# ESSURE

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# PHYSIOPATHOLOGIE : TOXICITÉ CUTANÉE

## NICKEL :

## allergène de contact le plus fréquent en Europe et pays industrialisés

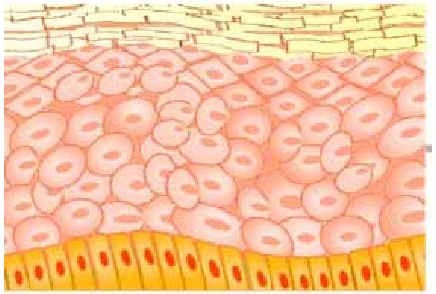
*(Ahlström et al. Contact Dermatitis, 2019)*

- **Allergie au métal**
- **Allergie aux sels de nickel soluble**
- **Allergie concomitante aux métaux : nickel, chrome, cobalt, palladium**
  - ➢ **Dermatite allergique de contact**
  - ➢ **Urticaire de contact**
  - ➢ **Dermatite de contact systémique**

*INRS, 2010, Yoshihisa & Shimizu, 2012)*

# CONSÉQUENCE DE L'EXPOSITION DE LA PEAU AUX ALLERGÈNES DE CONTACT

**Molécules allergisantes**
**=**
**haptènes**

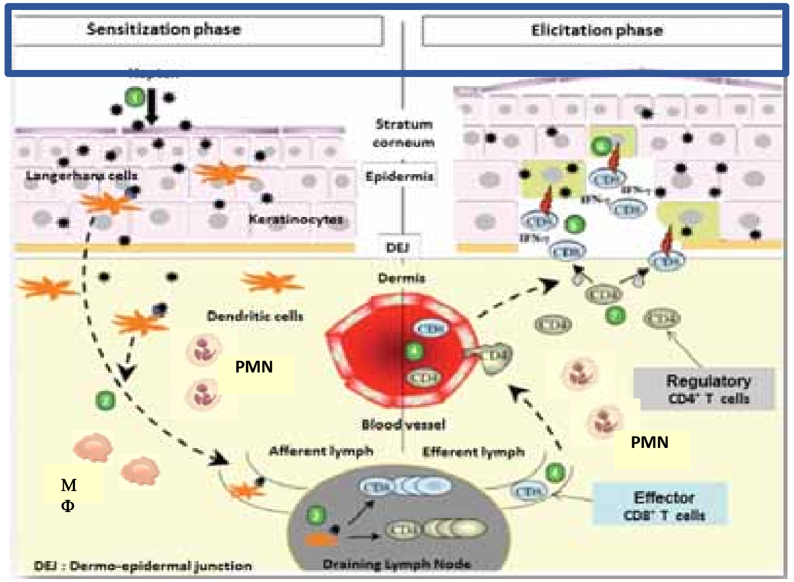



*Henna tattoo*

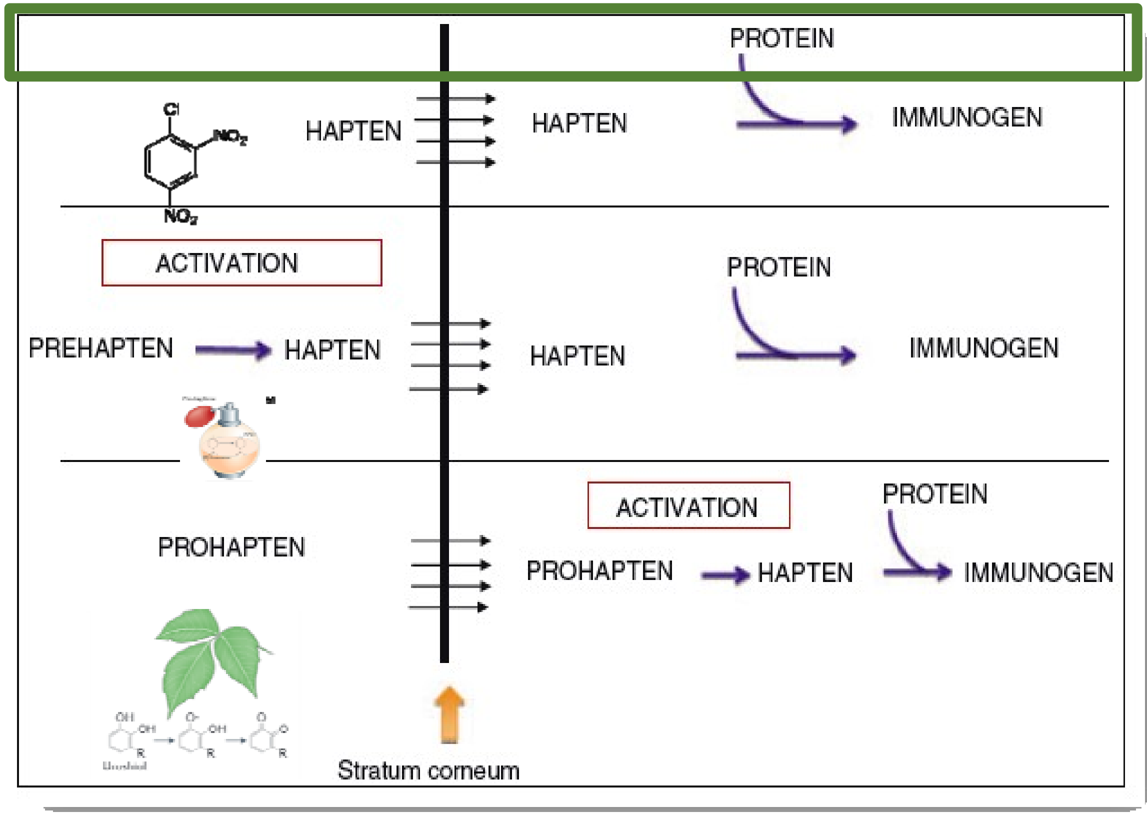
*Evans et al., New Eng. J. Med. 2008*

**Allergie cutanée**
**Dermatite allergique de contact (DAC)**

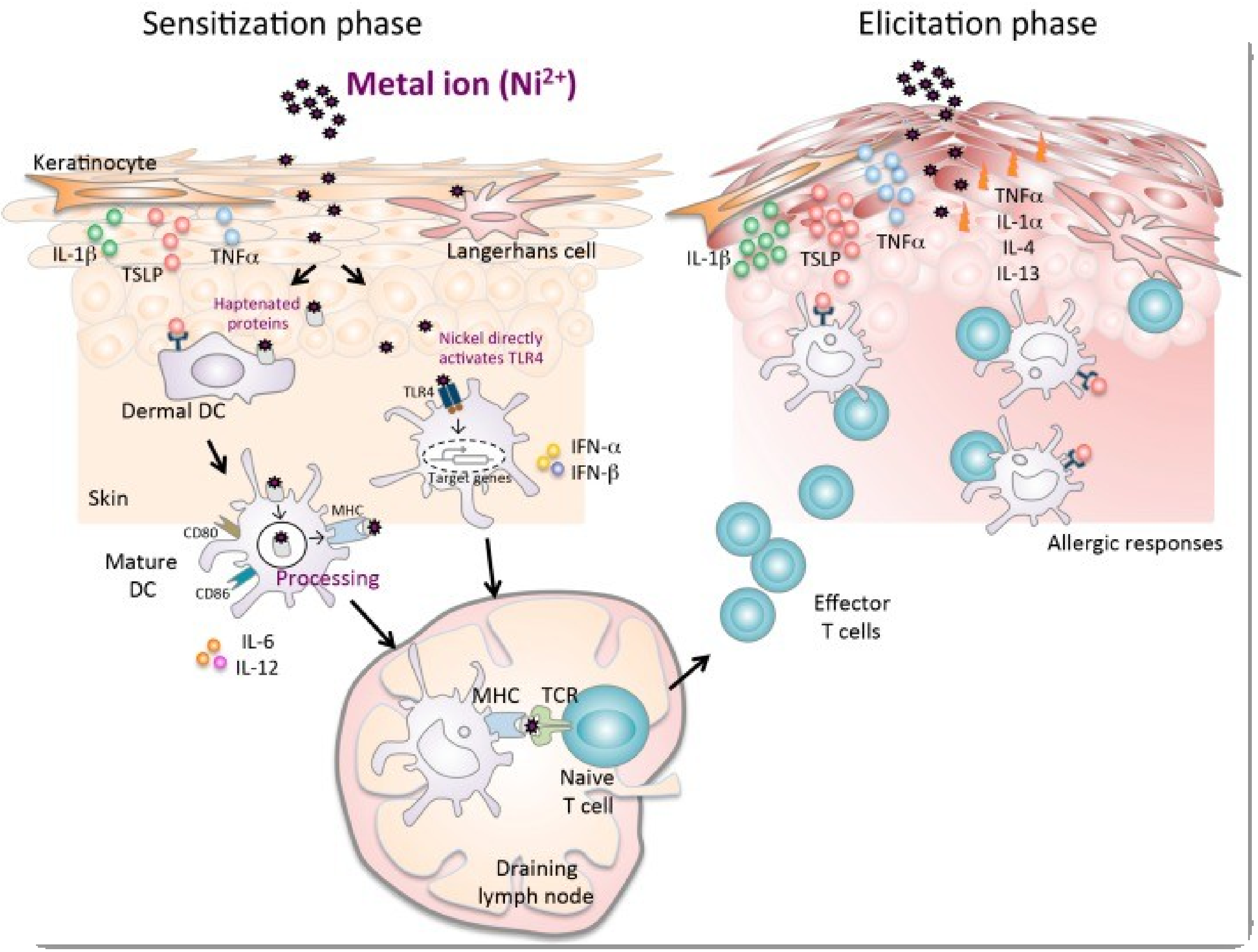
# DAC ET HAPTÈNES




La réactivité chimique joue un rôle important.

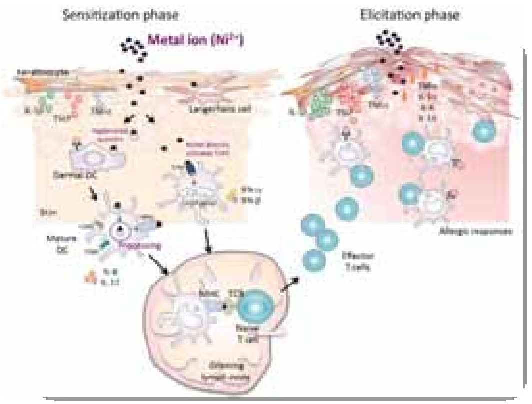


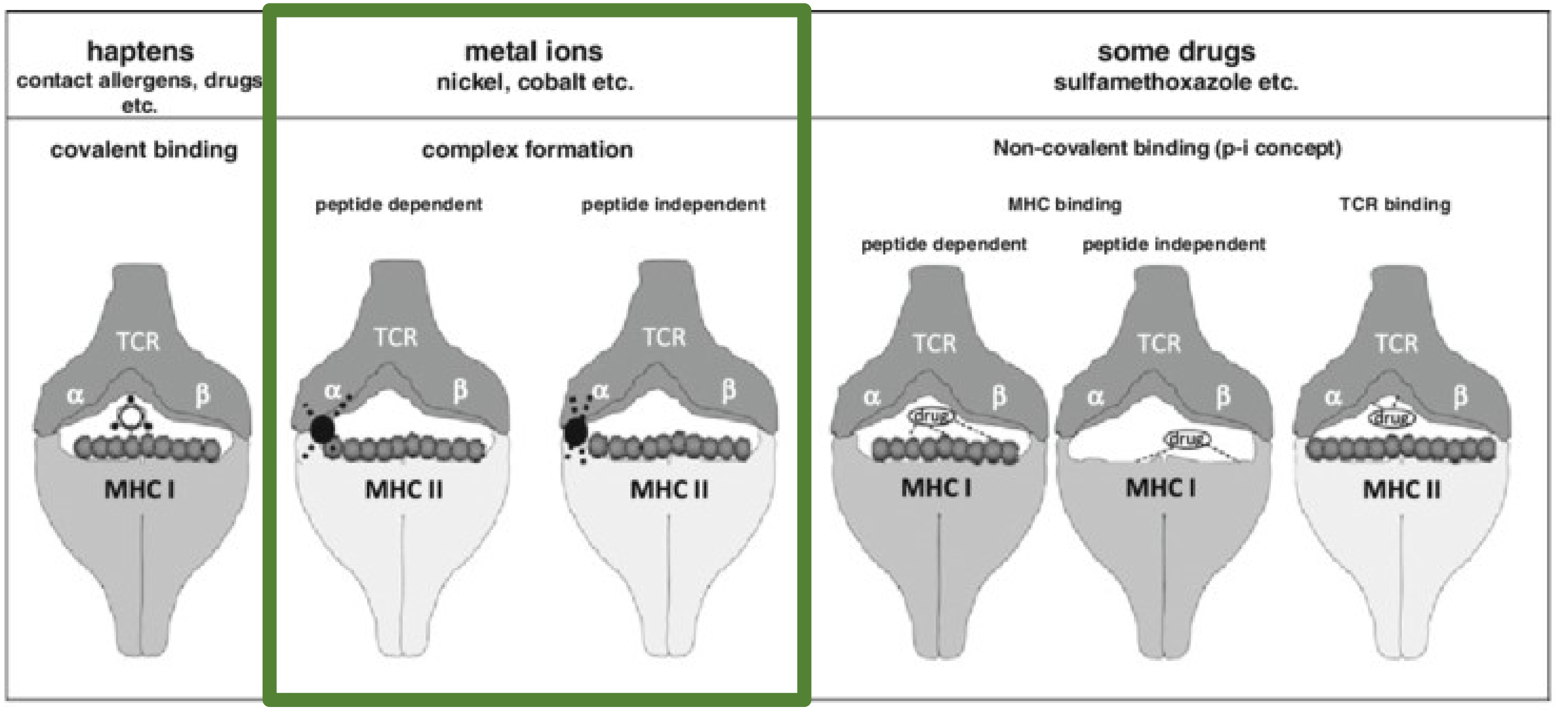
# Nickel et DAC




Saito et al., International J. of Molecular Sciences, 2016

# NICKEL ET DAC

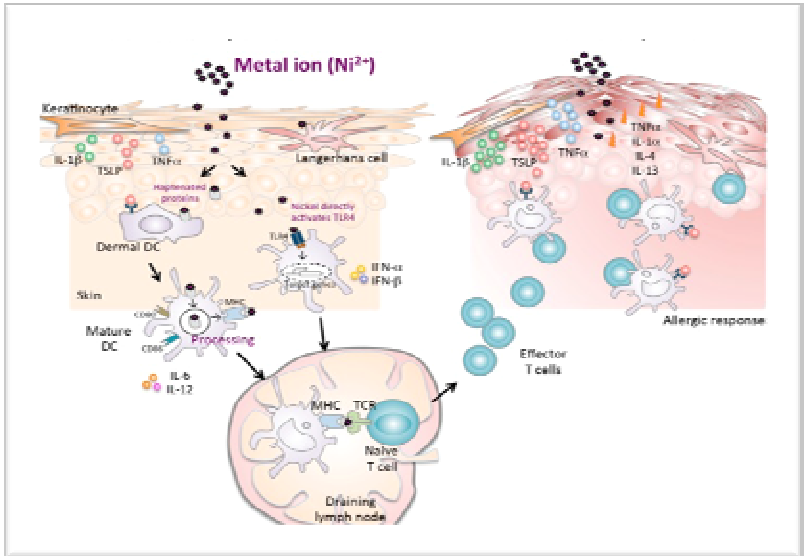


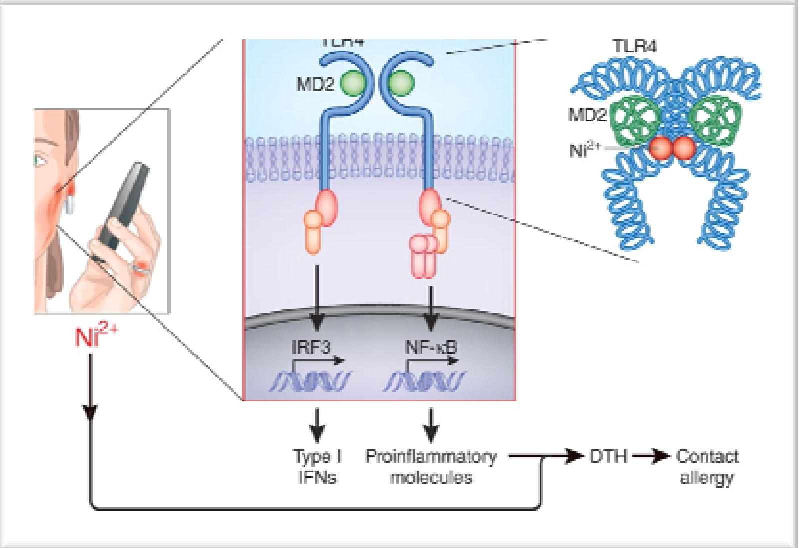

Saito et al., *International J. of Molecular Sciences*, 2016

# NICKEL ET DAC

Saito *et al.*, *International J. of Molecular Sciences*, 2016




Rothenberg, Nature Immunology, 2010




- Dermatite allergie de contact

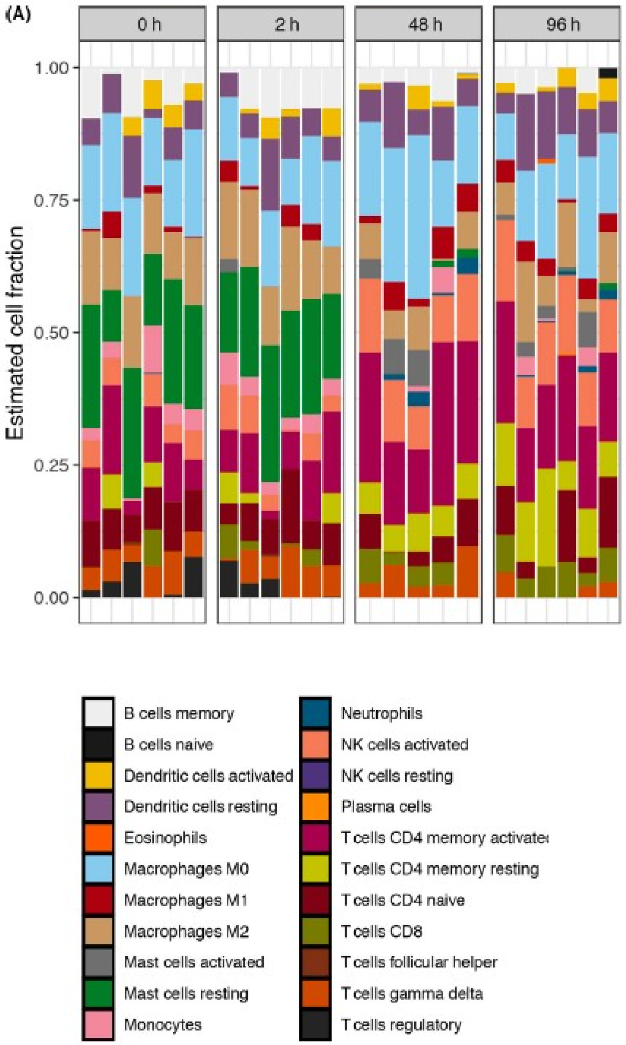
- Allergie systémique de contact

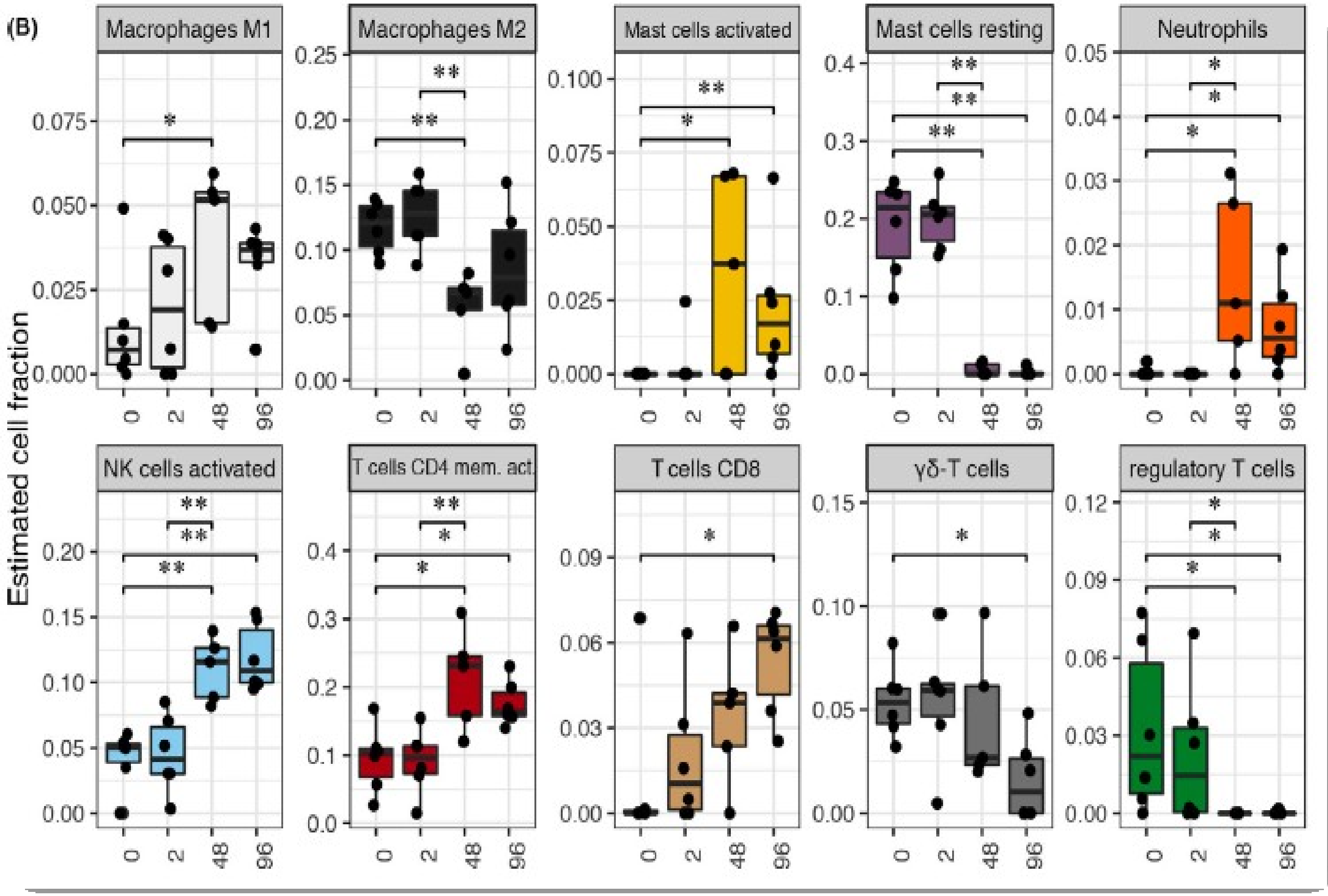
Aquino & Rosner, Clinical Reviews in Allergy & Immunology, 2018
Yoshibisa and Shimizu , Dermatology Research and Practice, 2012

La dermatite allergique de contact systémique :

affection cutanée dans laquelle un individu qui est sensibilisé par **voie cutanée** à un allergène réagira ultérieurement à ce même allergène ou à un allergène à réaction croisée par une **voie différente**

# Composition cellulaire de tissus cutanés de sujets allergiques



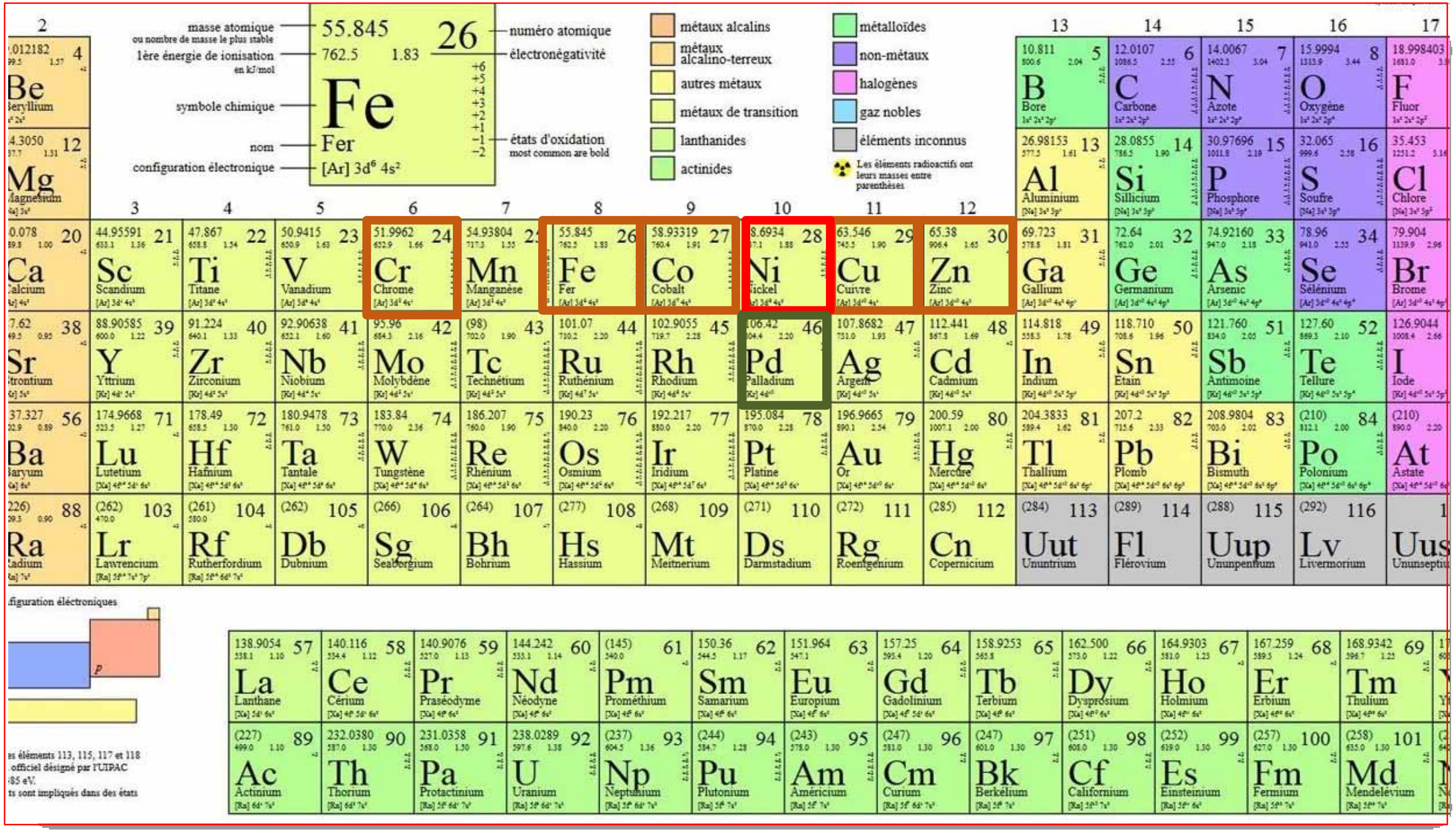




Nickel-induced contact allergy perturbates skin leukocyte composition. Estimated cell fractions from transcriptome-wide gene expression signatures, partitioned according to the investigated time point (A). Significantly changed cell populations over the allergen stimulation time course (B). *P < 0.05, **P < 0.01

Wisgrill *et al.*, Allergy, 2020

# Réactions croisées ?

## Tableau Périodique



# RÉACTIONS CROISÉES

## Cross-Reactivity of Human Nickel-Reactive T-Lymphocyte Clones with Copper and Palladium

Frank H.M. Pistoor,*† Martien L. Kapsenberg,† Jan D. Bos,* Marcus M.H.M. Meinardi,* B. Mary E. von Blomberg,‡ and Rik J. Scheper‡

*Department of Dermatology and †Laboratory of Cell Biology and Histology, Academic Medical Center, University of Amsterdam; and ‡Department of Pathology, Free University Hospital, Amsterdam, The Netherlands

**Twenty Ni-reactive T-lymphocyte clones were obtained from eight different donors and analyzed for their ability to cross-react with other metals. All Ni-reactive T-lymphocyte clones were CD4$^{+}$CD8$^{-}$ and recognized Ni in association with either HLA-DR or -DQ molecules. Based on the periodic table of the elements, the metals Cr, Fe, Co, Cu, and Zn from the same horizontal row as Ni, and Pd and Pt from the same vertical row, were selected to study T-lymphocyte clone cross-reactivity. Distinct cross-reactivity patterns were found that could be divided into three major groups: Ni-reactive T-lymphocyte clones i) cross-reacting with Cu, ii) cross-reacting with Pd, or iii) without cross-reactivity. Major histocompatibility complex class II–restriction patterns of Cu- and Pd-induced proliferative responses did not differ from those for the Ni-induced responses. *In vitro* cross-reactivities with Cu and Pd may be favored by their bivalency and location next to Ni in the periodic table, and the similarity of these metals to Ni in binding to histidine residues of peptides in the pocket of major histocompatibility complex class II molecules. The present findings suggest that Cu and Pd hypersensitivities, which are occasionally observed in Ni-allergic patients, may be due to cross-reactivities at the T-cell clonal level rather than to concomitant sensitization. *Key words: allergic contact dermatitis/T cells/metals/proliferation. J Invest Dermatol 105:92–95, 1995***

Toxicology in Vitro 23 (2009) 227–234

Contents lists available at ScienceDirect

Toxicology in Vitro

journal homepage: www.elsevier.com/locate/toxinvit

## Metallic haptens induce differential phenotype of human dendritic cells through activation of mitogen-activated protein kinase and NF-κB pathways

Diane Antonios[a,b,c], Nadège Ade[a,b], Saadia Kerdine-Römer[a,b], Hind Assaf-Vandecasteele[a,b], Alexandre Larangé[a,b], Hayat Azouri[c], Marc Pallardy[a,b,*]

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MAPK
NF-κB

ABSTRACT

Dendritic cells (DCs) play a major role in the regulation of immune responses to a variety of antigens (A... and haptens which participate in the process of DC maturation. Indeed, metallic haptens are able ... induce DC maturation in vitro but the mechanism of this maturation is not well understood. We a... others have already shown that $NiSO_4$ activates p38 mitogen-activated protein kinases (p38MAPK... c-jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK) and the transcription fac... NF-κB during the early events of DCs maturation. However, the effect of other metallic haptens on D... maturation is still poorly understood. In the present study, using dendritic cells derived from CD34$^{+}$ co... blood cells, we showed that both $NiSO_4$ and $CoCl_2$ induced the expression of CD86, CD83, HLA-DR a... CD40 and the production of IL-6 in human DCs while $K_2Cr_2O_7$ induced only a slight upregulation ... CD86. Interestingly, only $NiSO_4$ was able to induce the production of IL-12p40. $NiSO_4$ and $CoCl_2$ b... not $K_2Cr_2O_7$ were able to activate the MAPK pathway and the transcription factor NF-κB. The role ... MAPKs in metals-induced DC maturation was then evaluated using well-described pharmacologic... inhibitors. Our results suggest that p38MAPK activation regulates the expression of CD86 and CD... induced by $NiSO_4$ while it only affects the expression of CD83 induced by $CoCl_2$. IL-6 production induc... by $NiSO_4$ and $CoCl_2$ strongly depended on all MAPKs. IL-12p40 synthesis after $NiSO_4$ treatment w... regulated by both p38MAPK and JNK pathways whereas ERK may play an inhibitory role. Our resul... show that both $NiSO_4$ and $CoCl_2$ activate similar signaling pathways that are playing different roles ... DC maturation depending on the hapten used.

Contact Dermatitis • Original Article

COD
Contact Dermatitis

## Transition metal sensing by Toll-like receptor-4: next to nickel, cobalt and palladium are potent human dendritic cell stimulators

**Dessy Rachmawati[1,2], Hetty J. Bontkes[1], Marleen I. Verstege[3], Joris Muris[4], B. Mary E. von Blomberg[1], Rik J. Scheper[1] and Ingrid M. W. van Hoogstraten[1]**

*[1] Department of Pathology, VU University Medical Centre, 1081 HV Amsterdam, The Netherlands, [2] Department of Biomedical Science, Jember University, 68121 Jember, Indonesia, [3] Department of Molecular Cell Biology, VU University, 1081 Amsterdam, The Netherlands, and [4] Department of Dental Materials Science, Academic Centre for Dentistry Amsterdam (ACTA), 1081 Amsterdam, The Netherlands*

doi:10.1111/cod.12042

**Summary**

**Background.** Nickel was recently identified as a potent activator of dendritic cells through ligating with human Toll-like receptor (TLR)-4.

**Objectives.** Here, we studied an extended panel of transition metals neighbouring nickel in the periodic table of elements, for their capacity to activate human monocyte-derived dendritic cells (MoDCs).

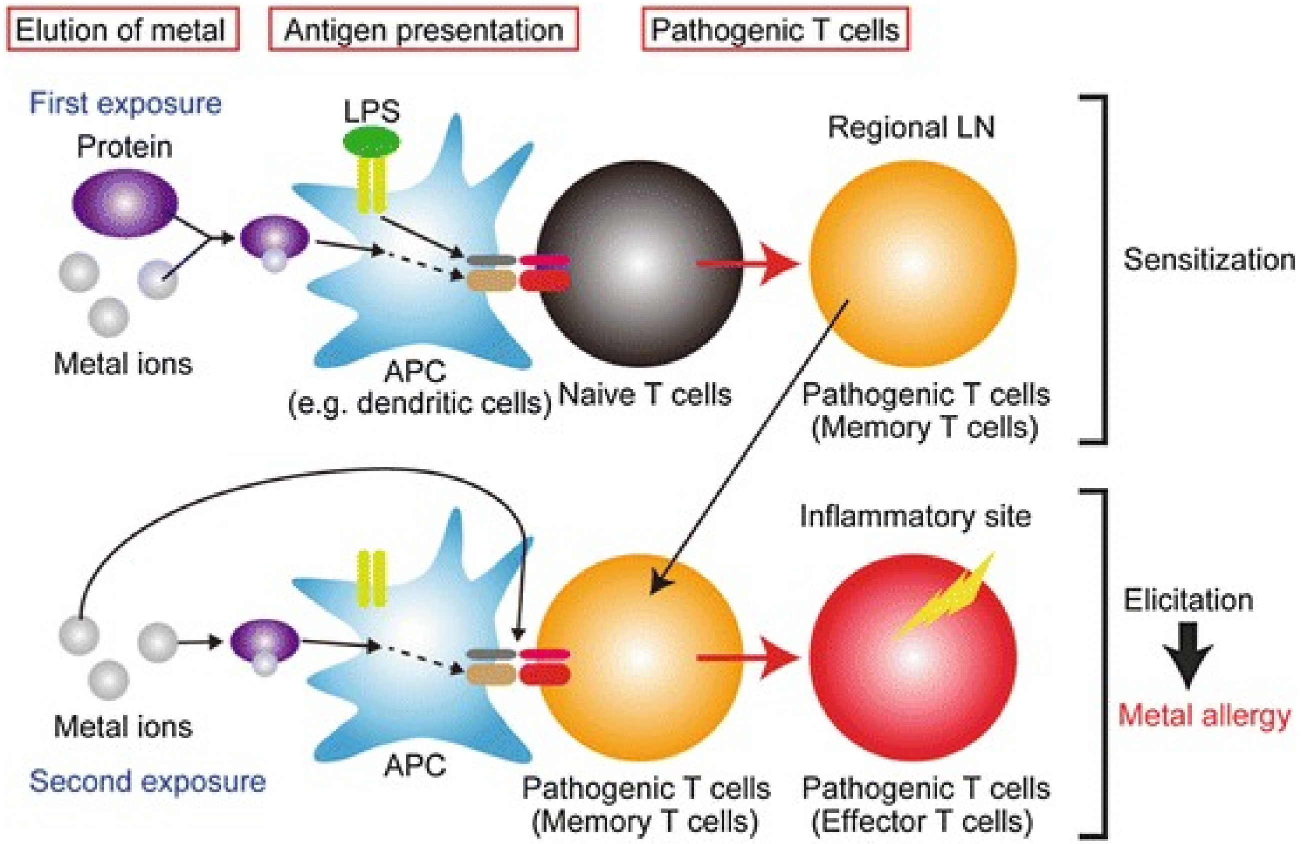
**Methods.** The panel included chromium, cobalt, and palladium, all of which are known to be frequent clinical sensitizers. MoDC activation was monitored by assessment of release of the pro-inflammatory mediator interleukin (IL)-8, a major downstream result of TLR ligation.

**Results.** The data obtained in the present study show that cobalt and palladium also have potent MoDC-activating capacities, whereas copper and zinc, but not iron and chromium, have low but distinct MoDC-activating potential. Involvement of endotoxin contamination in MoDC activation was excluded by *Limulus* assays and consistent stimulation in the presence of polymyxin B. The critical role of TLR4 in nickel-induced, cobalt-induced and palladium-induced activation was confirmed by essentially similar stimulatory patterns obtained in an HEK293 TLR4/MD2 transfectant cell line.

**Conclusions.** Given the adjuvant role of costimulatory danger signals, the development of contact allergies to the stimulatory metals may be facilitated by signals from direct TLR4 ligation, whereas other metal sensitizers, such as chromium, may rather depend on microbial or tissue-derived cofactors to induce clinical sensitization.

**Key words:** contact allergy, dendritic cells, TLR4, transition metals.

# Quel rôle des Lymphocytes T ?




Kawano et al., Advances in Metallic Biomaterials, 2015

# ASSOCIATION AU HLA ?

**Tableau 2. Association entre l'hypersensibilité aux médicaments et les allèles HLA correspondants**
RMP: rash maculo-papuleux; SJS: syndrome de Stevens-Johnson; NET: nécrolyse épidermique toxique.

| Médicaments | Allèle HLA | Manifestations cliniques | Population | OR (IC 95%) |
|---|---|---|---|---|
| **Pénicilline** | HLA-A2<br>DRw52 | RMP | Européenne | – |
| **Abacavir** | HLA-B*57 : 01 | DRESS (syndrome d'hypersensibilité à l'abacavir) | Australie<br>Australie | 117 (29-481)<br>960 |
| **Flucloxacilline** | HLA-B*57 : 01 | Atteinte hépatique | Européenne | 80 (23-285) |
| **Carbamazépine** | HLA-B*15 : 02<br>HLA-A*31 : 01 | SJS/NET<br>SJS/NET<br>SJS/NET<br>RMP<br>RMP | Chinoise Han<br>Japonaise<br>Européenne<br>Chinoise Han<br>Européenne | 1357 (193-8838)<br>33,9 (3,9-295)<br>25,93 (4,93-116,18)<br>17,5 (4,6-66,5)<br>8,33 (3,59-19,36) |
| **Allopurinol** | HLA-B*58 : 01 | SJS/NET/DRESS<br>SJS/NET | Chinoise Han<br>Européenne | 580 (34-9781)<br>80 (34-187) |

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Letters

## HLA-DR53 (DRB4*01) associates with nickel sensitization

Yan Zhang PhD [*, †], Kirsten M. Anderson PhD [*, †], Brian M. Freed PhD [‡], Shaodong Dai PhD [*, †], Karin A. Pacheco MD, MSPH [§, ‖]

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# Questions

- Allergie au nickel ?
- Allergie aux produits de relarguage ?
- Inflammation ?
- Effets systémiques ?