

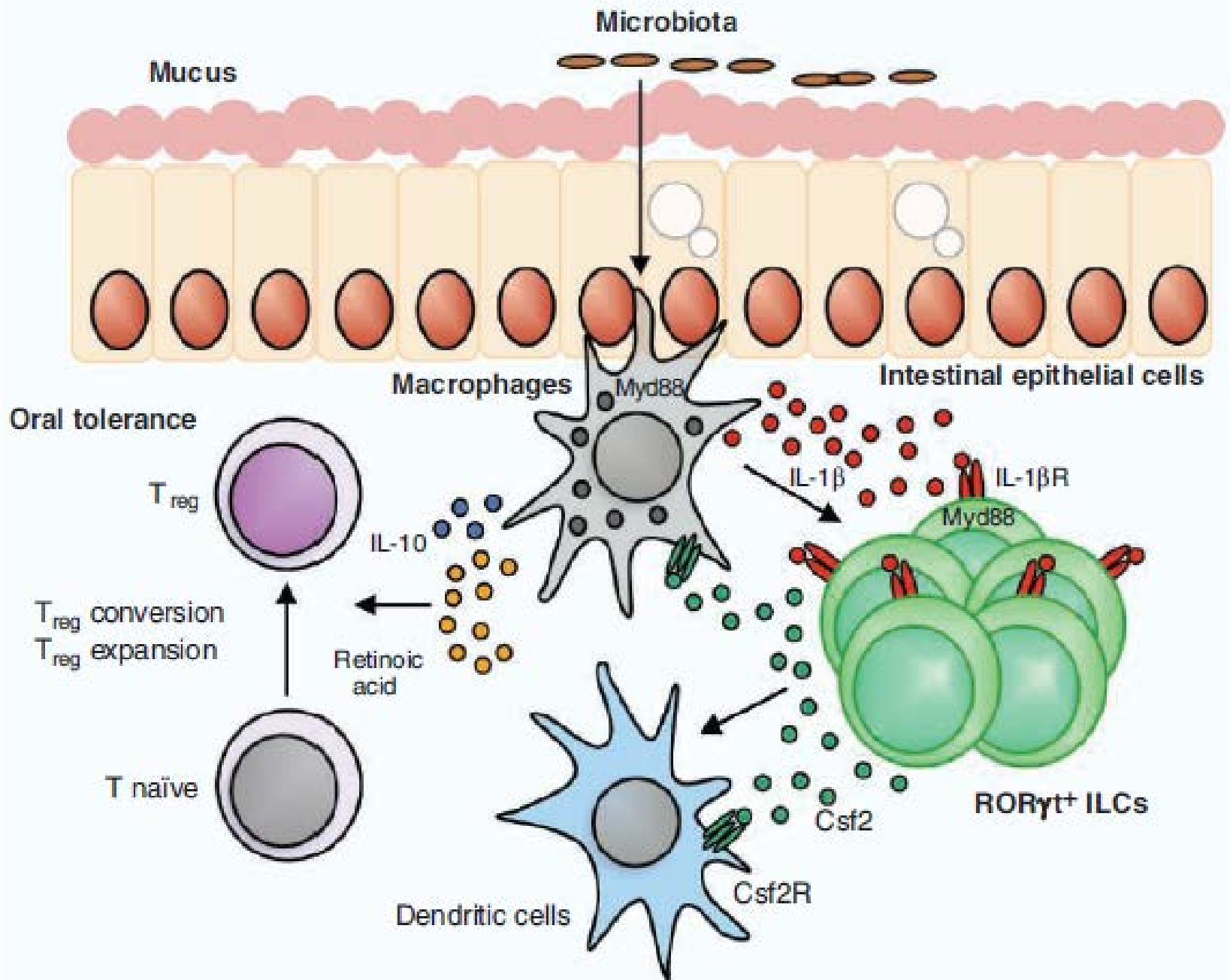
Microbiota-Dependent Crosstalk Between Macrophages and ILC3 Promotes Intestinal Homeostasis

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Facts

- Author: Arthur Mortha from the Department of Oncological Sciences, NY-USA
- published in Nature
- published on the 28th of March 2014



Introduction

- GIT -> large number of commensal microbes exposed to ingested antigens & potential pathogens
- Regulation of intestinal tolerance -> very important
- Accumulated evidence suggests -> gut commensals -> ability to control T lymphocytes and modulate inflammatory responses -> through Tregs and IL-10 production
- MNPs (incl. MPs and DCs) -> detect microbial signals -> capture, process and present extracellular antigenic material to T-lymphocytes

Rationale

- GM-CSF = CSF2-> required for the optimal function of tissue MNPs
Csf2 deficient mice -> reduced number of steady-state nonlymphoid tissue-resident DCs in small intestine -> reduction of Treg
- They used detailed profiling studies & functional immune assays of the MNP and lymphocyte compartment in the gut, as well as genetically engineered mice

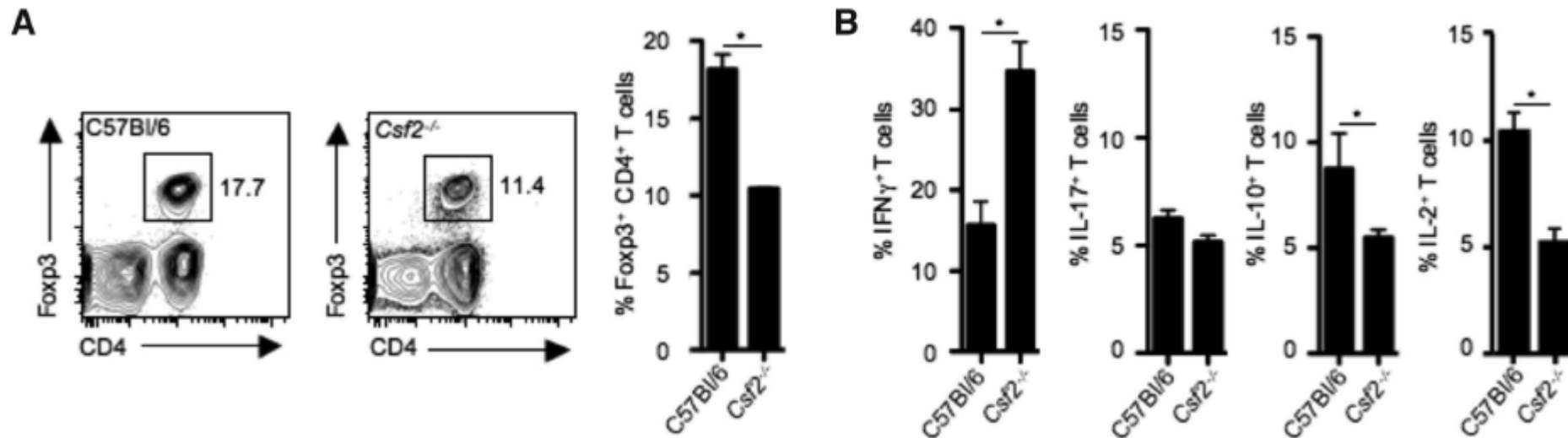
Results

Revealed a crosstalk between IL-1 β -secreting MPs and CSF2-producing ROR- γ -t⁺ type3 innate lymphoid cells (ILC3) in the intestinal mucosa

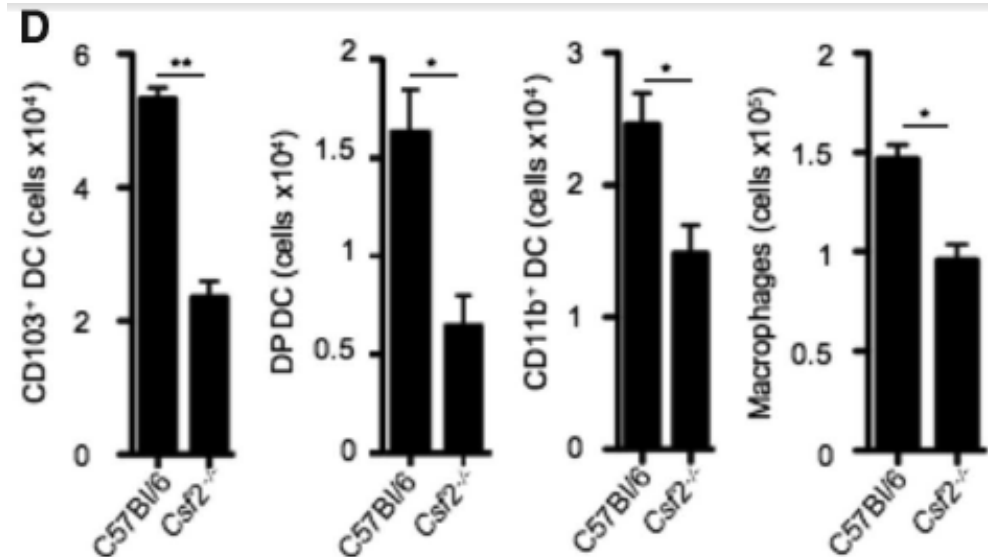
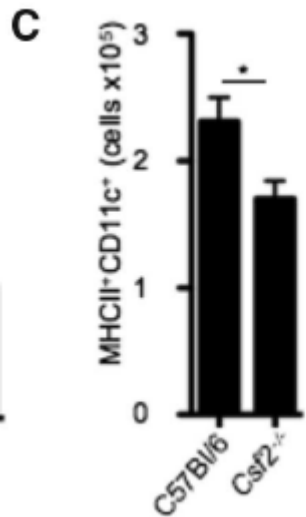
Conclusion

- This study established the commensal-driven MNP-ILC-Csf2 axis as a key regulator of intestinal T cell homeostasis in the mouse intestine.
- Disturbance of this axis radically altered MNP effector function, resulting in impaired oral tolerance to dietary antigens.
- These results represent an important advance in our understanding of how commensal microbes can regulate host intestinal immunity and may inform the design of novel immunotherapies für patients with inflammatory intestinal diseases with impaired GM-CSF function.

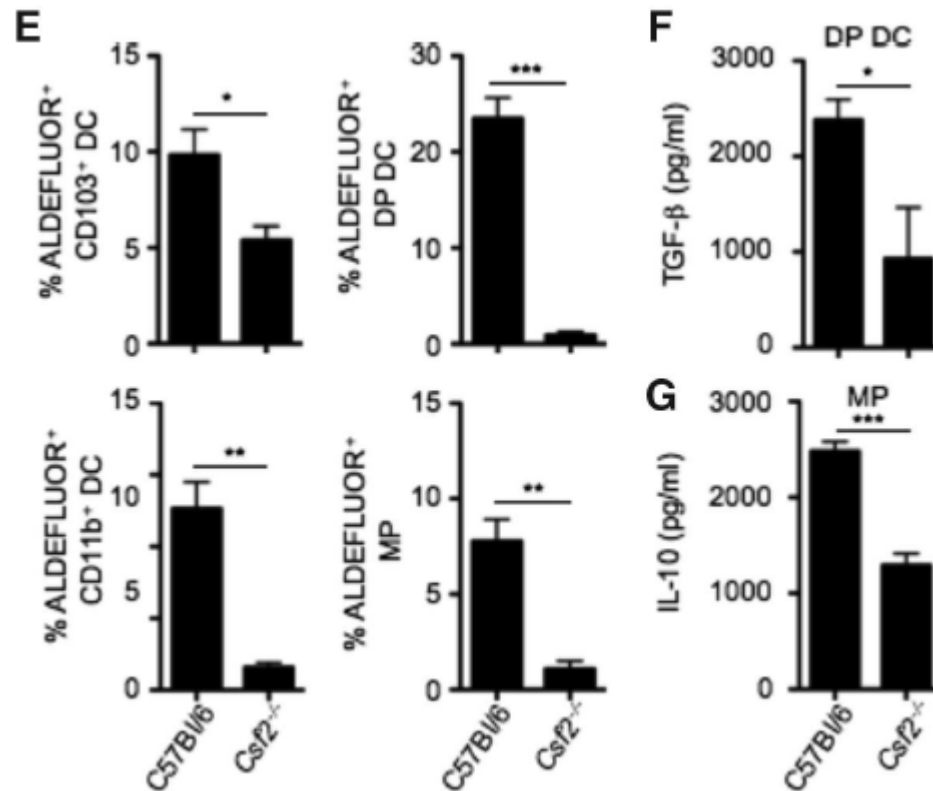
Regulation of Gut DC, Macrophage, and T_{reg} Cell Homeostasis by Csf



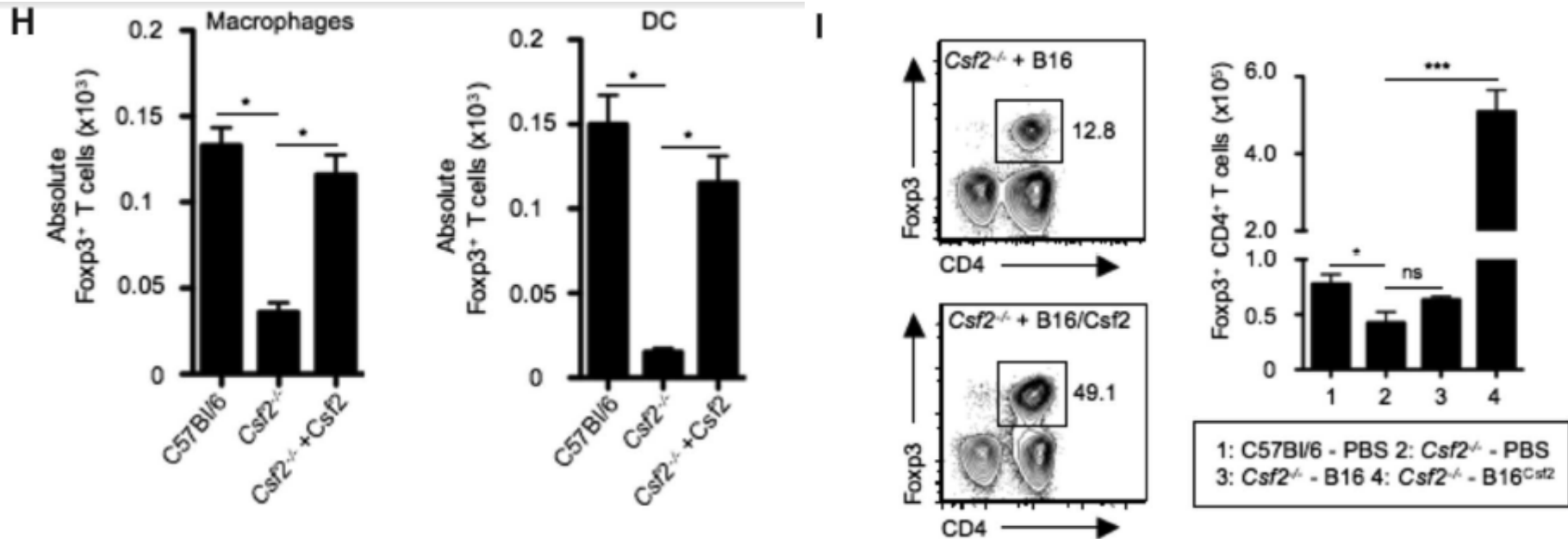
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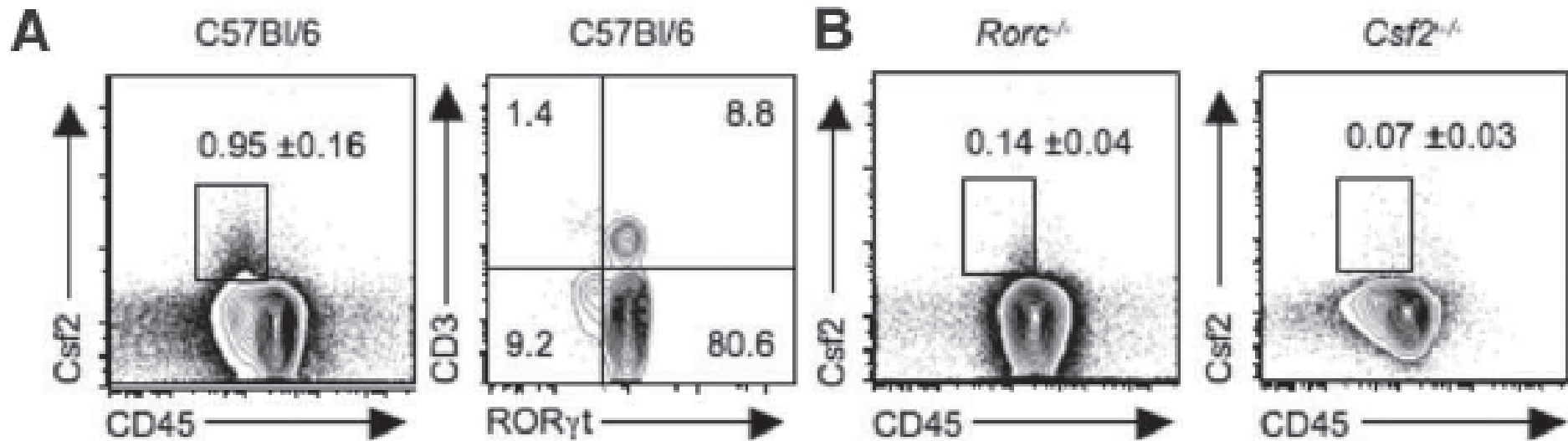
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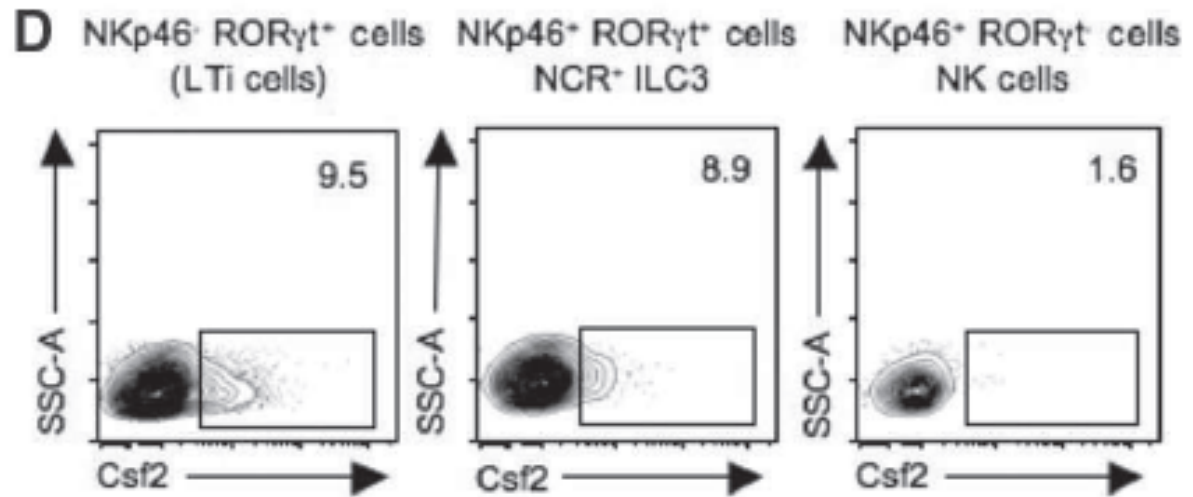
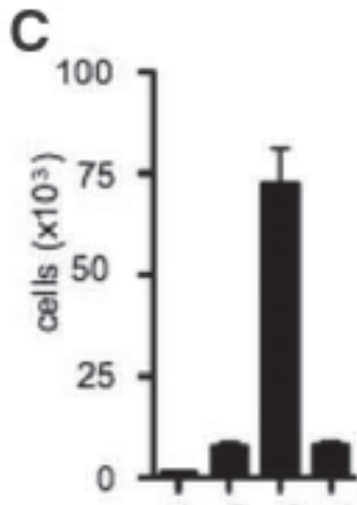
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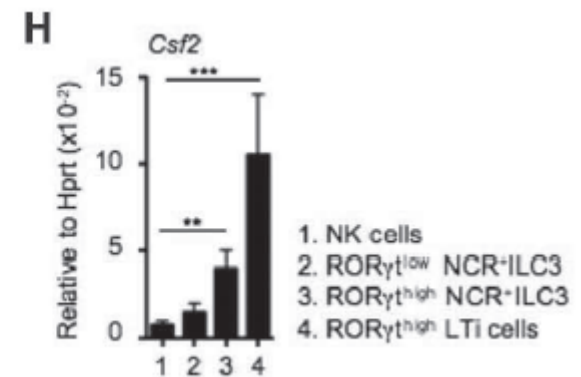
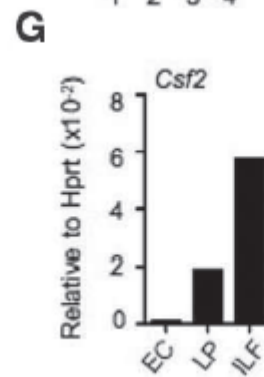
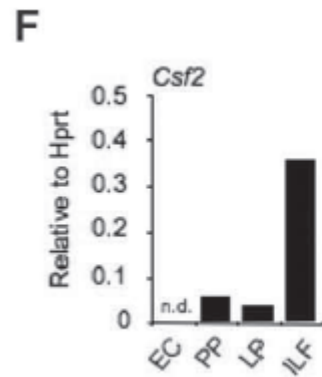
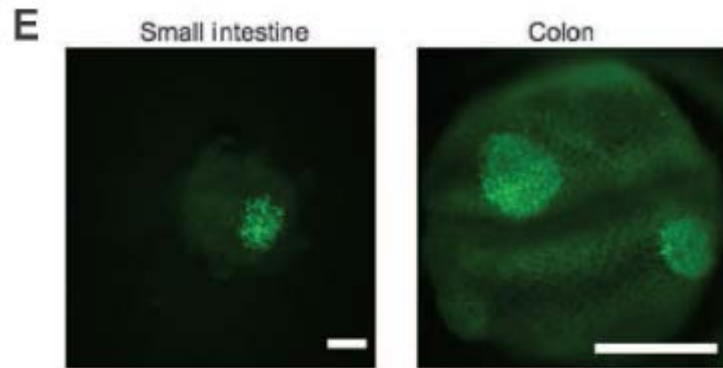
CSF is produced by ROR γ t⁺ ILC3



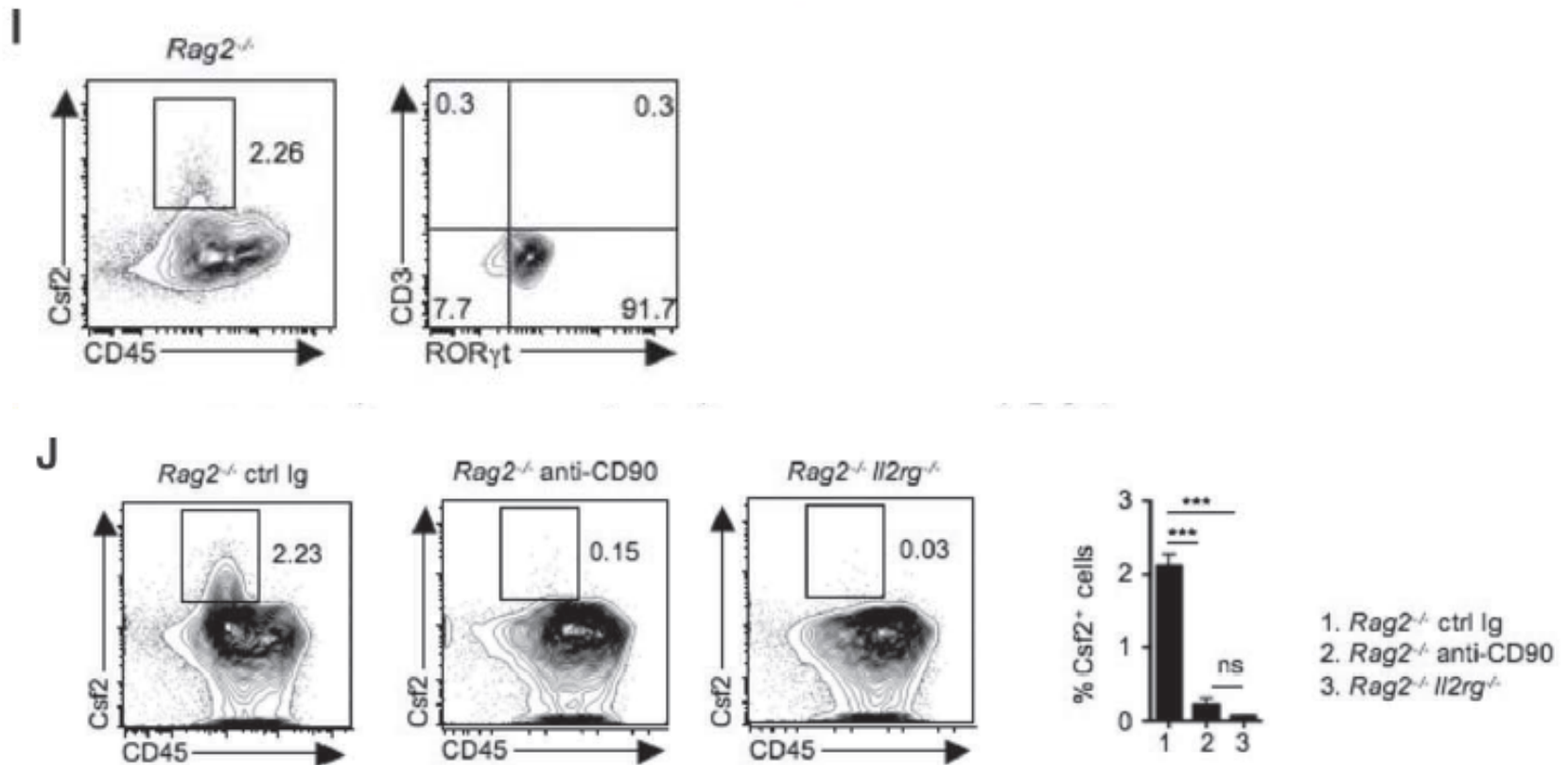
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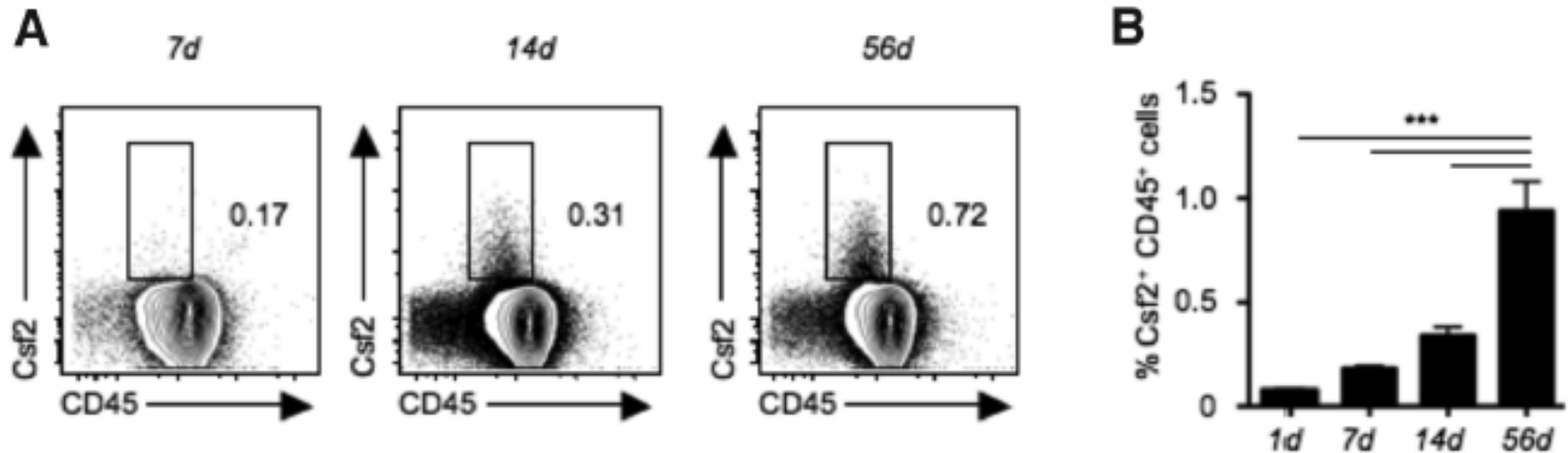
CSF is produced by ROR γ ^t ILC3



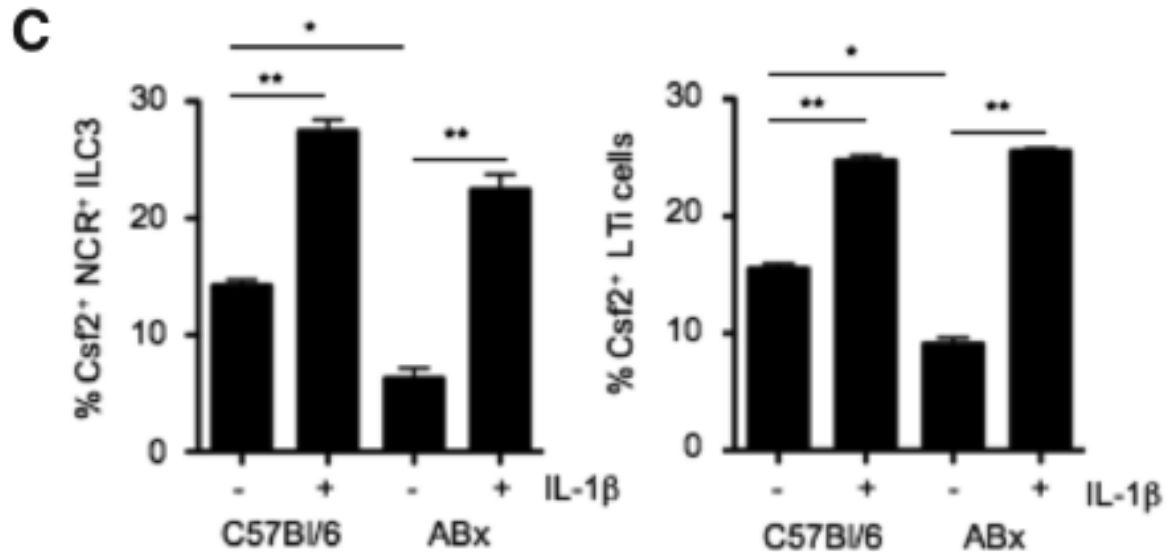
CSF is produced by ROR γ t⁺ ILC3



CSF2 production is dependent on microbial Signals

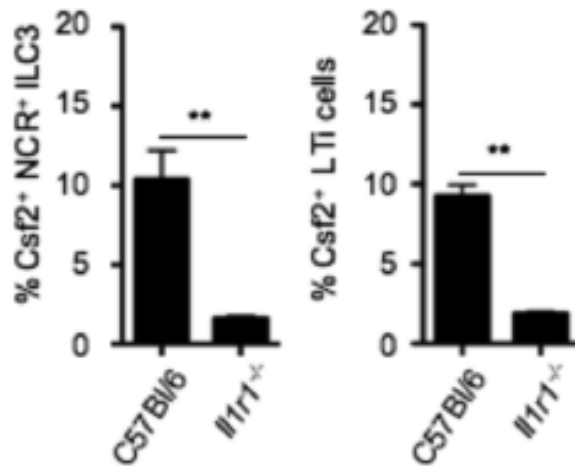


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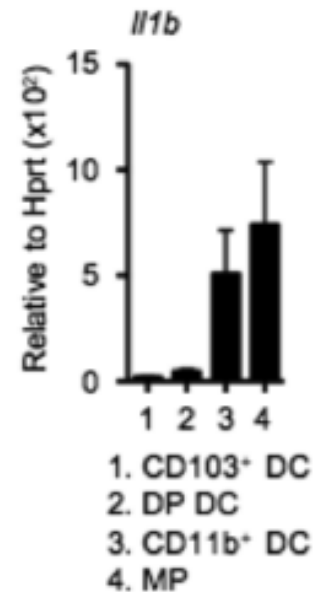


CSF2 production is dependent on microbial Signals

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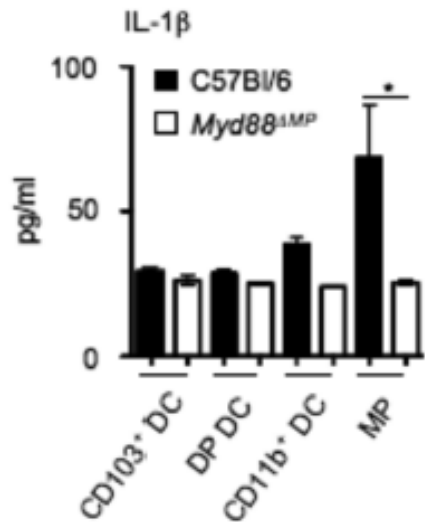


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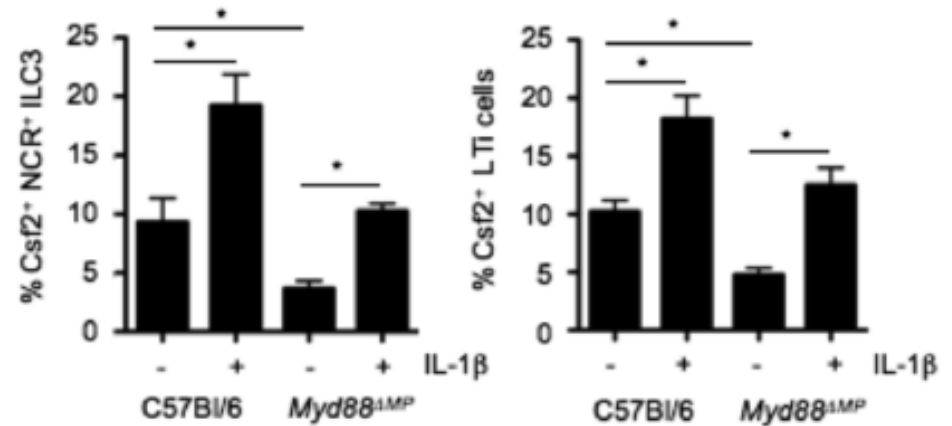


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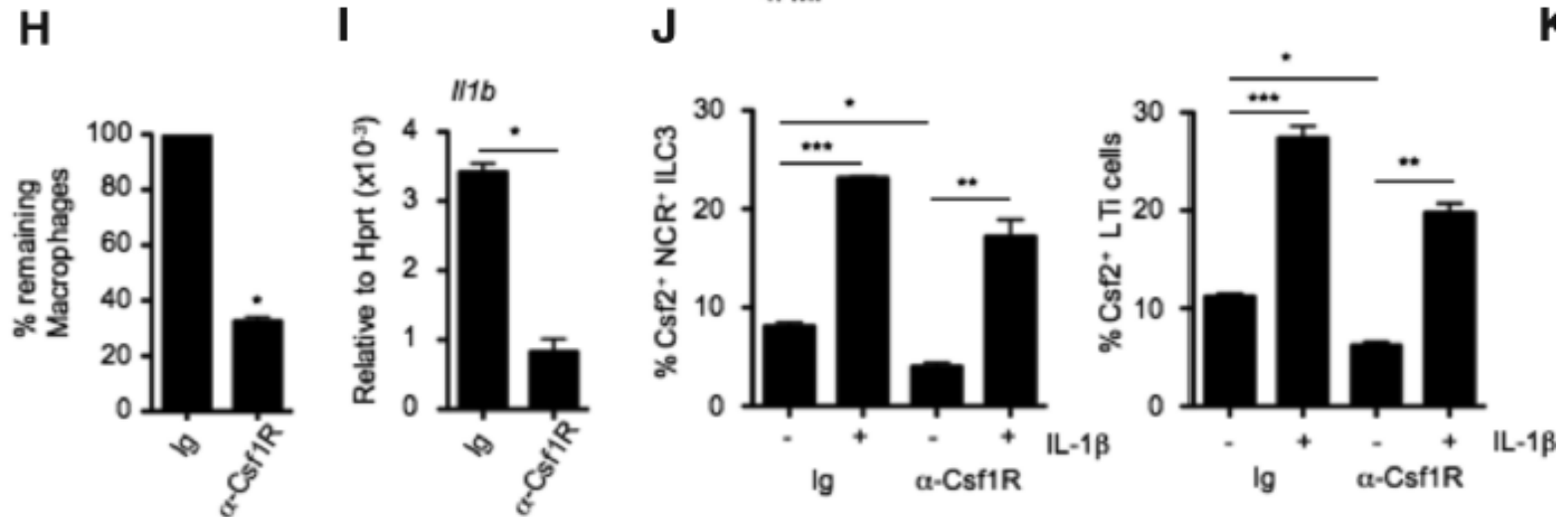
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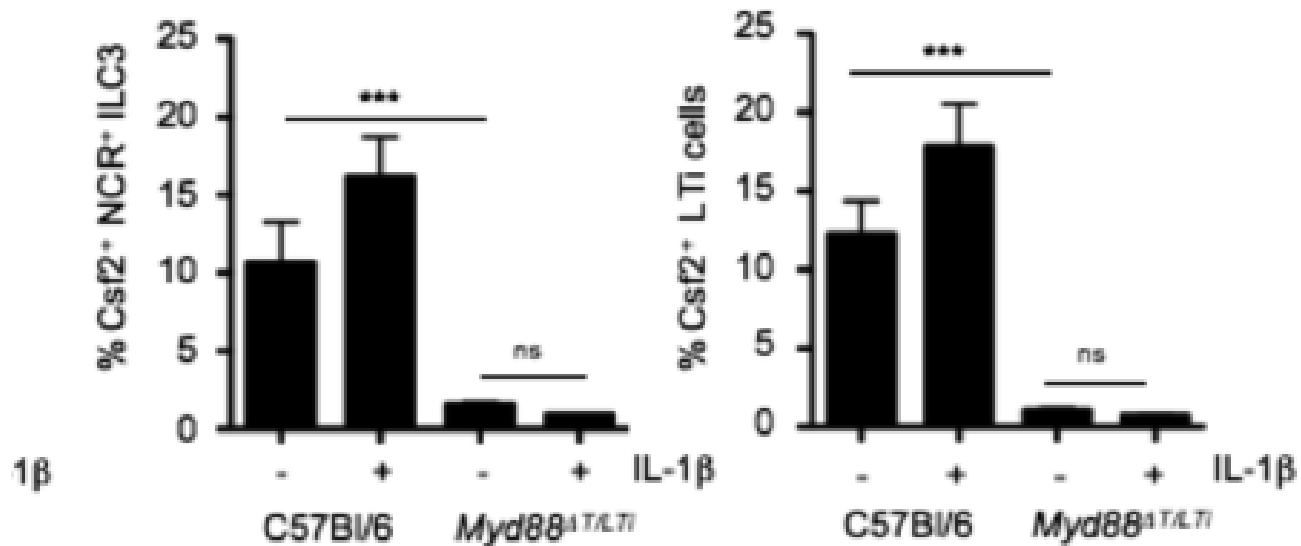


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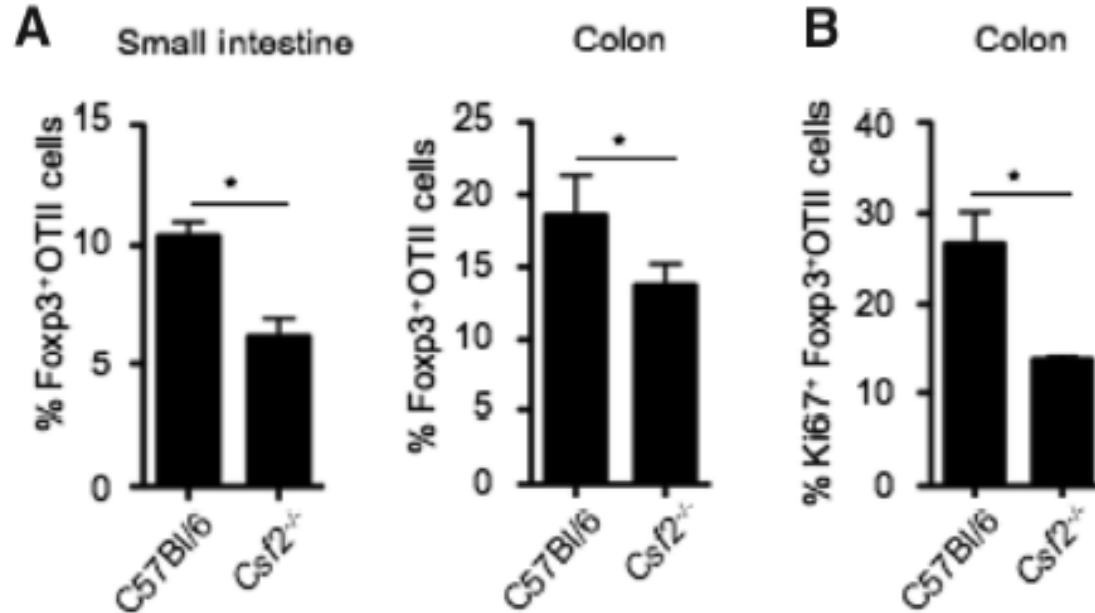


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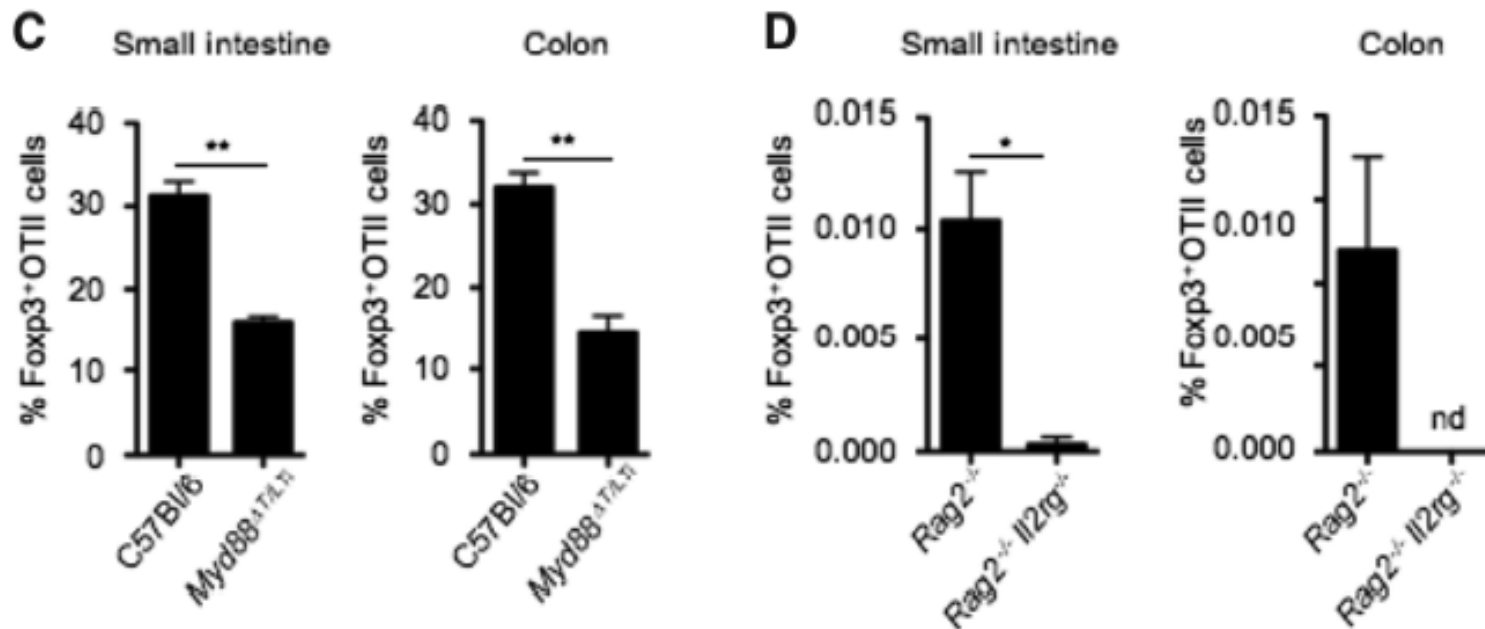
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CSF2 promotes Oral Tolerance of Fed Antigens

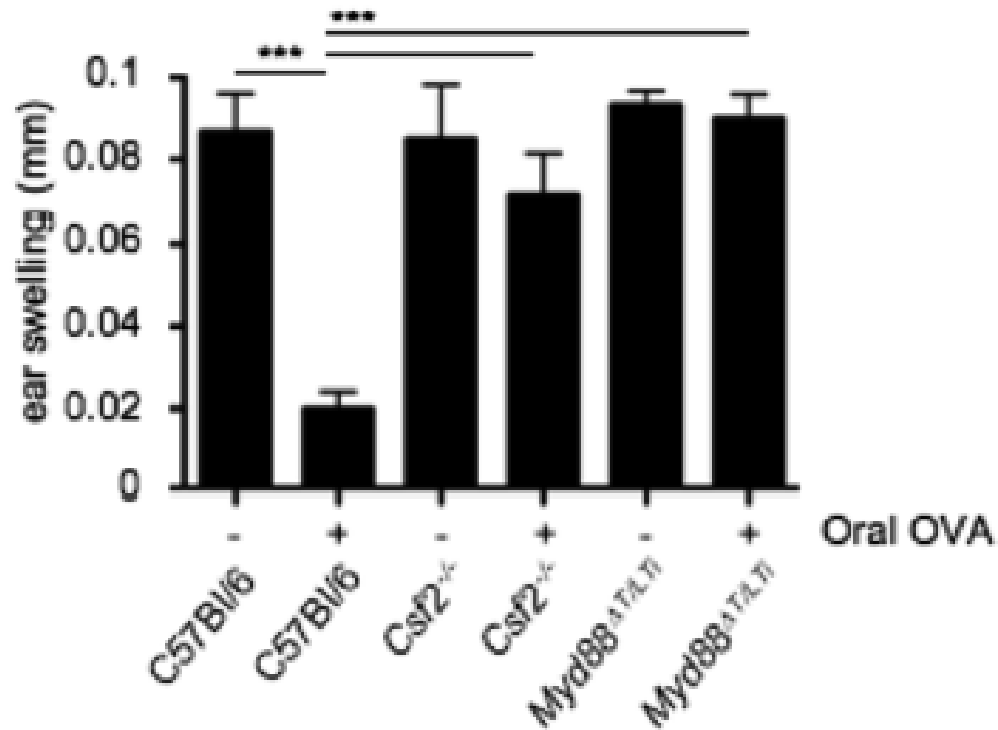


CSF2 promotes Oral Tolerance of Fed Antigens

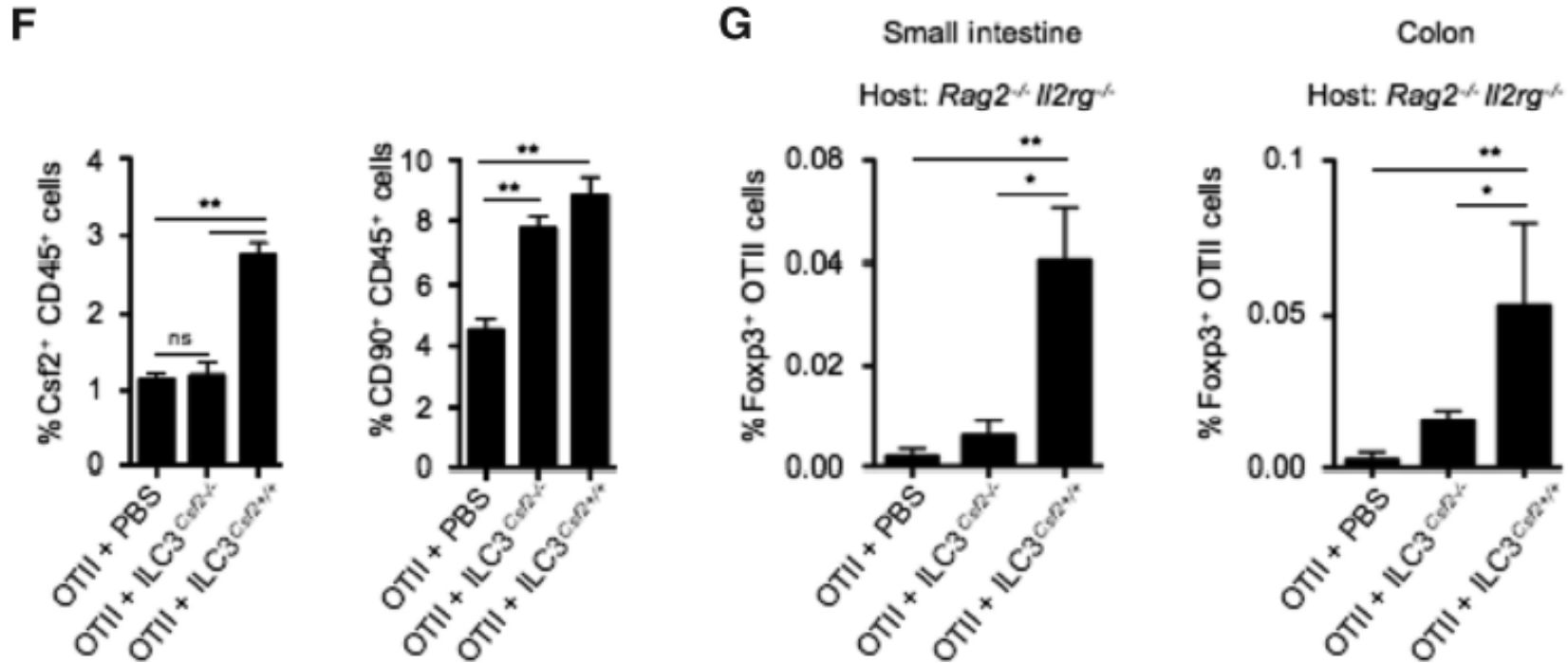


CSF2 promotes Oral Tolerance of Fed Antigens

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CSF2 promotes Oral Tolerance of Fed Antigens



Discussion

- Represents mechanism by which the gut microbiota mucosa promotes intestinal homeostasis
- Ablation of CSF2 -> disrupted Treg homeostasis
- Ablation of IL-1-dependent signaling in ROR γ t ILC3 -> abrogated oral tolerance to dietary antigens
- Gut commensal flora promotes immune homeostasis in the host

Discussion

- Commensal-driven MNP-ILC-CSF axis -> key regulator of Tcell homeostasis
- Disturbance of this axis -> altered MNP function, resulting in impaired oral tolerance to dietary antigens
- May inform the design of new immunotherapie for the use in patients with subtypes of IBD