IMMUNITE INNEE / ALLERGIE / INFLAMMATION MECANISMES GENERAUX DE LA TOLERANCE / REGULATION DE LA REPONSE IMMUNE

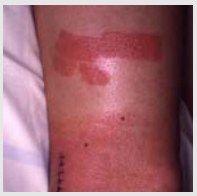
Marc VOCANSON
Jean-François NICOLAS
INSERM U1111 – CIRI
LYON - France

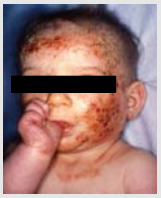
Team: IMMUNOLOGY OF SKIN ALLERGY / VACCINATION

Research activities

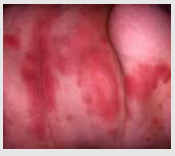
Pathophysiological research

Skin allergic diseases





Allergic contact dermatitis (ACD) Atopic dermatitis (AD)
ECZEMAS



MILD - Exanthema SEVERE – Blistering disease
DRUG ALLERGIES

Translational research

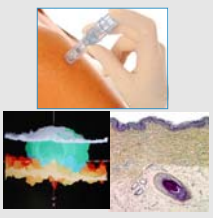
New immunological assays

Diagnosis

Prediction of allergenicity

Assessment of new therapies

Intradermal vaccination



PLAN

- La peau
- Bases immunologiques de la réponse inflammatoire cutanée
- Allergie cutanée : l'exemple de l'eczéma de contact
- Mécanismes de tolérance/régulation de la réponse immune

PLAN

- La peau
- Bases immunologiques de la réponse inflammatoire cutanée
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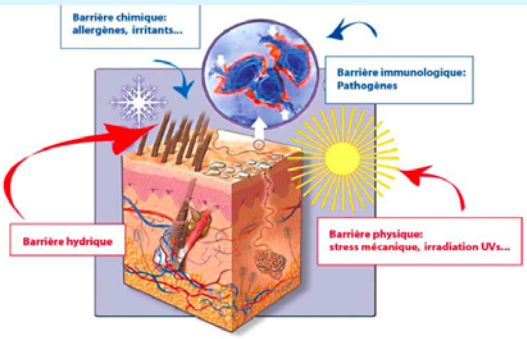
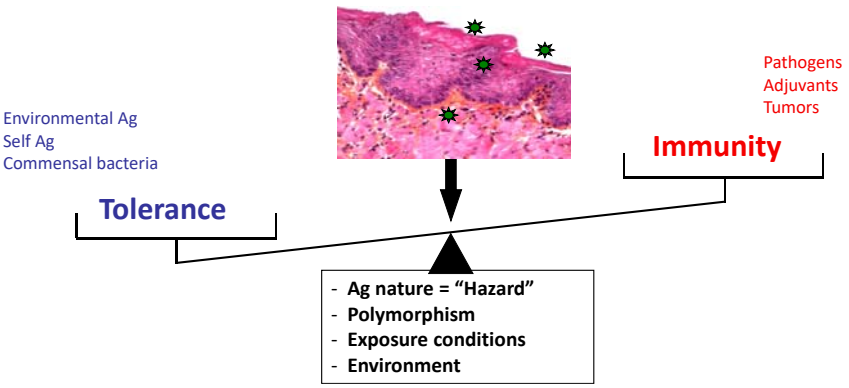
- Principes généraux / Mécanismes de tolérance/régulation de la réponse d'eczéma

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

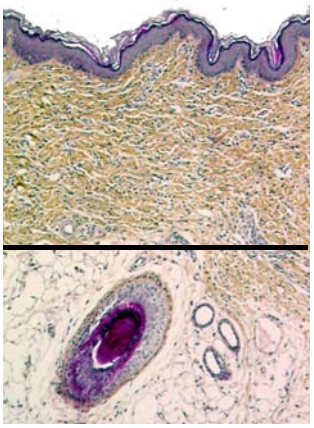


- Serves as an immuno-protective organ that actively defends deeper body tissues against infectious agents. Privileged site for vaccination
- Maintains self-tolerance, preventing allergens and inhibiting autoimmunity

Anatomy of the skin

SKIN

SUB-CUTANEOUS TISSUE

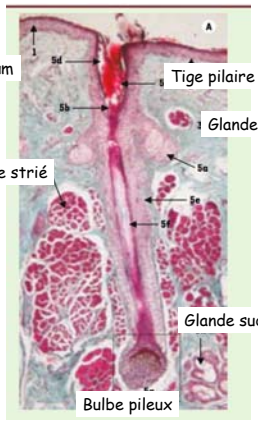


Epidermis

Papillary dermis

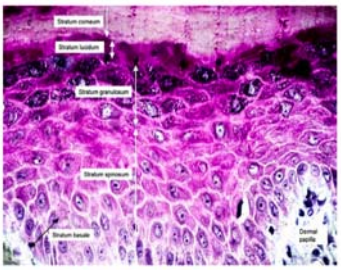
Reticular dermis

Hypodermis

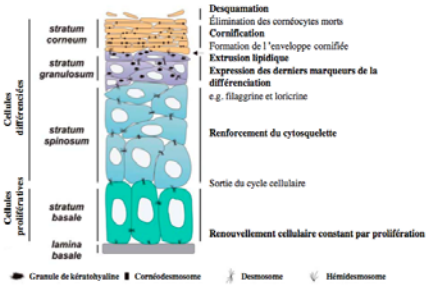


Follicule pilo-sebacé

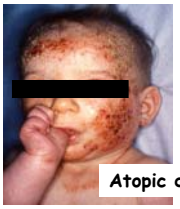
Anatomy of the epidermis



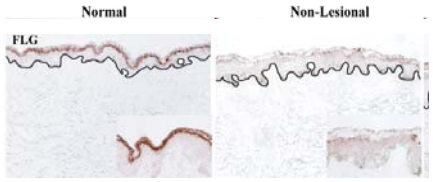
Epiderme - coloration Hematoxylline-Eosine



Différentiation épidermique - schéma

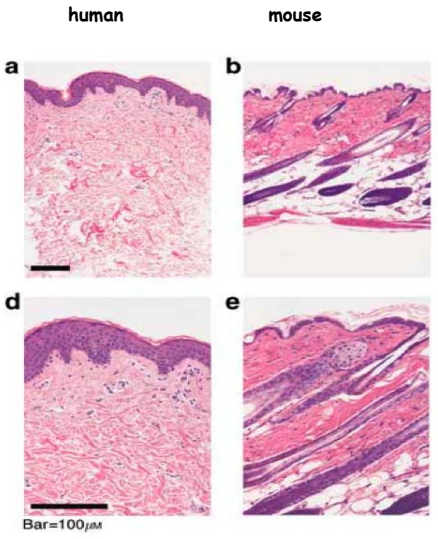


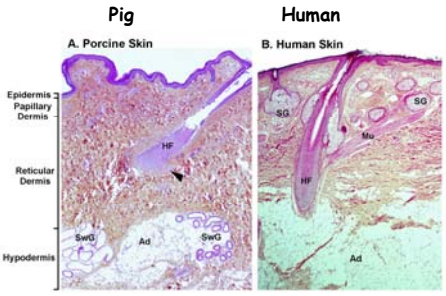
Atopic dermatitis



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

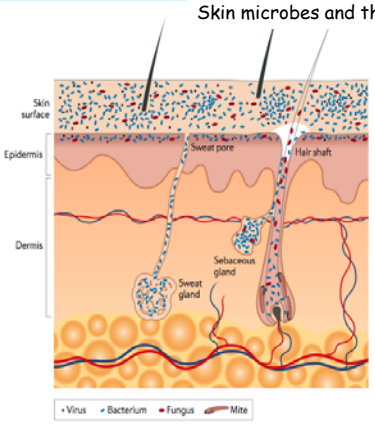
dermis: less follicles

Inter-folliclar area: no rete-ridges in human

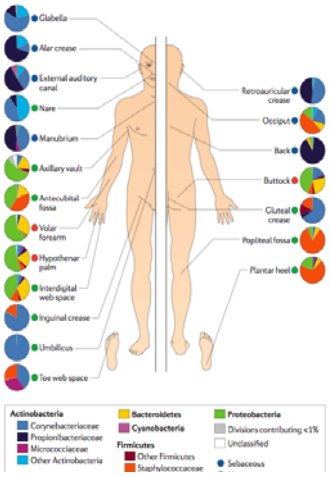
Mouse->entire muscle layer:panniculus carnosus

The skin microbiome

Skin microbes and their regional localisations



Grice et al. Nat rev microb 2011



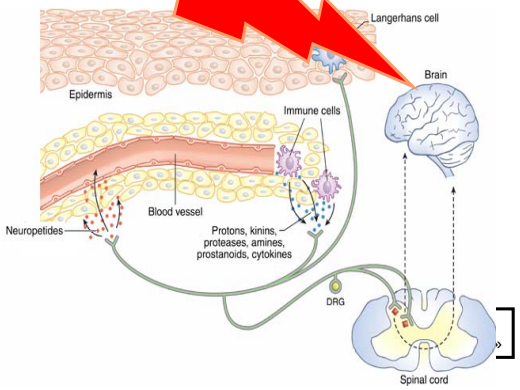
Up to 10^{12} resident bacteria/m^2

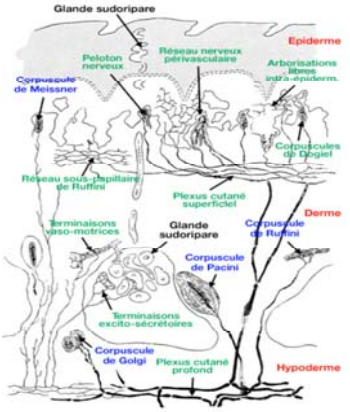
3 species particularly well-adapted to the acidic PH environment and host AMPs: *Staphylococcus, Propionibacterium, Corynebacterium*

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, chimioreceptors

The cellular effector of the skin

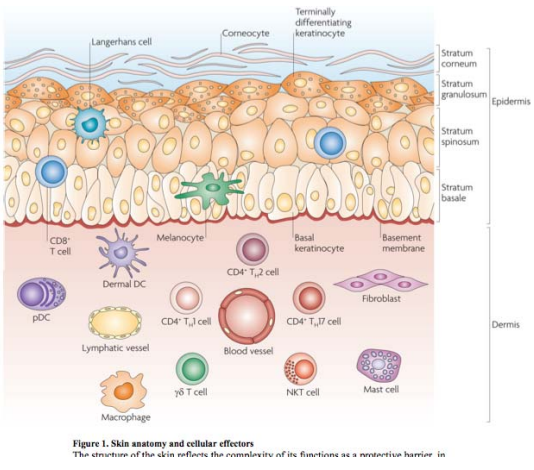
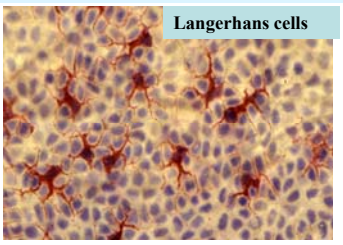
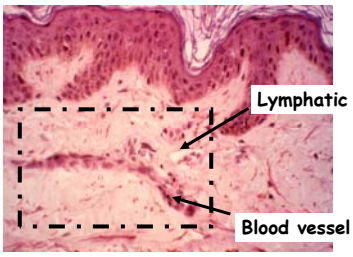


Figure 1. Skin anatomy and cellular effectors
The structure of the skin reflects the complexity of its functions as a protective barrier, in

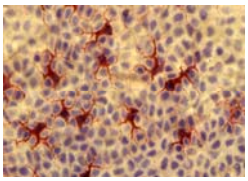




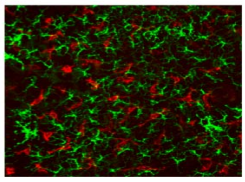
Numerous immune cells reside, traffic into the skin and travel to the lymph nodes: Langerhans cells, dermal dendritic cells, macrophages, mast cells,Tconv (Tregs), Tgd cells, innate cells such as ILC.

Skin immune cells - Differences human / mouse

Human epidermis

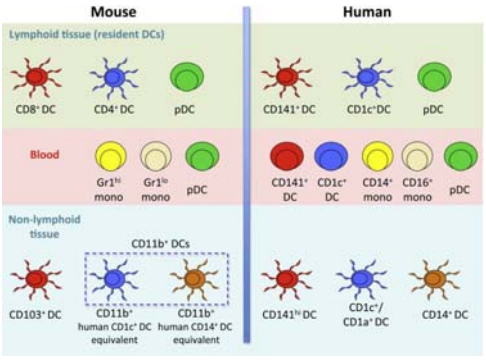


Mouse epidermis



Numerous Tγ5+δ1+ cells into the mouse epidermis (DETC, about 90% of T cells)

Dendritic cell subsets



Phenotypic differences in DC subsets
Recent studies identify subsets with functional homologies

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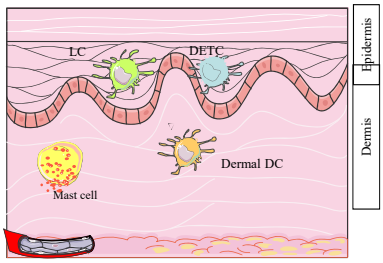
Induction of systemic immunity upon skin exposure/immunization

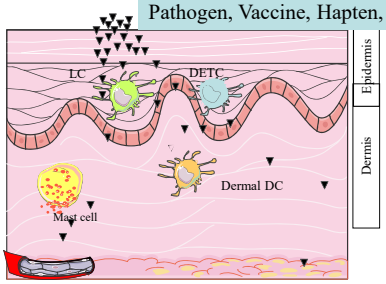
Skin exposure, immunization



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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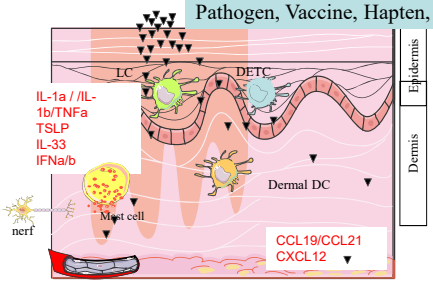


Innate immunity -> 1st line of defence

Release of inflammatory mediators

Inflammation
General scheme

4 major inflammatory components

Inducers

Microbes, Allergens AlloAg

Tissue damage
Cell-derived
Plasma-derived
ECM-derived

Sensors

P(athogen)AMPs
TLR, NLR…

D(amage)AMPs
TLR, NLR, RAGE…

Nociceptors

Mediators

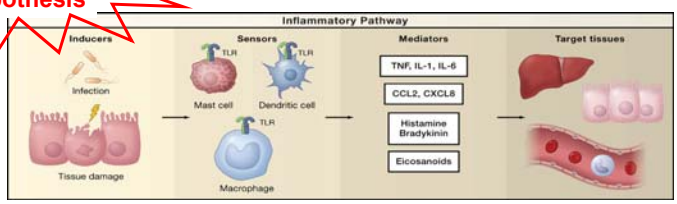
Cellular
Neutrophils, Eosinophils, Monocytes/Macrophages, T & B cells…

Molecular
Cytokines and chemokines,
Vasoactive amines or peptides
Complement fragments
lipide mediators
proteolytic enzymes

Target tissues

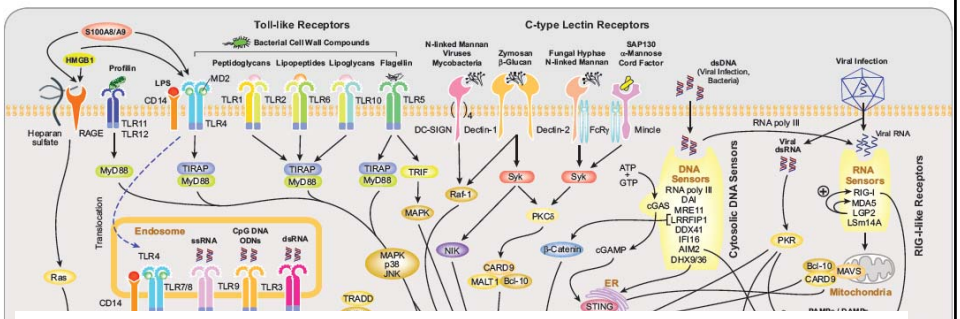
Redness/Oedema
Heat/Pain
Loss of function

DANGER Hypothesis



Pathogen recognition receptors (PRRs)

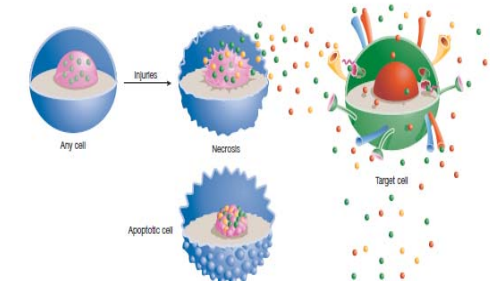
- Microbial Pattern Recognition Receptors: TLR, RLR, NLR, CLR signaling (examples)



- Recognition of specifc structures (polysach, nucleic acids, nucleotides lipoproteins, glycolipids)
- Cell comptarment 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

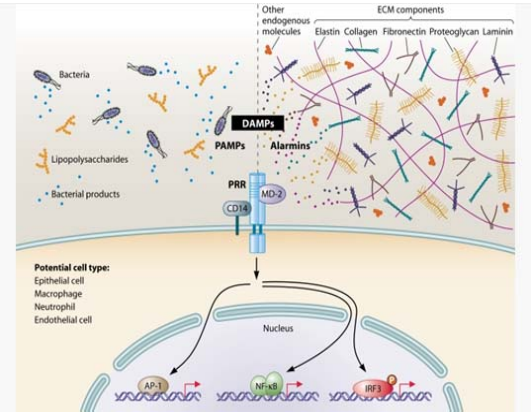


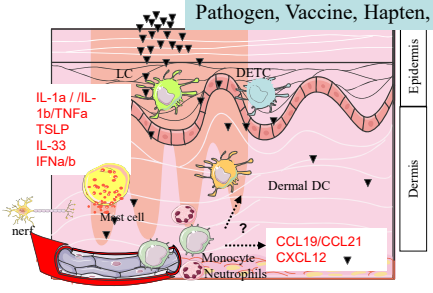
Table 2 | **Adjuvant and pro-inflammatory activity of extracel**

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

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



Innate immunity -> 1st line of defence
Release of inflammatory mediators
Coordinated cross-talk between epithelial and immune cells
Infiltration of blood leucocytes

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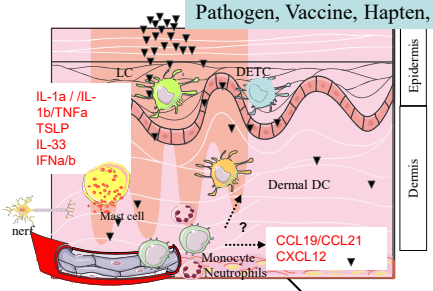
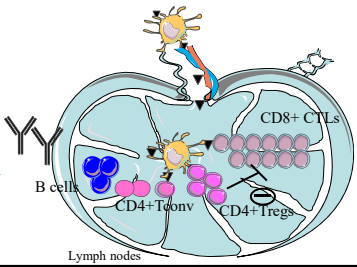


Innate response



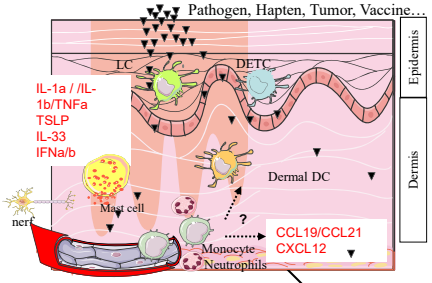
Adaptative immunity

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

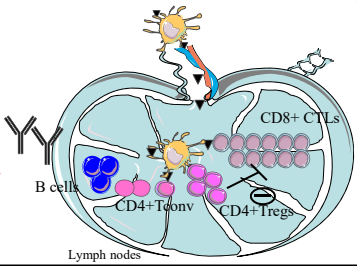
Induction of systemic immunity upon skin exposure/immunization

Skin exposure, immunization

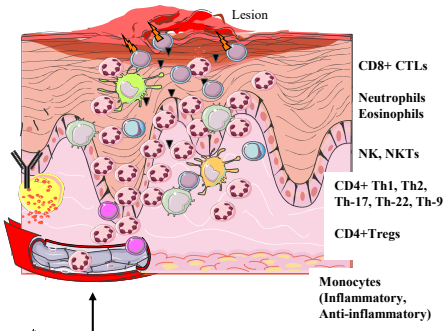
Persistance / Re-exposure → delayed-response (days)
Skin inflammation, elimination of infected cells
Tissue response/repair



Innate response

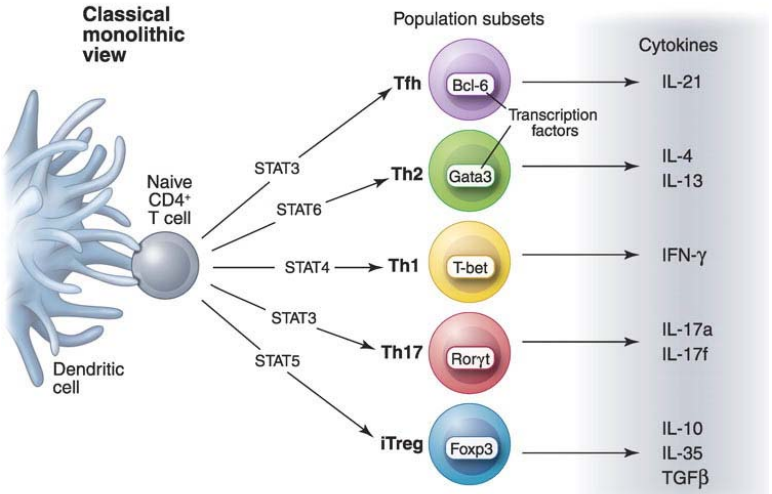


Adaptative immunity



Effector & memory response -> 2nd line of defence

Distinct T cells



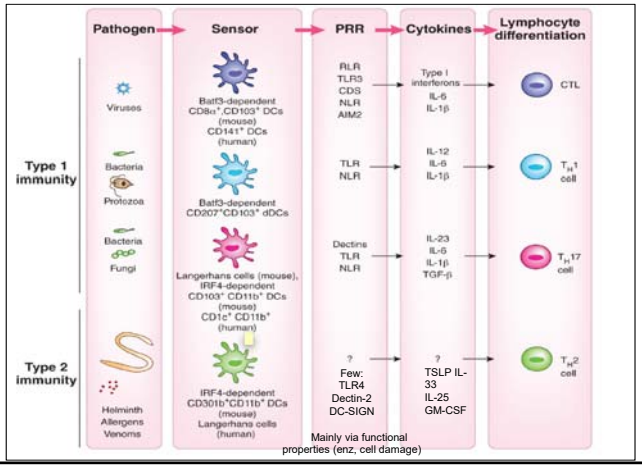
O'Shea and Paul. 2010. *Science*

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

Published in final edited form as:
Nat Immunol. 2015 April ; 16(4): 343–353. doi:10.1038/ni.3123.

Control of adaptive immunity by the innate immune system

Akiko Iwasaki and **Ruslan Medzhitov**
Howard Hughes Medical Institute, Department of Immunobiology, Yale University School of Medicine, New Haven, Connecticut, USA



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

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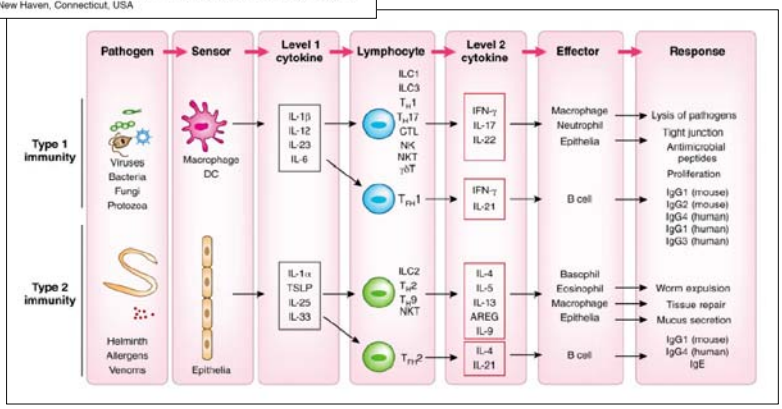
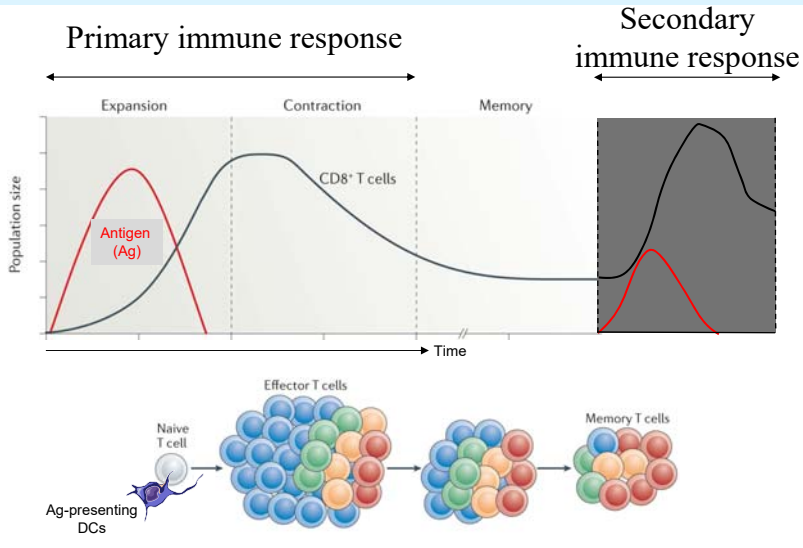


The development of T cell memory



Antigen-specific memory T cells =

- **more numerous**
- **poised for more rapid and more potent action**

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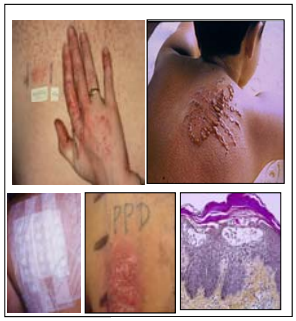
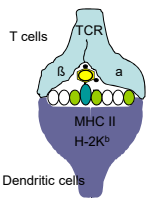
- Principes généraux / Mécanismes de tolérance/régulation de la réponse d'eczéma

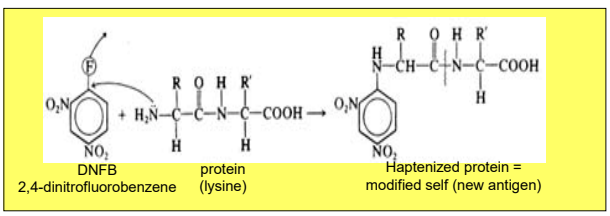
Allergic Contact Dermatitis (ACD): Generalities



Features

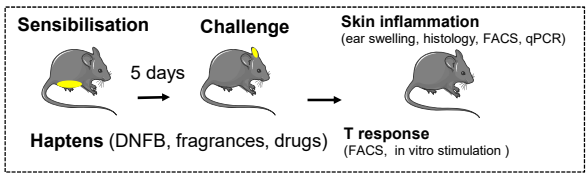
- High prevalence,1st occupationnal disease
- Repeated exposure to environmental allergens (cosmetics, jewels, drugs…)
- Breakdown of skin tolerance
- Delayed-type allergy:
  → infiltration and activation of allergen-specific T cells

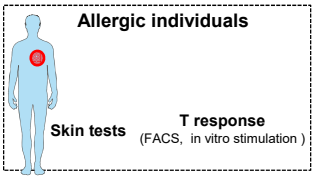




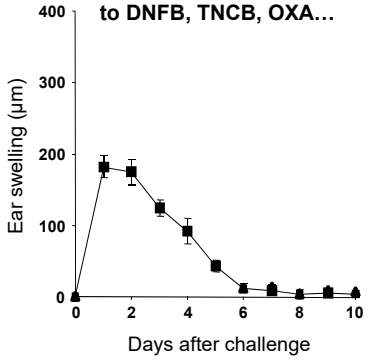
Presentation of haptenized peptides

Experimental models of ACD in mouse, in human

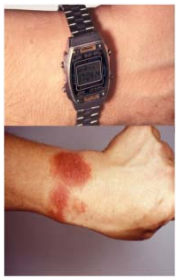




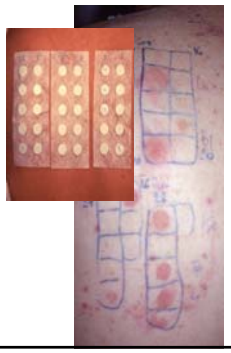
CHS (= ACD) response to DNFB, TNCB, OXA…



ACD lesions



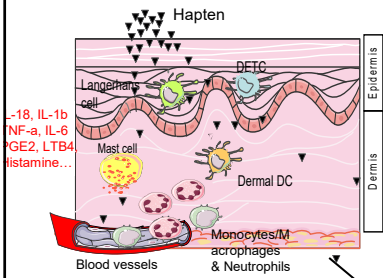
Positive patch-tests to reference allergens



Pathophysiology of Allergic Contact Dermatitis (ACD)

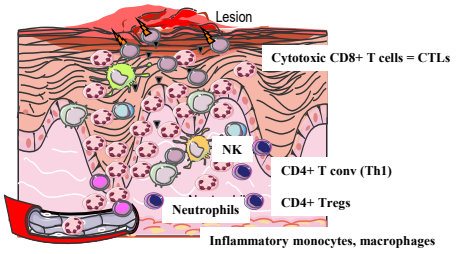
1- Sensitization phase

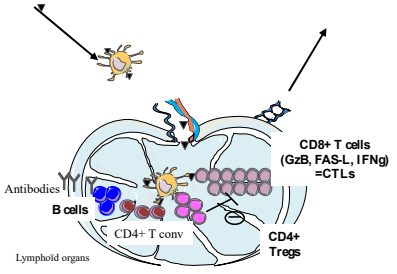
Innate immunity/ T cell priming



2- Elicitation phase

Effector response/ Polymorphic recruitment





BOUR et al. *Eur J Immunol*, 1995
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VOCANSON et al., *Allergy*, 2009
VOCANSON et al. *J Allergy Clin Immunol*, 2010
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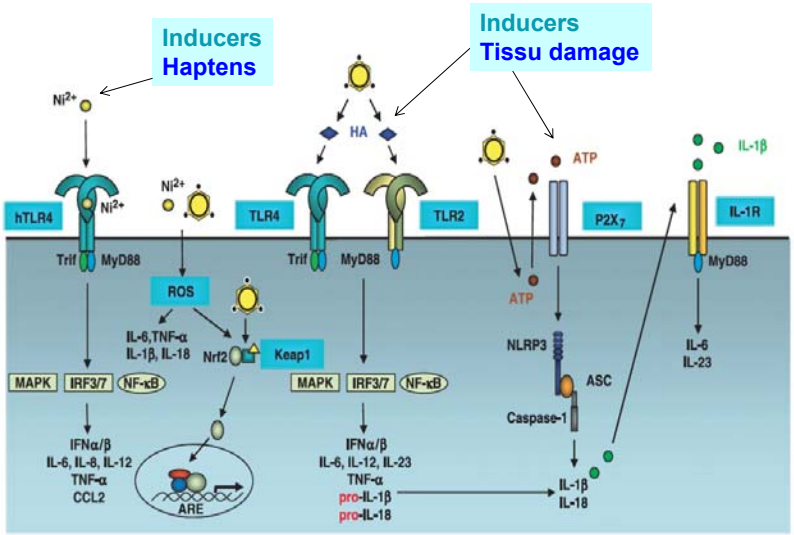
ROUZAIRE et al. *Eur J Immunol*, 2012
GOUBIER et al. *J Invest Dermatol*, 2013
CORTIAL et al. *Nanomedicine*, 2015

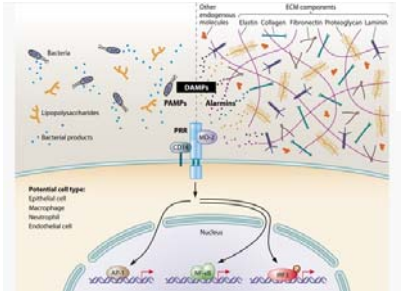
How haptens activate innate immunity?



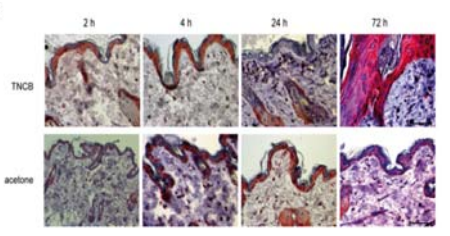
SF Martin et al, Allergy, 2011

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

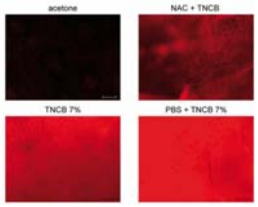
- Impact des médiateurs reconnus par les TLRs sur le développement de la réponse d'EAC



Esser P, Plos One 2012



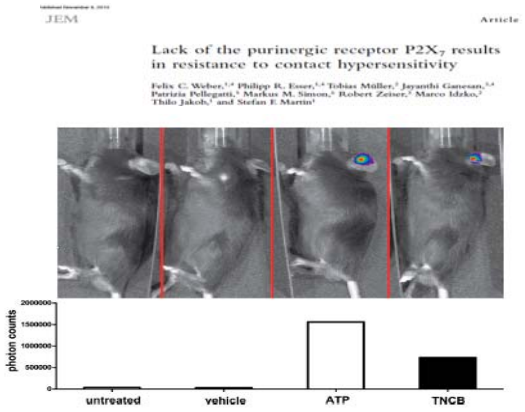
Dégradation Acide Hyaluronique ht PW, 24h après application



Production ROS, peau challengée

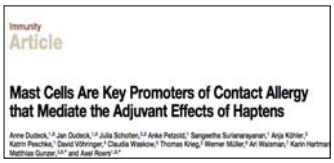
Les diverses étapes de la sensibilisation : activation de l'immunité innée

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

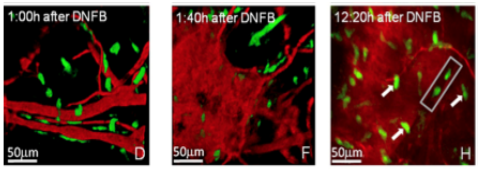


Relargage ATP, peau challengée

Contribution of innate cells? Mast cells

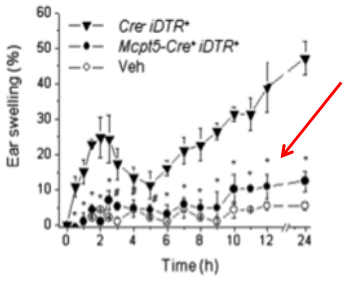


Ear skin mast cells and blood vessels respond to hapten

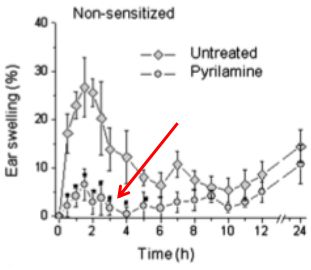


Dramatic decrease of CHS response in animals conditionally depleted in mast cells

CHS response



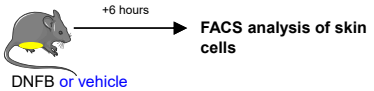
Skin inflammation is histamine-dependent

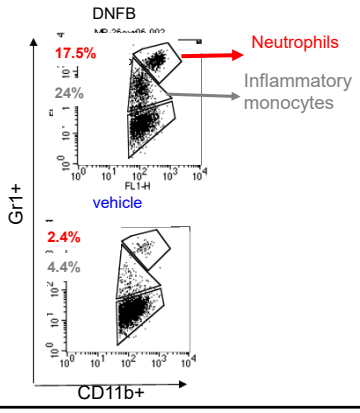


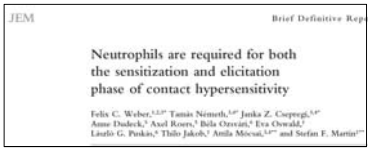
Contribution of innate cells? Neutrophils

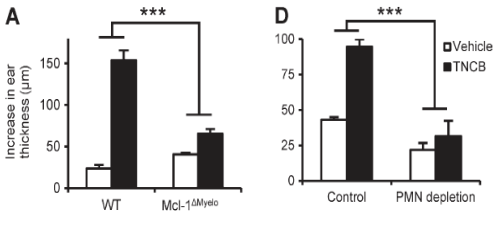
Large infiltration of neutrophils
in the hours following hapten application

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

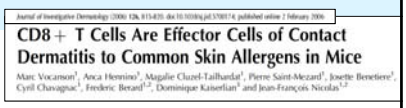


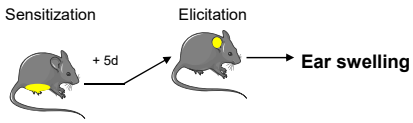






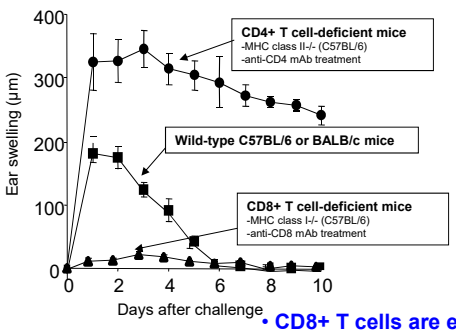
Main effectors? CD8+ CTLs

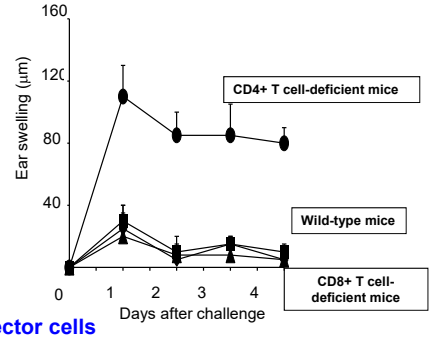




Strong haptens: DNFB, OXA...

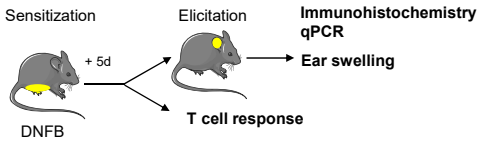
Weak haptens
→ Fragrances (Hexylcinnamaldehyde, Hydroxycitronellal, Eugenol, Dihydrocoumarin, Isoeugenol),
→ Dye (paraphenylenediamine)
→ Drugs (Amoxicillin, Rosephin, Phenytoin, Sulfasalazin)

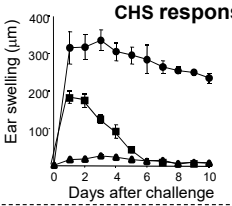


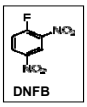


- **CD8+ T cells are effector cells**
- **CD4+ T cells comprise regulatory T cells**

Main effectors? CD8+ CTLs



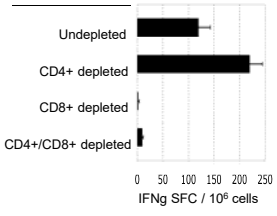




Priming of IFNg-producing CD8+ T cells

T cell response
(draining lymph nodes)

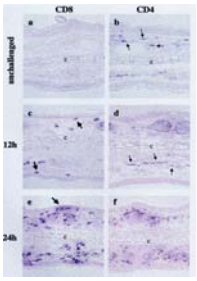
Elispot assay



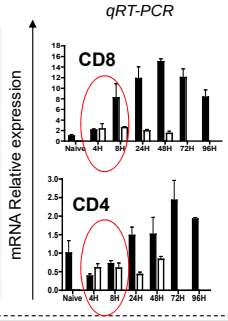
Early recruitment of CD8+ T cells initiates eczema

T cells recruitment
(challenged ears)

Immunostaining

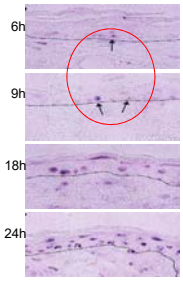


qRT-PCR



Keratinocytes: target of CTLs

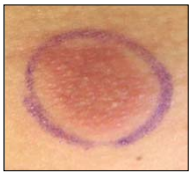
TUNEL



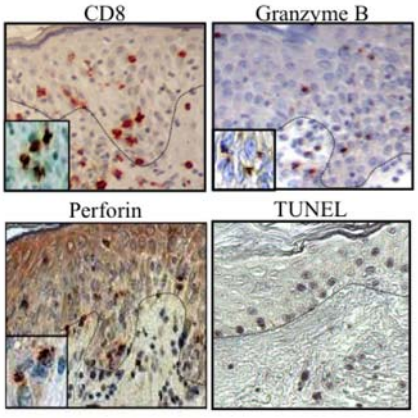
Main effectors? CD8+ CTLs

Allergic individual

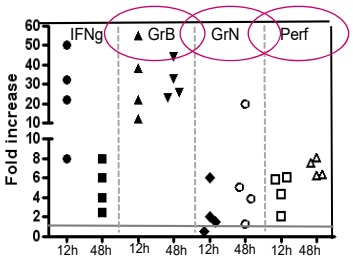
Patch-test



Immunohistochemistry



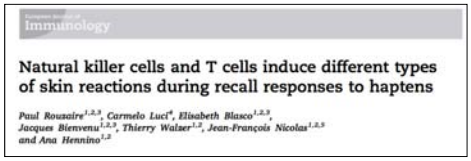
qPCR



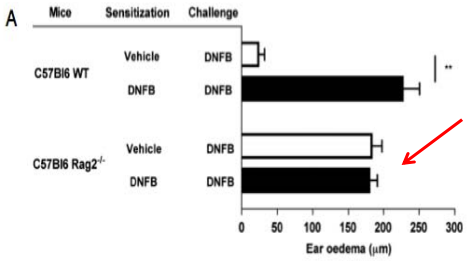
Rozières A. manuscript in preparation
Nosbaum A. manuscript in preparation

Main effectors? NK cells

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

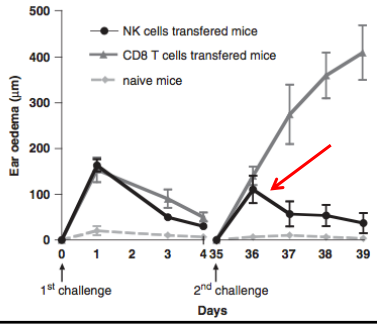


No CHS response in T cell-deficient strains



- *Paulst S. Nat Immunol 2011*

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



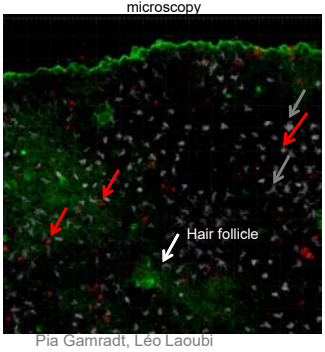
Main effectors? CD8+ CTLs
Recurrence, chronicity

Healthy skin

Healed lesion

allergic animal

Epidermal sheet, Confocal microscopy

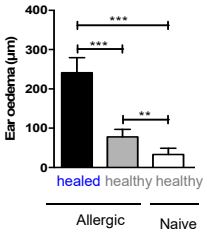


Skin edge

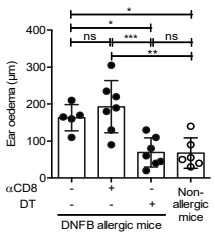
CD8+ T cells
Ag = DNP moities
DETC

Pia Gamradt, Léo Laoubi

Flare-up reaction



Acute depletion of CD8+Trm abrogates flares



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

Pathophysiology of Allergic Contact Dermatitis (ACD)

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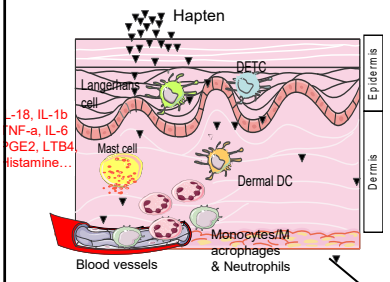
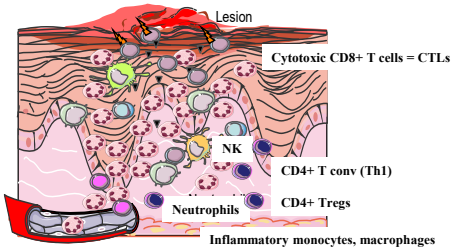
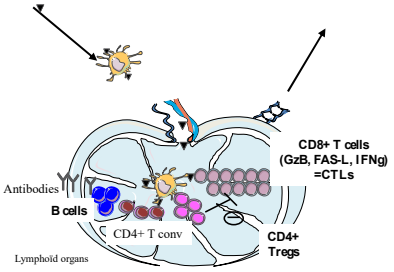
Innate immunity/ T cell priming



2- Elicitation phase

Effector response/ Polymorphic recruitment





BOUR et al. *Eur J Immunol*, 1995
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ROUZAIRE et al. *Eur J Immunol*, 2012
GOUBIER et al. *J Invest Dermatol*, 2013
CORTIAL et al. *Nanomedicine*, 2015

Pourquoi l'allergie? → Bénéfique pour l'hôte même si parfois problématique si excessive

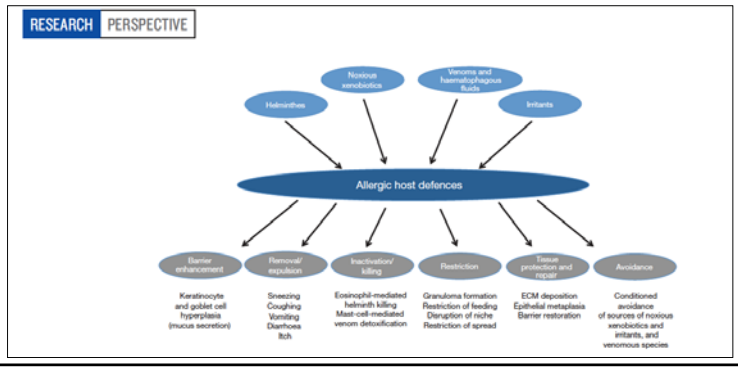
PERSPECTIVE

doi:10.1038/nature11047

Allergic host defences

Noah W. Palm[1]*, Rachel K. Rosenstein[1]* & Ruslan Medzhitov[1]

Allergies are generally thought to be a detrimental outcome of a mistargeted immune response that evolved to provide immunity to macroparasites. Here we present arguments to suggest that allergic immunity has an important role in host defence against noxious environmental substances, including venoms, haematophagous fluids, environmental xenobiotics and irritants. We argue that appropriately targeted allergic reactions are beneficial, although they can become detrimental when excessive. Furthermore, we suggest that allergic hypersensitivity evolved to elicit anticipatory responses and to promote avoidance of suboptimal environments.



Pourquoi l'allergie? → Bénéfique pour l'hôte même si parfois problématique si excessive

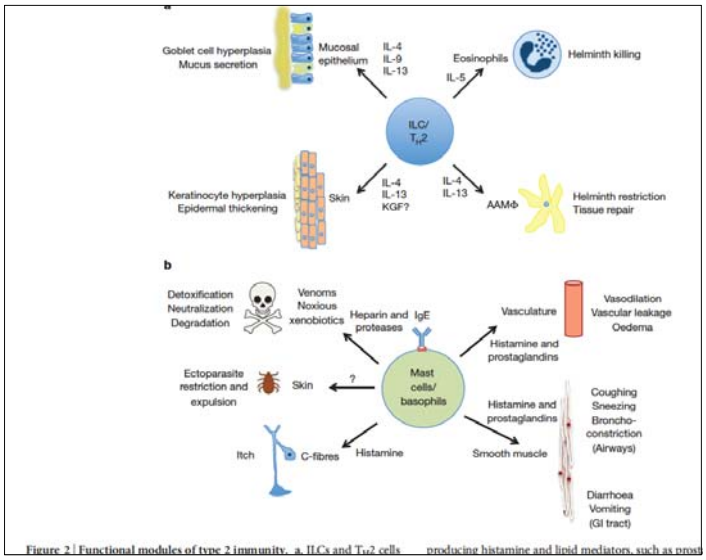
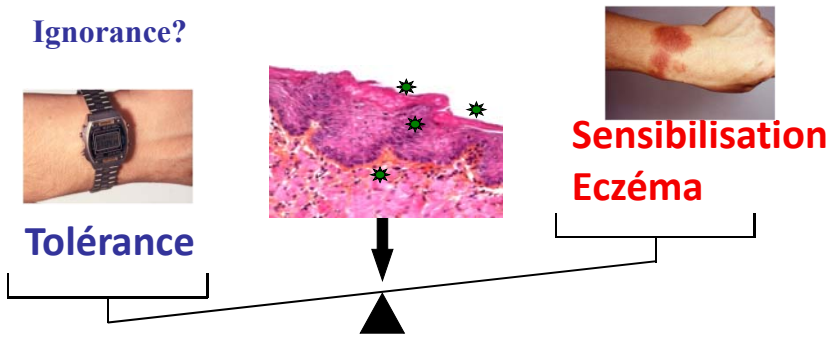


Figure 2 | Functional modules of type 2 immunity. a. ILCs and T_H2 cells producing histamine and lipid mediators, such as prost

PLAN

- La peau
- Bases immunologiques de la réponse inflammatoire cutanée
- Allergie cutanée : l'exemple de l'eczéma de contact
- Principes généraux / Mécanismes de tolérance/régulation de la réponse d'eczéma

Eczéma allergique de contact : les facteurs de risques



-> 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…)

Sensitizing potency of haptens

Chemical	Field	Sensitizing potency
Oxazolone	Chemistry	Extreme
2,4-Dinitrofluorobenzene	Chemistry	Extreme
2,4-Dinitrochlorobenzene	Chemistry	Extreme
Glutaraldehyde	Preservative, antiseptic	Strong
Formaldehyde	Cosmetic, Dye	Strong
Cinnamaldehyde	Perfum, Flavour	Moderate
Hexyl cinnamaldehyde	Cosmetic (fragrance)	Moderate/weak
Eugenol	Cosmetic (fragrance)	Weak
Hydroxycitronellal	Cosmetic (fragrance)	Weak
Linalool	Cosmetic (perfum)	Weak
Citral	Perfum, Flavour	Weak
Vanillin	Perfum, Flavour	Weak
2,4-Dinitrocyanobenzene	Chemistry	Weak
Amoxicillin, cyanamid, cetrimide	Drug	Weak

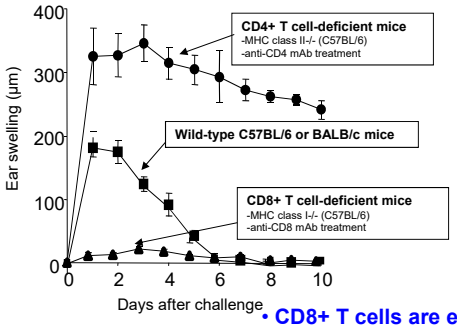
Main effectors? CD8+ CTLs

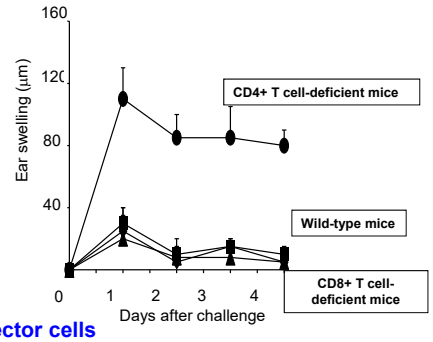
CD8+ T Cells Are Effector Cells of Contact Dermatitis to Common Skin Allergens in Mice

Sensitization → + 5d → Elicitation → Ear swelling

Strong haptens: DNFB, OXA...

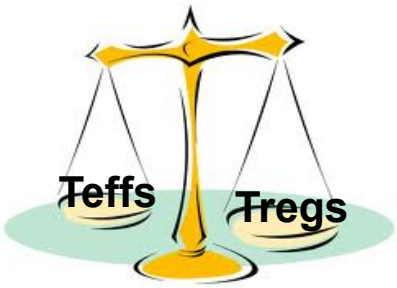
Weak haptens
→ Fragrances (Hexylcinnamaldehyde, Hydroxycitronellal, Eugenol, Dihydrocoumarin, Isoeugenol),
→ Dye (paraphenylenediamine)
→ Drugs (Amoxicillin, Rosephin, Phenytoin, Sulfasalazin)





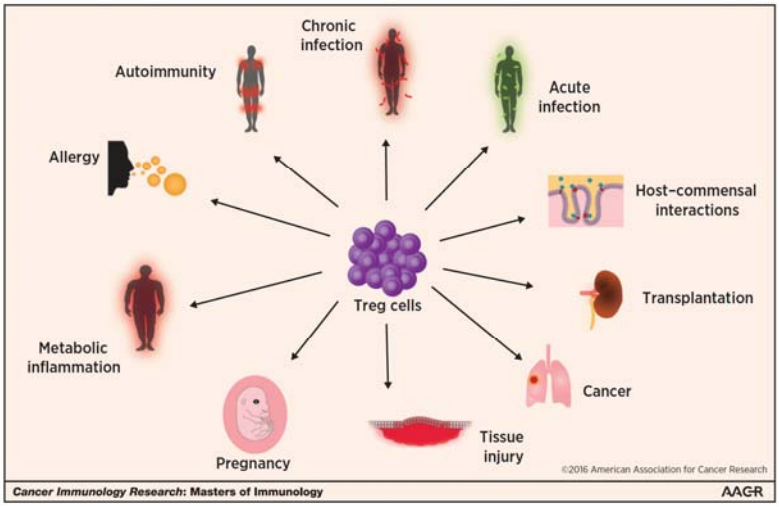
- CD8+ T cells are effector cells
- CD4+ T cells comprise regulatory T cells

L'équilibre immunologique - Une balance entre activation et contrôle lymphocytaire



Activation LT effecteurs	Tolérance LT régulateurs
Normale: réactions contre les pathogènes **Pathologique:** maladies inflammatoires: allergiques, autoimmunes	Pas de réponse contre le soi Réponses contrôlées contre les pathogènes

Regulatory T Cells (Tregs)



Plitas et al. AACR Journal 2016

De nombreux lymphocytes T régulateurs

Tregs FoxP3+ (CD25+)

nTregs — **pTregs ou iTreg FoxP3**

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

Thymus — *Périphérie - Voie orale Induit in vitro*

Ag du soi — Ag exogène

Tregs FoxP3- (CD25neg/low)

iTregs Tr1 — **iTregs Th3** — **LTh1** Producteurs **IFN-γ/IL-10**

IL-10 — *TGF-β* — IL-10

Périphérie - Tolérance — *Voie orale* — *Périphérie - Infection*

Ag exogène — Ag exogène — Ag exogène

LT CD4+ →

LT CD8+ → **FoxP3+** *thymus* — **Tr1-like** *périphérie*

LT CD4-/CD8- →

Cellules NKT → *thymus*

Main regulatory cells? FoxP3+Tregs

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

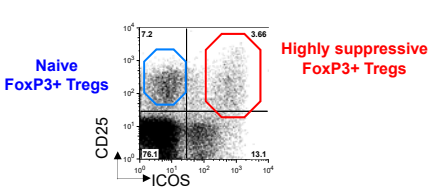
Inducible costimulator (ICOS) is a marker for highly suppressive antigen-specific T cells sharing features of T_H17/T_H1 and regulatory T cells

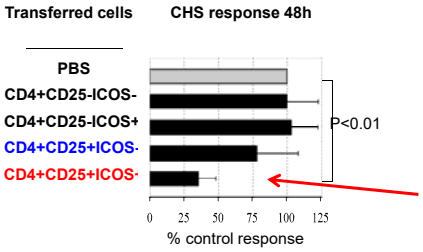
Marc Vocanson, PhD,[a,b,c] Aurore Rozieres, PhD,[a,b,c] Anca Hennino, PhD,[b,c] Gaelle Poyet, MSc,[a,b,c] Vincent Gaillard, BSc,[a,b,c] Sarah Renaudineau, MSc,[b,c] Amine Achachi, PhD,[b,c] Josette Benetiere, BSc,[a,b,c] Dominique Kaiserlian, PhD,[b,c] Bertrand Dubois, PhD,[b,c] and Jean-François Nicolas,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



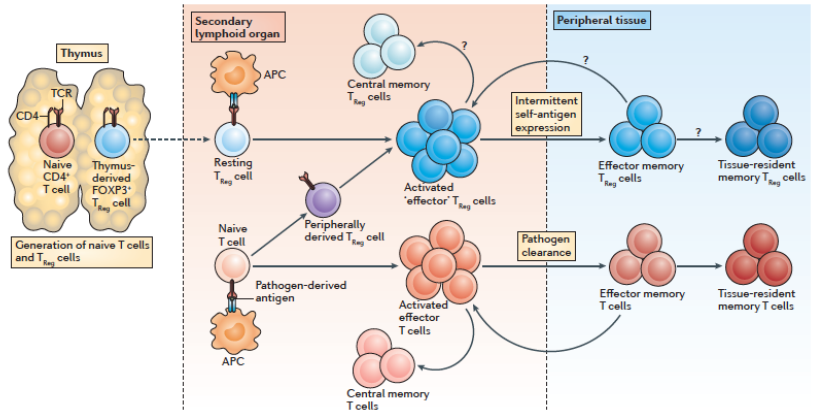


Regulatory T Cells (Tregs)

Les Tregs sont des LT CD4+ Foxp3+ $CD25^{hi}$

- Générés après reconnaissance d'auto-antigènes dans le thymus ou dans les tissus périphériques
- Leur génération requière le facteur de transcription Foxp3
  - Sa mutation cause des maladies auto-immunes sévères chez l'homme (syndrome IPEX- Immune dysregulation Polyendocrinopathy autoimmune enteropathy X-linked) et chez la souris scurfy.
  - Peut être exprimé transitoirement par les LT activés **chez l'homme**
  - Expression stable chez la souris

Ontogeny: Life Cycle of Regulatory and Conventional T cells



Rosenblum Ann Rev Immunol 2016

Foxp3-expressing Treg Subsets

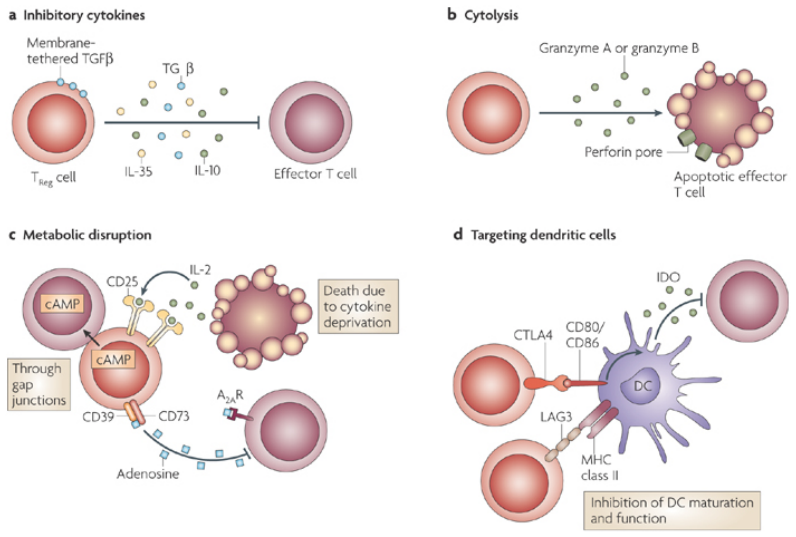
- Several subsets on the basis of
  - **The sites in which they are generated**
    - Thymus-derived Treg cells (tTregs)
    - Peripherally-derived Treg cells (pTregs)
    - In vitro induced (iTregs) also called Tr1
    - No reliable marker to differentiate these subsets in the skin
  - **Their relative differentiation state**
    - Naive or resting Treg cells versus effector or memory Treg cells
    - Good markers to differentiate these subsets in the skin
  - **The tissues in which they primarily reside**

Selected markers for resting, effector and memory T cell subsets

	Conventional T cells			Regulatory T cells		
	Resting	Activated effector	Memory	Resting	Activated effector	Memory
Selected phenotypic markers	$CD25^{low}$ $CD44^{low}$ $CD45RA^{hi‡}$ $CD45RO^{low‡}$ $CD69^{low}$ L-$selectin^{hi}$ $CD127^{high}$ $Ki67^{low}$ $BCL\text{-}2^{hi}$	$CD25^{hi}$ $CD44^{hi}$ CD45RA expression variable‡ CD45RO expression variable‡ $CD69^{hi}$ L-$selectin^{low}$ $CD127^{low}$ $Ki67^{hi}$ $BCL\text{-}2^{low}$ $KLRG1^{hi}$	$CD25^{low}$ $CD44^{hi}$ $CD45RA^{low‡}$ $CD45RO^{hi‡}$ CD69 expression variable L-selectin expression variable $CD127^{hi}$ $CD27^{hi}$ $Ki67^{low}$ $BCL\text{-}2^{hi}$	$CD25^{hi}$ $CD44^{hi}$ $CD45RA^{hi‡}$ $CD45RO^{low‡}$ $CD69^{low}$ L-$selectin^{hi}$ $CD127^{low}$ $CTLA4^{low}$ $ICOS^{low}$ $HLA\text{-}DR^{low‡}$ $Ki67^{low}$ $BCL\text{-}2^{hi}$	CD25 expression variable $CD44^{hi}$ $CD45RA^{low‡}$ $CD45RO^{hi‡}$ $CD69^{hi}$ L-$selectin^{low}$ $CD127^{low}$ $CTLA4^{hi}$ $ICOS^{hi}$ $HLA\text{-}DR^{hi‡}$ $Ki67^{hi}$ $BCL\text{-}2^{low}$ $KLRG1^{hi}$	$CD25^{hi}$ $CD44^{hi}$ $CD45RA^{low‡}$ $CD45RO^{hi‡}$ CD69 expression unknown L-$selectin^{low}$ $CD127^{hi§}$ $CTLA\text{-}4^{hi}$ $ICOS^{hi}$ HLA-DR expression not defined $CD27^{hi}$ $Ki67^{low}$ $BCL\text{-}2^{hi}$ KLRG1 expression not defined

Rosenblum Ann Rev Immunol 2016

Suppressive mechanisms used by Tregs



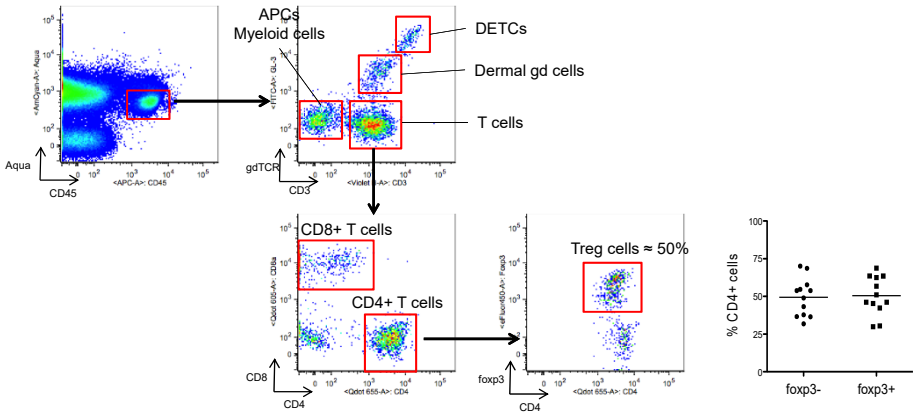
Vignali et al. *Nature Reviews Immunology 20*

Fonctions « non immunologiques » des Tregs dans les tissus

- Régulation du métabolisme lipide dans le tissu adipeux
- Production de facteurs de croissance dans le muscle, la peau et le poumon pour favoriser la réparation tissulaire (traumatisme, dystrophie musculaire, infection)
- Adaptation des Tregs à leur environnement ou existence de différents types de Tregs selon le tissu?

Tregs And The Cutaneous Immune System in Mouse

Mouse Skin Gating strategy in Flow Cytometry

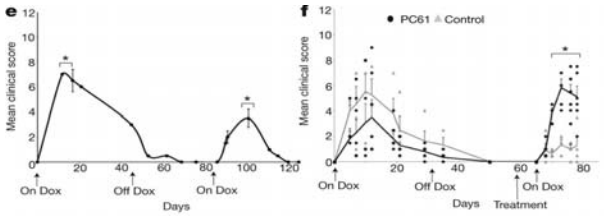


- Could be considered as tissue resident cells

Gratz et al. J Immunol 2013

Treg Functions in Skin (1/4)

- **To limiting skin auto-immunity**
  - Memory T_{reg} cells attenuate skin disease upon re-expression of tissue antigen.

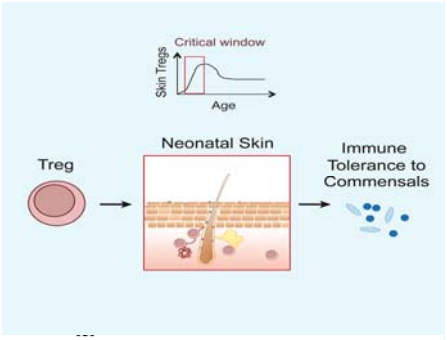


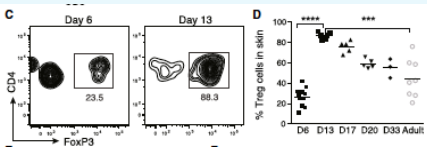
  - Exposure to tissue autoantigens leads to the activation of self-reactive Treg cells
  - Those Tregs are generated by self-antigen expression in the thymus.
  - Activated Treg cells persist in the target tissue and suppress autoimmune responses upon repeated or chronic encounters with tissue autoantigen

Rosenblum Nature 2011

Treg Functions in Skin (2/4)

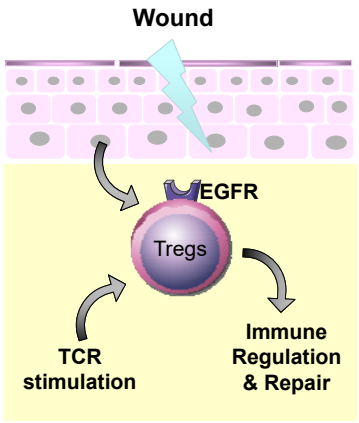
- **Promoting tolerance to commensal bacteria**
  - Skin bacteria activate antigen-specific T cells across an intact skin barrier
  - Tolerance to skin commensal bacteria is preferentially established in neonatal life
  - A unique wave of activated regulatory T cells enters skin in this critical window
  - Blocking entry of Treg cells into neonatal skin prevents tolerance to commensals



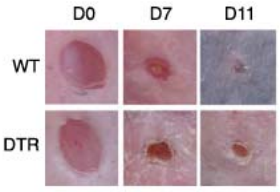


Scharschmidt, Nosbaum et al Immunity 2016

Treg Functions in Skin (3/4)

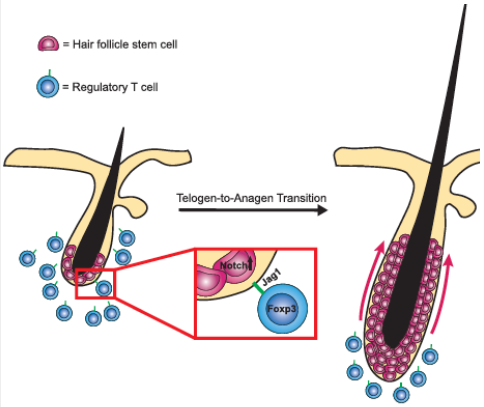


- **Facilitating cutaneous wound healing**
- At the cellular level, Tregs regulate inflammatory macrophage accumulation in wounded skin
- At the molecular level, Tregs utilize the EGFR pathway to facilitate wound healing



Nosbaum J Immunol 2016

Treg Functions in Skin (4/4)



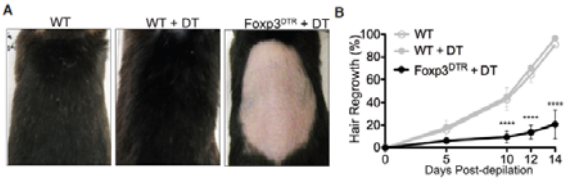
- **Facilitating epithelial stem cell differentiation**

Treg activation in skin closely correlates with the HF cycle

Tregs localize to HFSCs and play a major role in HF regeneration

Tregs facilitate HFSC proliferation and differentiation to initiate HF cycling

Treg expression of Jagged 1 is required for efficient hair regeneration



Ali, Nosbaum et al Cell 2017

De nombreux lymphocytes T régulateurs

Tregs FoxP3+ (CD25+)

nTregs — **pTregs ou iTreg FoxP3**

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

Thymus — *Périphérie - Voie orale Induit in vitro*

Ag du soi — Ag exogène

Tregs FoxP3- (CD25neg/low)

iTregs Tr1 — **iTregs Th3** — **LTh1**

Producteurs **IFN-γ/IL-10**

IL-10 — *TGF-β* — IL-10

Périphérie - Tolérance — *Voie orale* — *Périphérie - Infection*

Ag exogène — Ag exogène — Ag exogène

LT CD4+ →

LT CD8+ → **FoxP3+** *thymus* / **Tr1-like** *périphérie*

LT CD4-/CD8- →

Cellules NKT → *thymus*

Other regulatory cells? iNKT cells

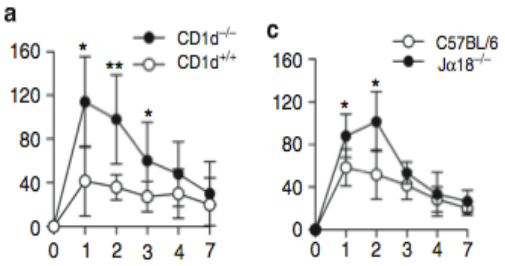
- iNKT cells are non-redondant downregulators of CTL-mediated CHS responses

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]

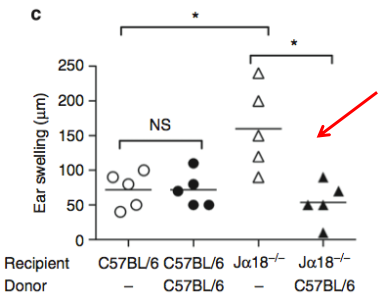
Journal of Investigative Dermatology (2013) **133**, 980–987; doi:10.1038/jid.2012.404; published online 29 November 2012

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



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

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

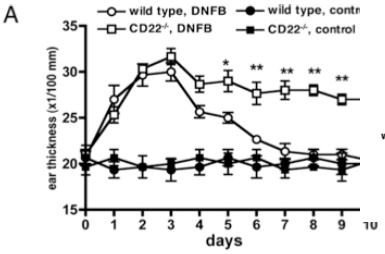
This information is current as of June 24, 2014.

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

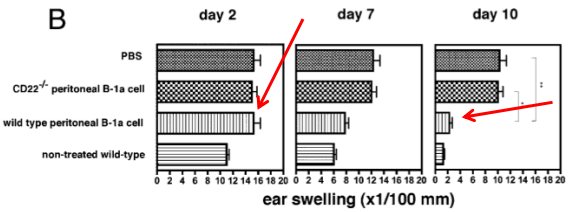
Hiroko Nakashima, Yasuhito Hamaguchi, Rei Watanabe, Nobuko Ishiura, Yoshihiro Kuwano, Hitoshi Okochi, Yoshimasa Takahashi, Kunihiko Tamaki, Shinichi Sato, Thomas F. Tedder and Manabu Fujimoto

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

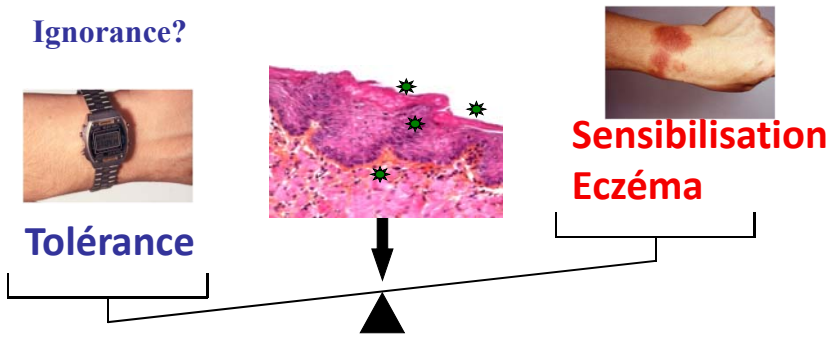
Absence of CHS resolution in CD22-/- animals



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

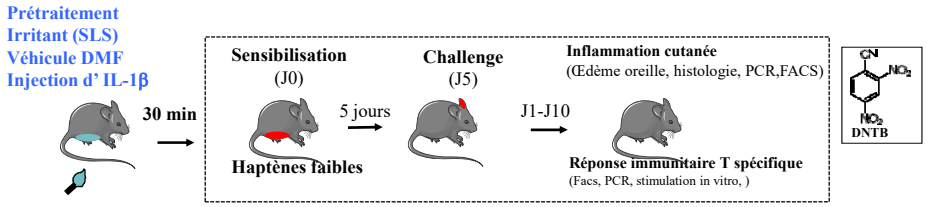


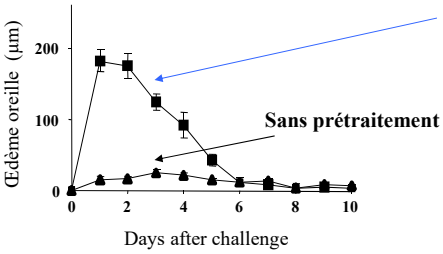
Eczéma allergique de contact : les facteurs de risques



-> 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…)

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



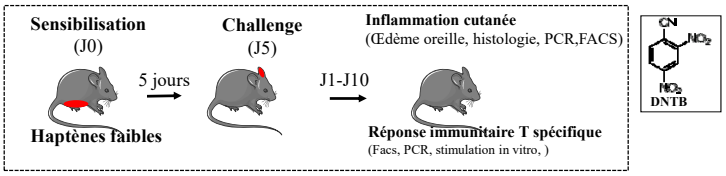


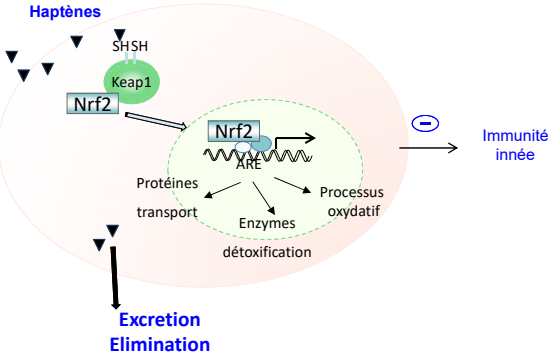
Yasukawa et al., Nat Comm, 2014
Watanabe et al. JI, 2008

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

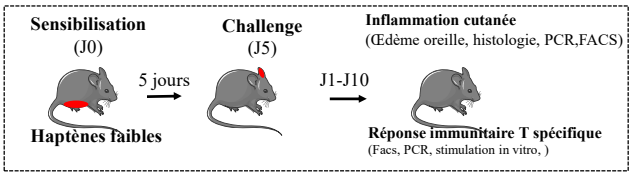
L'inverse est vrai pour un haptène fort : bloquer la production d'IL-1β prévient la sensibilisation et favorise la tolérance

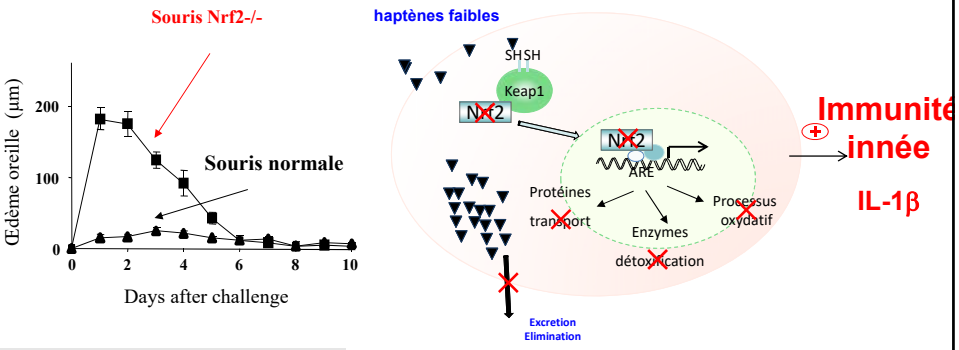
Un défaut de détoxification conduit à une rupture de tolérance vis-à-vis des haptènes faibles





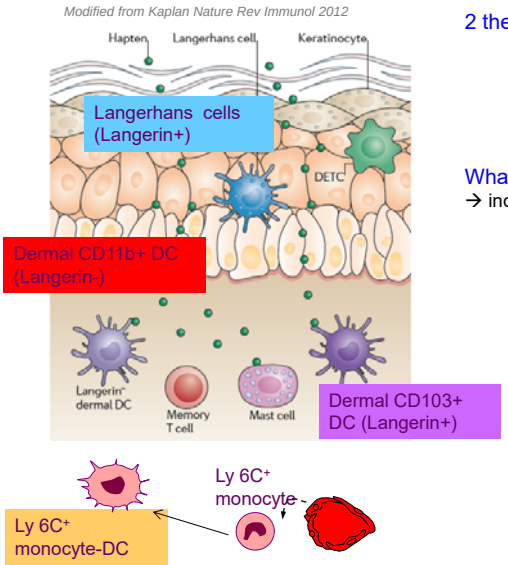
Un défaut de détoxification conduit à une rupture de tolérance vis-à-vis des haptènes faibles





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

2-What skin DC subsets for T cell priming?



2 theories:
- Functional specialization
- Plasticity

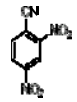
What contribution for Langerhans cells?
→ incongruent results

- *Kaplan D. Immunity 2005*
- *Kissenpfennig A. Immunity. 2005*
- *Bursch LS. J Exp Med. 2007*
- *Honda T. J Allergy Clin Immunol. 2010*

Collaboration Dubois B., Kaiserlian D.

What role for Langerhans cells: Tolerance or Sensitization?

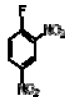
DNTB



Weak hapten = DNTB
AOO as vehicle
NO ALLERGY (TOLERANCE)

Weak hapten = DNTB
DMF as vehicle
ALLERGY

DNFB



Strong hapten = DNFB
AOO as vehicle
ALLERGY

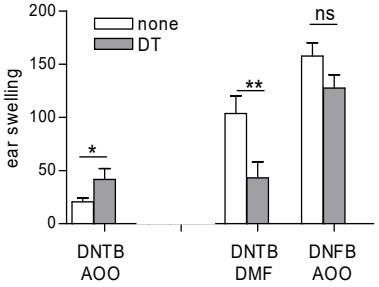
Langerhans cells = tolerogenic, immunostimulatory
Major, minor contribution

Research article

Langerhans cells protect from allergic contact dermatitis in mice by tolerizing CD8+ T cells and activating Foxp3+ regulatory T cells

Dubois B., unpublished data

CHS response in animals conditionally depleted in Langerhans cells



Immunosuppressive mechanisms of tolerogenic dendritic cells?

Tolerance through Education: How Tolerogenic Dendritic Cells Shape Immunity

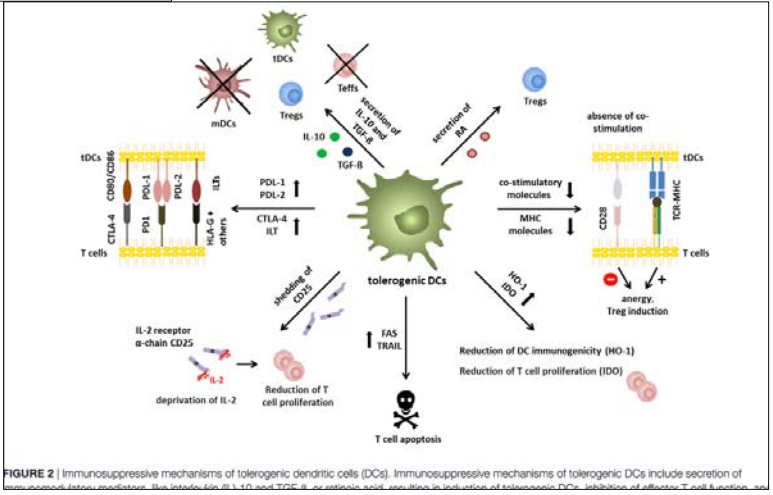
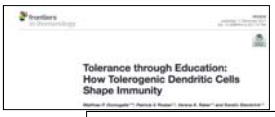


FIGURE 2 | Immunosuppressive mechanisms of tolerogenic dendritic cells (DCs). Immunosuppressive mechanisms of tolerogenic DCs include secretion of

How to induce tolerogenic phenotype/functions ?


Tolerance through Education:
How Tolerogenic Dendritic Cells
Shape Immunity

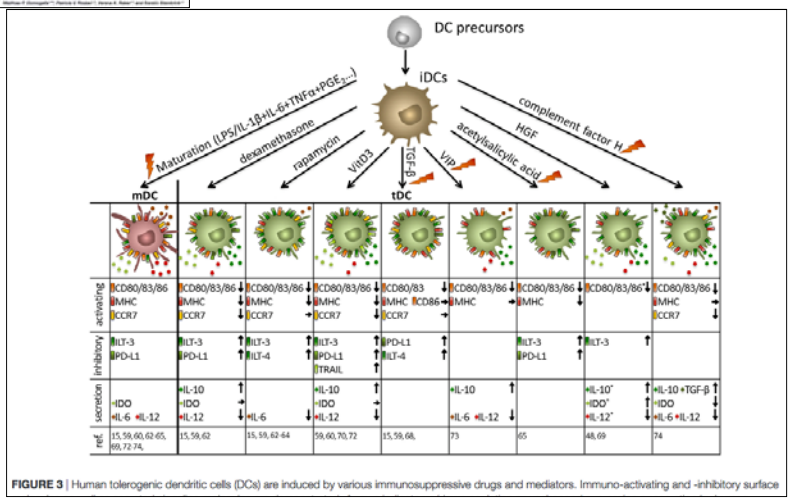
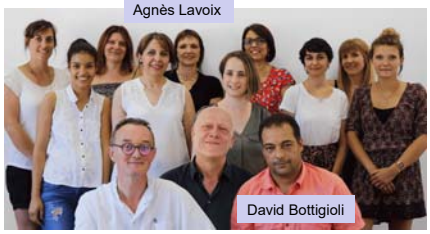


FIGURE 3 | Human tolerogenic dendritic cells (DCs) are induced by various immunosuppressive drugs and mediators. Immuno-activating and -inhibitory surface

Département d'Immuno-Allergologie

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

Equipe 17 – INSERM U1111 - 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
Faculté de Médecine LYON SUD
Hôpitaux de Lyon