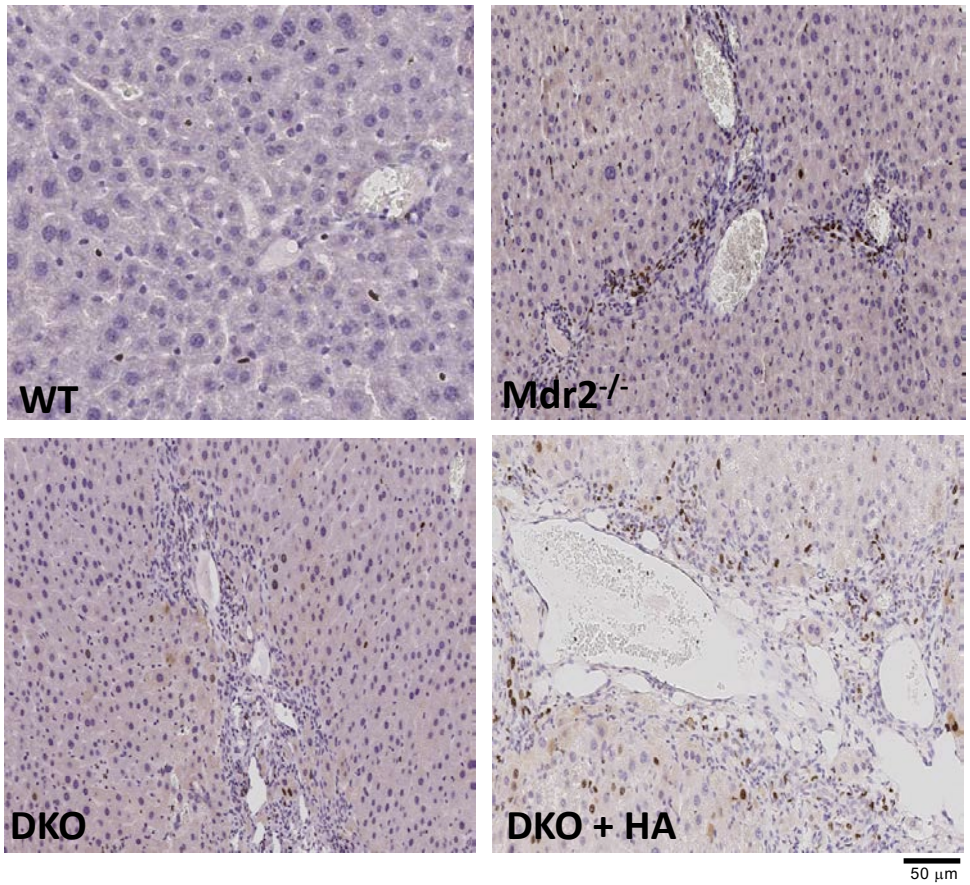
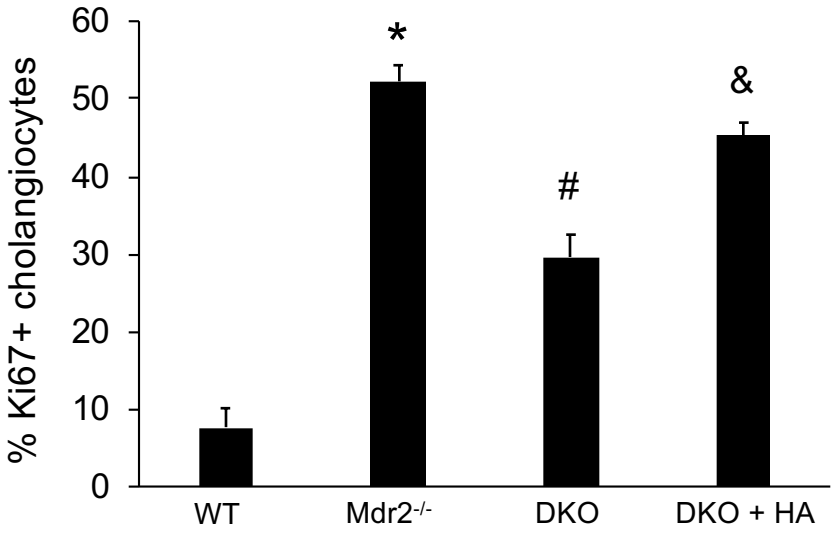
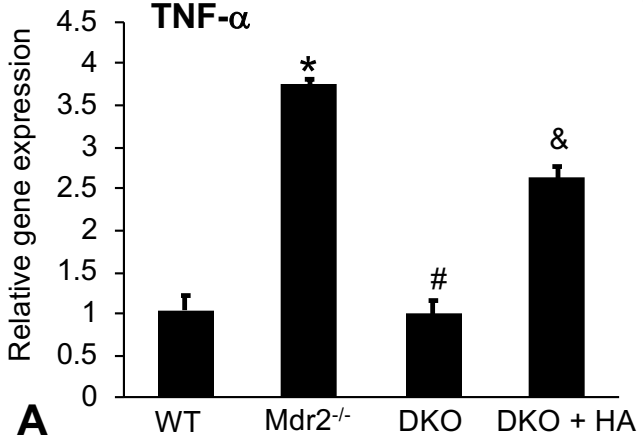
Supplemental Figure 1

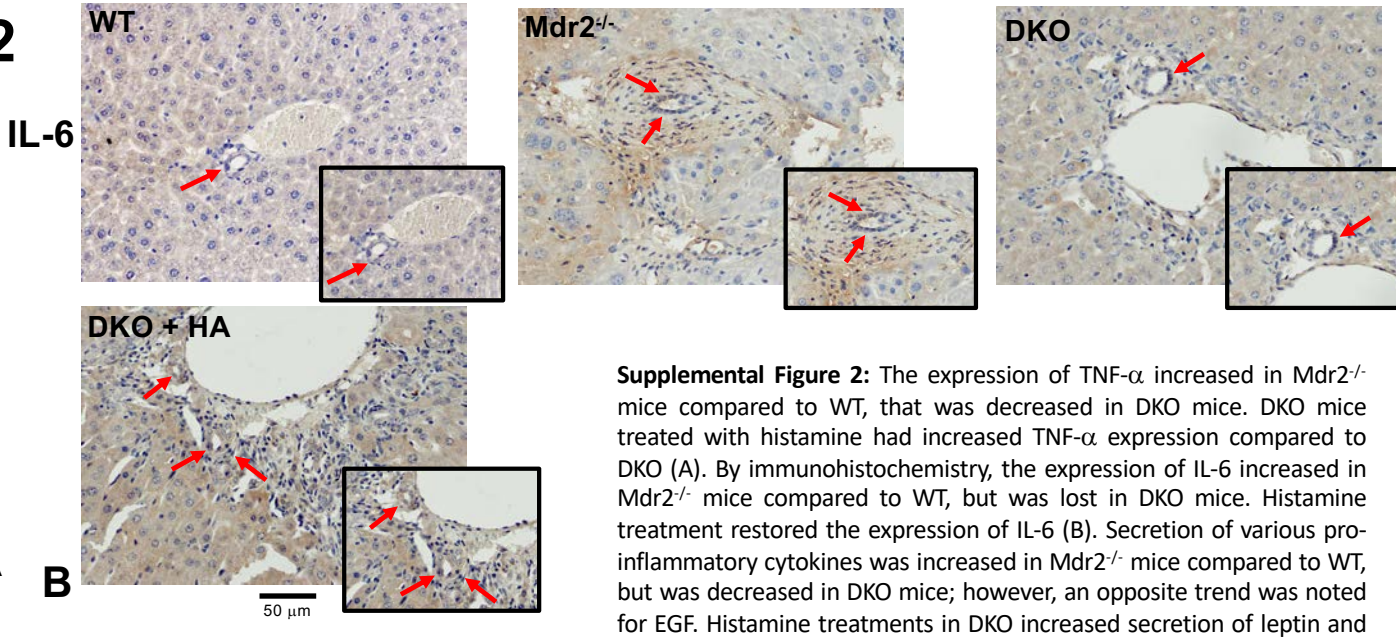




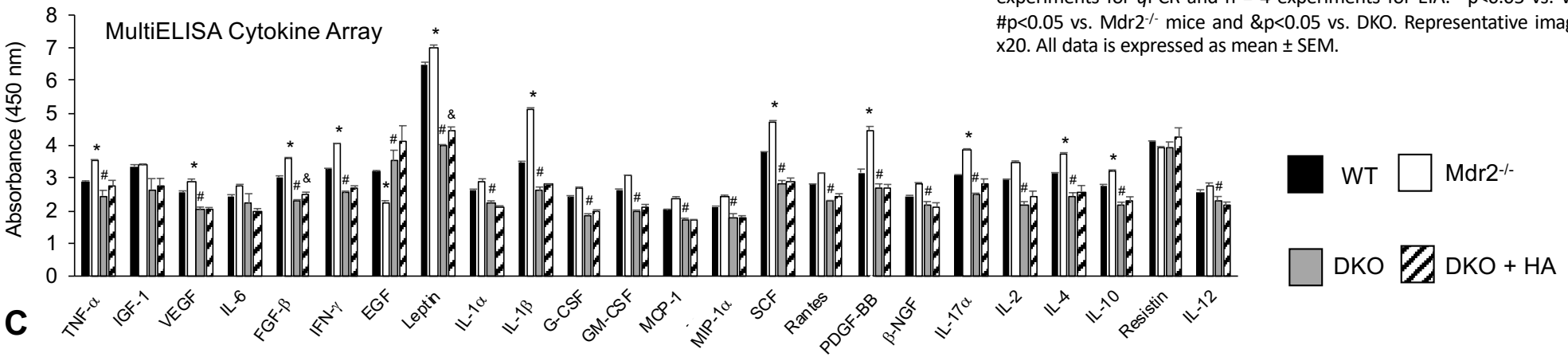
Supplemental Figure 1: Evaluation of biliary proliferation. Cholangiocyte proliferation was measured by immunohistochemistry for Ki-67. Biliary proliferation increased in $Mdr2^{-/-}$ mice compared to WT, which was decreased in DKO mice. When DKO mice were treated with histamine, biliary proliferation increased. Data are mean ± SEM of n = 10 representative images from n = 6 mice for each group. *p<0.05 vs. WT; #p<0.05 vs. $Mdr2^{-/-}$ mice and &p<0.05 vs. DKO. Representative images x20.

Supplemental Figure 2

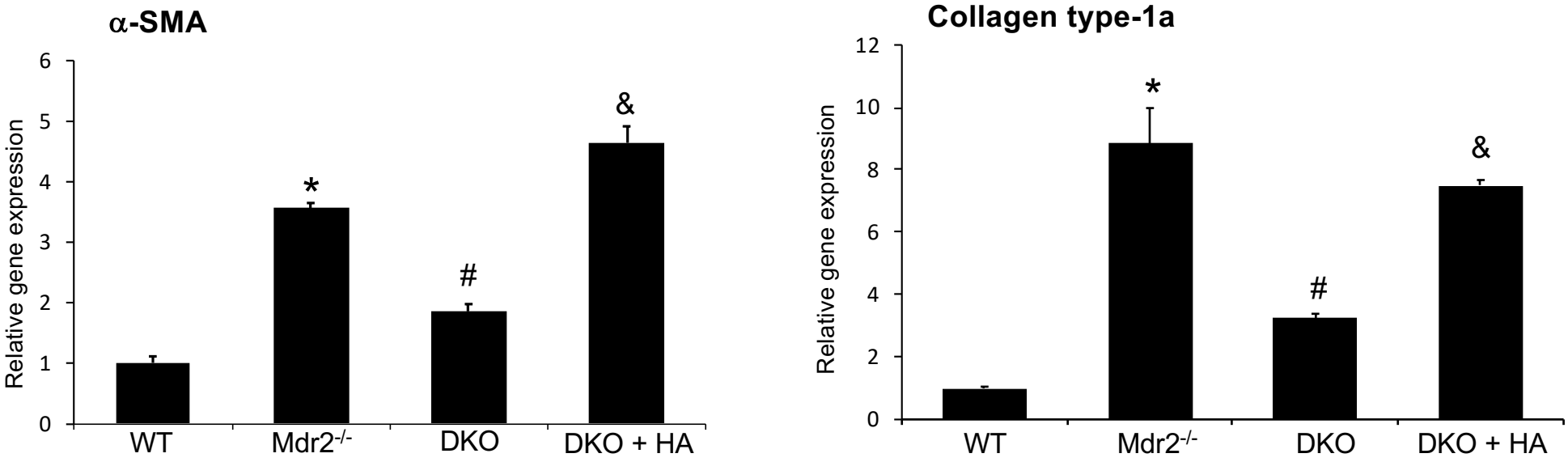




Supplemental Figure 2: The expression of TNF-α increased in Mdr2$^{-/-}$ mice compared to WT, that was decreased in DKO mice. DKO mice treated with histamine had increased TNF-α expression compared to DKO (A). By immunohistochemistry, the expression of IL-6 increased in Mdr2$^{-/-}$ mice compared to WT, but was lost in DKO mice. Histamine treatment restored the expression of IL-6 (B). Secretion of various pro-inflammatory cytokines was increased in Mdr2$^{-/-}$ mice compared to WT, but was decreased in DKO mice; however, an opposite trend was noted for EGF. Histamine treatments in DKO increased secretion of leptin and FGF-β compared to DKO. (C). Data are mean ± SEM of n = 12 experiments for *q*PCR and n = 4 experiments for EIA. *p<0.05 vs. WT; #p<0.05 vs. Mdr2$^{-/-}$ mice and &p<0.05 vs. DKO. Representative images x20. All data is expressed as mean ± SEM.

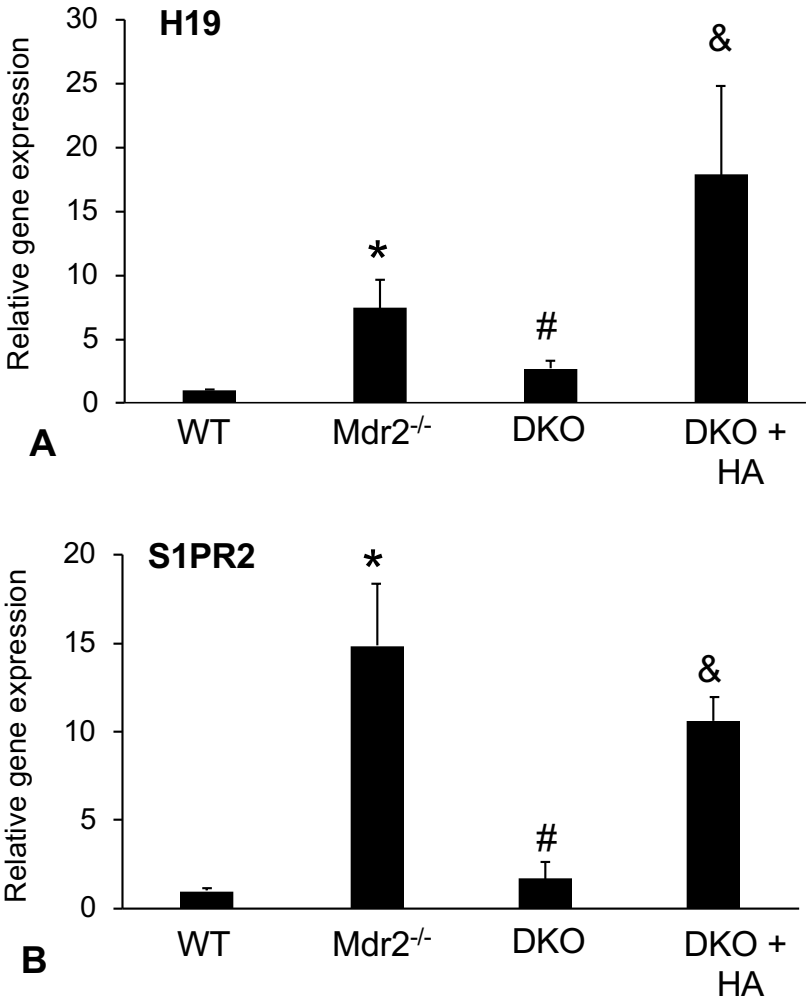


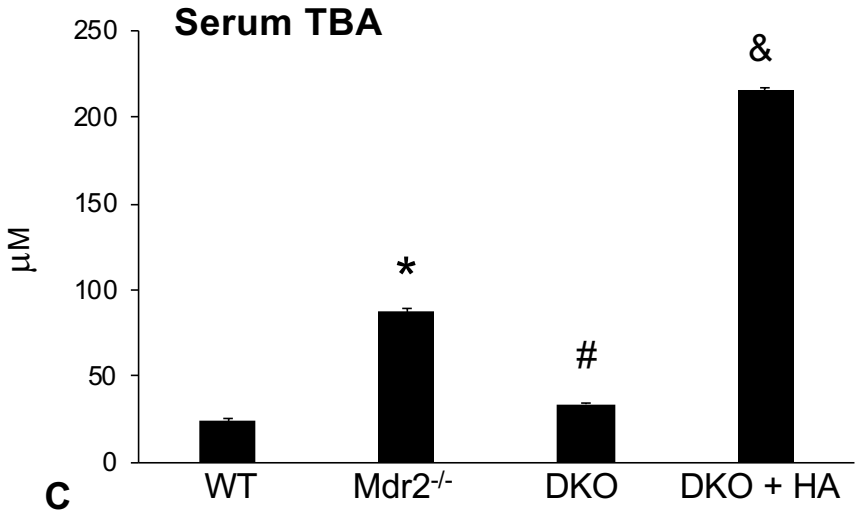
Supplemental Figure 3



Supplemental Figure 3: The expression of fibrogenic markers was determined by real-time PCR for collagen type-1a and α-SMA. The expression of collagen type-1a and α-SMA increased in Mdr2$^{-/-}$ mice compared to WT, that was decreased in DKO mice. DKO mice treated with histamine had increased gene expression of fibrotic markers compared to DKO. Data are mean ± SEM of n = 10 experiments. *p<0.05 vs. WT; #p<0.05 vs. Mdr2$^{-/-}$ mice and &p<0.05 vs. DKO.

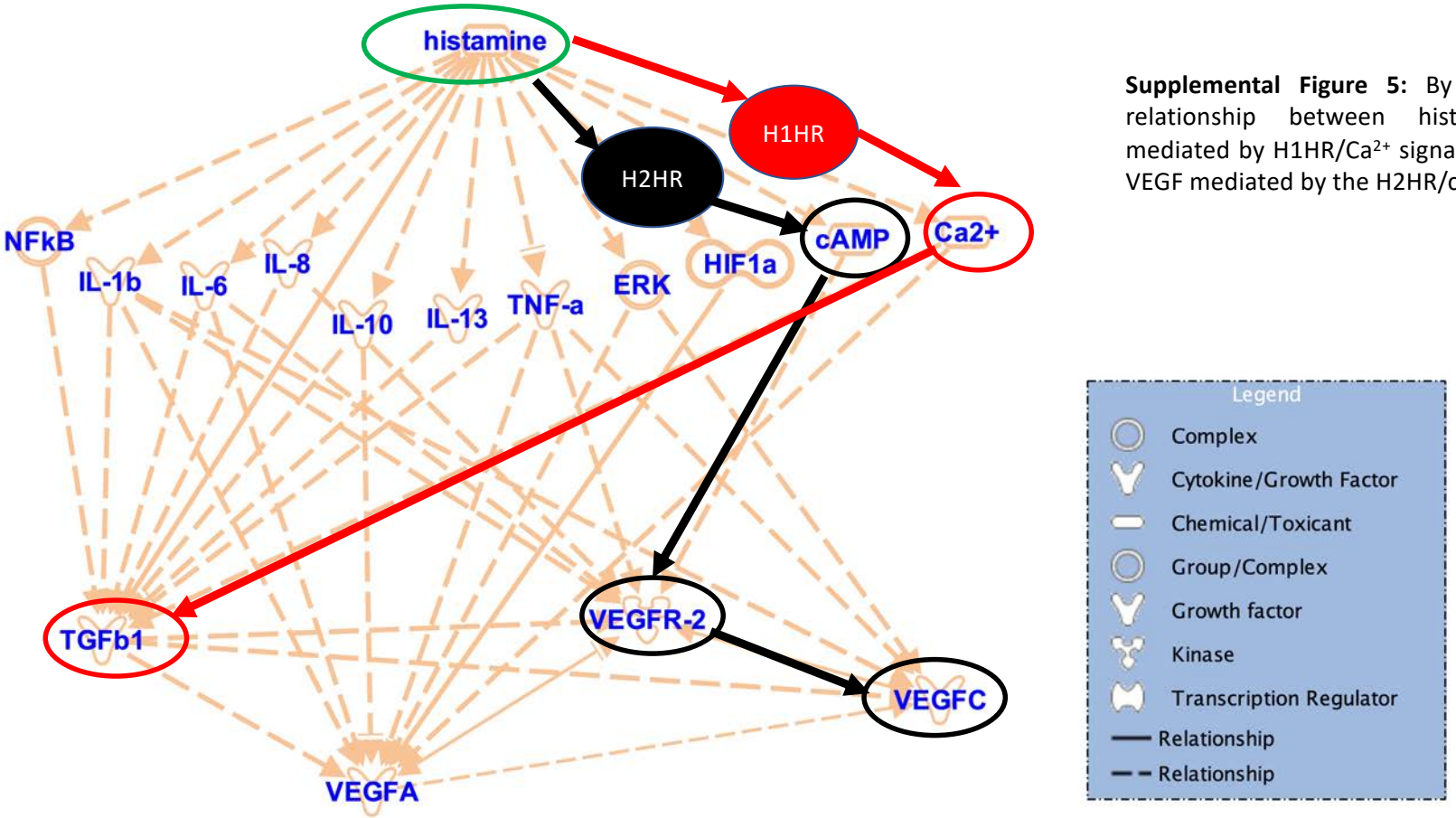
Supplemental Figure 4





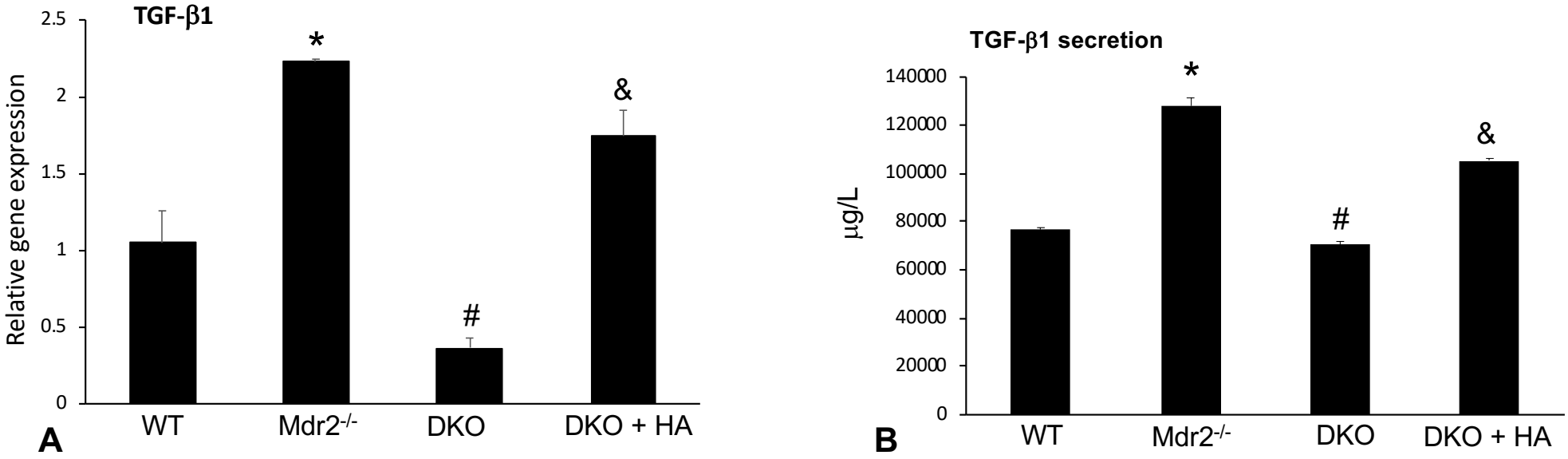
Supplemental Figure 4: Gene expression of H19 and S1PR2 was measured by real-time PCR and we found an increase in Mdr2$^{-/-}$ mice compared to WT, which was reduced in the DKO mice (A, B). Administration of histamine to DKO mice increased the expression of these factors (A, B). Serum TBA levels were measured by EIA, and we found an increase in serum TBA in Mdr2$^{-/-}$ mice that was decreased in DKO mice; however, histamine treatment significantly increased serum TBA in DKO mice (C). Data are mean ± SEM of n = 9-12 experiments for *q*PCR and n = 4 experiments for EIA. $p<0.05$ vs. WT; #$p<0.05$ vs. Mdr2$^{-/-}$ mice and &$p<0.05$ vs. DKO.

Supplemental Figure 5



Supplemental Figure 5: By IPA we identified a relationship between histamine and TGF-β1 mediated by H1HR/Ca^{2+} signaling and histamine and VEGF mediated by the H2HR/cAMP/pERK pathway.

Supplemental Figure 6



Supplemental Figure 6: Gene expression of TGF-β1 was measured by real-time PCR and we found an increase in Mdr2$^{-/-}$ mice compared to WT that was ablated in the DKO mice (A). Treatment with histamine to DKO mice increased the expression of TGF-β1 (A). Serum secretion of TGF-β1 was measured by EIA and demonstrates increased levels in Mdr2$^{-/-}$ mice, which is ablated in DKO mice. Histamine treatment restored the levels of TGF-β1 in DKO mice (B). Data are mean ± SEM of n = 9 experiments for *q*PCR and n = 12 experiments for EIA. $p<0.05$ vs. WT; #$p<0.05$ vs. Mdr2$^{-/-}$ mice and &$p<0.05$ vs. DKO.