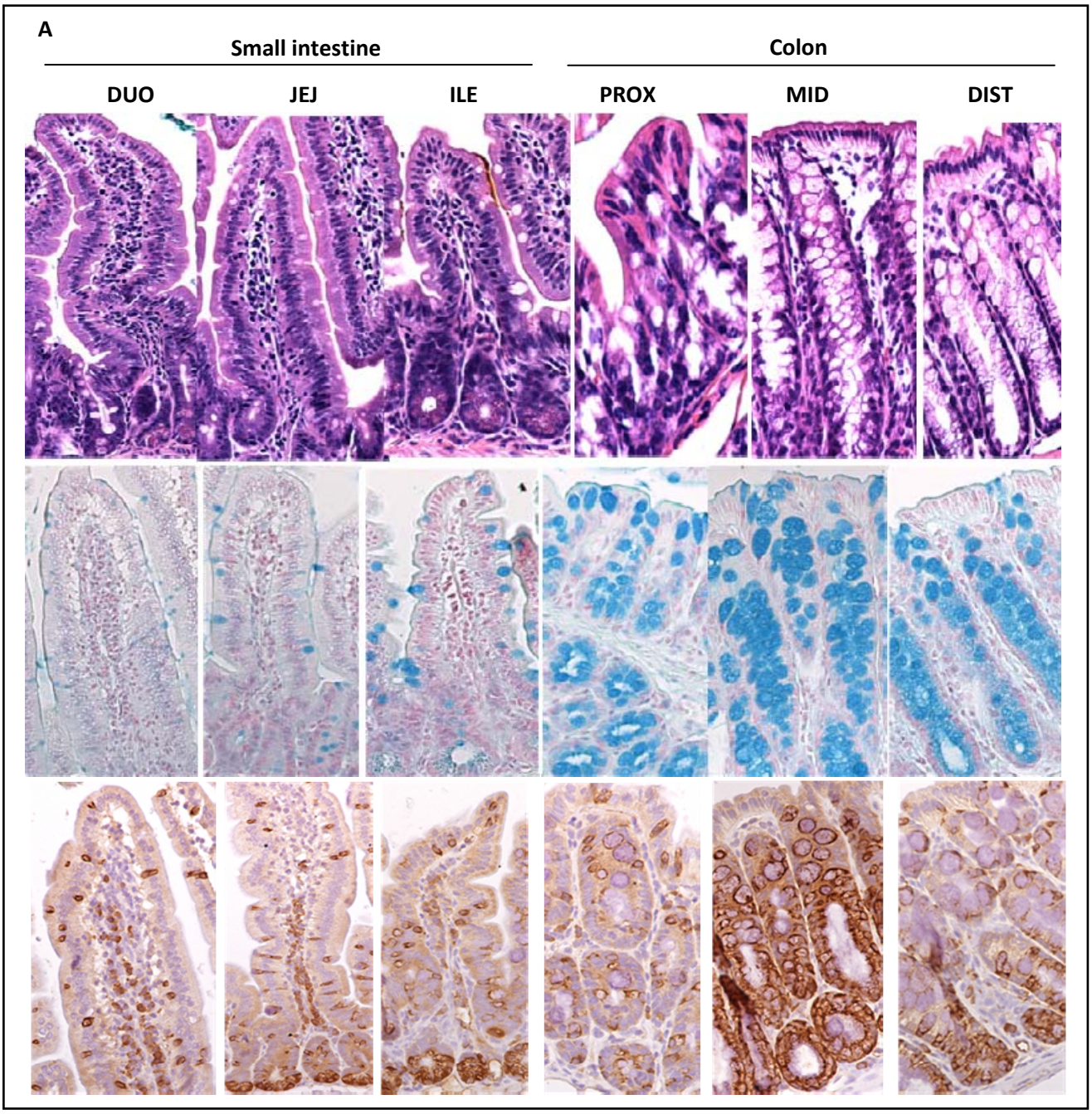


Figure 3. Paneth cell specific marker-positive cells migrate to the villi in germline *Agr2-/-* mice. Paneth cells localized at the base of the crypts of Lieberkühn in the small intestine express Paneth cell markers Sox9, MMP7 and lysozyme in wild type mice (left panel). In germline *Agr2-/-* mice, multiple cells that are immunopositive for Sox9, MMP7 and lysozyme that have migrated to the villi are seen in addition to cells at the crypt base. Sox9 immunostaining is predominantly nuclear (middle panel, higher magnification images are shown in the right panel).



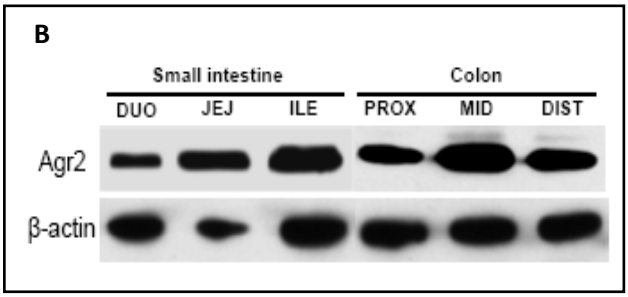


Figure. 4 Agr2 expression gradient in intestine epithelium is consistent with that of mucin-secreted goblet cells (A)Top row shows H+E staining of different parts of mouse intestine. The middle row illustrates mucin expression revealed by Alcian blue (pH2.5) staining. The bottom row is Immunohistochemical staining for *Agr2* which reveals *Agr2* protein is increased from proximal to distal in small intestine and throughout the colon. (B) Agr2 protein expression levels in different parts of mouse intestine by Western blot.

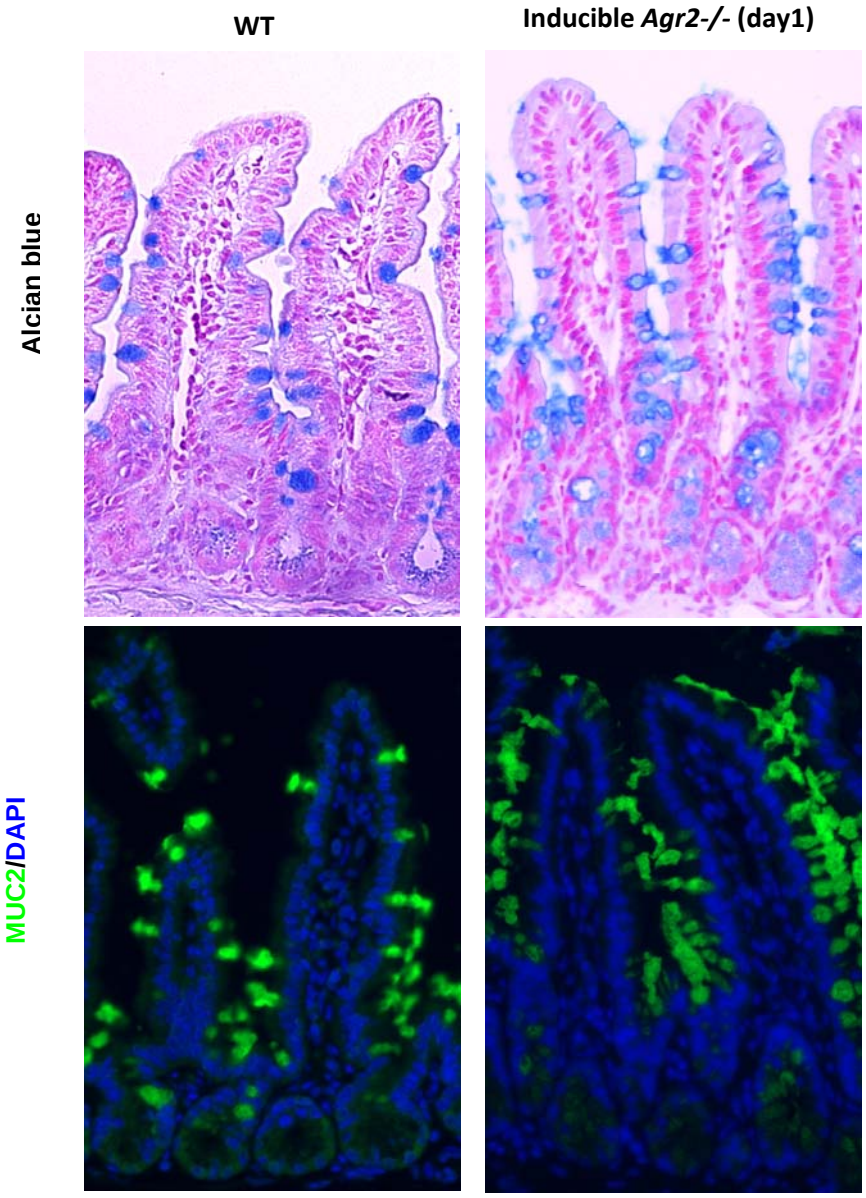


Figure 5. Muc2 and Alcian blue staining in wt and day 1 inducible *Agr2-/-* mice. Compared to Wt mice, Alcian blue and MUC2 positive cells are not decreased in the inducible *Agr2-/-* small intestine at day 1 (24hours after tamoxifen injection).

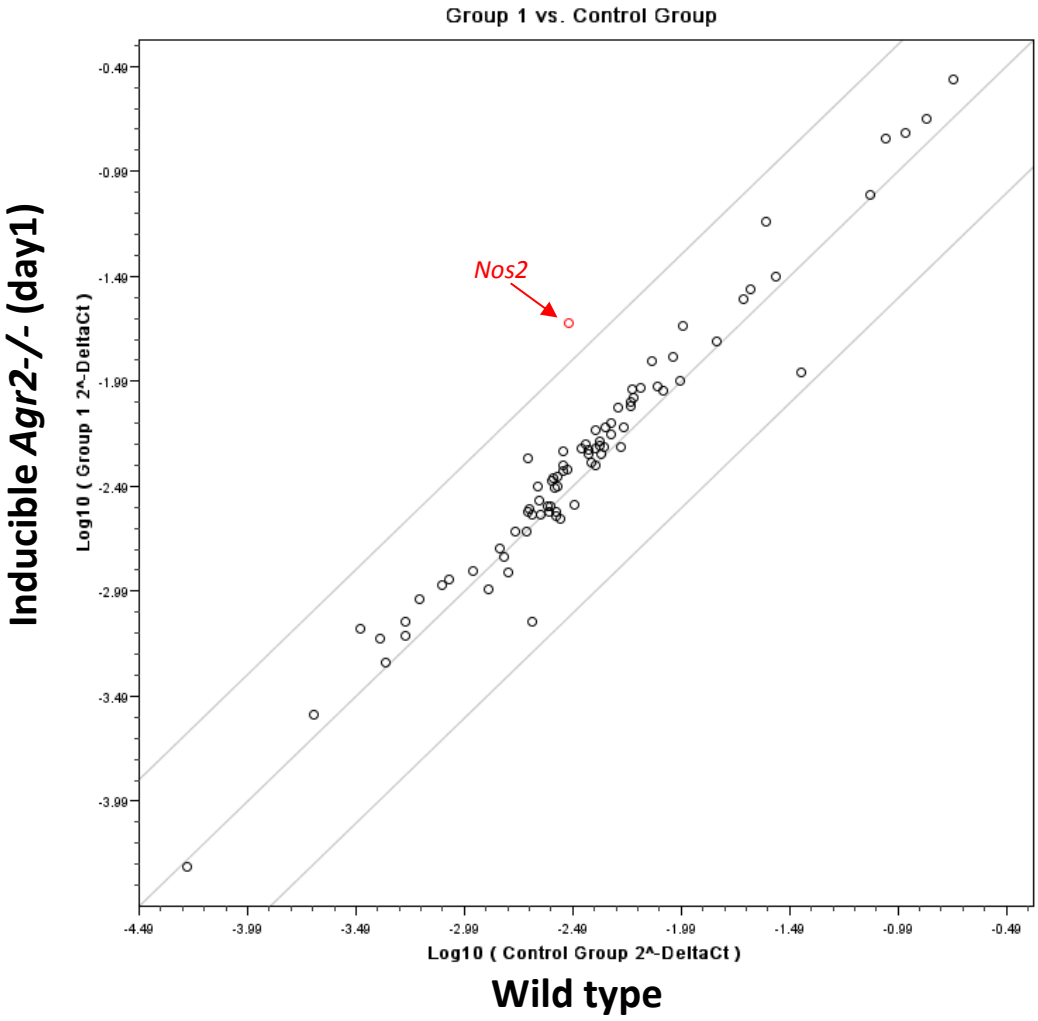


Figure 6. SuperArray expression profile of mouse inflammatory genes in wild type and *Agr2-/-* mice. Expressions of 82 key genes involved in mouse inflammatory responses were analyzed by SYBR green real time RT-PCR using SuperArray RT² Profiler™ PCR Array (catalog: PAMM-077). Data was analyzed by PCR Array Data Analysis Web Portal (http://www.sabiosciences.com/pcrarraydataanalysis.php) and using the default set format. As showing in the above scatter plot, of 82 genes analyzed, there is only one significantly misregulated gene (*Nos2*, fold regulation 6.25) in day1 (24 hours after tamoxifen treatment) inducible *Agr2-/-* small intestine epithelium compared to Wt mice.

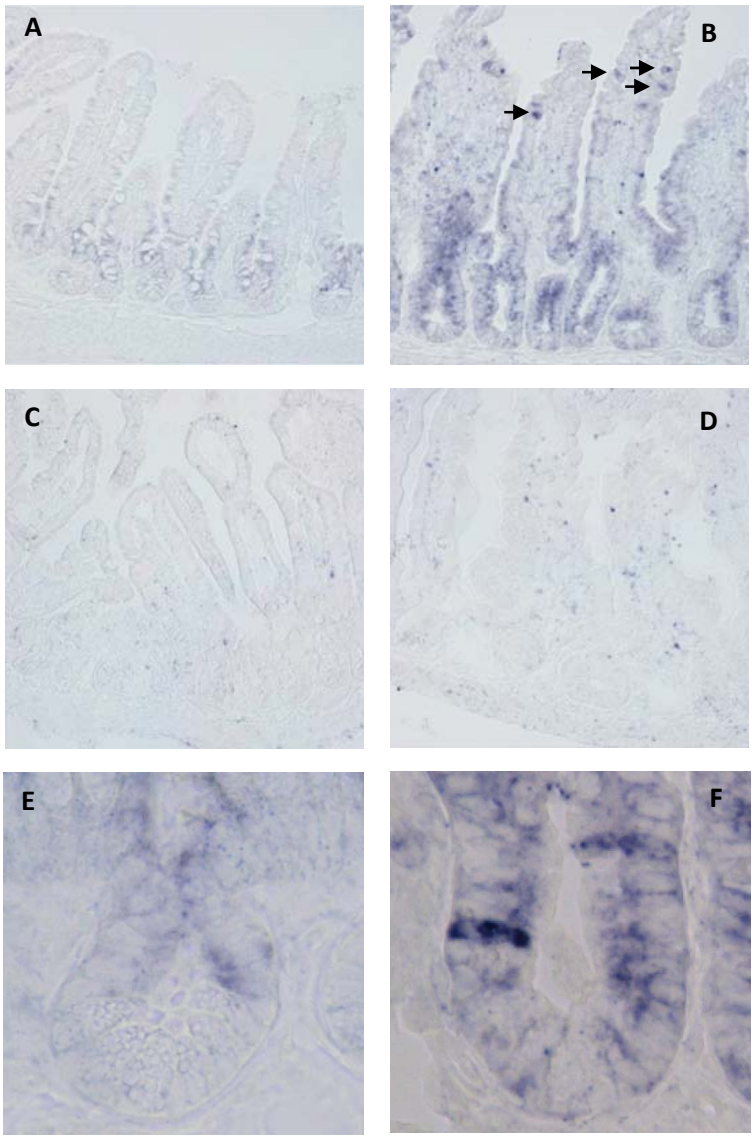


Figure 7. BiP expression increased in germline *Agr2-/-* mice. Digoxigenin-labeled antisense RNA probe and sense control probe specific for BiP were hybridized to 10-µm frozen sections of small intestine derived from wild type and germline *Agr2-/-* mice. Hybridization signal of BiP antisense probe was detected in the upper crypt and crypt-villus junction in wild type mice (**A**). The intensity of BiP antisense probe in the same region was increased in germline *Agr2-/-* mice (**B**). Additionally, BiP hybridization signals are increased in some epithelia cells in the upper villi (**B, black arrows**) as well as cells adjacent to Paneth cells both near and at the crypt base in germline *Agr2-/-* intestine (**F**). No detectable signal was seen at the wild type crypt base (**E**). No expression was detected with BiP sense control probe in either wild type (**C**) or germline *Agr2-/-* mice (**D**).

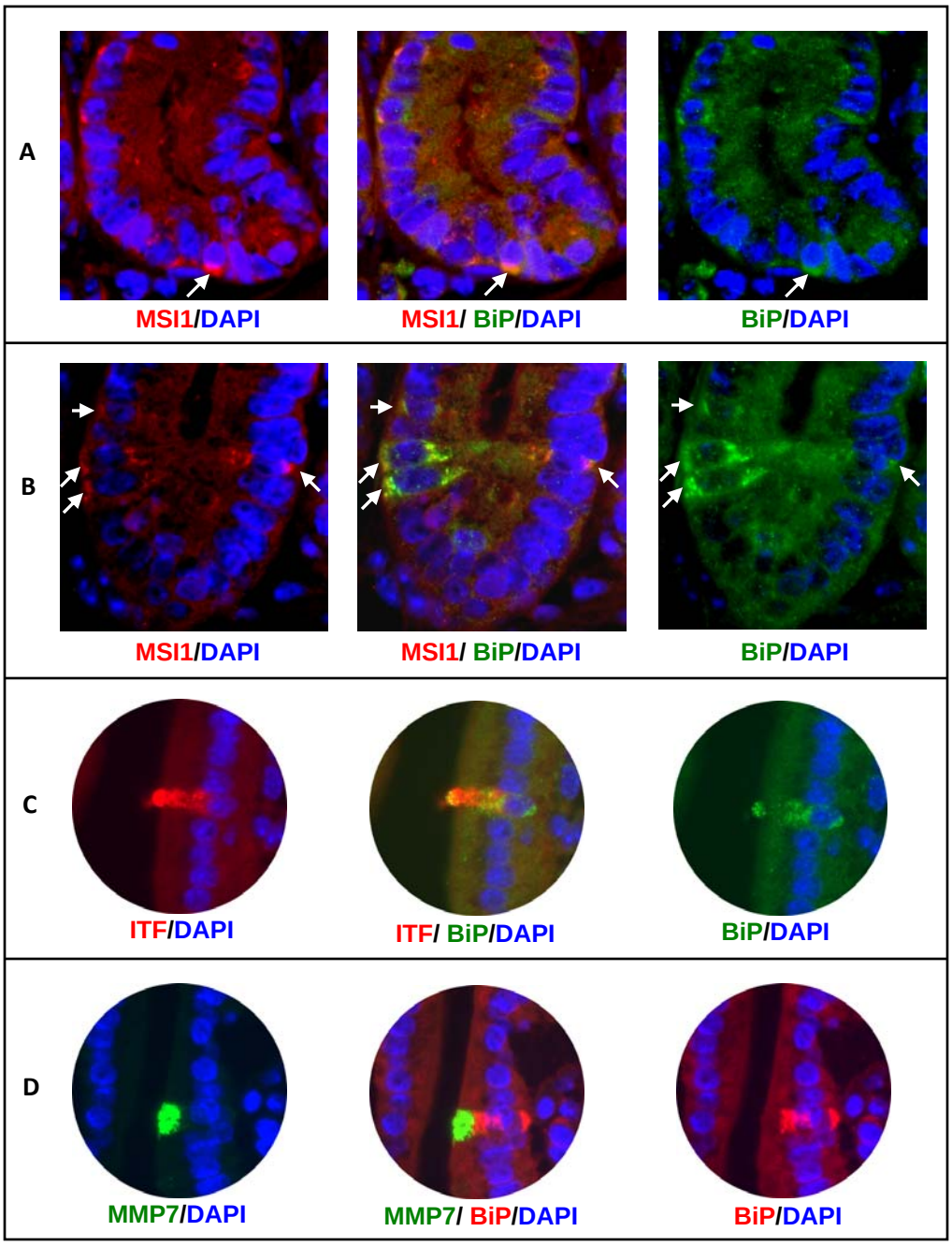


Figure 8. BiP expression pattern in germline *Agr2-/-* small intestine. Immunofluorescence co-staining shows MSI1-positive stem cells at the crypt base (A) and early progenitor cells in the mid-crypt/proliferating zone (B) have increased BiP expression. ITF-positive or MMP7-positive cells in the villi also have increased BiP expression (C, D).