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Immunity
Article

Group 2 Innate Lymphoid Cells Are Critical for the Initiation of Adaptive T Helper 2 Cell-Mediated Allergic Lung Inflammation

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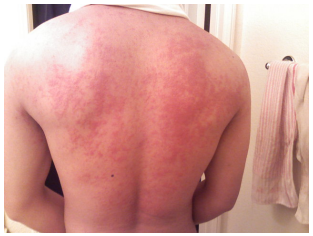
http://dx.doi.org/10.1016/j.immuni.2014.01.011

Allergy



•Allergy is one the most common health problems in the industrialized world.

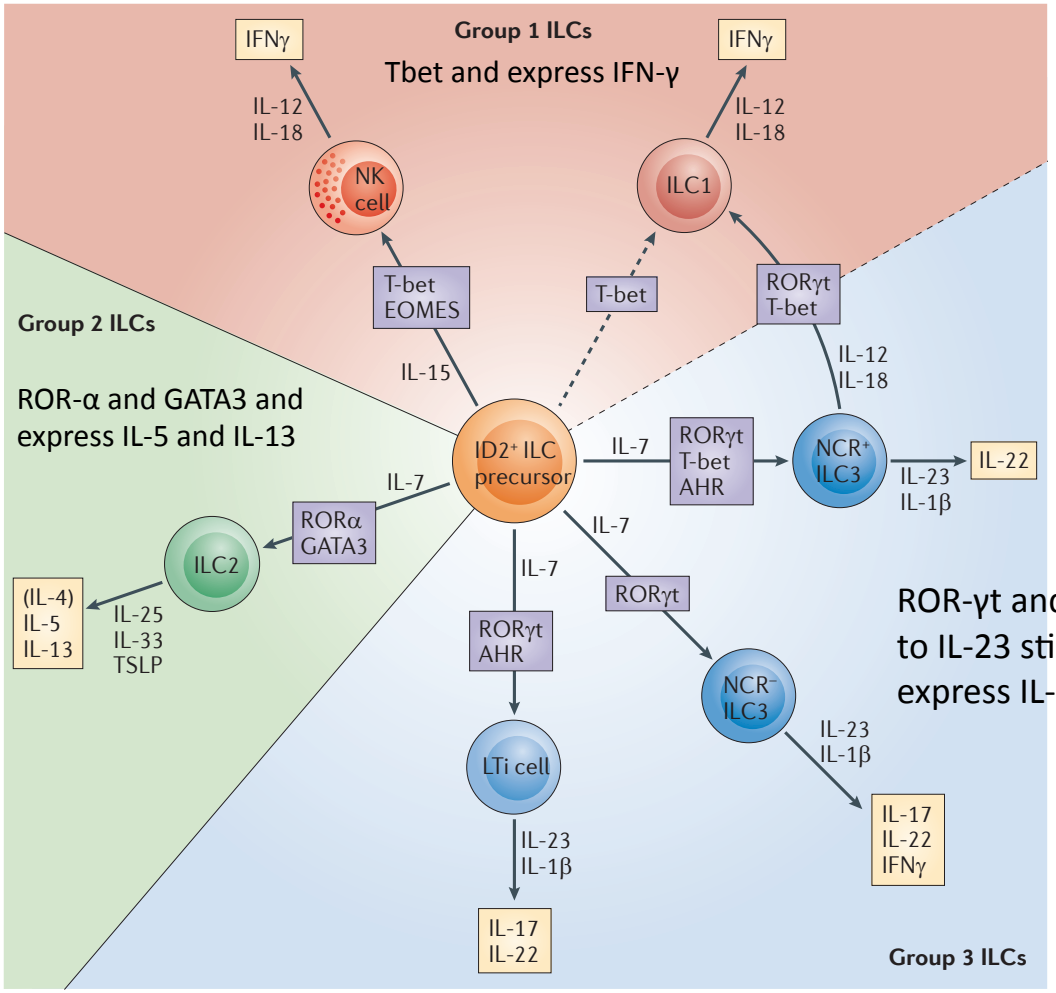
•A type 2 immune response is responsible for most of the allergen-induced inflammation at mucosal surfaces, and is characterized by the overproduction of Th2 cytokines and IgE.

•In sensitized individuals, reexposure to the same allergens, induce a memory Th2 response, characterized by the secretion of IL-4, IL-5, IL-9 and IL-13.

•Mechanisms by which allergens initiate the differentiation of naïve CD4+ T cells into Th2 cells during the sensitization phase are not well understood.

Innate lymphoid cells (ILCs)

Rapid and potent producers of type 2 cytokines IL-5 and IL-13



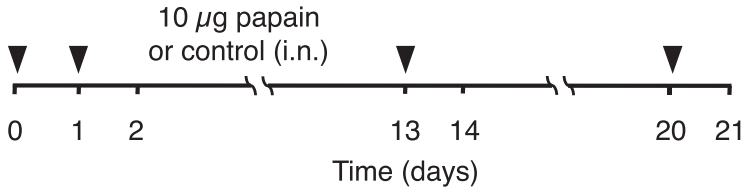
ROR-γt and in response to IL-23 stimulation express IL-17A and IL-22

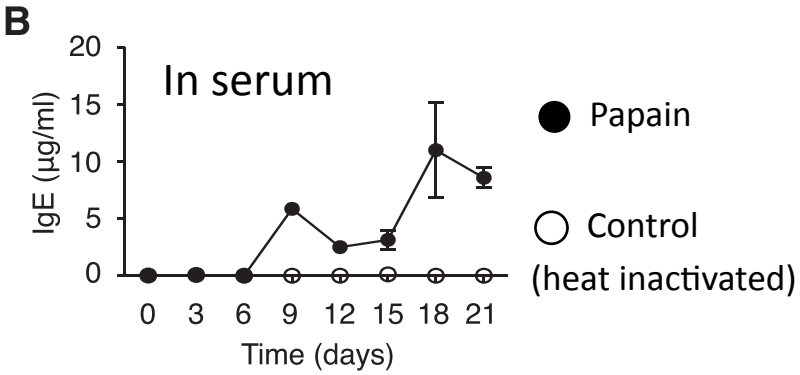
Spits et al. Nature reviews Immunology 2013

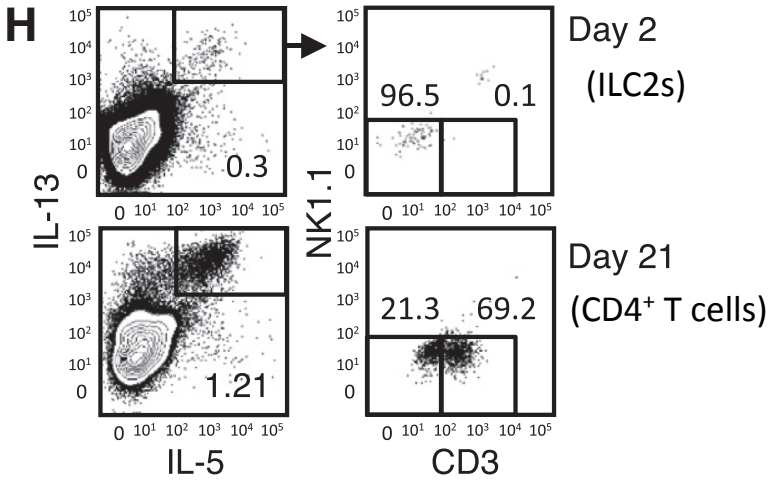
- Intranasal administration of papain induces lung IL-5 and IL-13 producing ILC2S in RAG deficient mice.
- ILC2 activation can induce T cell and IgE independent acute allergic lung inflammation
- RORα deficient Staggerer ($Rora^{sg/sg}$) bone marrow transplanted mice are specifically deficient in ILC2s and fail to develop type 2 lung inflammation after sensitization with papain.

- Since ILC2s are potent source of type 2 cytokines, how do these cells influence the downstream Th2 response ?

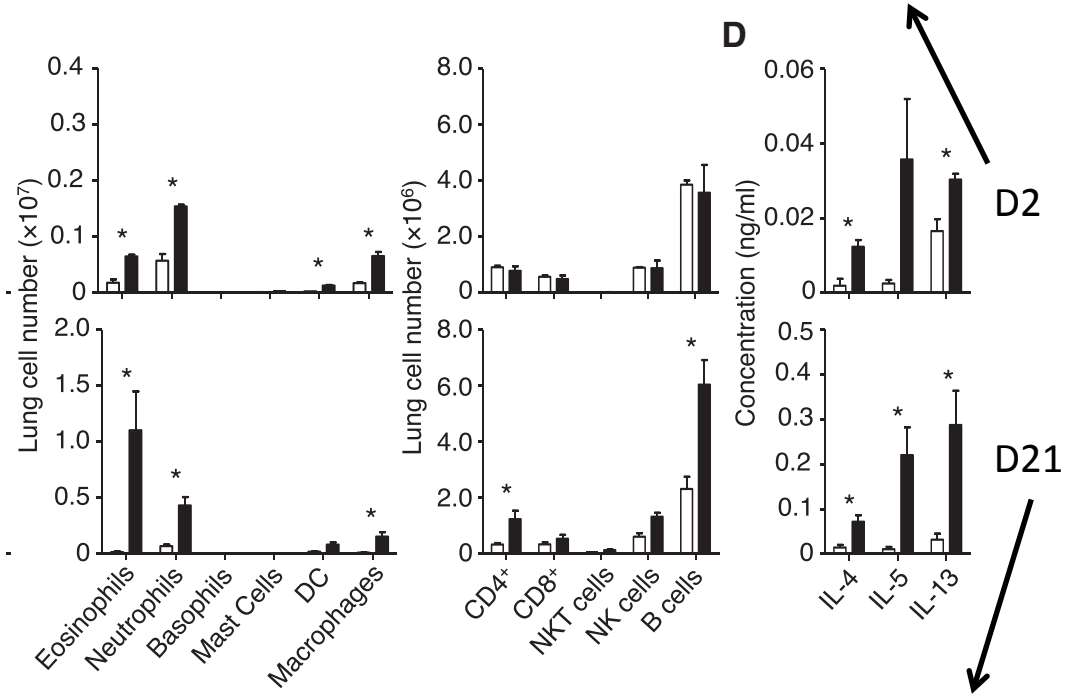
Innate and adaptive immune response to protease-allergen papain







Activated ILC2s rather than Th2 cells mediated these early effects since similar responses were observed in Rag1-/- (FigS1A-C)

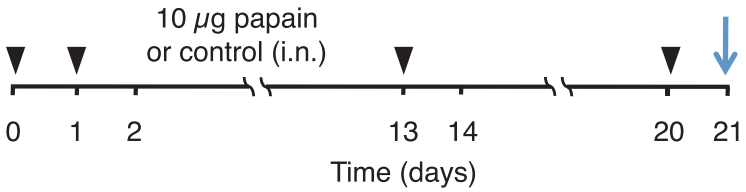


No augmented in Rag1-/- mice (FigS1A-C)

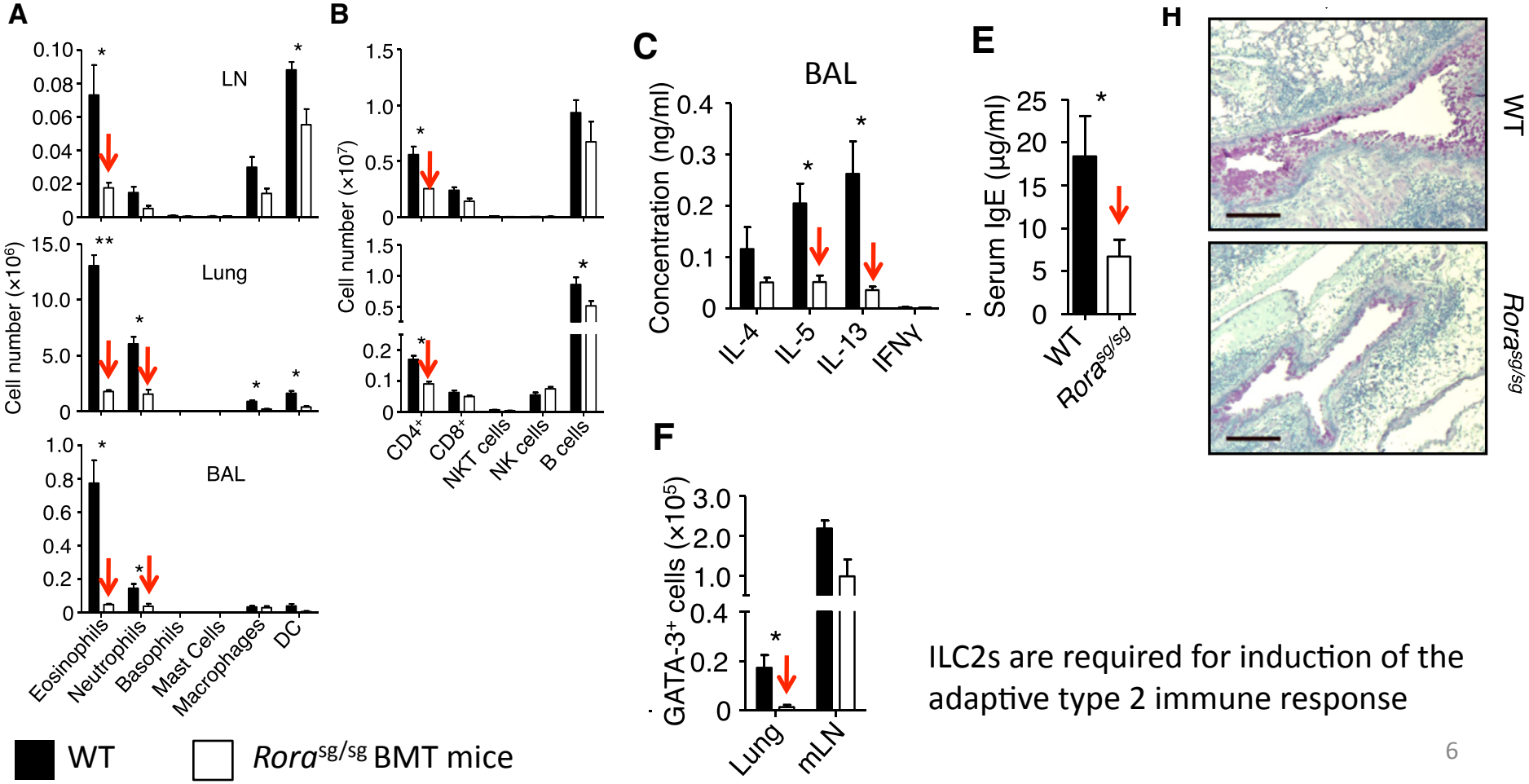
Protease-allergen papain induced a strong innate and adaptive type 2 immune response

Effects of ILC2 deficiency on Th2 responses to papain (D21)

ILC2-deficient
Rora$^{sg/sg}$ BMT mice

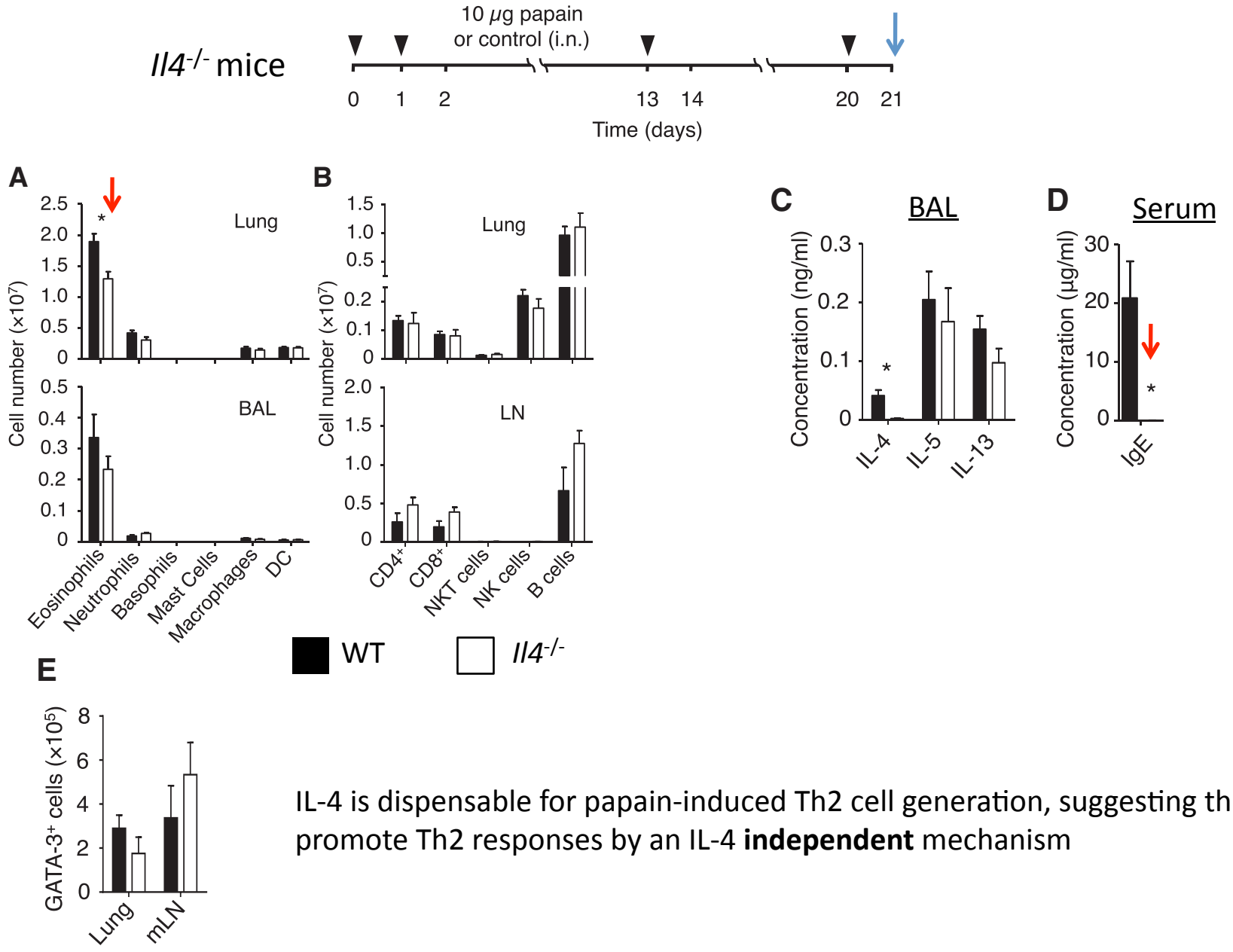


- Transcription factor RORα is required for ILC2 development but not for Th2 differentiation.
- Transplantation of BM from RORα mutant Rora$^{sg/sg}$ into irradiated WT mice generates ILC2-deficient mice



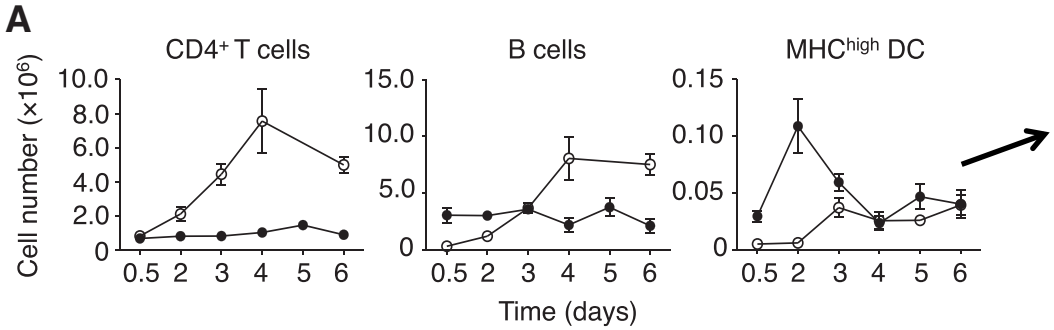
ILC2s are required for induction of the adaptive type 2 immune response

Role of IL-4 in Th2 response to inhaled protease allergen

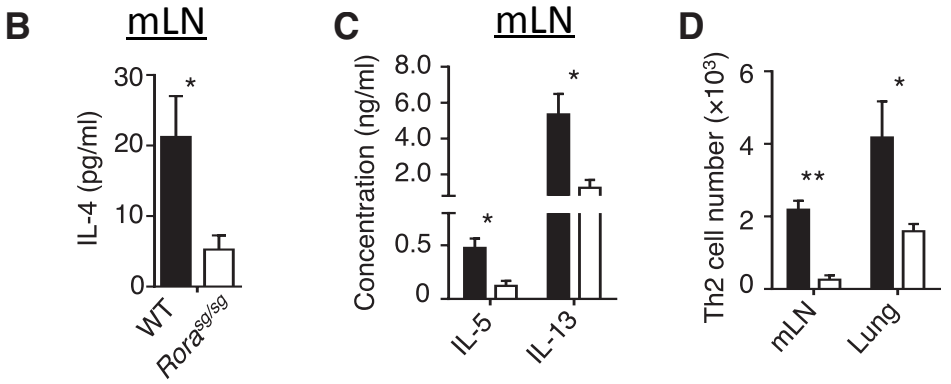


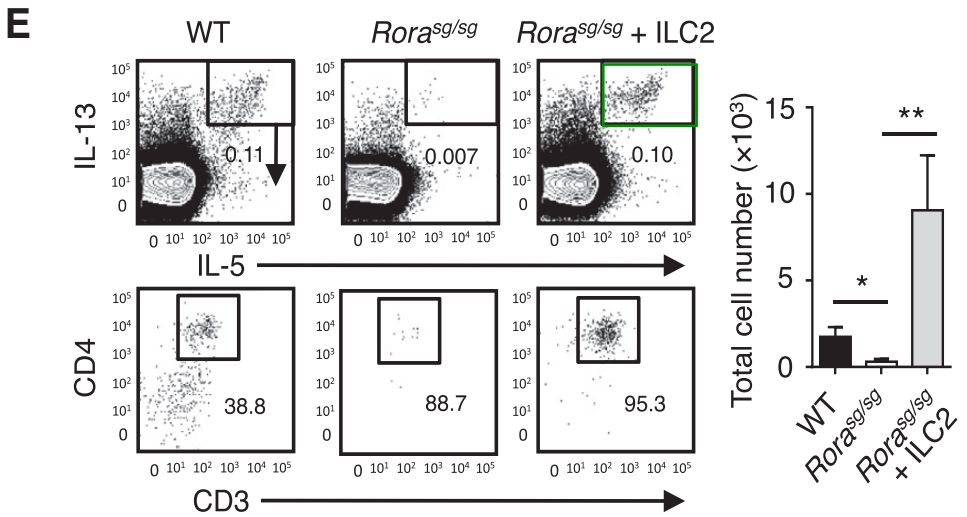
IL-4 is dispensable for papain-induced Th2 cell generation, suggesting that ILC2s promote Th2 responses by an IL-4 **independent** mechanism

Role of ILC2s in the induction of Th2 cells in the mLN



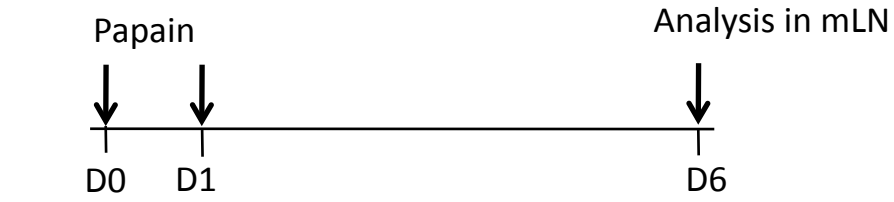
Papain activated lung DCs likely migrated into the draining mLN where they stimulated naïve CD4⁺ T cells

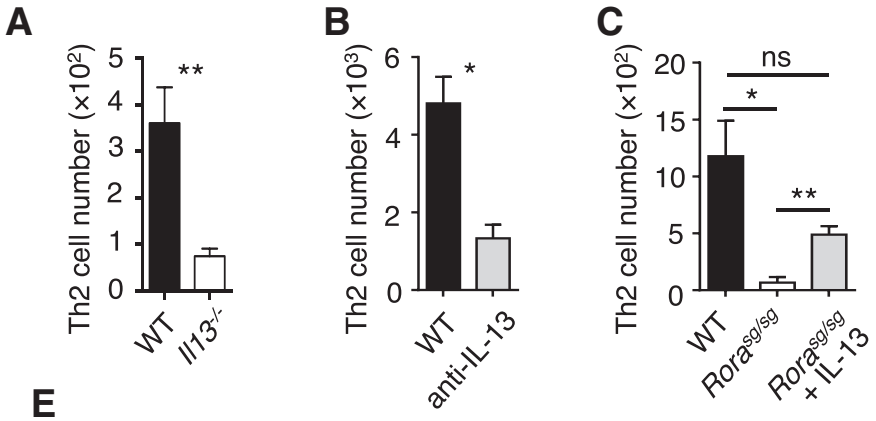


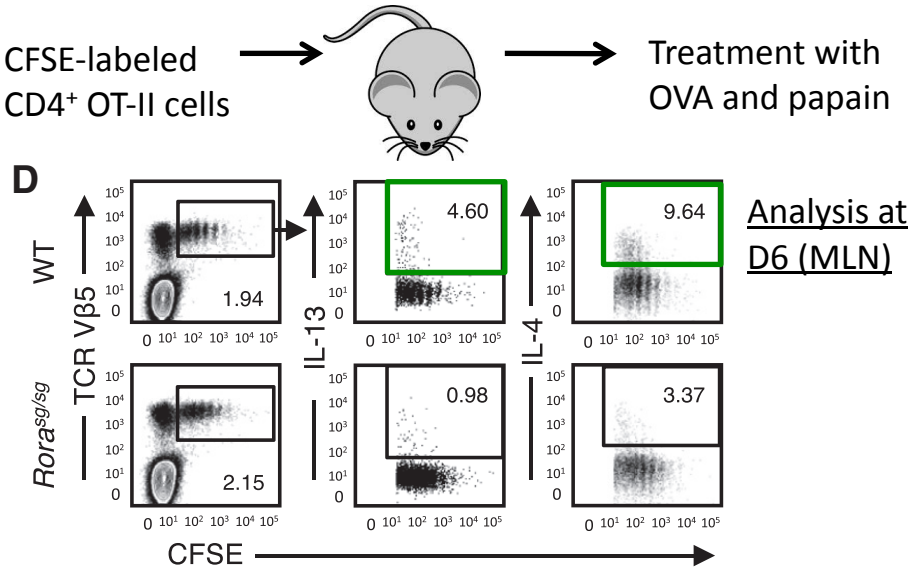


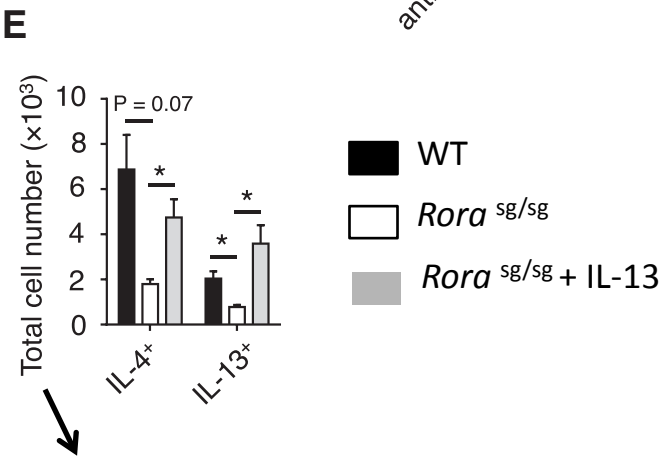
ILC2s are instrumental for induction of Th2 cells in the mLN

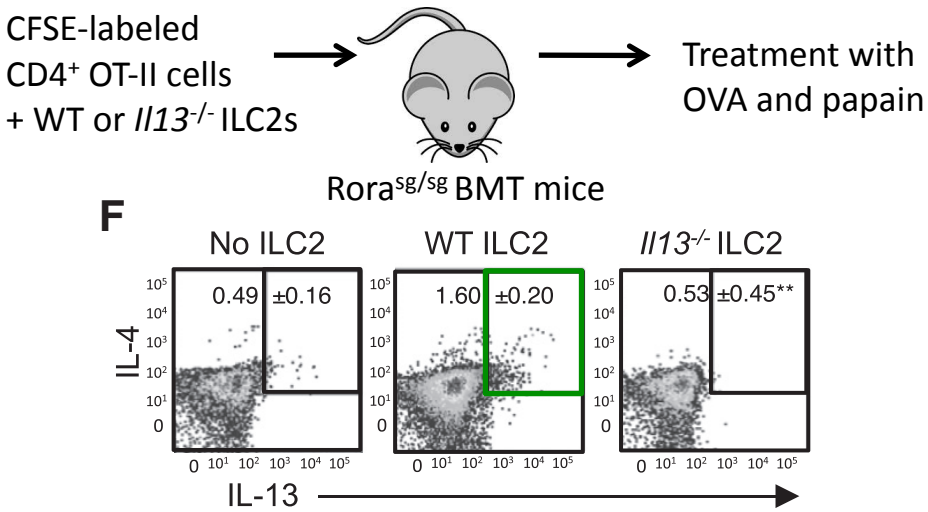
Requirement for IL-13 for the induction of Th2 cells





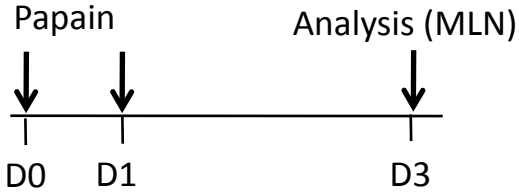


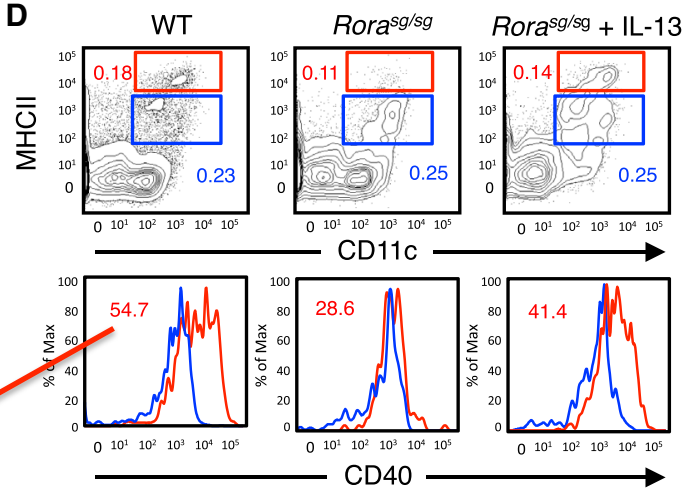


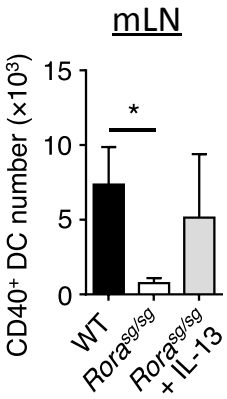


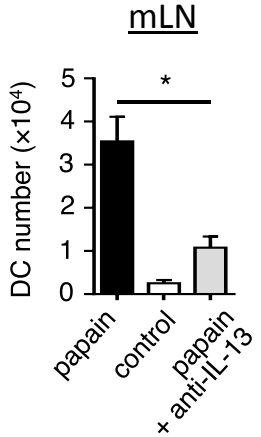
IL-13 is required for the induction of Th2 cells

Role of ILC2-derived IL-13 on DC function





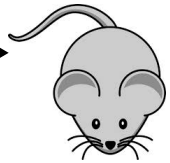




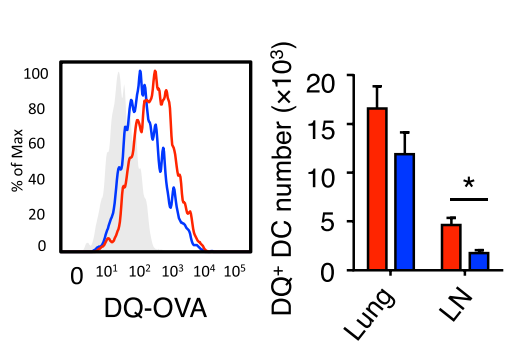
(CD40: critical for Th2 differentiation)

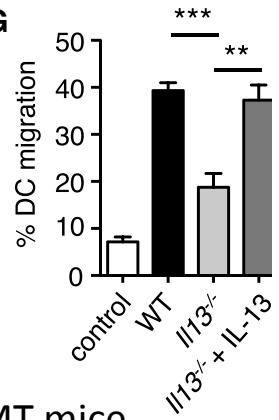
DQ-OVA become fluorescent upon processing by APC

Traceable DQ-OVA + papain



Analysis for DQ+CD11c+MHCIIhi DCs





Lung tissue explants were made from papain stimulated mice on d3. Tissue explants cultured and exposed to a CCL21 chemokine gradient for 14hr.

ILC2-derived IL-13 promote DC migration to the draining lymph node

WT Rorasg/sg BMT mice

Summary

- ILC2s are required for efficient Th2 cell mediated allergic lung inflammation.
- Th2 cell promoting effect of ILC2s appeared to be mediated by IL-13.
- IL-13 had no effect on Th2 cell differentiation, indicating that IL-13 is unlikely to act directly on naïve T cells.
- DCs are the main target of ILC2-derive IL-13 in papain treated mice

Immunity
Article

Toll-like Receptor and Inflammasome Signals Converge to Amplify the Innate Bactericidal Capacity of T Helper 1 Cells

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Introduction

•Pathogen-specific lymphocytes recirculate at low frequency and undergo rapid expansion in response to infection.

•The expansion of individual T cell clones are tightly regulated by pathogen specific TCRs that recognize microbial peptides on MHC molecules.

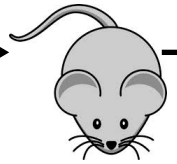
•However, a lower threshold for stimulating activated effector T cells might be advantageous when the host confronts a replicating pathogen.

•IL-12 and IL-18 cause noncognate stimulation of effector $CD8^+$ T cells .

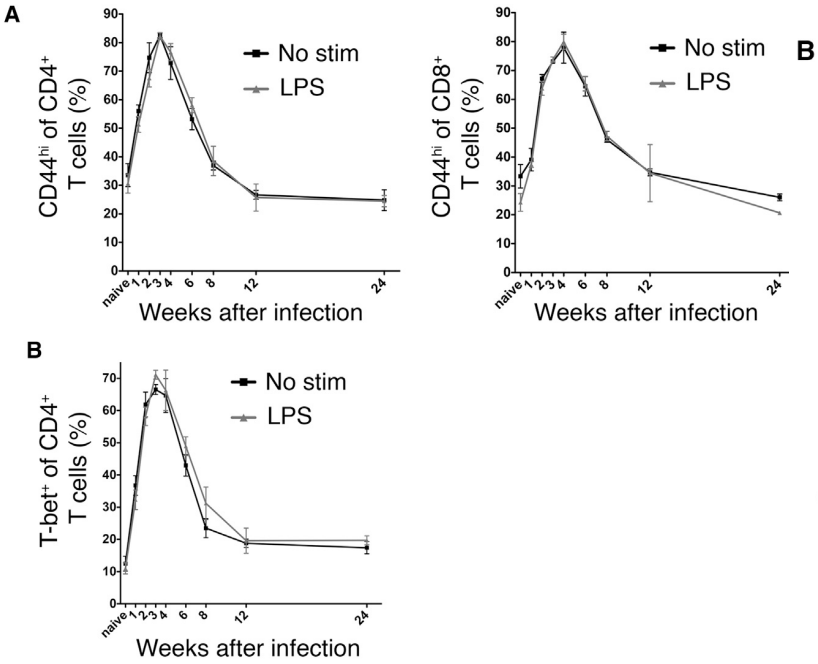
•$CD4^+$ Th1 cells can activate macrophages in the absence of cognate stimuli and also provide cross-protection against unrelated co-infecting microbes.

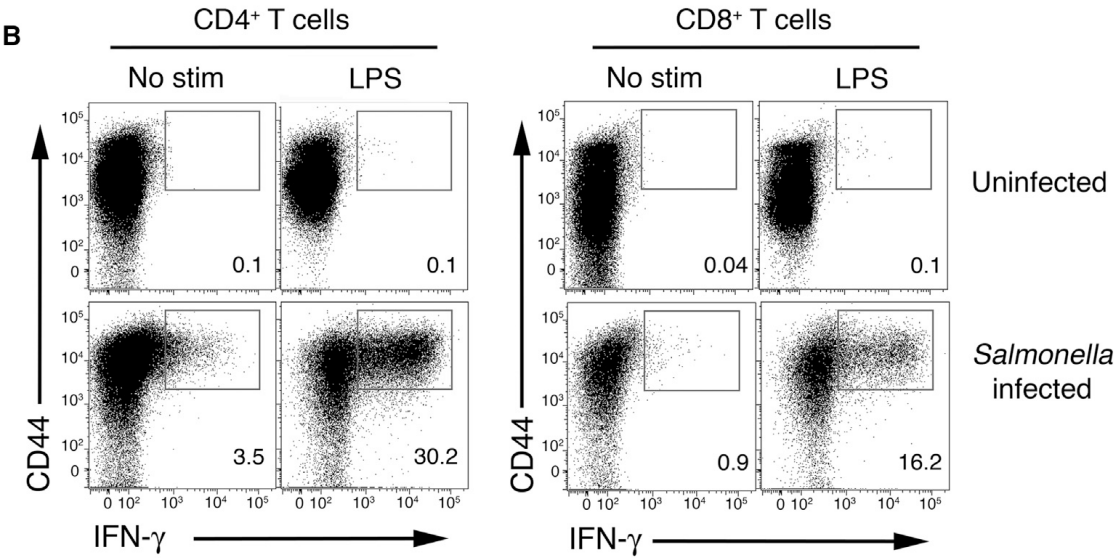
- What are the signals that drive noncognate stimulation of $CD4^+$ Th1 cells ?
- How do noncognate stimulation of $CD4^+$ Th1 cells contribute to bacterial clearance ?

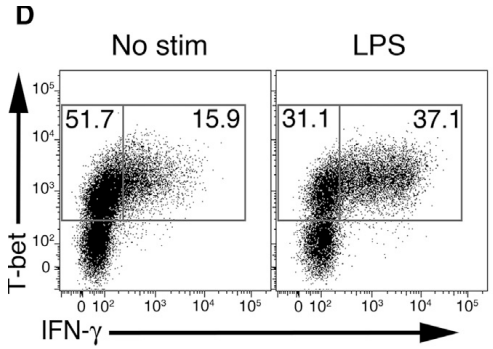
Expanded CD4⁺ Th1 and CD8+ T cells acquire the ability to respond to innate stimulation

5x10^5 *Salmonella* i.v →  → 4 hrs prior to analysis, 10 ug LPS i.v → T cell response in the spleen

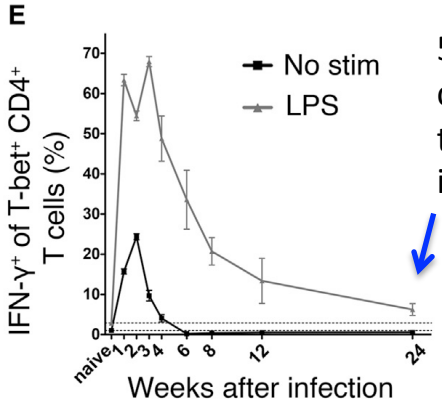
14 days post-infection



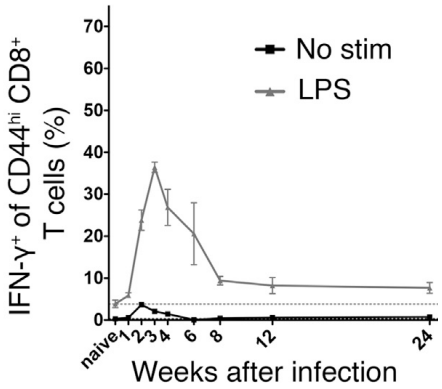




LPS-induced IFN-γ production confined to T-bet⁺ cells

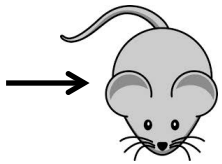


5-10% T-bet+ CD4+ T cells retained the ability to respond rapidly to innate stimuli



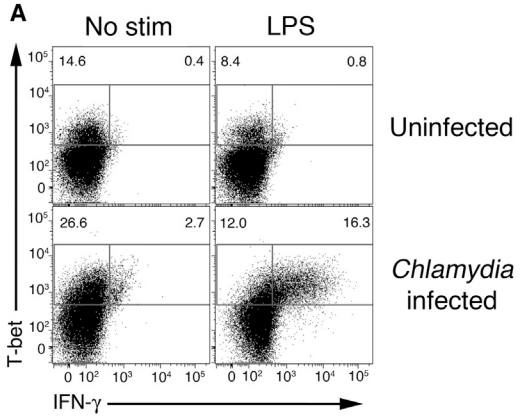
Amplification of CD4$^+$ Th1 and CD8$^+$ T cell responses occurs with multiple innate ligands

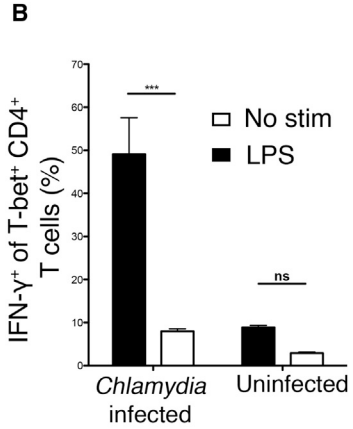
Infection with 5x10^5 *Salmonella* (2 weeks)
or
Infection with 1x10^7 *Chlamydia muridarum* (1 week)



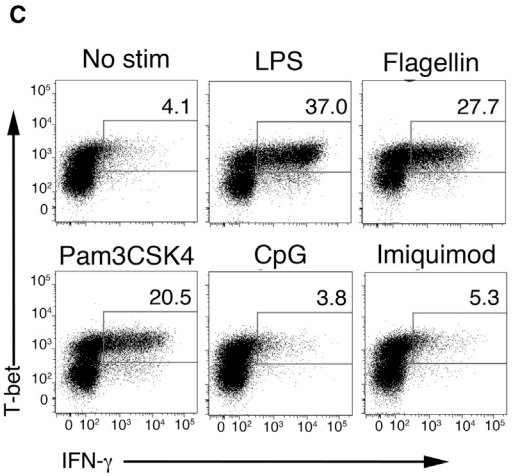
4 hrs prior to analysis, 10 ug LPS or innate receptor ligands i.v

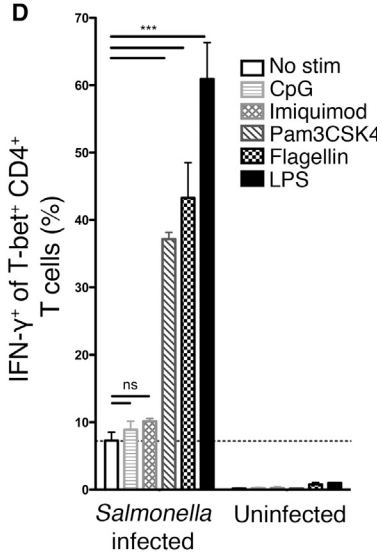
T cell response in the spleen

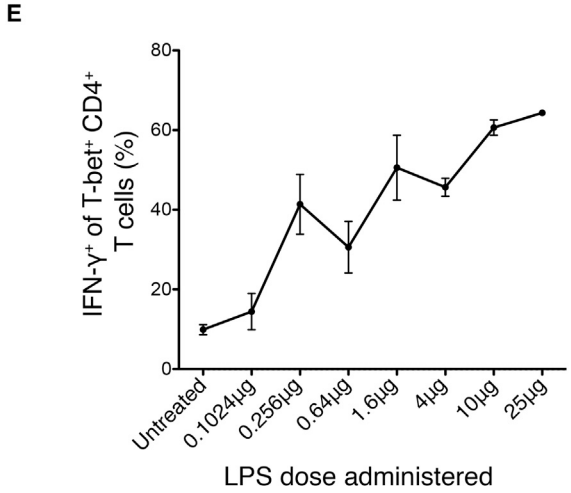




Salmonella infection

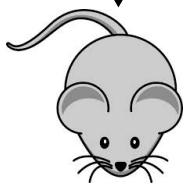






T cells require expression of MyD88 for innate amplification

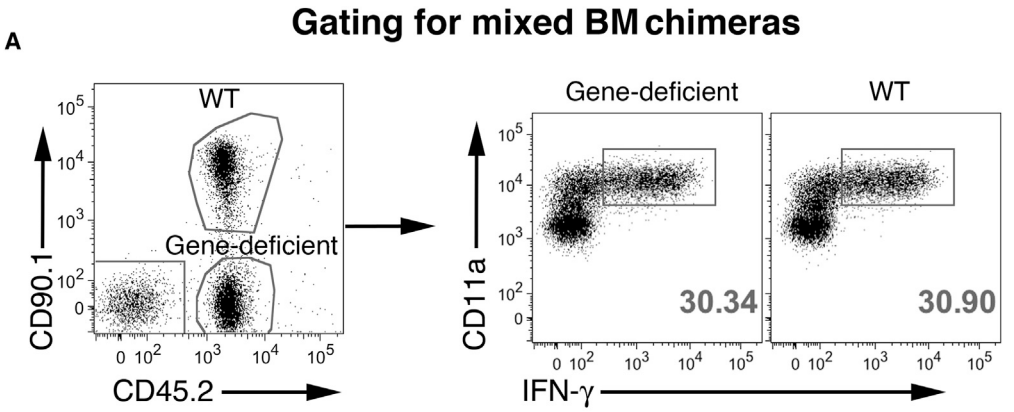
1:1 mixture of BM from
WT (CD90.1⁺CD45.2⁺) and
gene deficient (CD90.2⁺CD45.2⁺)

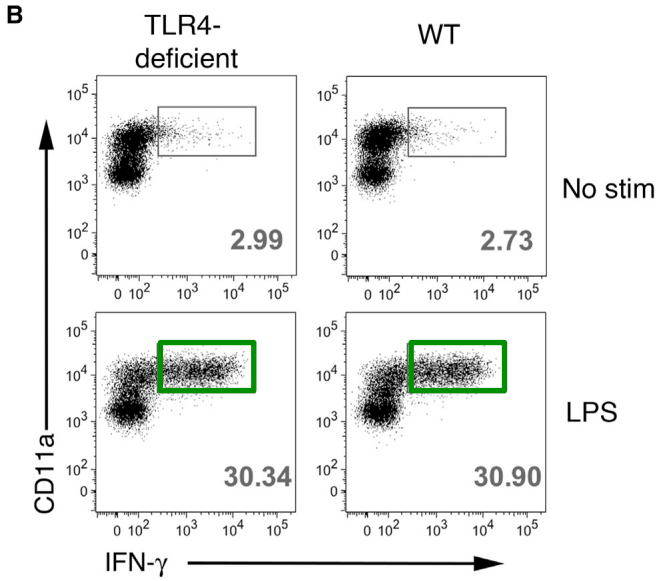


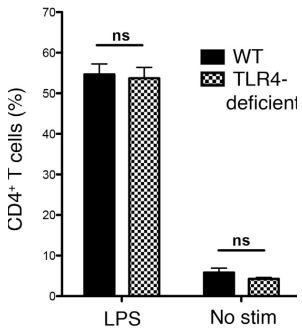
CD90.2⁺CD45.1⁺ recipient

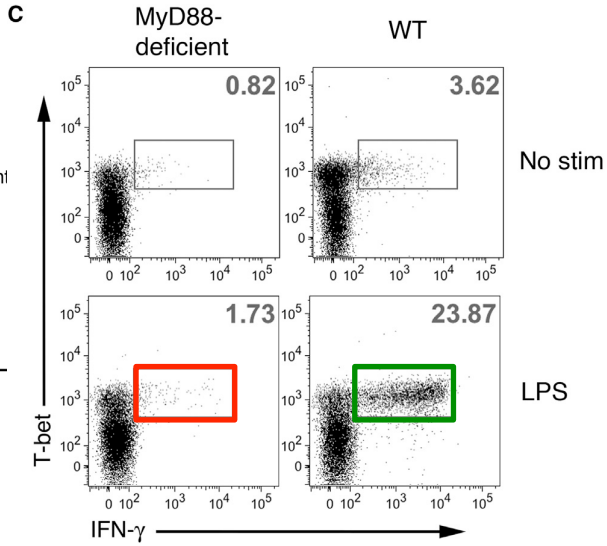
6-8 weeks

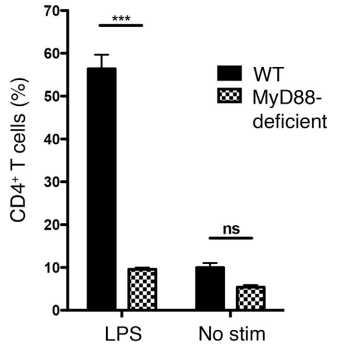
Infect with *Salmonella*





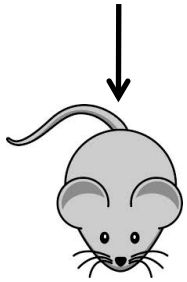




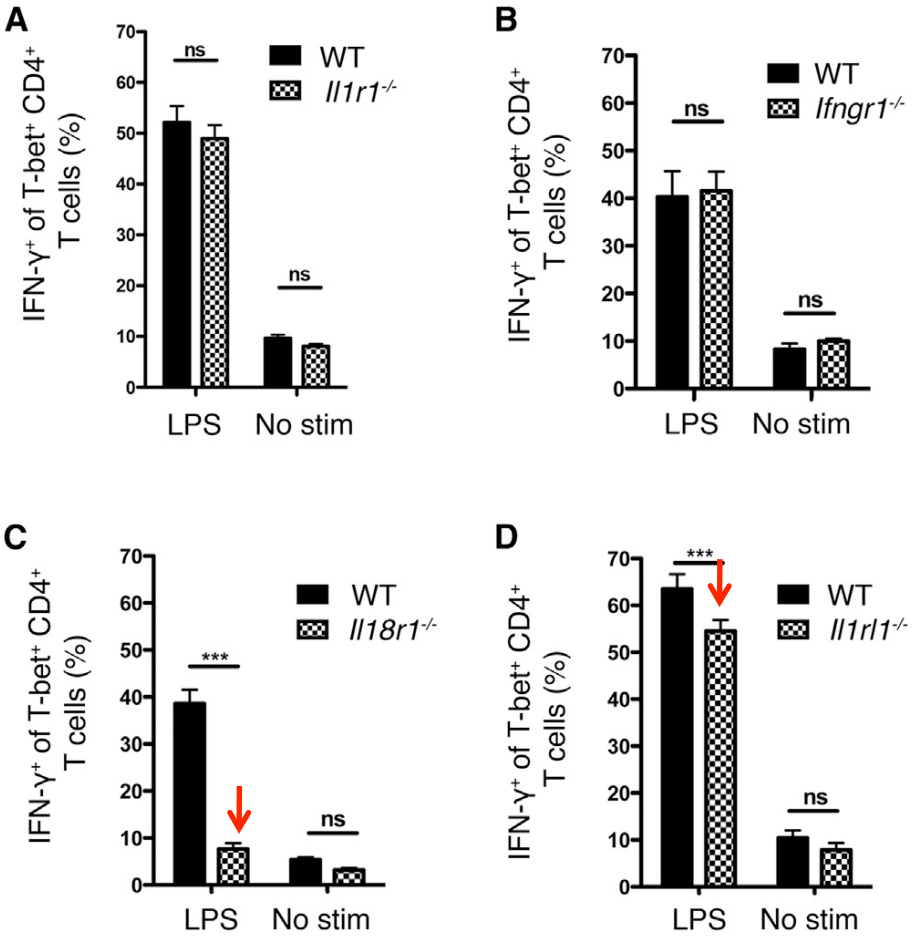


CD4$^+$ T cell expression of IL-18R and IL-33R is required for maximal innate responses

1:1 mixture of BM from
WT (CD90.1$^+$CD45.2$^+$) and
gene deficient (CD90.2$^+$CD45.2$^+$)

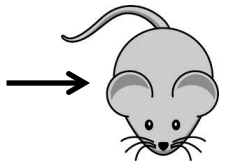


CD90.2$^+$CD45.1$^+$ recipient → 6-8 weeks → Infect with *Salmonella*



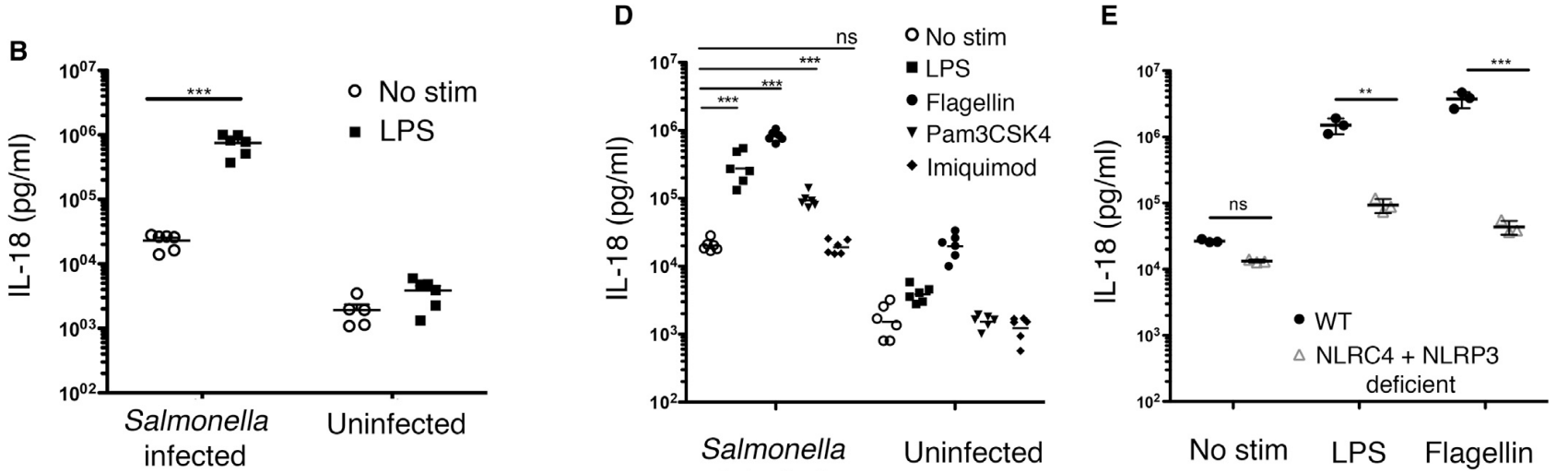
LPS induction of IL-18 requires inflammasome activity in *Salmonella*-infected mice

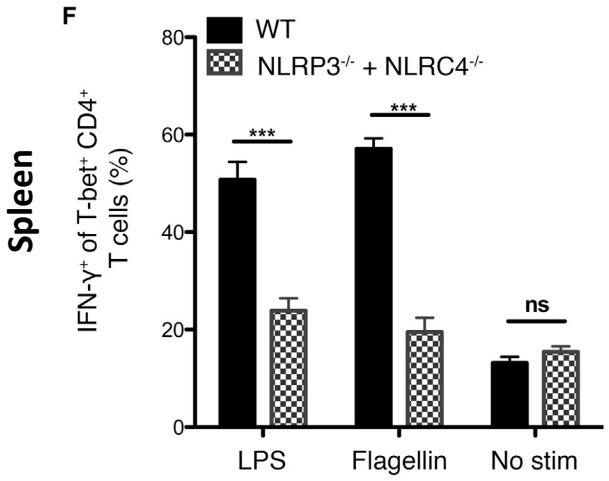
Infection with
5x10^5 *Salmonella* (2 weeks)

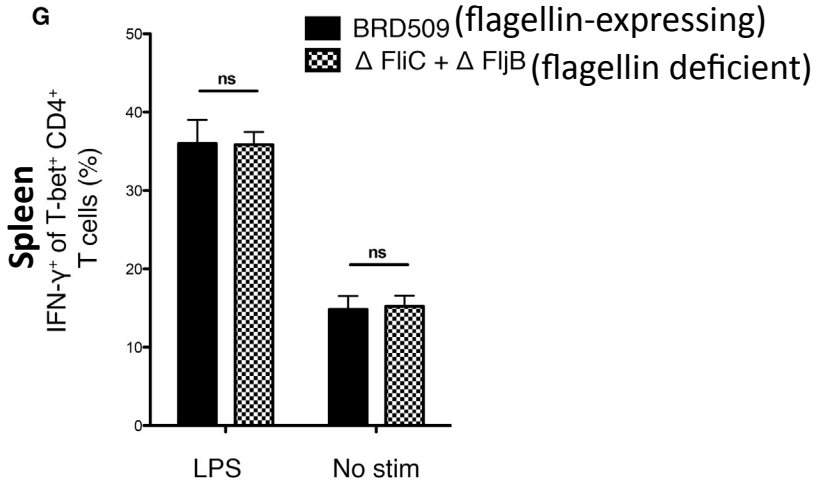


4 hrs prior to analysis,
10 ug LPS or innate
receptor ligands i.v

In serum

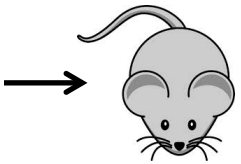




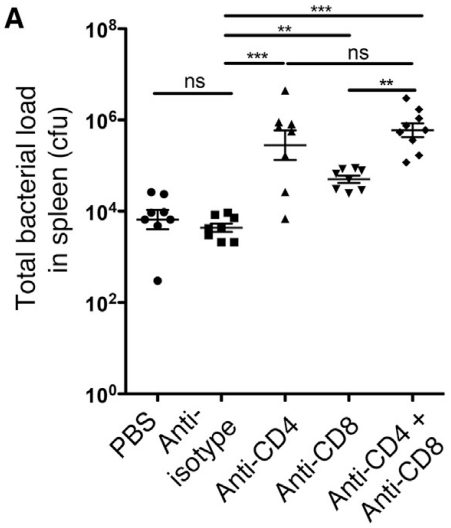


Noncognate stimulation of T cells contributes to bacterial clearance

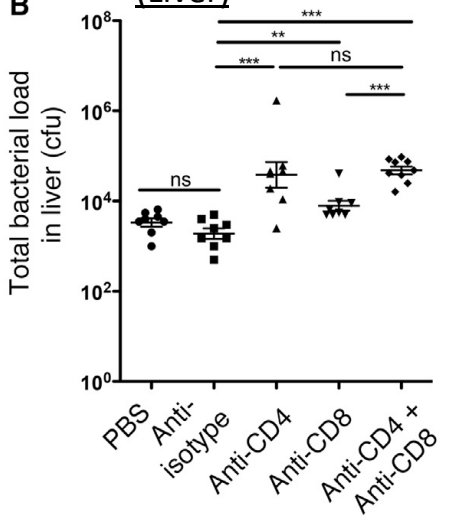
Infection with
5x10^5 *Salmonella*

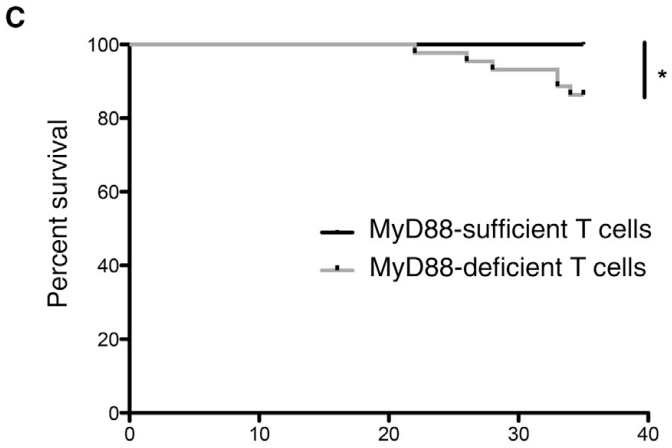


30 days postinfection (Spleen)



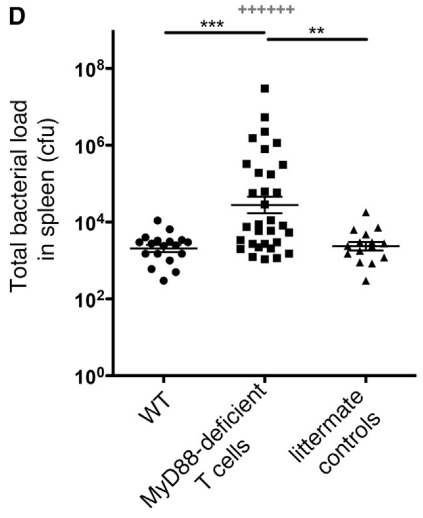
30 days postinfection (Liver)



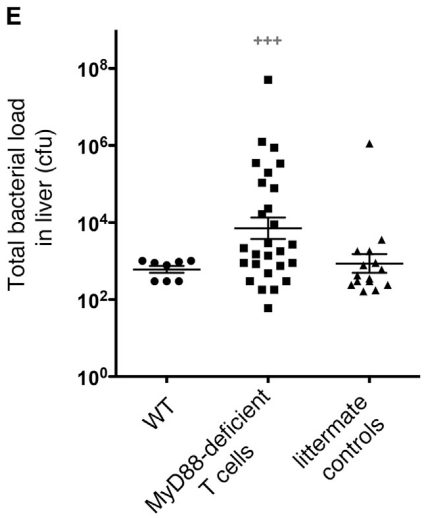


*Myd88*fl$^{fl/WT}$ *Lck-cre heterozygous*
Myd88$^{fl/fl}$ *Lck-cre* homozygous

5 weeks post infection (Spleen)



5 weeks post infection (Liver)



Summary

•During active *Salmonella* infection, effector $CD4^+$ Th1 cells have reduced threshold for stimulation.

•The ability to induce effector functions without a requirement for recognizing cognate antigen and MHC on an infected cell probably evolved to enhance the efficiency of adaptive response to infection.

•Inflammasome sensing of intracellular bacterial components synergizes with TLR recognition of MAMPs to induce cytokine production.