Étude de la coopération entre les cellules dendritiques et les lymphocytes T dans les allergies aux produits chimiques – FPH42

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Chemical allergy: major public health concern

Chemical allergy

- 15-20 % of the general population suffer from allergic contact dermatitis.

Peiser *et al*. Cell Mol Life Sci, 2012

- Major cause of occupational skin disease → estimated newly reported annual incident of 0.5-1.9 ‰ in Europe.

Kaplan *et al*. Nat Rev Immunol, 2012

- **Nickel** is the most frequent contact allergen (18.1%) followed by **cobalt** (5.9%) and chromium (3%) as diagnosed by patch testing.

Uter *et al*. J. Eur. Acad. Dermatol. Venereol, 2017

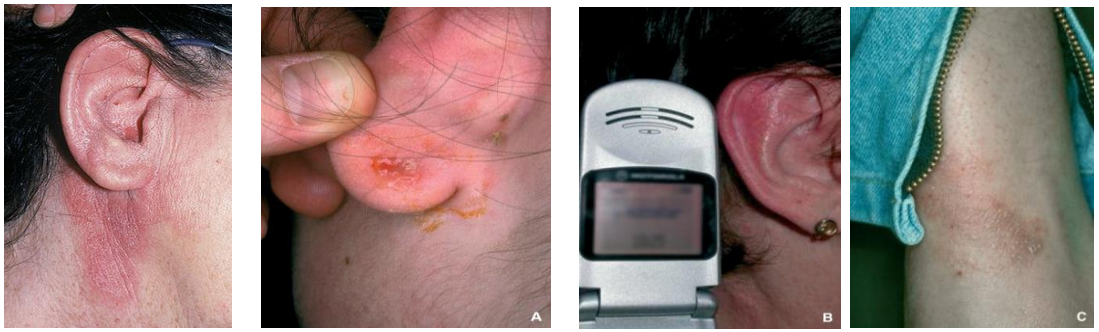
- In Europe, an estimated 65 million people may be allergic to **nickel**.

Diepgen *et al*. Contact dermatitis, 2013

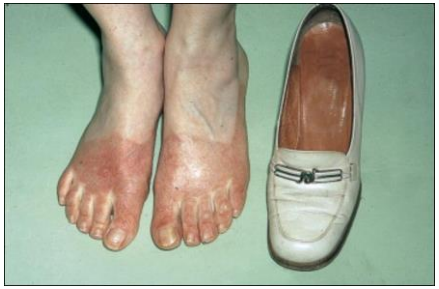
Chemical allergy: major public health concern

T-cell mediated reactions *(Gell-Coombs Type IV)*

Varying degrees of erythema, edema and vesiculation

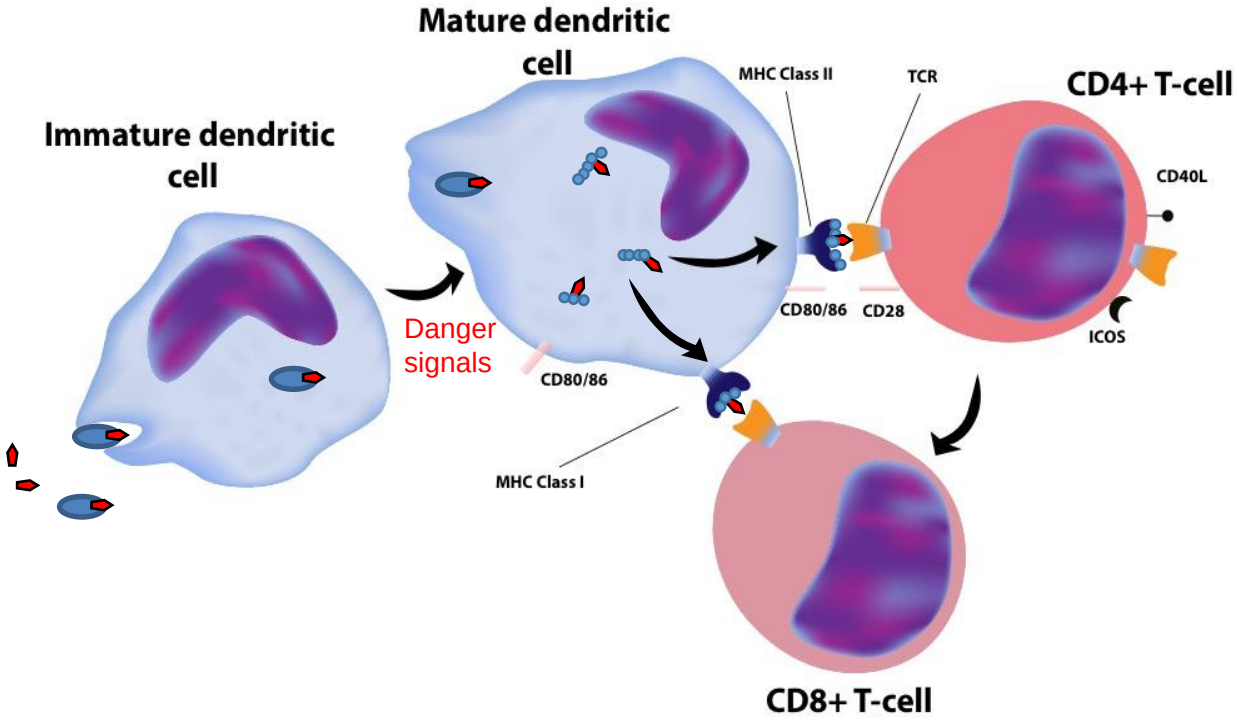


ACD caused by nickel / cobalt



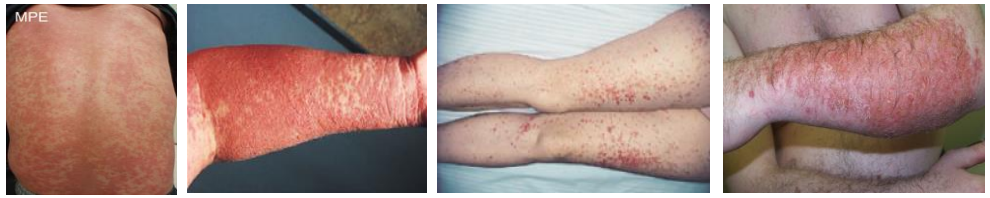
ACD caused by chromium

Drug and chemical allergy: complex mechanism



Second exposure

T-cell mediated reactions

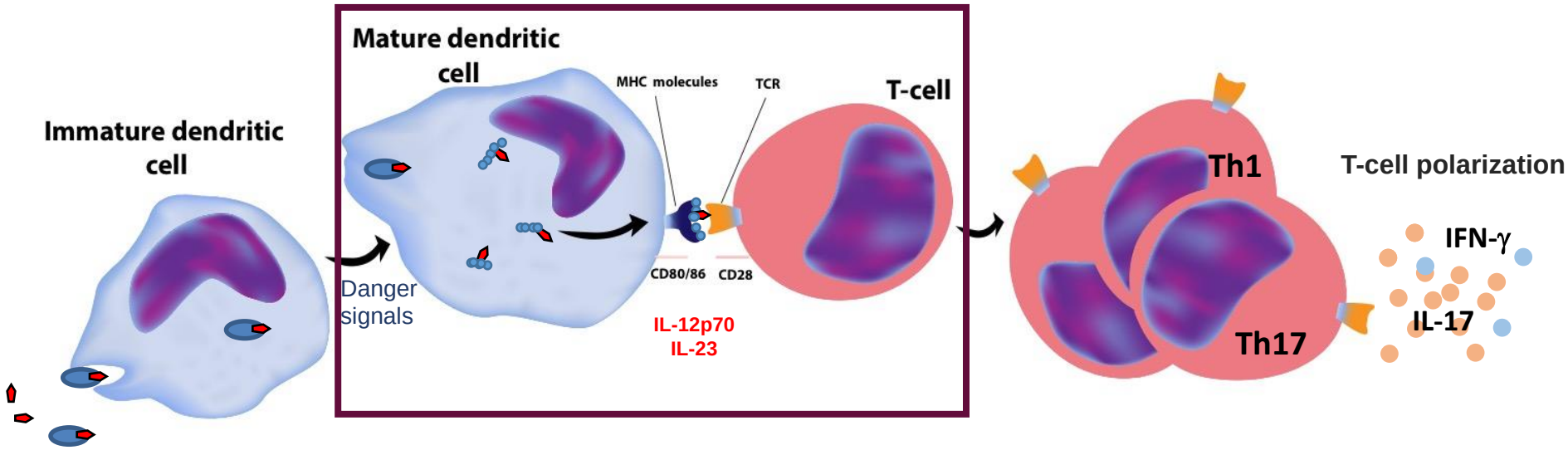


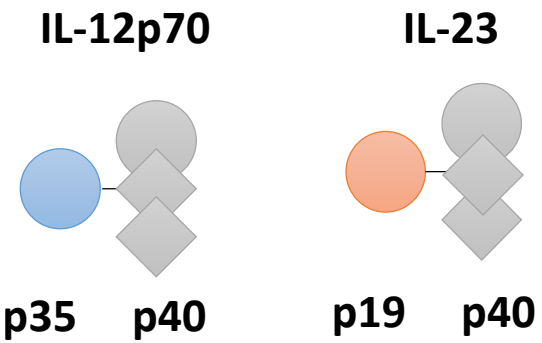
Maculopapular exanthema induced by β-lactams

Pustulosis exanthema

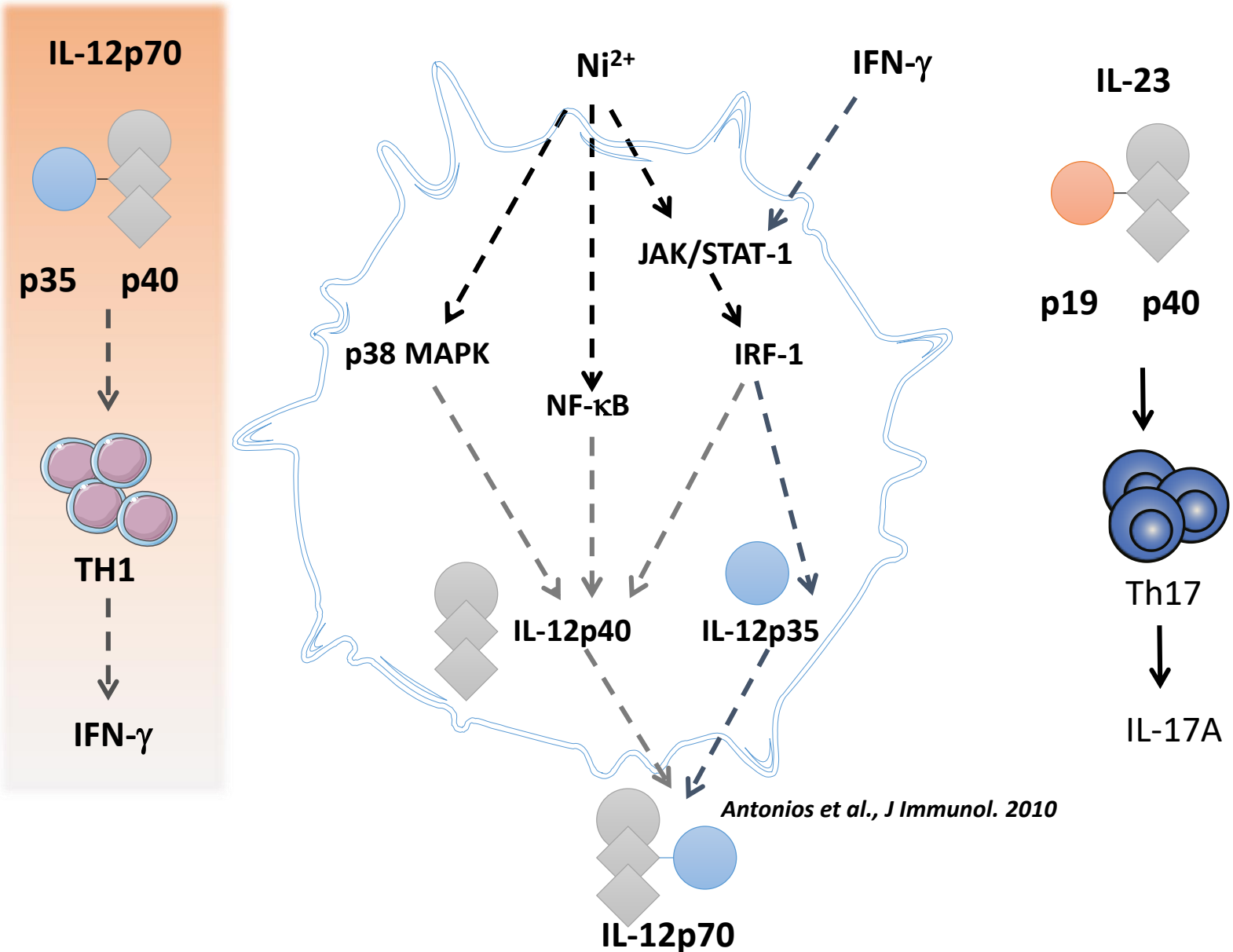
Allergic contact dermatitis

Dendritic cells and T-cells interaction





Dendritic cells and T-cells interaction

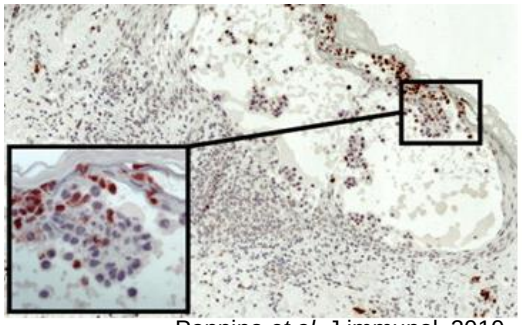


Antonios et al., J Immunol. 2010

Background

- **Nickel-specific Th1 and Th17 cells were found in the blood and skin of nickel allergic patients.**

Peiser, Clin Dev Immunol, 2013
Dyring-Andersen B *et al*. Contact dermatitis, 2013
Pennino *et al*. J immunol, 2010
Larsen *et al*. J Allergy Clin Immunol, 2009



Pennino *et al*. J immunol, 2010

Intraepidermal **CD3+ **IL-17+** cells, mostly distributed at the site of epidermal spongiosis and microvesiculation*

- **IL-17 amplifies allergic contact dermatitis:**
  - *ACD clinical score correlated with the epidermal accumulation of IL-17A- producing T-cells.*

Schmidt *et al*. Contact dermatitis, 2017

  - *IL-17 deficient mice demonstrated strongly reduced ear swelling response (CHS) to contact allergens*

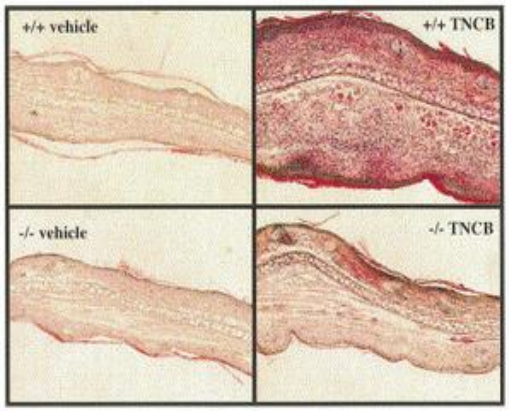
Nakae *et al*. Immunity, 2002
He *et al*. J Immunol, 2006

  - *Induction of chemokines (CXCL-8, CXCL1) and cytokines (IL-6, IL-1) release from keratinocytes*

Peiser, Clin Dev Immunol, 2013

  - *Intensification of the ICAM-1–dependent keratinocyte-T cell interaction → promoting nonspecific T cell-induced keratinocyte apoptosis.*

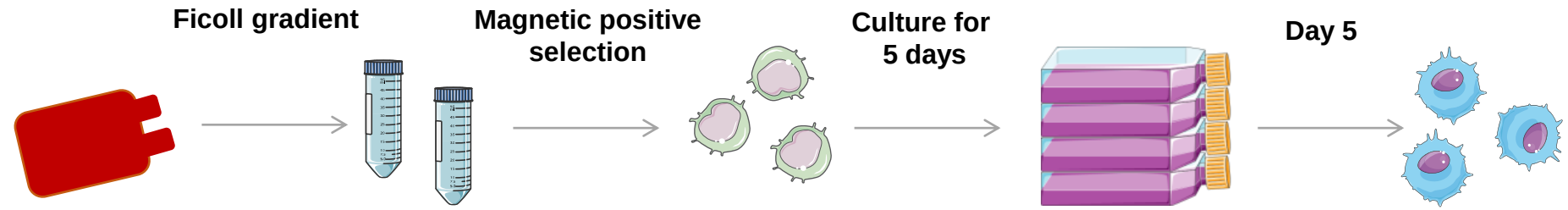
Pennino *et al*. J immunol, 2010



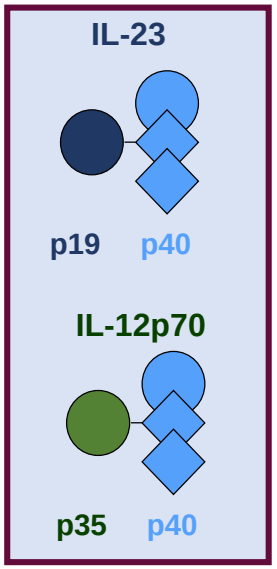
Nakae *et al*. Immunity, 2002

What are the mechanisms behind nickel-induced Th17 cells development ?

Generation of human monocyte-derived dendritic cells (MoDC)

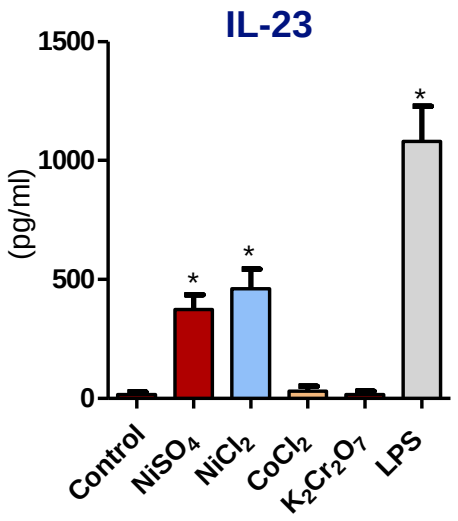


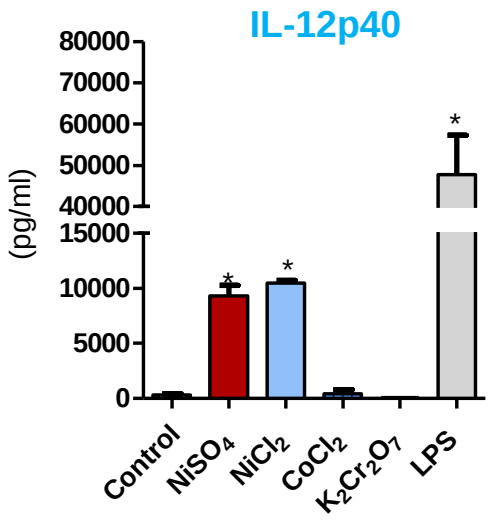
Ni^{2+} induces the production of IL-23, IL-12p40 and IL-12p70 by human MoDC

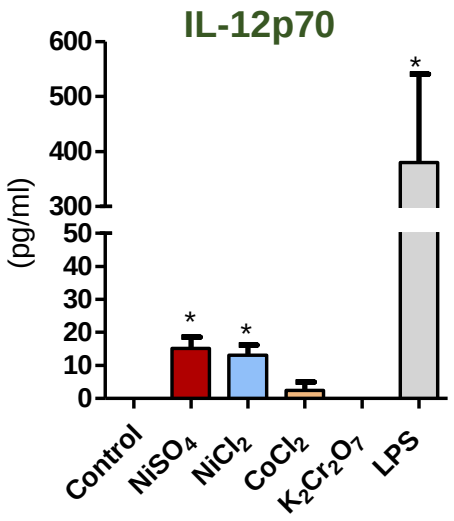


A

ELISA-24hrs ($NiSO_4$ *500 µM*; $NiCl_2$ *500 µM*; $CoCl_2$ *500 µM*; $K_2Cr_2O_7$ *5 µM*; LPS *25 ng/ml*)







*N=4; * p ≤0.05, Mann-Whitney*

Bechara R. *et al*. J Invest Dermatol. 2017

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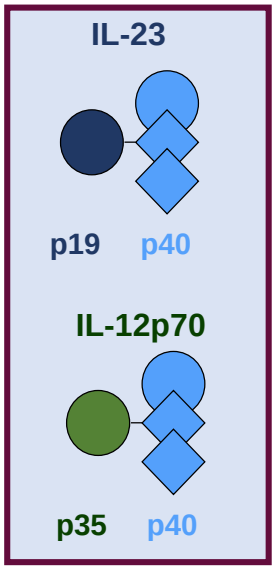

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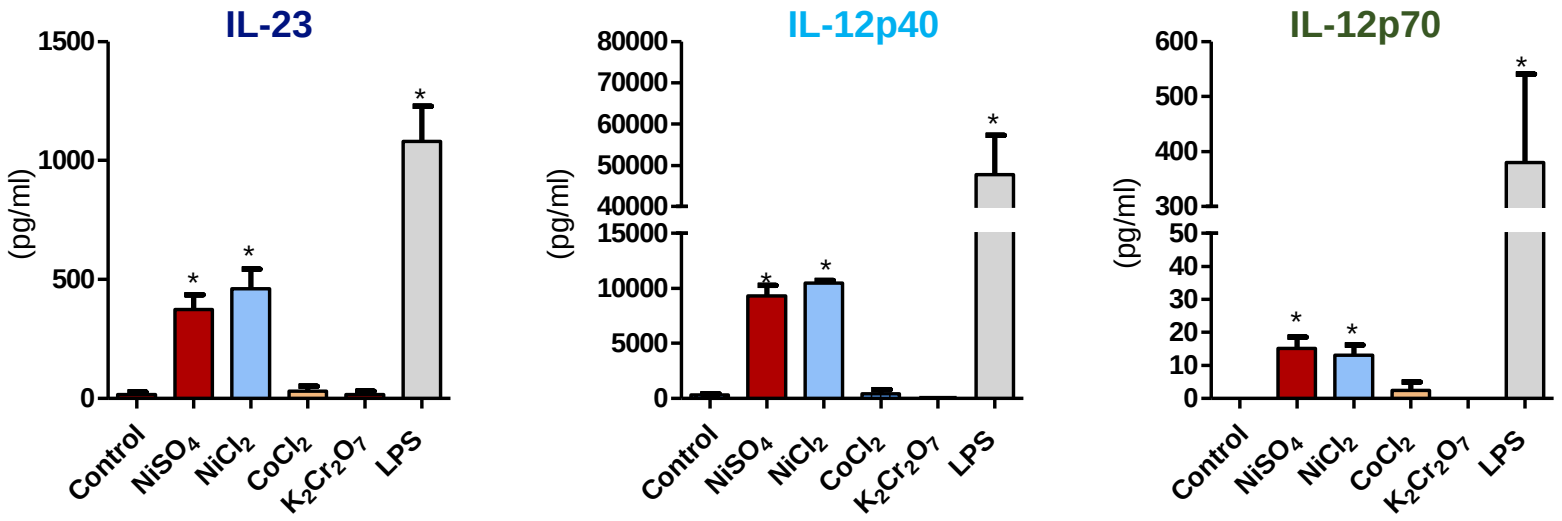
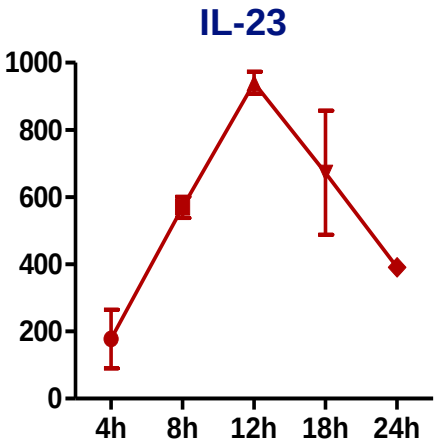


B ELISA ($NiSO_4$ *500 µM*)



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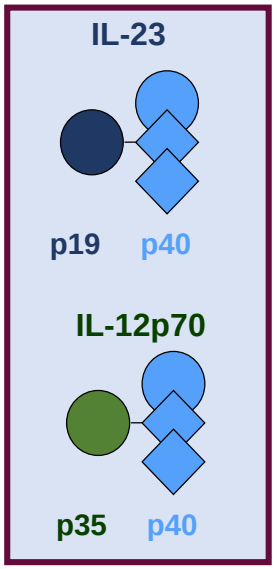

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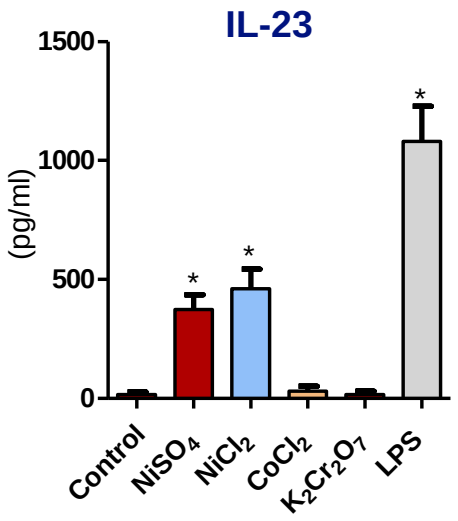
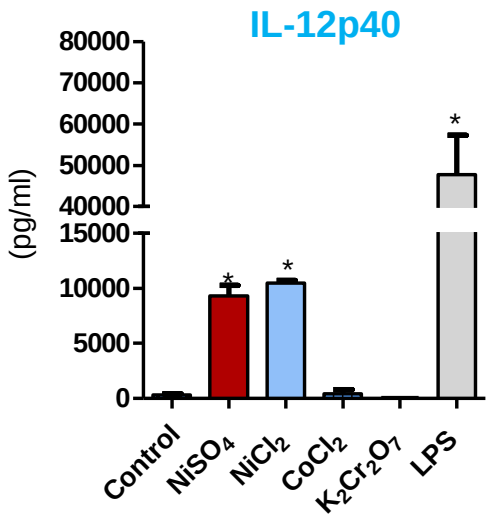
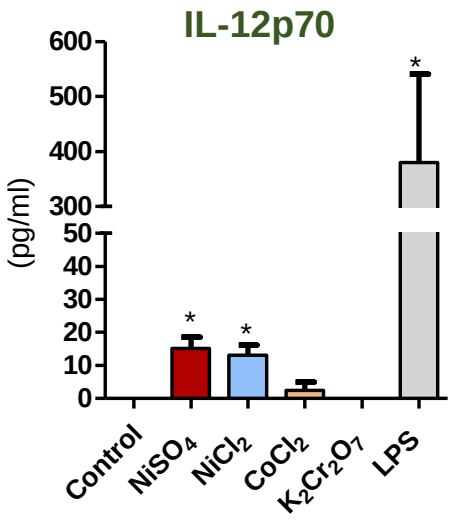
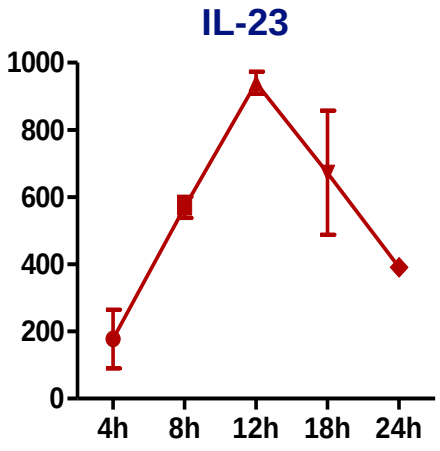






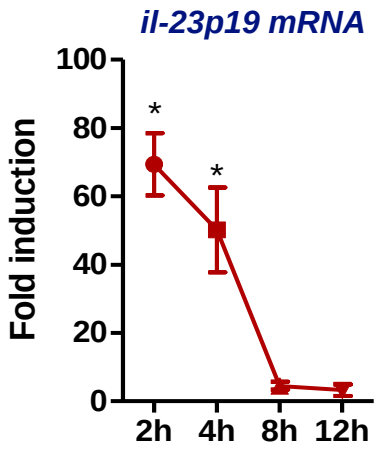
B

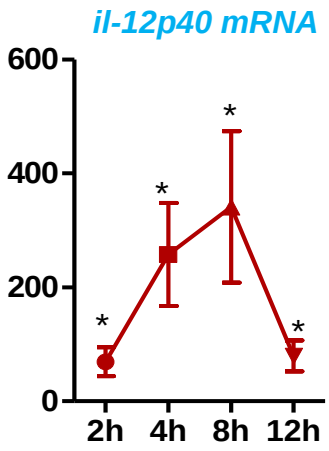
ELISA ($NiSO_4$ *500 µM*)

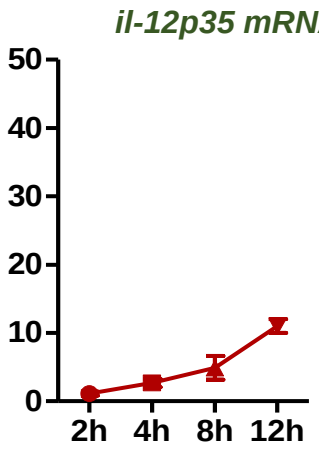


C

RT-qPCR ($NiSO_4$ *500 µM*)





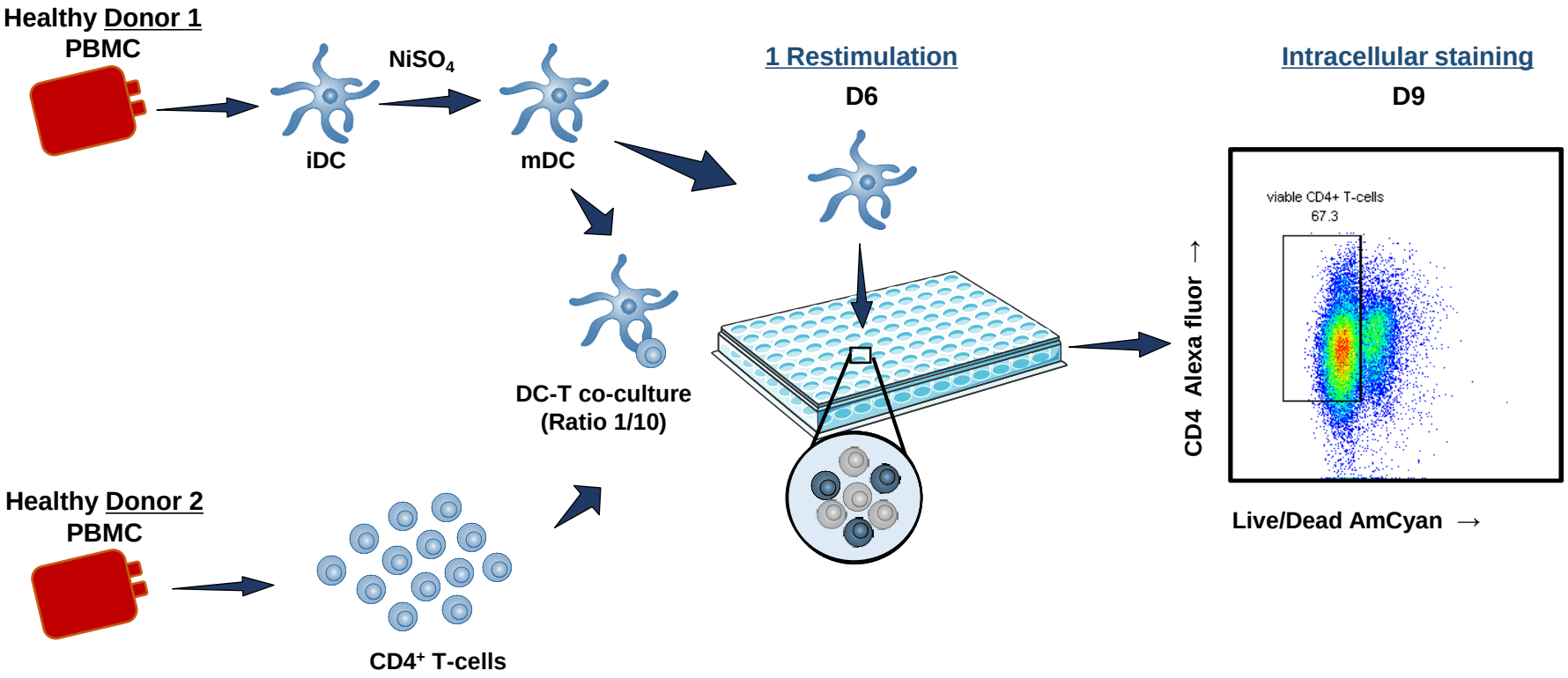


*N=4; * p ≤0.05, Mann-Whitney*

Bechara R. *et al*. J Invest Dermatol. 2017

$NiSO_4$-treated MoDCs promote IL-17A producing CD4+ T-cells via IL-23 production

Co-culture of MoDCs and allogeneic $CD4^+$ T-cells (R=1/10) → Restimulation at Day 6 → Intracellular cytokine production at Day 9 after Ionomycin/PMA activation



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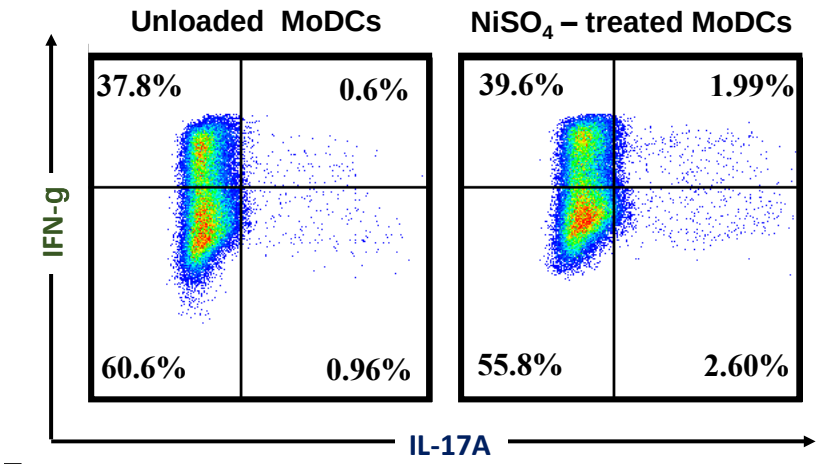

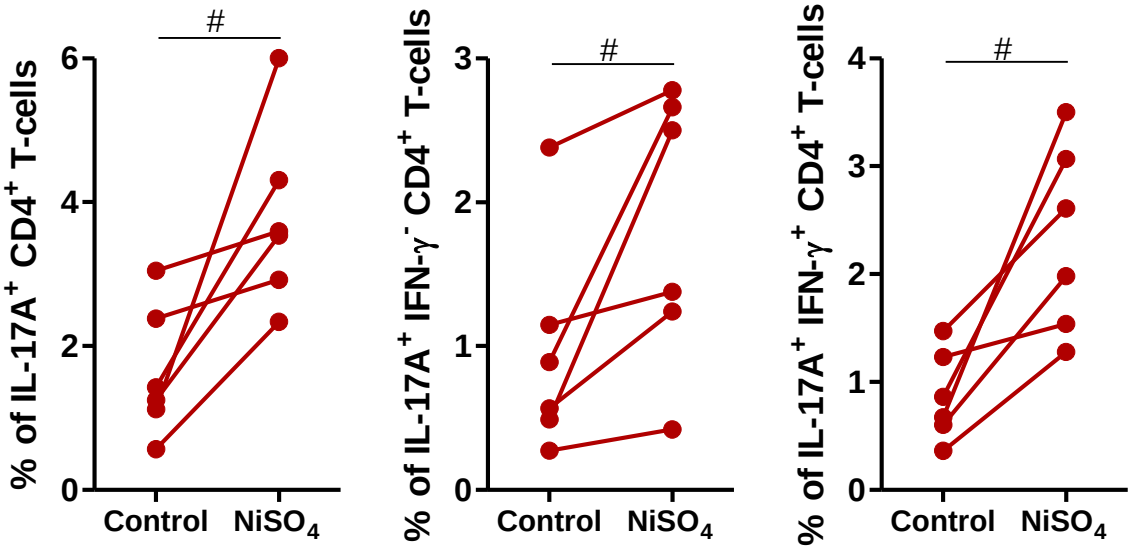

*N=6; * p ≤0.05, Wilcoxon*

Bechara R. *et al*. J Invest Dermatol. 2017

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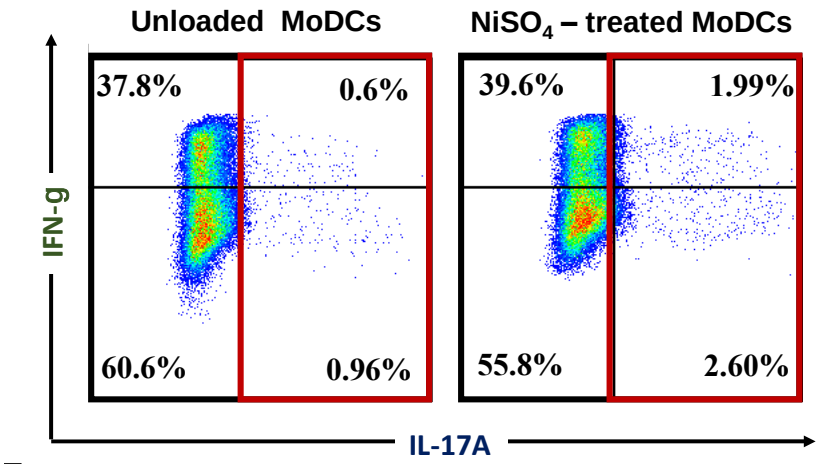

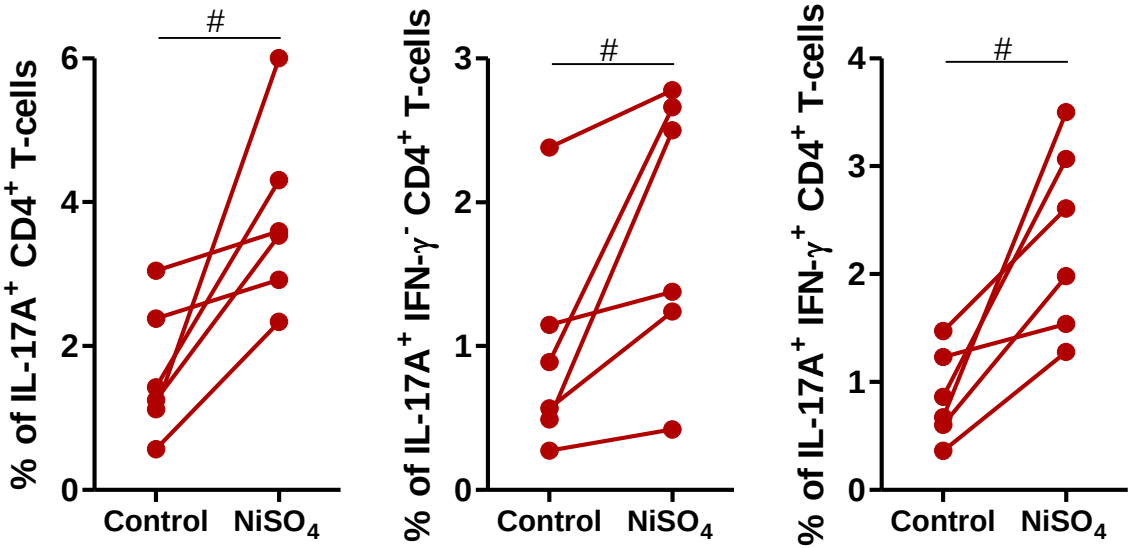

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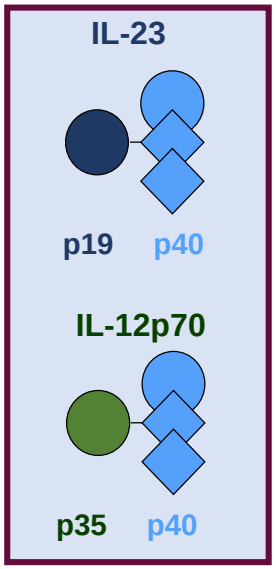
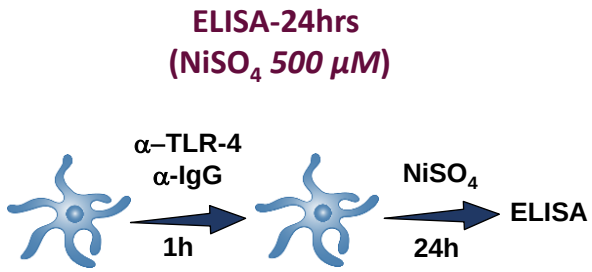
Bechara R. *et al*. J Invest Dermatol. 2017

TLR4 pathway is implicated in $NiSO_4$-induced IL-23, IL-12p40 and IL-12p70 production





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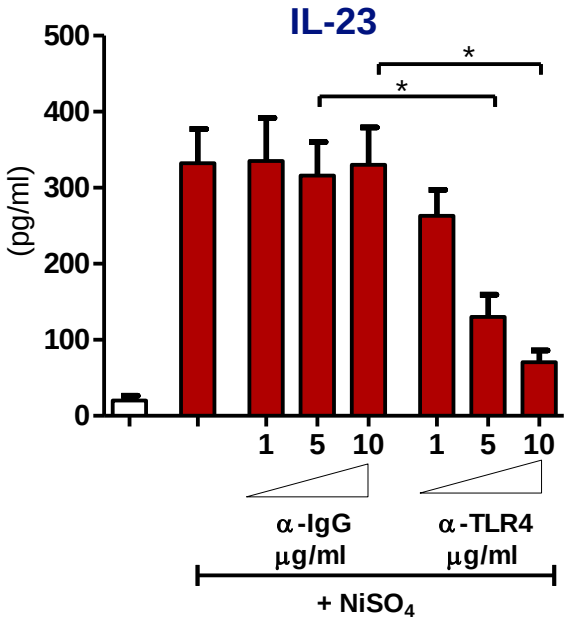
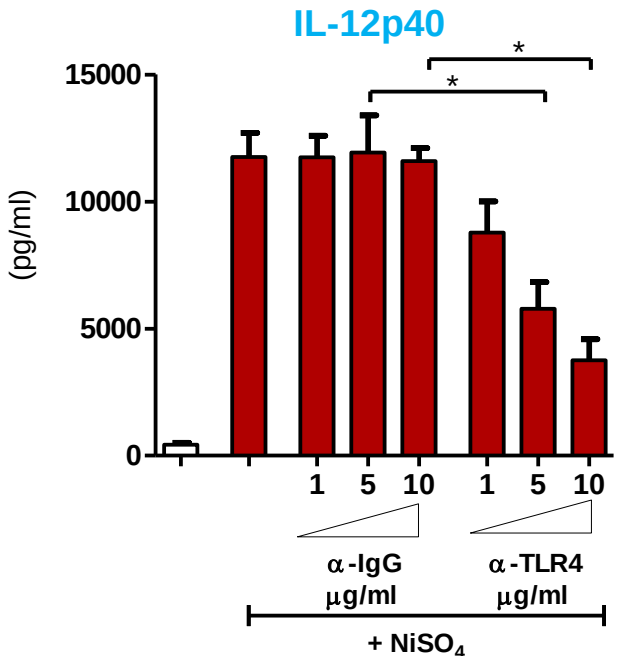
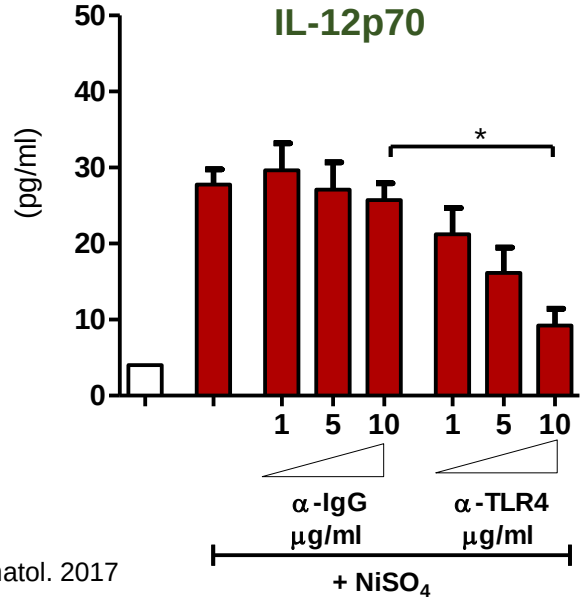
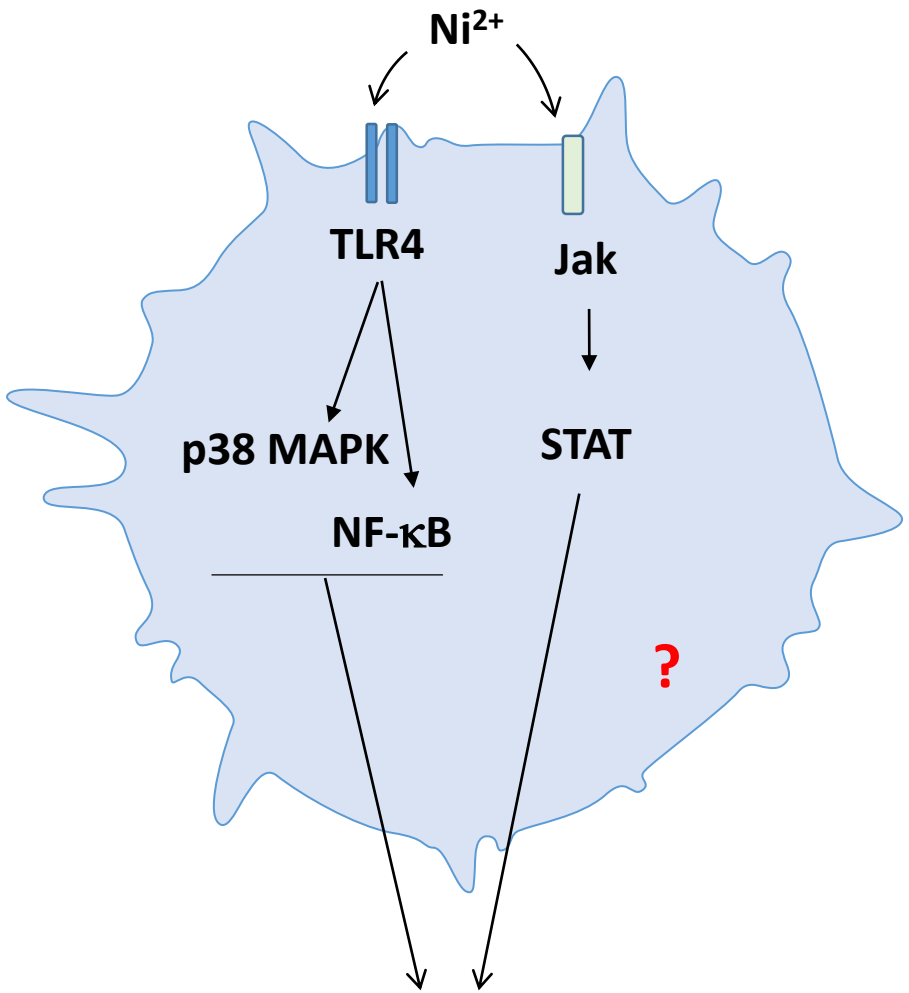






Bechara R. *et al*. J Invest Dermatol. 2017

The Jak-STAT pathway regulates the IL-23/IL-12p70 balance in $NiSO_4$-treated MoDCs

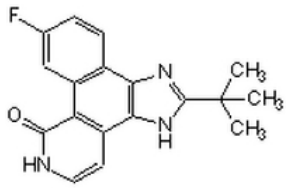


Ni^{2+} → STAT-1 → IRF-1 → IL-12p35

Antonios et al. J immunol. 2010

JAK Inhibitor I (0.5 µM)

ATP-competitive inhibitor of Janus protein tyrosine kinases (JAKs).



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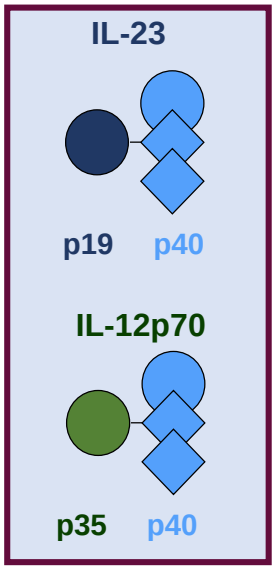
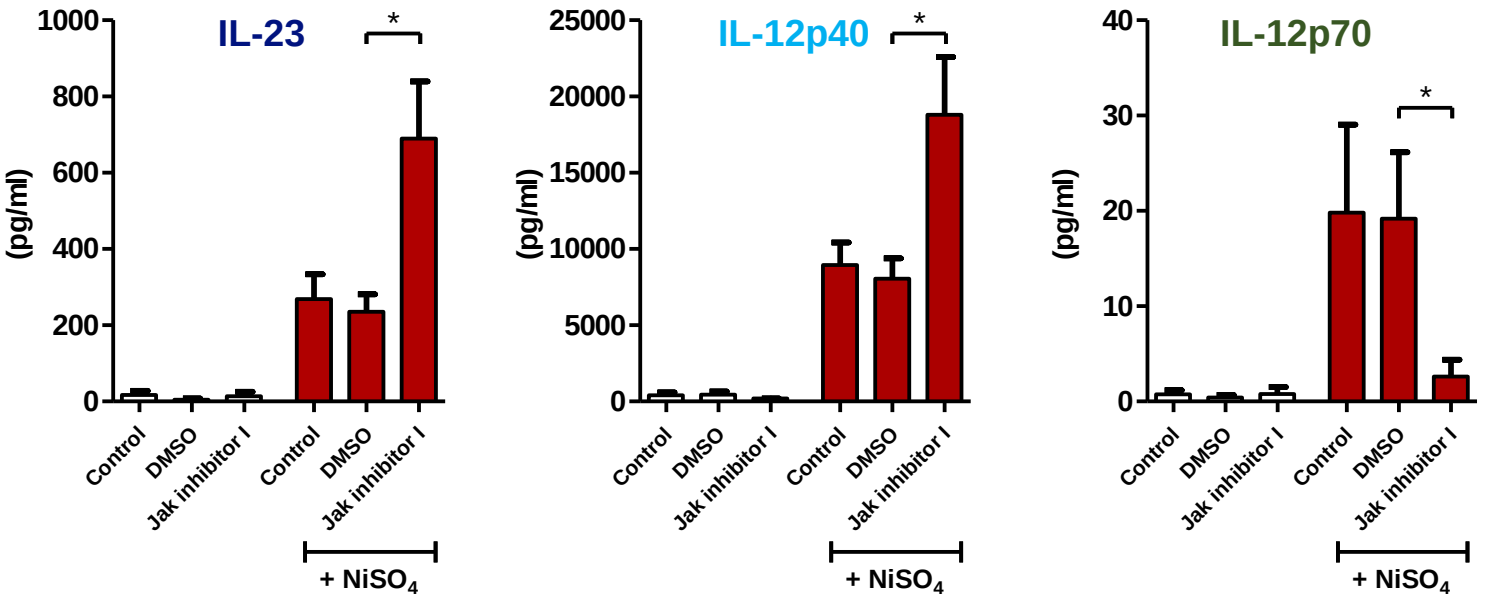
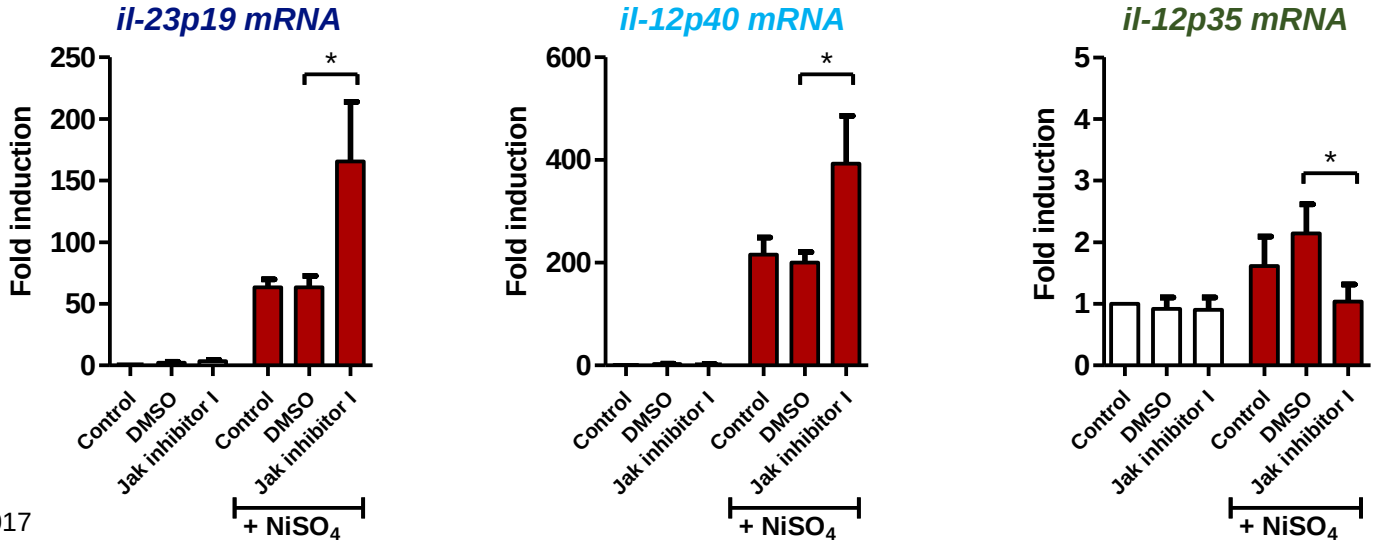


A ELISA-24hrs ($NiSO_4$ *500 µM*; Jak Inhibitor I *0.5 µM*)



B RT-qPCR-4hrs
($NiSO_4$ *500 µM;*
Jak Inhibitor I *0.5 µM)*



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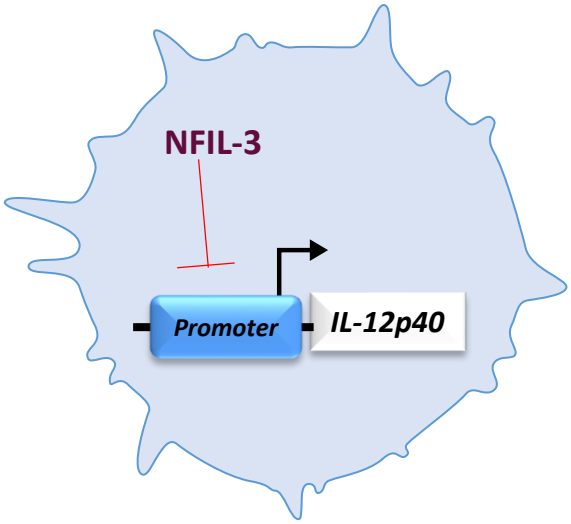
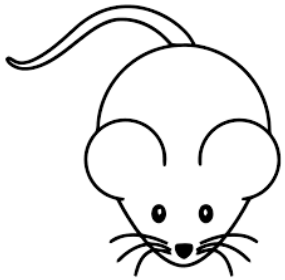
Bechara R. *et al*. J Invest Dermatol. 2017

What are the mechanisms mediating the increase in $NiSO_4$-induced IL-23 and IL-12p40 production following Jak-STAT inhibition?

- NFIL-3 (*Nuclear Factor, Interleukin 3 Regulated*) is a basic leucine zipper transcription factor.
- NFIL-3 serves as a key regulator in the development and functions of immune cells.
- NFIL-3 plays a crucial role in various immune-mediated diseases.



Kobayashi et al. J immunol. 2011
Smith et al. J Biol Chem 2011



NFIL-3 $^{-/-}$

↑ IL-23
↑ IL-12p40

Colitis

Kobayashi et al. J immunol. 2014

- NFIL-3 is a transcriptional repressor of IL-12p40 in macrophages and mucosal immunity

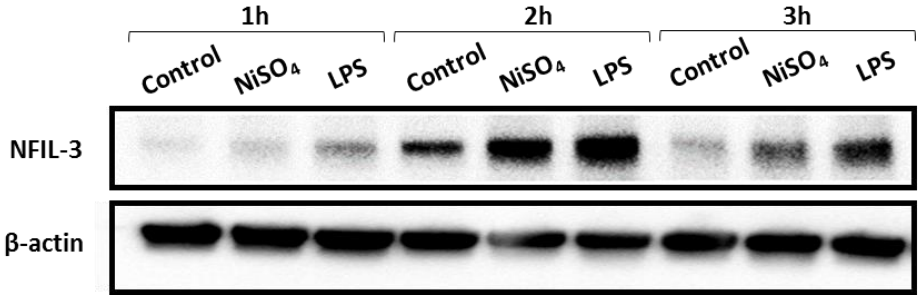
Kobayashi et al. J immunol. 2011
Smith et al. J Biol Chem 2011

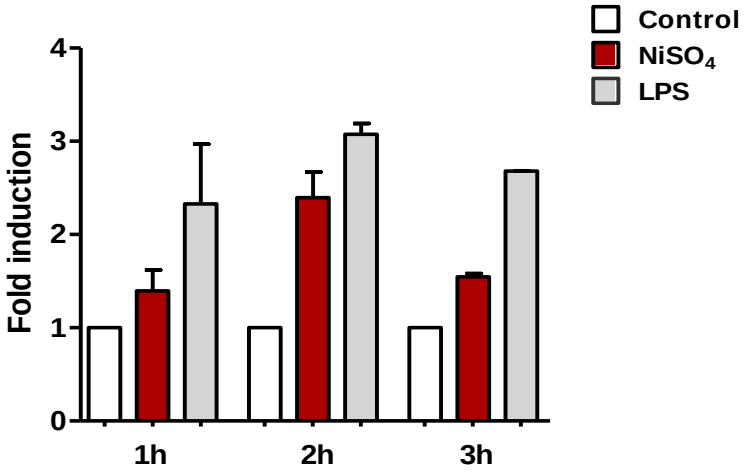
- NFIL-3-deficient macrophages expressed higher IL-12p40 and IL-23p19 compared to WT

Kobayashi et al. J immunol. 2014

What are the mechanisms mediating the increase in $NiSO_4$-induced IL-23 and IL-12p40 production following Jak-STAT inhibition?

1- $NiSO_4$ induces NFIL-3 expression in human MoDCs





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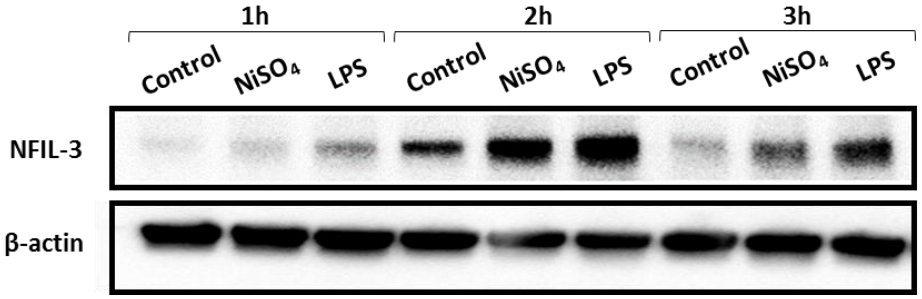
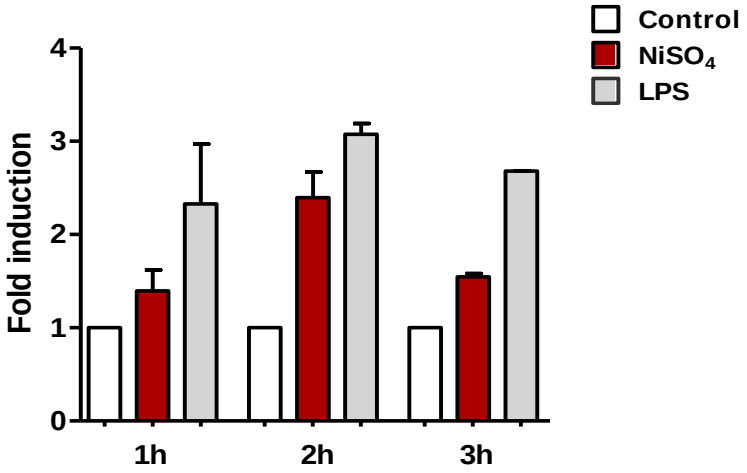
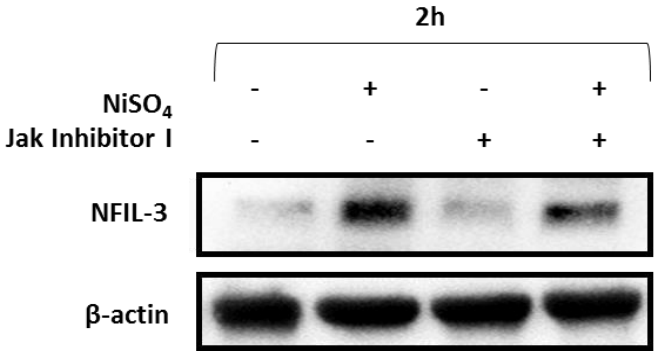
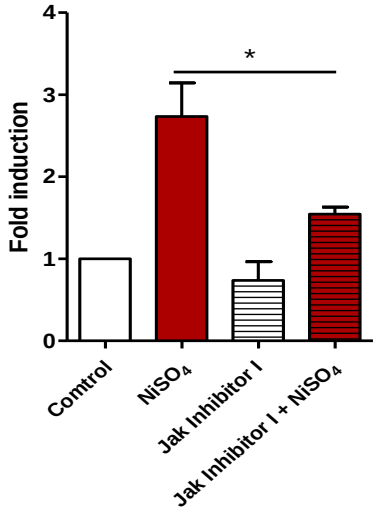
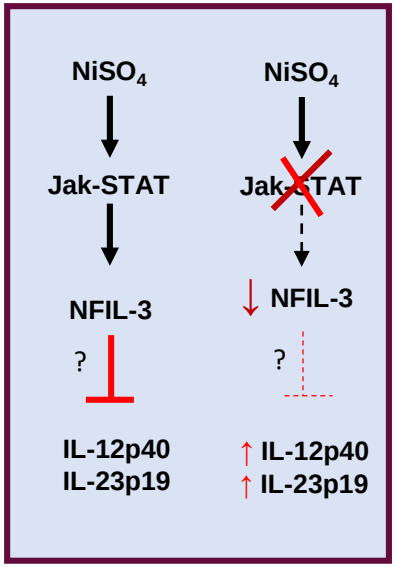




2- NFIL-3 expression is mediated by the Jak-STAT pathway







*N=4; * p ≤0.05, Mann-Whitney*

-Conclusions:

-$NiSO_4$ induces the production of IL-23 and the expression of *il-23p19* and *il-12p40* mRNA,

-p38MAPK, NF-κB and TLR4 were involved in IL-23 production induced by nickel.

-Nickel contributes to NFIL-3 expression in human MoDCs and JAK/STAT limit the production of IL-23 by promoting Th1 polarization

-**Publications:**

-Nickel Sulfate Promotes IL-17A Producing CD4+ T Cells by an IL-23-Dependent Mechanism Regulated by TLR4 and Jak-STAT Pathways.
Bechara R, Antonios D, Azouri H, Pallardy M.
J Invest Dermatol. 2017 Oct;137(10):2140-2148. doi: 10.1016/j.jid.2017.05.025. Epub 2017 Jun 17. IF =6.28

-2 publications *in preparation.*

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