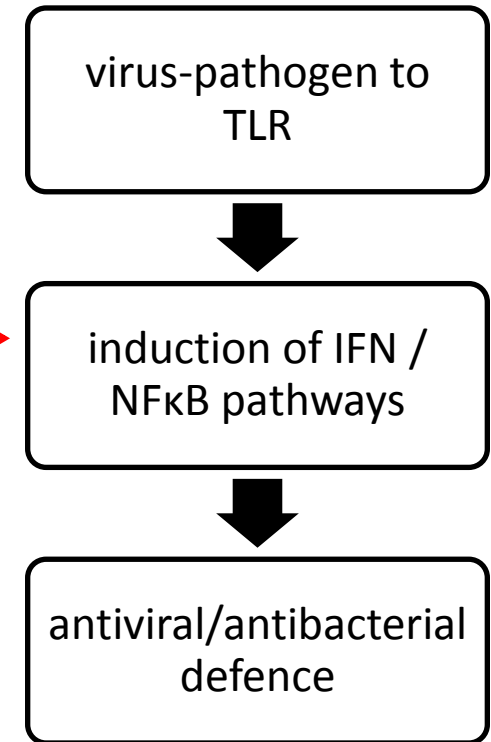


The methyltransferase Setdb2 mediates virus-induced susceptibility to bacterial superinfection

Schliehe C, Flynn EK, Vilagos B, et al; Nature Immunology; Jan. 2015

Overview

- Virus-induced immune response
 - multiple layers of regulation
 - maintain balance
 - methyltransferases as regulatory factors e.g. Setdb1 (cancer, proviral silencing)
- particularly relevant in virus-induced susceptibility to bacterial superinfection
 - IFN-mediated interference with NFκB pathway
 - example: secondary bacterial pneumonia & influenza



Overview

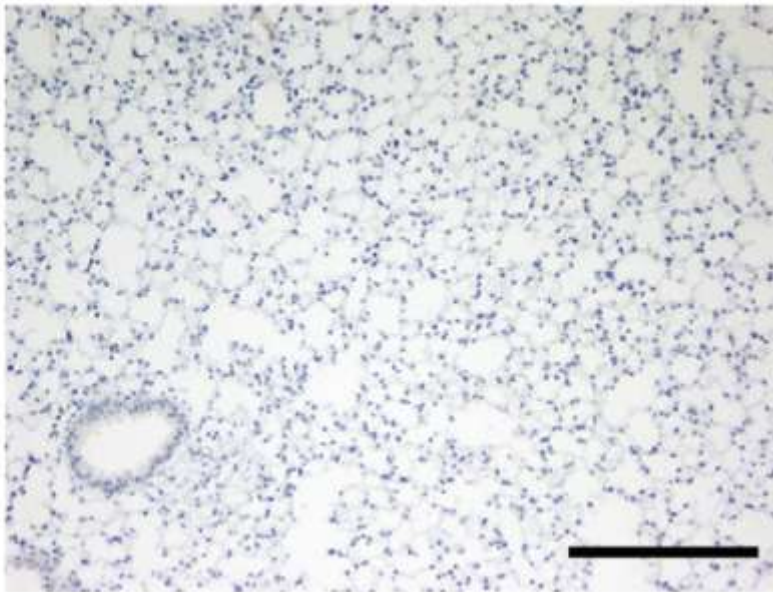
- Setdb2 (= Suvar 3-9-enhancer-of-zeste-trithorax domain bifurcated 2)
 - interferon-stimulated
 - modulates expression of gene-subset which are targets of NFκB
 - through transferring methyl (-CH₃) residues and catalyzing Histone (H3K9) methylation
 - silencing of transcription

Results

- Induction of Setdb2 expression by infection with influenza virus

- pulmonary tissue of influenza-infected mice 18h post infection vs. mice left uninfected

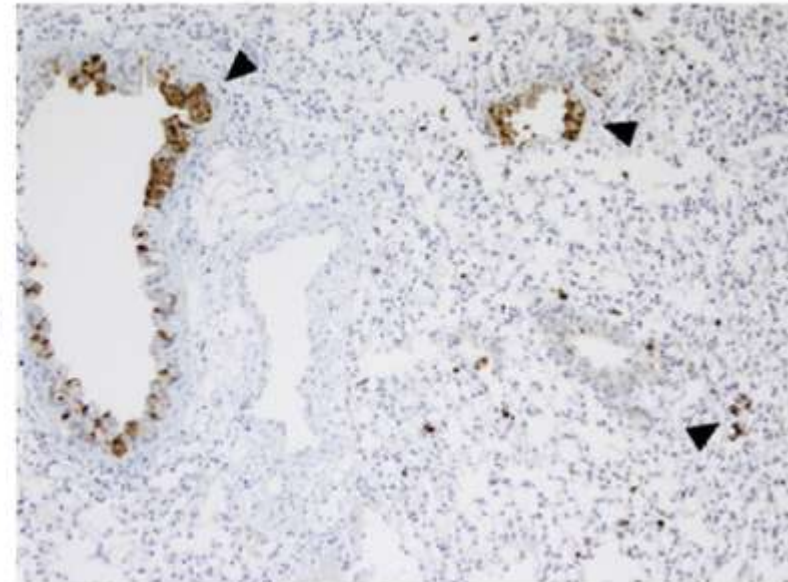
UI



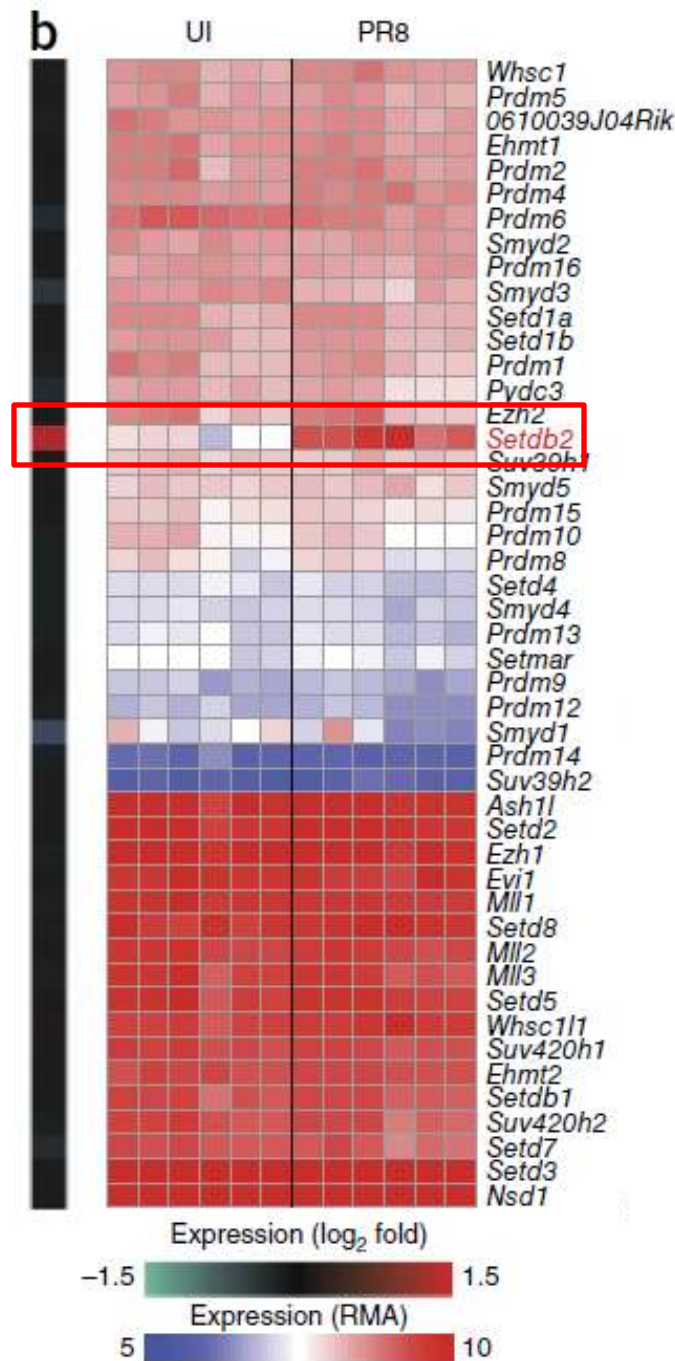
a

Anti-H1N1

PR8
(18 h)



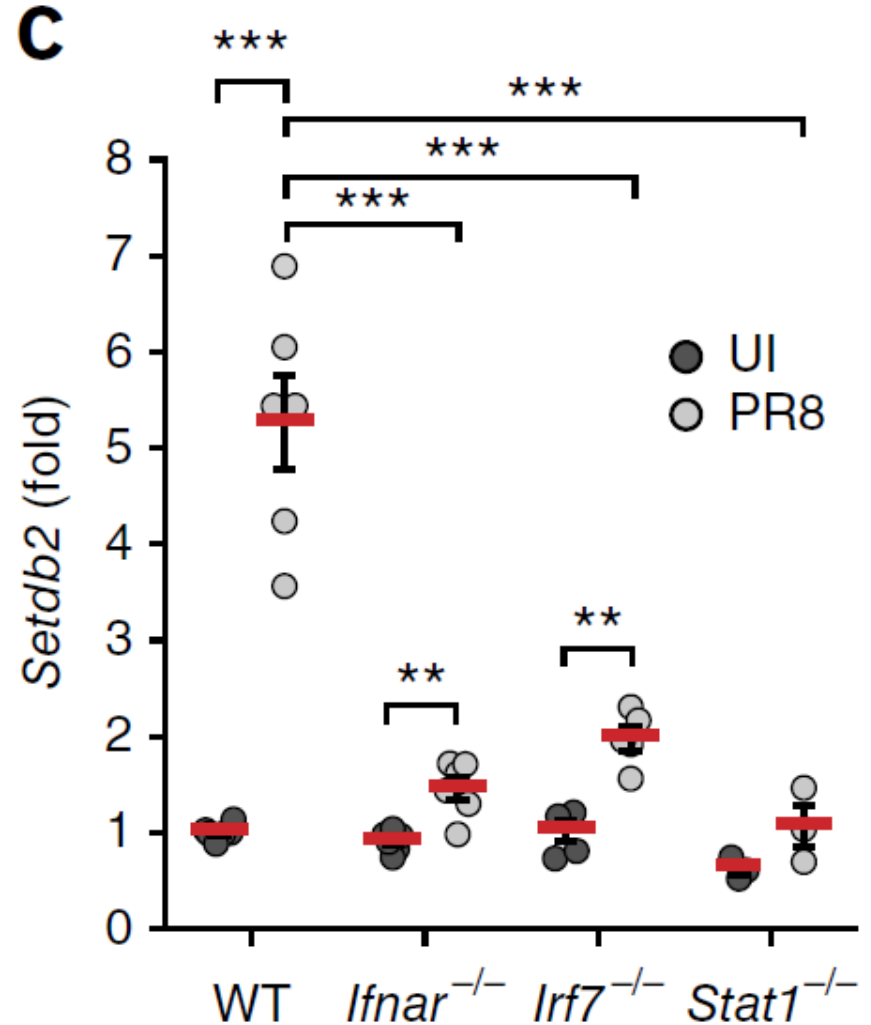
- gene expression



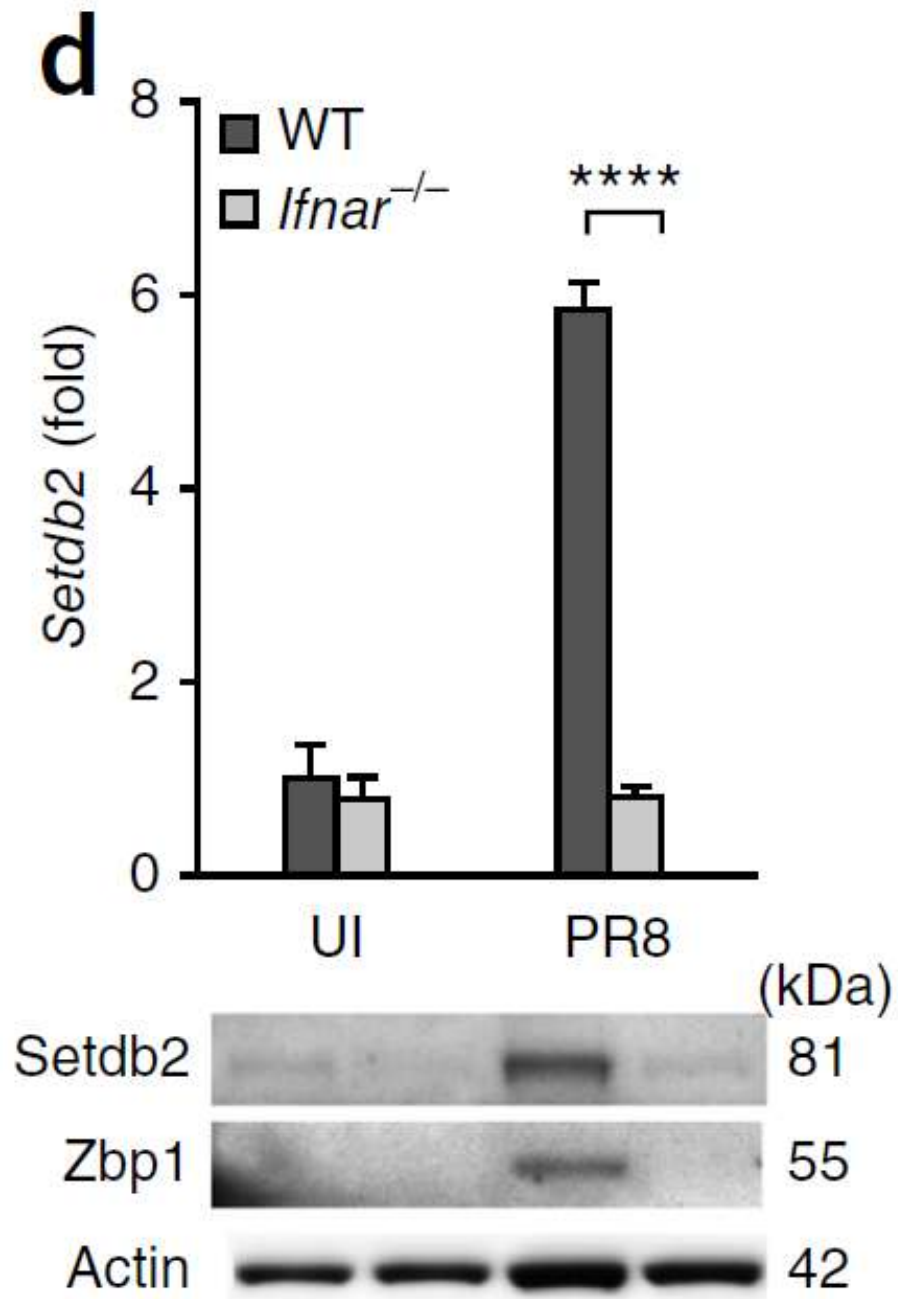
Results

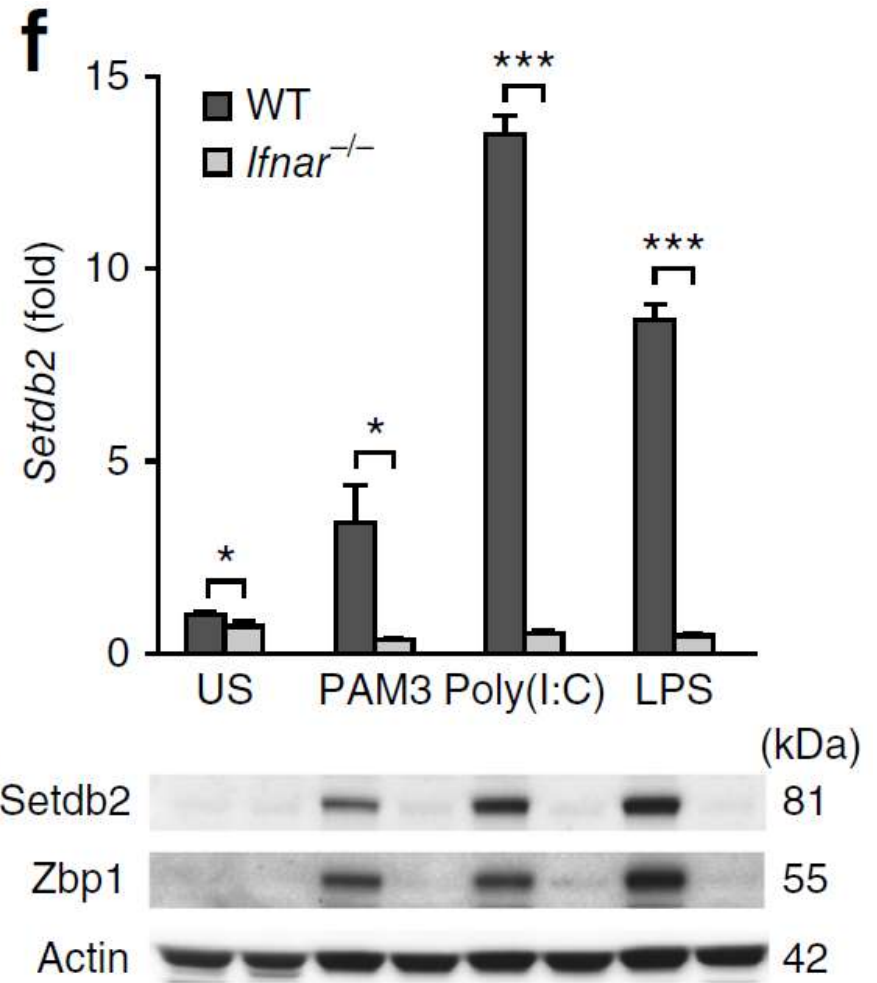
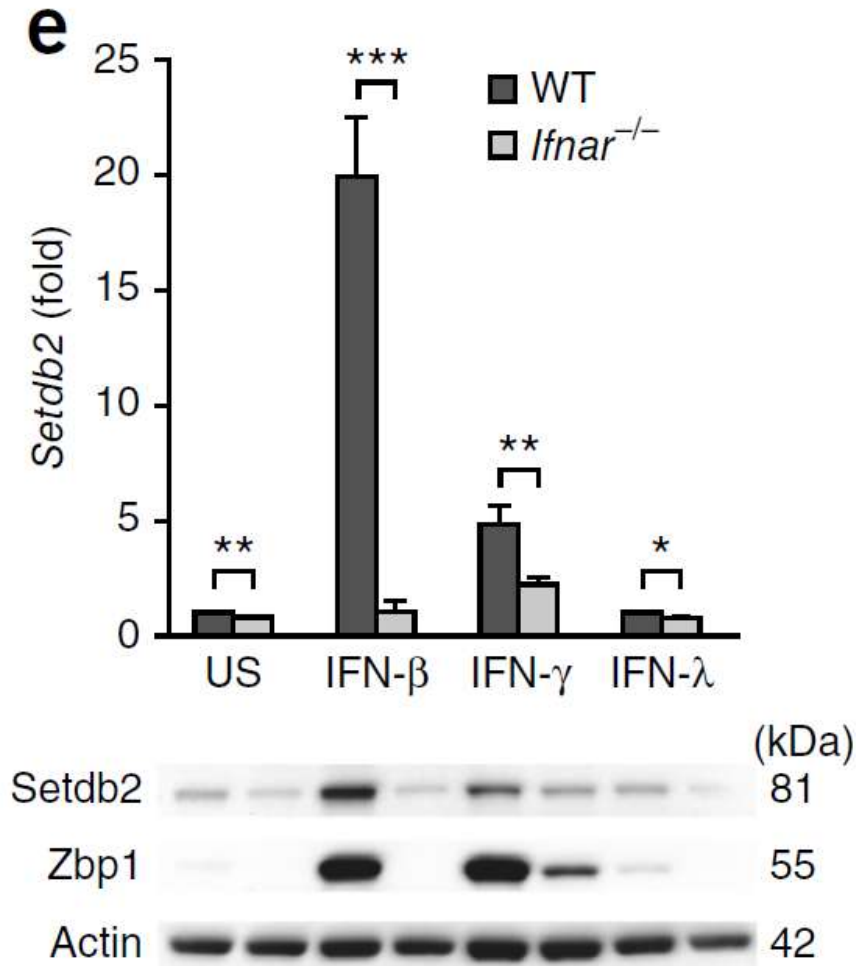
- Setdb2 expression is driven by type I interferon signaling

- Setdb2 expression in wildtype mice vs. mice deficient of different molecules from the IFN pathway, infected (PR8) vs. uninfected (UI)



- mouse BMDM vs. IFNAR1 depleted macrophages

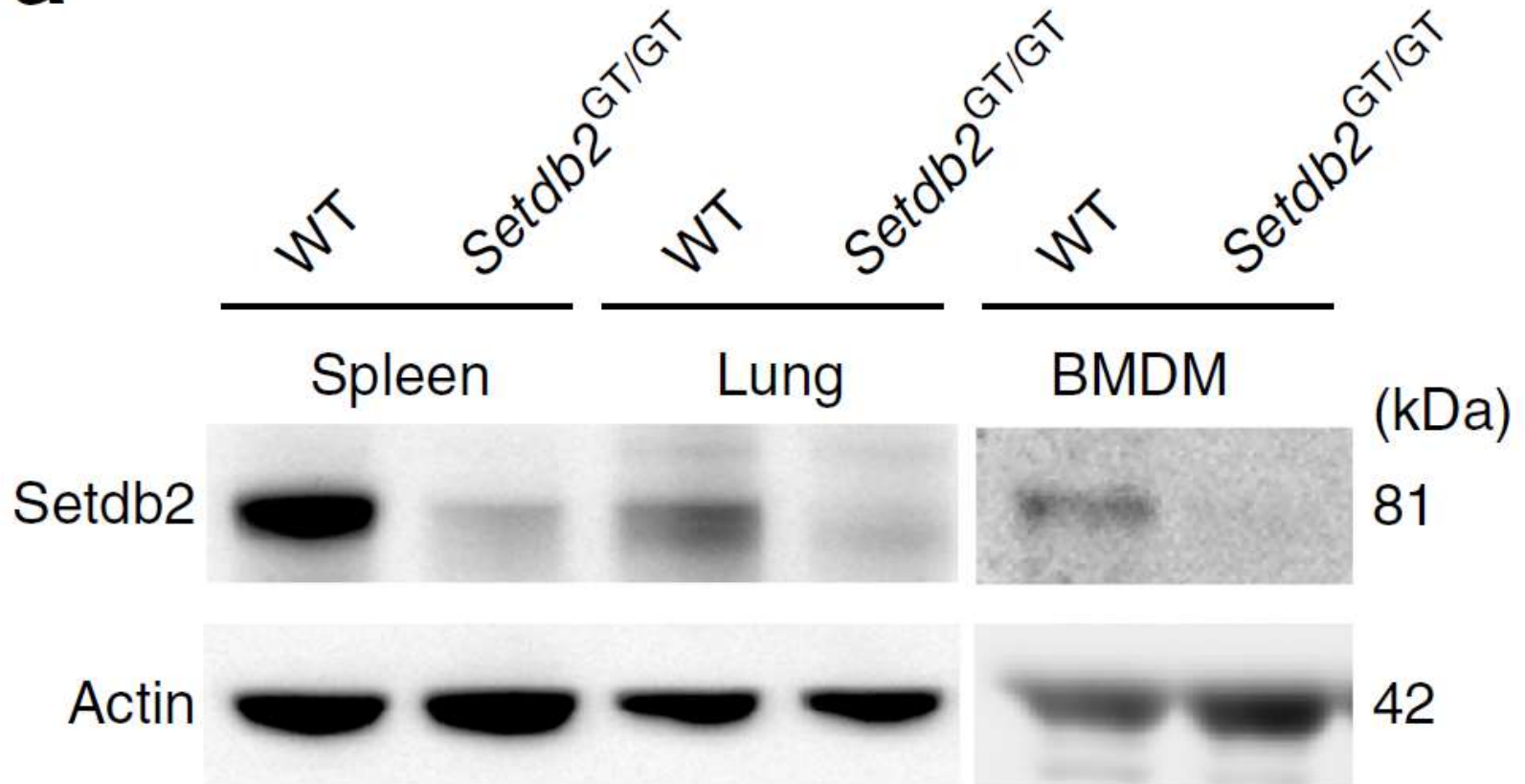




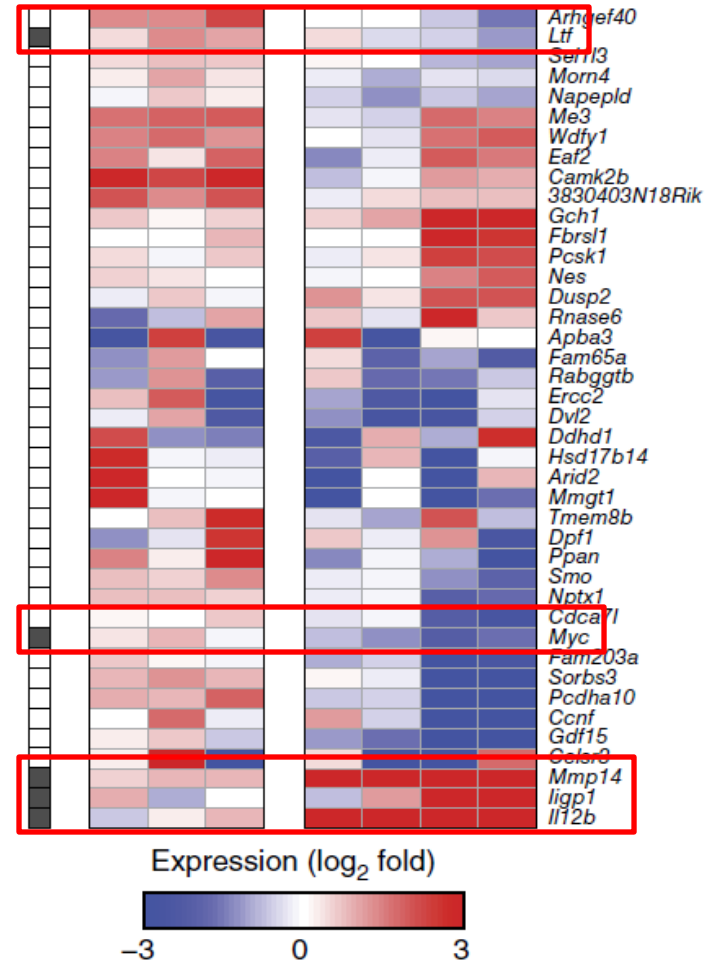
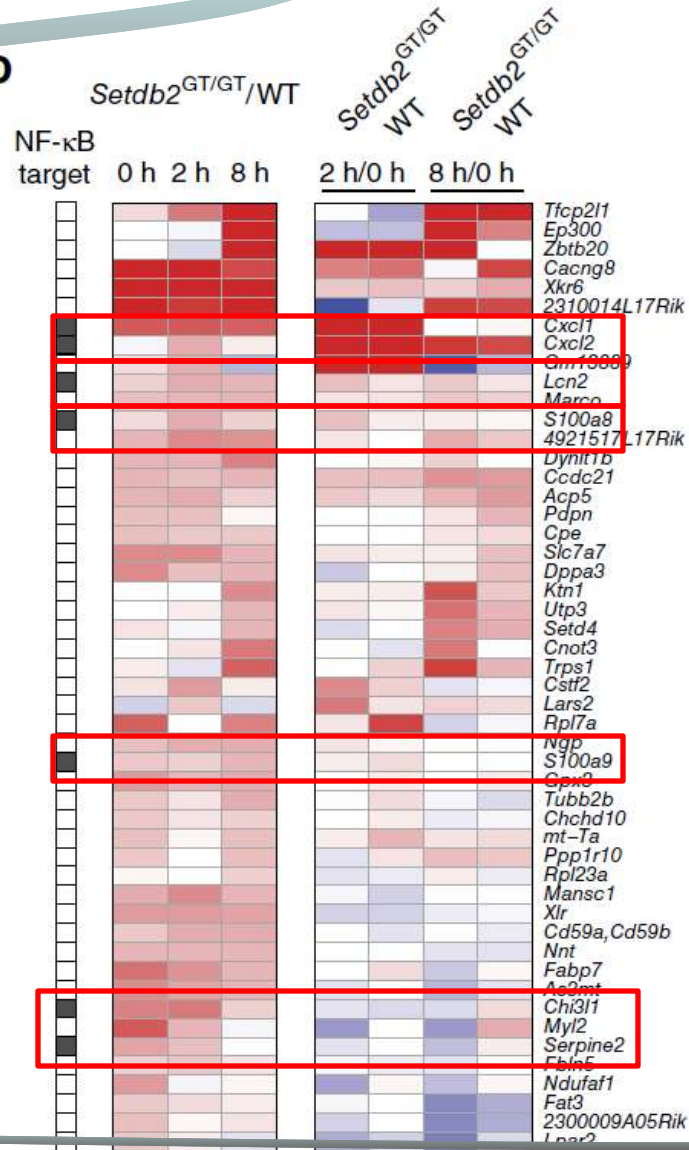
Results

- Expression of NF- κ B target genes is modulated by Setdb2

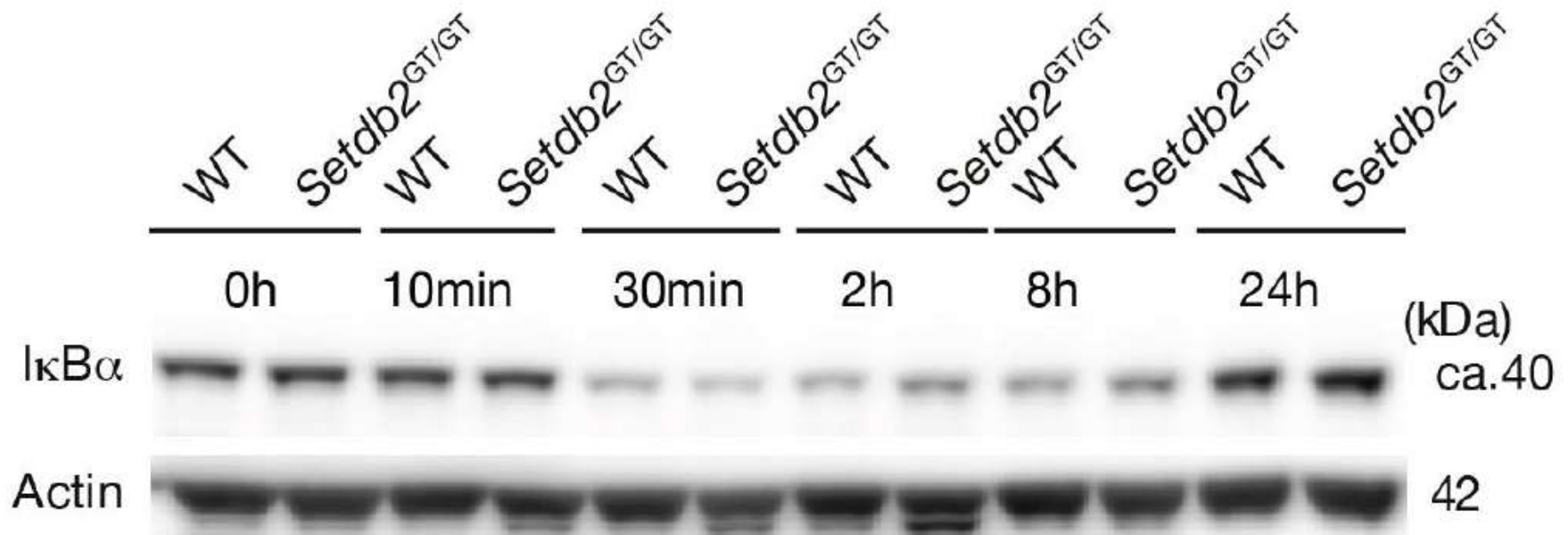
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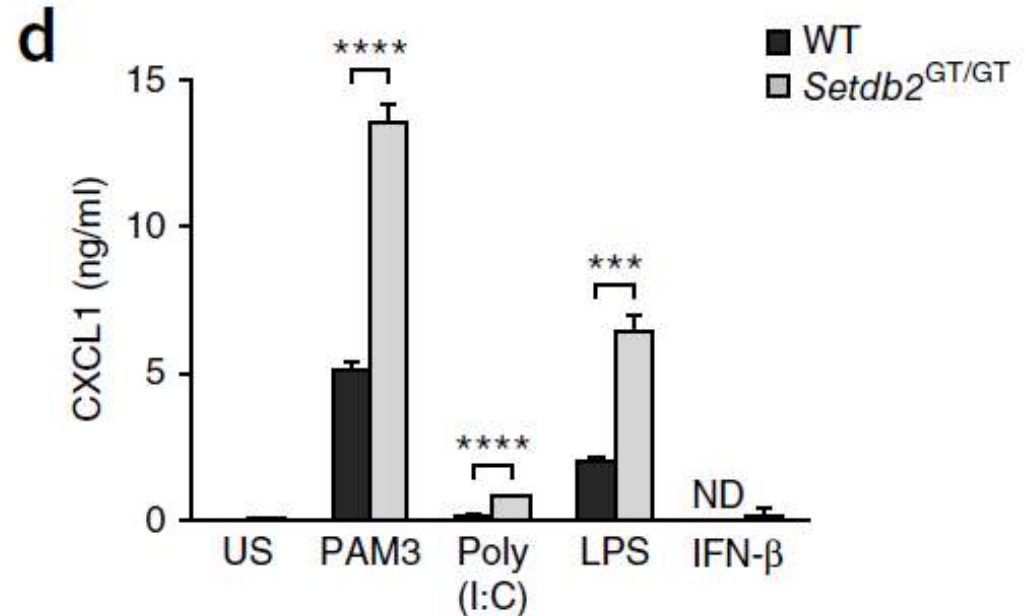
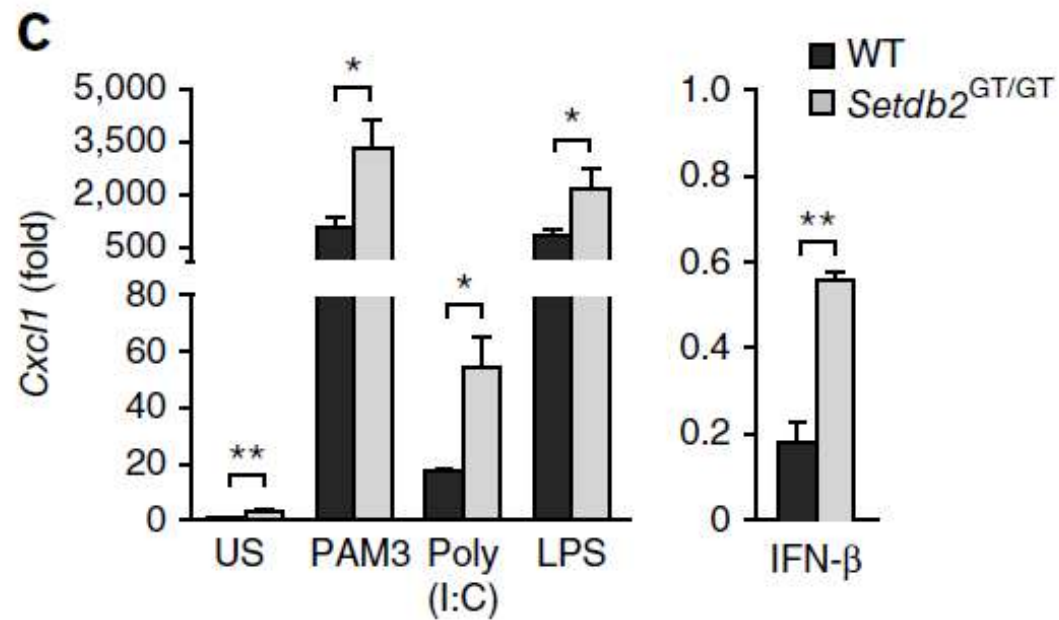
b



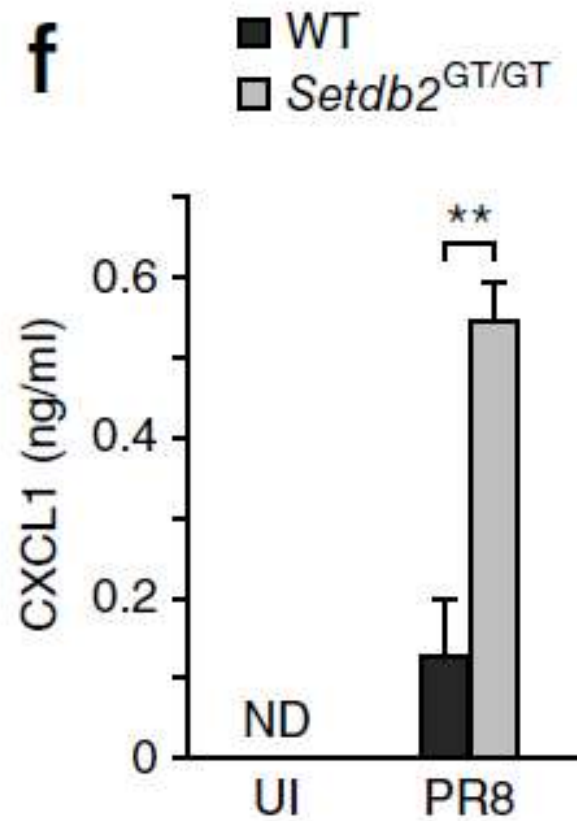
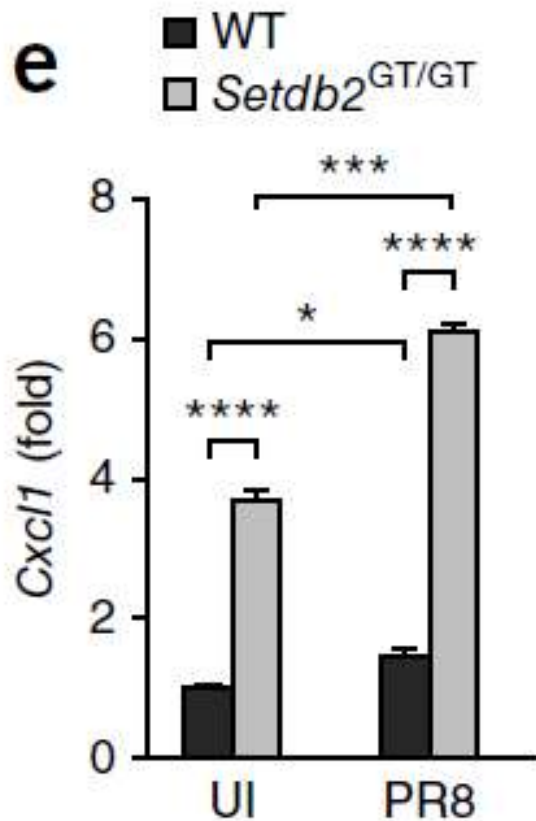
- Setdb2 acts downstream of NF κ B regulation by I κ B α



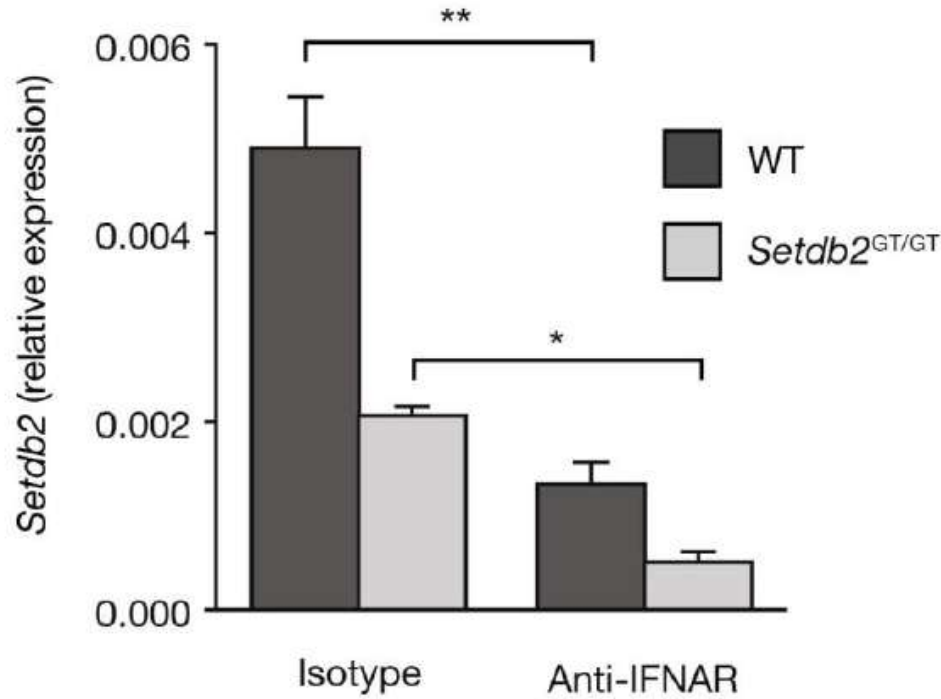
- Cxcl1*-expression is significantly higher in *Setdb2*^{GT/GT} BMDM after stimulation with TLR agonists



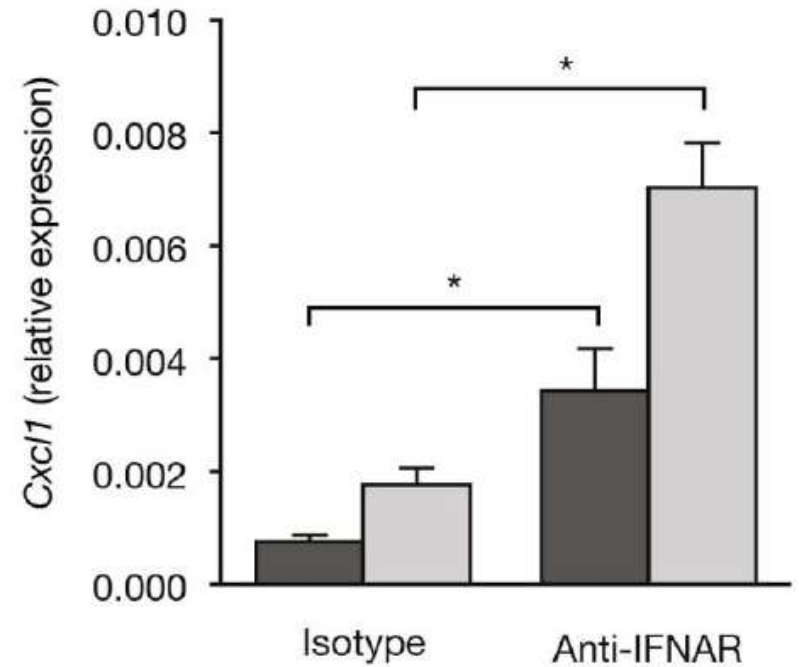
- Cxcl1*-expression is significantly higher in *Setdb2*^{GT/GT} BMDM after infection with influenza virus PR8



a

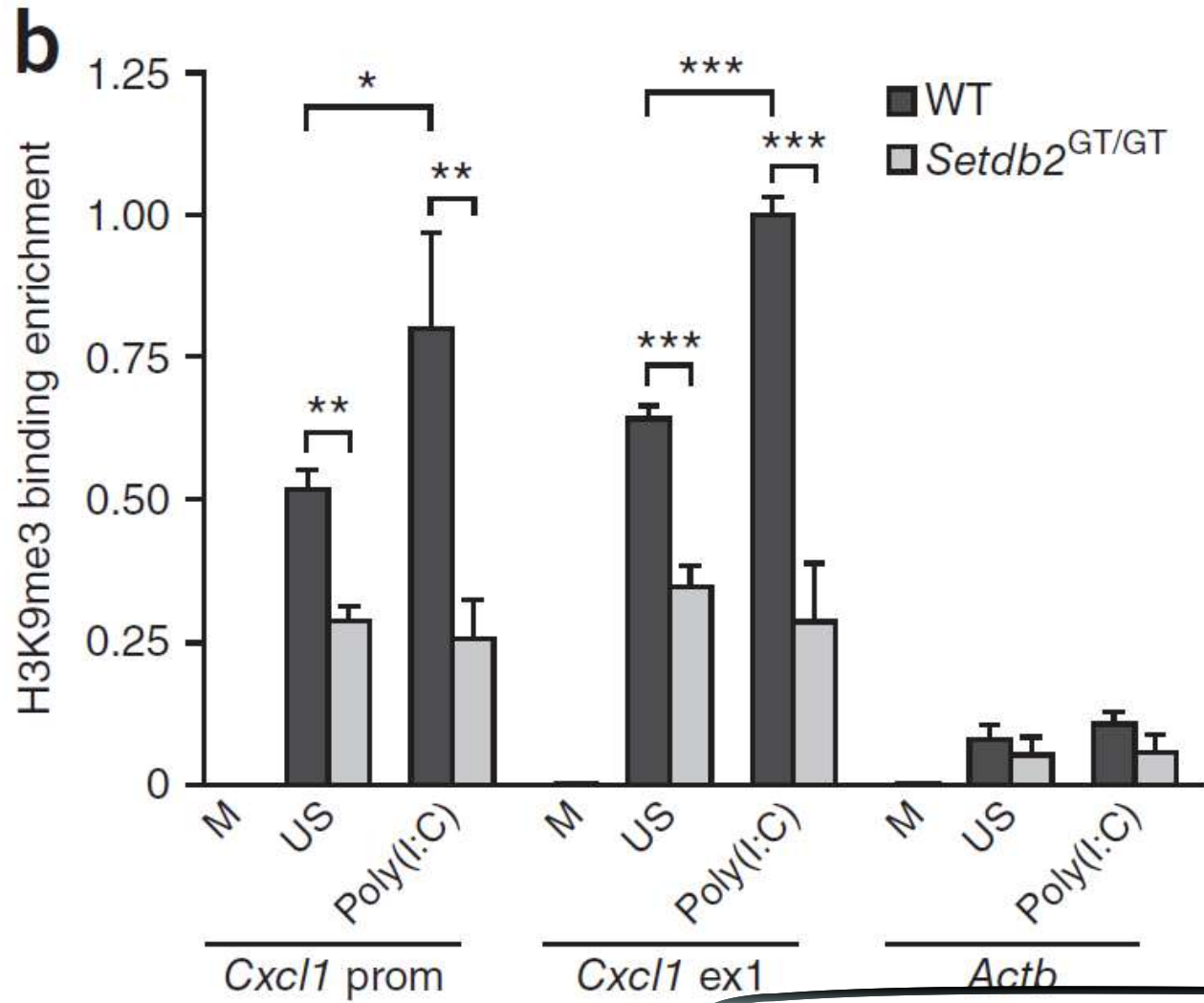
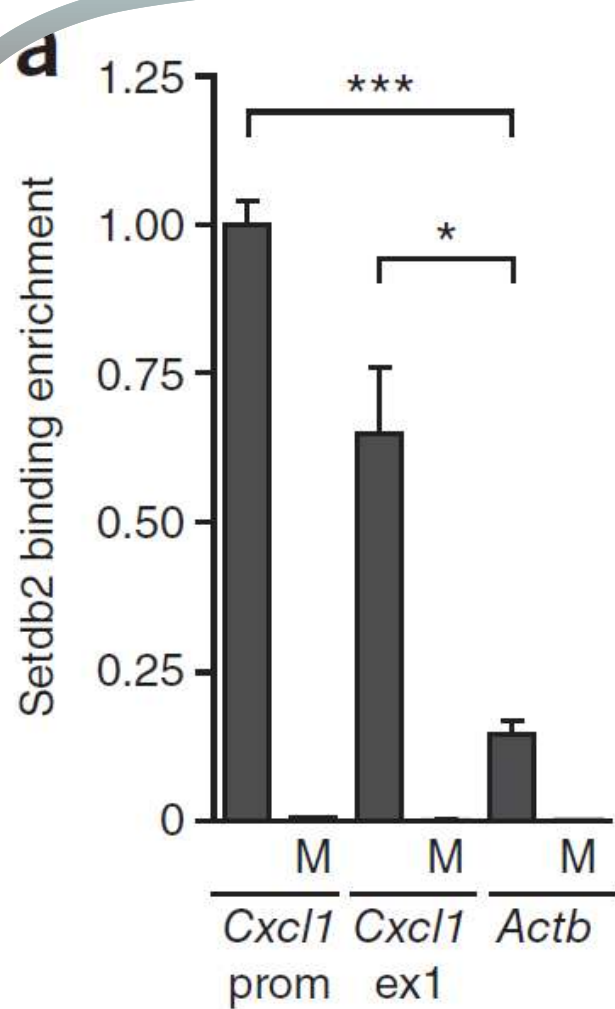


b



Results

- Setdb2 mediates trimethylation of H3K9 at the Cxcl1 promoter



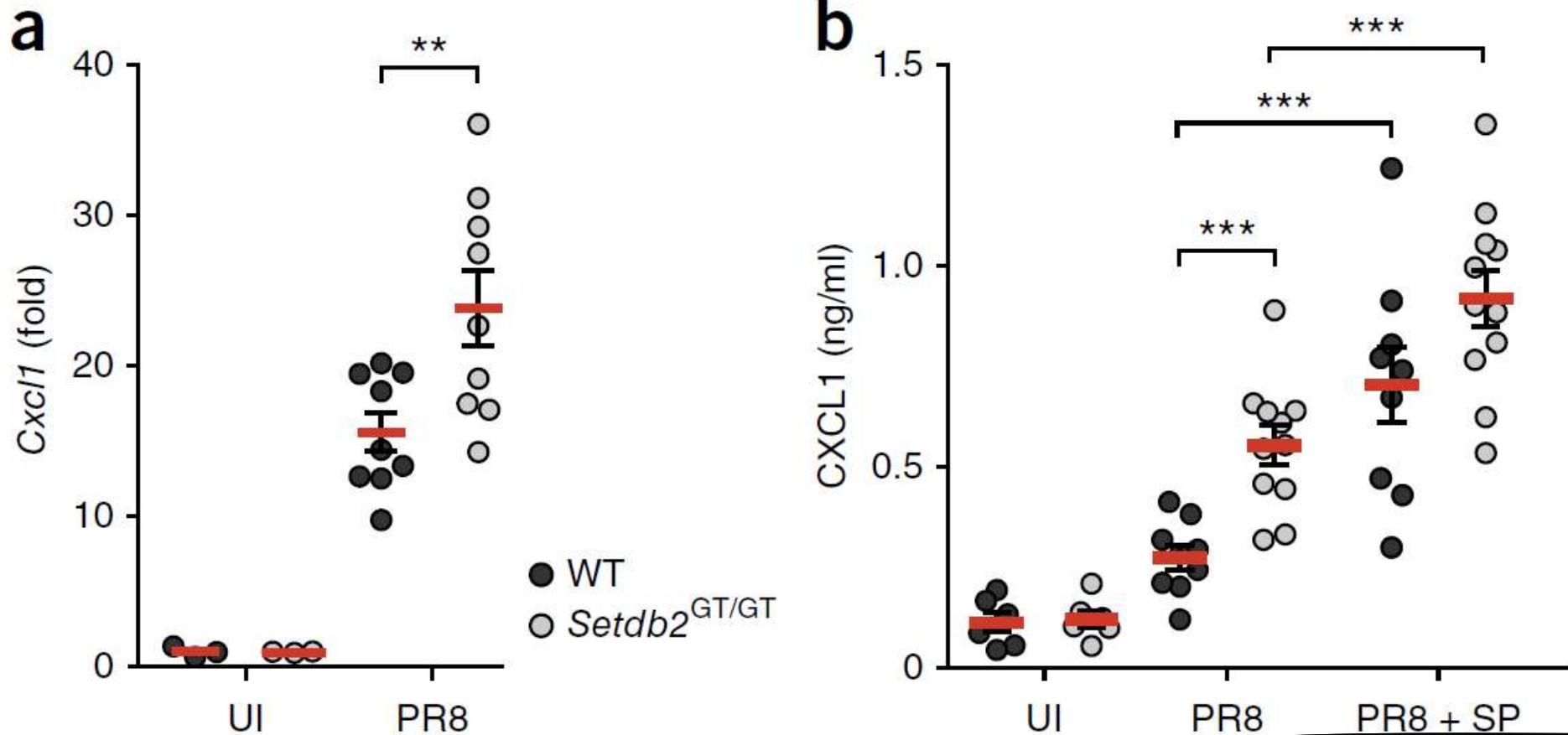
Results

- Setdb2 deficiency results in exacerbated lung inflammation

Results

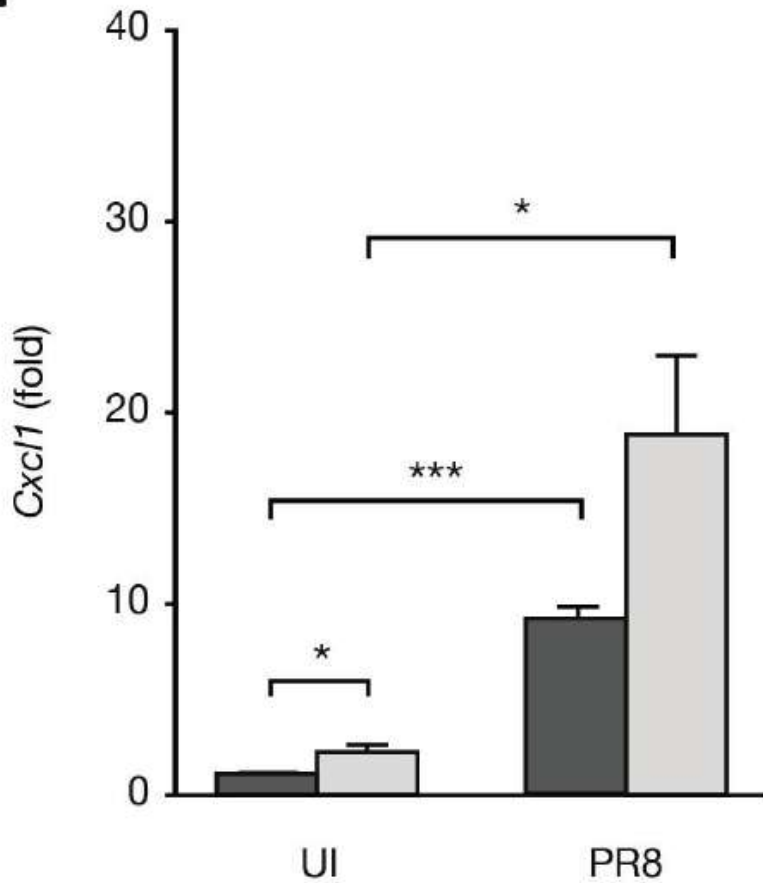
- Setdb2 mediates susceptibility to bacterial superinfection

- Increased CXCL1 expression after infection (influenza-virus / superinfection)

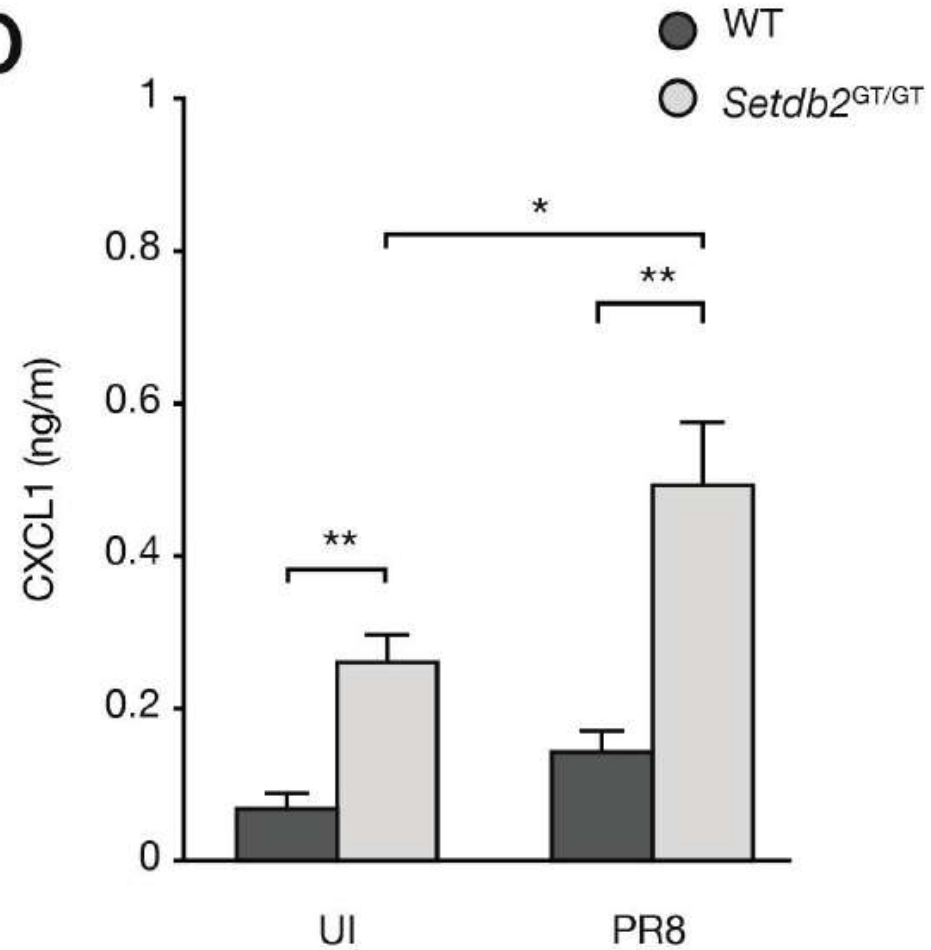


- pulmonary macrophages as a source of CXCL1

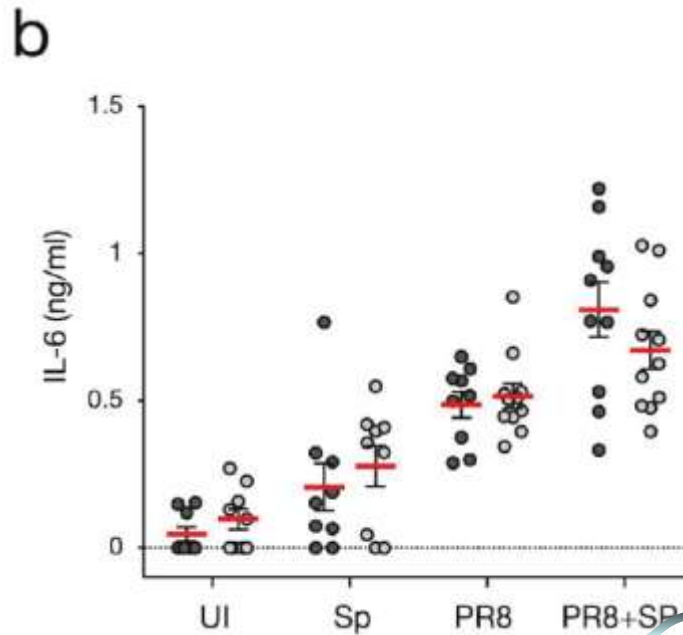
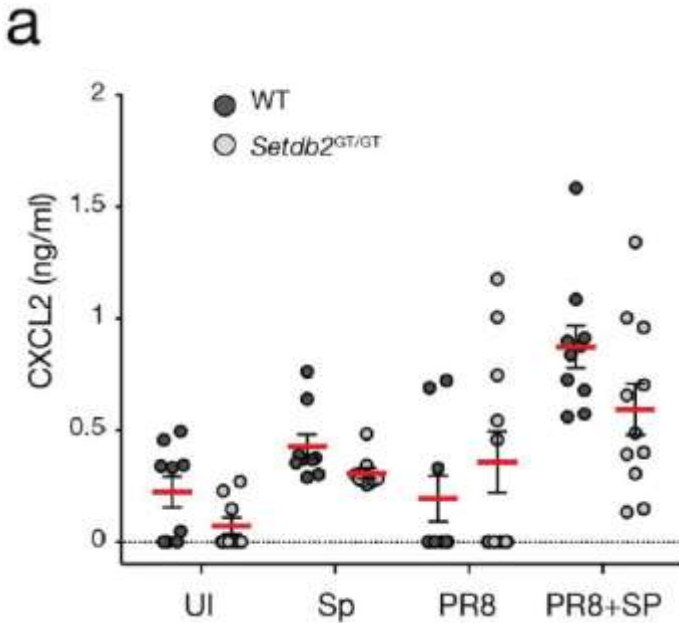
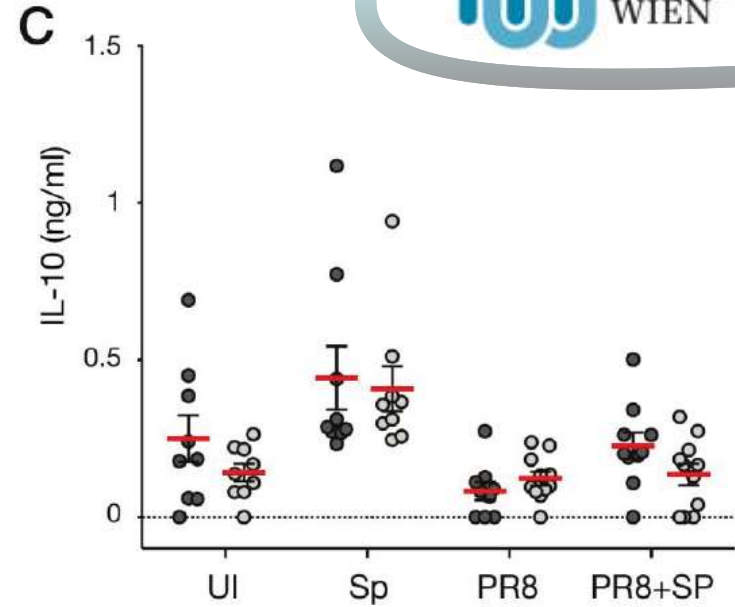
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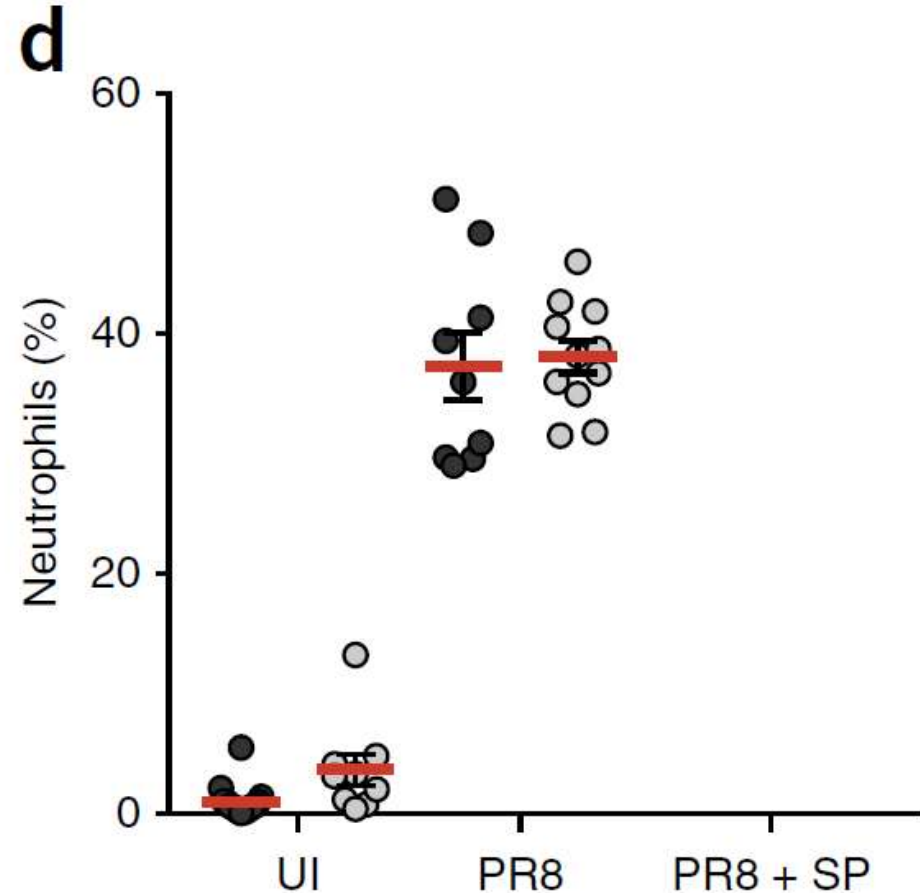
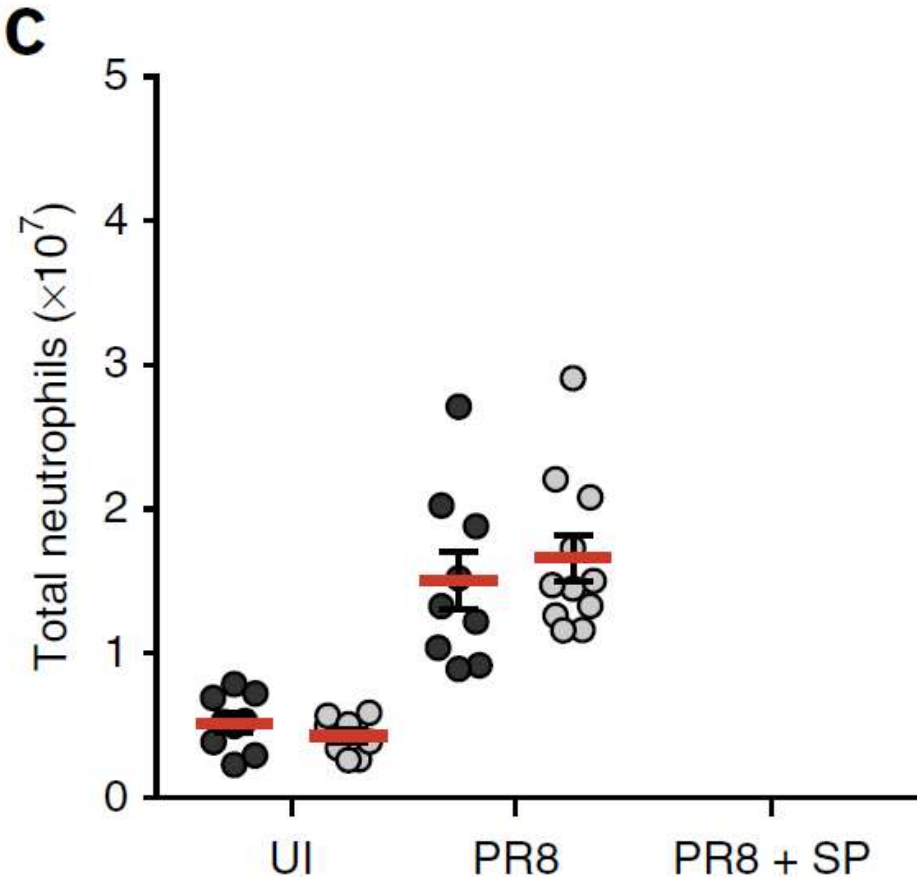
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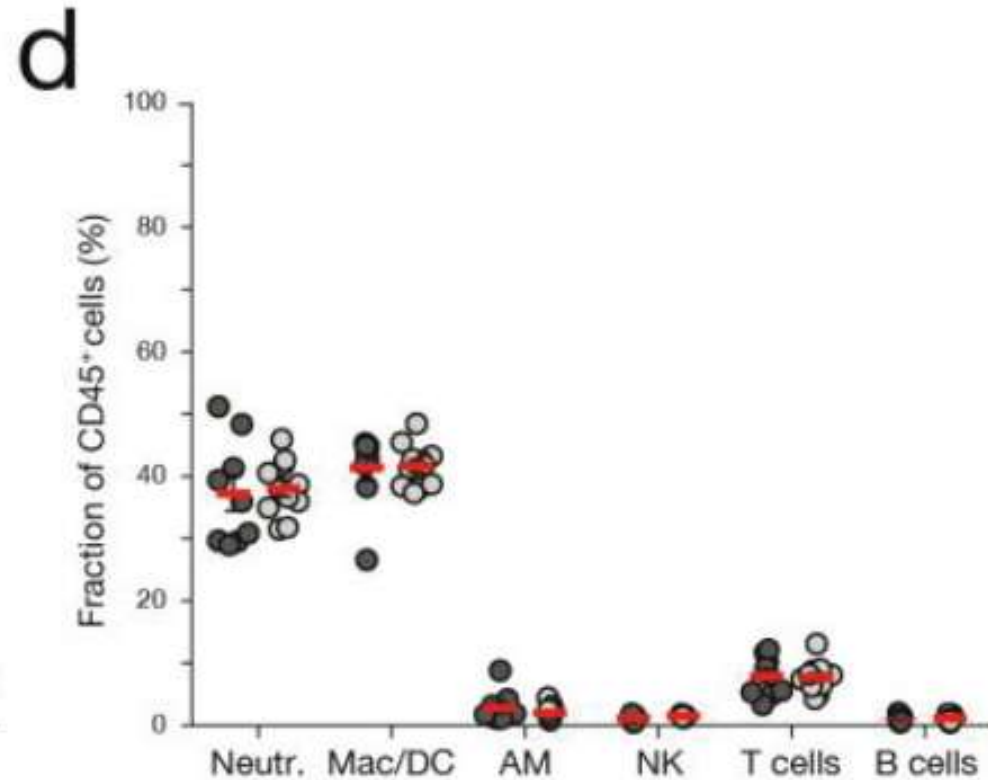
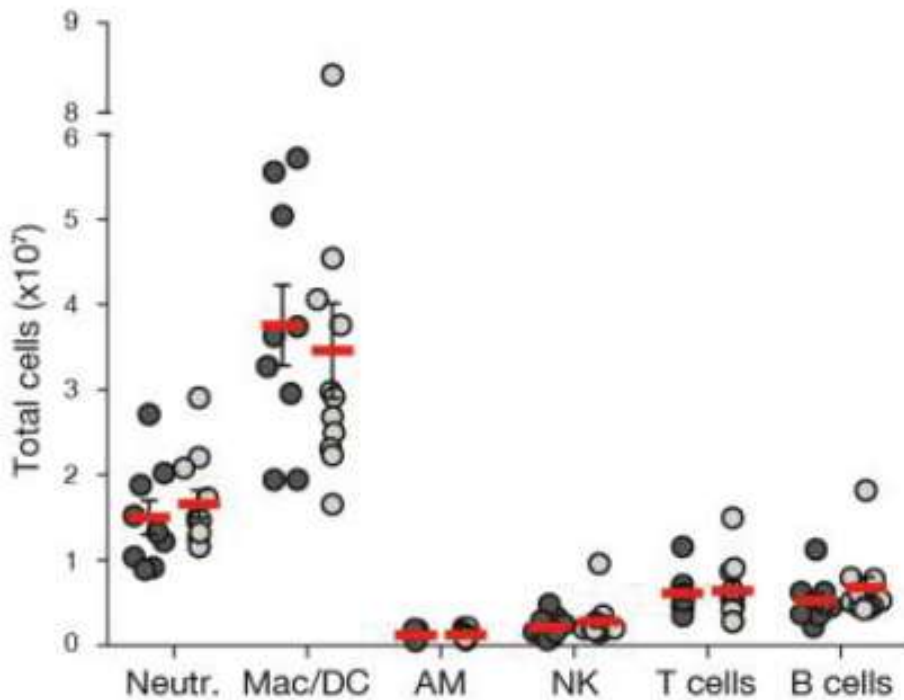


- levels of other known cytokines after infection

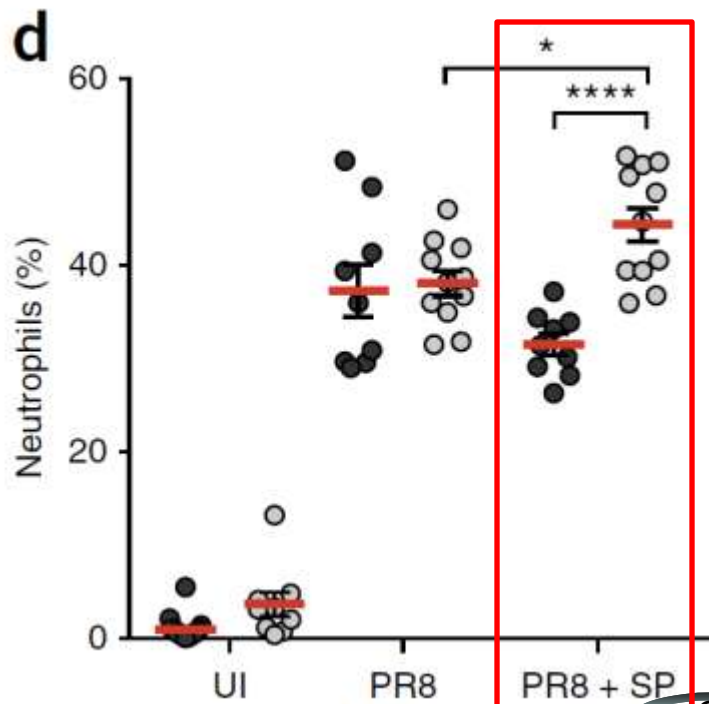
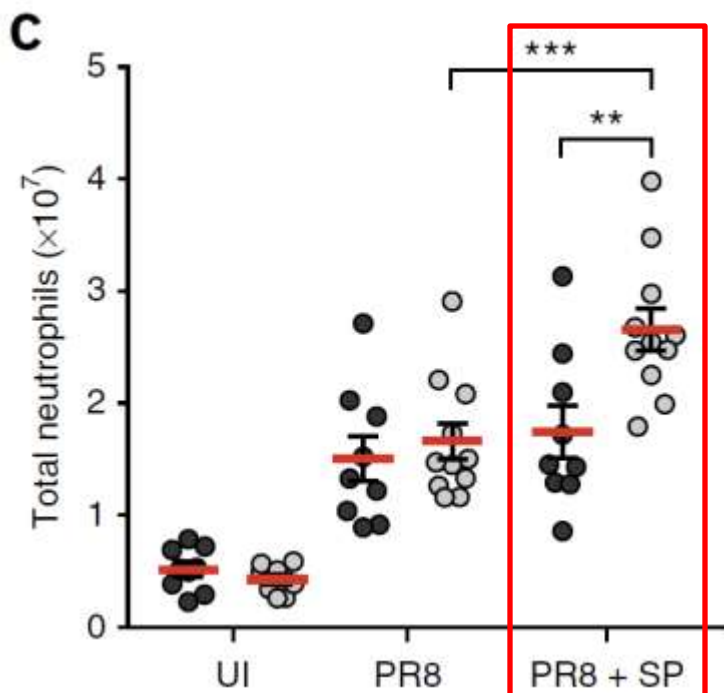
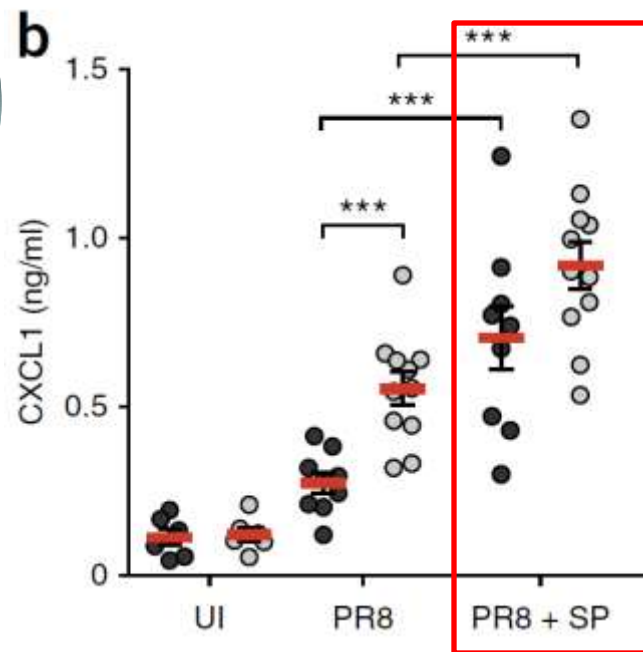


- Infiltration with immune cells after infection with influenza-virus (PR8)



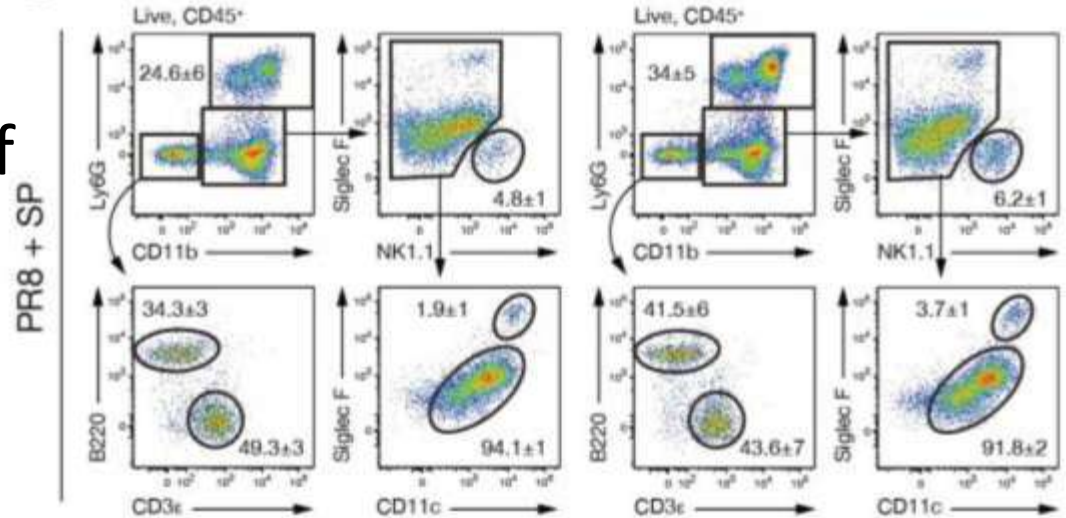


- Infiltration of immune cells after infection with influenza-virus (PR8)

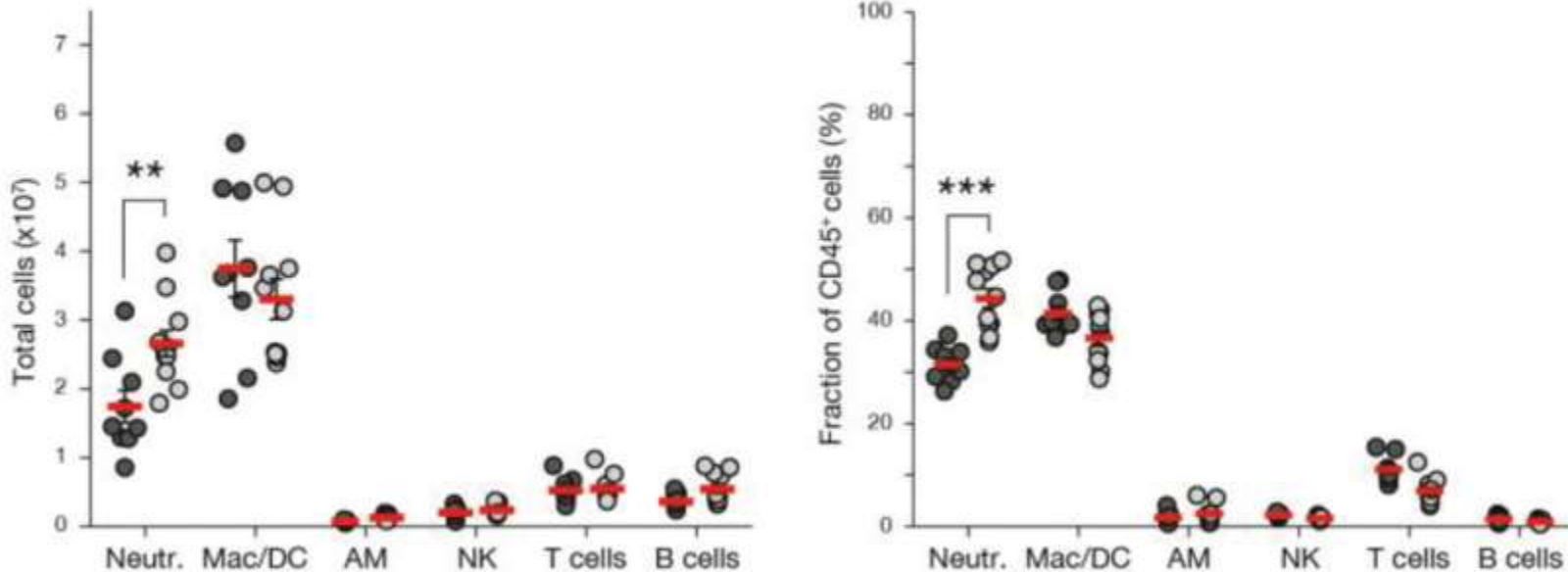


- increased infiltration of neutrophils into lung tissue

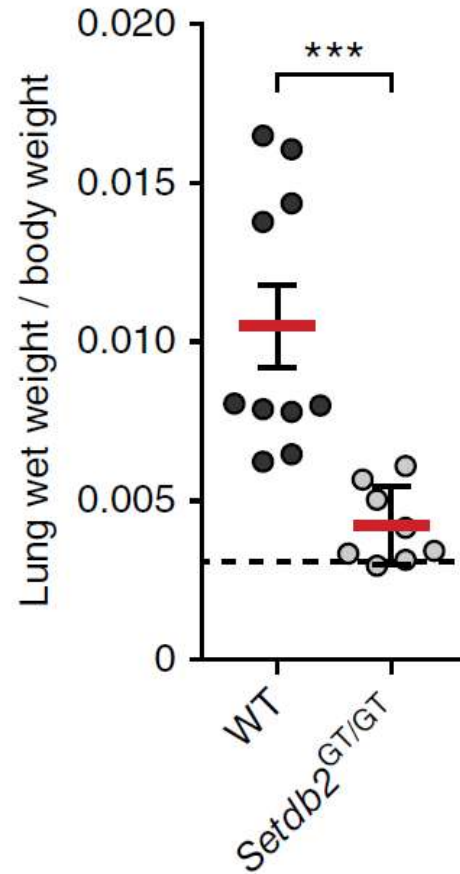
g



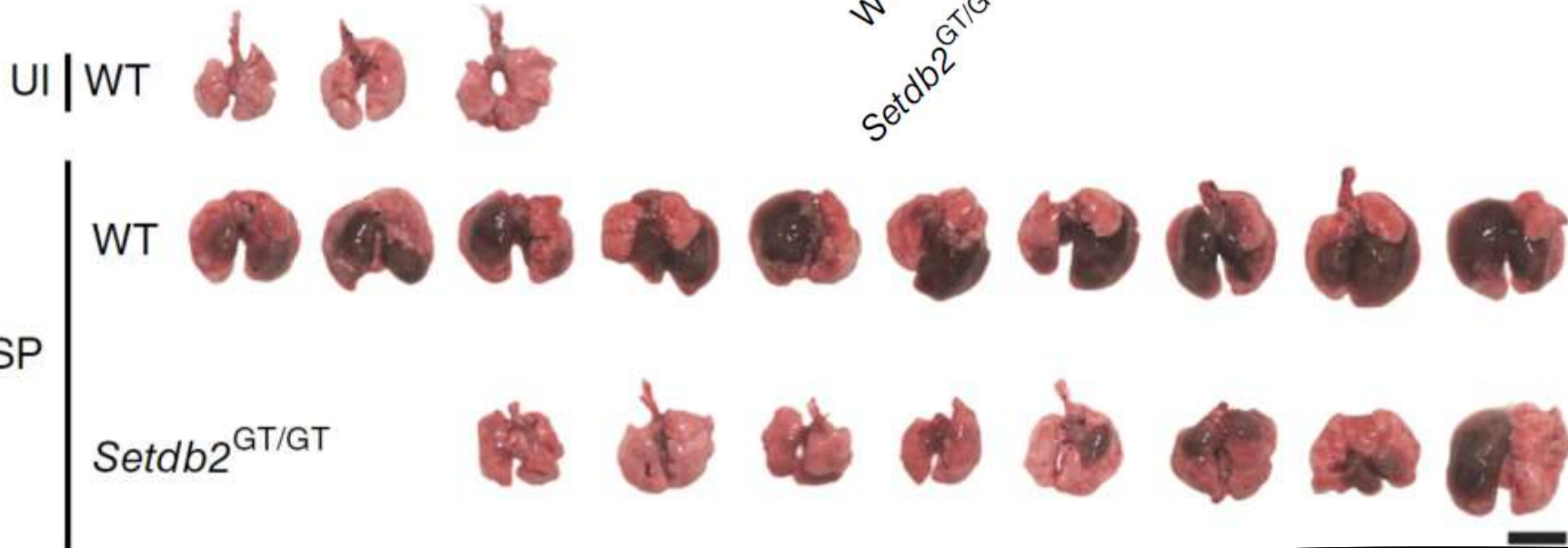
h



- gross pathological appearance of superinfected lungs



e



- histopathological scoring of superinfected lungs

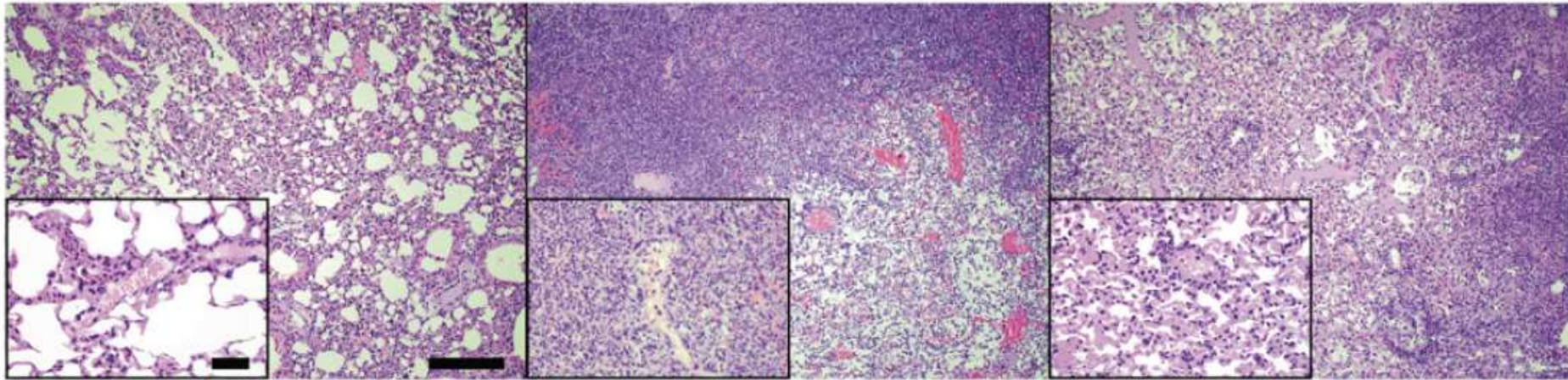
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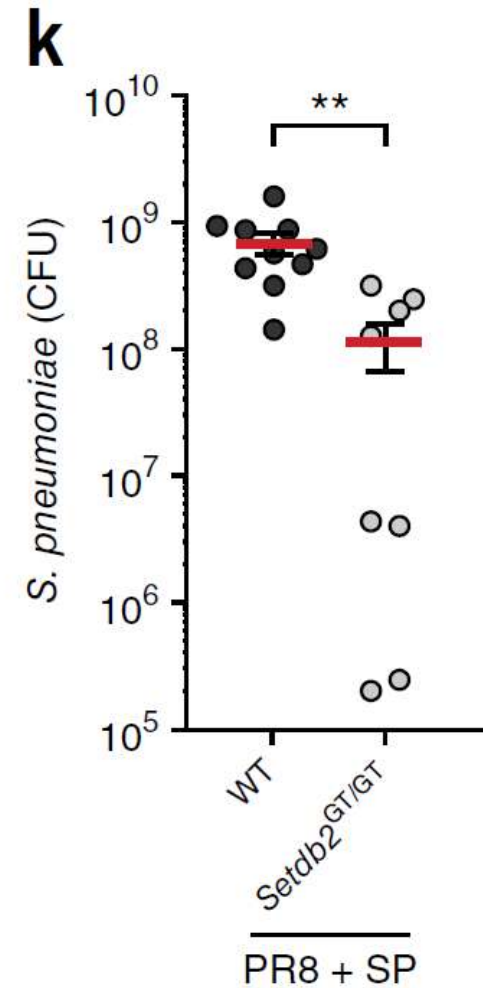
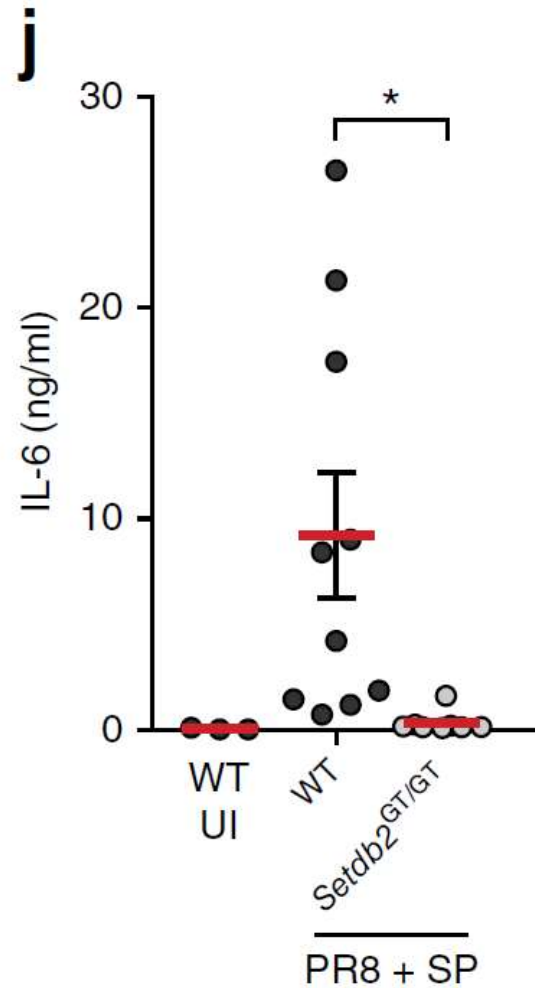
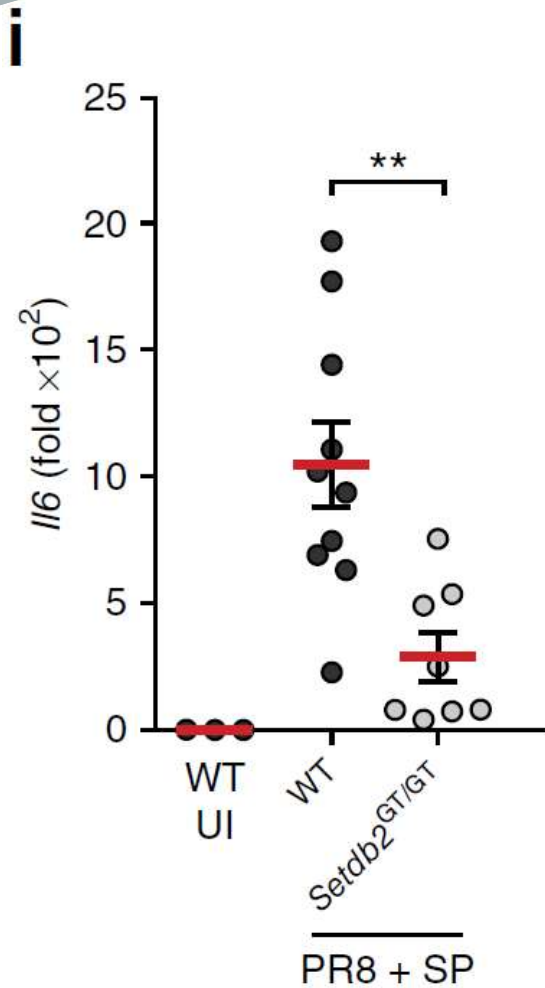
PR8 + SP

WT UI

WT

Setdb2^{GT/GT}





Discussion

- Interferon-I and NFκB pathways interact closely in immunoregulation
- chromatin modifiers are crucial mediators and effectors, silencing and/or activating gene expression
- Setdb2 catalyzes trimethylation at H3K9 -> silencing

Discussion

- Setdb2 increases significantly in WT mice after infection with influenza-virus
- Expression of CXCL1 shows an inverse correlation with expression of Setdb2
- less CXCL1 means less chemotaxis for neutrophils
- Results in decreased bacterial clearance
→ promoted superinfection after infection with influenza virus

**THANK YOU FOR YOUR
ATTENTION!**