MasterClass
Module 0 « Immunologie de l'allergie»
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Le système immunitaire en action
Induction et régulation
de l'inflammation cutanée

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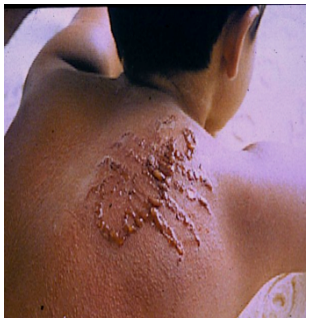
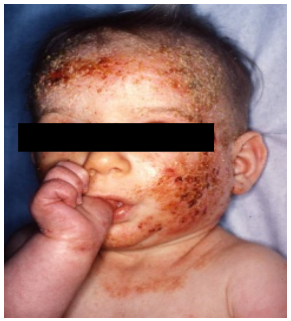
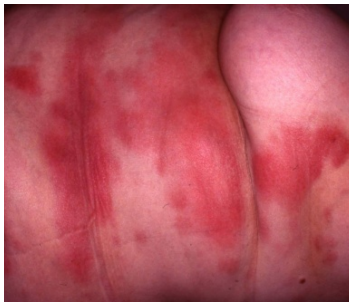
Team “Epidermal Immunity & Allergy”
Research activities

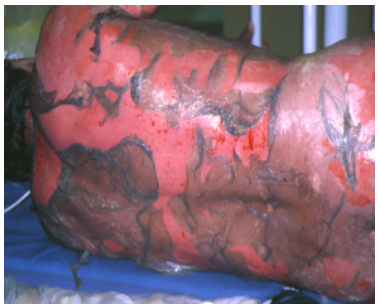




Allergic Contact Dermatitis (ACD) Atopic Dermatitis (AD)

ECZEMAS





Benign - Exanthema Severe – Bullous diseases

DRUG ALLERGY (DA)

Main Features

- High prevalence
  - 10% of children (AD)
  - 1st occupational disease (ACD)
- Benign to very severe
- Localized acute or chronic lesions
- Delayed-type allergy / Specific T cells
- Breakdown of tolerance

Allergens

- Chemicals/haptens & proteins
- Endowed with antigenic & adjuvant properties
- Skin or systemic route

Objectives

- Decipher the pathophysiology
- Develop new diagnostic/predictive assays
- Develop new therapeutic strategies to restaure skin tolerance

Key words: Immunology, skin allergy, T cells

PLAN

- Bases immunologiques de la réponse à l'interface cutanée

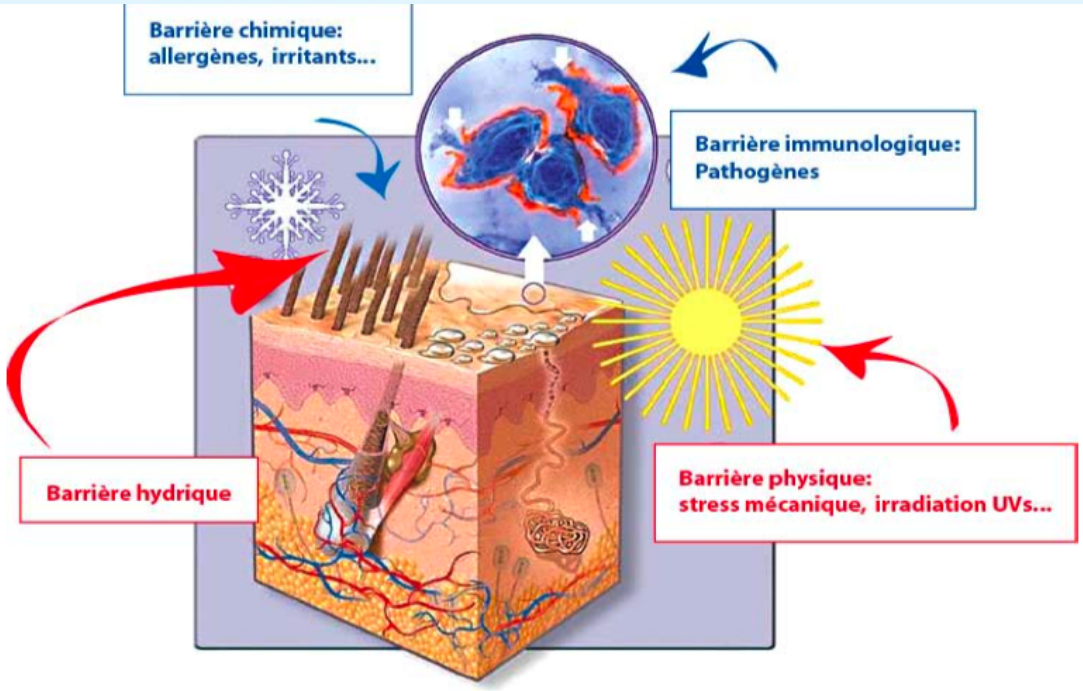
- Induction & régulation de l'inflammation cutanée : *exemple de l'eczéma de contact*

PLAN

- Bases immunologiques de la réponse à l'interface cutanée

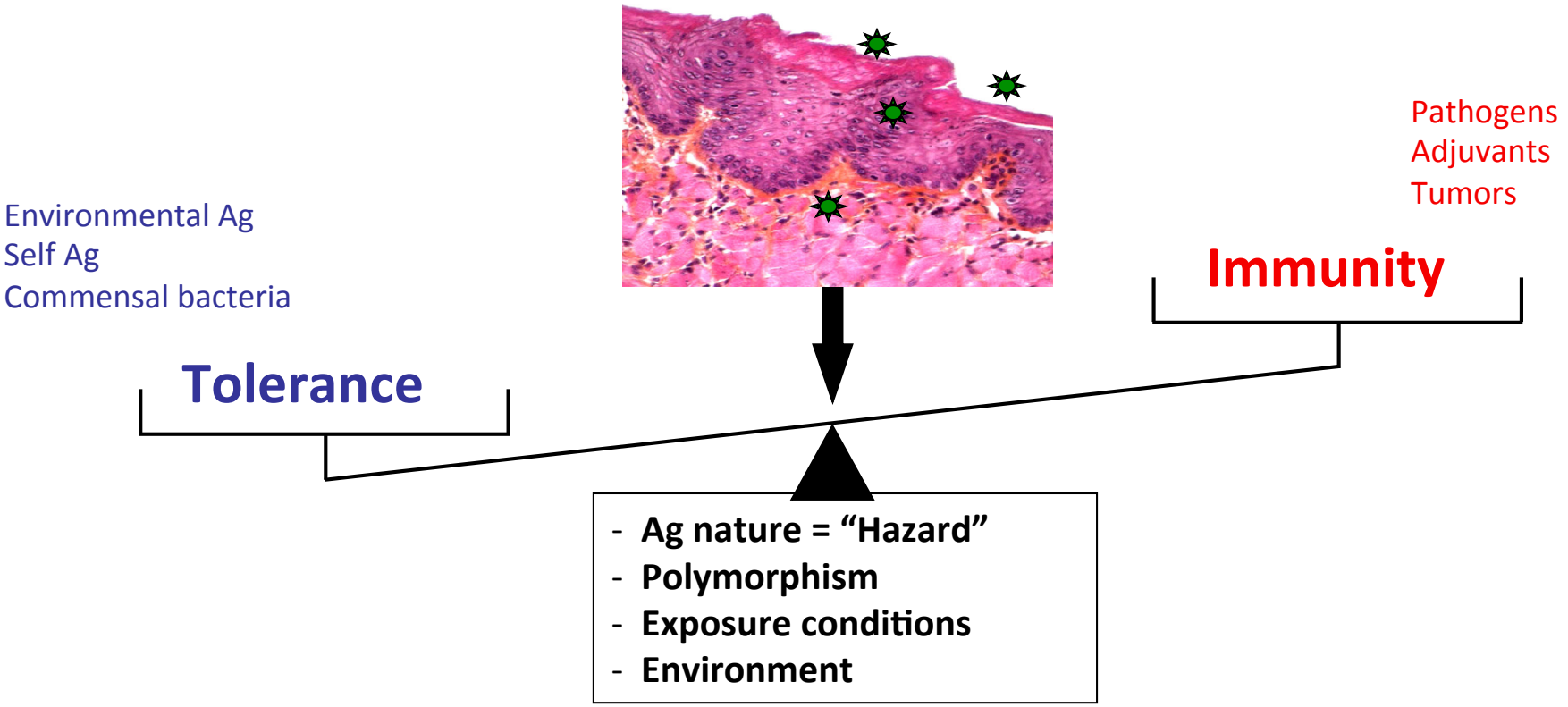
- Induction & régulation de l'inflammation cutanée : *exemple de l'eczéma de contact*

The skin: the multitasking organ



- Skin area=1.8 m2
- Being constantly exposed to potential hazards -> maintain homeostasis
- Examples of the non-immune functions of the skin:
  - Physical and biochemical barrier
  - Sensory-receptive area
  - Ensures hydratation
  - Allows synthesis of vitamins, hormones

The skin: an immuno-protective organ

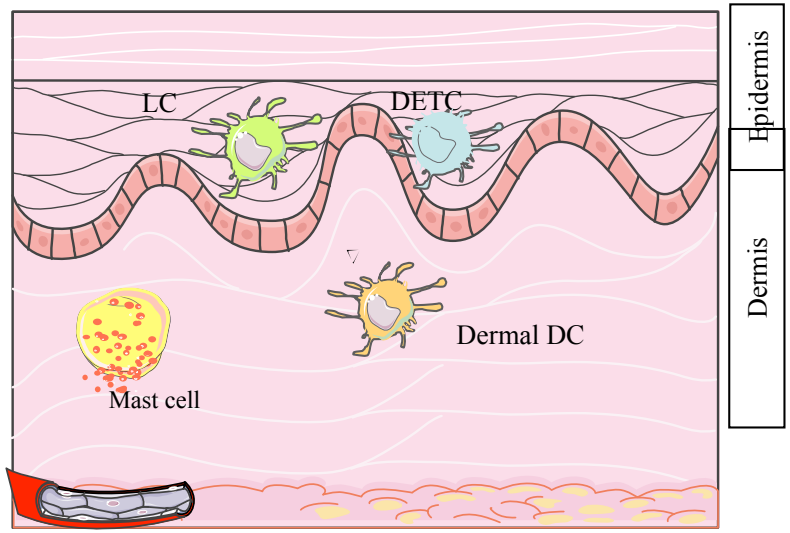


- Serves as an immuno-protective organ that actively defends deeper body tissues against infectious agents. Privileged site for vaccination

- Maintains self-tolerance, preventing allergens and inhibiting autoimmunity

Induction of systemic immunity upon skin exposure/immunization

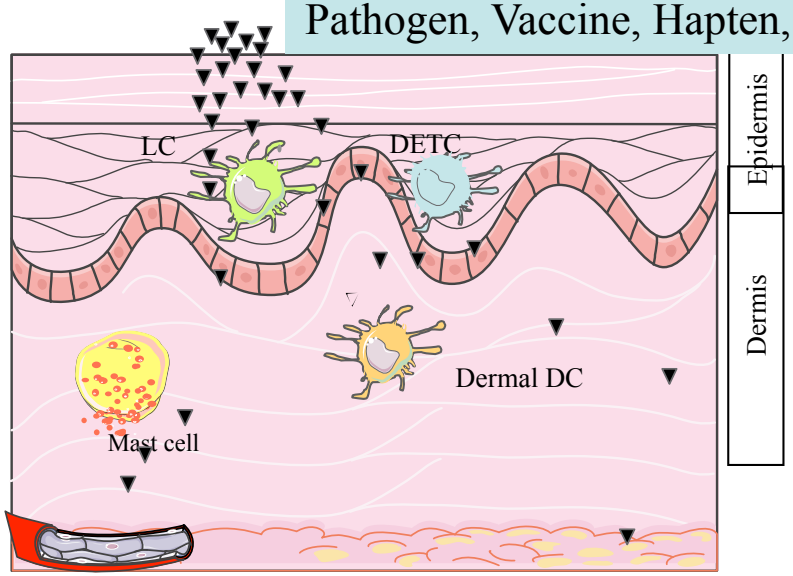
Skin exposure, immunization



Induction of systemic immunity upon skin exposure/immunization

Skin exposure, immunization

Pathogen, Vaccine, Hapten, Tumor, Allo-Ag, Commensal Microbiota, Auto-Ag



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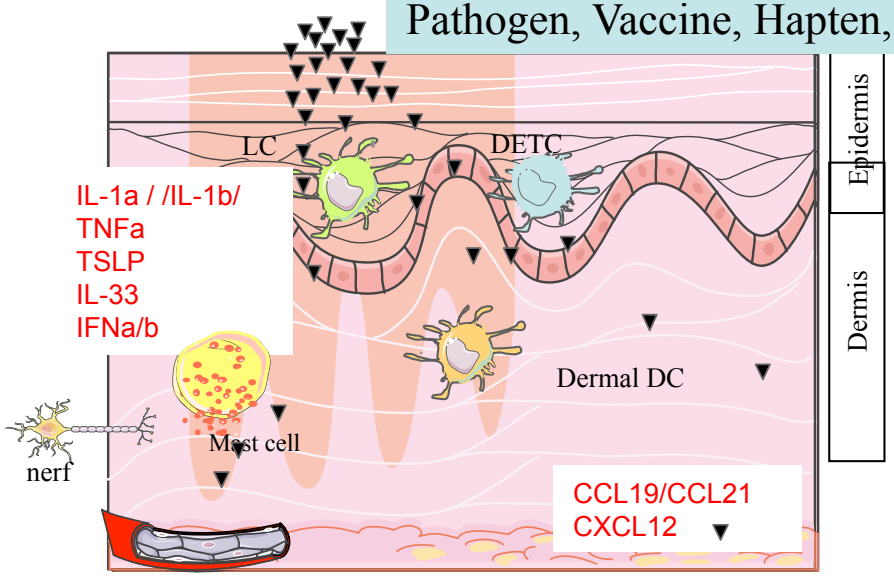
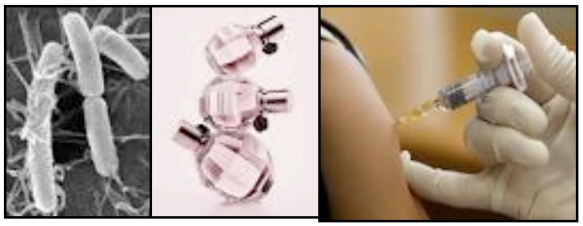




Innate immunity -> 1st line of defence

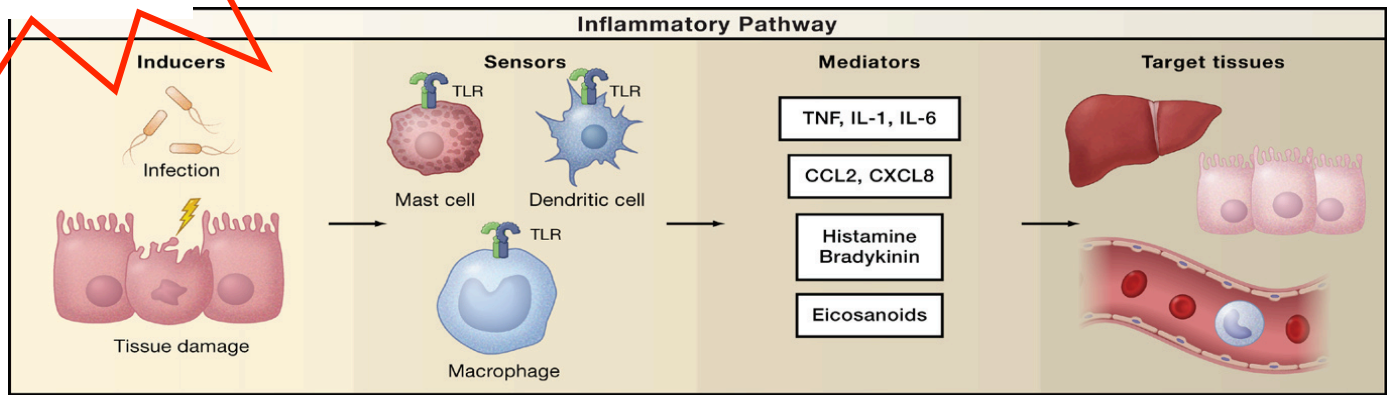
Release of inflammatory mediators

Inflammation
General scheme

4 major inflammatory components

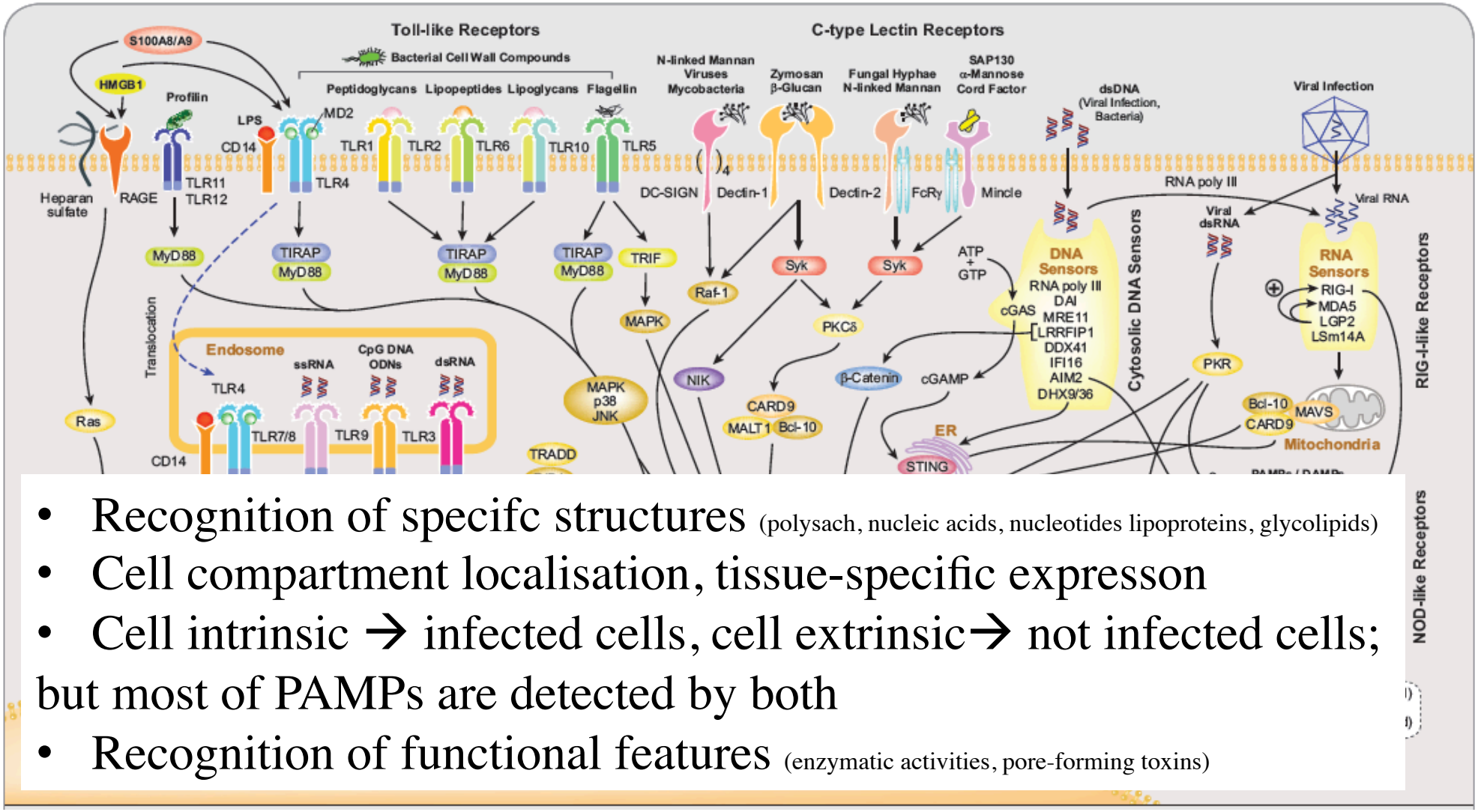
Inducers	Sensors	Mediators	Target tissues
Microbes, Allergens AlloAg	**P(athogen)AMPs** TLR, NLR…	**Cellular** Neutrophils, Eosinophils, Monocytes/Macrophages, T & B cells…	**Redness/Oedema Heat/Pain Loss of function**
Tissue damage Cell-derived Plasma-derived ECM-derived	**D(amage)AMPs** TLR, NLR, RAGE…	**Molecular** Cytokines and chemokines, Vasoactive amines or peptides Complement fragments lipide mediators proteolytic enzymes	
	~~Nociceptors~~		

DANGER Hypothesis



Pathogen recognition receptors (PRRs)

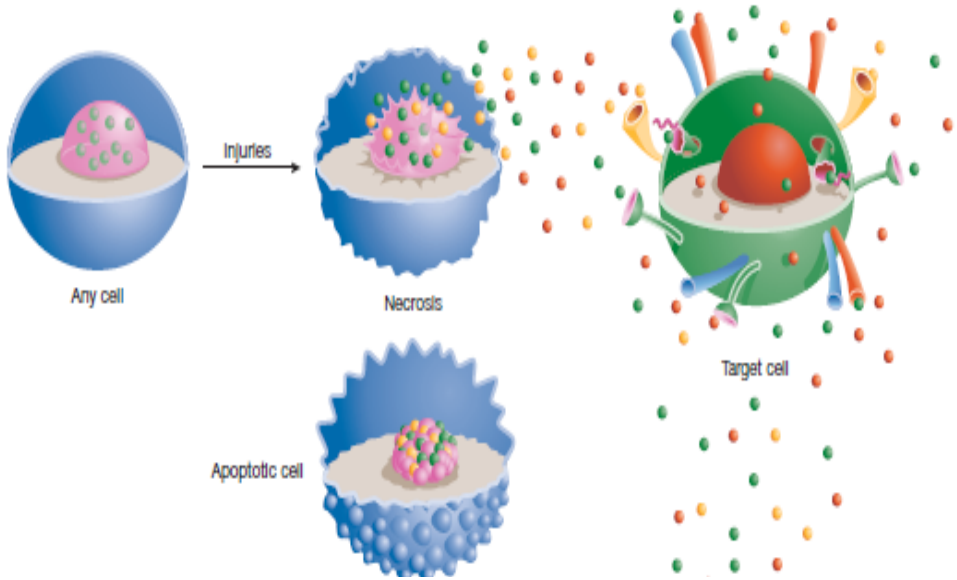
- Microbial Pattern Recognition Receptors: TLR, RLR, NLR, CLR signaling (examples)



- Recognition of specifc structures (polysach, nucleic acids, nucleotides lipoproteins, glycolipids)
- Cell compartment localisation, tissue-specific expresson
- Cell intrinsic → infected cells, cell extrinsic→ not infected cells; but most of PAMPs are detected by both
- Recognition of functional features (enzymatic activities, pore-forming toxins)

Inflammation
PAMPs – DAMPs and their sensors

Intracellular DAMPs



DAMP	Adjuvant activity
HMGB1	*In vivo*: adjuvant activity of purified molecule; adjuvant activity shown by selective depletion
	In vitro: DC activation
Uric acid (MSU)	*In vivo*: adjuvant activity shown by injection of purified molecule and selective depletion
	In vitro: DC activation
Chromatin, nucleosomes and DNA	*In vivo*: DC maturation induced by purified molecule
	In vitro: DC activation induced by chromatin–IgG complexes
HSPs	*In vivo*: tumour immunogenicity enhanced by overexpressed molecule or addition of purified molecule (HSP70); DC migration to lymph nodes induced by purified molecule (gp96)
	In vitro: DC maturation (gp96 and HSP70)
Adenosine and ATP	*In vivo*: exacerbation or abrogation of bronchial asthma by purified molecule or specific inhibition, respectively
	In vitro: DC maturation
Galectins	*In vivo*: ND
	In vitro: DC maturation
Thioredoxin	ND
S100 proteins	ND
Cathelicidins	*In vitro*: DC maturation; DC activation induced by LL37–self-DNA complex
Defensins	*In vivo*: adjuvant activity by co-administration of purified molecule
	In vitro: DC maturation
N-formylated peptides	*In vivo*: ND
	In vitro: DC chemotaxis

Inflammation
PAMPs – DAMPs and their sensors

Extracellular DAMPs

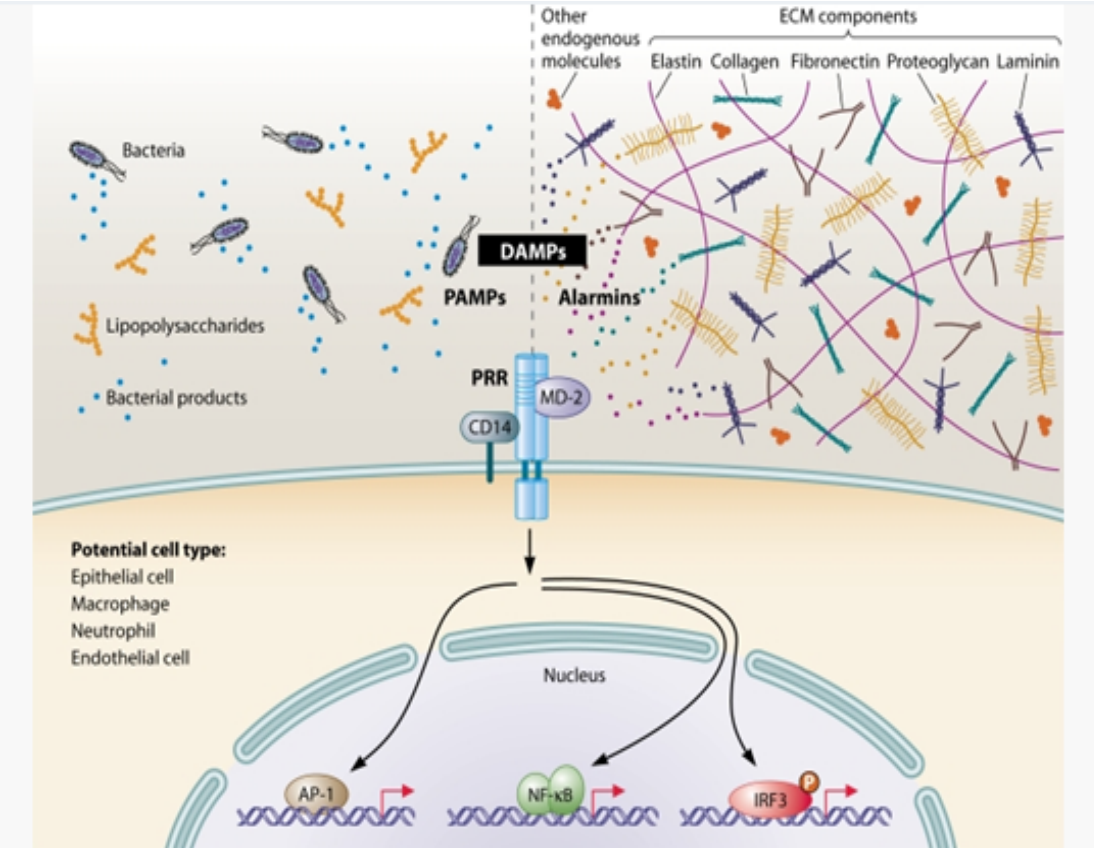
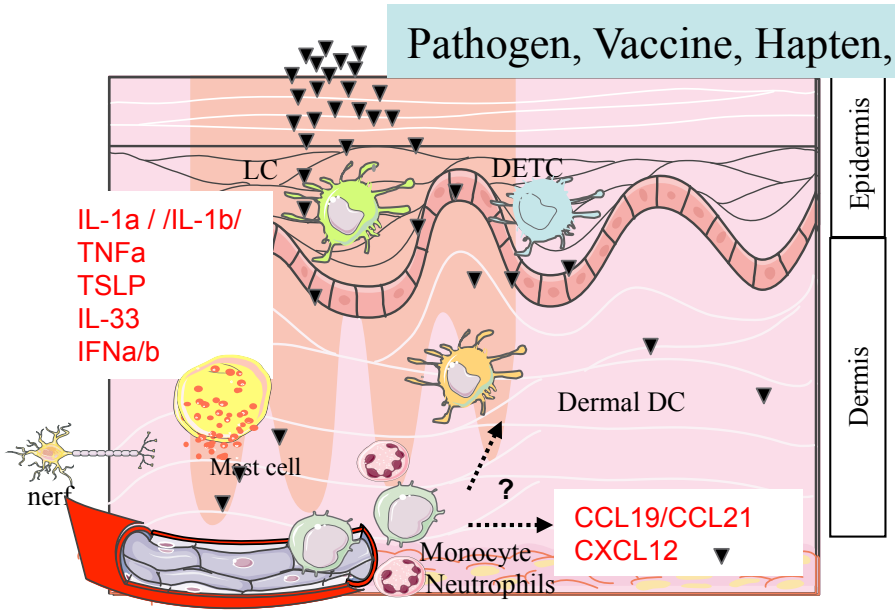


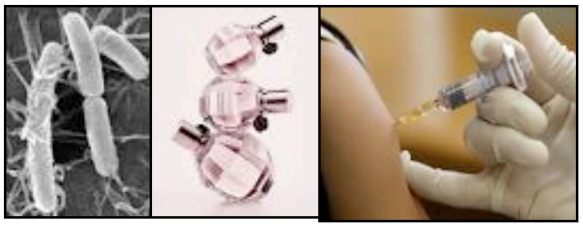
Table 2 | **Adjuvant and pro-inflammatory activity of extracel**

DAMP	Adjuvant activity
Hyaluronic acid	*In vivo*: inhibition of Langerhans-cell maturation by blocking peptide; adjuvant activity by administration of purified molecule
	In vitro: DC maturation
Heparan sulphate	*In vitro*: DC maturation
Fibrinogen	*In vitro*: DC maturation
Collagen-derived peptides	*In vivo*: ND
	In vitro: DC maturation
Fibronectin	*In vitro*: DC maturation
Elastin-derived peptides	*In vivo*: ND
	In vitro: ND
Laminin	*In vivo*: ND
	In vitro: ND

Induction of systemic immunity upon skin exposure/immunization

Skin exposure, immunization





Innate immunity -> 1st line of defence

Release of inflammatory mediators

Coordinated cross-talk between epithelial and immune cells

Infiltration of blood leucocytes

Induction of systemic immunity upon skin exposure/immunization

Skin exposure, immunization

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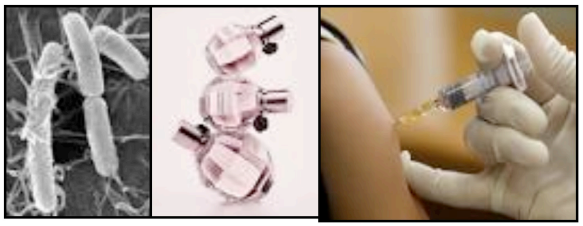
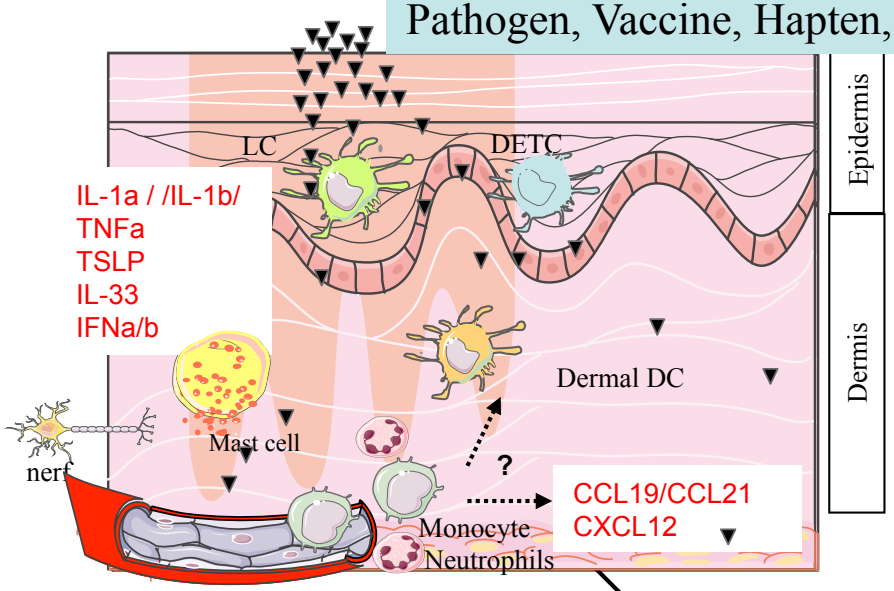
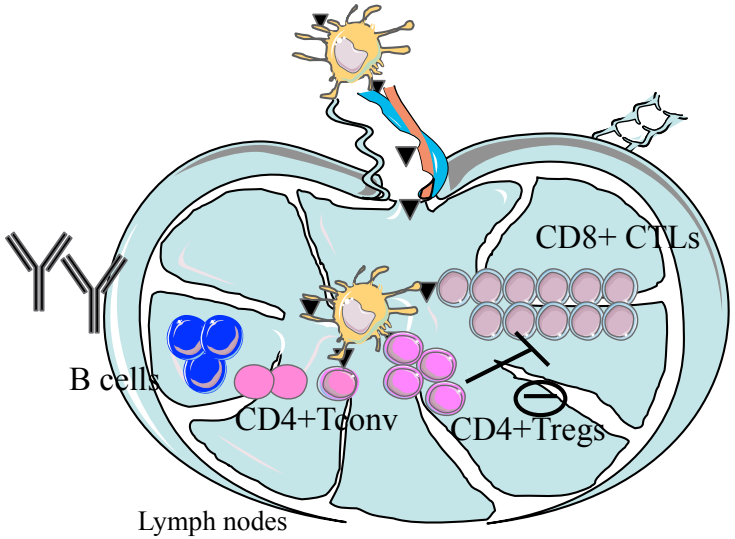




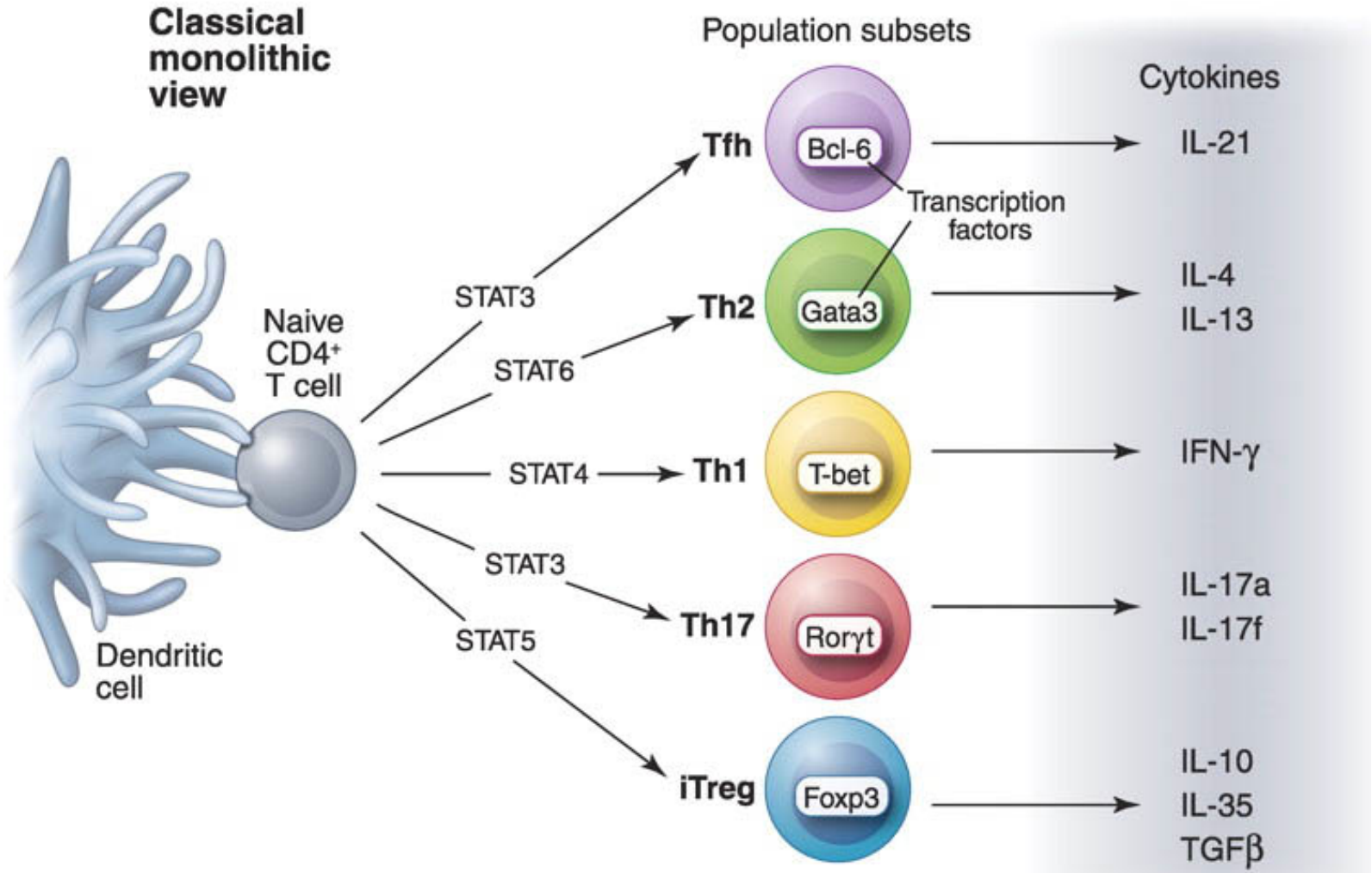
Innate response



Adaptative immunity

Antibody production
Effector CD4+ & CD8+ T cells
Memory T cells, B cells & plasma cells

Distinct T cells

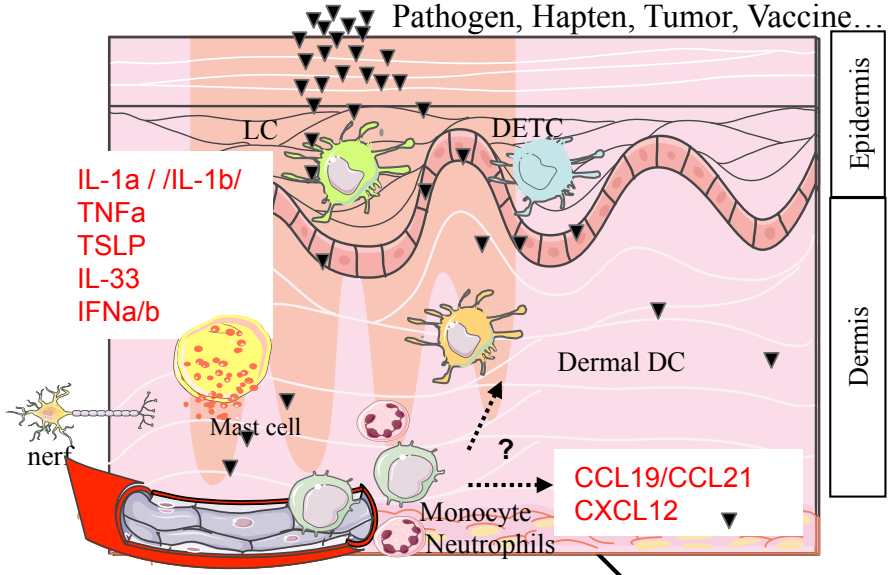


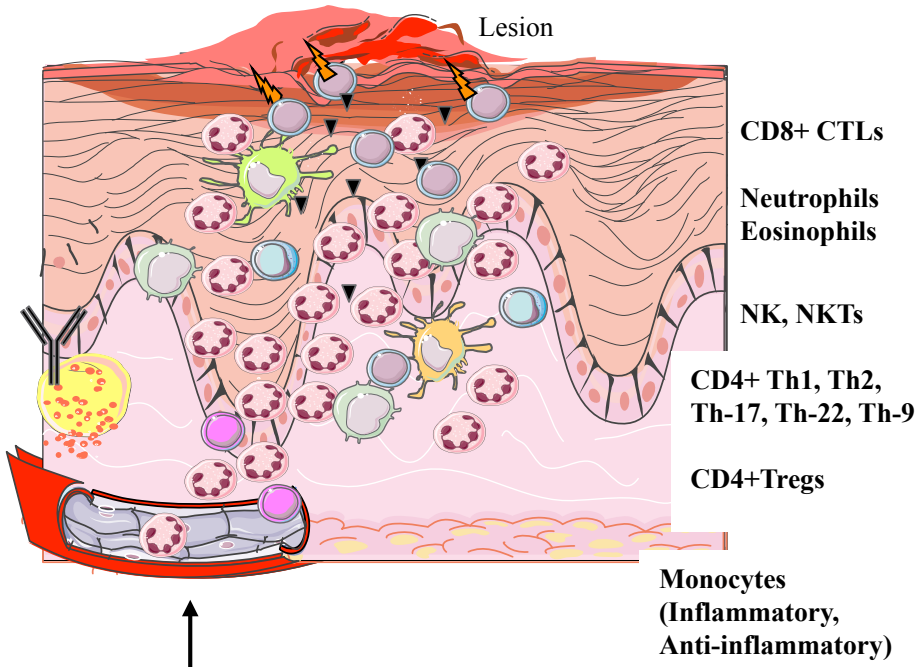
O'Shea and Paul. 2010. *Science*

Induction of systemic immunity upon skin exposure/immunization

Skin exposure, immunization

Persistance / Re-exposure → delayed-response (days)
Skin inflammation, elimination of infected cells
Tissue response/repair





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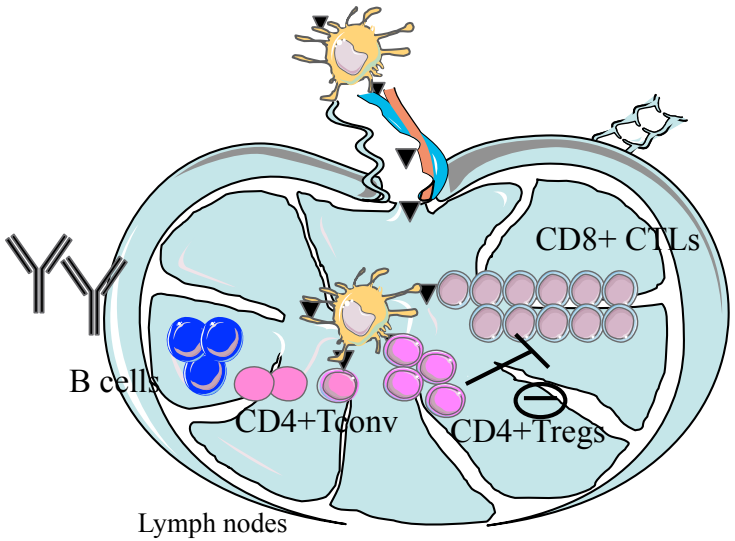
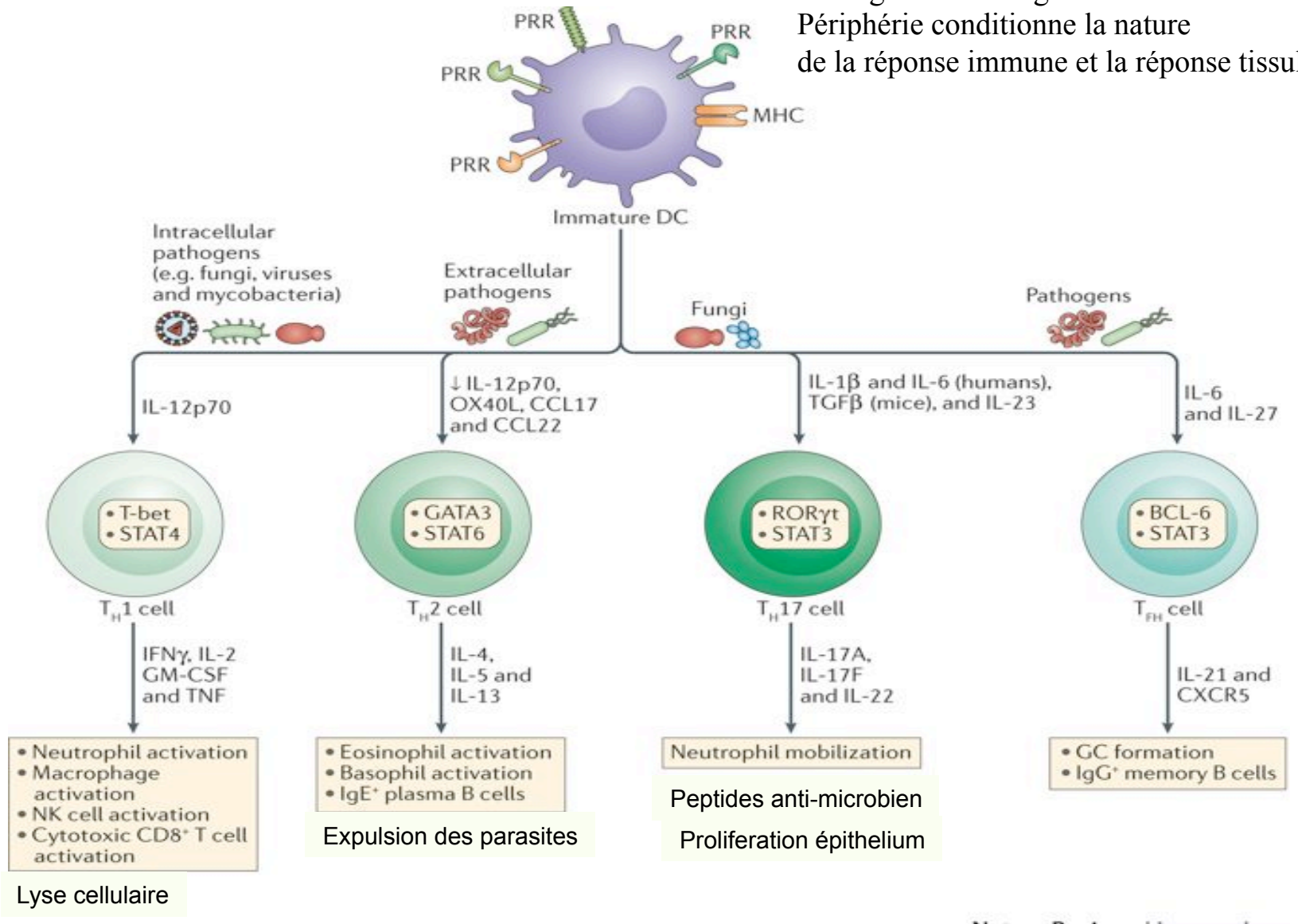


Adaptative immunity

Effector & memory response -> 2nd line of defence

Different mode of recognition by the innate immunity → different layers of sensing by the immune system → different effector response

L'intégration des signaux de la Périphérie conditionne la nature de la réponse immune et la réponse tissulaire

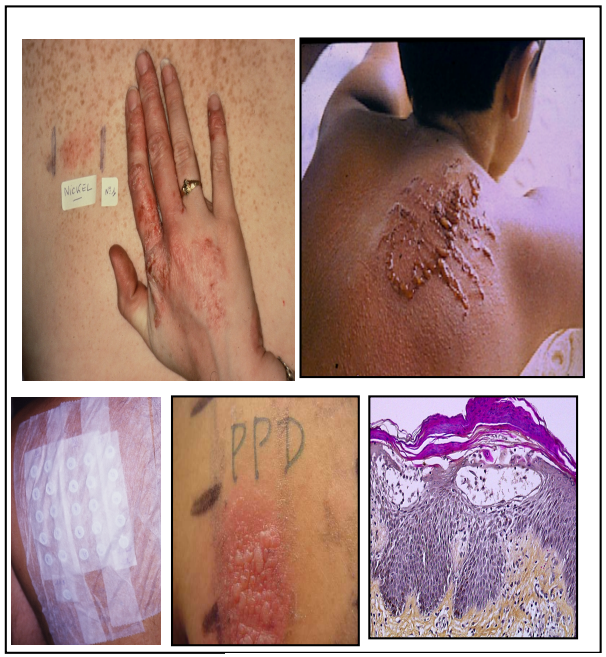


PLAN

- Bases immunologiques de la réponse à l'interface cutanée

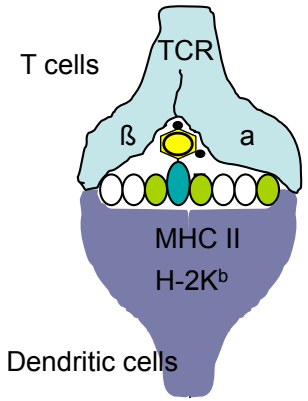
- Induction & régulation de l'inflammation cutanée : exemple de l'eczéma de contact

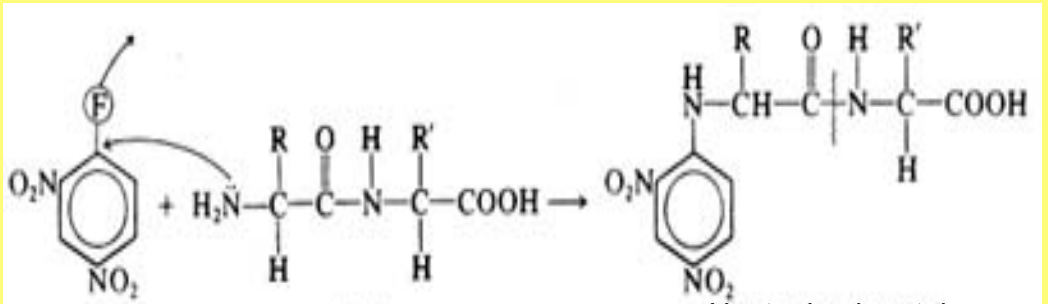
Allergic Contact Dermatitis (ACD): Generalities



Features

- High prevalence,1st occupationnal disease
- Repeated exposure to environmental allergens (cosmetics, jewels, drugs…)
- Breakdown of skin tolerance
- Delayed-type allergy:
  → infiltration and activation of allergen-specific T cells





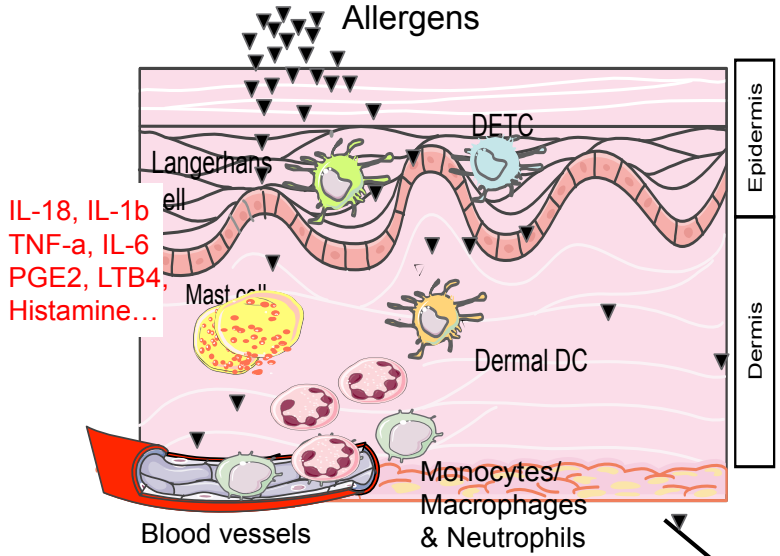
Presentation of haptenized peptides

Pathophysiology of skin allergy

Vocanson M. et al, Allergy, 2009

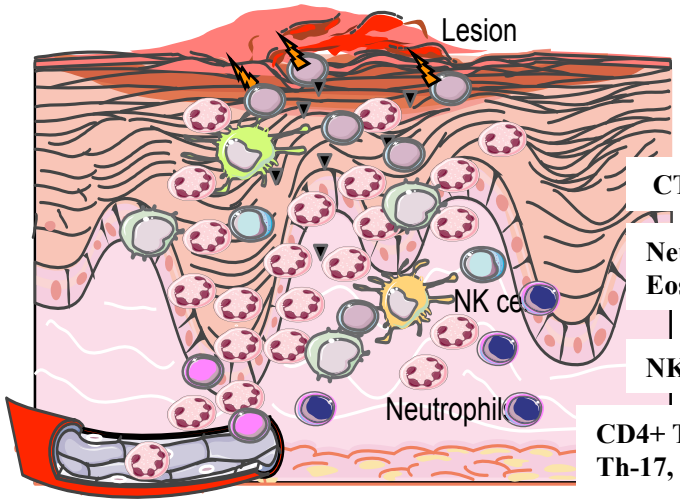
1- Sensitization phase

Innate immunity/ T cell priming

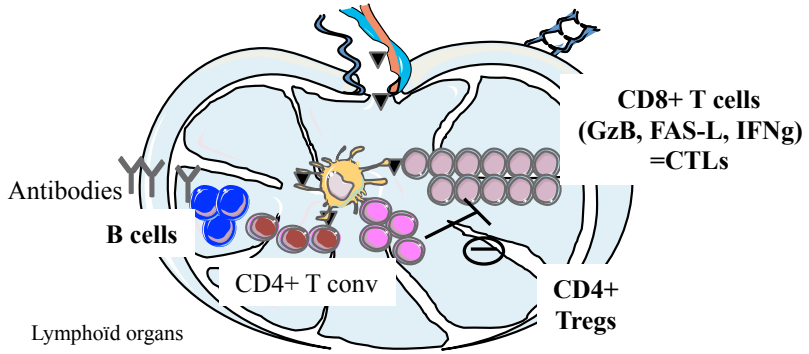


2- Elicitation phase

Effector response/ Polymorphic recruitment



Monocytes (Inflammatory, Anti-inflammatory)



BOUR et al. *Eur J Immunol,* 1995
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CORTIAL et al. *Nanomedicine,* 2015
GAMRADT *J Allergy Clin Immunol* 2019

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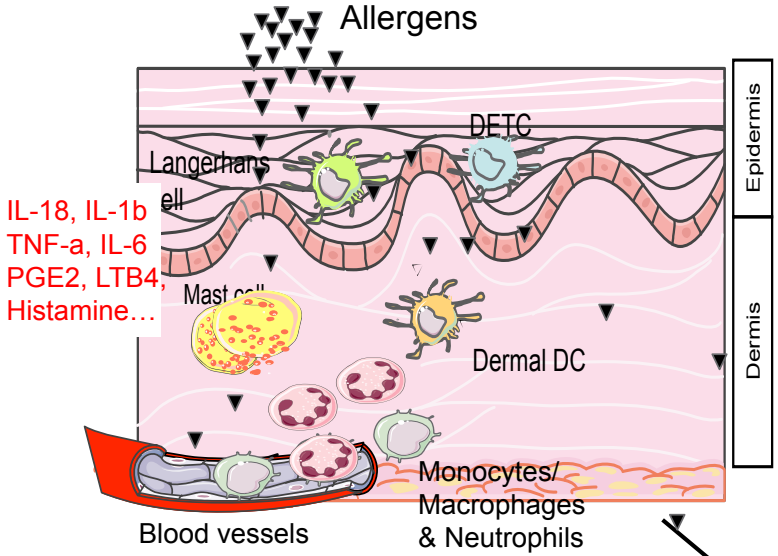
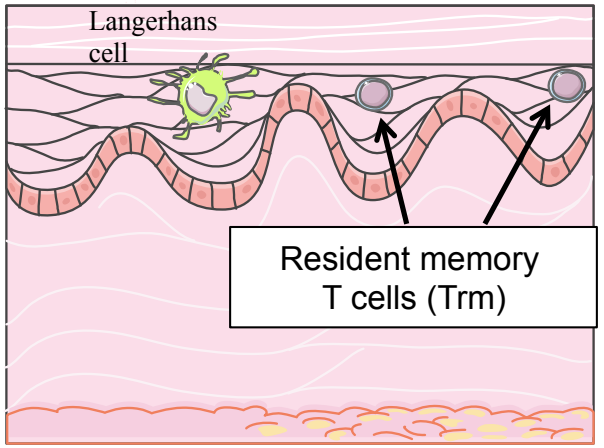
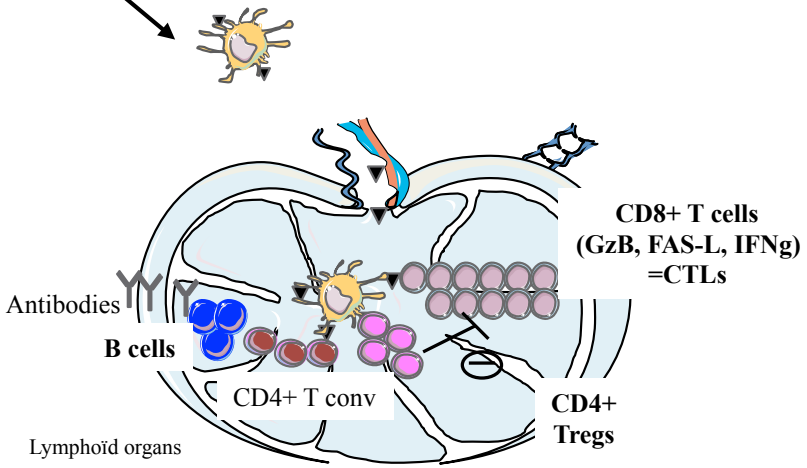


3- Resolution of skin inflammation

Healed lesion/ Persistence of skin Trm





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Pathophysiology of skin allergy

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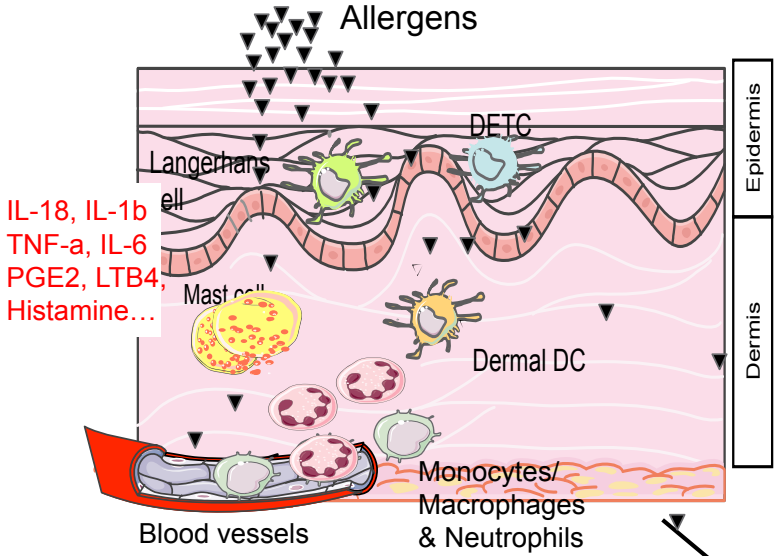
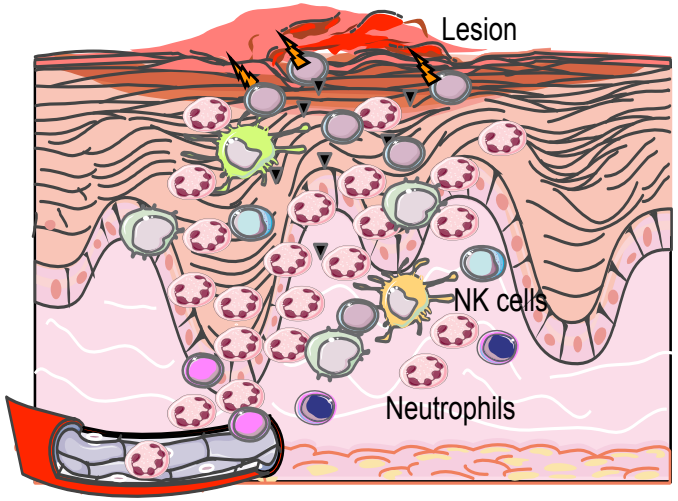
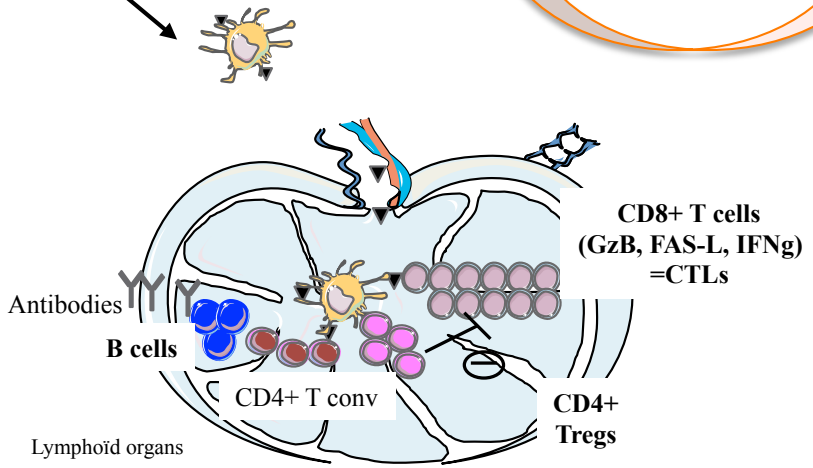


4- Recurrence / Severity / Chronicity

New exposure / Flares





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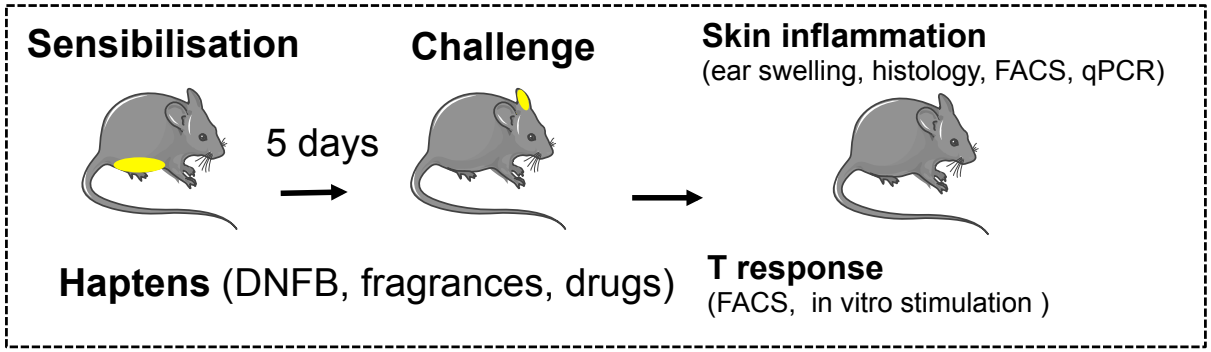
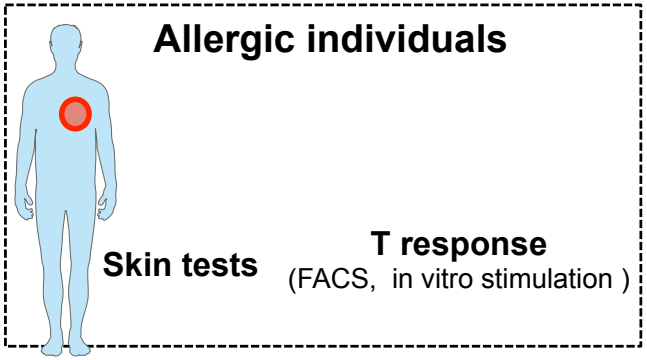
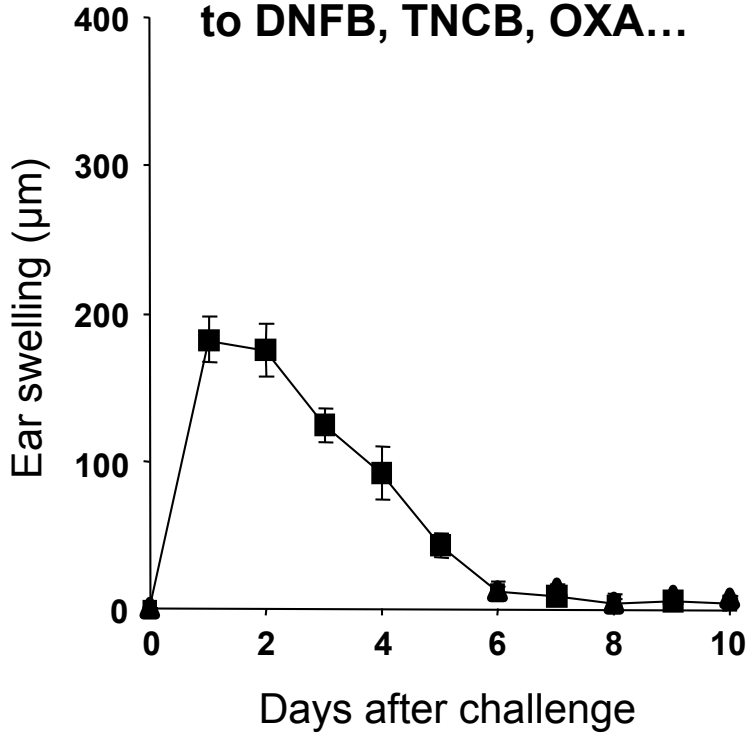
Experimental models of ACD in mouse, in human

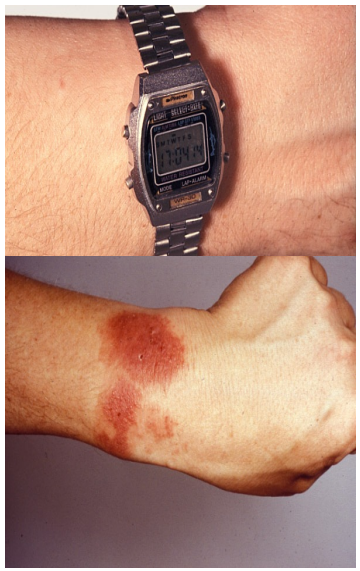




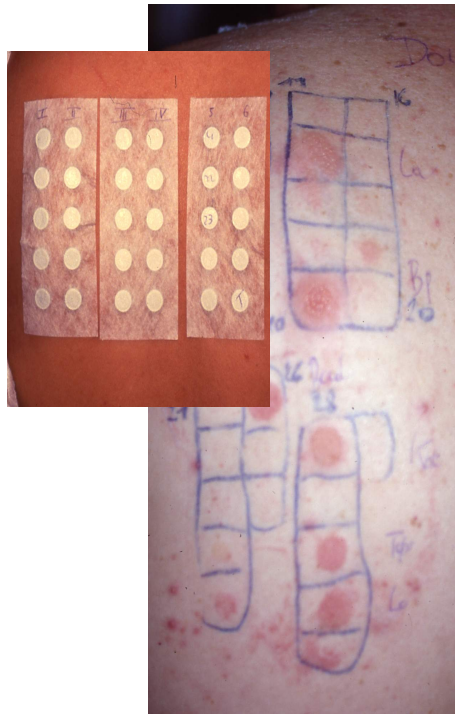
CHS (= ACD) response to DNFB, TNCB, OXA…



ACD lesions



Positive patch-tests to reference allergens



Permeation of haptens into the skin

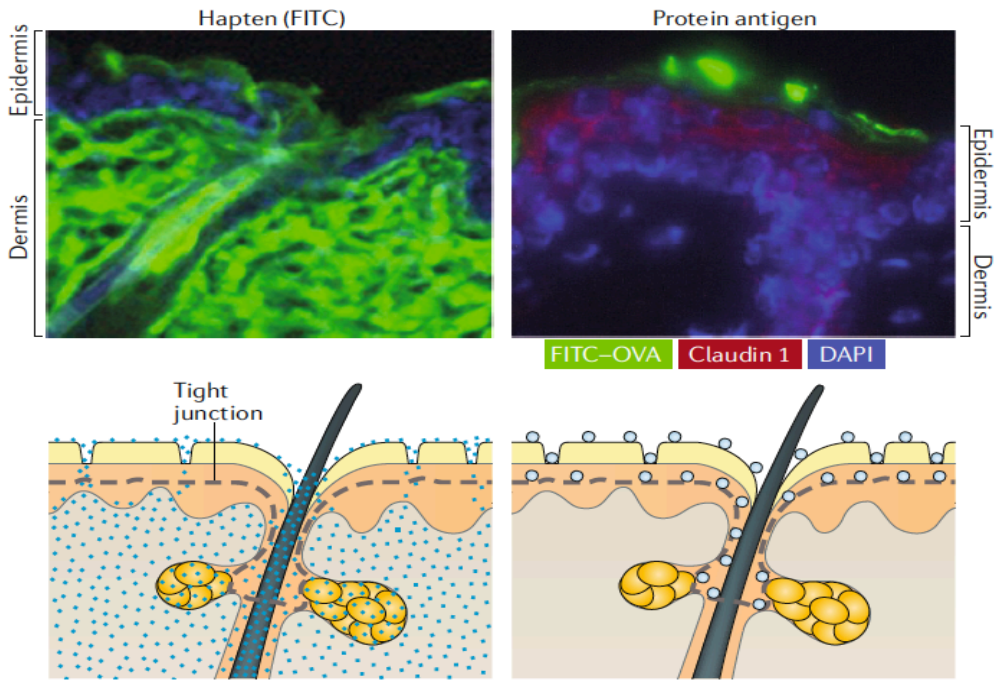


Fig. 4 | **Penetration of hapten and proteins into the skin.** A hapten (fluorescein isothiocyanate (FITC); molecular mass = 389; left) or FITC-conjugated ovalbumin (FITC–

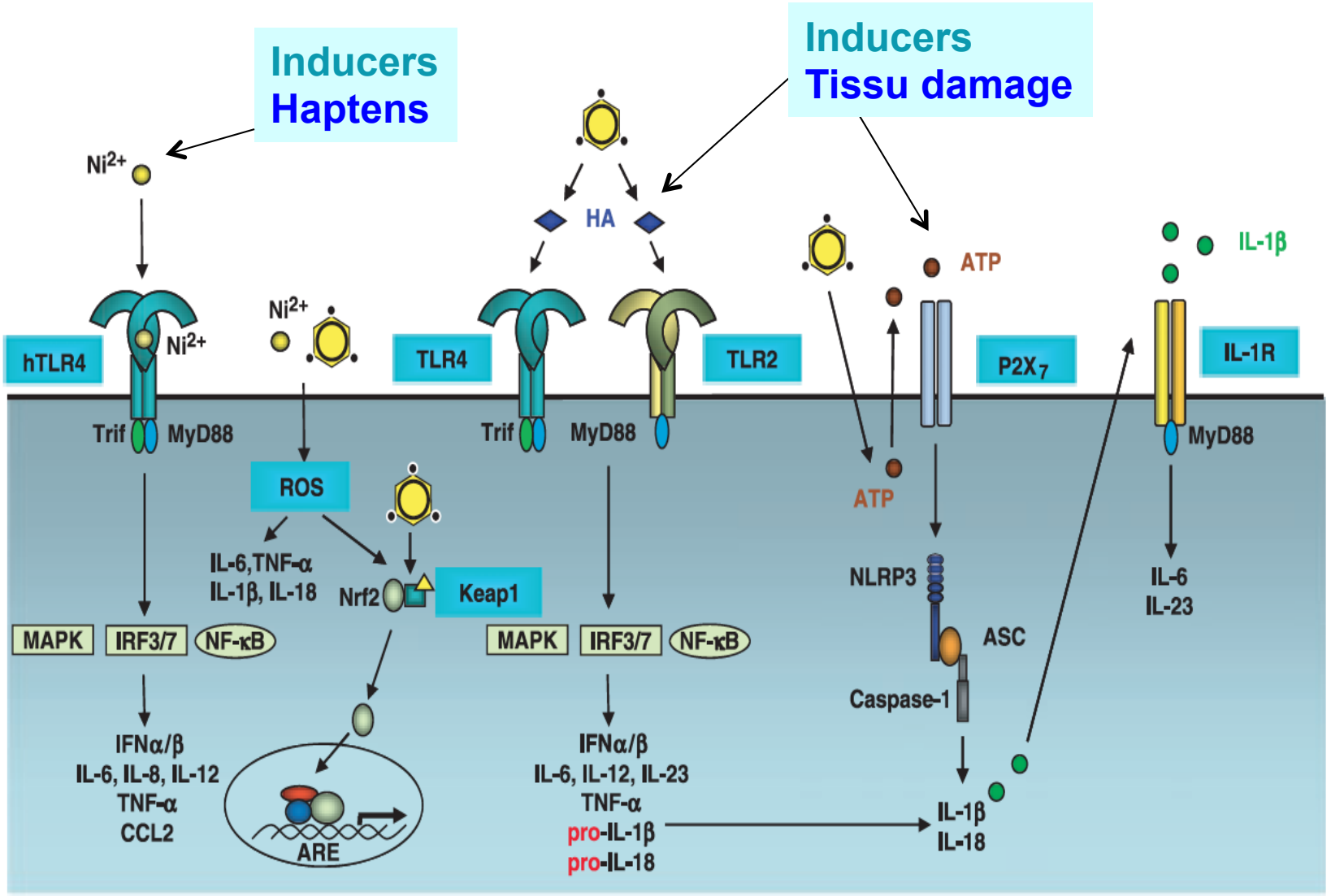
➢Les haptènes sont pour la plus part des substances hydrophobes

➢Pénétration dépend de l'hydrophobicité (LogP), mais aussi de la présence de groupes chargés, la taille (poids moléculaire < 1000 Daltons), la forme moléculaire et du véhicule.

➢Les peaux altérées (blessures physiques, chimiques ou anormalité génétique) favorisent l'apparition d'un eczéma de contact

Kabashima et al. Nature Rev immunol 2019

How haptens activate innate immunity?



SF Martin et al, Allergy, 2011

Les diverses étapes de la sensibilisation : activation de l'immunité innée

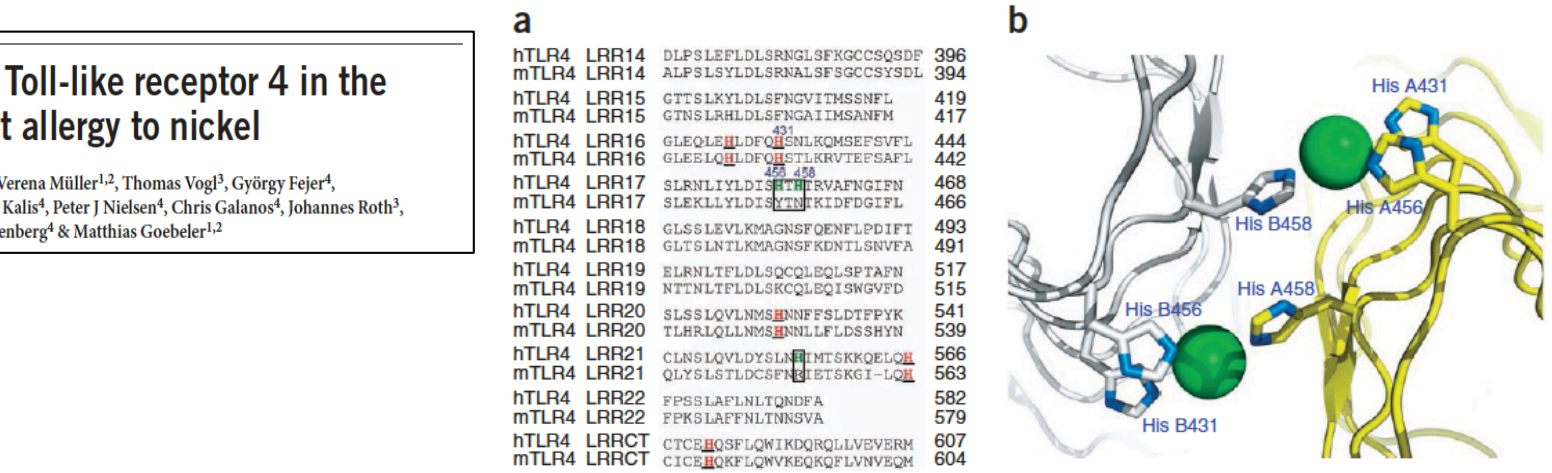
- Rôle crucial de la structure du TLR4 humain sur le développement de la réponse d'EAC

Conserved histidines on human TLR4 as potential binding sites for nickel

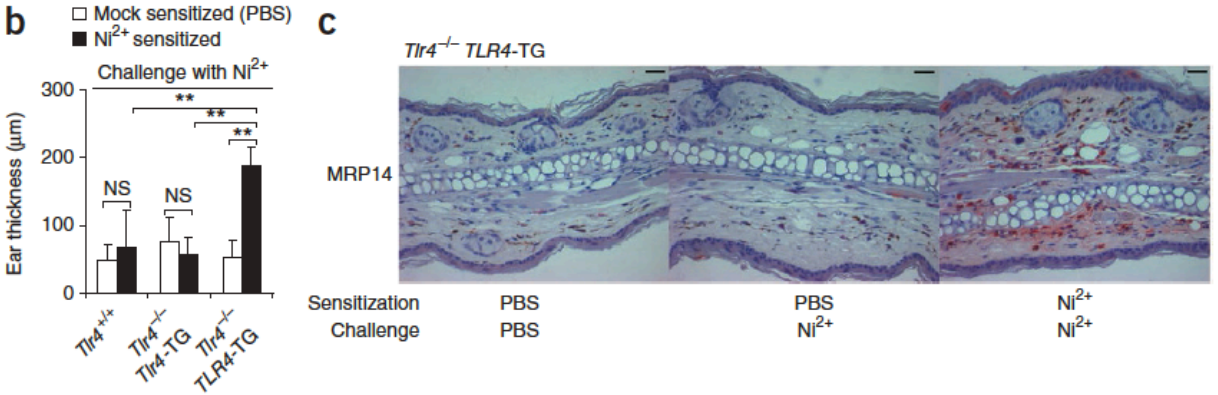
nature immunology

Crucial role for human Toll-like receptor 4 in the development of contact allergy to nickel

Marc Schmidt[1,2], Badrinarayanan Raghavan[1,2], Verena Müller[1,2], Thomas Vogl[3], György Fejer[4], Sandrine Tchaptchet[4], Simone Keck[4], Christoph Kalis[4], Peter J Nielsen[4], Chris Galanos[4], Johannes Roth[3], Arne Skerra[5], Stefan F Martin[6], Marina A Freudenberg[4] & Matthias Goebeler[1,2]

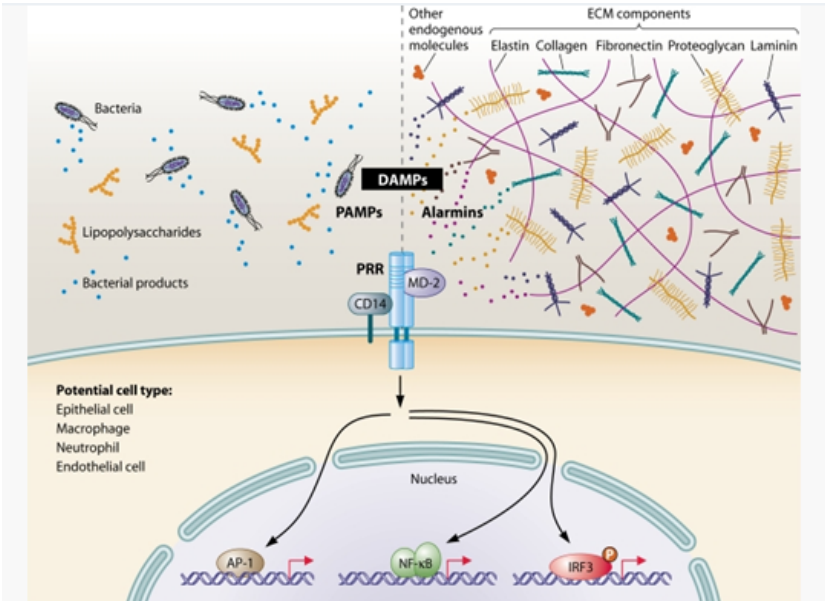


Transgenic expression of human TLR4 in mice confers reactivity toward nickel



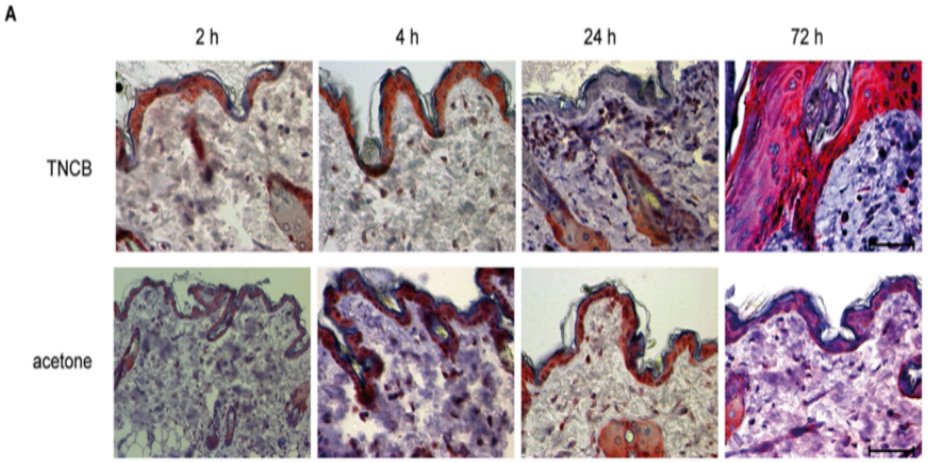
Les diverses étapes de la sensibilisation : activation de l'immunité innée

- Impact des médiateurs reconnus par les TLRs sur le développement de la réponse d'EAC

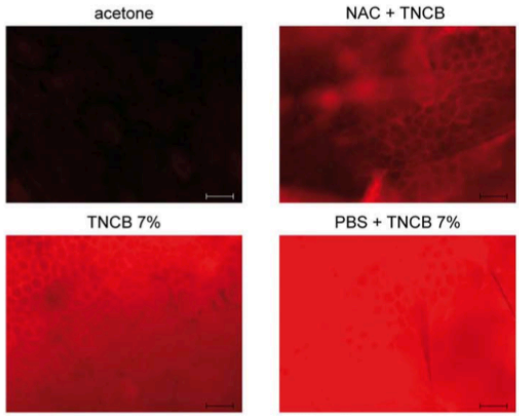


Esser P, Plos One 2012

Dégradation Acide Hyaluronique ht PW, 24h après application



Production ROS, peau challengée



Les diverses étapes de la sensibilisation : activation de l'immunité innée

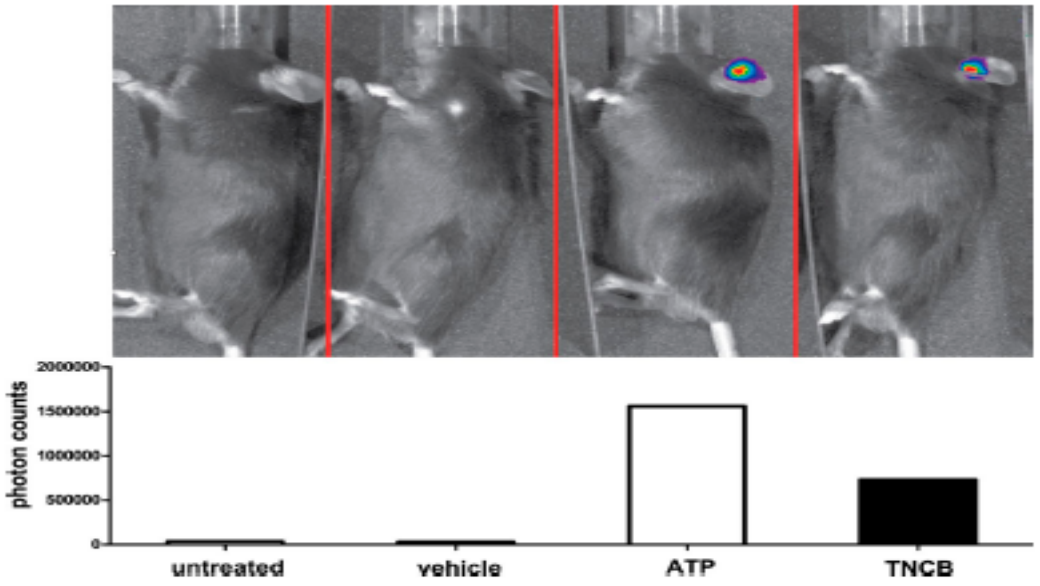
- Impact des médiateurs reconnus par les NLRs sur le développement de la réponse d'EAC

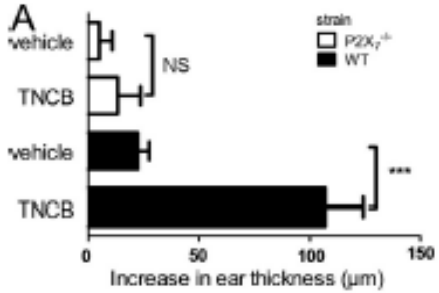
Published November 8, 2010

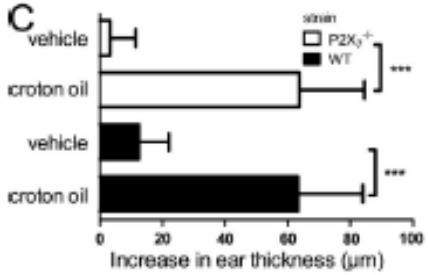
JEM Article

Lack of the purinergic receptor $P2X_7$ results in resistance to contact hypersensitivity

Felix C. Weber,[1,4] Philipp R. Esser,[1,4] Tobias Müller,[2] Jayanthi Ganesan,[3,4] Patrizia Pellegatti,[5] Markus M. Simon,[6] Robert Zeiser,[3] Marco Idzko,[2] Thilo Jakob,[1] and Stefan F. Martin[1]







Relargage ATP, peau challengée

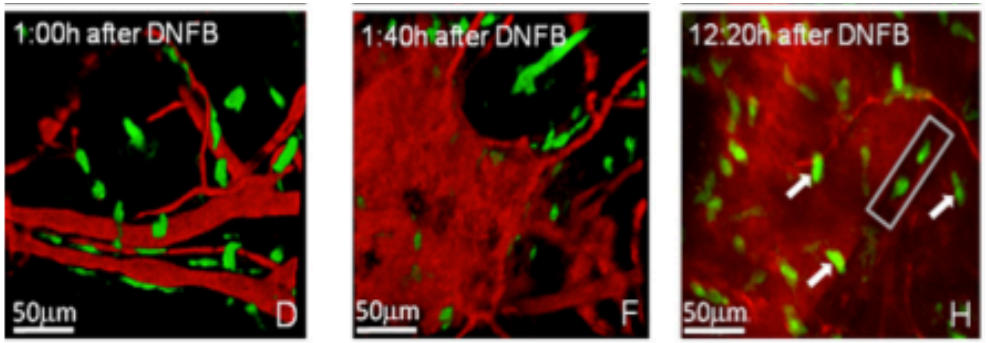
Contribution of innate cells? Mast cells

Immunity
Article

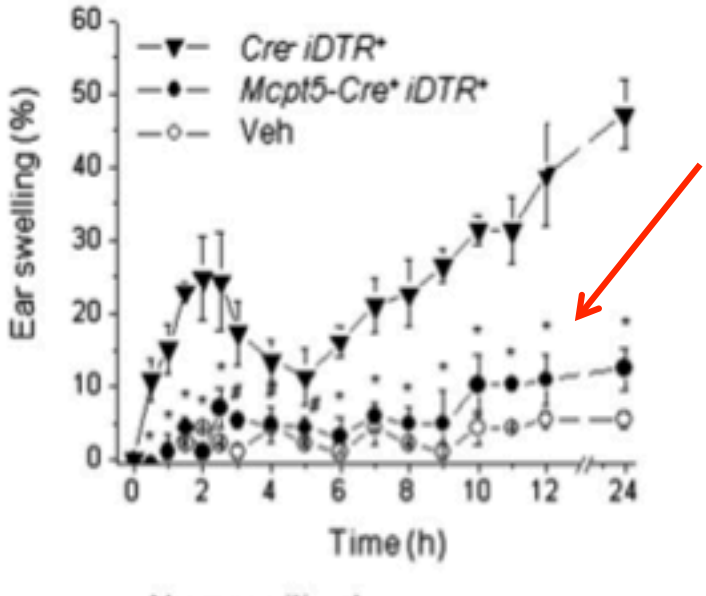
Mast Cells Are Key Promoters of Contact Allergy that Mediate the Adjuvant Effects of Haptens

Anne Dudeck,[1,8] Jan Dudeck,[1,8] Julia Scholten,[2,8] Anke Petzold,[1] Sangeetha Surianarayanan,[1] Anja Köhler,[3] Katrin Peschke,[1] David Vöhringer,[4] Claudia Waskow,[5] Thomas Krieg,[2] Werner Müller,[6] Ari Waisman,[7] Karin Hartmann, Matthias Gunzer,[3,8,*] and Axel Roers[1,8,*]

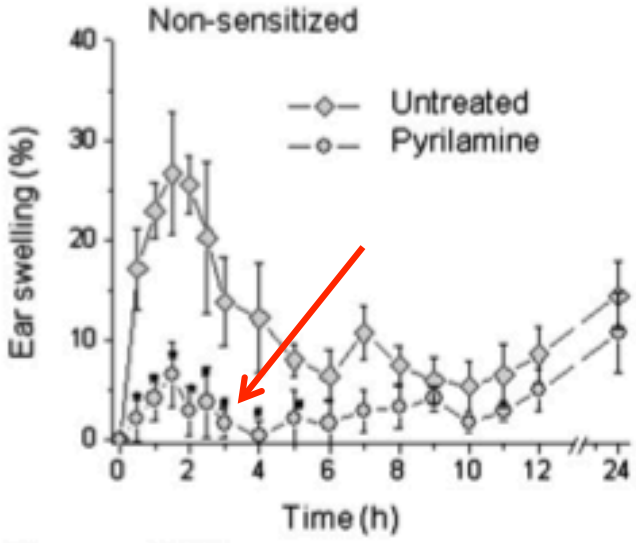
Ear skin mast cells and blood vessels respond to hapten



Dramatic decrease of ACD response in animals conditionally depleted in mast cells



Skin inflammation is histamine-dependent

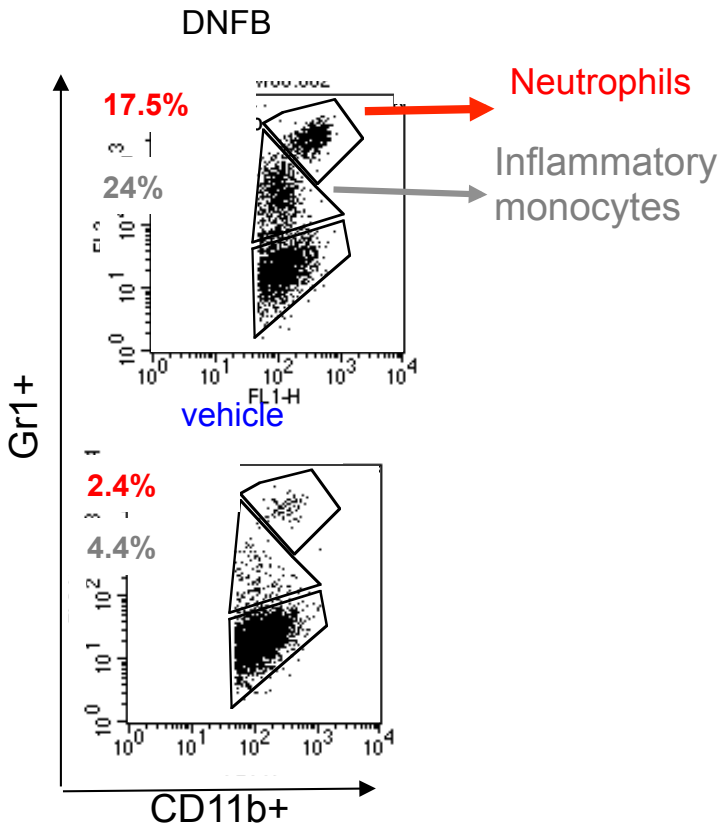


Contribution of innate cells? Neutrophils

Large infiltration of neutrophils
in the hours following hapten application

+6 hours → **FACS analysis of skin cells**

DNFB or vehicle

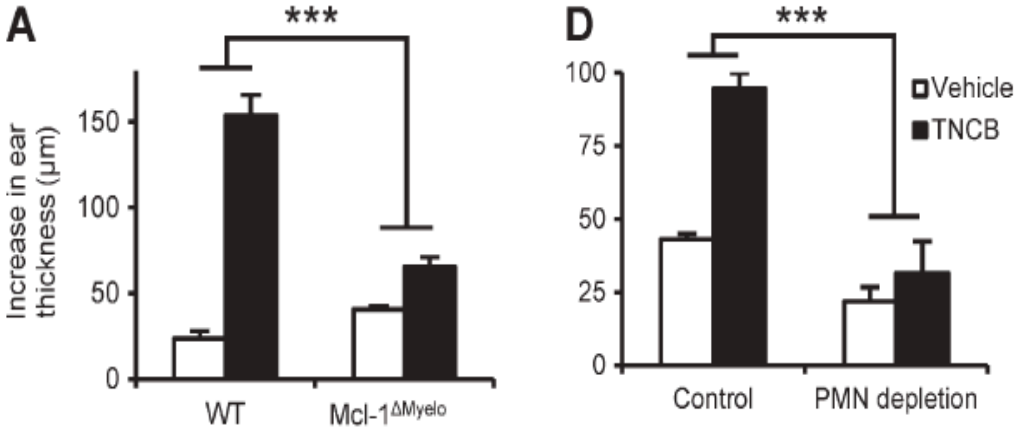


Lack of neutrophils (depletion, transgenic animals) prevents T cell priming and development of skin inflammation

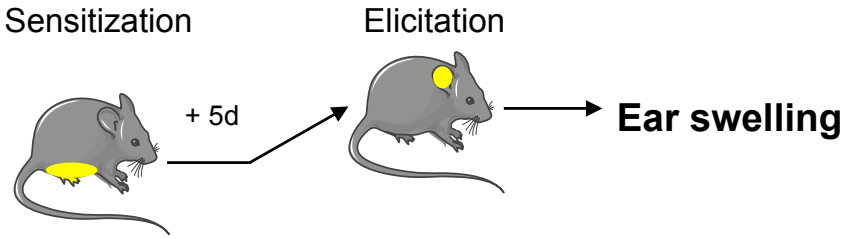
JEM Brief Definitive Repo

Neutrophils are required for both the sensitization and elicitation phase of contact hypersensitivity

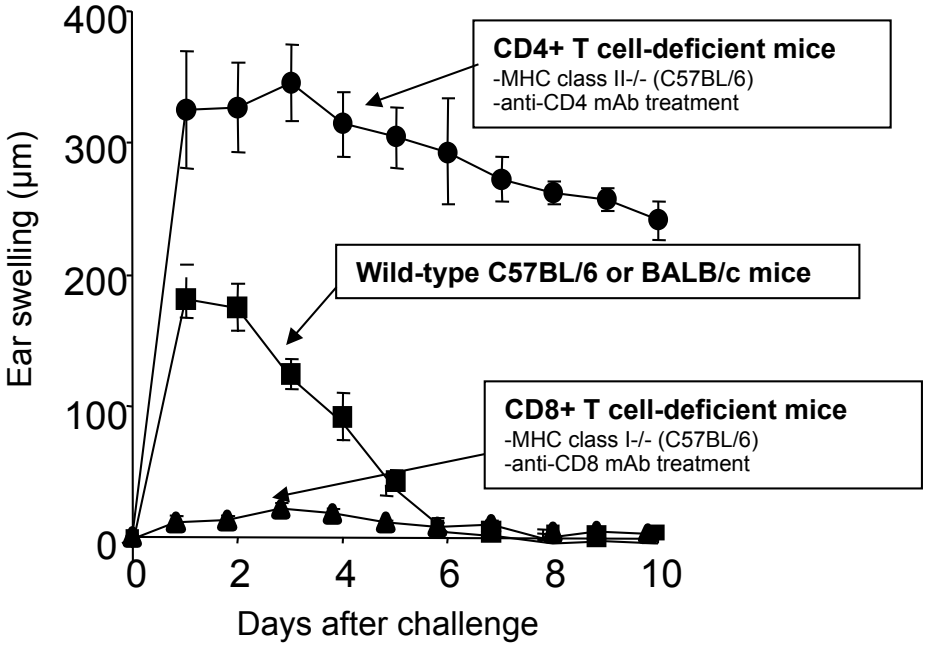
Felix C. Weber,[1,2,3*] Tamás Németh,[3,4*] Janka Z. Csepregi,[3,4*] Anne Dudeck,[5] Axel Roers,[5] Béla Ozsvári,[6] Eva Oswald,[1] László G. Puskás,[6] Thilo Jakob,[1] Attila Mócsai,[3,4**] and Stefan F. Martin[1**]



Main effectors? CD8+ CTLs

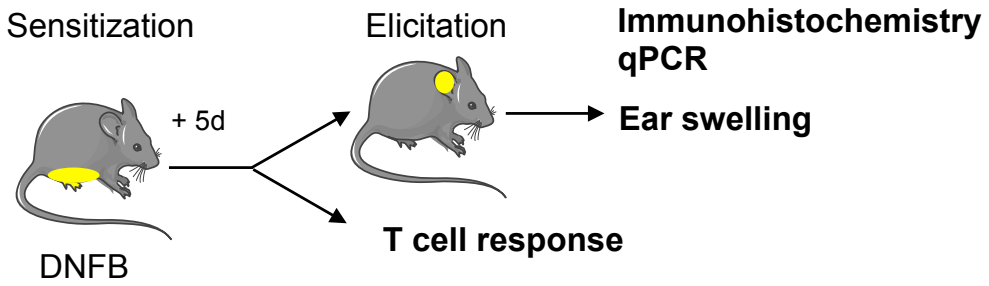


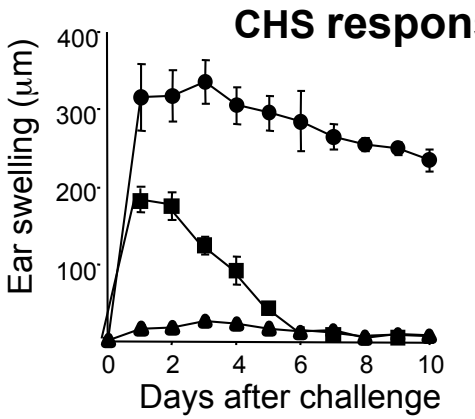
Strong haptens: DNFB, TNCB, OXAZOLONE…

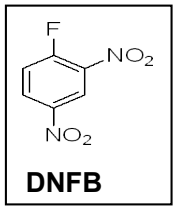


- CD8+ T cells are effector cells
- CD4+ T cells comprise regulatory T cells

Main effectors? CD8+ CTLs





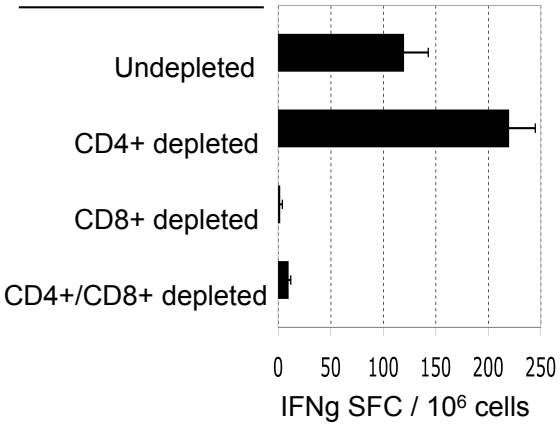


Priming of IFNg-producing CD8+ T cells

T cell response
(draining lymph nodes)

Elispot assay

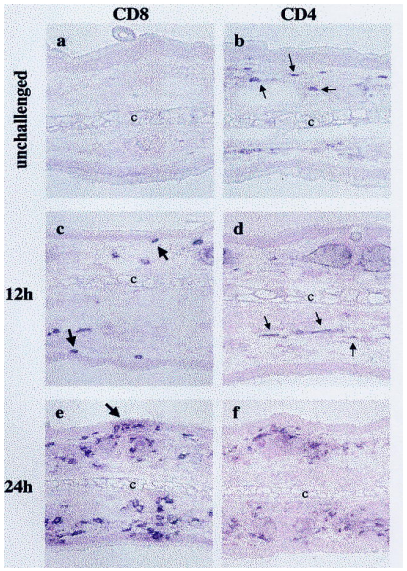
mAb Treatment



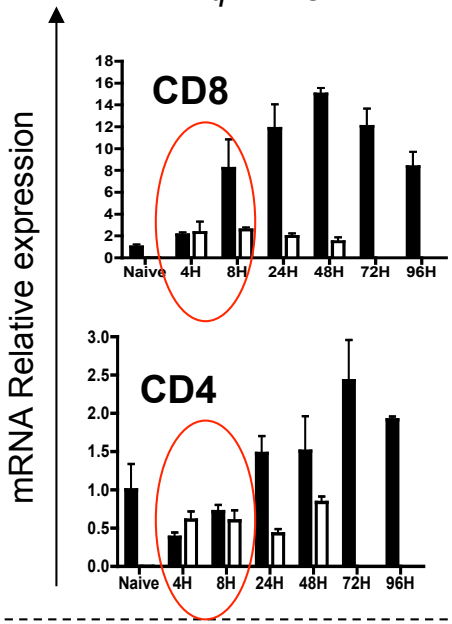
Early recruitment of CD8+ T cells initiates eczema

T cells recruitment
(challenged ears)

Immunostaining

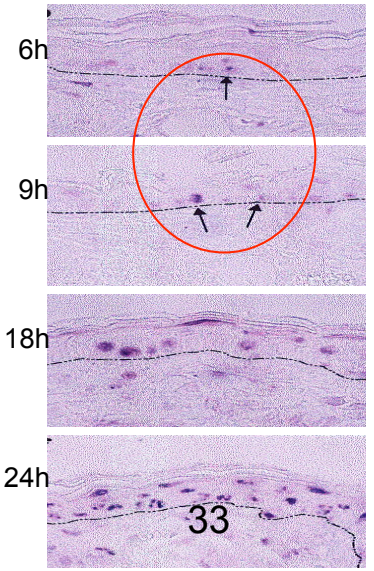


qRT-PCR



Keratinocytes: target of CTLs

TUNEL



Main effectors? CD8+ CTLs
Recurrence, chronicity

Inhibitory checkpoint receptors control CD8+ resident memory T cells to prevent skin allergy

J ALLERGY CLIN IMMUNOL 2019

Pia Gamradt, PhD,[a,b,c,d,e*] Léo Laoubi, MSc,[a,b,c,d,e*] Audrey Nosbaum, MD, PhD,[a,b,c,d,e] Virginie Mutez, MSc,[a,b,c,d,e] Vanina Lenief, MSc,[a,b,c,d,e] Sophie Grande, MD,[f] Daniel Redoulès, PhD,[g] Anne-Marie Schmitt, MD, PhD,[h] Jean-François Nicolas, MD, PhD,[a,b,c,d,e,f] and Marc Vocanson, PhD[a,b,c,d,e]

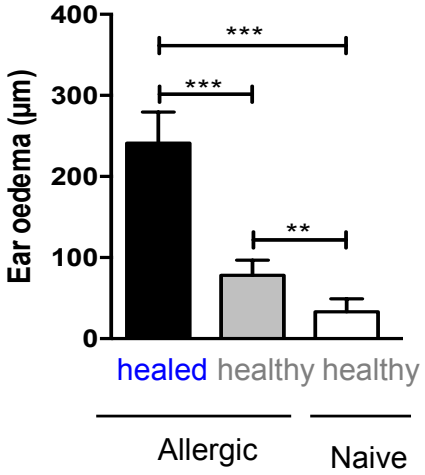
Lyon, Pierre-Benite, and Toulouse, France

Healthy skin

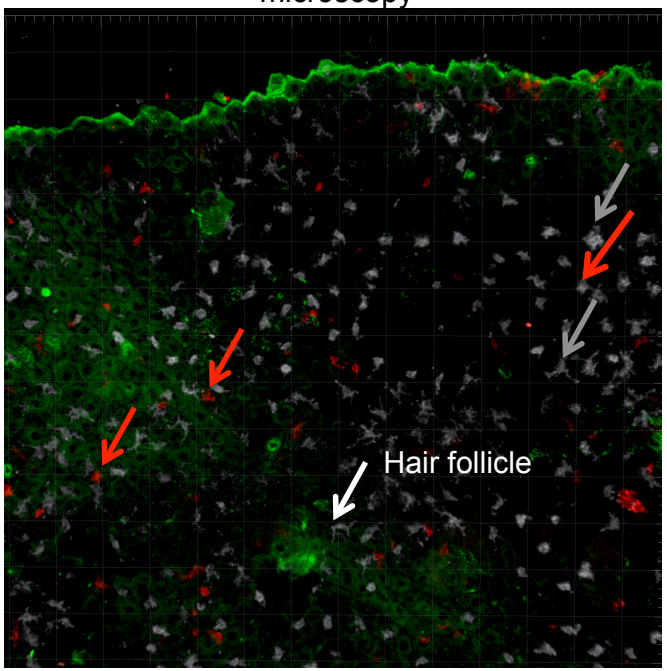
Healed lesion

allergic animal

Flare-up reaction



Epidermal sheet, Confocal microscopy



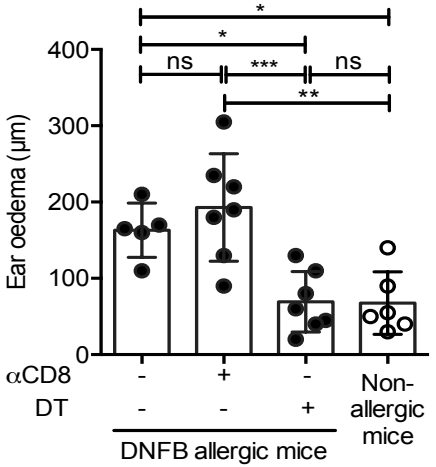
Skin edge

CD8+ T cells

Ag = DNP moities

DETC

Acute depletion of CD8+Trm abrogates flares



Injection of diphteria toxin or anti-CD8+ mAbs
IDTR transgenic animals

Main effectors? NK cells

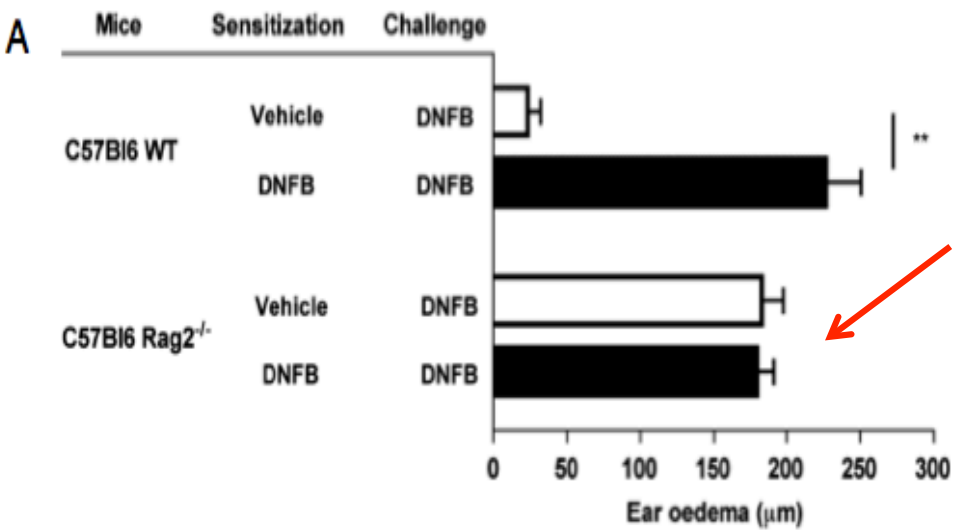
- **NK cells are far less important than CD8+ CTLs for eczema**

European Journal of Immunology

Natural killer cells and T cells induce different types of skin reactions during recall responses to haptens

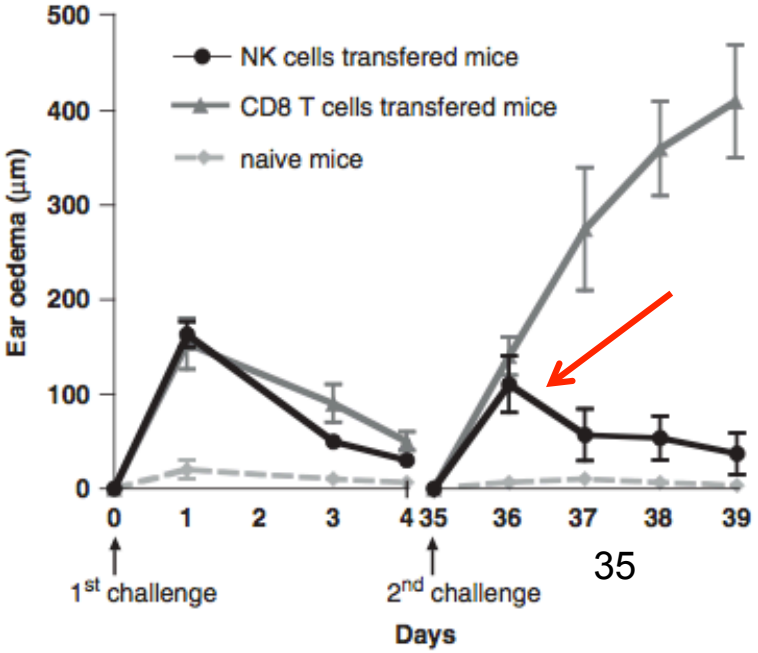
Paul Rouzaire[1,2,3], Carmelo Luci[4], Elisabeth Blasco[1,2,3], Jacques Bienvenu[1,2,3], Thierry Walzer[1,2], Jean-François Nicolas[1,2,5] and Ana Hennino[1,2]

No CHS response in T cell-deficient strains

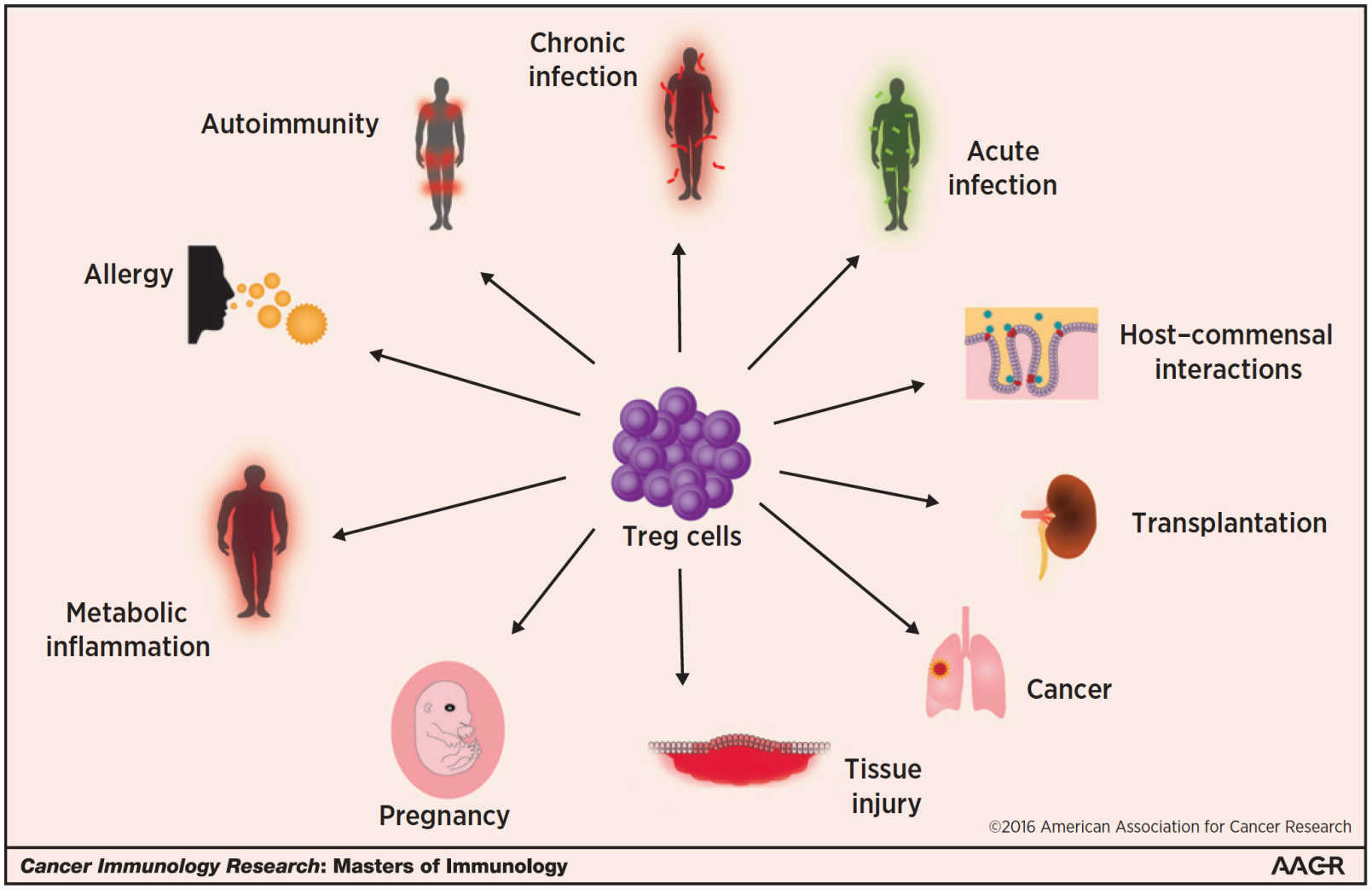


Paulst S. Nat Immunol 2011

NK cells confer CHS and recall responses, when extracted from liver and transferred into recipient animals
-> NK cell « memory »



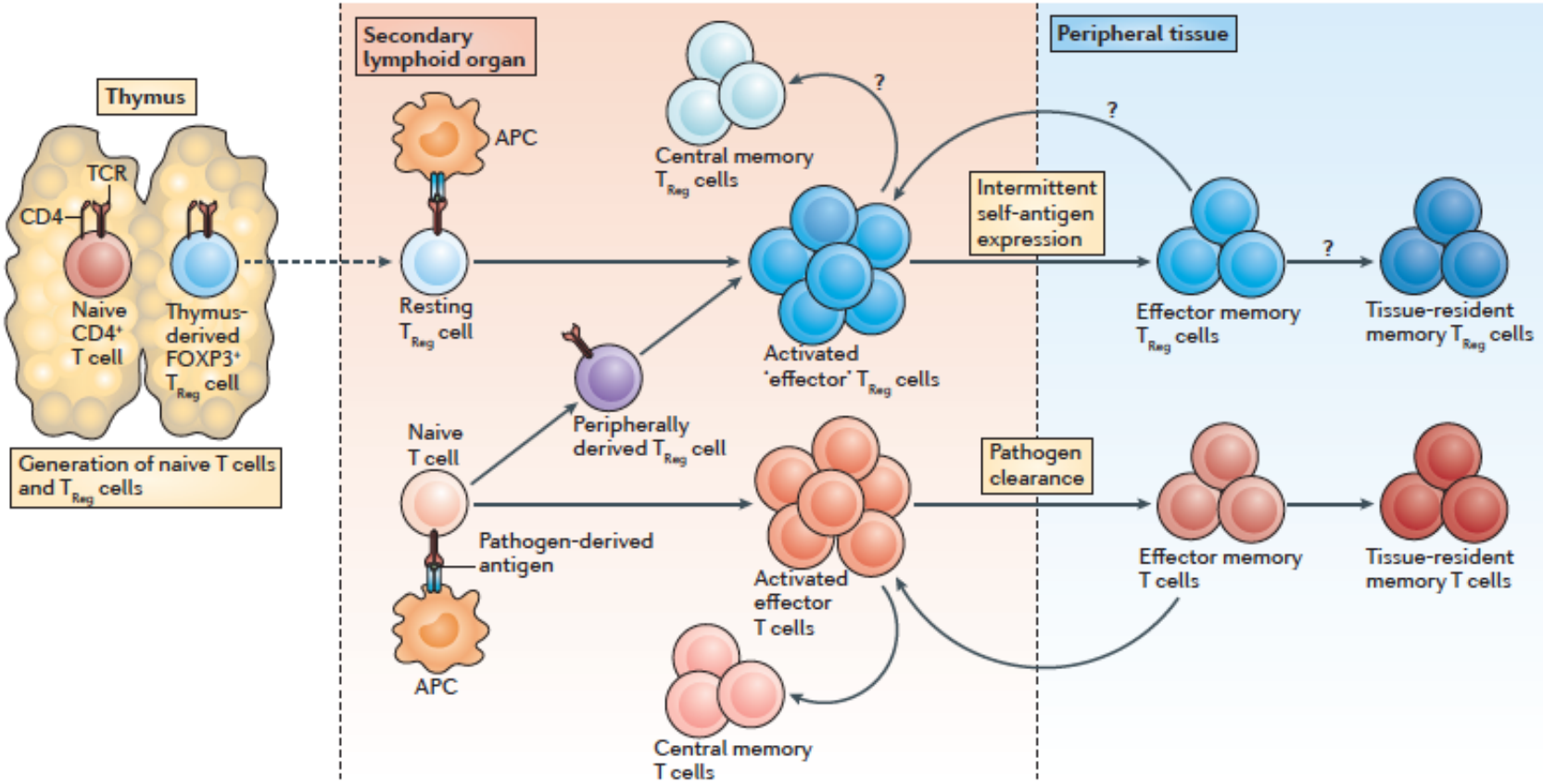
Les lymphocytes T régulateurs FoxP3+



Plitas et al. AACR Journal 2016

Les lymphocytes T régulateurs FoxP3+

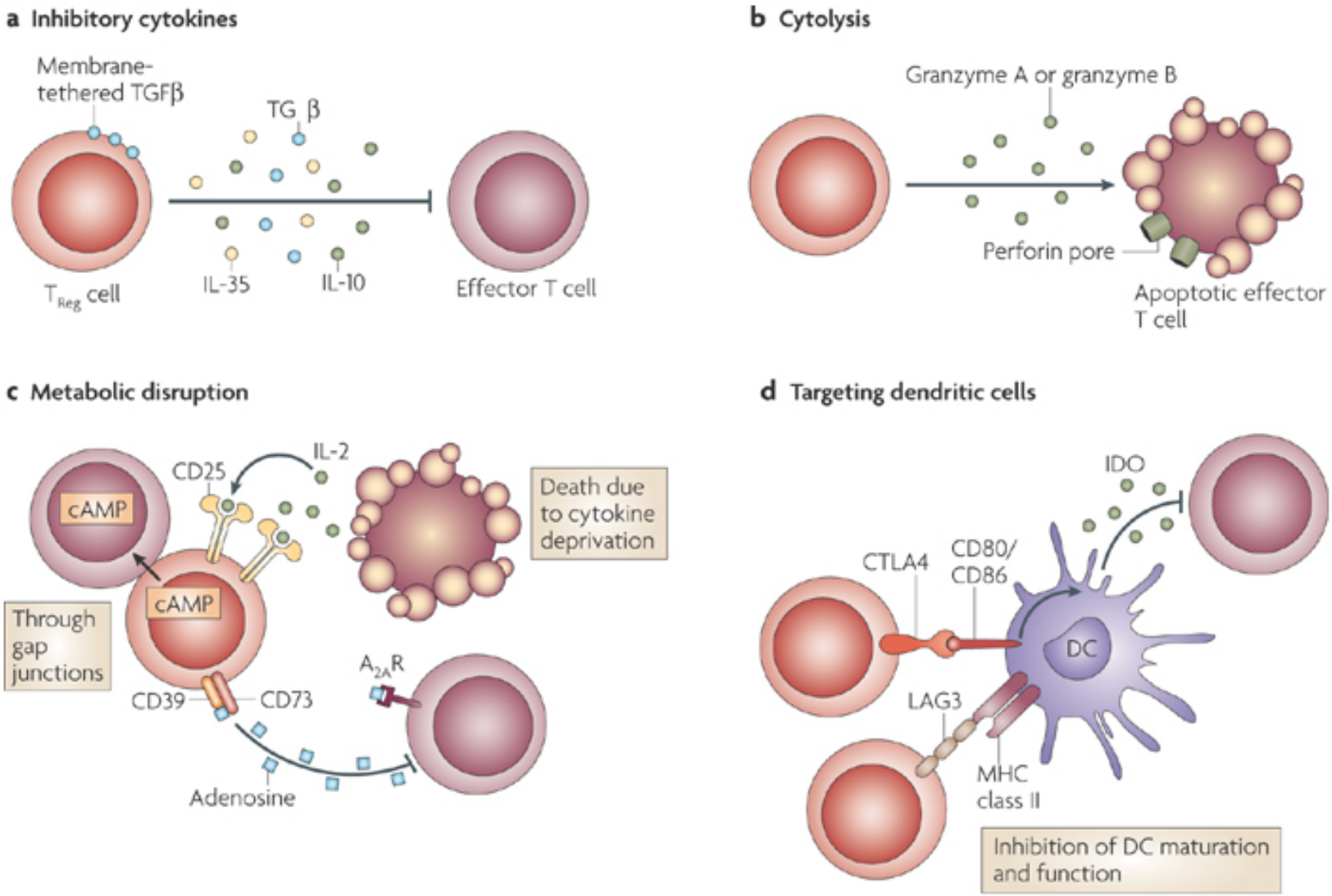
Ontogeny: Life Cycle of Regulatory and Conventional T cells



Rosenblum Ann Rev Immunol 2016

Les lymphocytes T régulateurs FoxP3+

Suppressive mechanisms used by Tregs



Vignali et al. Nature Reviews Immunology 2008

Main regulatory cells? FoxP3+Tregs

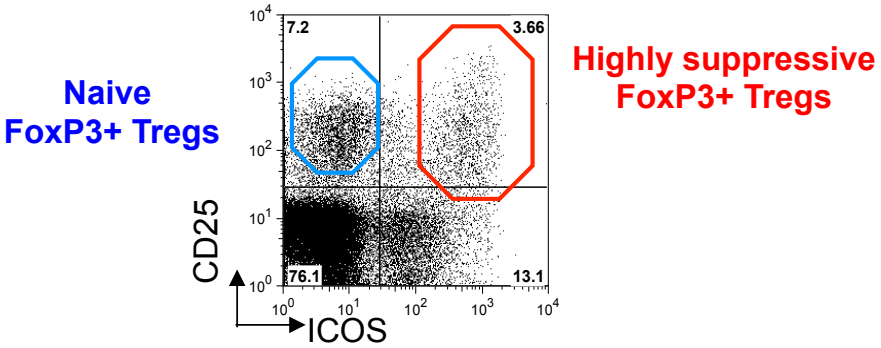
- **Multifunctional FoxP3+ICOS+ regulatory T cells control CTL-induced skin inflammation**

Inducible costimulator (ICOS) is a marker for highly suppressive antigen-specific T cells sharing features of T_H17/T_H1 and regulatory T cells

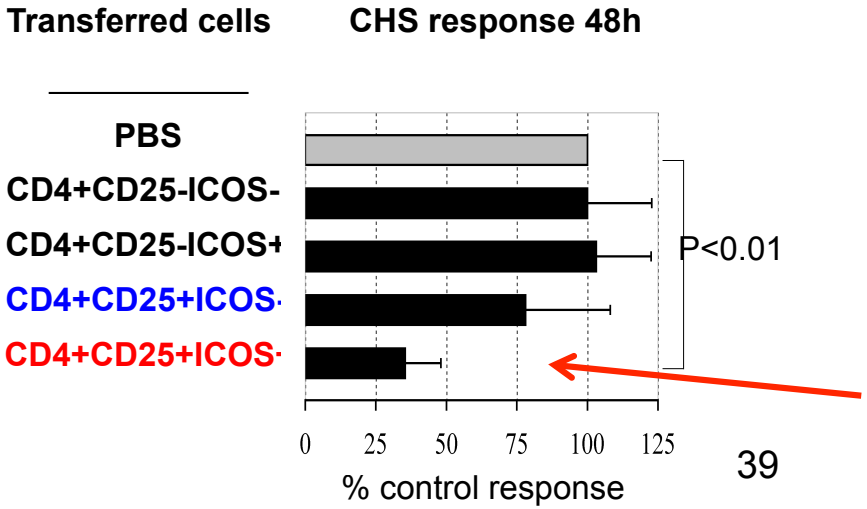
Marc Vocanson, PhD,[a,b,c] Aurore Rozieres, PhD,[a,b,c] Anca Hennino, PhD,[b,c] Gaelle Poyet, MSc,[a,b,c] Vincent Gaillard, BSc,[a,b,c] Sarah Renaudineau, MSc,[b,c] Amine Achachi, PhD,[b,c] Josette Benetiere, BSc,[a,b,c] Dominique Kaiserlian, PhD,[b,c] Bertrand Dubois, PhD,[b,c] and Jean-François Nicolas, MD, PhD[a,b,c,d] *Lyon, France*

J ALLERGY CLIN IMMUNOL
VOLUME 126, NUMBER 2

Activation of CD4+CD25+FoxP3+ICOS+ Tregs in the draining lymph nodes of hapten-sensitized mice



Transfer of FoxP3+ICOS+ Tregs prevents the priming of CD8+ CTLs and the developement of skin inflammation in an antigen-dependant manner



De nombreux lymphocytes régulateurs

Tregs FoxP3+ (CD25+)

nTregs — *CTLA-4/LAG-3/AMPc / IL-10/TGF-β/IL-35/ adénosine / cytotoxicité / privation IL-2*

Thymus

Ag du soi

pTregs ou iTreg FoxP3 — *CTLA-4/LAG-3/AMPc / IL-10/TGF-β/IL-35/ adénosine / cytotoxicité / privation IL-2*

Périphérie - Voie orale
Induit in vitro

Ag exogène

Tregs FoxP3- (CD25neg/low)

iTregs Tr1 — IL-10

Périphérie - Tolérance

Ag exogène

iTregs Th3 — *TGF-β*

Voie orale

Ag exogène

LTh1 — Producteurs IFN-γ/IL-10

IL-10

Périphérie - Infection

Ag exogène

LT CD4+ →

LT CD8+ →

FoxP3+ *thymus*

Tr1-like *périphérie*

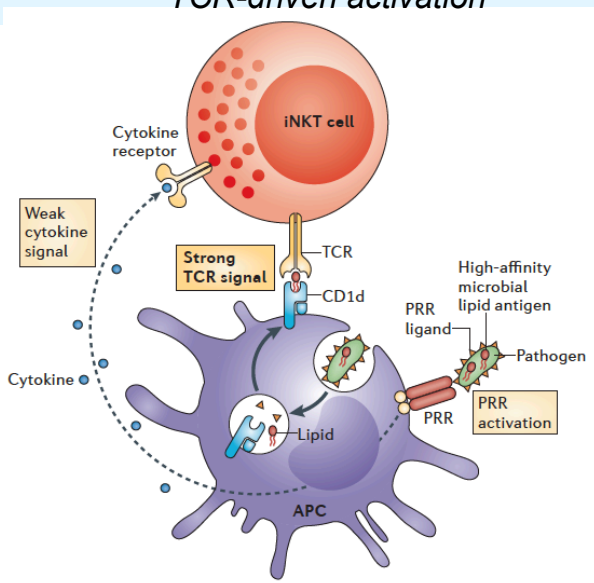
LT CD4-/CD8- →

Cellules NKT →

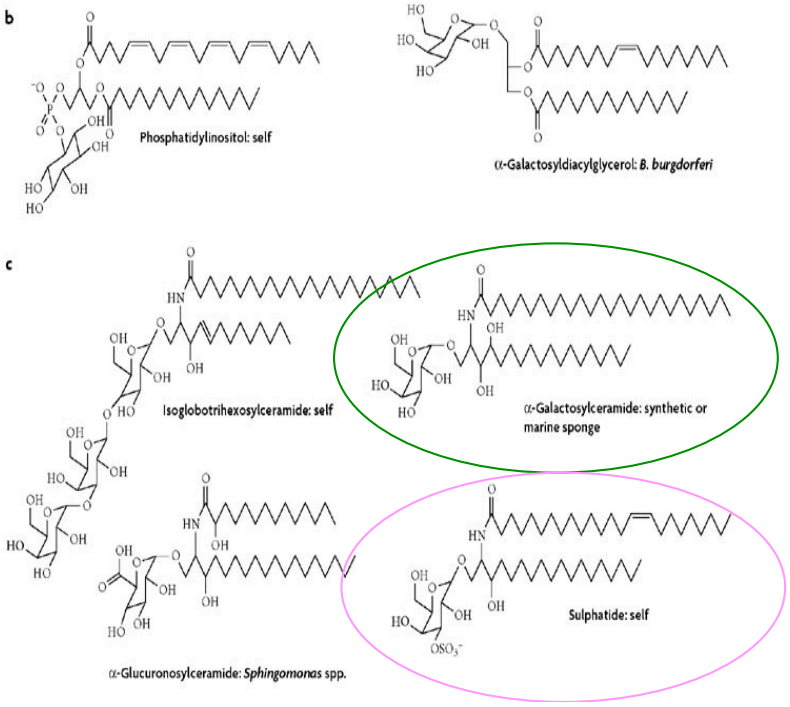
thymus

Les lymphocytes non conventionnels : les cellules NKTs

TCR-driven activation



Main recognized lipids



Main features

- 2 groups of NKT cells:
  - ✓ invariant NKT cells (iNKT cells) = TCR Vα24Jα18 and mainly Vβ11
  - ✓ non-invariant NKT cells (oligoclonal)
- iNKT predominant in mice, few in humans
- NKT cells promote immunity against cancers and microbes but suppress autoimmunity
- Functional versatility → different subsets (NKT1, NKT2, NK17, NKT_{FH}…)
- iNKT cells respond to self and microbial lipids similar to the glycosphingolipid α-GalCer
- Non-invariant NKT cells respond to lipids similar to sulfatide
- CD1d-restriction

From Brennan et al. Nat Rev Immunol 2013

Other regulatory cells? iNKT cells

- **iNKT cells are non-redondant downregulators of CTL-mediated CHS responses**

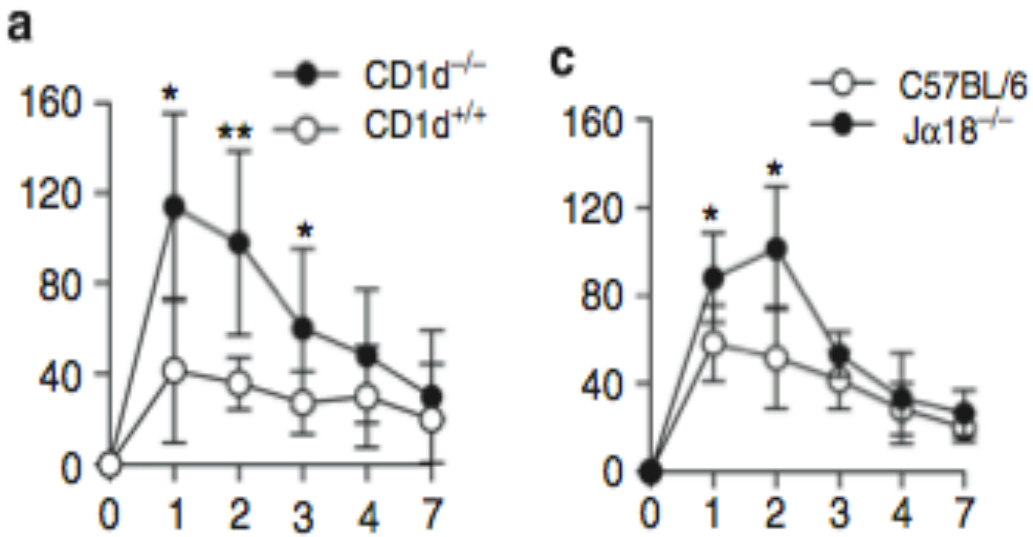
Invariant NKT Cells Suppress CD8$^+$ T-Cell–Mediated Allergic Contact Dermatitis Independently of Regulatory CD4$^+$ T Cells

Anne Goubier[1,2,3,6], Marc Vocanson[1,2,3,6], Claire Macari[1,2,3], Gaelle Poyet[1,2,3], André Herbelin[4,5], Jean- François Nicolas[1,2,3], Bertrand Dubois[1,2,3,6] and Dominique Kaiserlian[1,2,3,6]

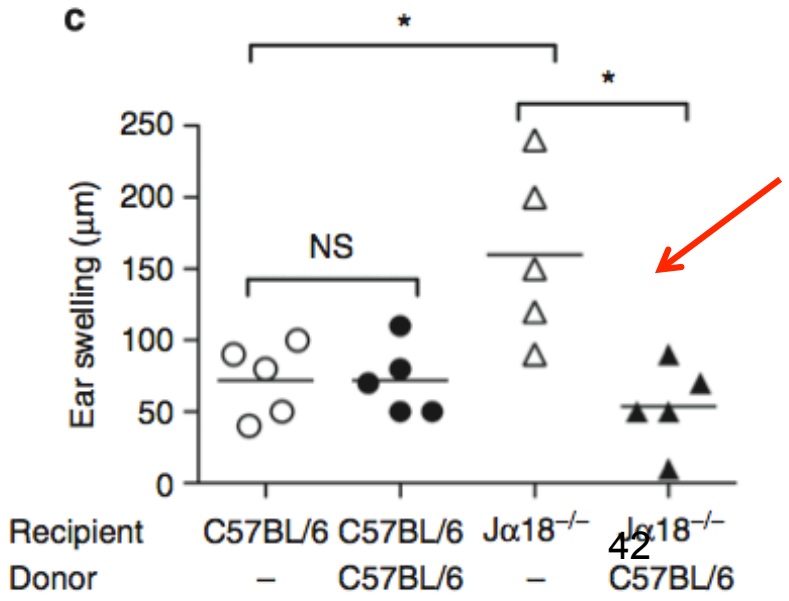
Journal of Investigative Dermatology (2013) **133,** 980–987; doi:10.1038/jid.2012.404; published online 29 November 2012

Other studies argues against the regulatory functions of iNKT cells and suggest stimulatory functions

Decreased CHS to DNFB response in NKT deficient mice (B6)



Adoptive transfer of iNKT in Ja18-/- mice normalises CHS response



Other regulatory cells? B cell subsets

- Other regulatory cells (peritoneal B-1a cells) participate to the resolution of skin inflammation

THE JOURNAL OF IMMUNOLOGY

This information is current as of June 24, 2014.

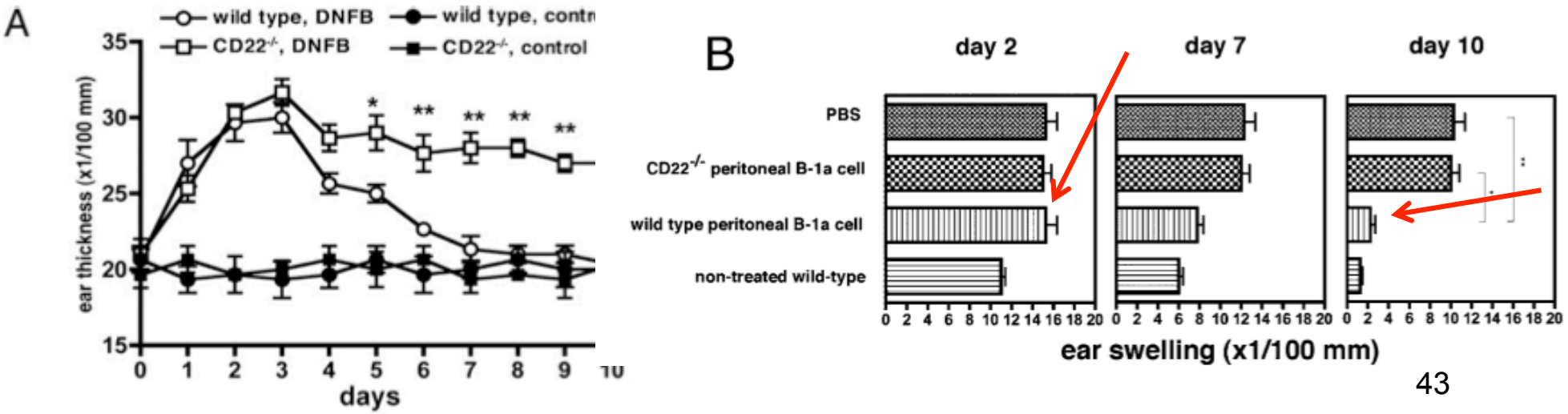
CD22 Expression Mediates the Regulatory Functions of Peritoneal B-1a Cells during the Remission Phase of Contact Hypersensitivity Reactions

Hiroko Nakashima, Yasuhito Hamaguchi, Rei Watanabe, Nobuko Ishiura, Yoshihiro Kuwano, Hitoshi Okochi, Yoshimasa Takahashi, Kunihiko Tamaki, Shinichi Sato, Thomas F. Tedder and Manabu Fujimoto

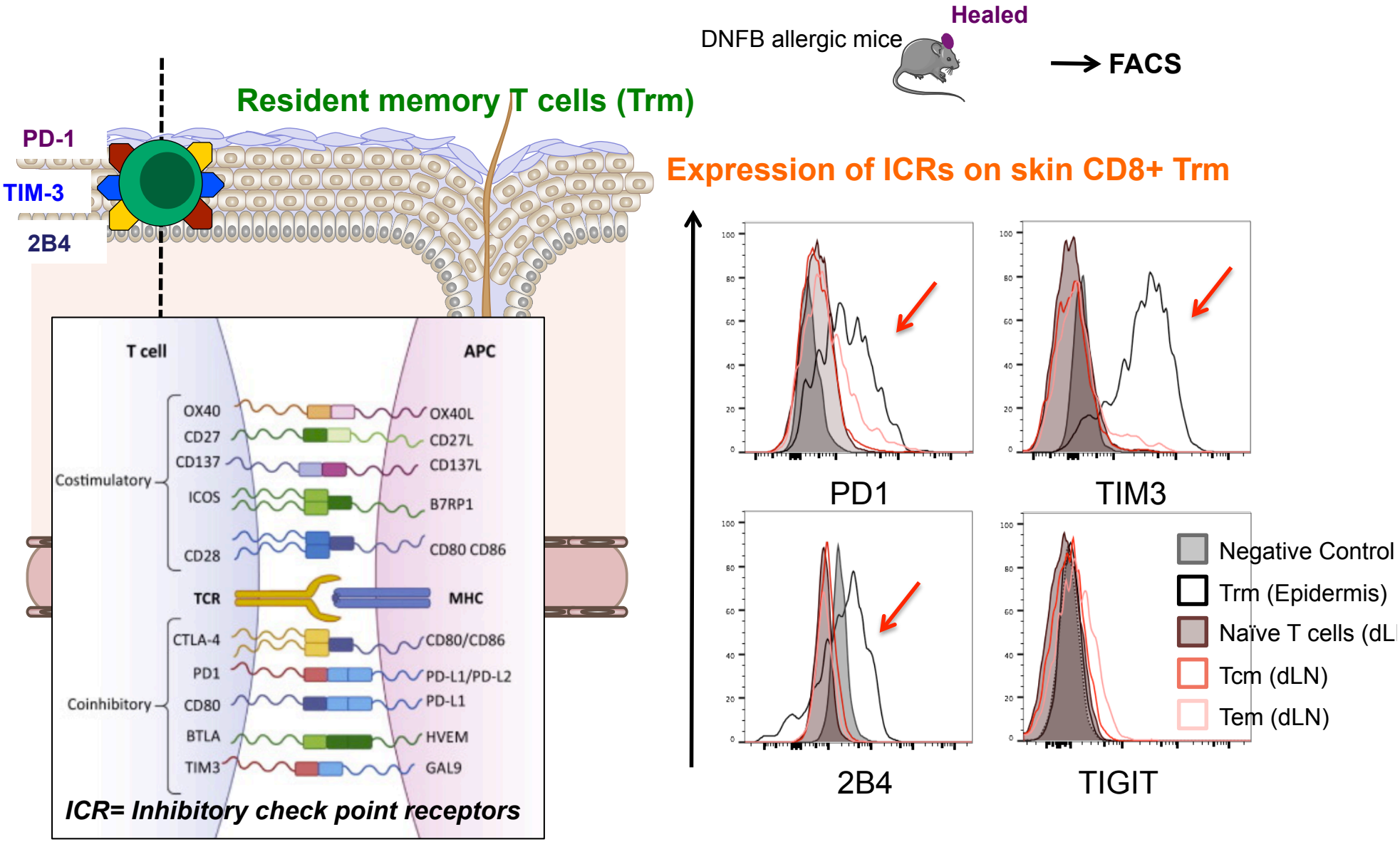
J Immunol 2010; 184:4637-4645; Prepublished online 24 March 2010;
doi: 10.4049/jimmunol.0901719
http://www.jimmunol.org/content/184/9/4637

Absence of CHS resolution in CD22-/- animals

Adoptive transfer of B1-a cell promotes the resolution of skin inflammation in CD22-/- animals



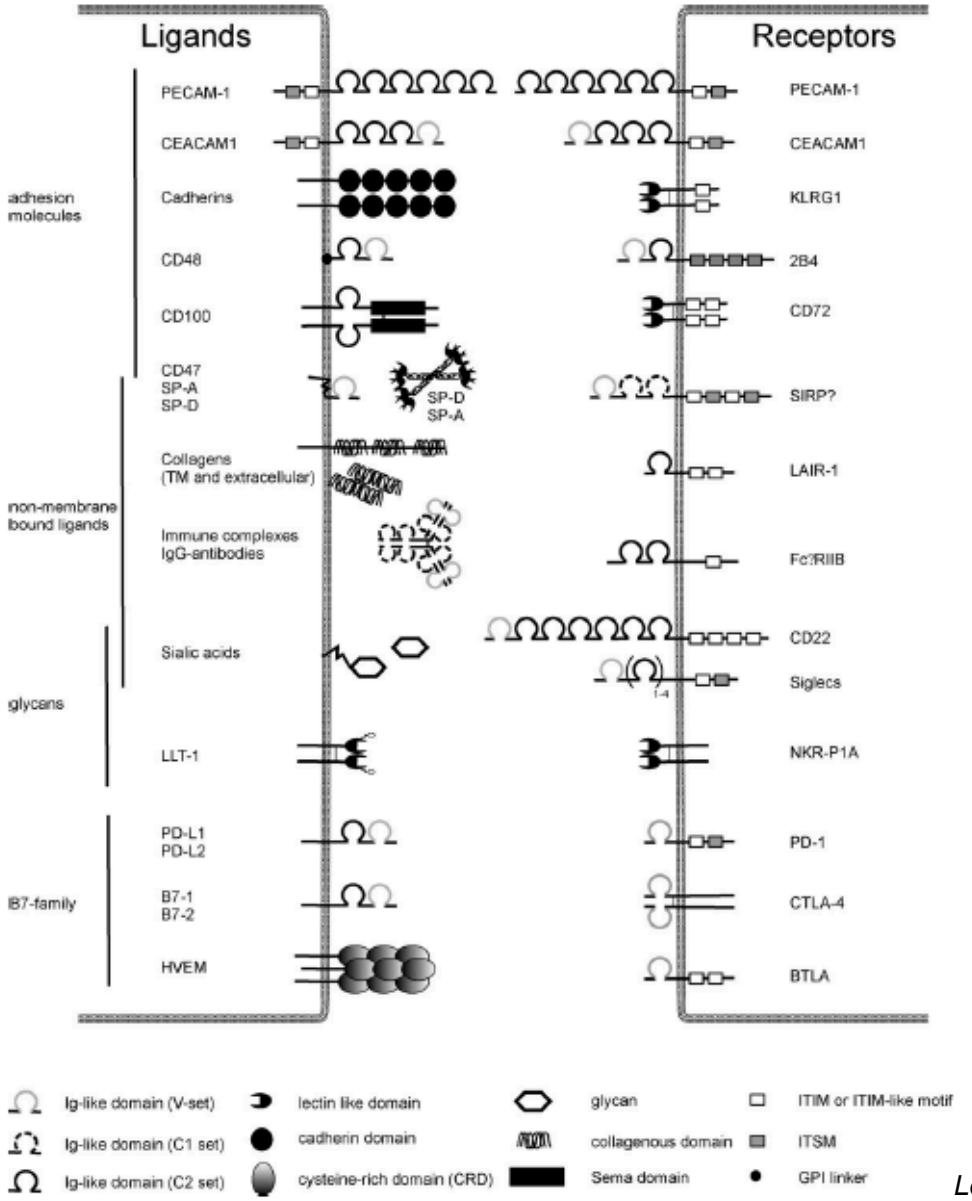
Les mécanismes de régulation intrinsèques:
Les récepteurs inhibiteurs



- **Certain ICRs are expressed on skin CD8+ Trm**

but not on circulating memory T cells→ they limited recurrences & exacerbations

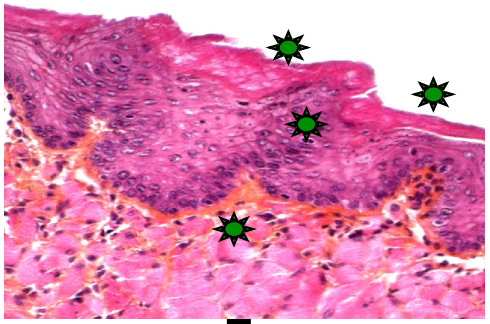
D’autres mécanismes de régulation par le tissu?

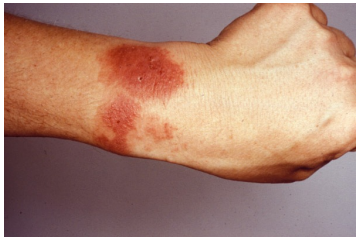


Lebbink et al. Mol Immunol 2007

Eczéma allergique de contact : les facteurs de risques

Ignorance?





Sensibilisation

Eczéma

Tolérance

-> la nature de l'antigène = "le danger"
-> les conditions d'exposition (dose, fréquence, durée, route)
-> le polymorphisme génétique (barrière cutanée, enzymes de détoxification…), âge, sexe
-> l'environnement (maladie sous-jacente, stress, pollution…)

Les facteurs génétiques

5. Studies on probably functionally relevant polymorphisms in contact allergic patients from ou
), from more recent studies (columns I–IV, rows 1, 5, 6, and 9), and replication studies (column V

II	III
Polymorphisms	Results
Filaggrin null mutations (combined	Results inconclusive:

Table 3. Difference in sensitization rates between children of sensitized and non-sensitized parents. 'The potent allergen DNCB is probably overpowering genetic influences'; Walker et al. (21)

	Percentage of children sensitized	
Status of parents	DNCB	NDMA
Sensitized	65	51
Not sensitized	52	29
	$p < 0.10$	$p < 0.01$

DCNB, 2,4-dinitrochlorobenzene; NDMA, p-nitroso-dimethylaniline.

Cytokines: *ILB*−511, *ILB* +3953, *ILRA*, *IL6*−174, *TNFA*−238, *TNFA*−308	*TNFA*−308 (G→A): increased (in polysensitized individuals) *TNFA*−308 G/G and *ILRA* polymorphism (77) increased in Turkish patients ($n = 50$)
Cytokine: *IL-16*	*IL16*-295 (T→C) increased (in polysensitized individuals)
Cytokine *IL-4*	No difference between chromate allergics and controls with regard to *IL4*-590 polymorphism

Schnuch A, Contact Dermatitis 2010

Le pouvoir sensibilisant des haptènes varient en fonction de la nature des molécules

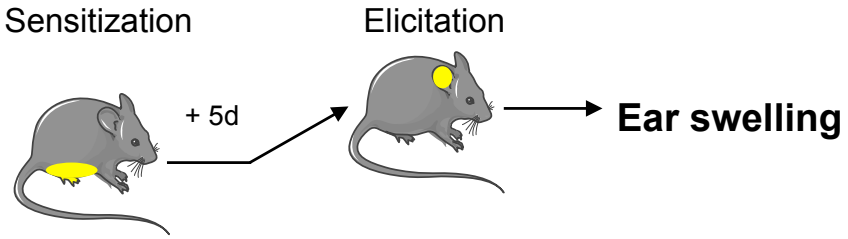
Chimique	Secteur	Pouvoir sensibilisant
Oxazolone	Chimie	Extreme
2,4-Dinitrofluorobenzene	Chimie	Extreme
2,4-Dinitrochlorobenzene	Chimie	Extreme
Glutaraldehyde	Conservateur, antiseptique	Fort
Formaldehyde	Cosmétique, Colorant	Fort
Cinnamaldehyde	Parfum, arôme	Modéré
Hexyl cinnamaldehyde	Cosmétique, Parfum	Modéré/Faible
Eugenol	Cosmétique, Parfum	Faible
Hydroxycitronellal	Cosmétique, Parfum	Faible
Linalool	Cosmétique	Faible
Citral	Parfum, arôme	Faible
Vanillin	Parfum, arôme	Faible
2,4-Dinitrocyanobenzene	Chimie	Faible
Amoxicilline, cyanamide, cetrimide	Médicament	Faible

Main effectors? CD8+ CTLs

Journal of Investigative Dermatology (2006) **126**, 815-820. doi:10.1038/sj.jid.5700174; published online 2 February 2006

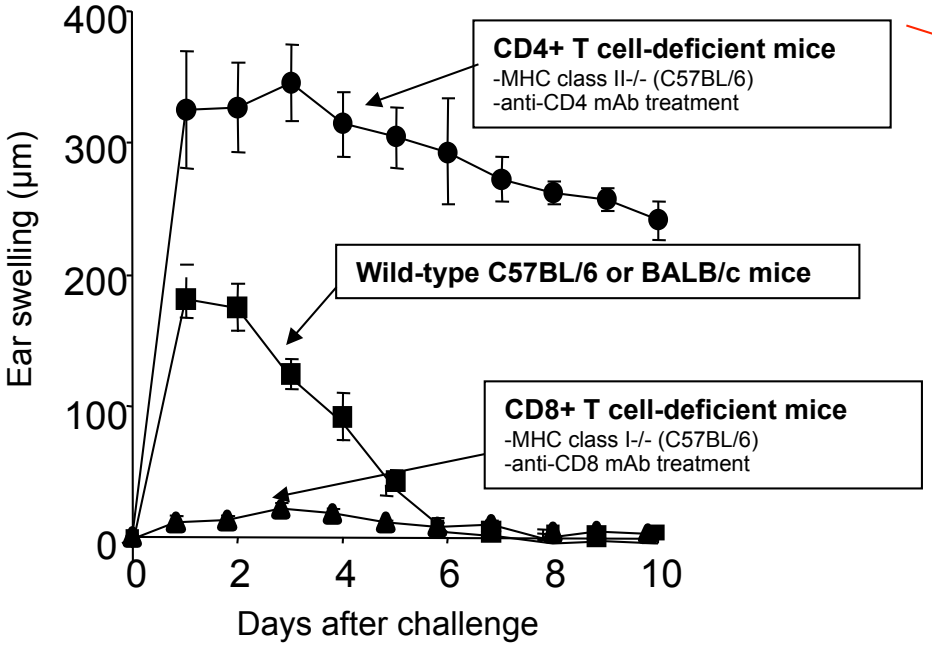
CD8+ T Cells Are Effector Cells of Contact Dermatitis to Common Skin Allergens in Mice

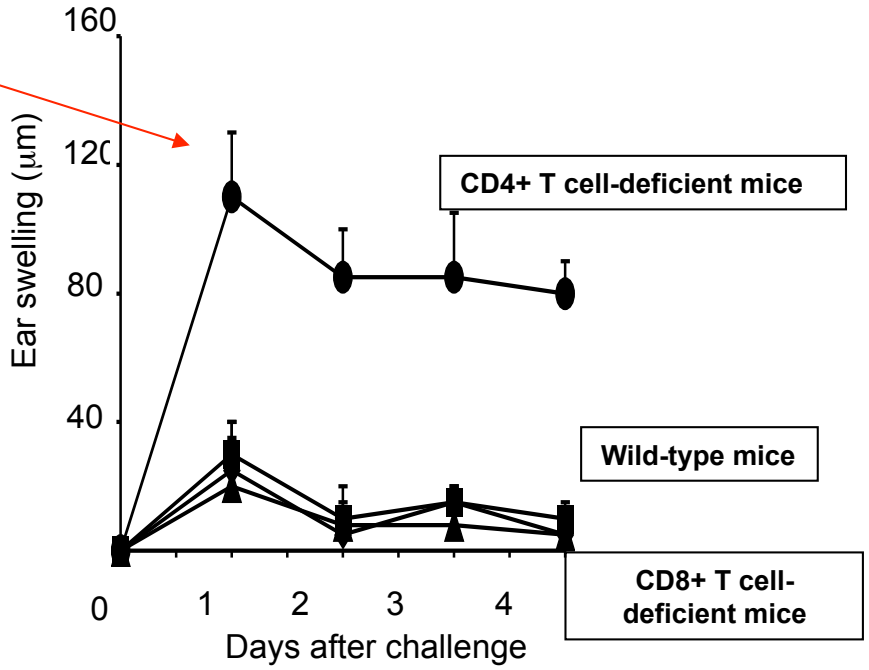
Marc Vocanson[1], Anca Hennino[1], Magalie Cluzel-Tailhardat[1], Pierre Saint-Mezard[1], Josette Benetiere[1], Cyril Chavagnac[1], Frederic Berard[1,2], Dominique Kaiserlian[3] and Jean-François Nicolas[1,2]



Strong haptens: DNFB, TNCB, OXAZOLONE…

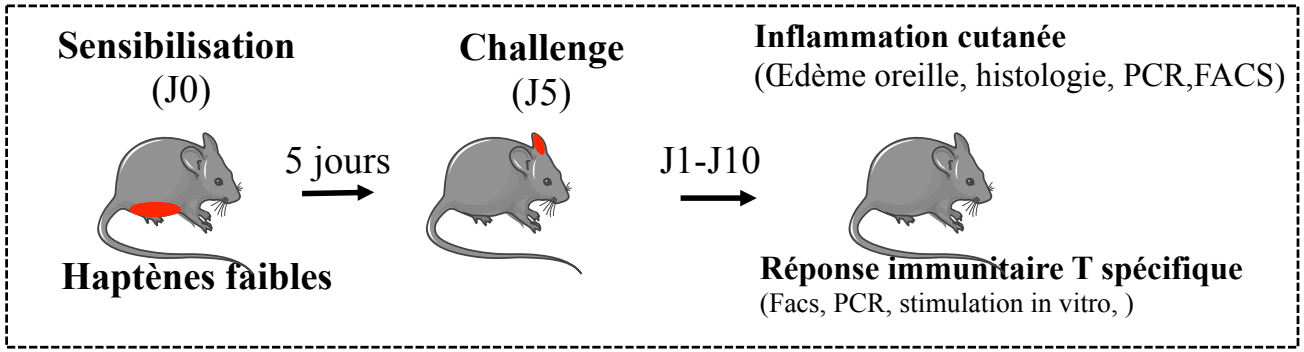
Weak haptens
→ Fragrances (Hexylcinnamaldehyde, Hydroxycitronellal, Eugenol, Dihydrocoumarin, Isoeugenol),
→ Dye (paraphenylenediamine)
→ Drugs (Amoxicillin, Rosephin, Phenytoin, Sulfasalazin)

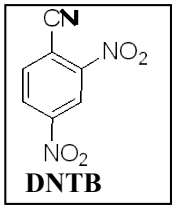


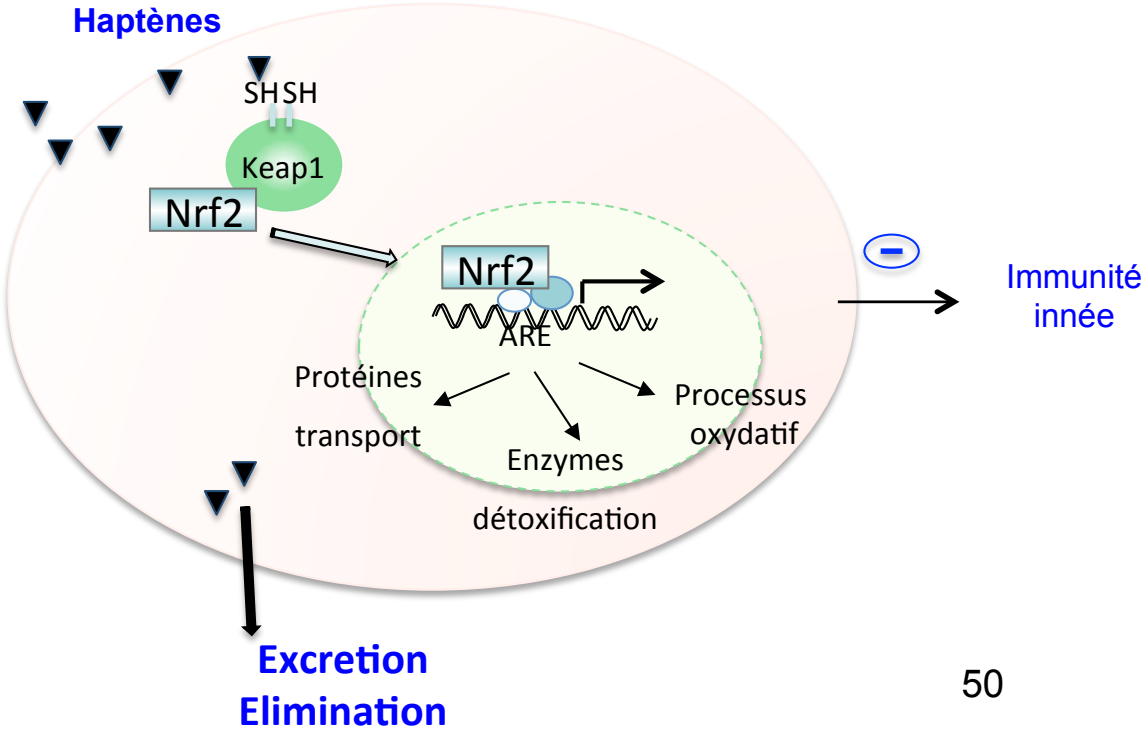


- CD8+ T cells are effector cells
- CD4+ T cells comprise regulatory T cells

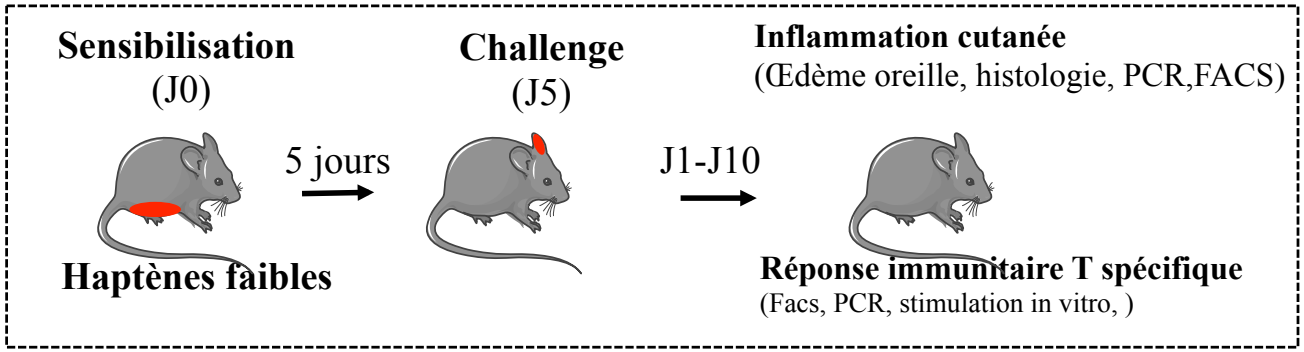
Un défaut de détoxification conduit à une rupture de tolérance vis-à-vis des haptènes faibles

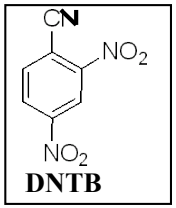


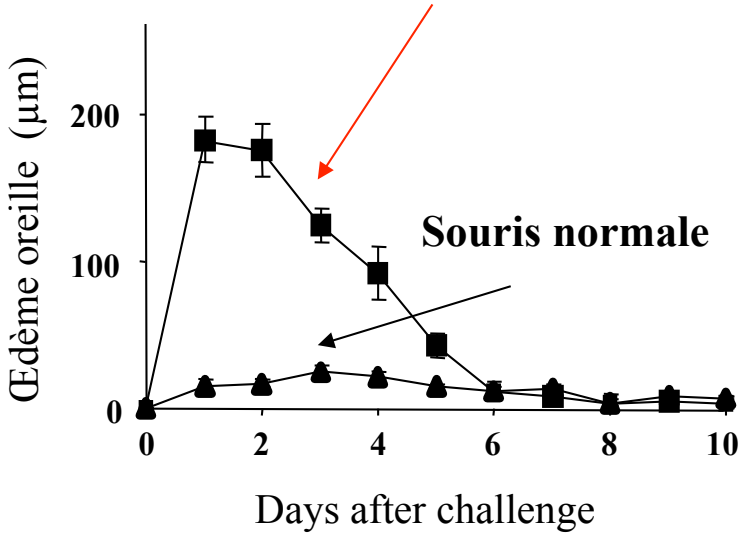


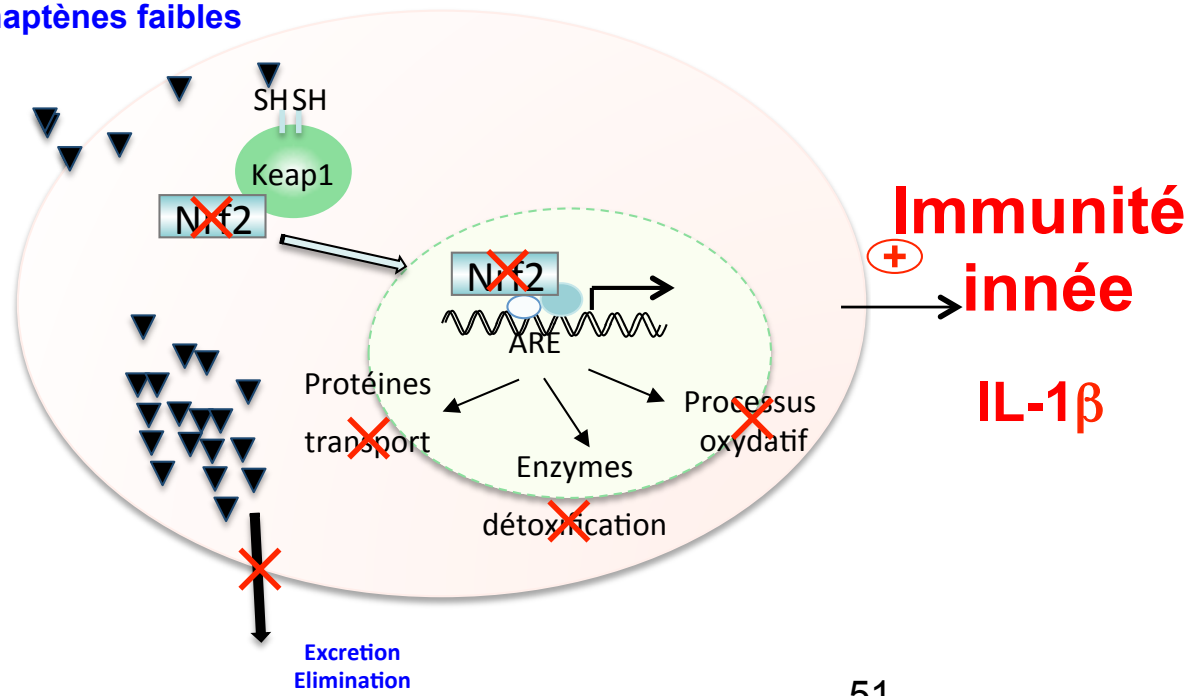


Un défaut de détoxification conduit à une rupture de tolérance vis-à-vis des haptènes faibles



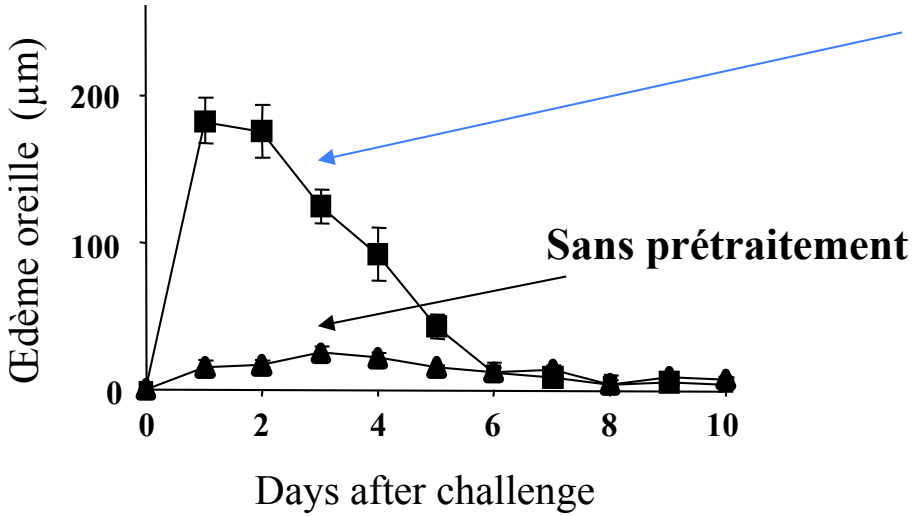






Zeina El Ali et al., Toxicol Sci, 2013
Kerdines-Romer & Vocanson et al, manuscript in preparation

L'irritation favorise la rupture de tolérance vis-à-vis des haptènes faibles

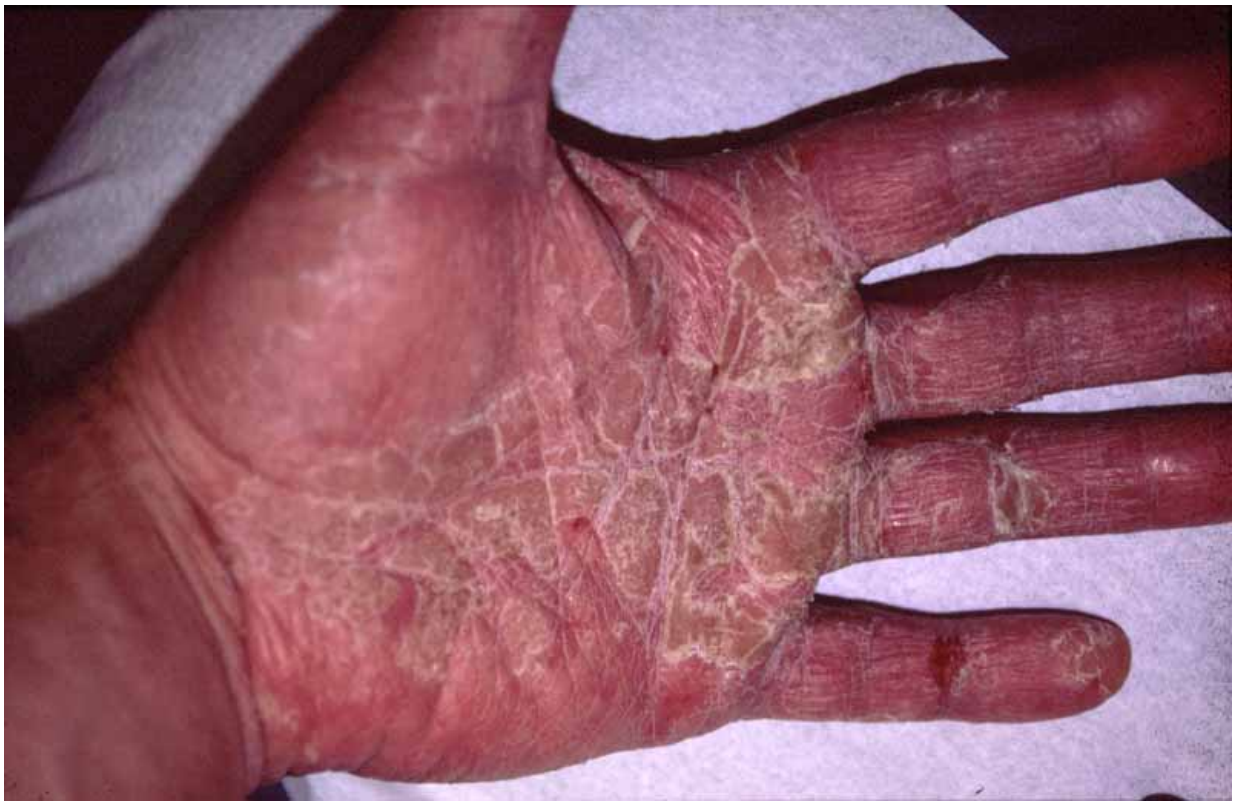


L'application d'un irritant SDS / un véhicule différent (DMF) / l'injection d'une cytokine proinflammatoire comme IL-1β avant la sensibilisation induit une réponse d'eczéma vis-à-vis d'un allergène faible

L'inverse est vrai pour un haptène fort : bloquer la production d'IL-1β prévient la sensibilisation et favorise la tolérance

Yasukawa et al., Nat Comm, 2014
Watanabe et al. JI, 2008

L’irritation fait le lit de l’allergie



Maçon de 48 ans,
eczéma de contact irritatif depuis des années,
aggravation depuis 3 mois
→ Eczéma allergique au chrome

Nosbaum et al. Eur J Dermatol 2011

Département d'Immuno-Allergologie

Département d'allergologie et d'immunologie clinique Lyon-Sud

Equipe 20 – CIRI

Unité de recherche Phase I, Lyrec- Lyon-Sud

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

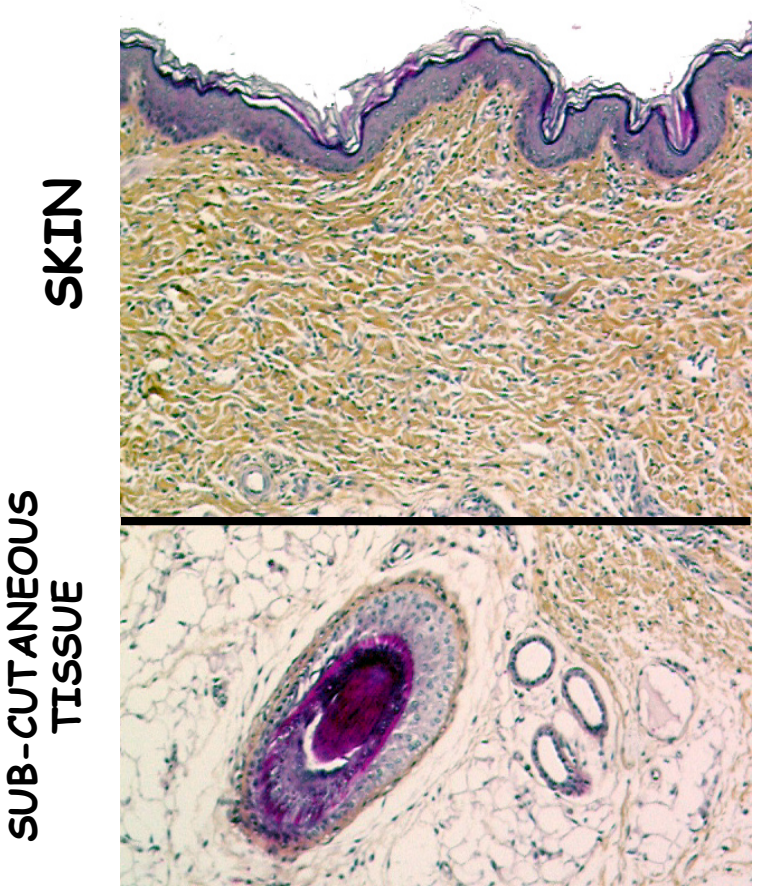
Lyon 1

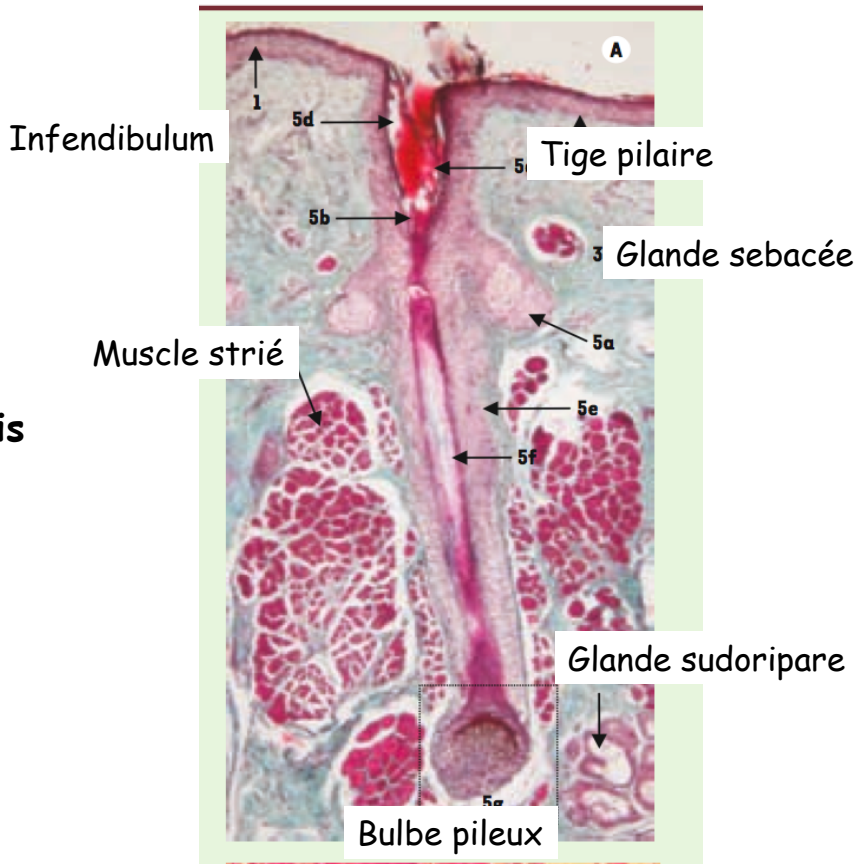
ciri Centre International de Recherche en Infectiologie

Faculté de Médecine LYON SUD

Hôpitaux de Lyon

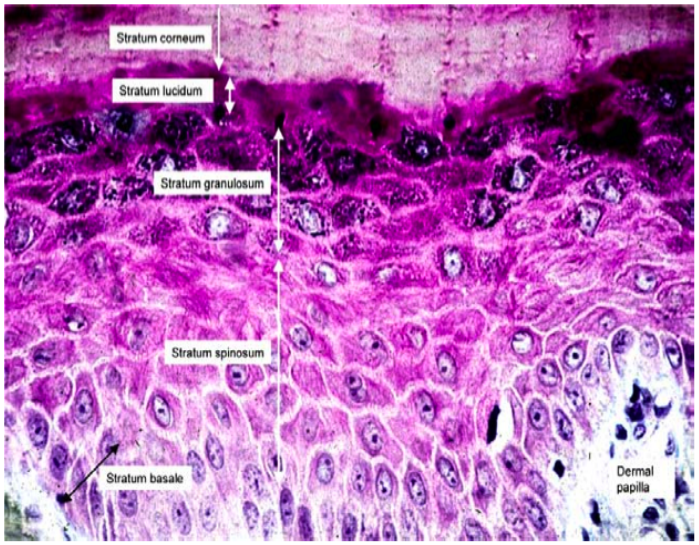
Anatomy of the skin



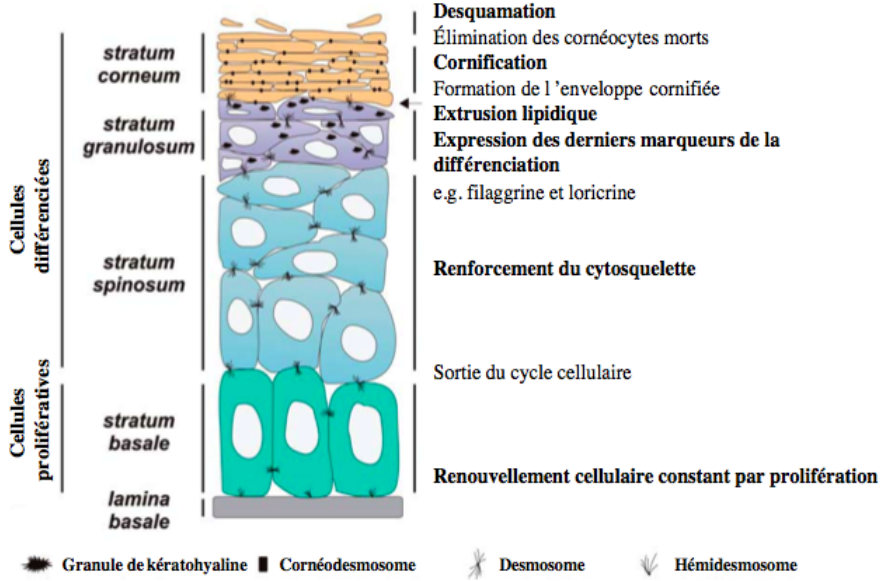


Follicule pilo-sebacé

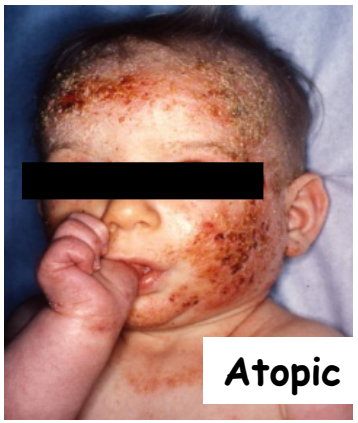
Anatomy of the epidermis



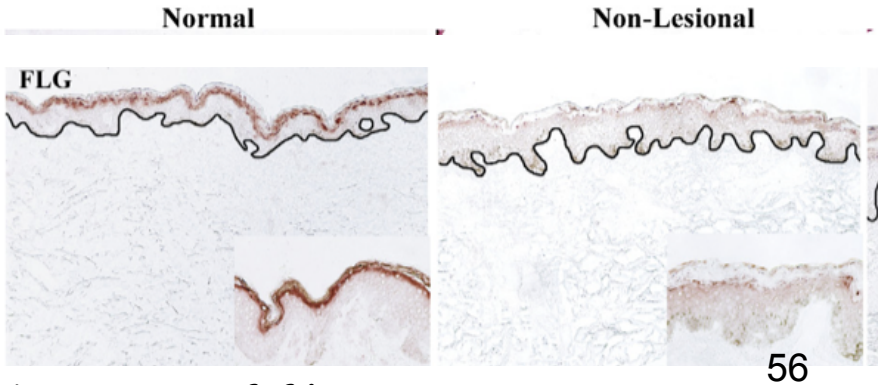
Epiderme - coloration Hematoxylline-Eosine



Différentiation épidermique - schéma

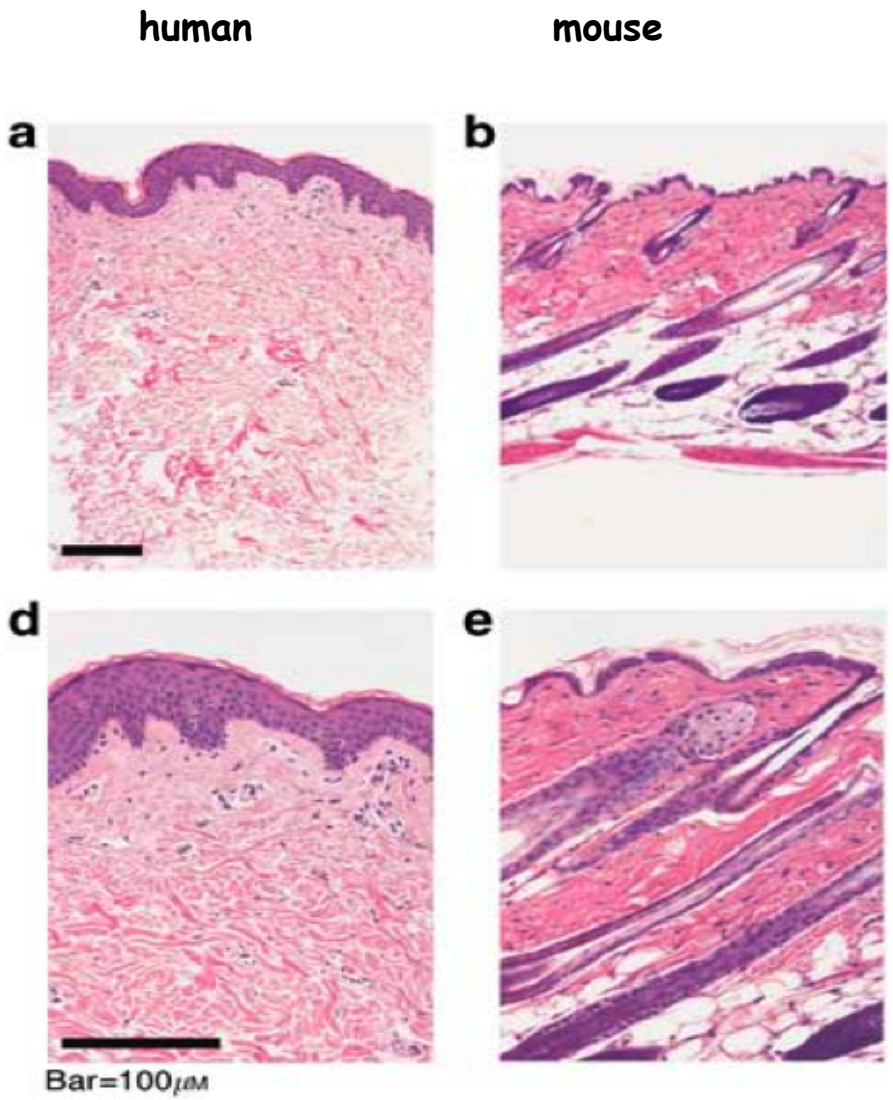


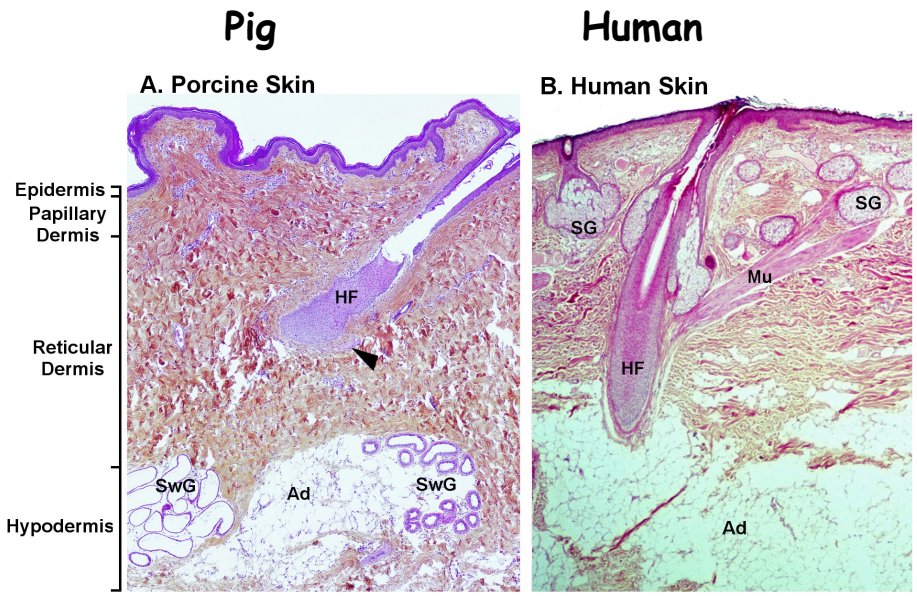
Atopic dermatitis



IHC staining of filaggrin, *Suarez-Farinas et al. JACI 2010*

Anatomy of the skin - Comparison human / mouse / Pig





Epidermis: 6-10 versus 3 layer of Keratinocytes

dermis: substantially thicker

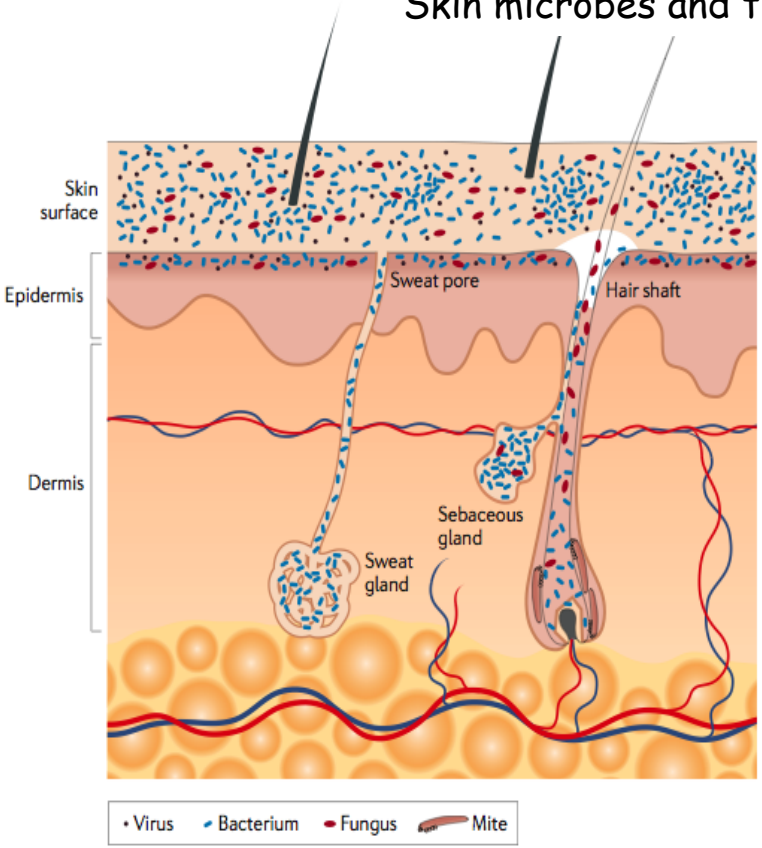
dermis: less follicles

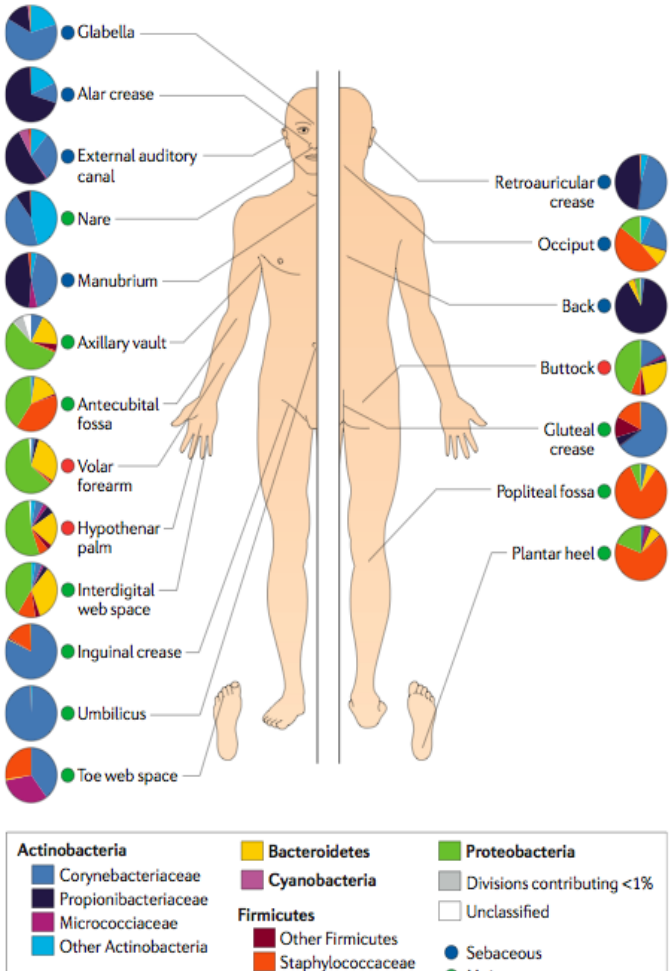
Inter-folliclar area: no rete-ridges in human

Mouse->entire muscle layer:panniculus carnosus

The skin microbiome

Skin microbes and their regional localisations





Grice et al. Nat rev microb 2011

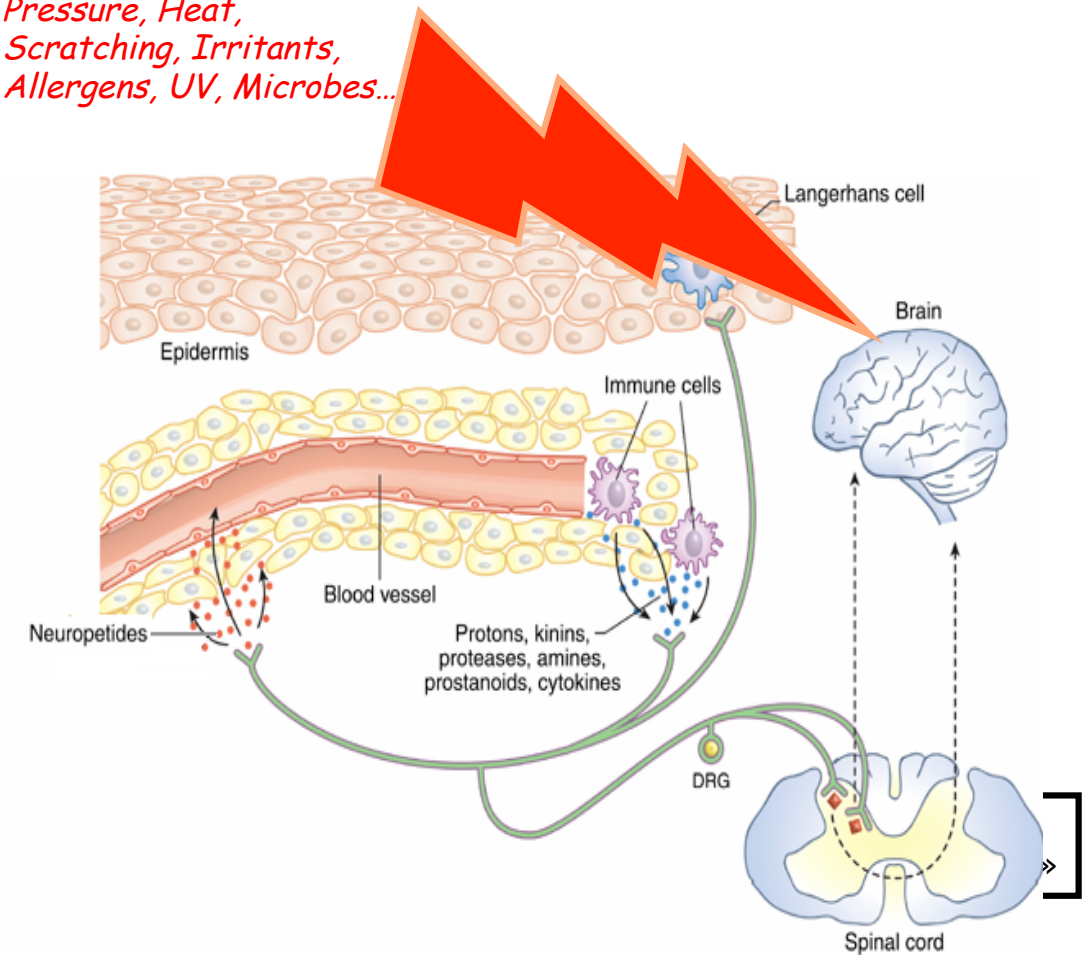
Up to 10^{12} resident bacteria/m^2

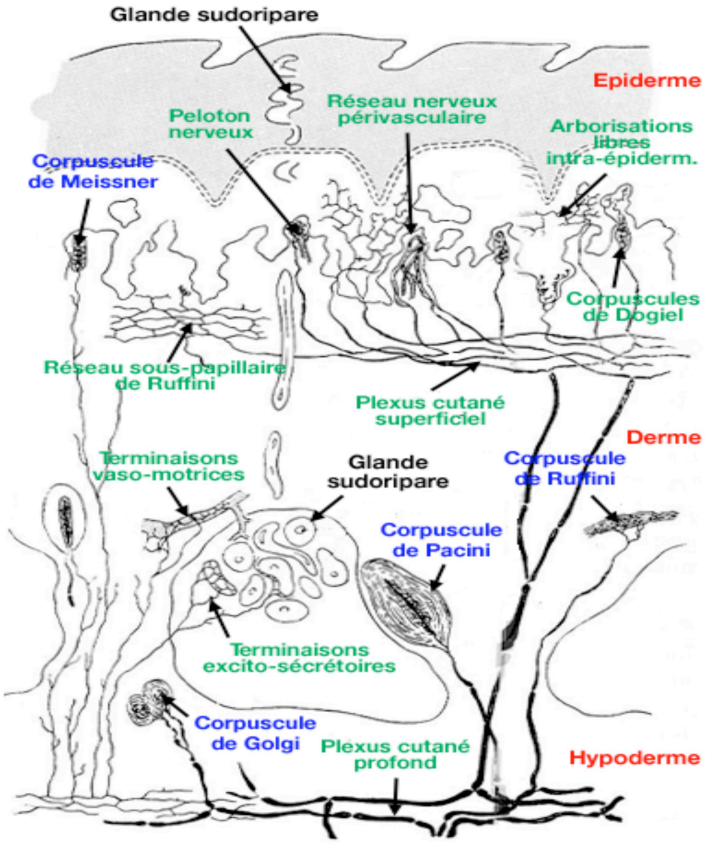
3 species particularly well-adapted to the acidic PH environment and host AMPs: *Staphylococcus, Propionibacterium, Corynebacterium*

Neurogenic connection of the skin

Pain, Pruritus, Sensorial… responses

Pressure, Heat,
Scratching, Irritants,
Allergens, UV, Microbes…





Récepteurs simples
- **-terminaisons nerveuses libres**
- **-organes terminaux encapsulés**

Mechano, thermo, chimiorecepteurs