

Psoriatic skin inflammation is promoted by c-Jun/AP-1-dependent CCL2 and IL-23 expression in dendritic cells

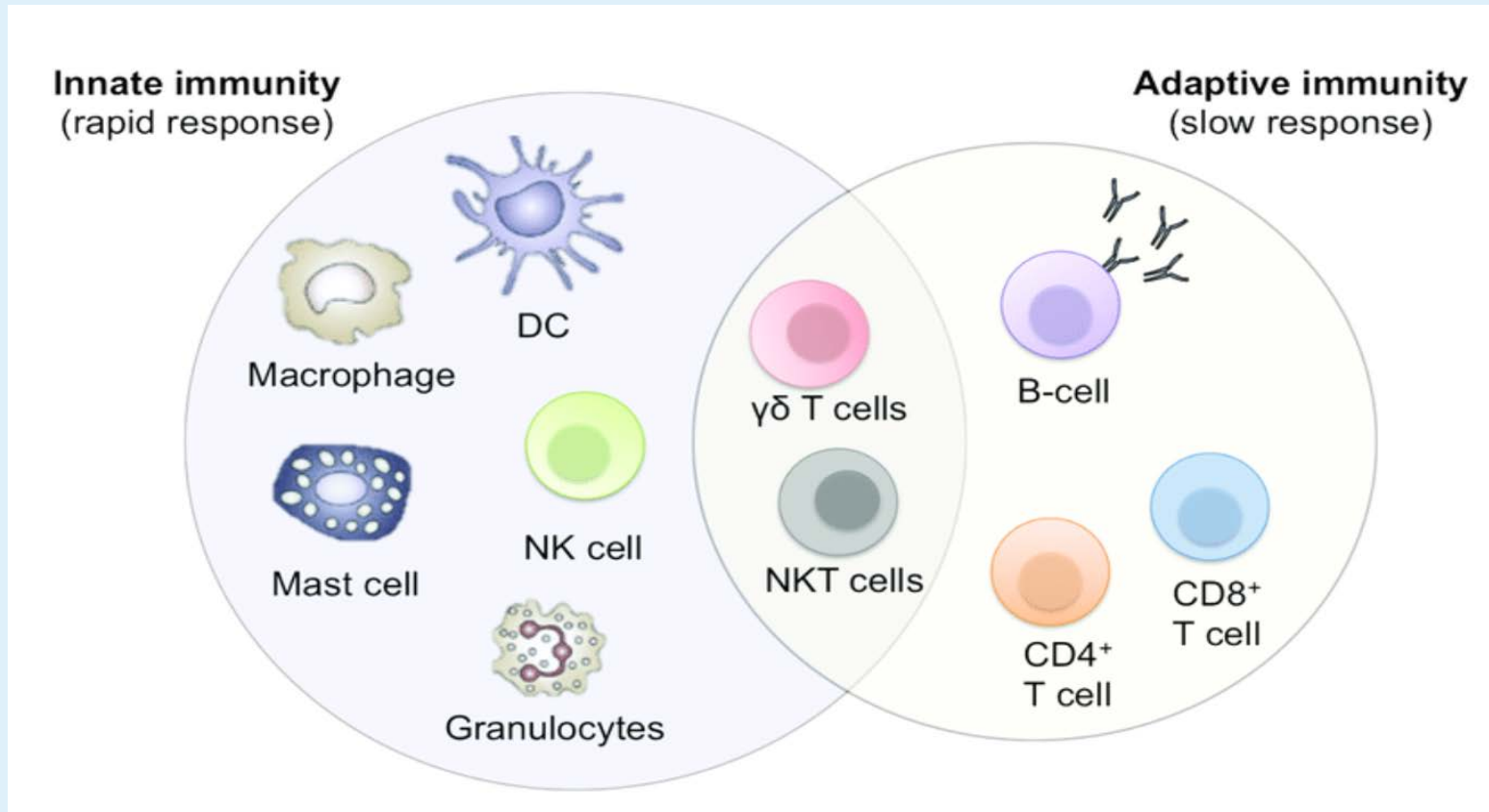
Philipp Novoszel et al., 2021

Department of Medicine I, Comprehensive Cancer Center, Institute of Cancer Research, Medical University of Vienna, Vienna, Austria

Journal Club (20220509)

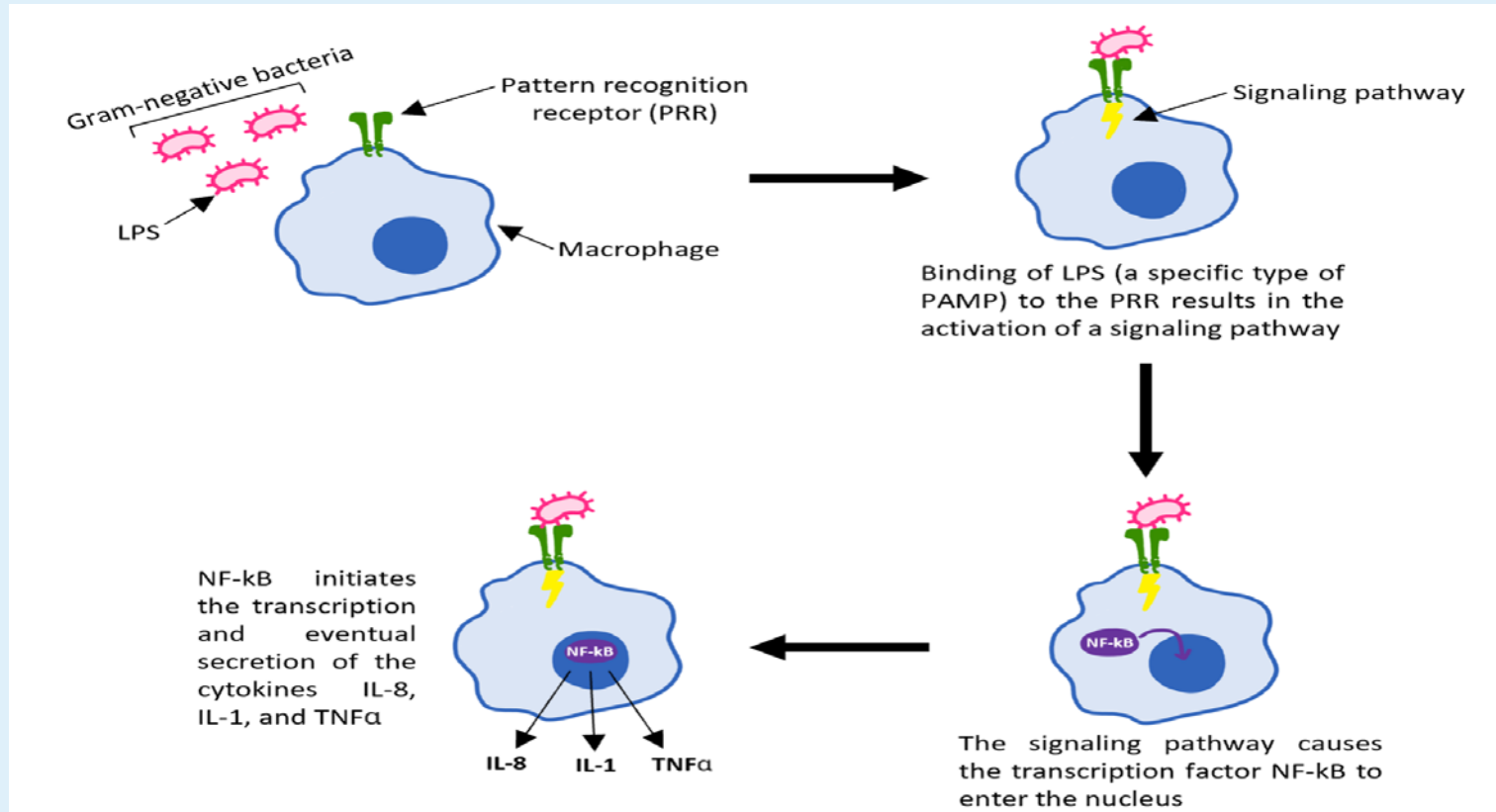
Fatemeh Hefzolehhe

Applied Immunology Lab/ARGE Prof. Ankersmit



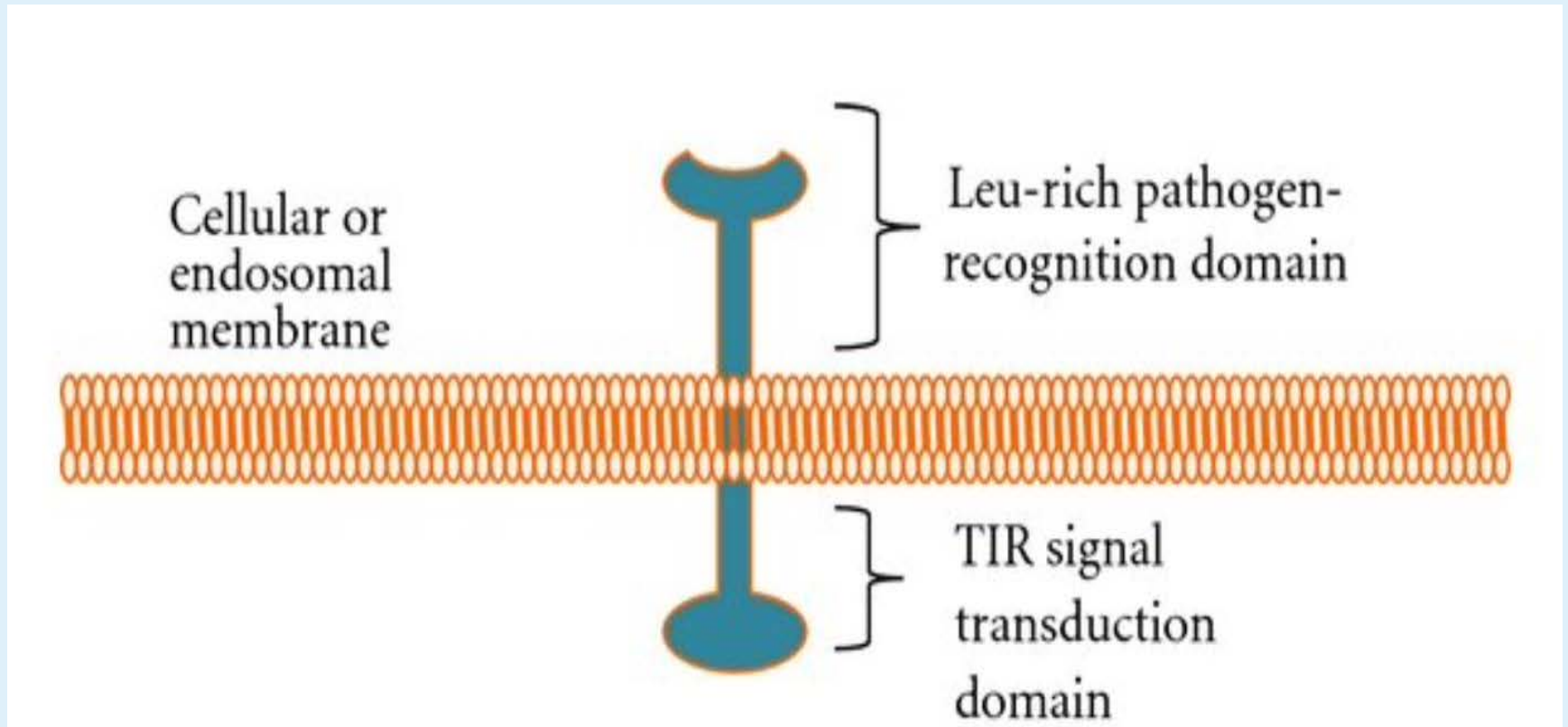
https://www.researchgate.net/profile/Cathrin-Ritter/publication/321936676_Scientific_basics_for_new_immunotherapeutic_approaches_towards_Merkel_cell_carcinoma/links/5cdc815d299bf14d959c4433/Scientific-basics-for-new-immunotherapeutic-approaches-towards-Merkel-cell-carcinoma.pdf

Innate Immune System



https://en.m.wikipedia.org/wiki/File:PAMPs_and_PRRs_in_the_Innate_Immune_System.png

Toll-like receptor (TLR)



<https://doi.org/10.5402/2012/642141>

Psoriasis

- Complex, chronic, multifactorial & inflammatory
- Genetik, environment & immune system
- 2% of the World Population
- „Psoriasis Vulgaris“ typical form ~ 90%
- High level of IL-23 in the injured skin
- Progression of psoriasis: injuring of ceratinocytes and releasing of DNA/RNA fragments
- Similar symptoms by some chemical drugs such as „Imiquimod“

- <https://doi.org/10.3390/ijms23010540>
- <https://emedicine.medscape.com/article/1943419-overview>

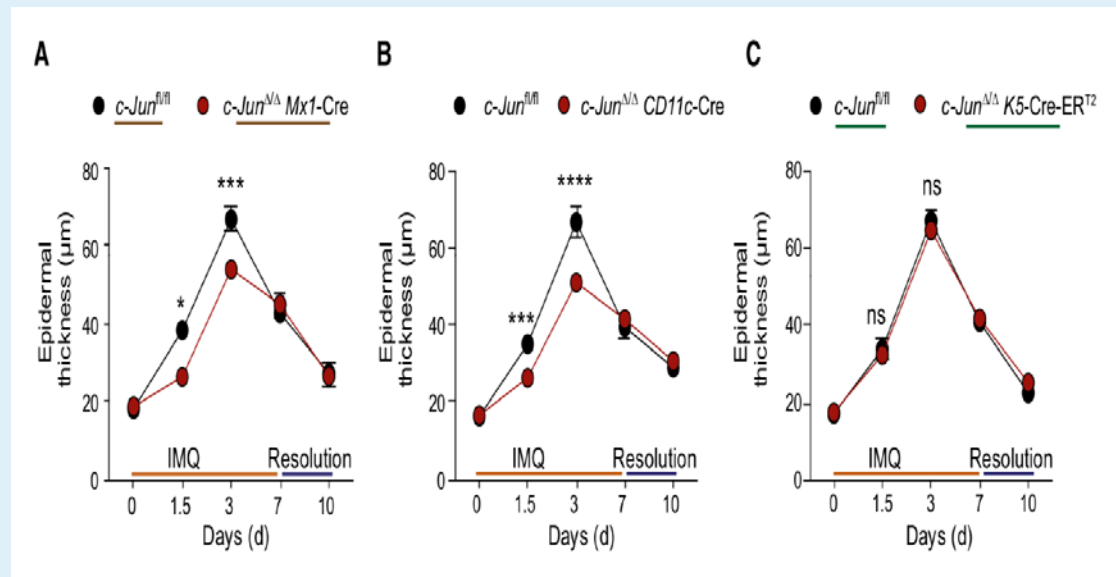


Studies & Results

1. IMQ-induced skin inflammation requires c-Jun in dendritic cells
2. CCL2-mediated recruitment of pDCs to IMQ-inflamed skin depends on c-Jun in DCs
3. c-Jun directly regulates IL-23 expression in DCs
4. c-Jun is essential in conventional type-2 DCs to control CCL2 and IL-23 expression
5. Blocking JNK/c-Jun signaling ameliorates IMQ-induced skin inflammation
6. c-Jun, CCL2, and IL-23 are co-expressed in type-2/inflammatory DCs of psoriatic lesions
7. JNK/AP-1 Inhibitors repress CCL2 and IL-23 expression in human mo-DCs

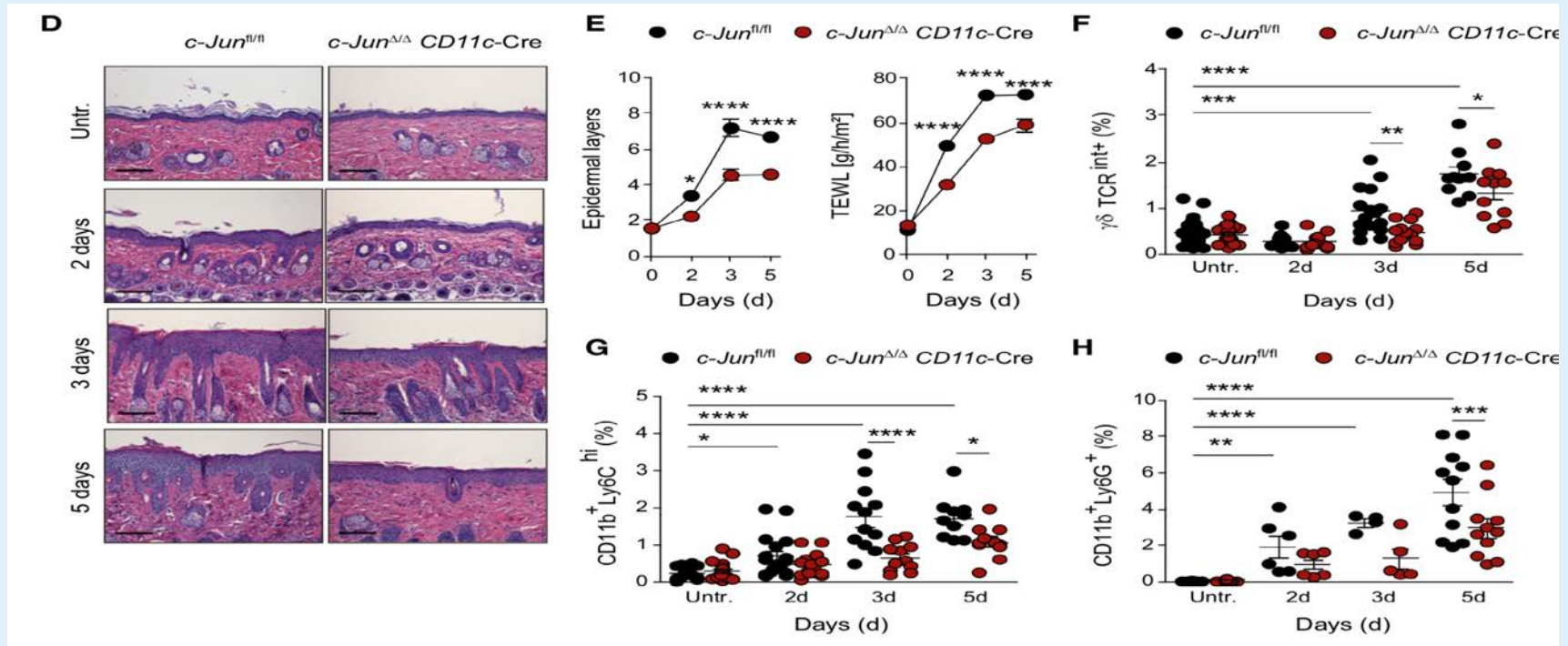
1: IMQ-induced skin inflammation requires c-Jun in dendritic cells

Experimental group	C-Jun inactivation
c-Jun Δ/Δ CD11c-Cre	Genetically via crossing (C-Jun ^{fl/fl} and mice with Cre recombinase)
c-Jun Δ/Δ K5-Cre-ERT2	Injection of Tamoxifen
c-Jun Δ/Δ Mx1-Cre	Injection of Poly I:C (polyinosinic:Polycytidylic acid)
Control group	
C-Jun ^{fl/fl}	-----



- Identify the role of C-Jun in the skin inflammation
- Epidermal thickness as inflammatory indicator

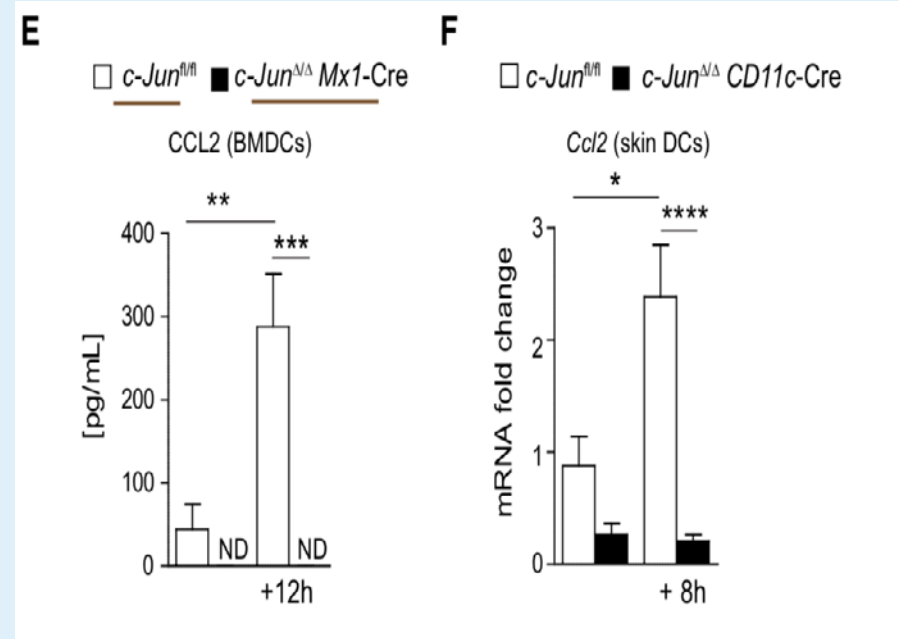
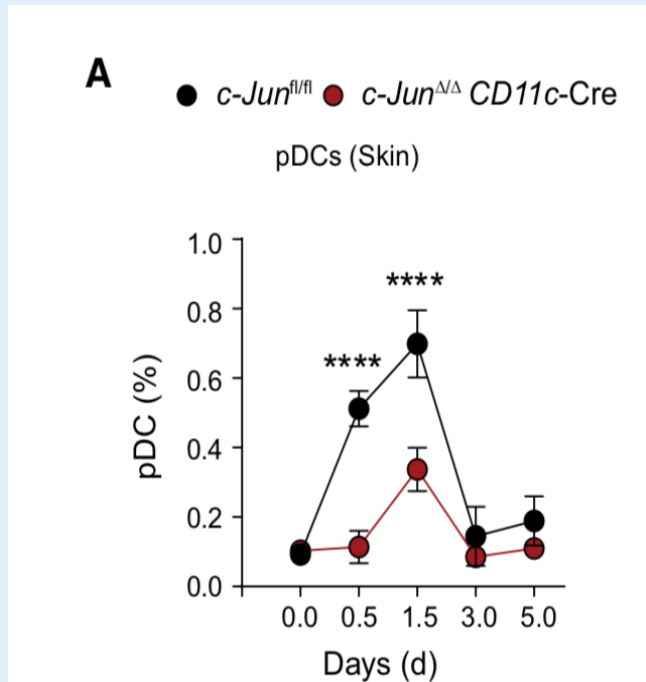
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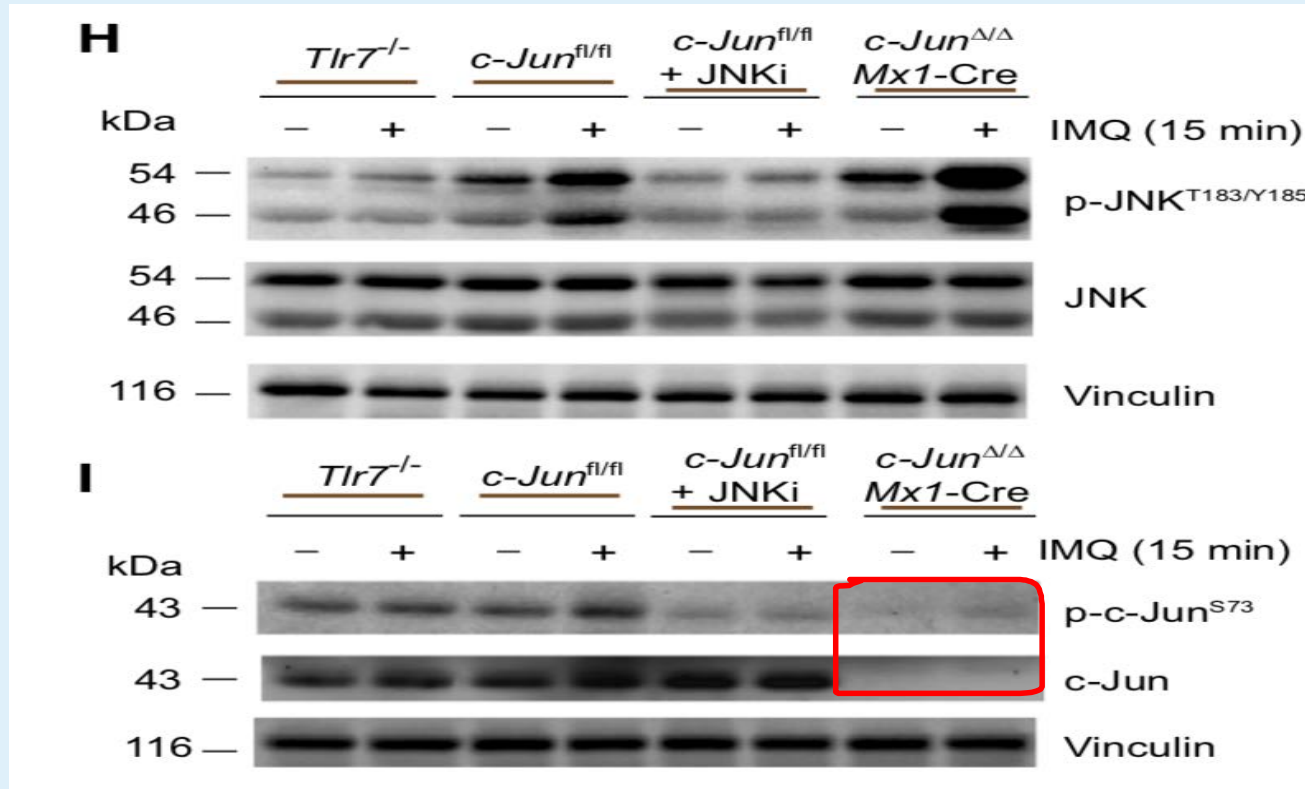
Inflammation indicators:

- Epidermal thickness/acanthosis
- Loss of barrier integrity (TEWL: Trans-epidermal Water Loss)
- Infiltration of immune cells (dermal $\gamma\delta$ -T cells & monocytes & neutrophils) into the skin of mice

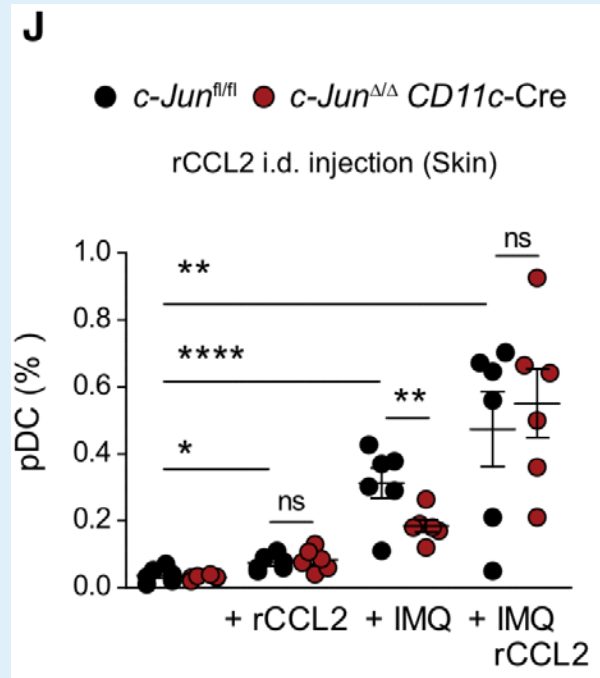
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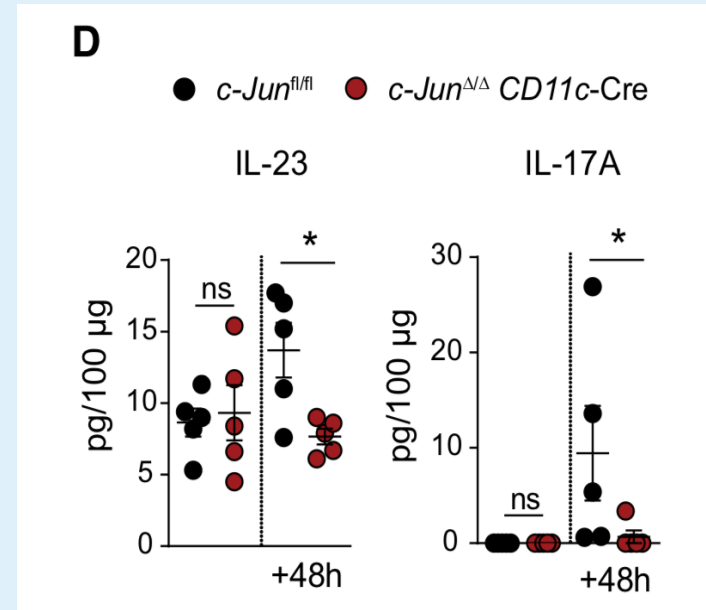
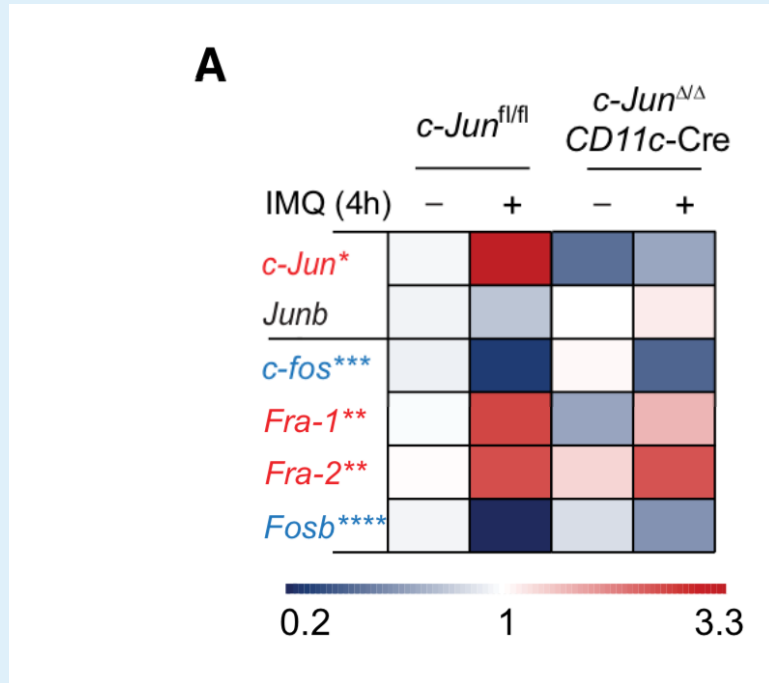


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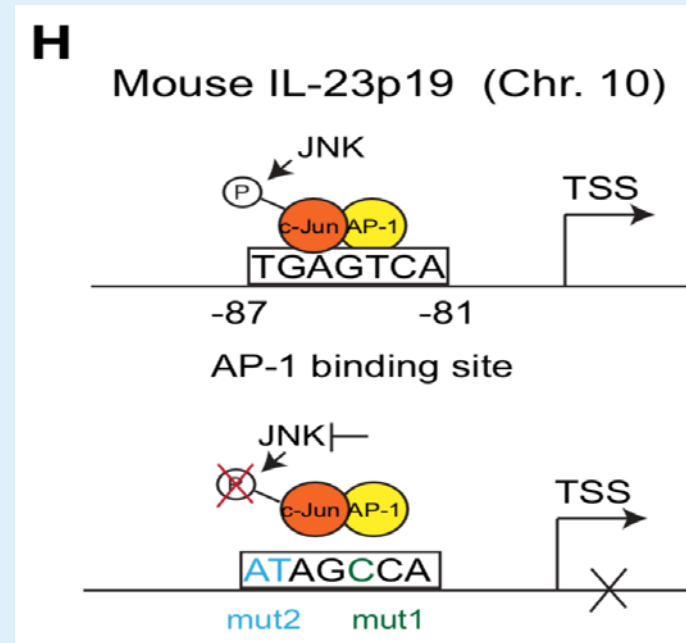
- Injection of recombinant CCL2 (rCCL2)

3: c-Jun directly regulates IL-23 expression in DCs

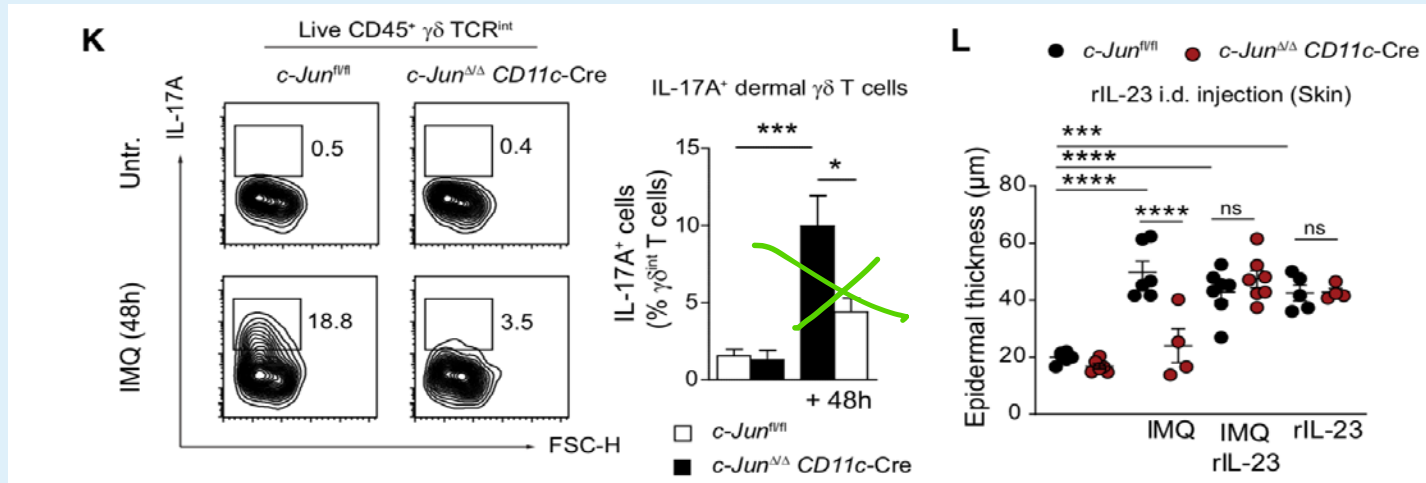


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- Genomic location & sequence of binding site of IL-23p19
- 2 ways for inhibition of C-Jun phosphorylation:
 1. Using JNK inhibitor
 2. Mutation in the base sequence



3: c-Jun directly regulates IL-23 expression in DCs



- Tortola et al. 2012: IL-23 induces IL-17A production in $\gamma\delta$ -T cells ,which contributes to IMQ-induced inflammation
- Recombinant IL-23 (rIL-23) to adjust the IL-23 deficiency

4: c-Jun is essential in conventional type-2 DCs to control CCL2 and IL-23 expression

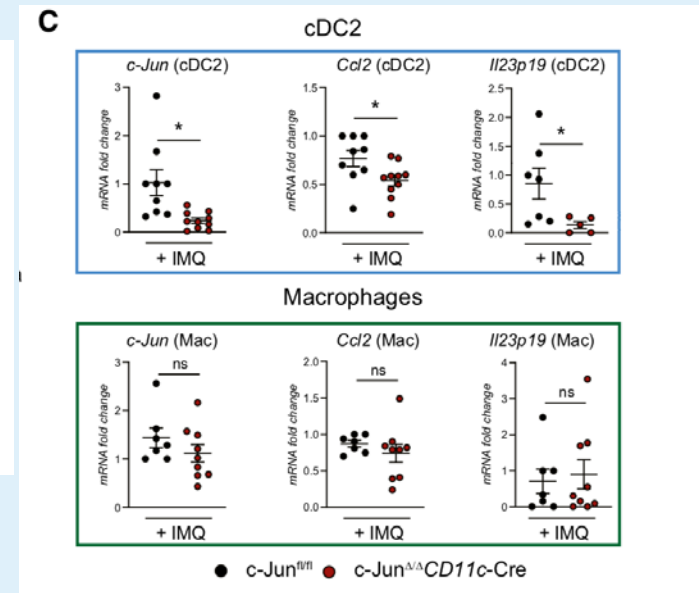
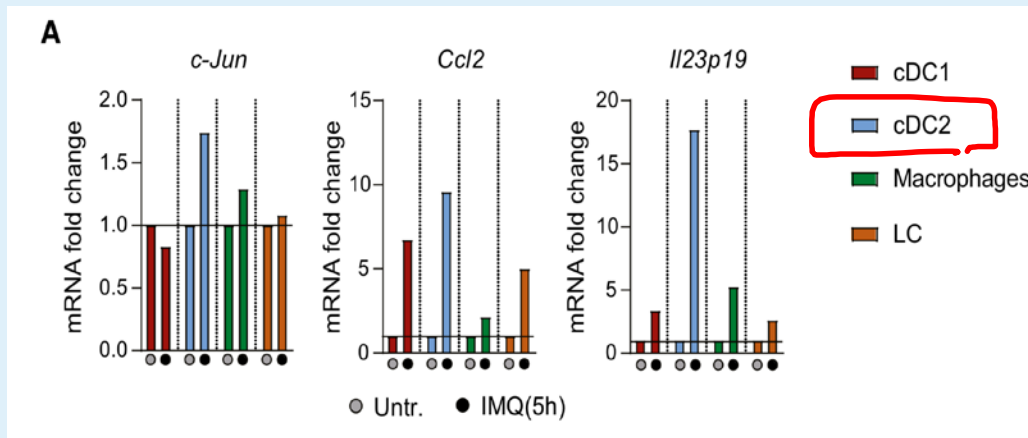
Dendritic cells (DCs) First description in (1973) by Steinmann and Cohn

3 main subdivision:

- Conventional Dendritic Cells (cDCs) —> **main Antigen-presenting cells**
type 1 & type 2
- Plasmacytoid Dendritic Cells (pDCs)
- Monocytes-derived Dendritic Cells (mo DCs)

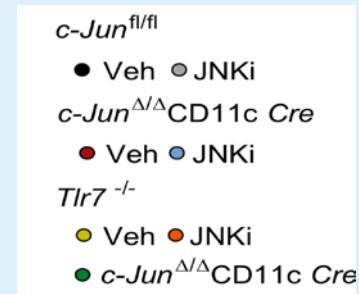
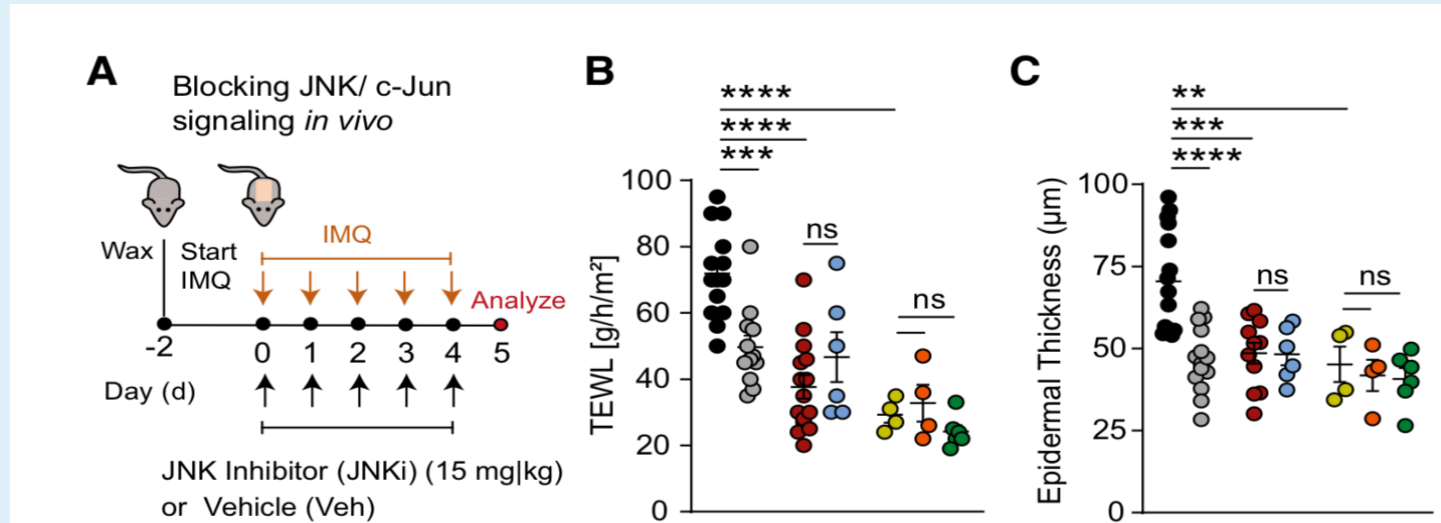
<https://doi.org/10.1038/mi.2017.8>

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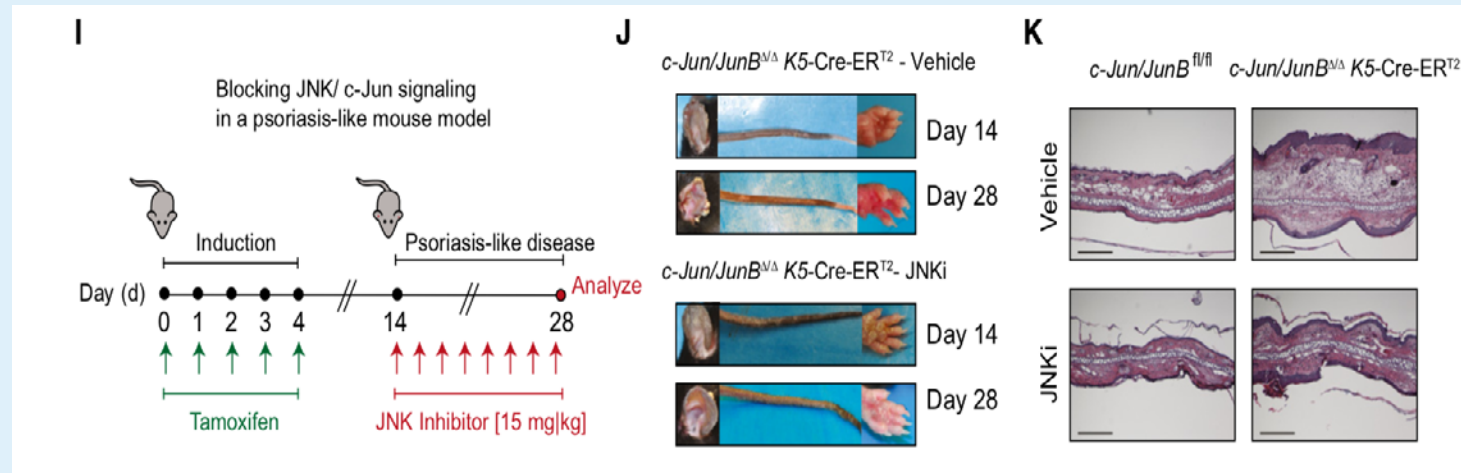


- A comparison between 4 immune cells regarding C-Jun, CCL2 & IL-23p19 expression
- Whether macrophages contribute to the expression of CCL2 and IL-23p19

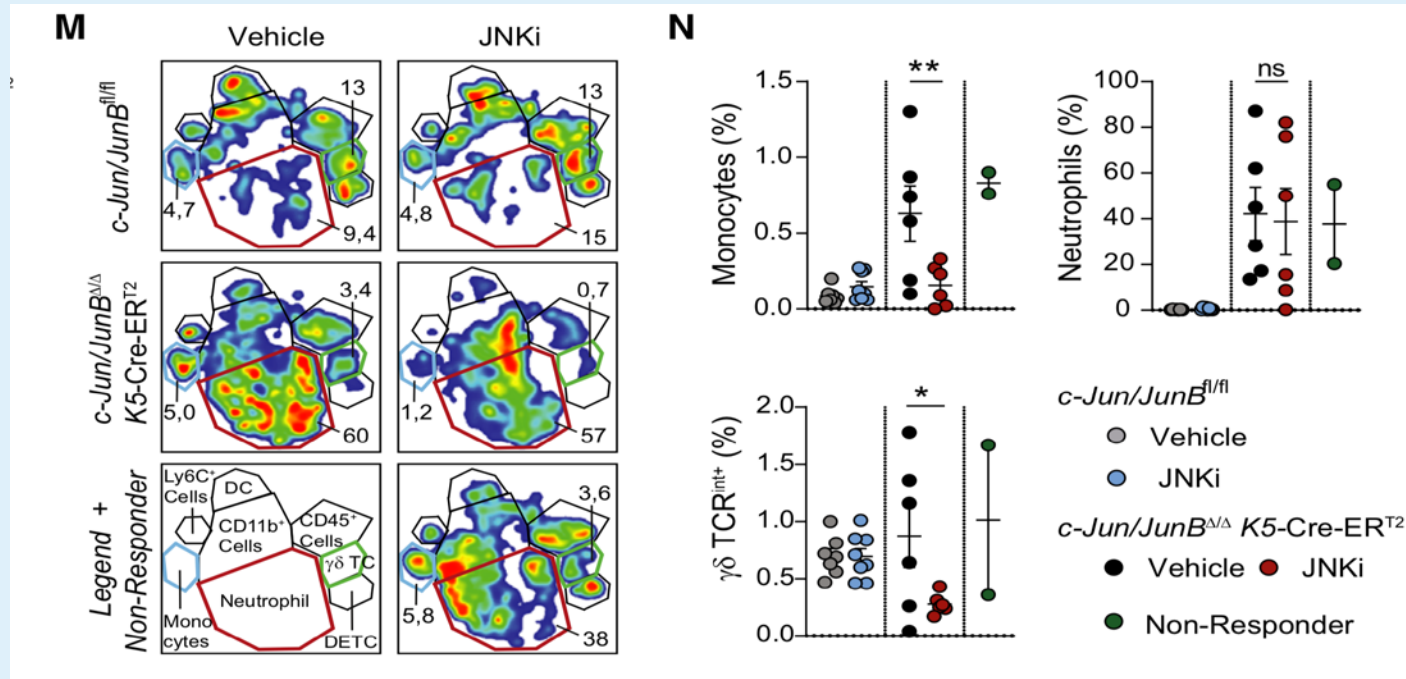
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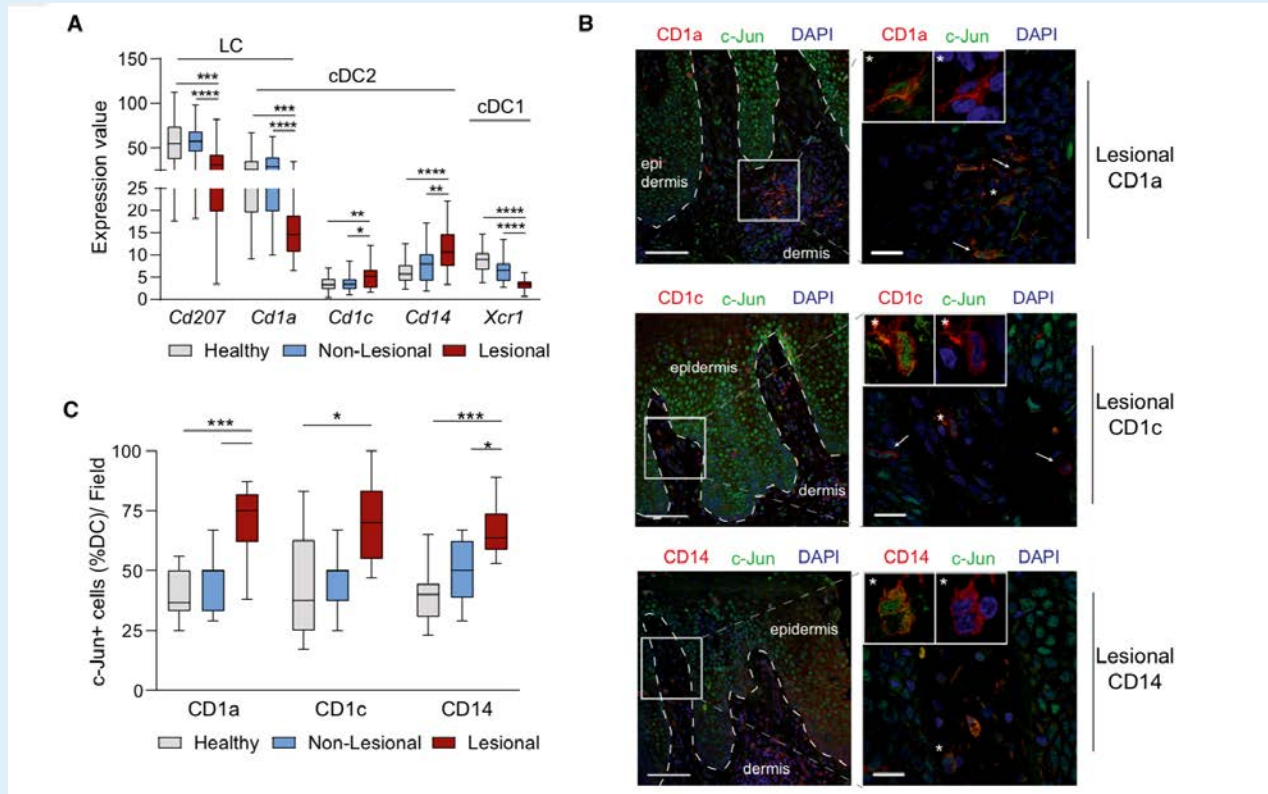


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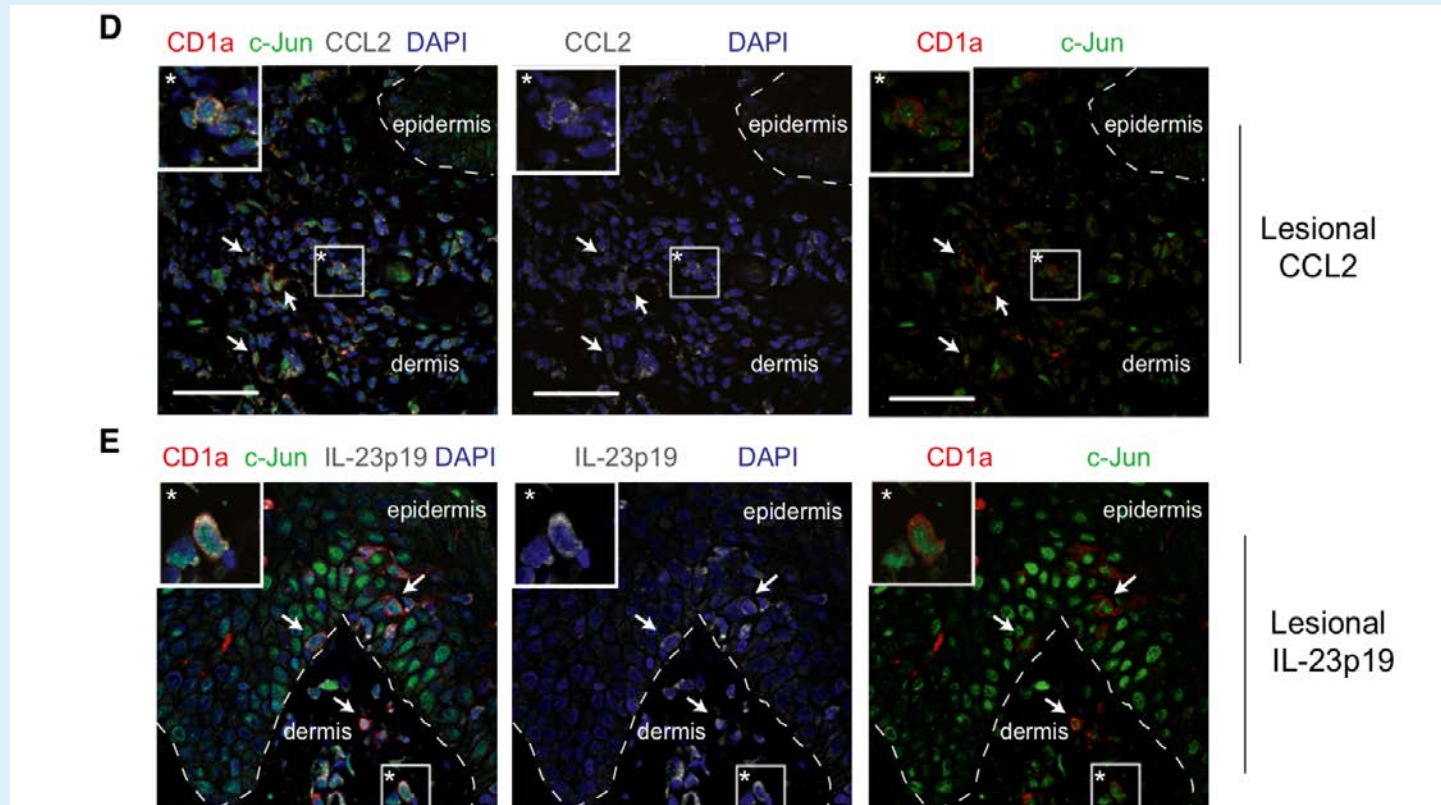


Statistic methode: t-SNE/ t-Distributed Stochastic Neighbor Embedding

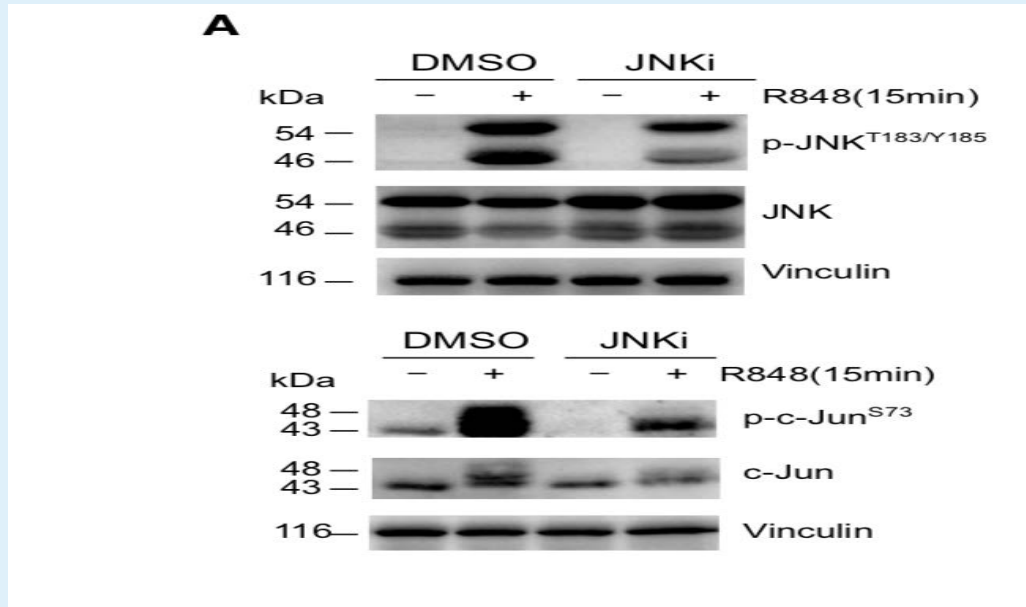
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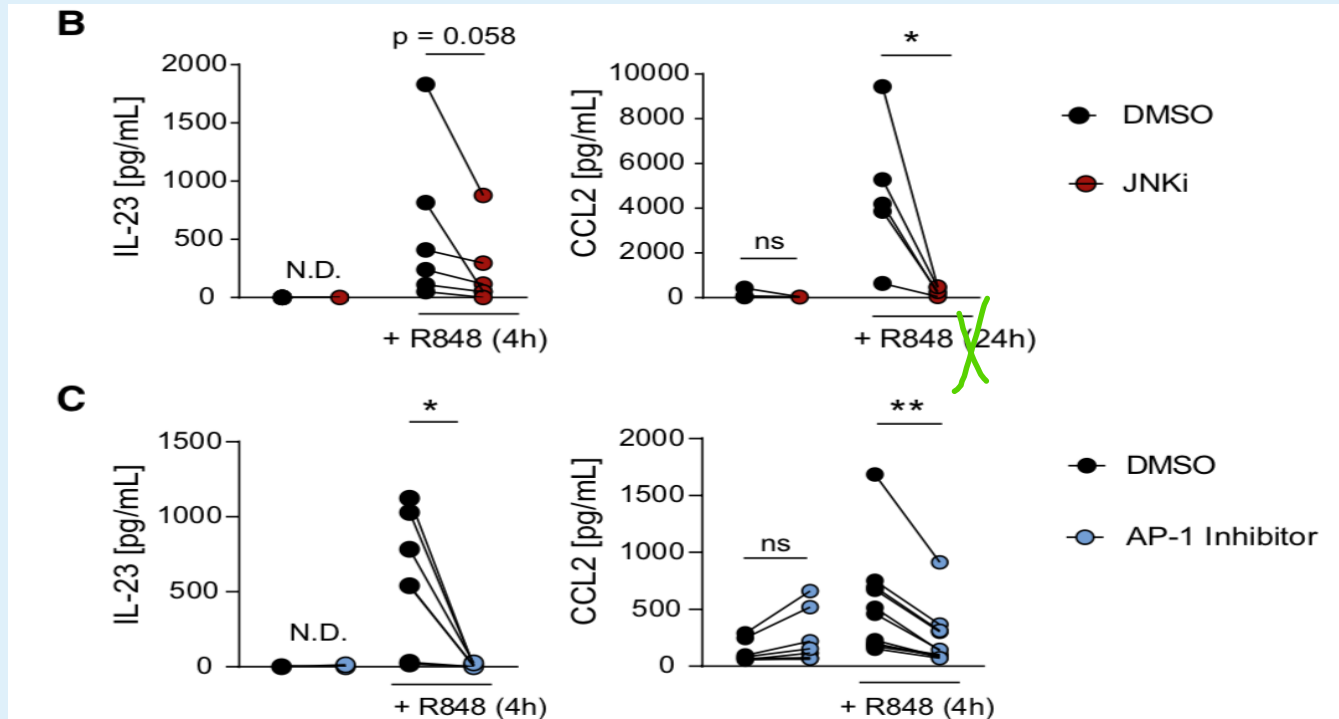


7: JNK/AP-1 Inhibitors repress CCL2 and IL-23 expression in human mo-DCs

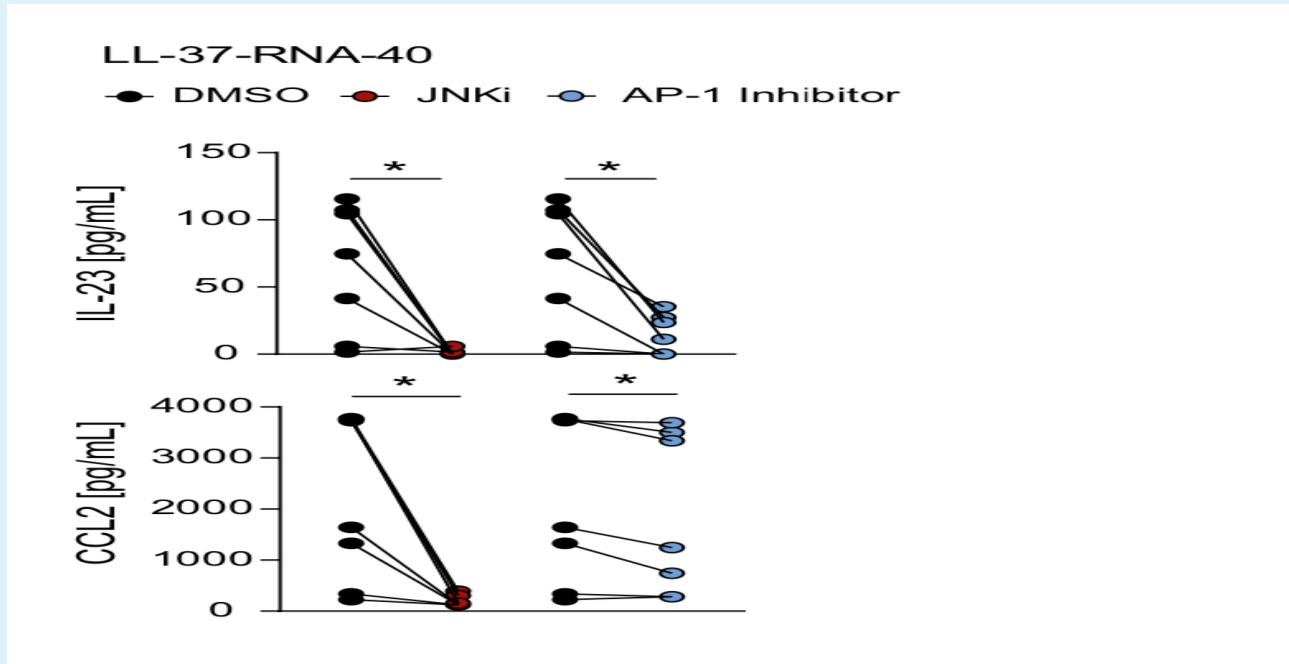


- **DMSO (Dimethylsulfoxid):** A solvent, which is often used for dissolution of drugs in animal studies
- **Resiquimod (R848):** TLR7/8 stimulating factor

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LL-37/RNA complex: Psoriasis promoting complex (disease-relevant agonist)

Discussion

Major discoveries in the study:

- C-Jun as a critical positive regulator of CCL2 and IL-23 expression in DCs
- Deletion of C-Jun in DCs attenuates psoriasis-like skin inflammation induced by the TLR7 agonist IMQ
- Expression of C-Jun in different DCs, suggesting a critical, disease-relevant role in this chronic, auto-immune skin disease
- C-Jun/AP-1 has a multi-faceted, cell-type specific function in the pathogenesis of psoriasis
- Disruption of JNK/C-Jun signaling by small molecules might be as a treatment option in psoriasis

TFYA!