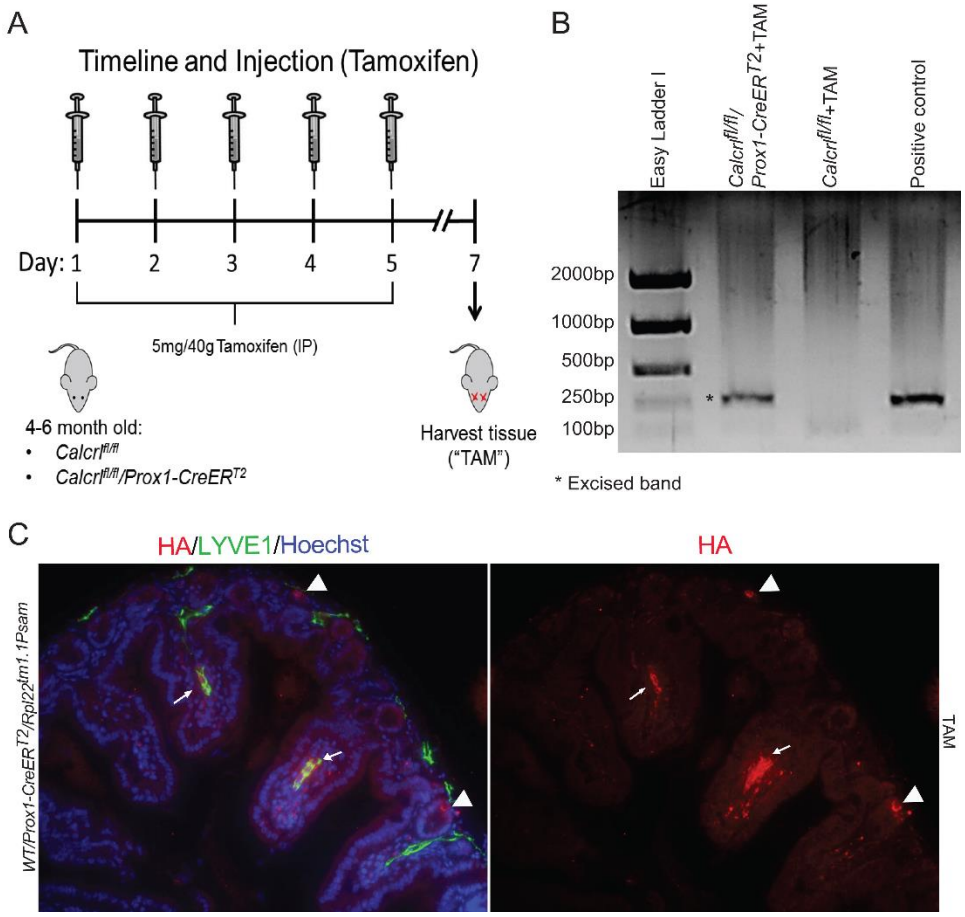
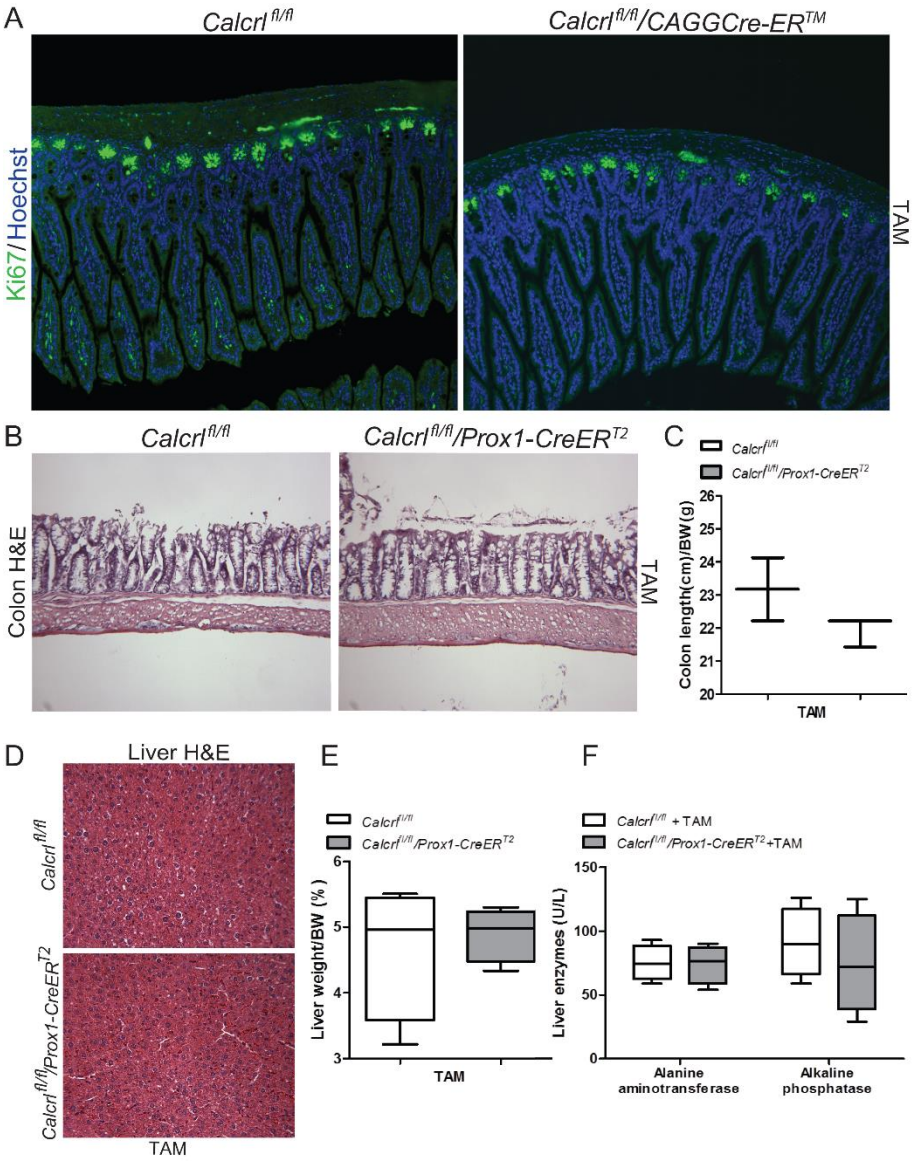
Supplementary Figure 1



***Prox1-CreER^{T2}* is expressed in intestinal lymphatic vessels and effectively deletes calcitonin receptor-like receptor upon tamoxifen induction.**

(A) Timeline and scheme of tamoxifen (TAM) injections **(B)** Calcitonin receptor-like receptor (CLR) excised band (*) as seen by PCR genotyping lung DNA obtained from tamoxifen (TAM) treated *Calcrl$^{fl/fl}$* and *Calcrl$^{fl/fl}$/Prox1-CreER^{T2}* **(C)** Representative image of HA and lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1) stained ileum of TAM treated *WT/Prox1-CreER^{T2}/Rpl22$^{tm1.1Psam}$* (ribotag mouse) indicating the expression of *Prox1-CreER^{T2}* in the gut. *n* = 3 animals in each group. Arrows point to lacteals and arrowheads indicate HA staining in enteroendocrine cells.

Supplementary Figure 2

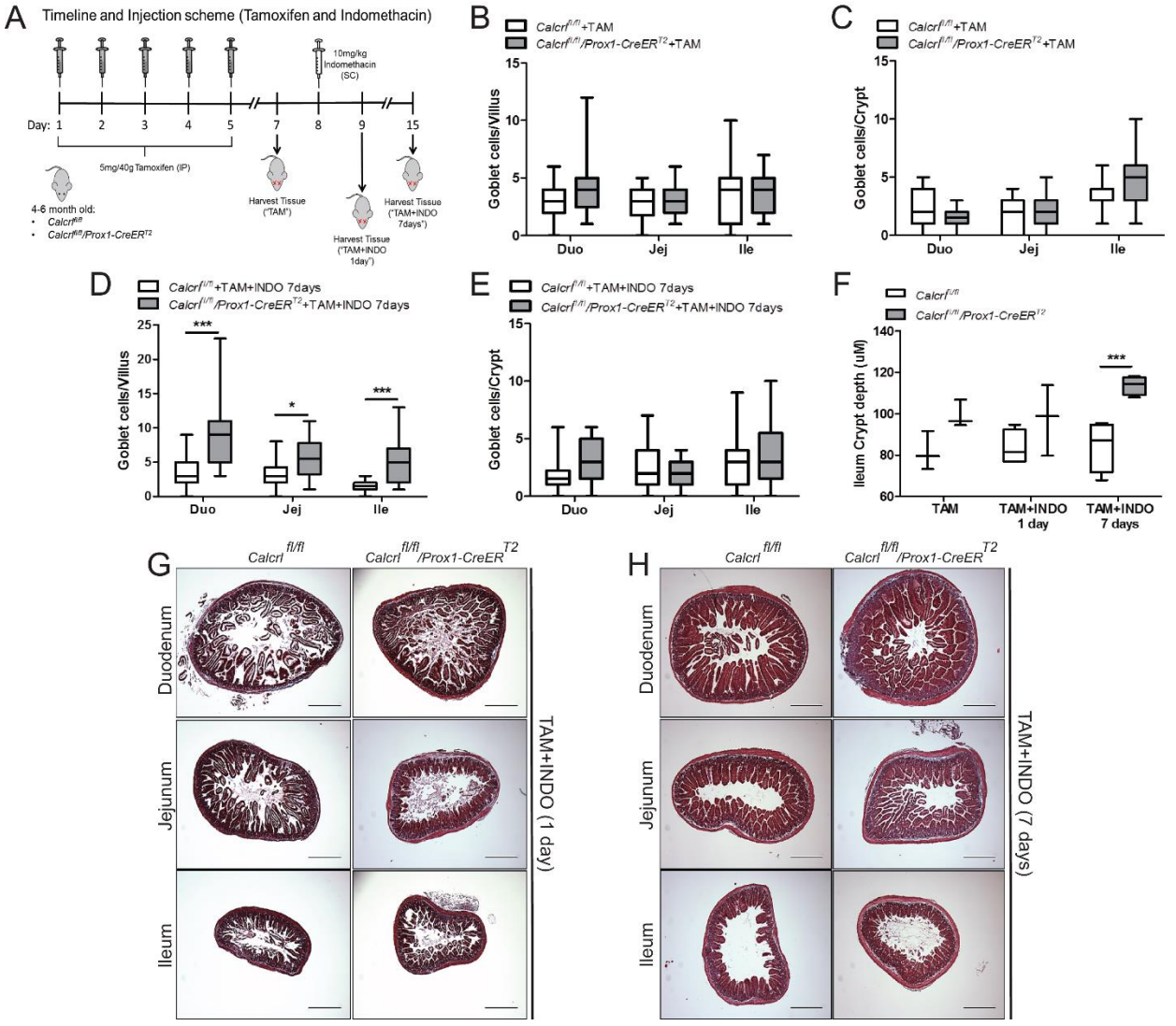


Tamoxifen induced loss of calcitonin receptor-like receptor does not induce drastic systemic changes and mice can survive long term in the absence of challenge.

(A) Representative image of Ki67 stained ileum of tamoxifen (TAM) treated aged (>1.5 years) *Calcrl*$^{fl/fl}$ and *Calcrl*$^{fl/fl}$*/CAGGCre-ER*^{TM}. *n* = 11-12 animals in each group. **(B)** Representative images of H&E stained colon of TAM treated *Calcrl*$^{fl/fl}$ and *Calcrl*$^{fl/fl}$*/Prox1-*

CreER^{T2}. *n* = 3 animals in each group. **(C)** Quantification of colon length measured from proximal to distal end normalized to body weight in *Calcrl*$^{fl/fl}$ and *Calcrl*$^{fl/fl}$*/Prox1-CreER*^{T2} after TAM treatment. *n* = 3 mice per group. Quantitative data is represented as box-and-whisker plot with bounds from 25th to 75th percentile, median line, and whiskers ranging from minimum to maximum values of colon length. Significance was determined by Student *t* test (tail=2, type=2). **(D)** Representative images of H&E stained liver of TAM treated *Calcrl*$^{fl/fl}$ and *Calcrl*$^{fl/fl}$*/Prox1-CreER*^{T2}. *n* = 4 animals in each group. **(E)** Quantification of liver weight normalized to body weight in *Calcrl*$^{fl/fl}$ and *Calcrl*$^{fl/fl}$*/Prox1-CreER*^{T2} after TAM treatment. *n* = 4 mice per group. Quantitative data is represented as box-and-whisker plot with bounds from 25th to 75th percentile, median line, and whiskers ranging from minimum to maximum weights. Significance was determined by Student *t* test (tail=2, type=2). **(F)** Quantification of liver enzymes present in serum of *Calcrl*$^{fl/fl}$ and *Calcrl*$^{fl/fl}$*/Prox1-CreER*^{T2} after TAM treatment. *n* = 4 mice per group. Quantitative data is represented as box-and-whisker plot with bounds from 25th to 75th percentile, median line, and whiskers ranging from minimum to maximum values. Significance was determined by two-way ANOVA.

Supplementary Figure 3

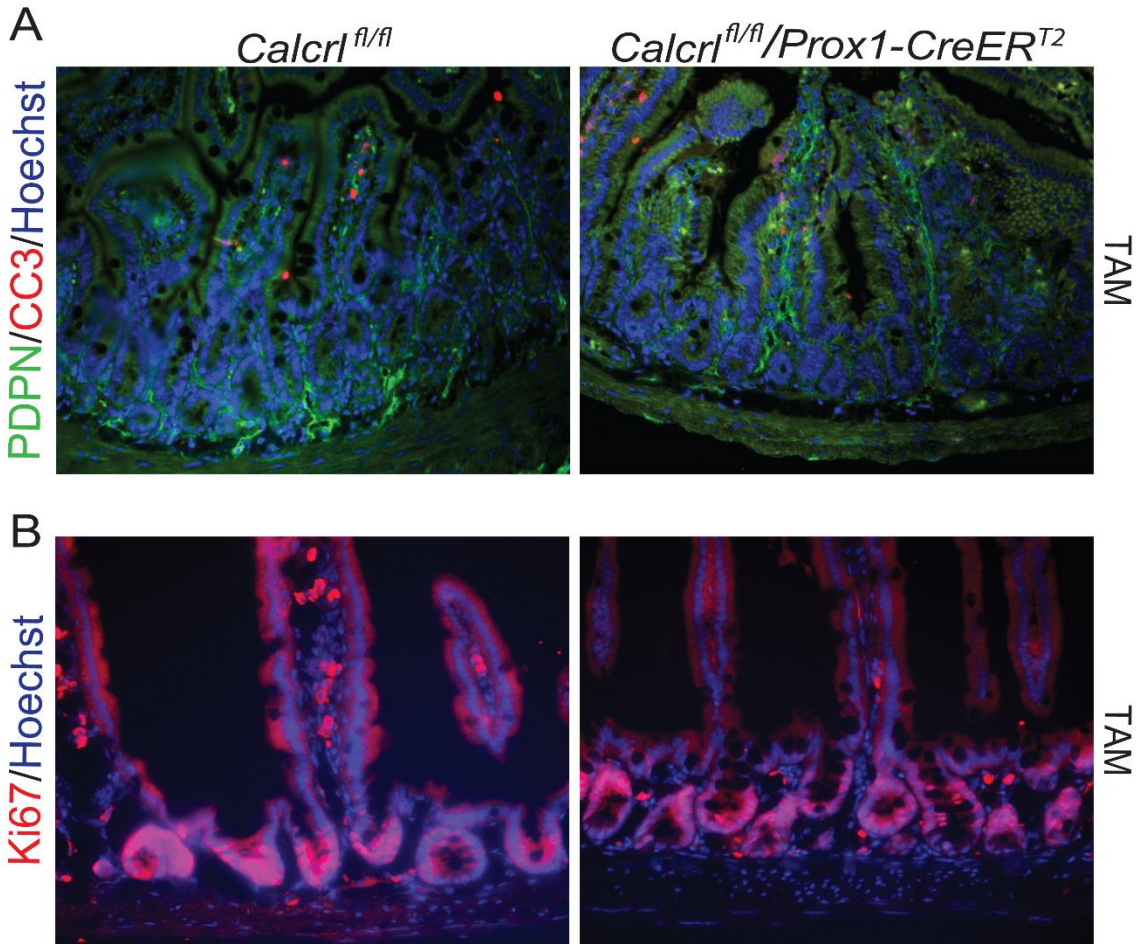


Indomethacin challenge leads to increased crypt depth, increase in goblet cells, and persistent fibrosis in intestines lacking lymphatic *Calcrl* after the 7 day recovery period.

(A) Timeline and scheme of tamoxifen (TAM) injections followed by indomethacin (INDO) challenge and recovery period **(B-E)** Quantification of goblet cells per villus (B,D) or per crypt (C,E) in *Calcrl*$^{fl/fl}$ and *Calcrl*$^{fl/fl}$*/Prox1-CreER*^{T2} after TAM treatment, and 7 days post

INDO challenge. *n* = 4-6 mice per group. Quantitative data is represented as box-and-whisker plot with bounds from 25th to 75th percentile, median line, and whiskers ranging from minimum to maximum number of goblet cells. Significance was determined by two-way ANOVA with **P* <0.05 and ****P* <0.001. **(F)** Quantification of ileum crypt depth in *Calcrl*$^{fl/fl}$ and *Calcrl*$^{fl/fl}$*/Prox1-CreER*^{T2} after TAM treatment, 1 day post INDO challenge, and 7 days post INDO challenge. *n* = 3-10 mice per group. Quantitative data is represented as box-and-whisker plot with bounds from 25th to 75th percentile, median line, and whiskers ranging from minimum to maximum depth. Significance was determined by two-way ANOVA with ****P* <0.001. **(G, H)** Representative images of Masson's trichrome stained duodenum, jejunum and ileum of TAM treated *Calcrl*$^{fl/fl}$ and *Calcrl*$^{fl/fl}$*/Prox1-CreER*^{T2} 1 day (G) and 7 days (H) post INDO challenge. n = 7-8 animals in each group. Scale Bars, 500 µm.

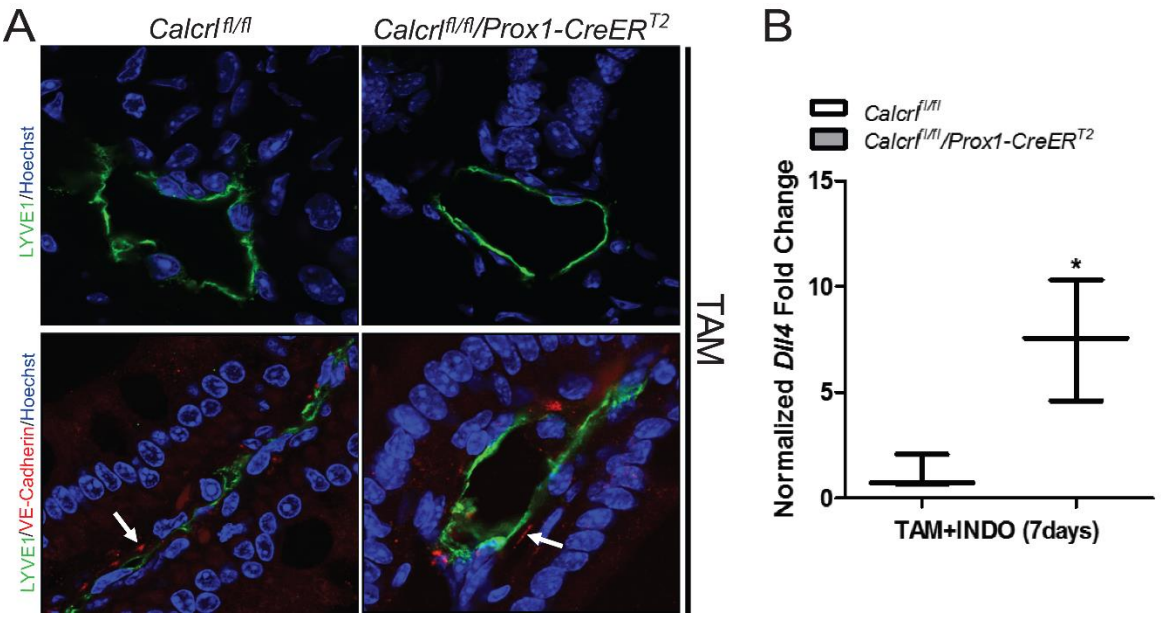
Supplementary Figure 4



Loss of lymphatic *Calcrl* does not change crypt proliferation or villus enterocyte apoptosis in the absence of inflammatory challenge.

(A) Representative image of podoplanin (PDPN) and cleaved caspase-3 (CC3) stained ileum of tamoxifen (TAM) treated *Calcrl*$^{fl/fl}$ and *Calcrl*$^{fl/fl}$*/Prox1-CreER*^{T2}. n = 3-6 animals in each group. **(B)** Representative image of Ki67 stained ileum of TAM treated *Calcrl*$^{fl/fl}$ and *Calcrl*$^{fl/fl}$*/Prox1-CreER*^{T2}. n = 3-6 animals in each group.

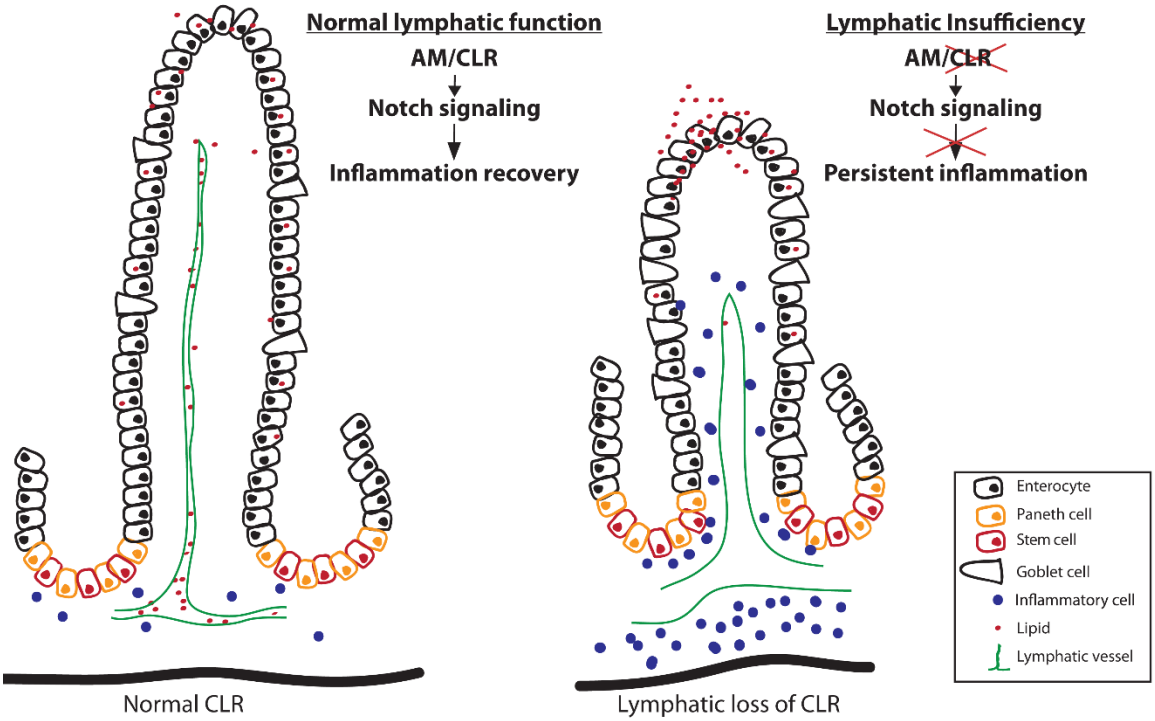
Supplementary Figure 5



No visible change in cell morphology in animals lacking lymphatic *Calcrl* but DLL4 expression is increased in whole gut upon indomethacin challenge.

(A) Representative images of lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1) stained submucosal lymphatic vessels (top panel) and LYVE1 and VE-Cadherin stained lacteals (lower panel) in ileum of tamoxifen (TAM) treated *Calcrl*$^{fl/fl}$ and *Calcrl*$^{fl/fl}$*/Prox1-CreER*^{T2}. Arrows point to VE-Cadherin stained junctions. n = 3-6 animals in each group. **(B)** Relative expression of delta like canonical Notch ligand 4 (DLL4) in whole gut of TAM treated *Calcrl*$^{fl/fl}$ and *Calcrl*$^{fl/fl}$*/Prox1-CreER*^{T2} 7 days post indomethacin (INDO) challenge. Quantitative data is represented as box-and-whisker plot with bounds from 25th to 75th percentile, median line, and whiskers ranging from minimum to maximum fold change from 3 independent studies. *GAPDH, RN18S* and *ACTB* were used as housekeeping controls. Significance was determined by Student *t* test (tail=2, type=2) with **P* <0.05.

Supplementary Figure 6



Model: Small intestinal lymphatic *Calcrl* is required for lacteal maintenance and function during acute mucosal injury. Upon normal adrenomedullin (AM) signaling through the calcitonin receptor-like receptor (CLR) in the small intestinal lymphatic vessels, lacteal junctions allow for the uptake of lipids and the clearing of inflammation. On the other hand, intestinal injury under the conditions of lymphatic insufficiency due to lack of lymphatic *Calcrl* leads to downregulated Notch signaling, inefficient lipid absorption, and persistence of inflammation after mucosal injury. Box shows legend.