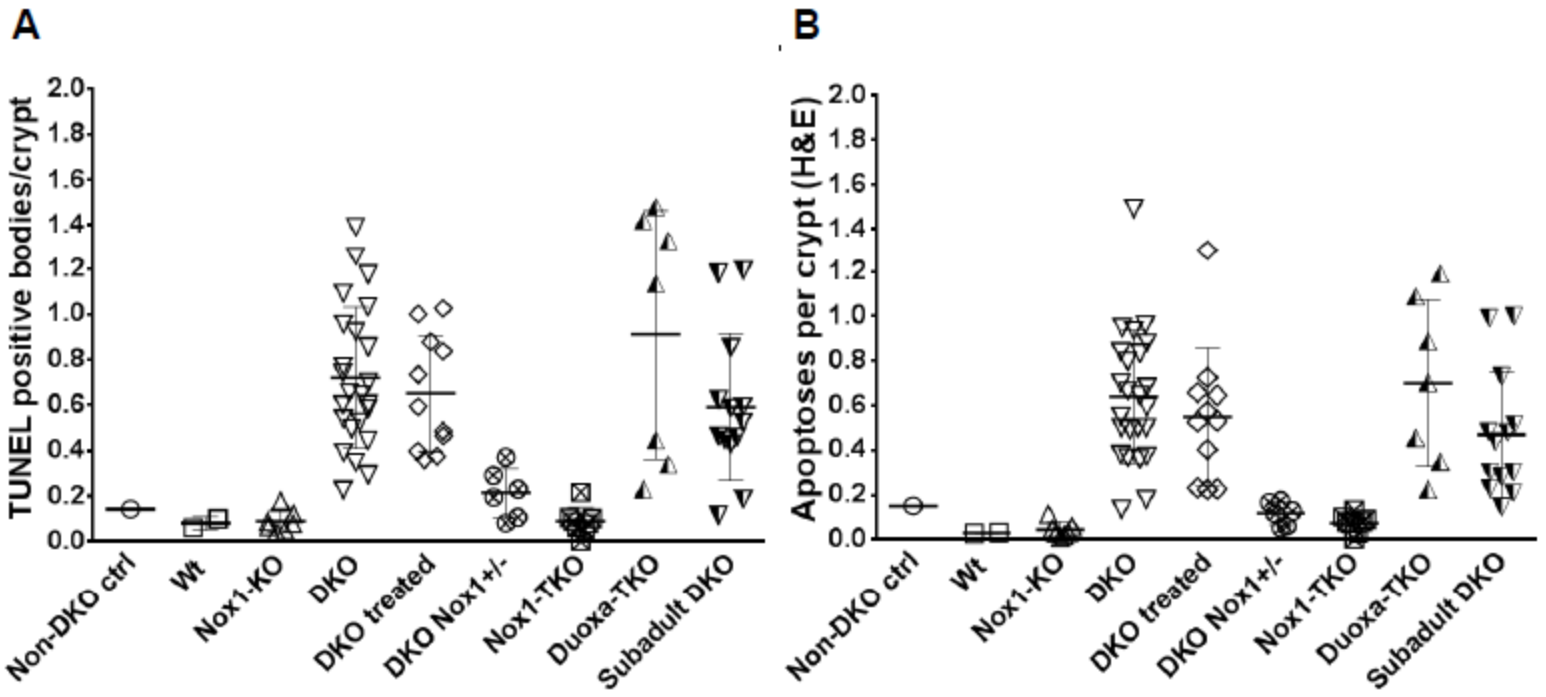
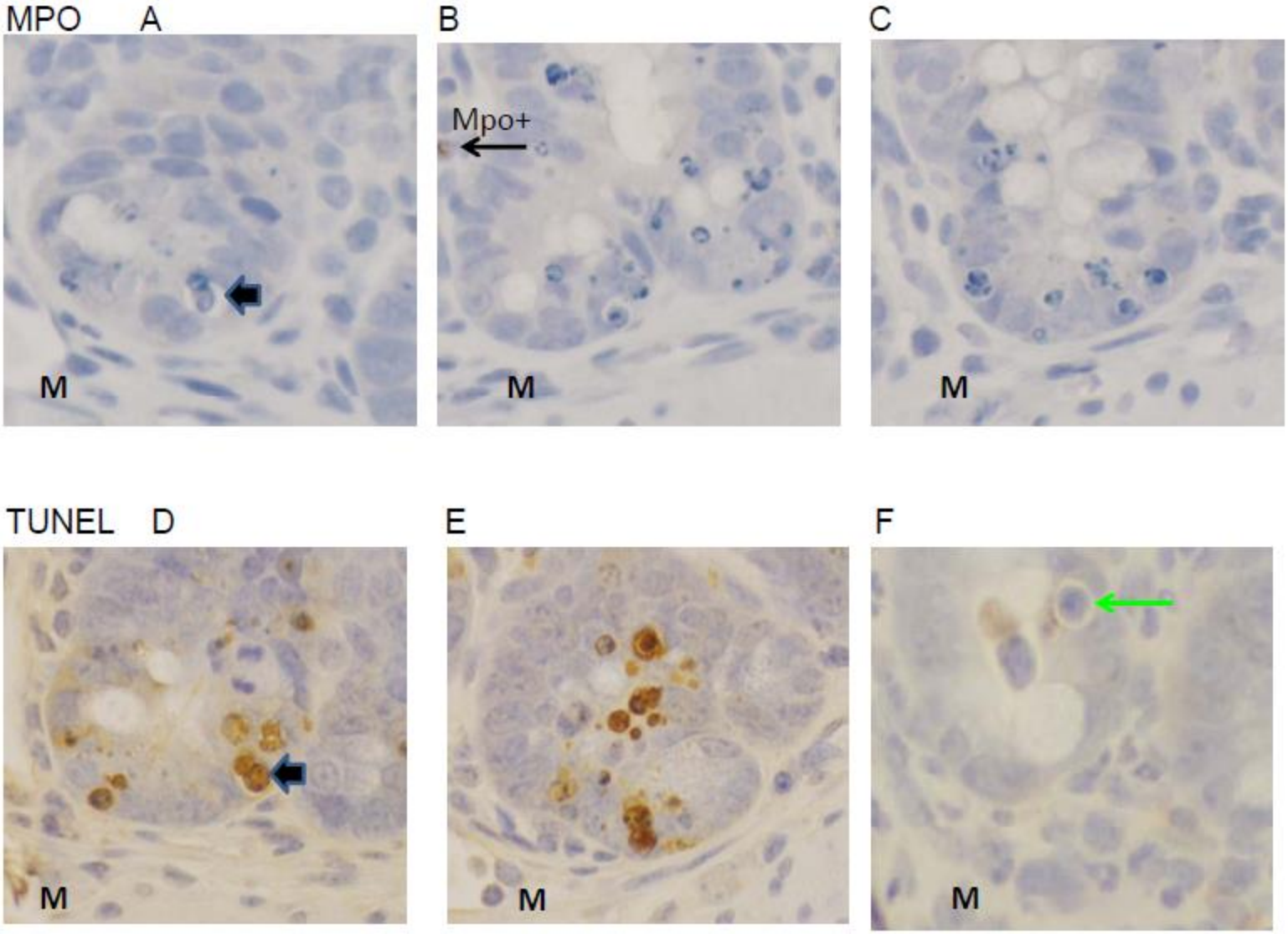
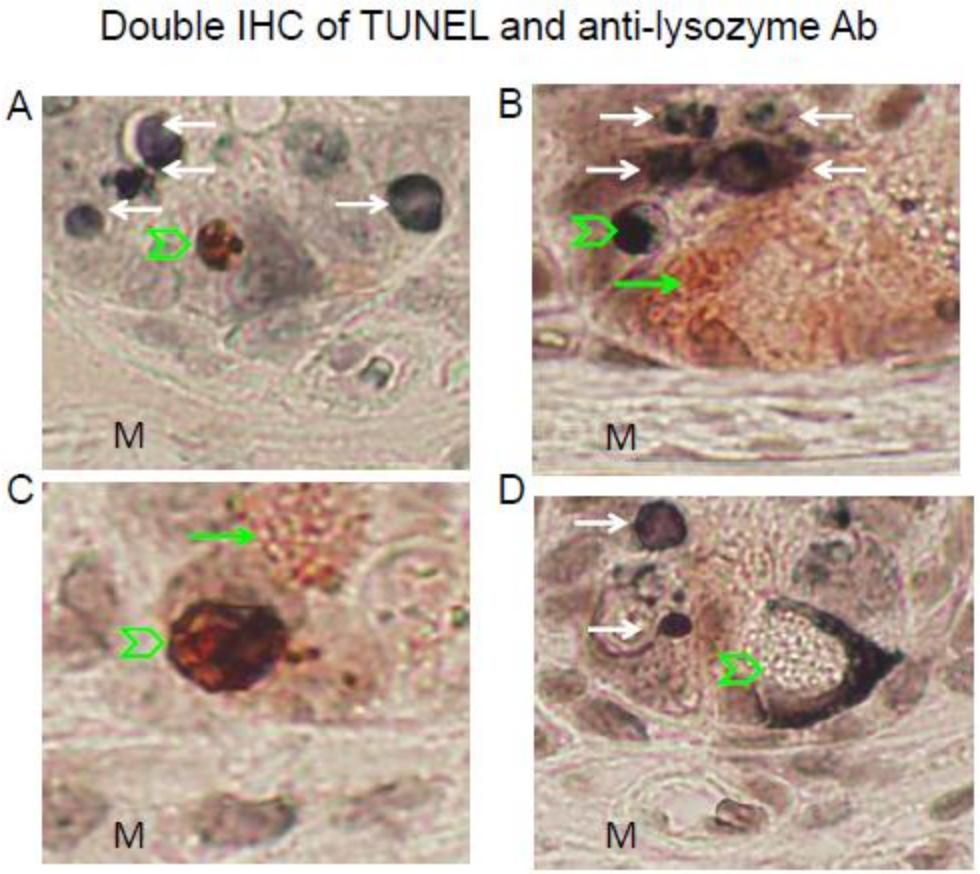


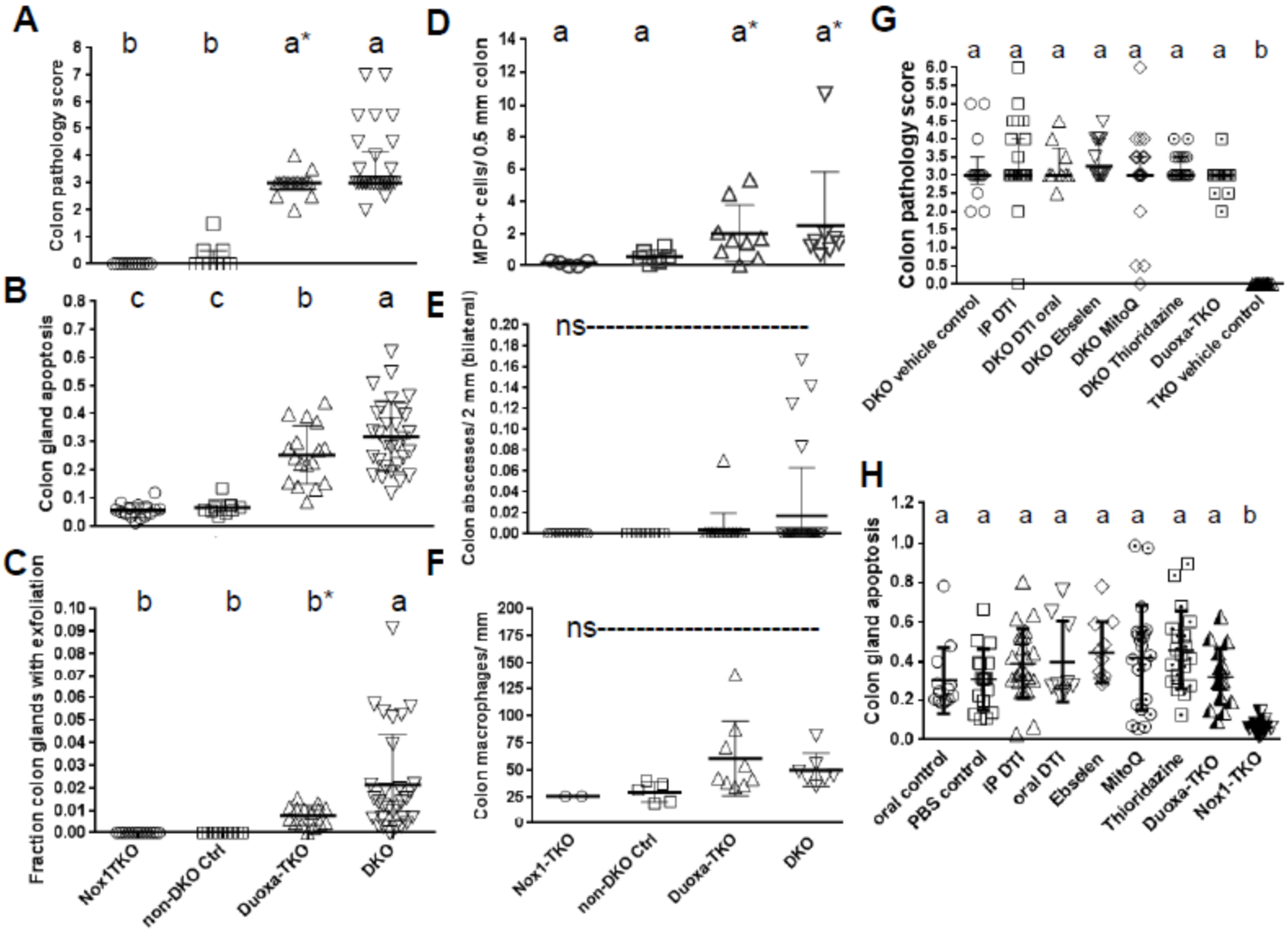

Supplementary Figure 1. Comparison of apoptosis levels quantified by TUNEL IHC and morphology on H&E stained sections. The ilea of 79 B6 mice of different genotypes or ages were evaluated for apoptosis by TUNEL (Panel A) and by apoptotic figures (Panel B). All mice except the Subadult DKOs were at least 35-day old. DKO treated refers to those DKO mice that received GKT 831 or DPI treatment. DKO Nox1+/- group has female DKO mice with *Nox1*$^{+/-}$ genotype *(Nox1* is on the X chromosome). Subadult DKO refers to DKO mice between 24 and 34 days of age. Each symbol represents one mouse.



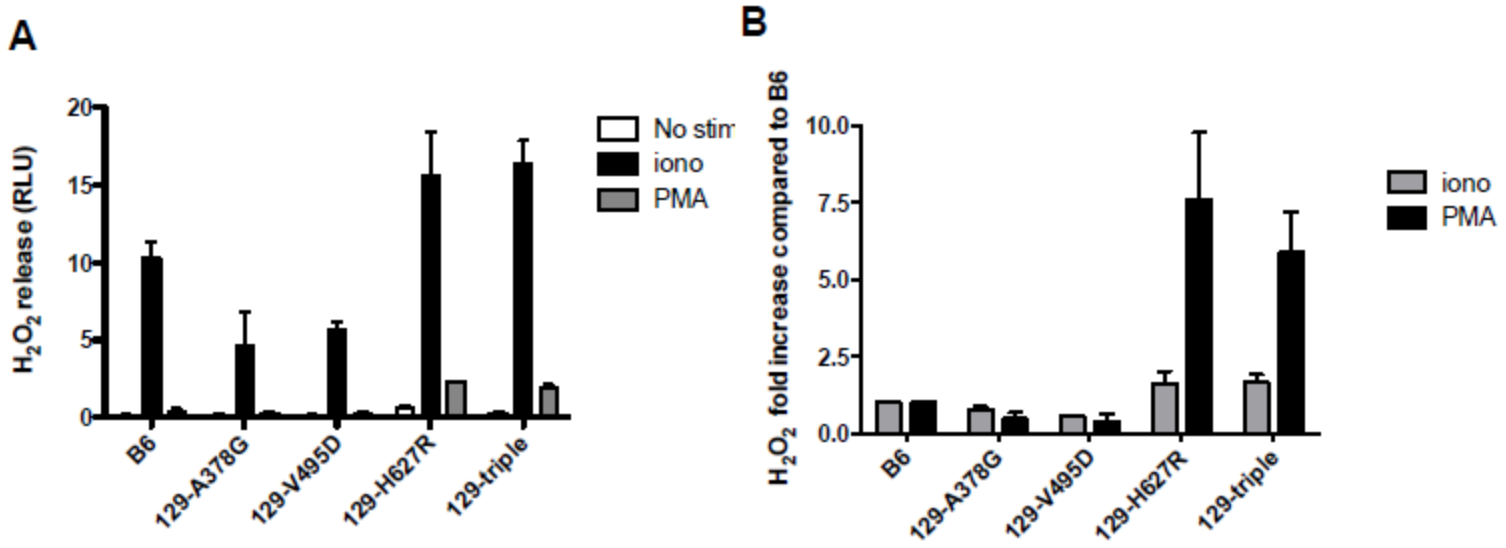

Supplementary Figure 2. Estimate of the potential misidentification of infiltrating lymphocytes as apoptotic bodies/figures in hematoxylin stained sections after anti-MPO IHC. The adjacent sections were processed for anti-MPO IHC (Panels A-C) and TUNEL IHC (Panels D-F). Apoptotic bodies are identified as shrunken bodies with condensed nuclei, which are largely confined to the crypt region (block arrow, Panel A). The TUNEL+ bodies share similar distribution and number (Panels D, block arrow and E). No putative apoptotic bodies were MPO+ (Black arrow, Panel B). A TUNEL- body resembling an infiltrating lymphocyte (green arrow, Panel F) which may be identified as an apoptotic cell. These lymphocyte-like bodies accounted for about 5-10% of the number of TUNEL+ bodies. M indicates muscle layer.




Supplementary Figure 3. Double IHC of TUNEL and anti-lysozyme Ab to show Paneth cells apoptosis, *in situ*. DKO mouse ileum was treated with TUNEL and then anti-lysozyme IHC sequentially. The white arrows point to the TUNEL+ apoptotic cells (blue-grey color). The green arrows point to the alkaline phosphatase product (red-brown color) detecting anti-lysozyme Ab, a marker of Paneth cells. The green arrowhead points to apoptotic Paneth cells. M indicates the muscle layer for orientation.




Supplementary Figure 4. Assessment of colon pathology by genotype (Panels A-F and H). The assessment parallels that of the ileum as presented in Figures 3 and 4 (see legends for Figures 3 and 4 for details). Panel G shows the impact of selected drugs on colon pathology. The selected drugs were those that demonstrated some impact on the ilea (see Figure 8A).




Supplementary Figure 5. 129 Duox2 allele has higher enzyme activity than B6 Duox2 allele. *Duox2* cDNA alleles tested included the native B6 allele, three nsSNP variants (at A378G, V495D and H627R residue) and the 129 allele (129-triple) constructed by combining the three nsSNPs. Assays were done after adding ionomycin (iono) or phorbol myristate acetate (PMA) as stimulants. Panel A shows integrated $H_2O_2$ output represented as GFP-normalized relative fluorescent units (RFU; mean ± SEM) from three independent assays. Panel B shows the 129 variant Duox2 activity relative to the B6 allele.