

Innate immune regulation of T-helper (Th) cell homeostasis in the intestine

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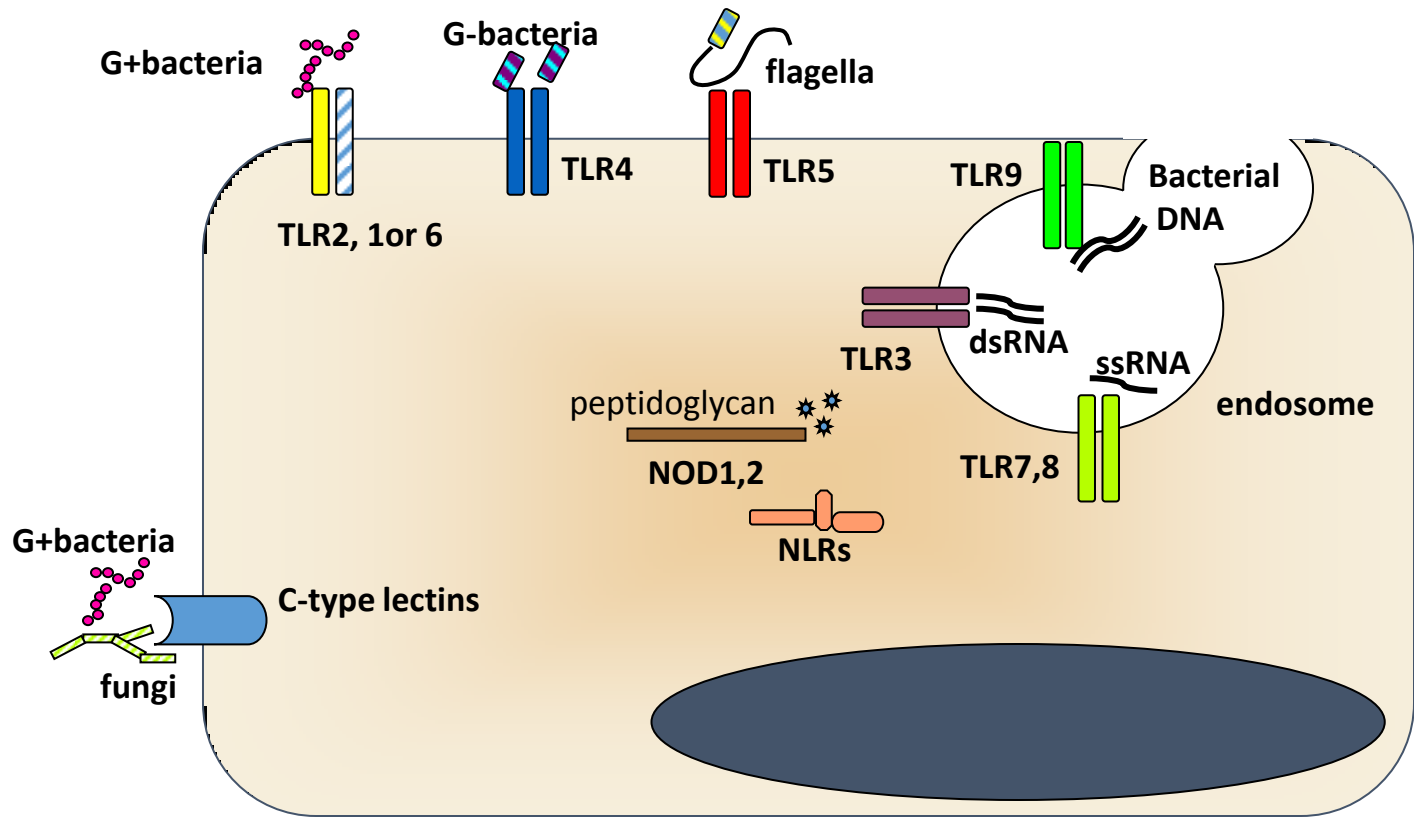
Two arms of immunity

Innate immunity

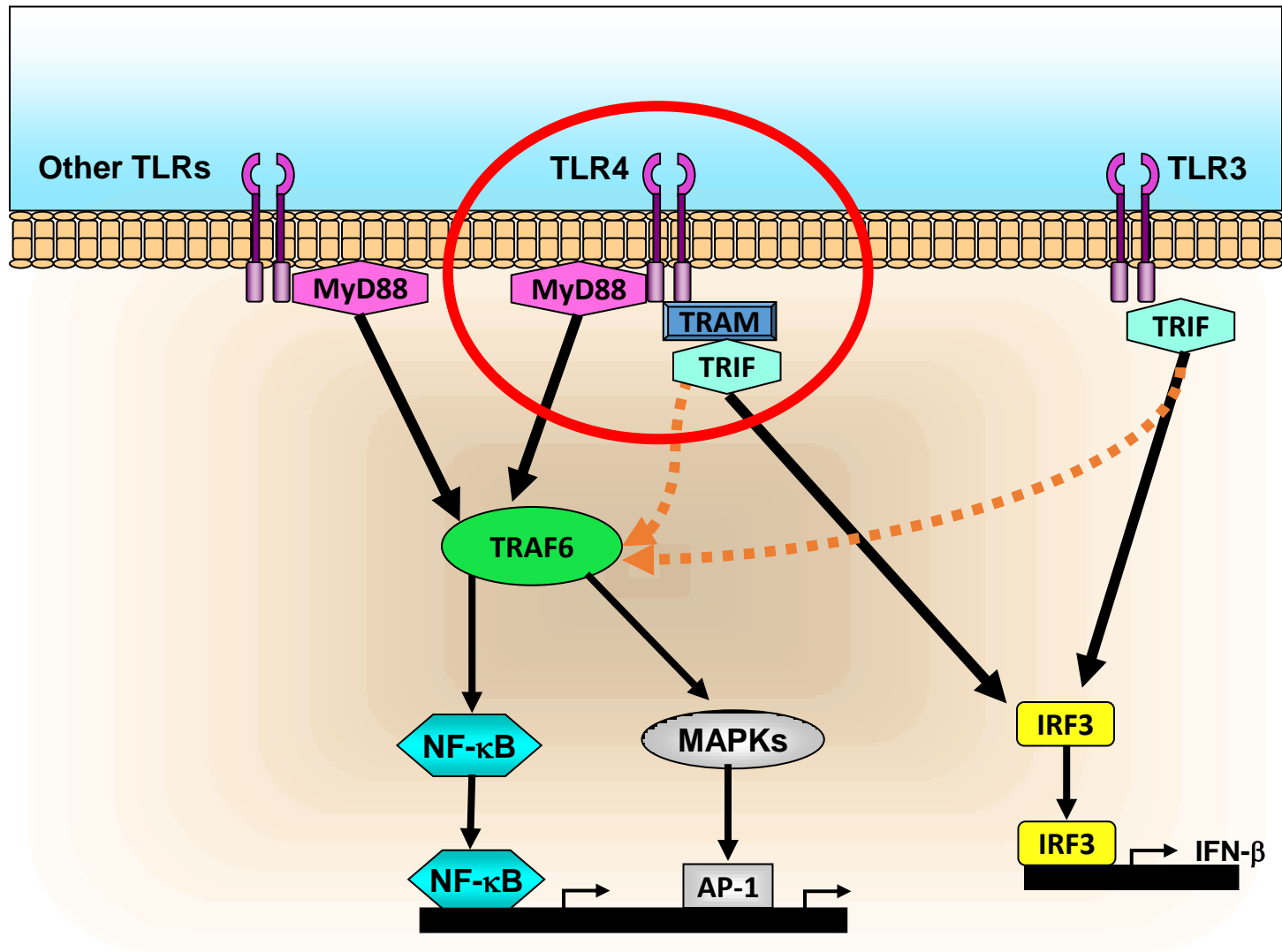
Adaptive immunity

Timing	Rapid (hours)	Slow (days)
Target	Broad	Specific
Main cells	APCs, PMN, NK, ILCs,	T cells, B cells
Location	Interface (mucosa, skin)	Internal (lymphoid organs)

Pattern recognition receptors (PRRs) recognize microorganisms

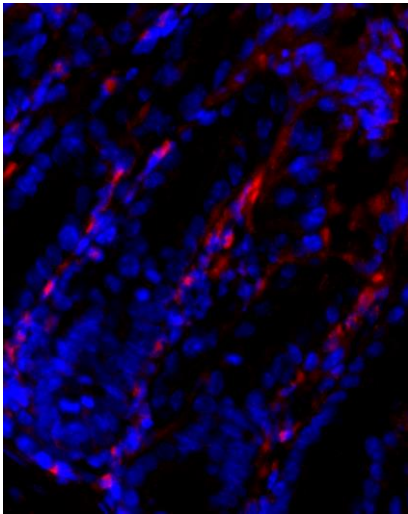


TLR signaling

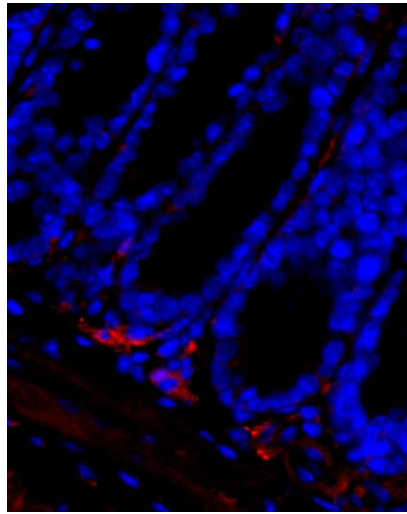


Innate immune cells in the intestine (mouse colon)

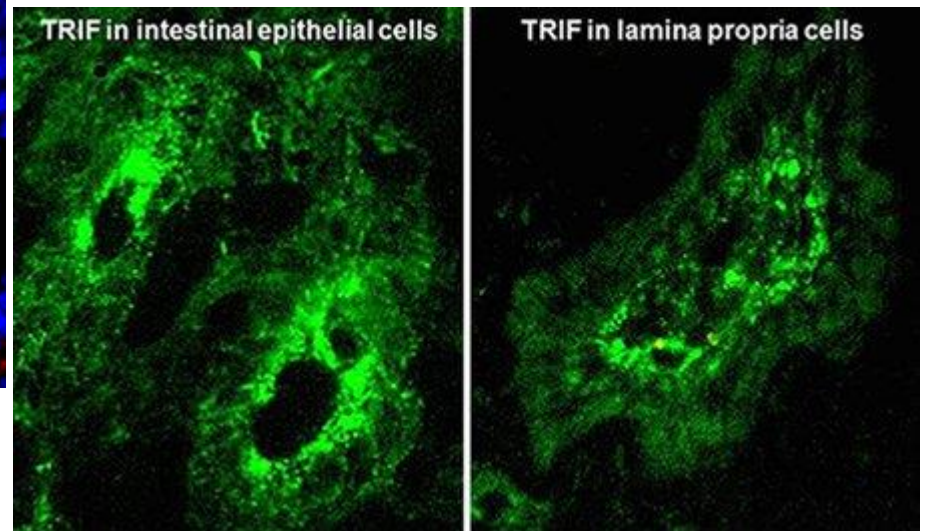
CD11c



F4/80

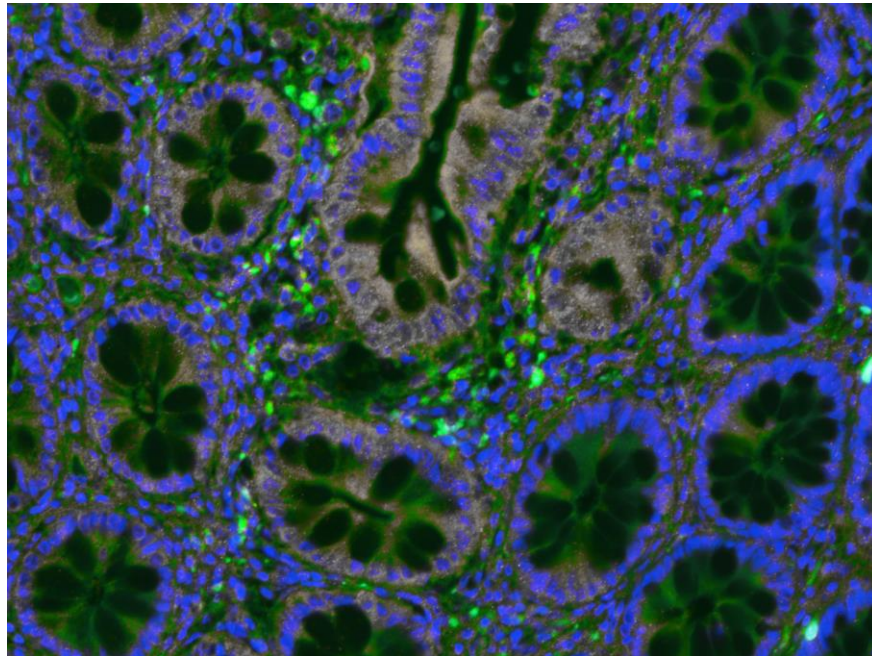


TRIF

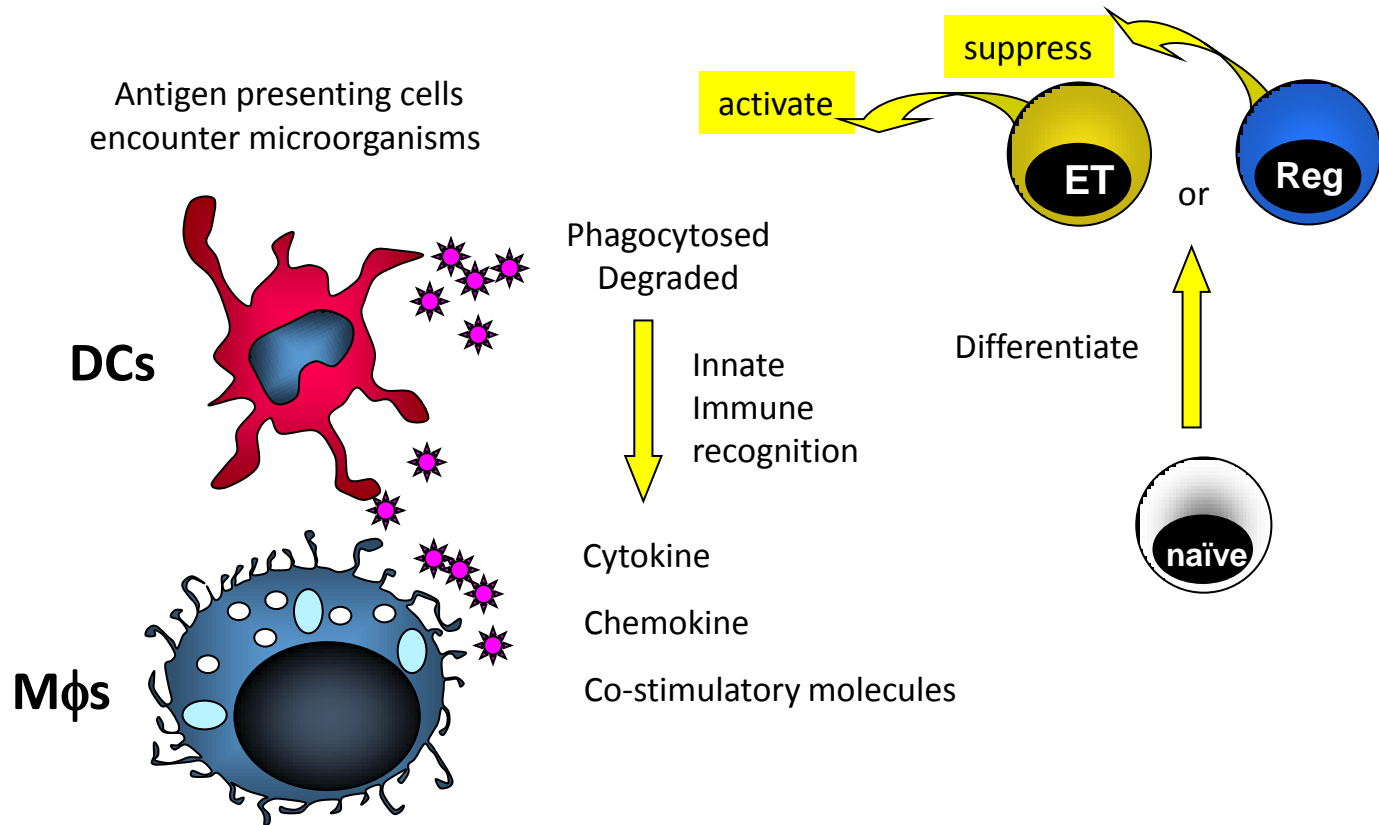


CD4+ cells in the intestine (normal human colon)

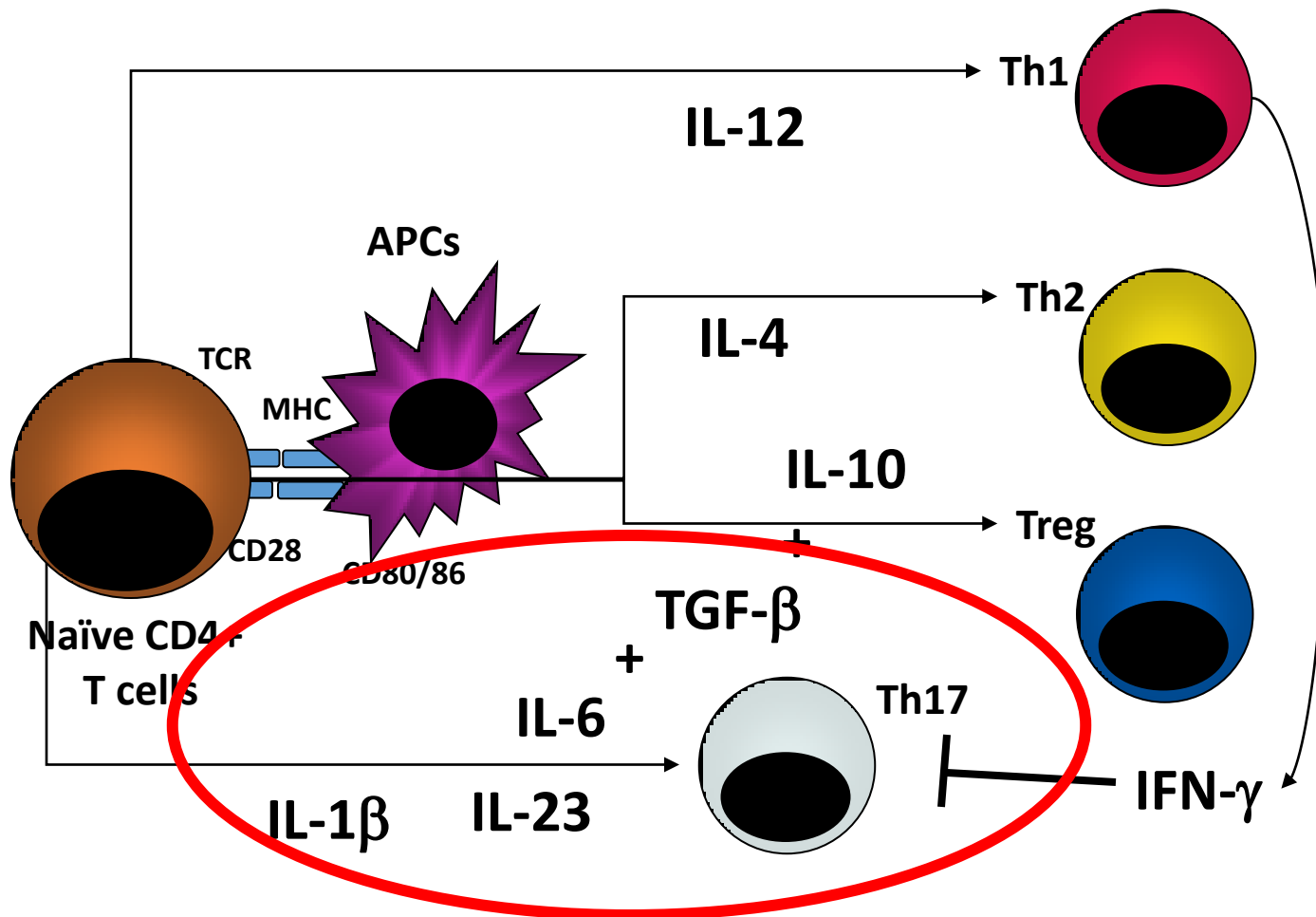
CD4



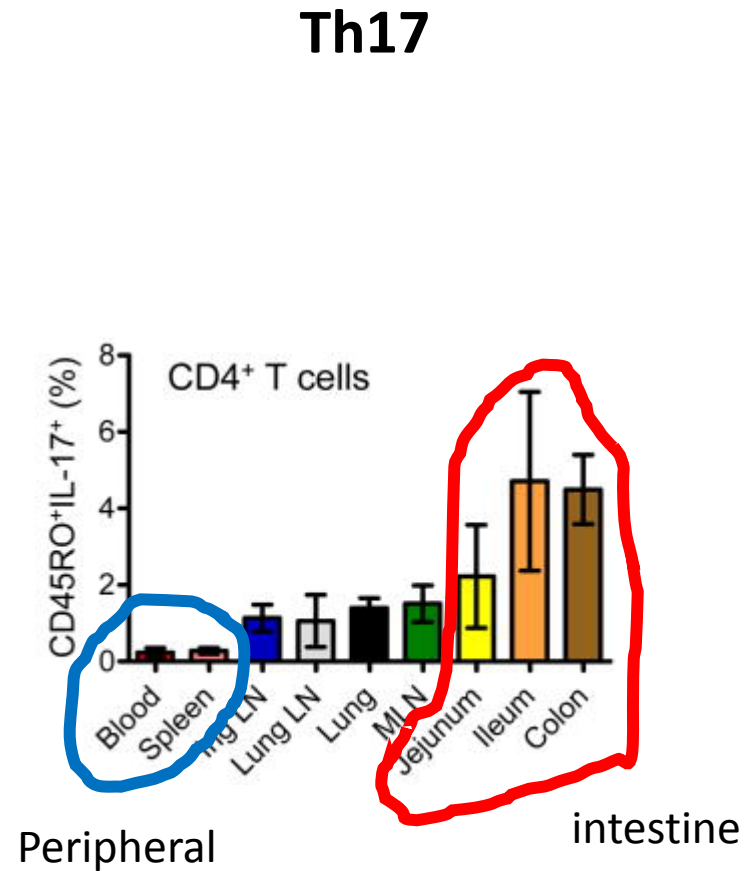
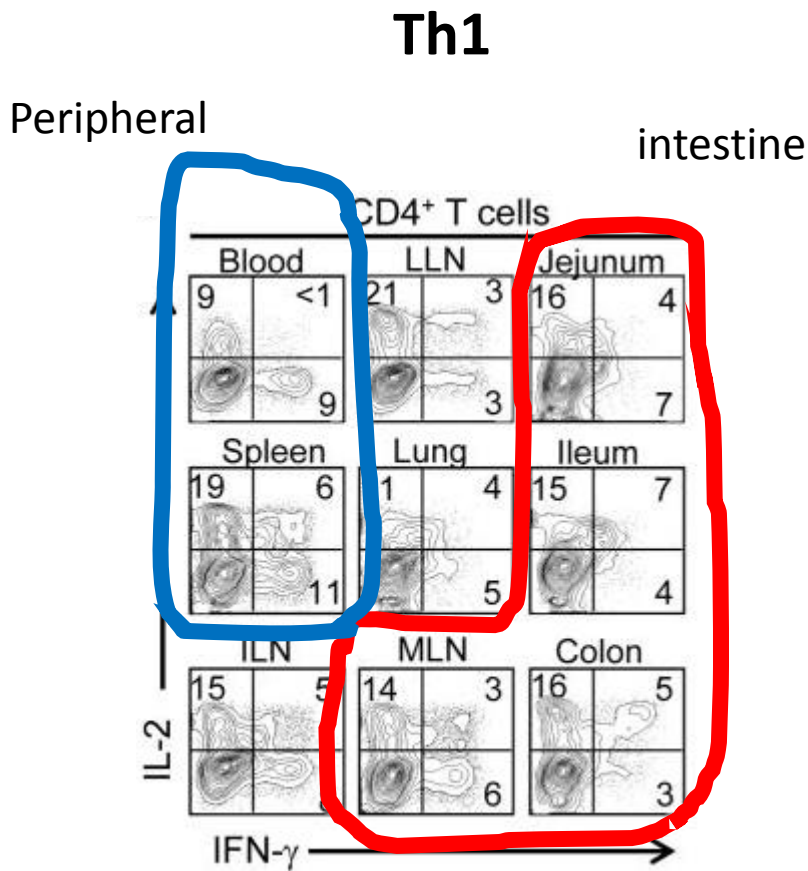
The interplay between innate and adaptive Th cell immunity



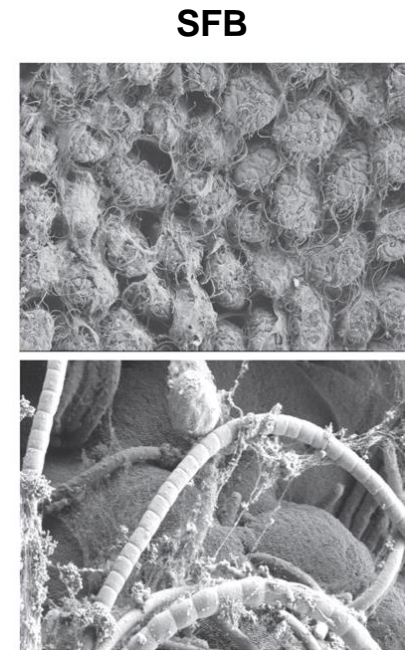
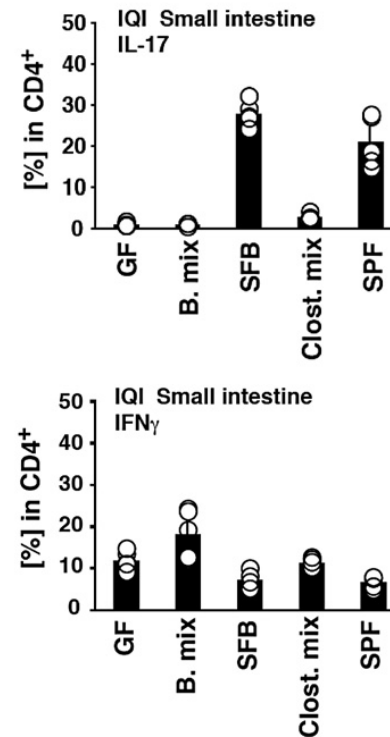
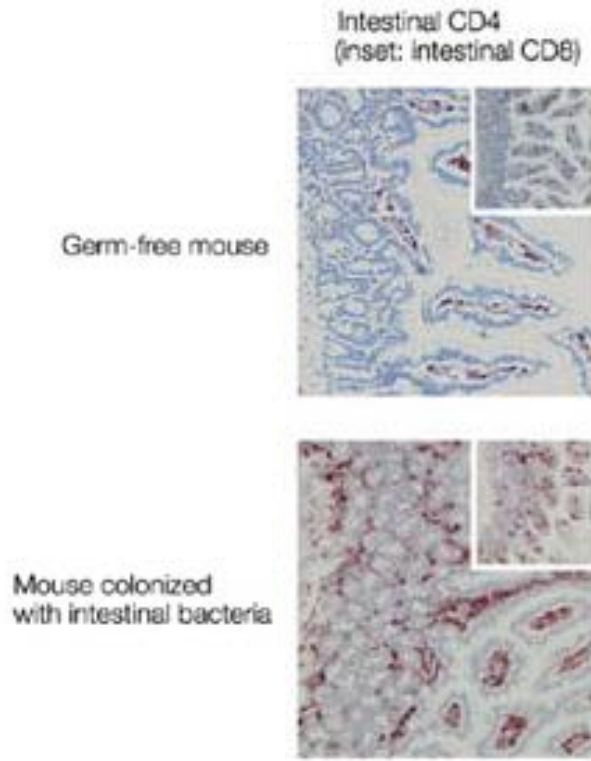
Th cell differentiation



Distribution difference in Th cell types



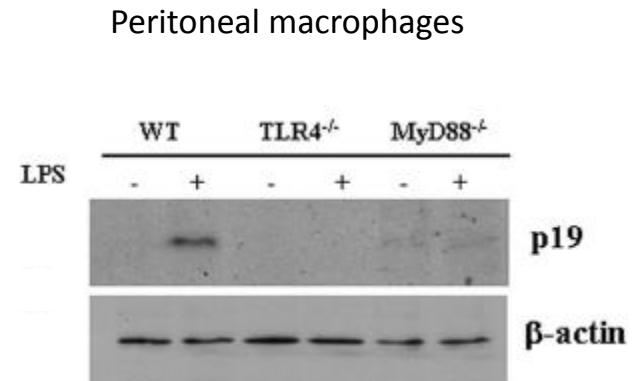
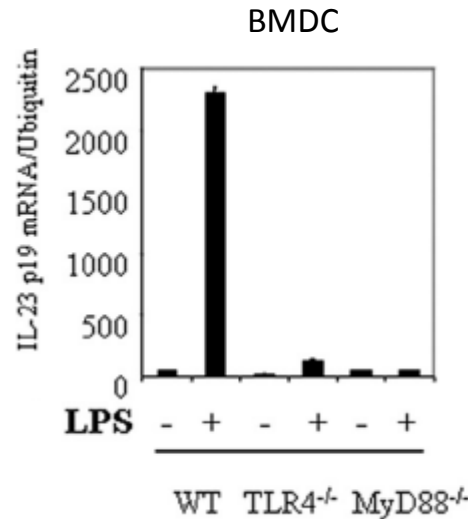
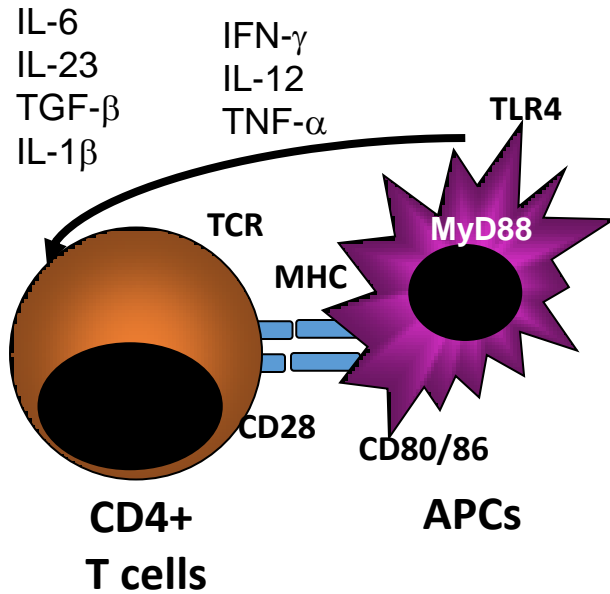
Intestinal commensal bacteria maintain mucosal Th cells especially Th17 type



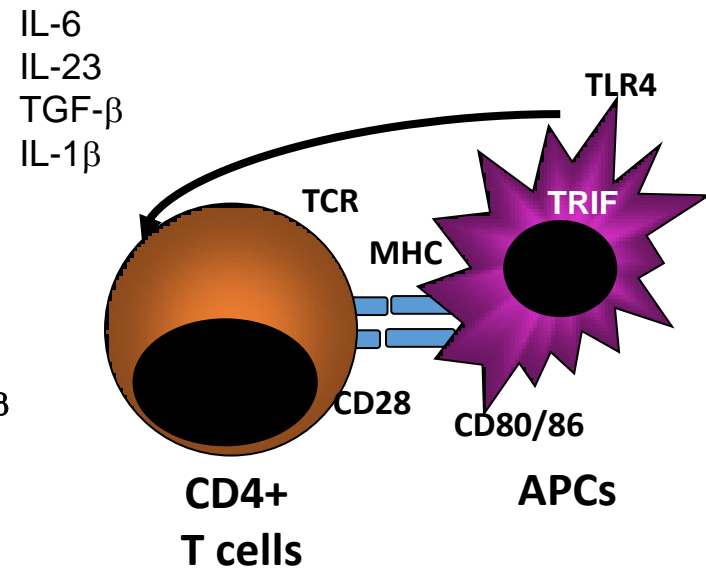
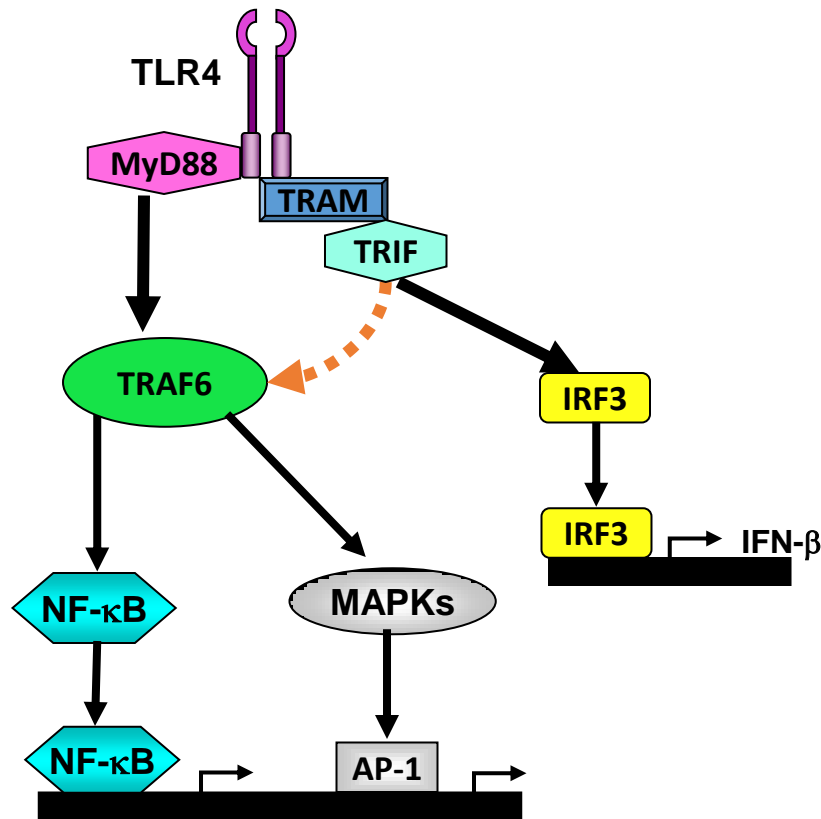
Function of Th17 cells

- Anti-fungal (filamentous fungi, candida, aspergillus)
- Anti-bacterial (especially extracellular bacteria)
- Induce chemotaxis (neutrophils, macrophages)
- Cell growth (in some tumor)
- Induce autoimmune diseases (MS, RA, etc)
- Induce cytokines (IL-17A, IL-17F, IL-22, IL-21, GM-CSF, CCL20, TNF)
- Lineage flexibility (plasticity)

MyD88-dependent TLR4 signaling induces IL-23p19 in APCs

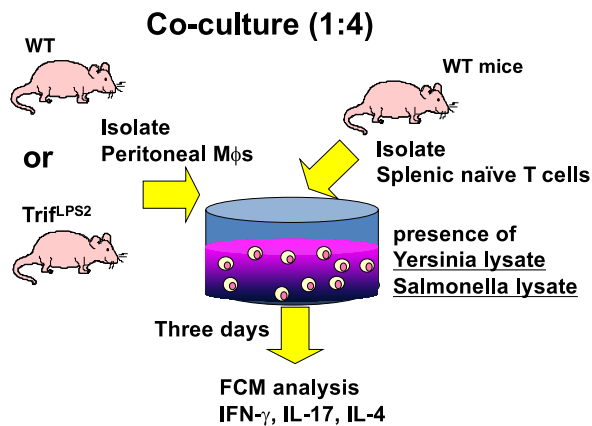


Does TRIF-dependent TLR4 signaling induce Th17 cell differentiation?

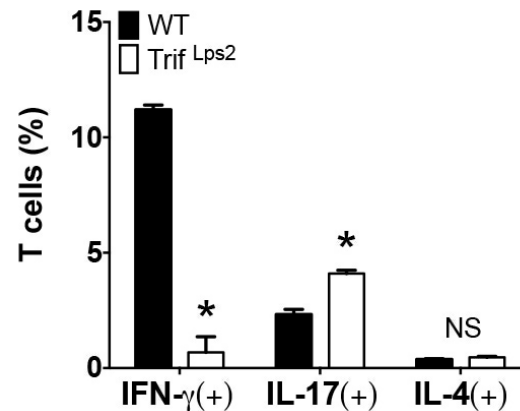


TRIF-dependent TLR4 signaling likely suppress Th17 cell differentiation

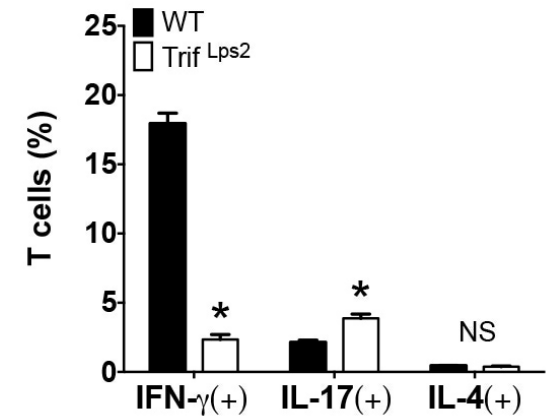
In vitro Th cell differentiation



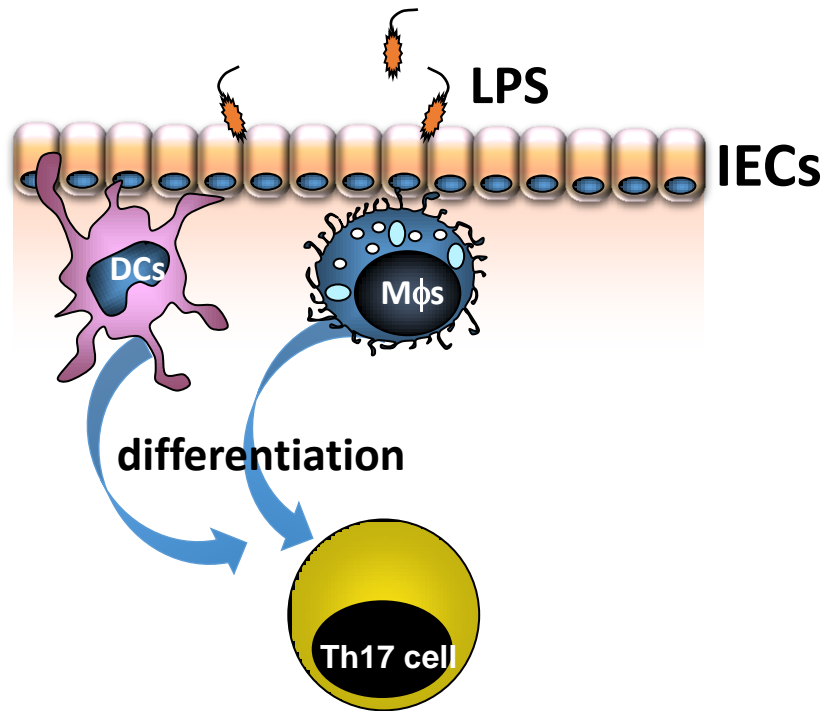
Y. enterocolitica



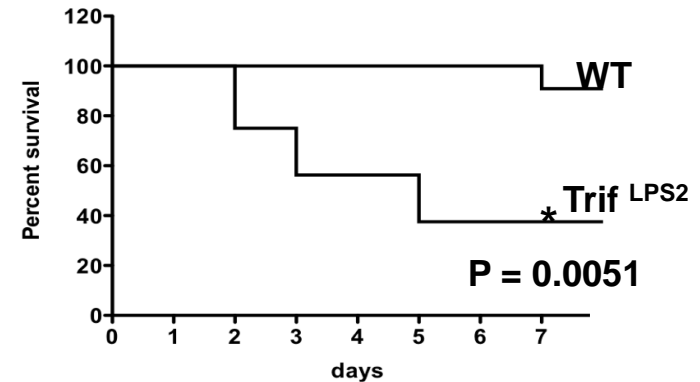
Salmonella



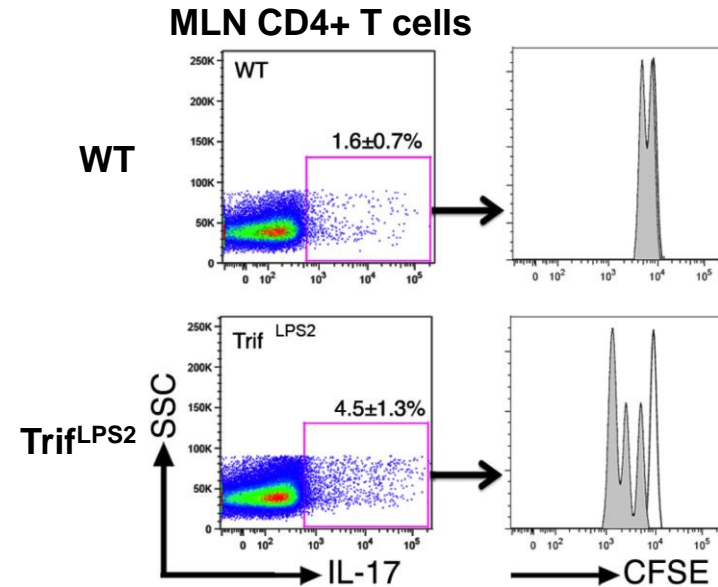
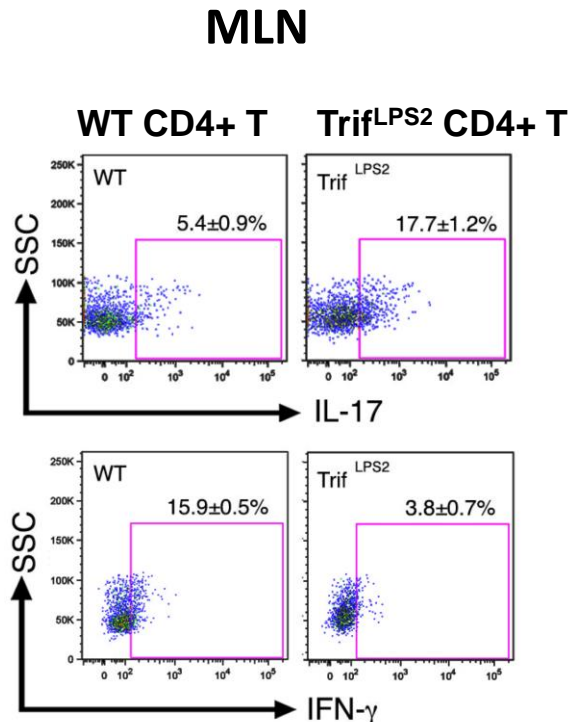
The role of TRIF signaling in the regulation of Th17 cells in the intestine



① **In host defense mechanism**
(*Y. enterocolitica* infection model)

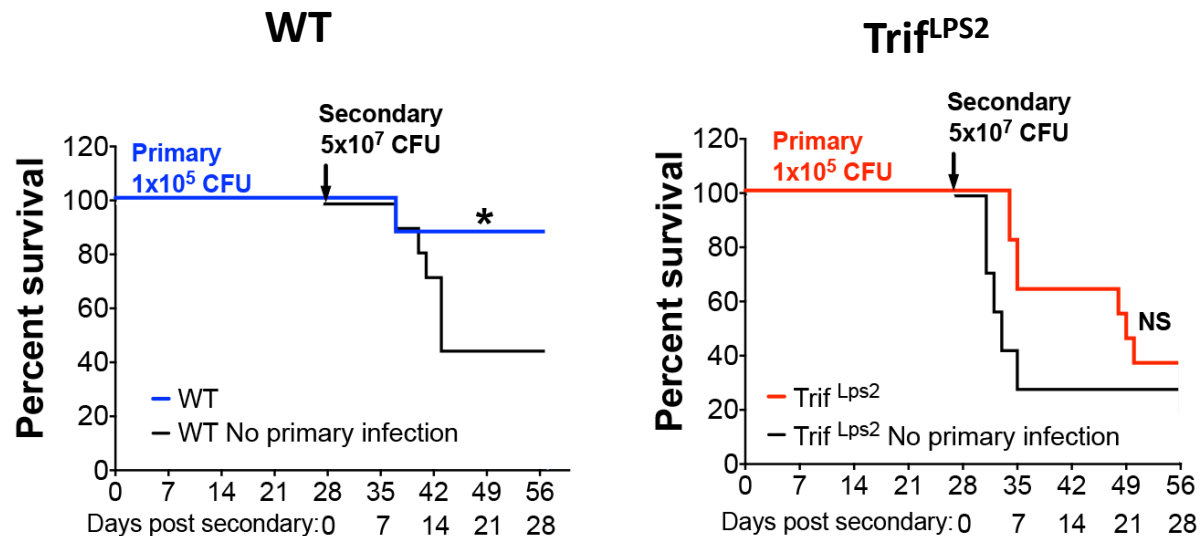


TRIF-deficient ($Trif^{LPS2}$) mice generate more Th17 cells and less Th1 cells in response to *Y. enterocolitica* infection (day 9)

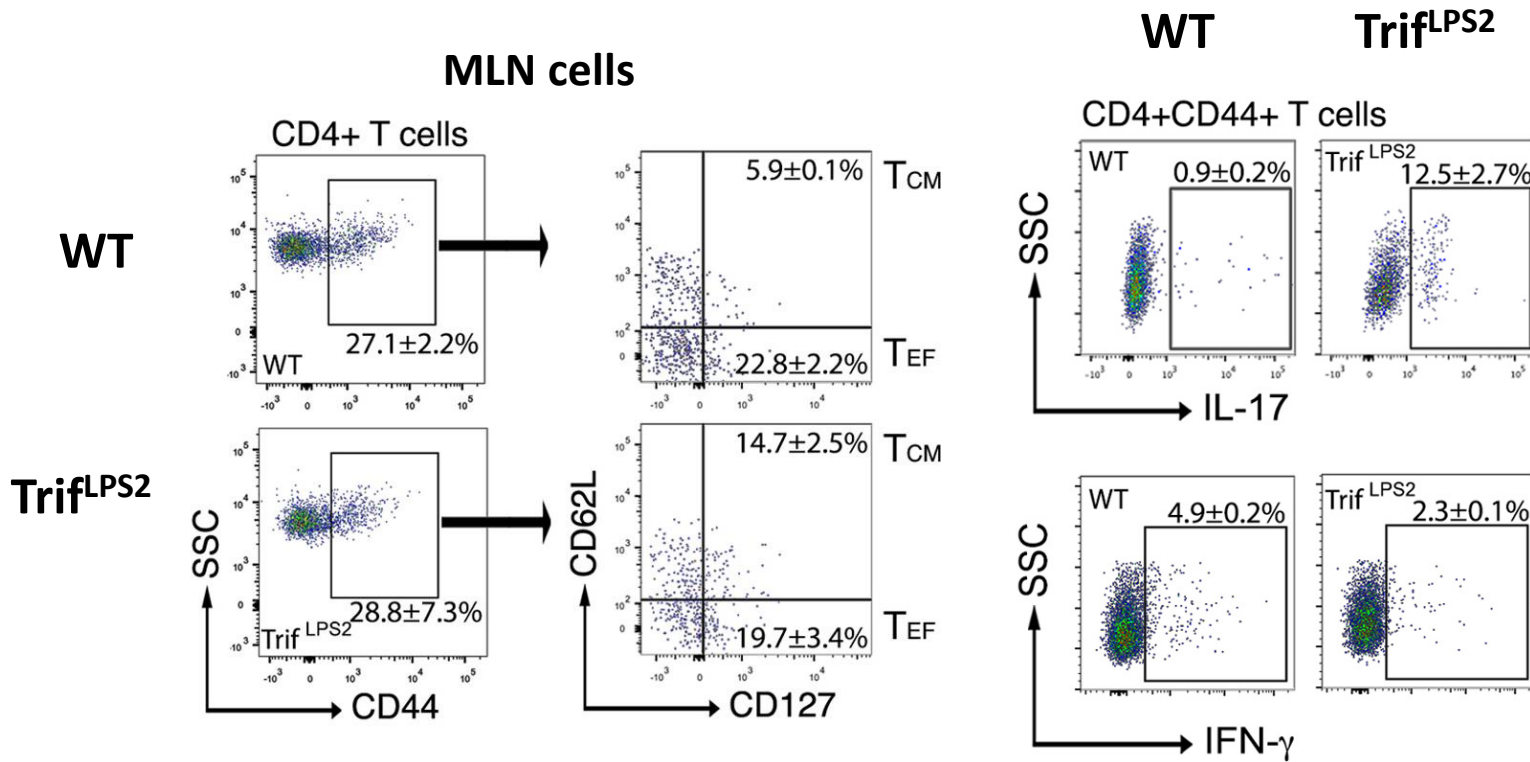


TRIF-deficient mice fail to establish effective immunological memory in the intestine

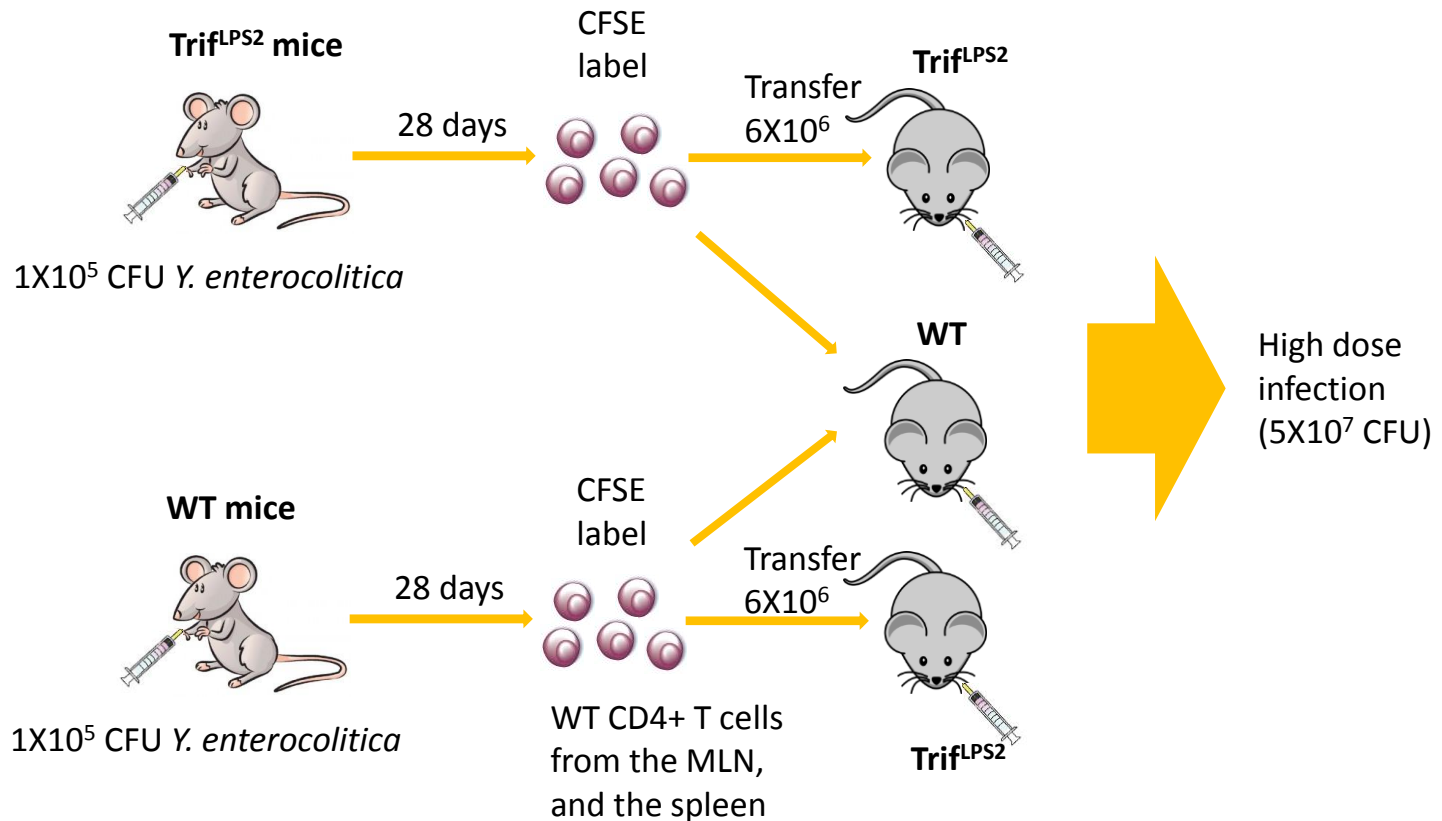
Y. enterocolitica re-infection model



Absence of TRIF skews memory T cells towards Th17 response (7 days post secondary infection)

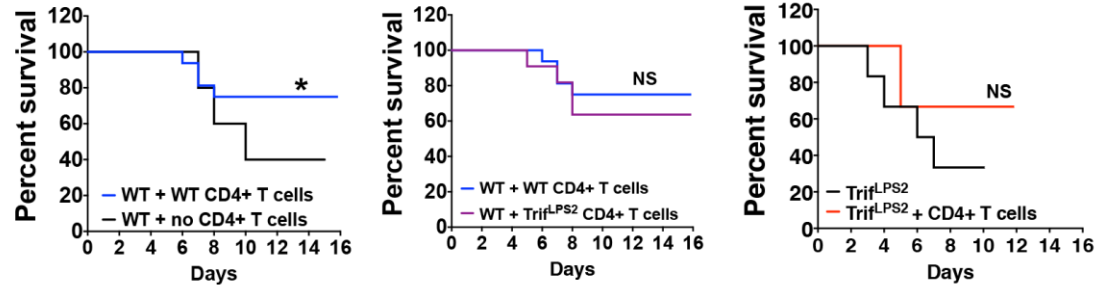


Transferring primed Th cells (role of TRIF in T cells or non T cells?)

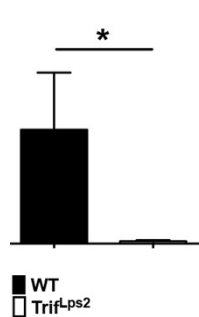


Primed T cells do not confer protective immunity without TRIF signaling during bacterial infection

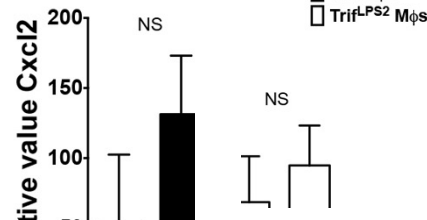
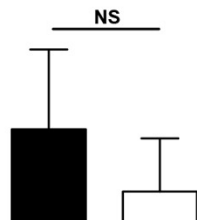
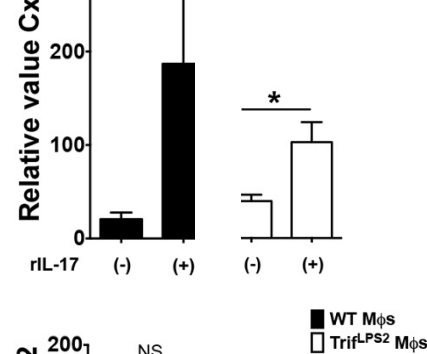
5x10⁷ CFU infection after primed T cell transfer



7 days post infection

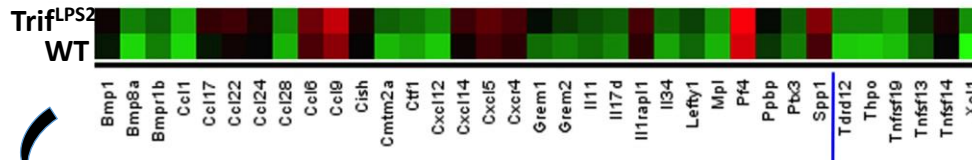
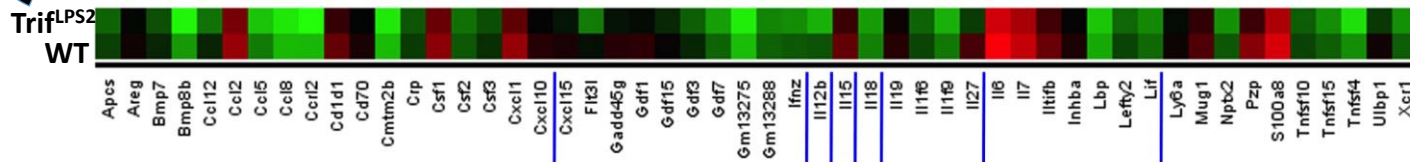


14 days post infection



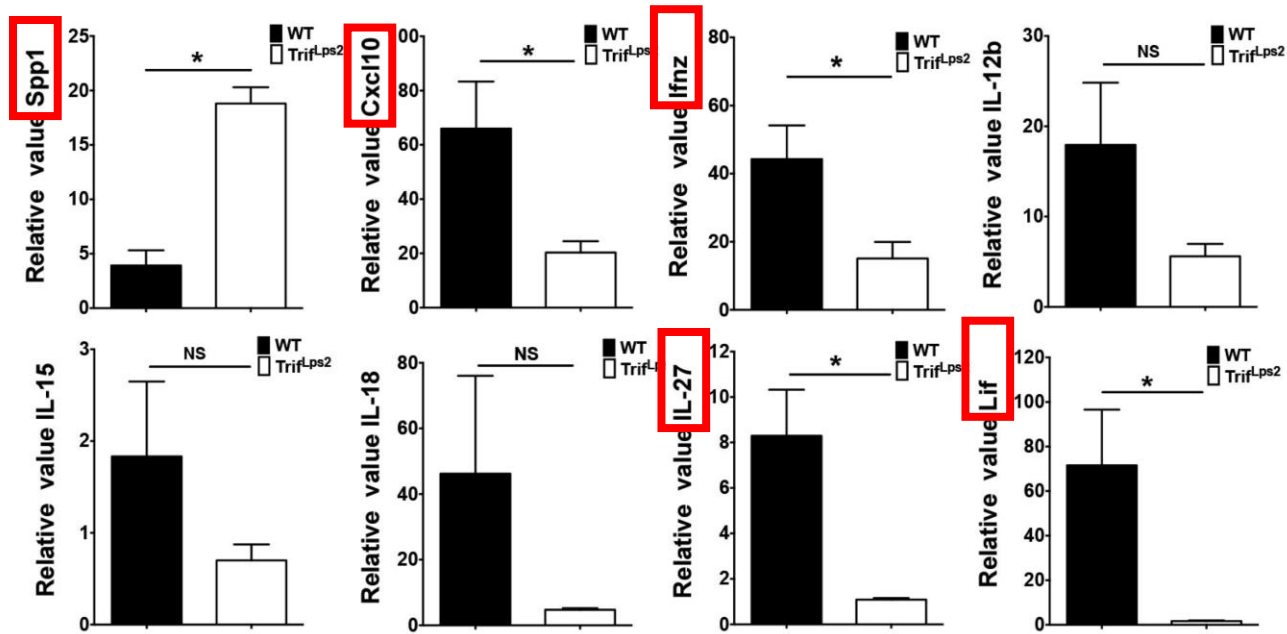
Trif^{LPS2} Mfs had an unique cytokine profile that supports Th17 cell differentiation

52 downregulated in Trif^{LPS2}



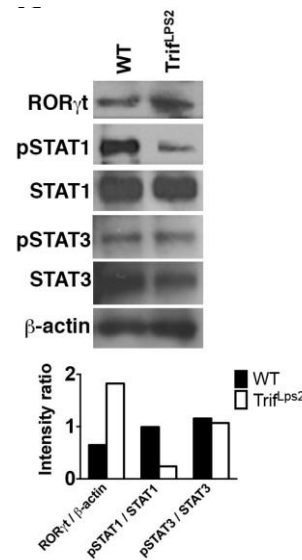
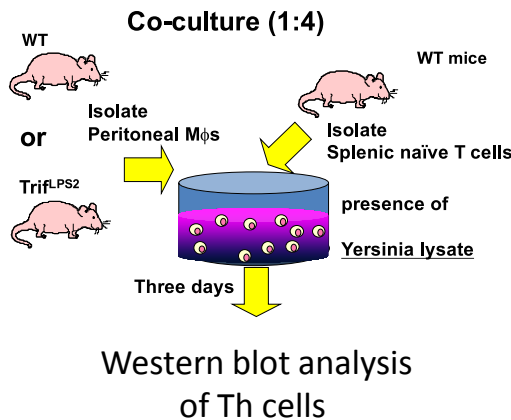
35 upregulated in Trif^{LPS2}

Consistent alteration of gene expression in the MLN during *Y. enterocolitica* infection

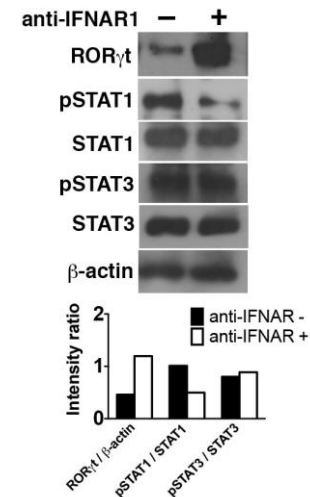


TRIF-dependent regulation of Th17 cell response involves type I IFN signaling

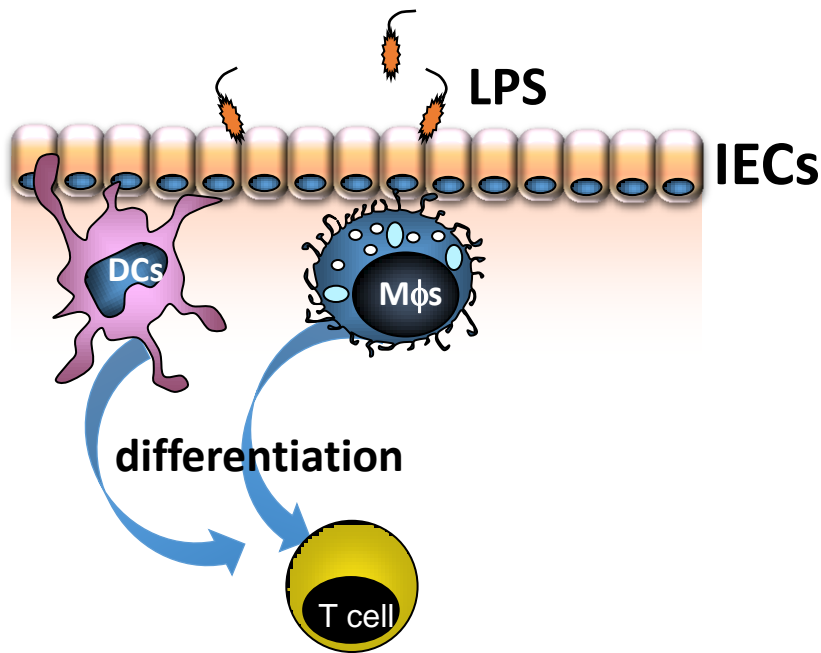
In vitro Th cell differentiation



WT Mφs + T cells + anti-IFNAR



The role of TRIF signaling in the regulation of Th17 cells in the intestine



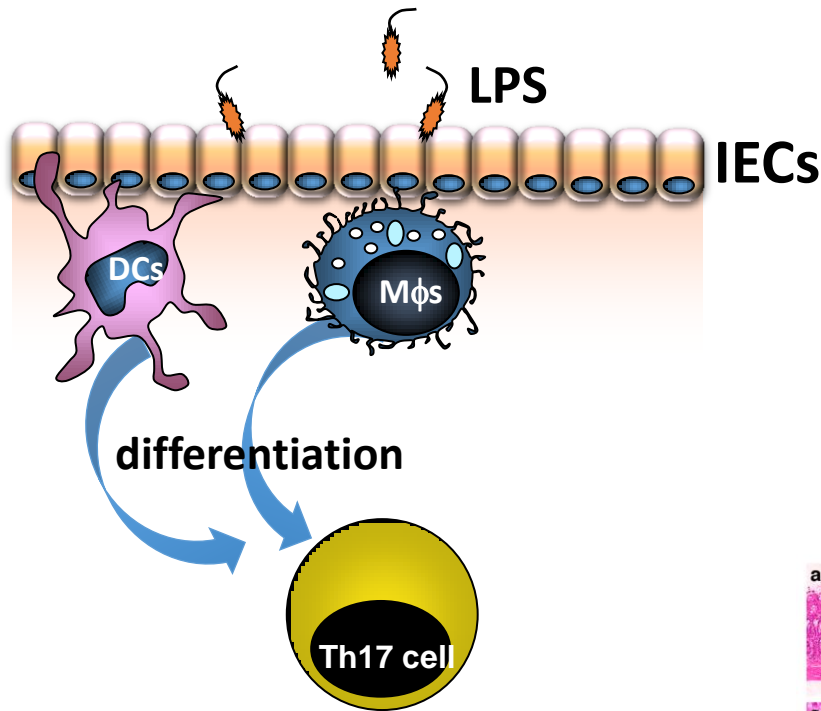
Summary

① In host defense mechanism

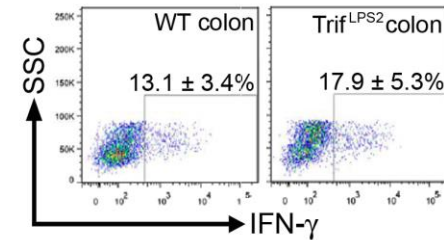
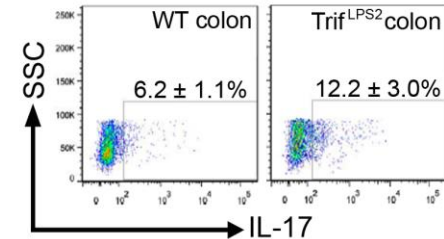
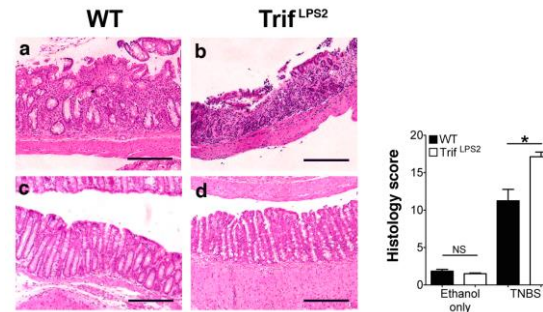
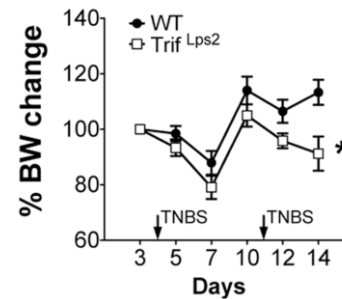
(*Y. enterocolitica* infection model)

1. TRIF suppresses Th17 cell generation and balances Th1 and Th17 cell responses against Gram-negative bacteria, *Y. enterocolitica*.
2. The maintenance of Th1 and Th17 cell balance also requires TRIF signaling and is involved in host resistance to *Y. enterocolitica*.
3. TRIF-dependent suppression of Th17 cell generation may be mediated by type I IFN signaling.

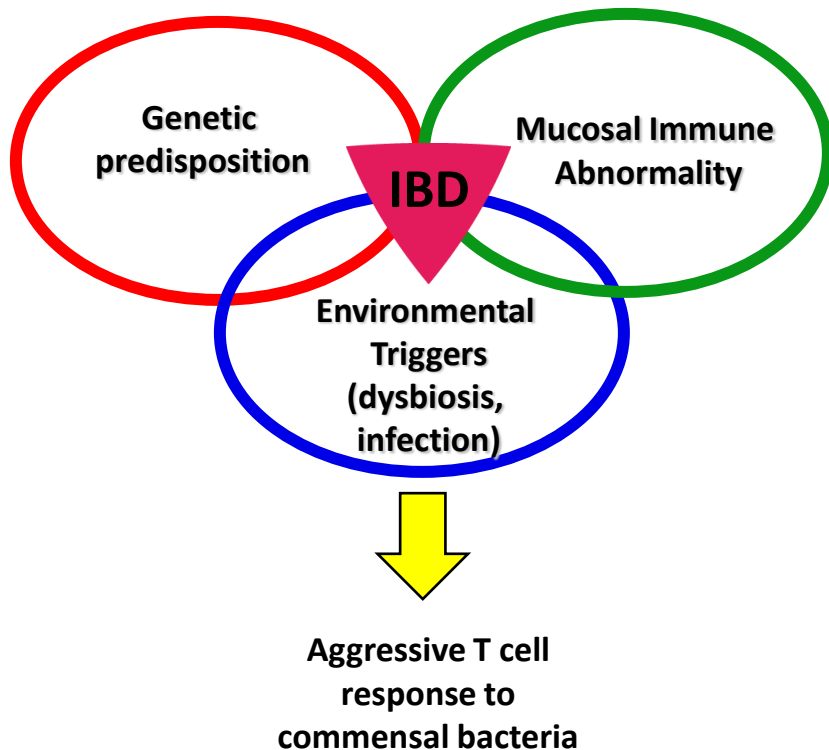
The role of TRIF signaling in the regulation of Th17 cells in the intestine



② In intestinal inflammation (TNBS colitis model)



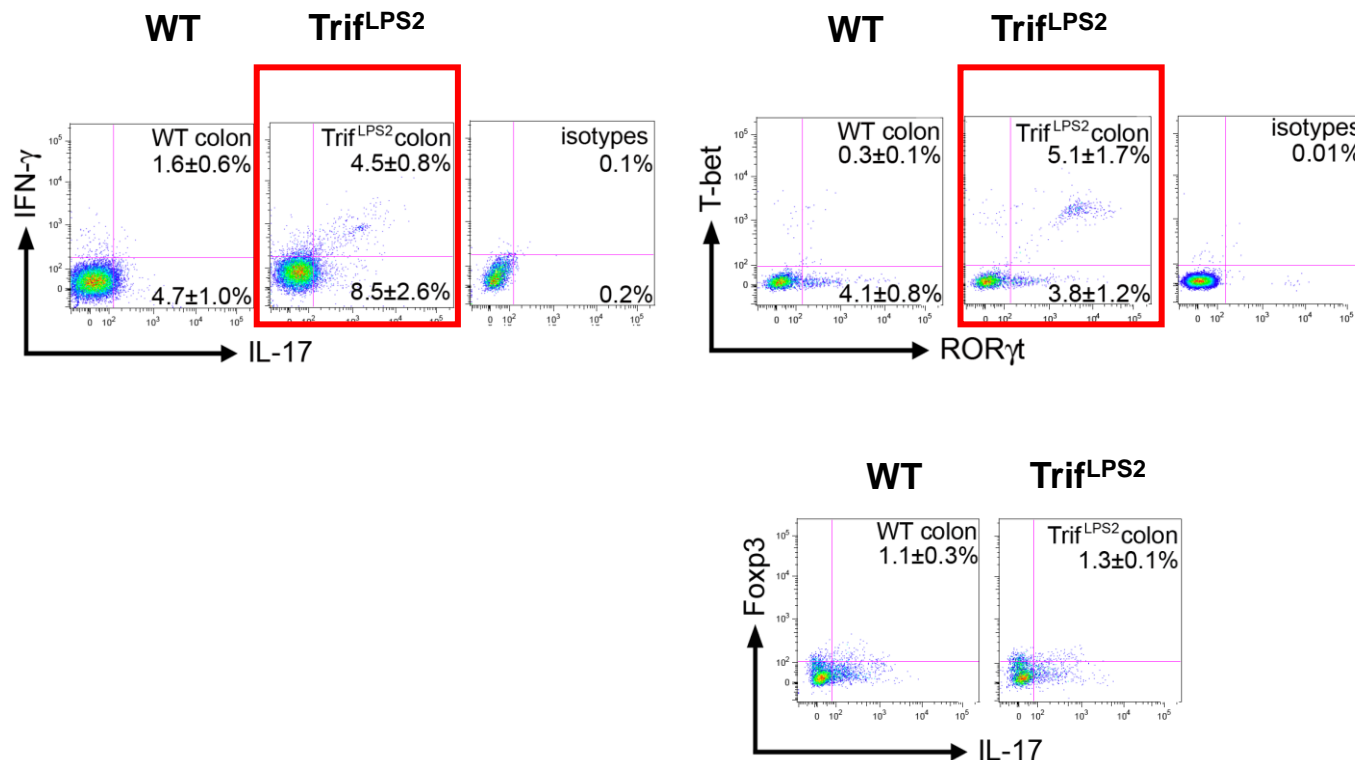
Pathogenesis of inflammatory bowel disease (IBD) involves host Th cell responses to commensal bacteria



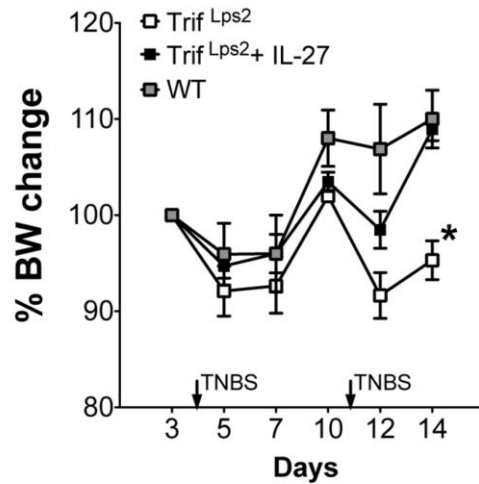
In patients with IBD

- Increased number of Th17 cells have been found in inflamed mucosa.
- Attempts have made blocking IL-17, a signature cytokine of Th17 cells in patients with CD; however, it failed to meet efficacy criteria.
- Animal studies have demonstrated inconsistent results with regard to pathogenic and regulatory phenotypes of Th17 cells in the intestine.
- The existence of IFN- γ (+) and Foxp3(+) Th17 cells in human and animal models of IBD suggests the fluctuant phenotype of Th17 cells in the intestine.
- IFN- γ (+)Th17 cells have been implicated in severity of colitis in human and animal models of IBD.

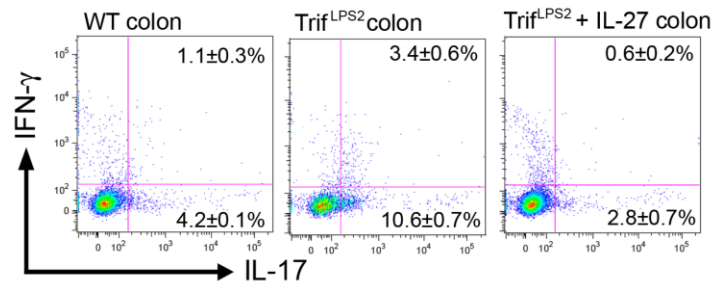
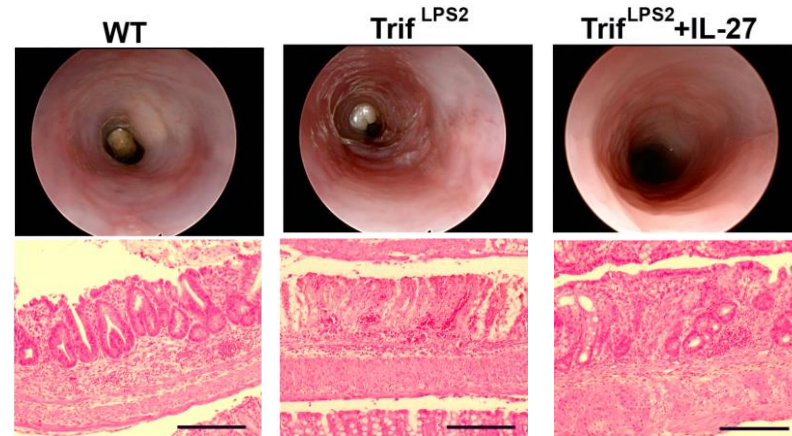
Trif^{LPS2} mice carry IFN- γ expressing Th17 cells in the intestine during TNBS colitis



IL-27 treatment reduces severity of TNBS colitis in $Trif^{LPS2}$ mice along with suppression of IFN- γ expressing Th17 cells in the lamina propria

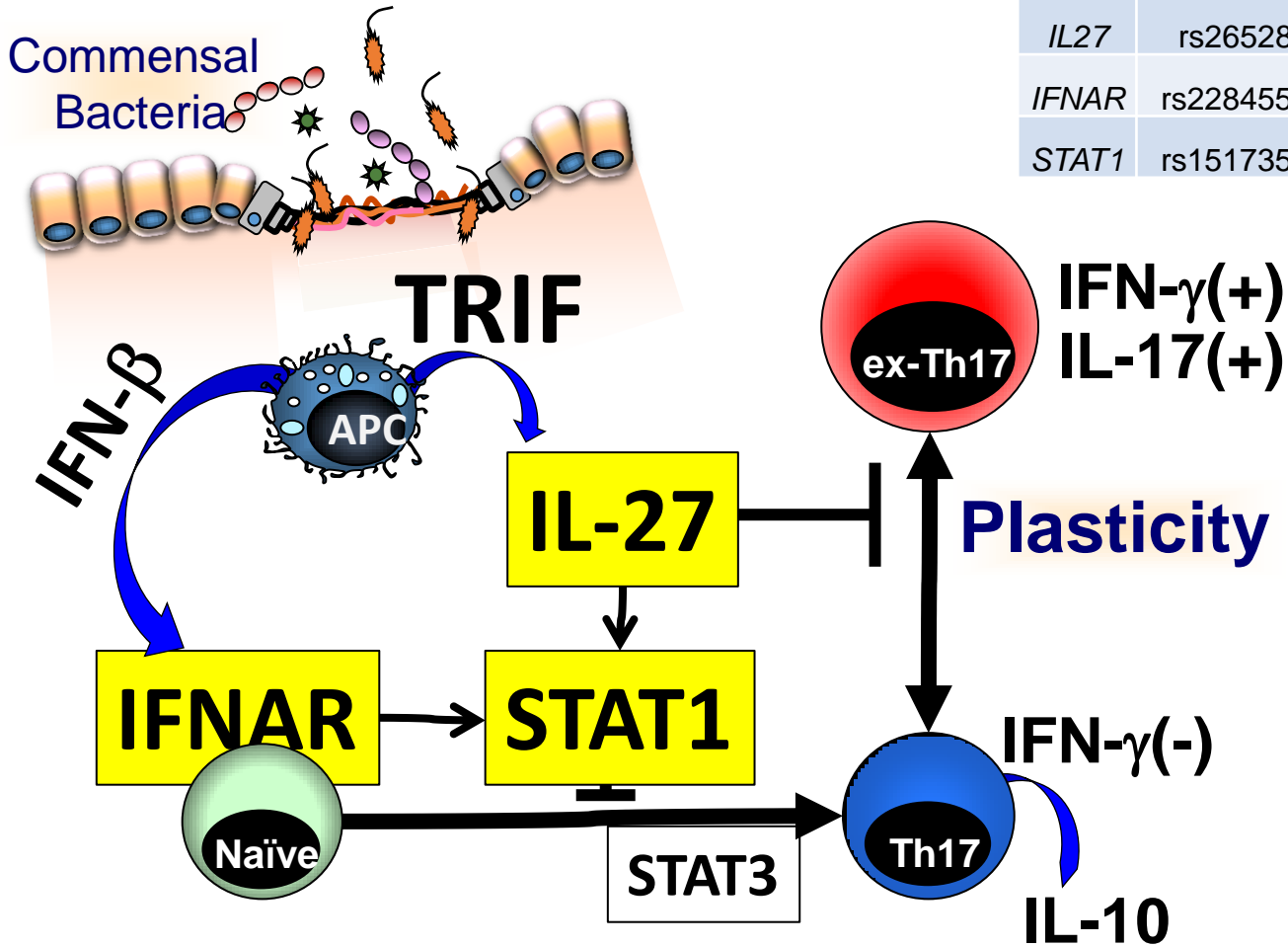


rIL-27 daily injection
(s.c, 0.25 μ g)



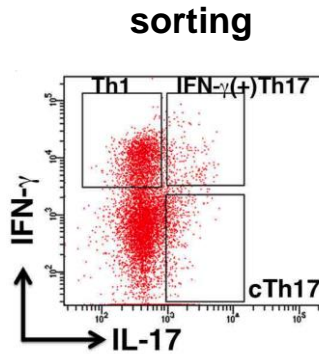
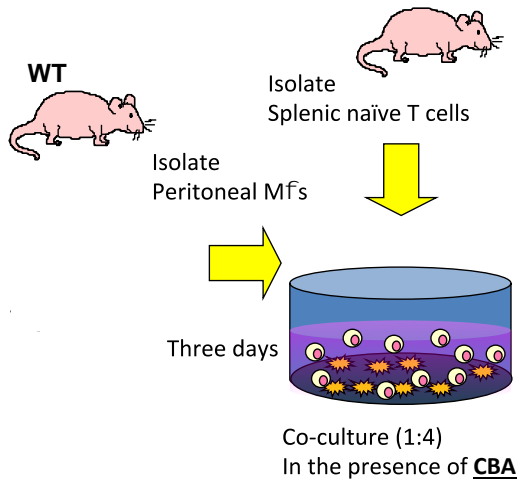
Th17 cell plasticity in Crohn's disease

Gene	SNP ID	Alleles	Allele frequency	P value
<i>IL27</i>	rs26528	G/A	45.1	9.7*10E-22
<i>IFNAR</i>	rs2284553	G/A	59.9	2.1*10E-16
<i>STAT1</i>	rs1517352	C/A	60.0	1.9*10E-10

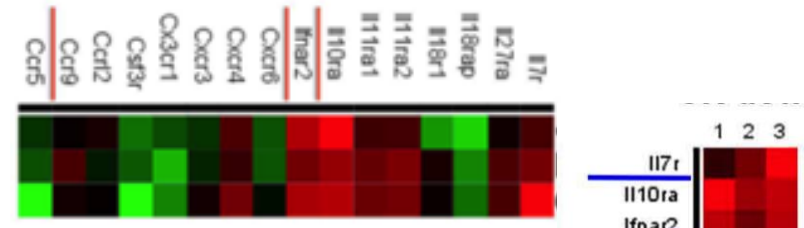


The altered expression of cytokine receptors in IFN- γ (+)Th17 cells

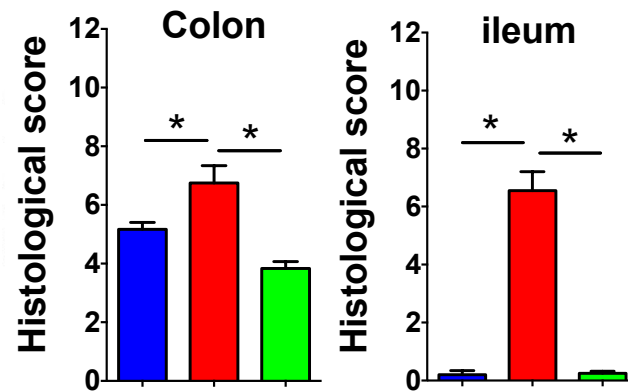
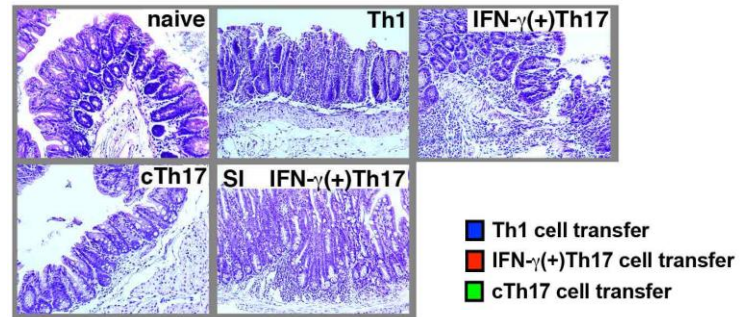
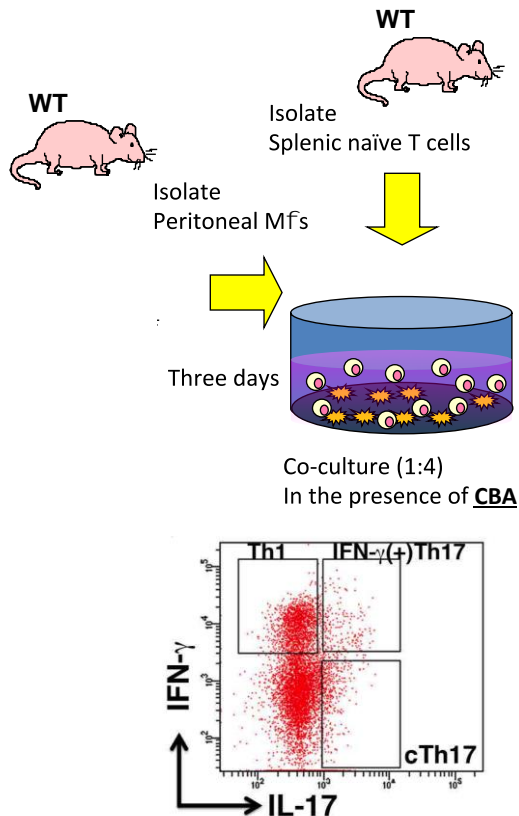
IFN- γ /IL-17A reporter mouse



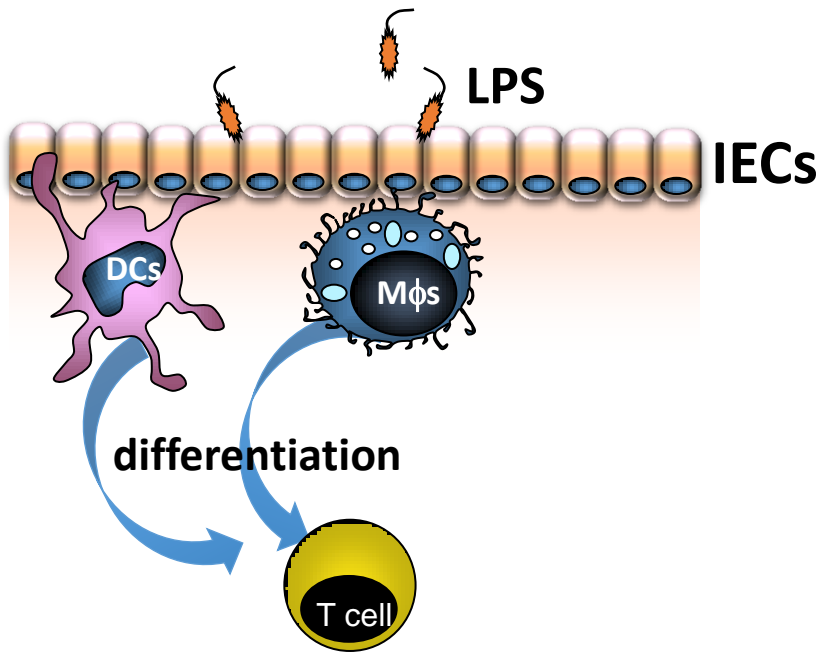
Microarray analysis



IFN- γ (+)Th17 cells (ex-Th17 cells) are more potent to induce colitis than IFN- γ (-)Th17 cells



The role of TRIF signaling in the regulation of Th17 cells in the intestine

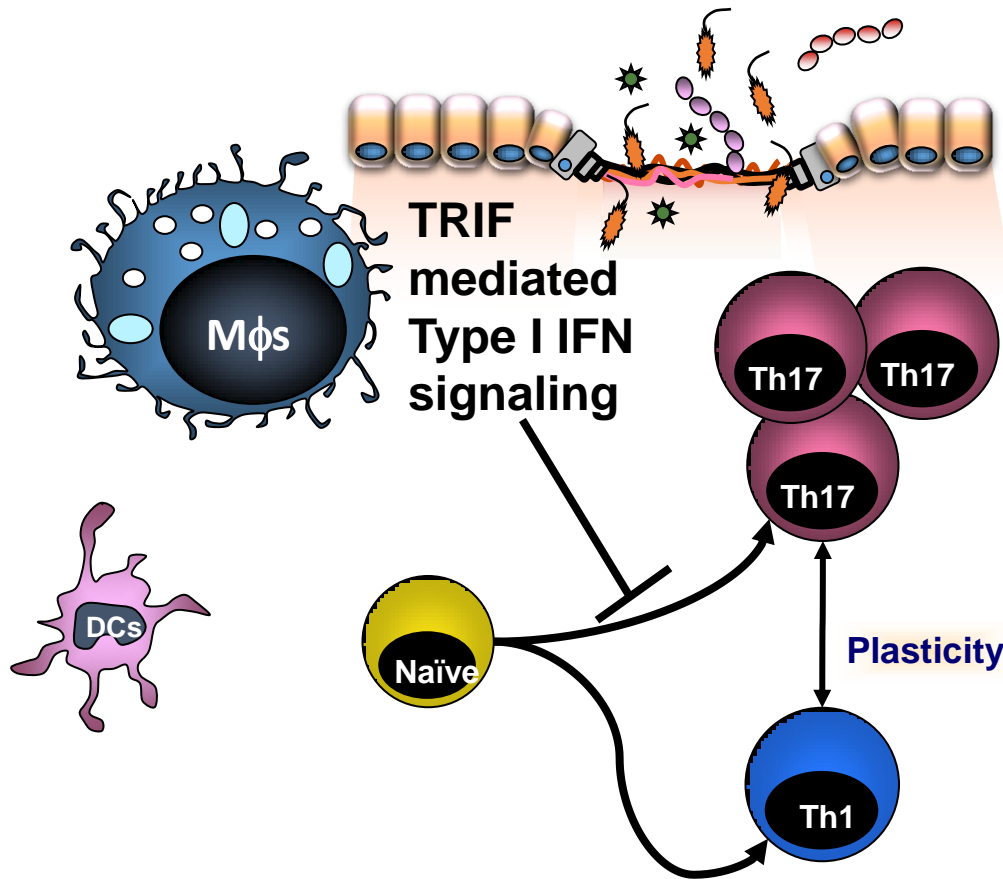


Summary

② **In intestinal inflammation** (TNBS colitis model)

1. TRIF suppresses Th17 cell generation and plasticity with Th1 cells in response to commensal bacteria (CBA).
2. The suppression of Th17 cell generation and plasticity by TRIF signaling involves IL-27, IFNAR, and STAT1.
3. SNPs of IL-27, IFNAR, and STAT1 were individually associated with human Crohn's disease.
4. IFN- γ (+)Th17 cells have strong inflammatory capacity especially in the ileum.

Summary



Th1 / Th17 imbalance

Impairs host
resistance to
infection

Exacerbates colitis