

IMMUNITE INNÉE / ALLERGIE / INFLAMMATION

MECANISMES GENERAUX DE LA TOLERANCE /

REGULATION DE LA REPONSE IMMUNE



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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

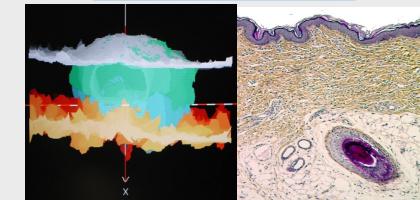
New immunological assays

Diagnosis

Prediction of allergenicity

Assessment of new therapies

Intradermal vaccination



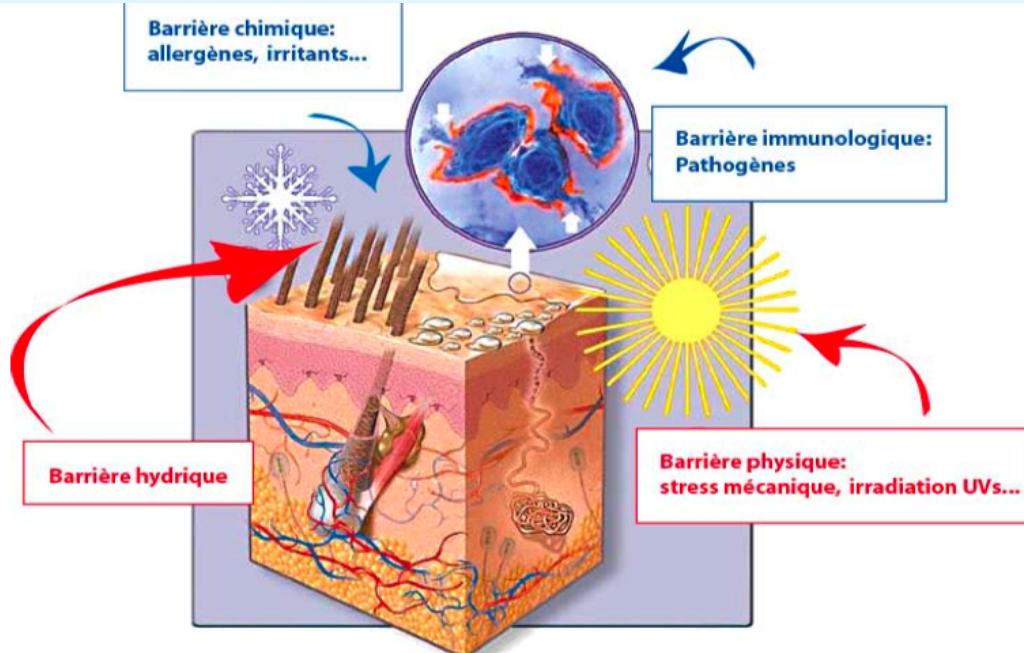
PLAN

- 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 immunitaire

PLAN

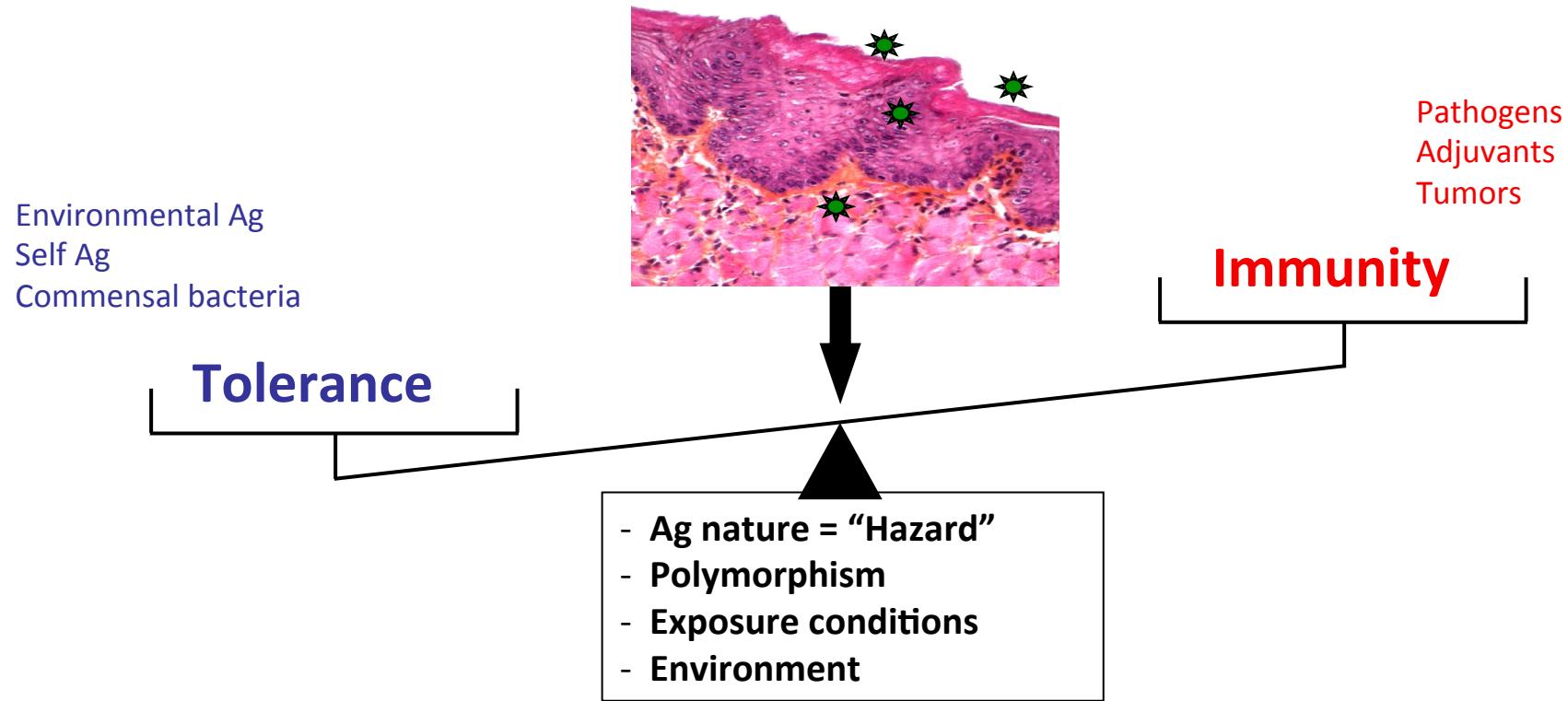
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The skin: the multitasking organ



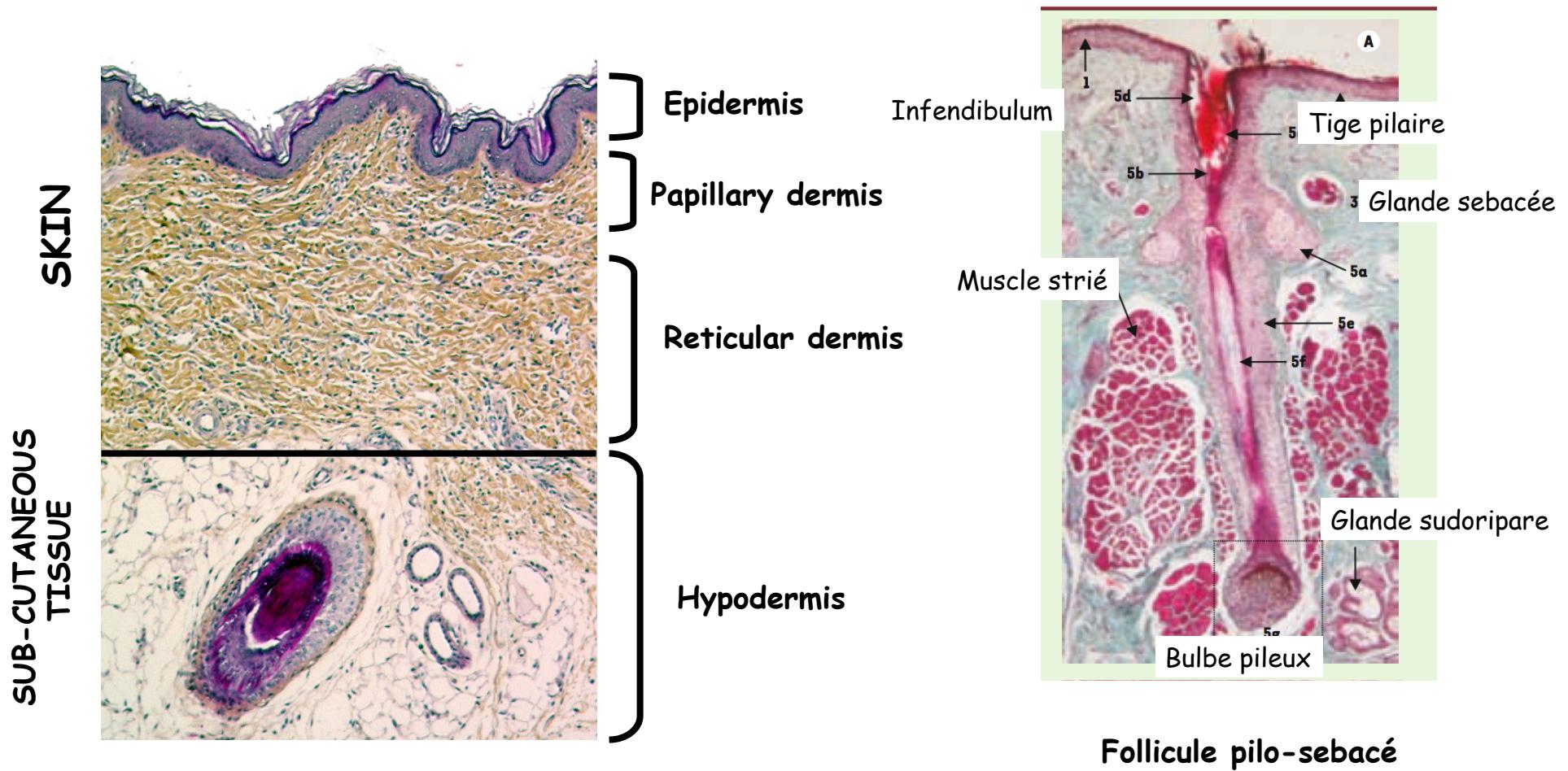
- Skin area=1.8 m²
- Being constantly exposed to potential hazards -> maintain homeostasis
- Examples of the non-immune functions of the skin:
 - Physical and biochemical barrier
 - Sensory-receptive area
 - Ensures hydration
 - Allows synthesis of vitamins, hormones

The skin: an immuno-protective organ

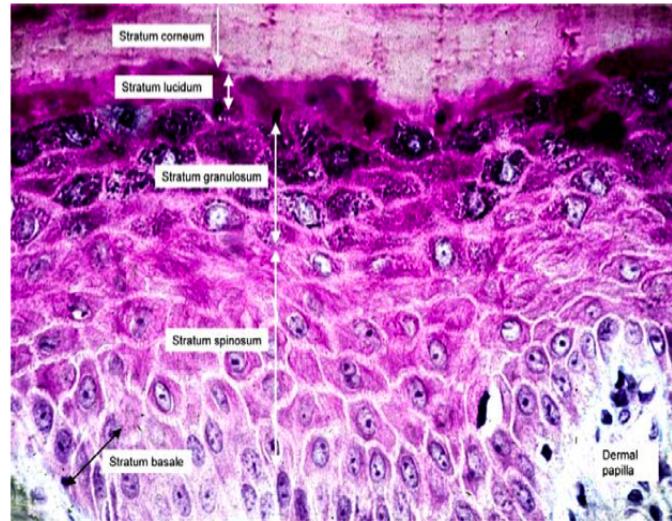


- Serves as an immuno-protective organ that actively defends deeper body tissues against infectious agents. Privileged site for vaccination
- Maintains self-tolerance, preventing allergens and inhibiting autoimmunity⁶

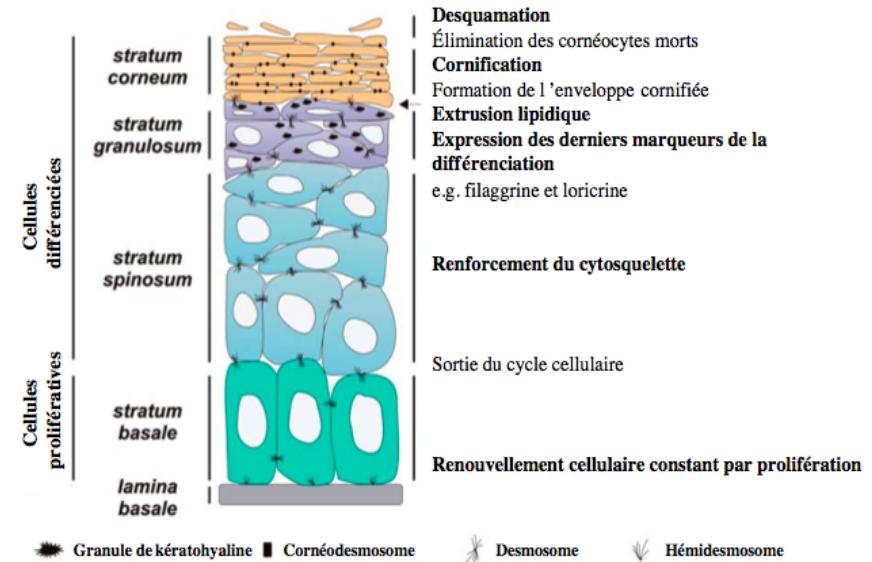
Anatomy of the skin



Anatomy of the epidermis



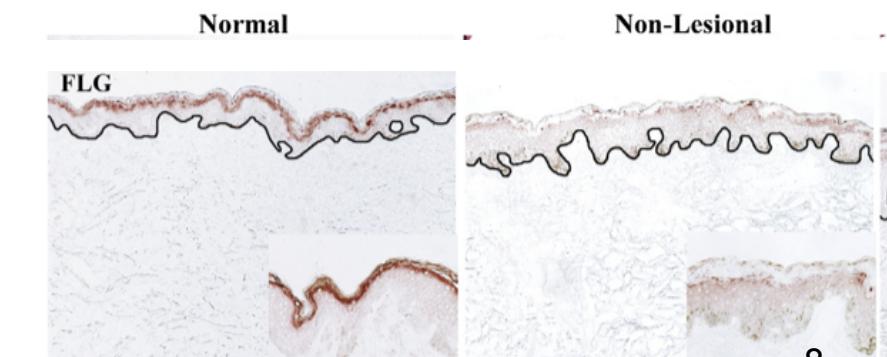
Epiderme - coloration Hematoxylline-Eosine



Différentiation épidermique - schéma

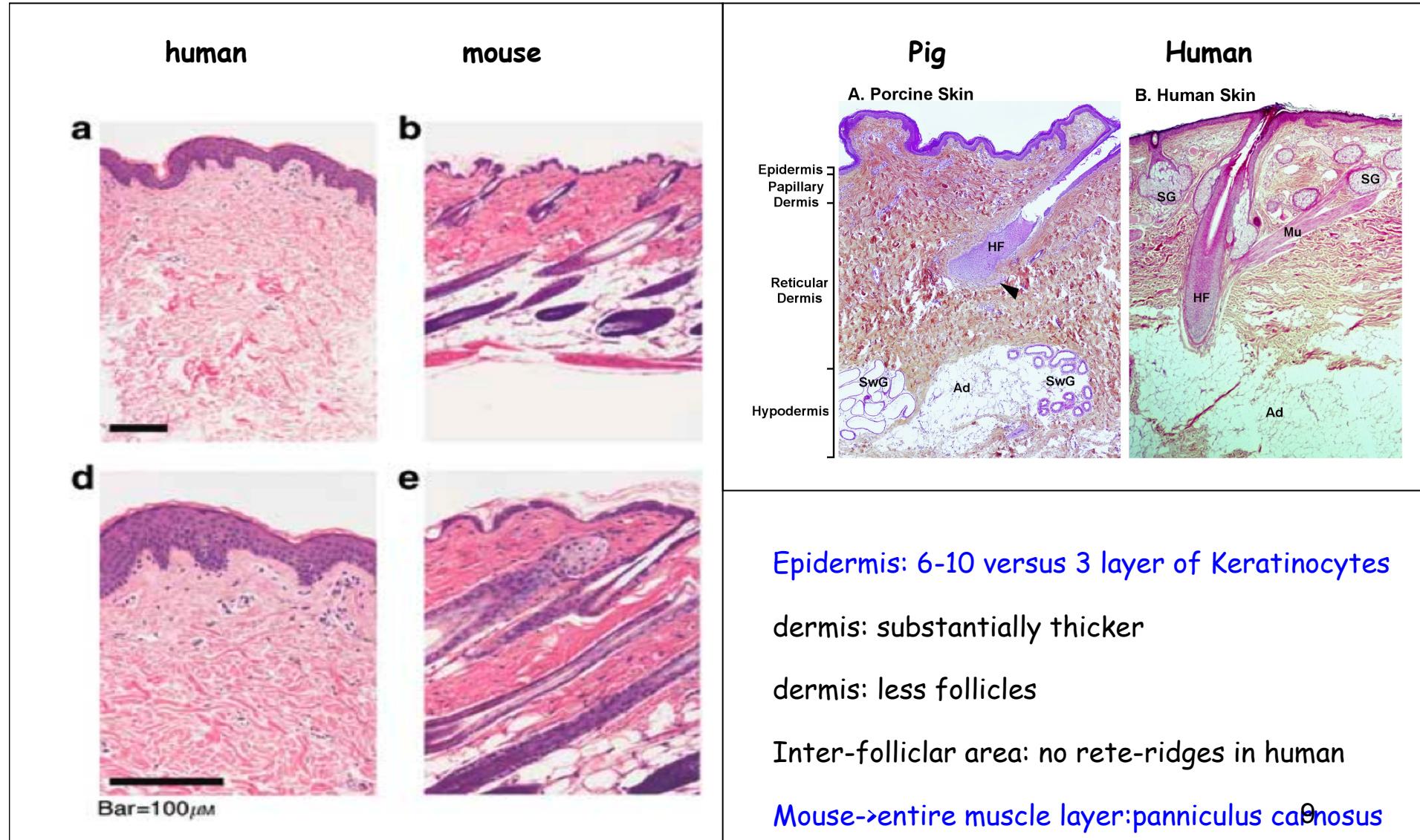


Atopic dermatitis

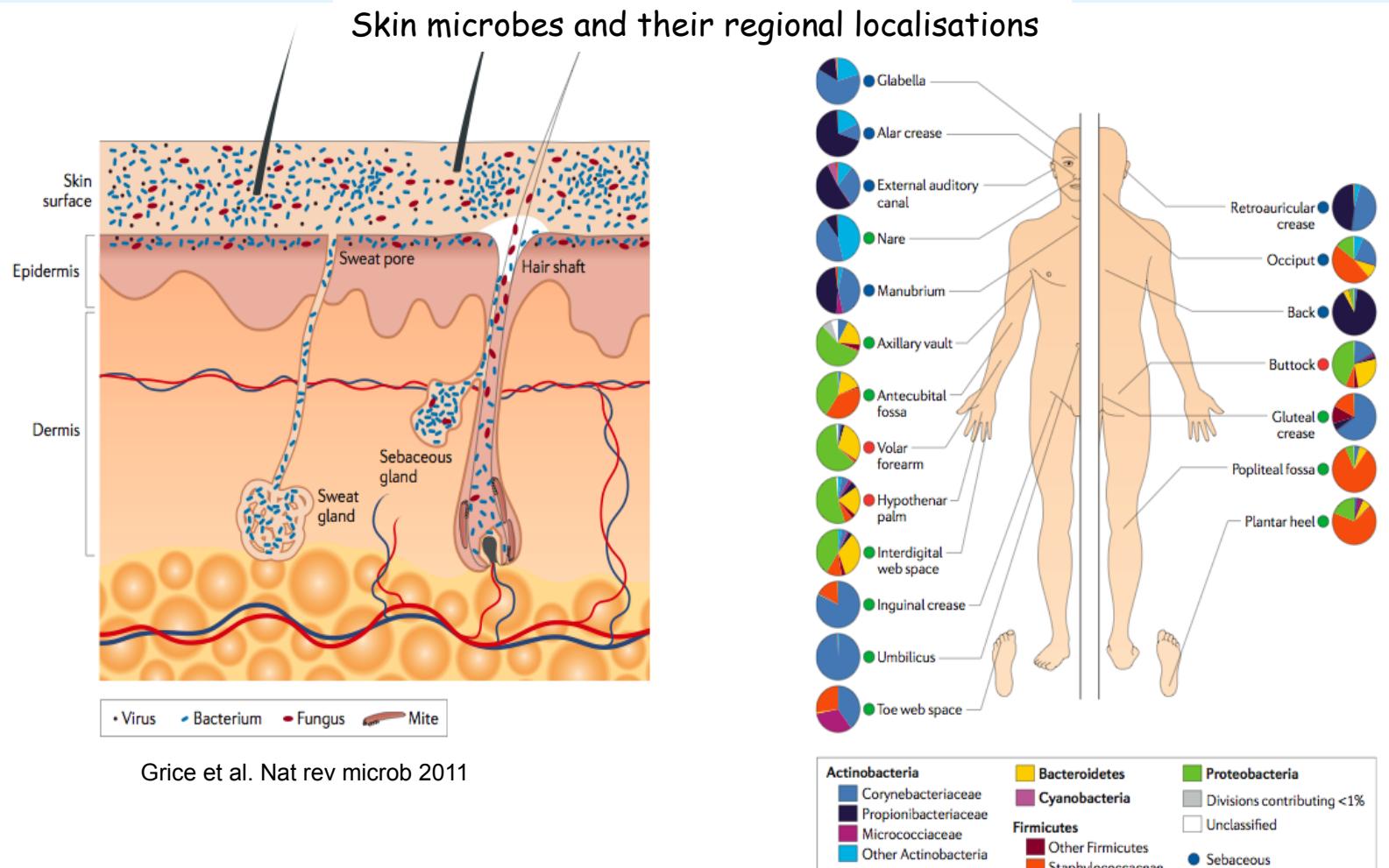


IHC staining of filaggrin, Suarez-Farinas et al. JACI 2010

Anatomy of the skin - Comparison human / mouse / Pig



The skin microbiome



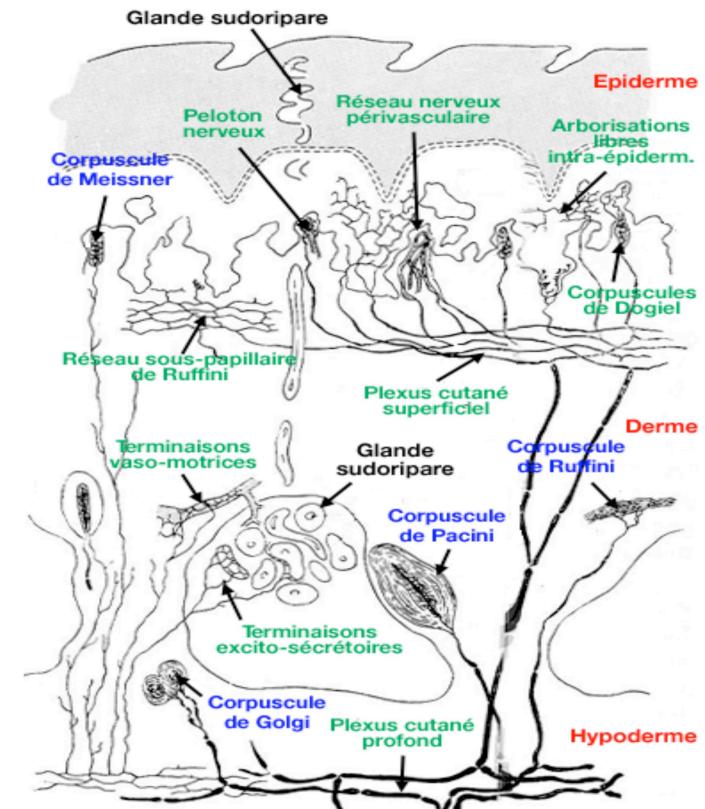
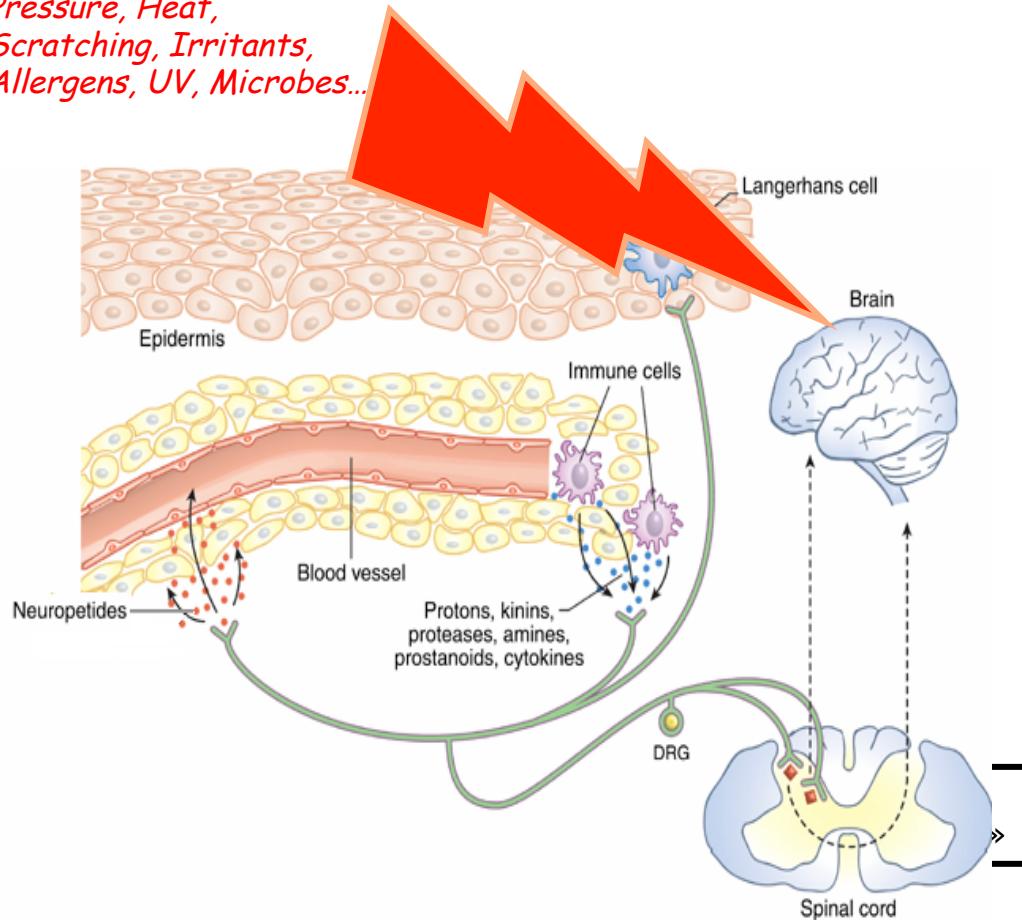
Up to 10^{12} resident bacteria/m²

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

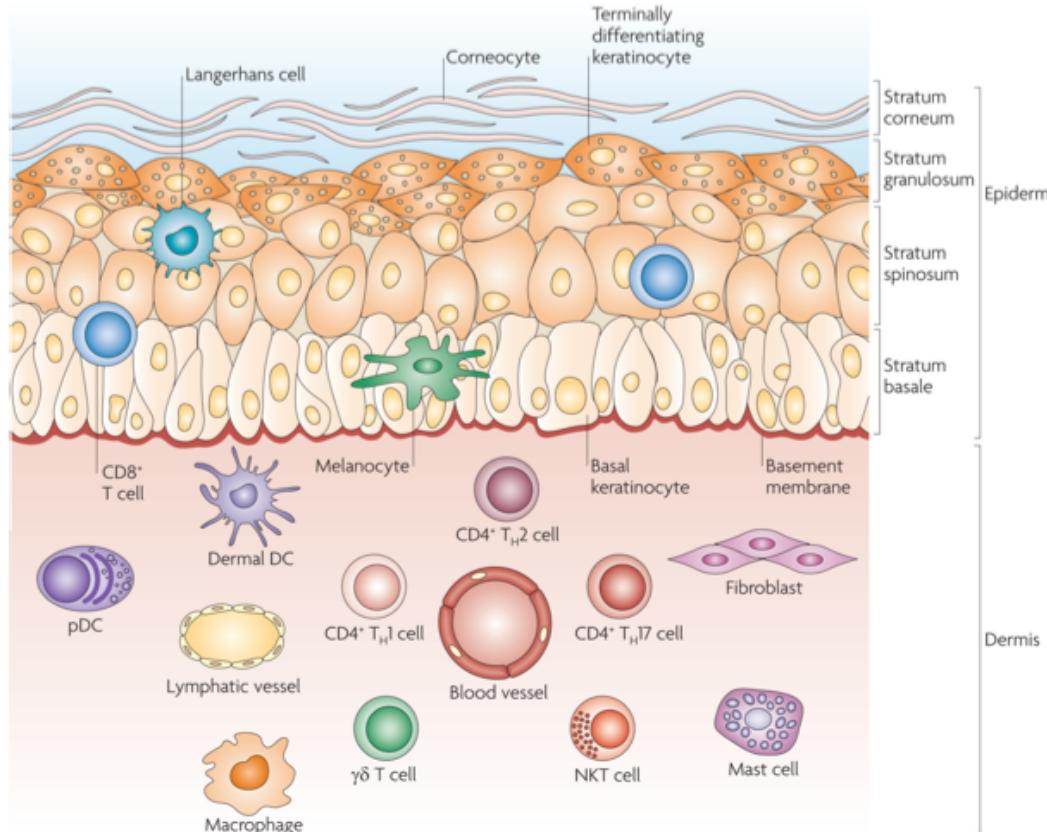
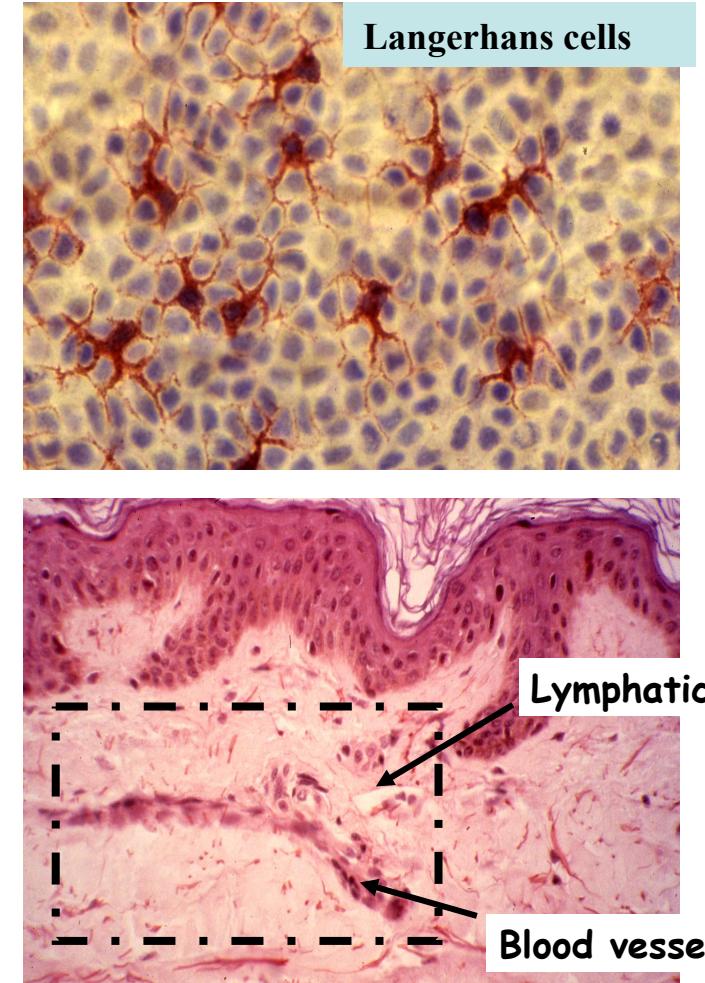


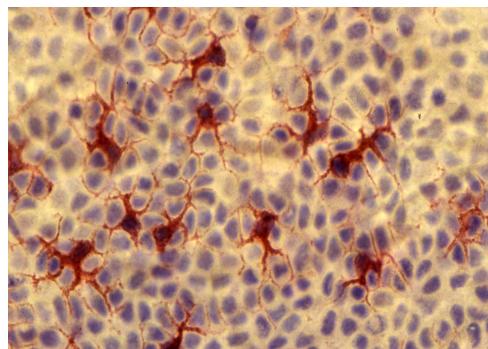
Figure 1. Skin anatomy and cellular effectors
The structure of the skin reflects the complexity of its functions as a protective barrier. In



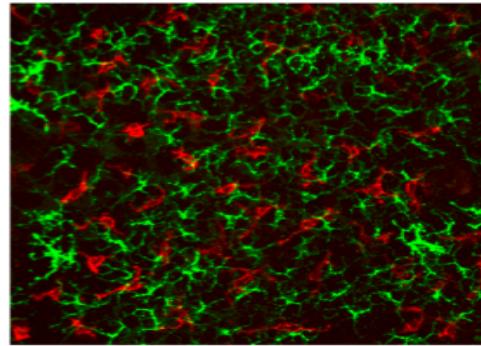
Numerous immune cells reside, traffic into the skin and travel to the lymph nodes:
 Langerhans cells, dermal dendritic cells, macrophages, mast cells, Tconv (Tregs), Tgd cells,
 innate cells such as ILC.

Skin immune cells - Differences human / mouse

Human epidermis

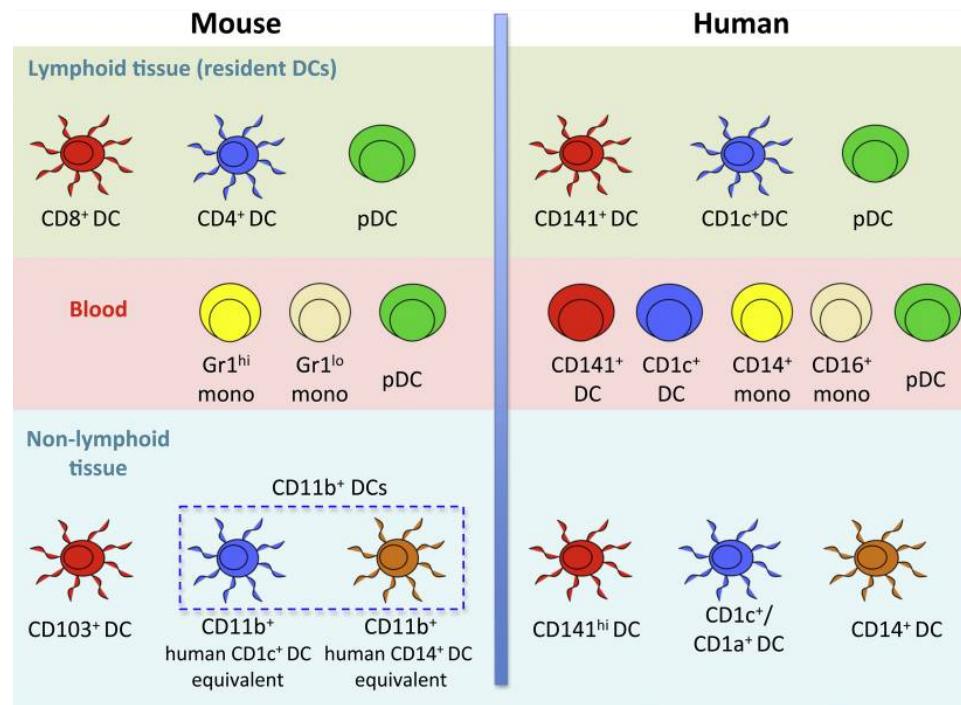


Mouse epidermis



Numerous $T\gamma 5+\delta 1+$ cells into the mouse epidermis (DETC, about 90% of T cells)

Dendritic cell subsets



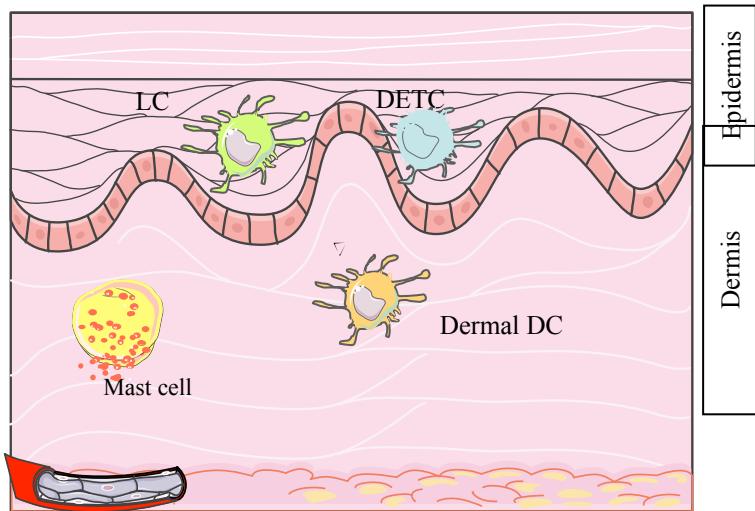
Phenotypic differences in DC subsets
Recent studies identify subsets with functional homologies

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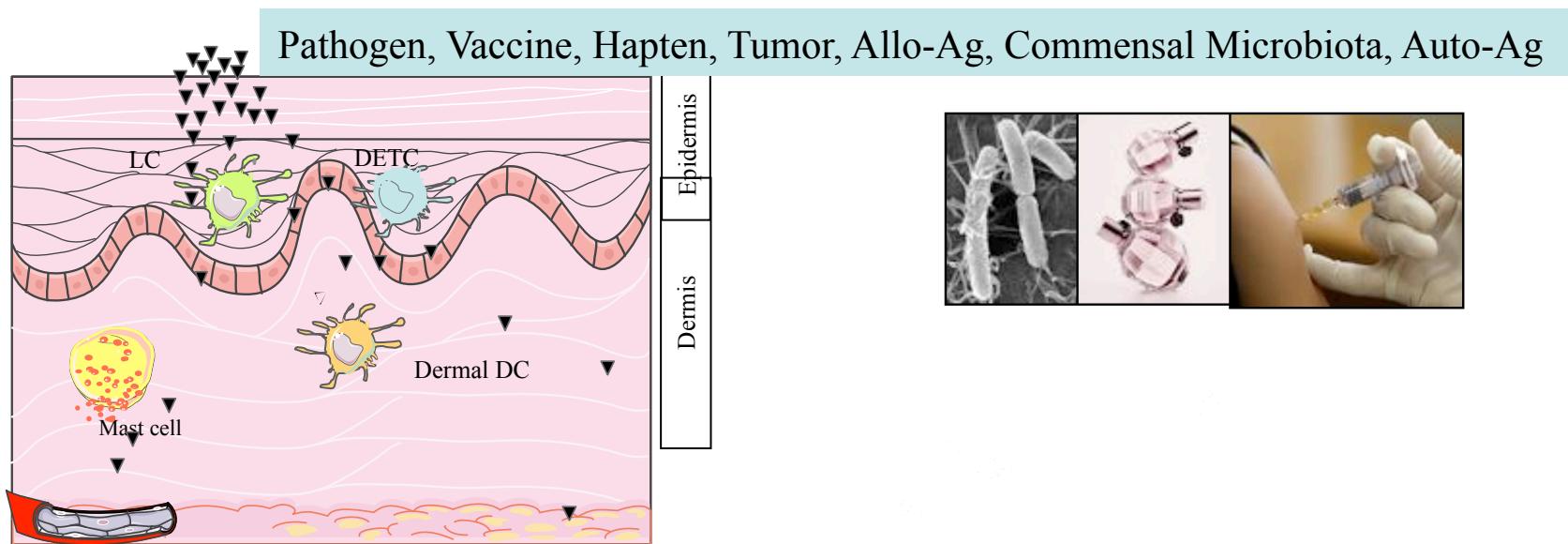
Induction of systemic immunity upon skin exposure/immunization

Skin exposure, immunization



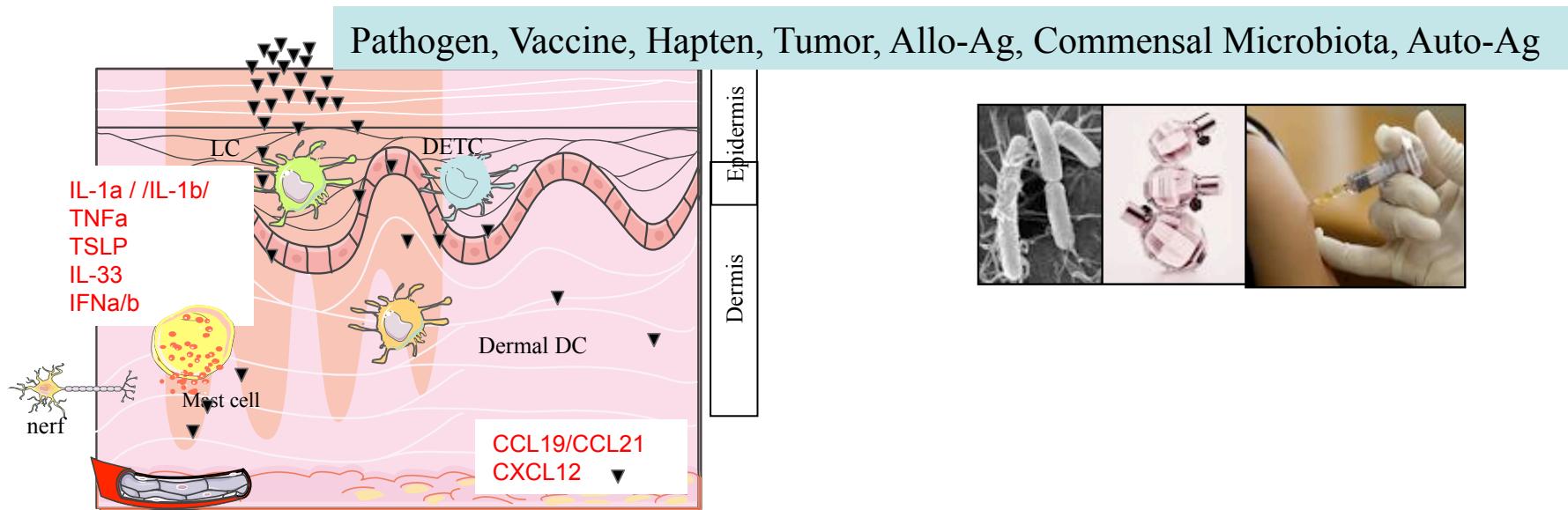
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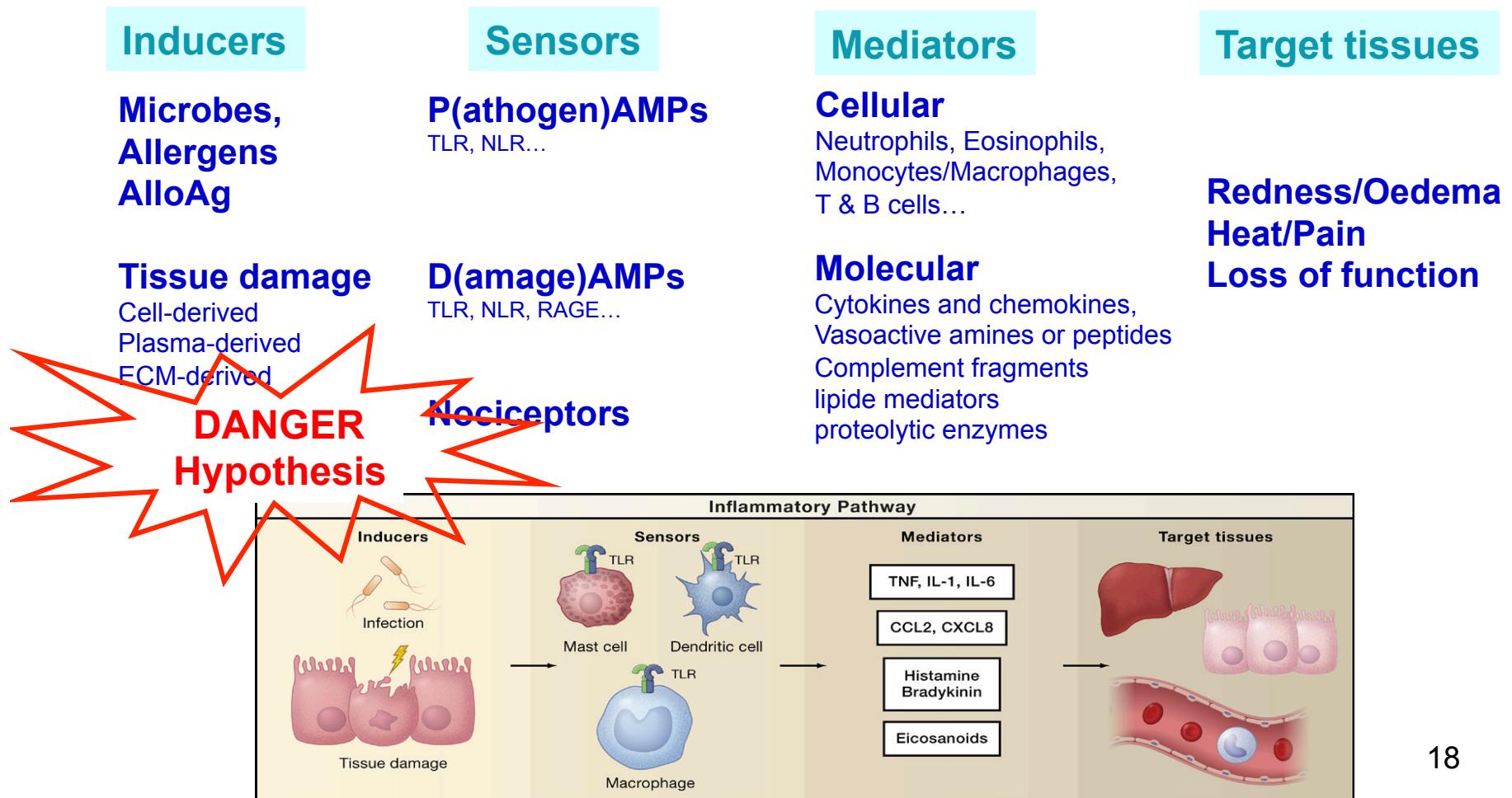
Innate immunity -> 1st line of defence

Release of inflammatory mediators

Inflammation

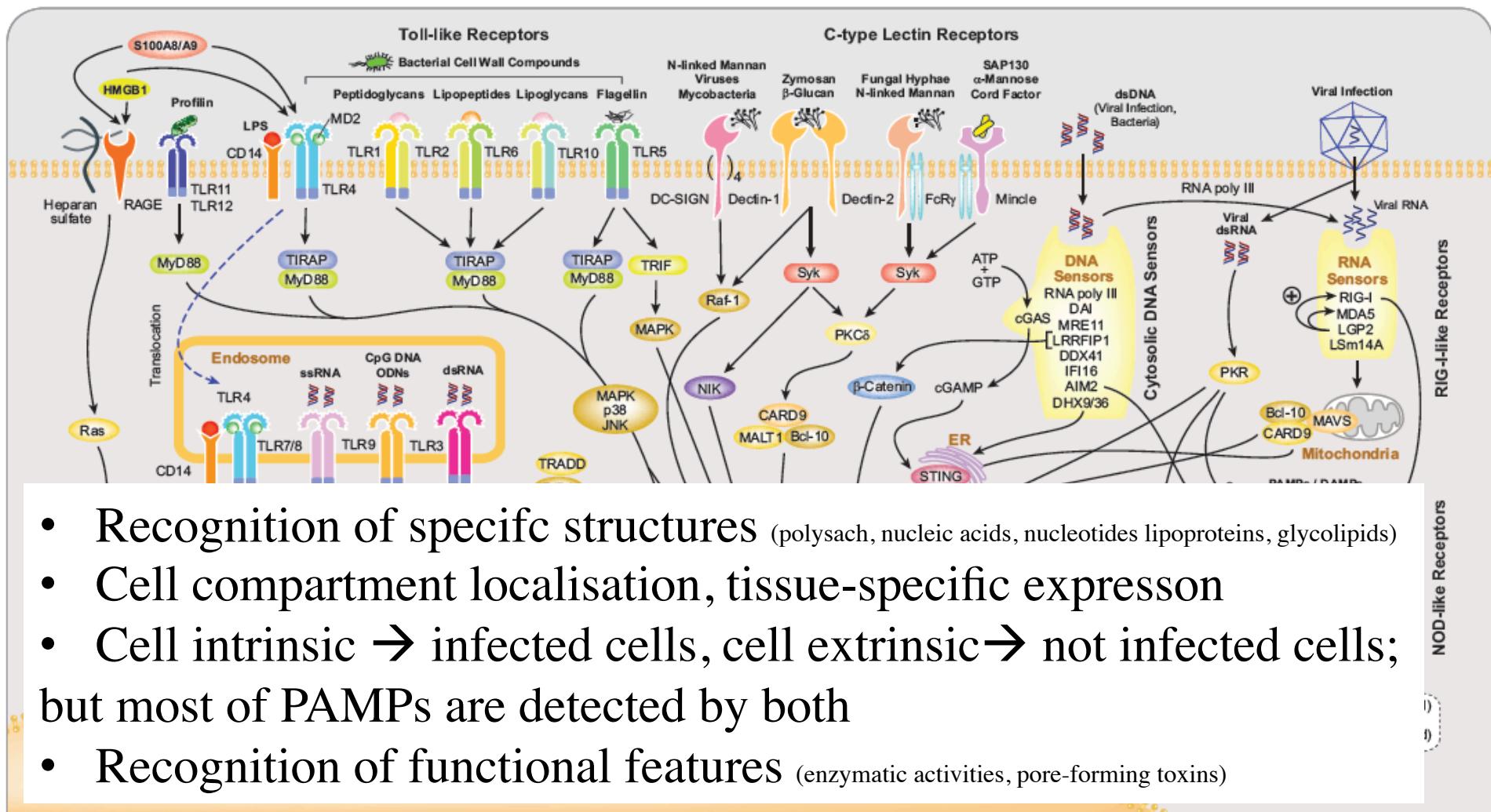
General scheme

4 major inflammatory components



Pathogen recognition receptors (PRRs)

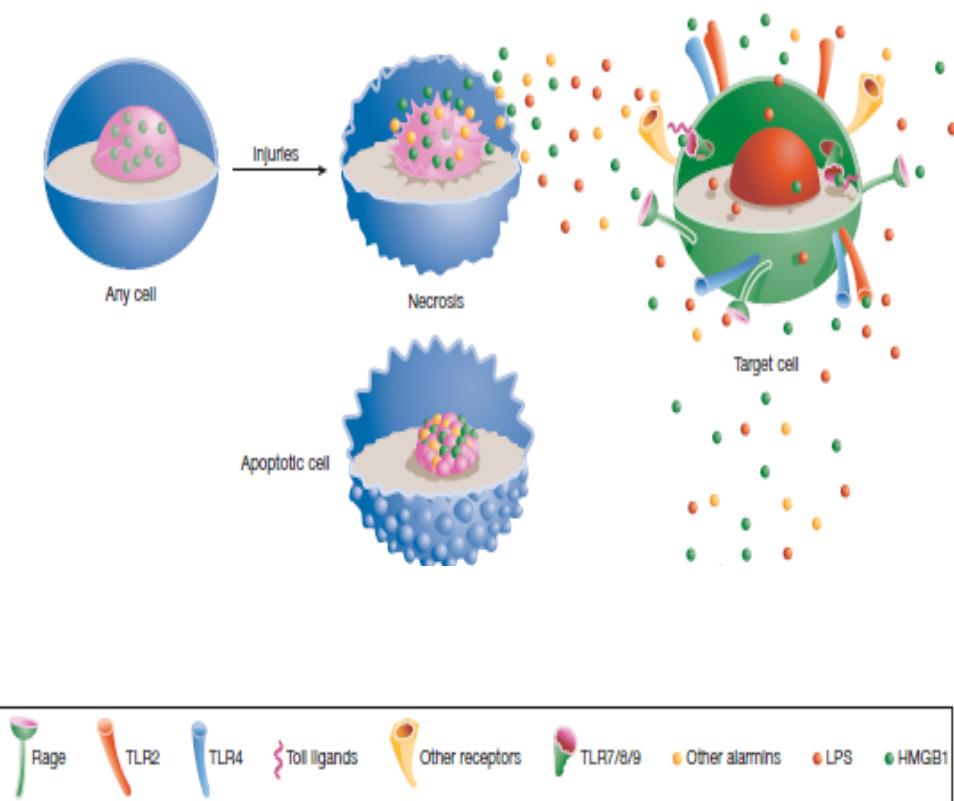
- Microbial Pattern Recognition Receptors: TLR, RLR, NLR, CLR signaling (examples)



Inflammation

PAMPs – DAMPs and their sensors

Intracellular DAMPs



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

Inflammation

PAMPs – DAMPs and their sensors

Extracellular DAMPs

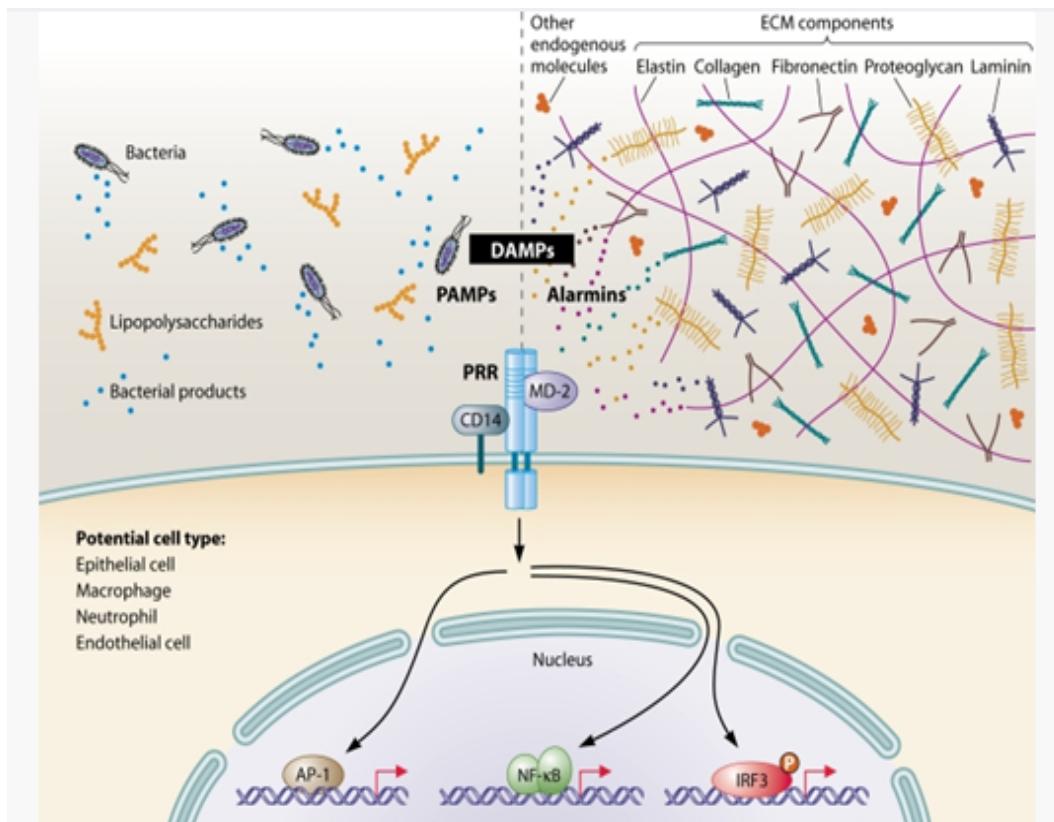
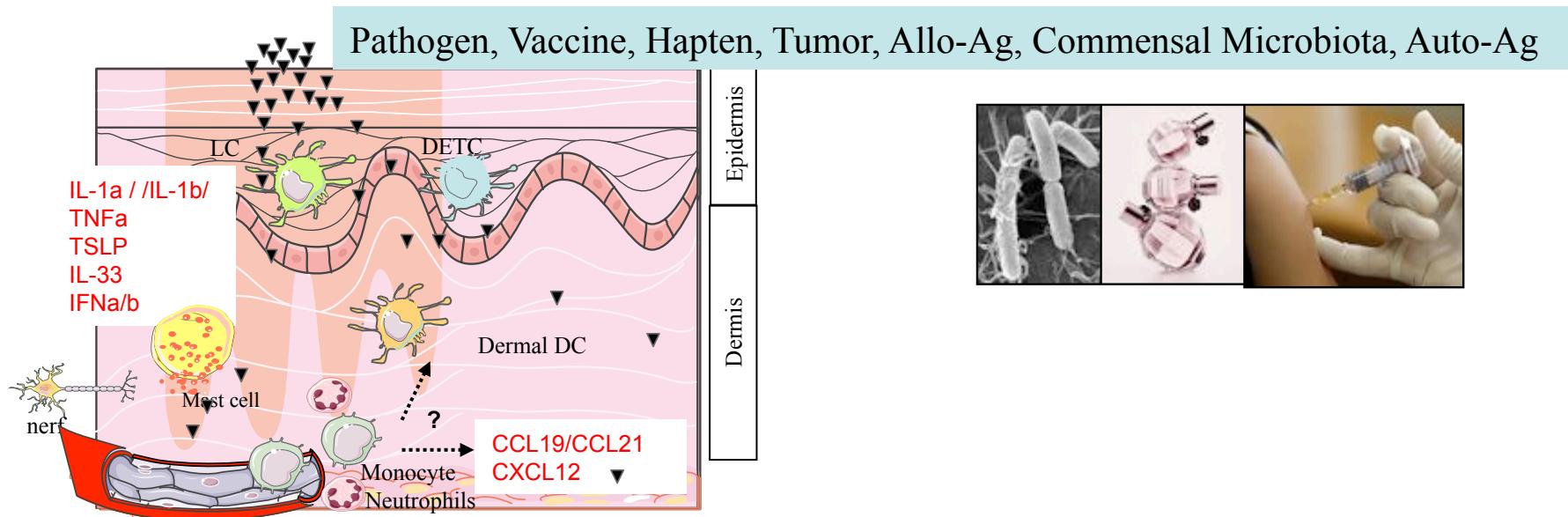


Table 2 | Adjuvant and pro-inflammatory activity of extracellular DAMPs

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

Induction of systemic immunity upon skin exposure/immunization

Skin exposure, immunization



Innate immunity -> 1st line of defence

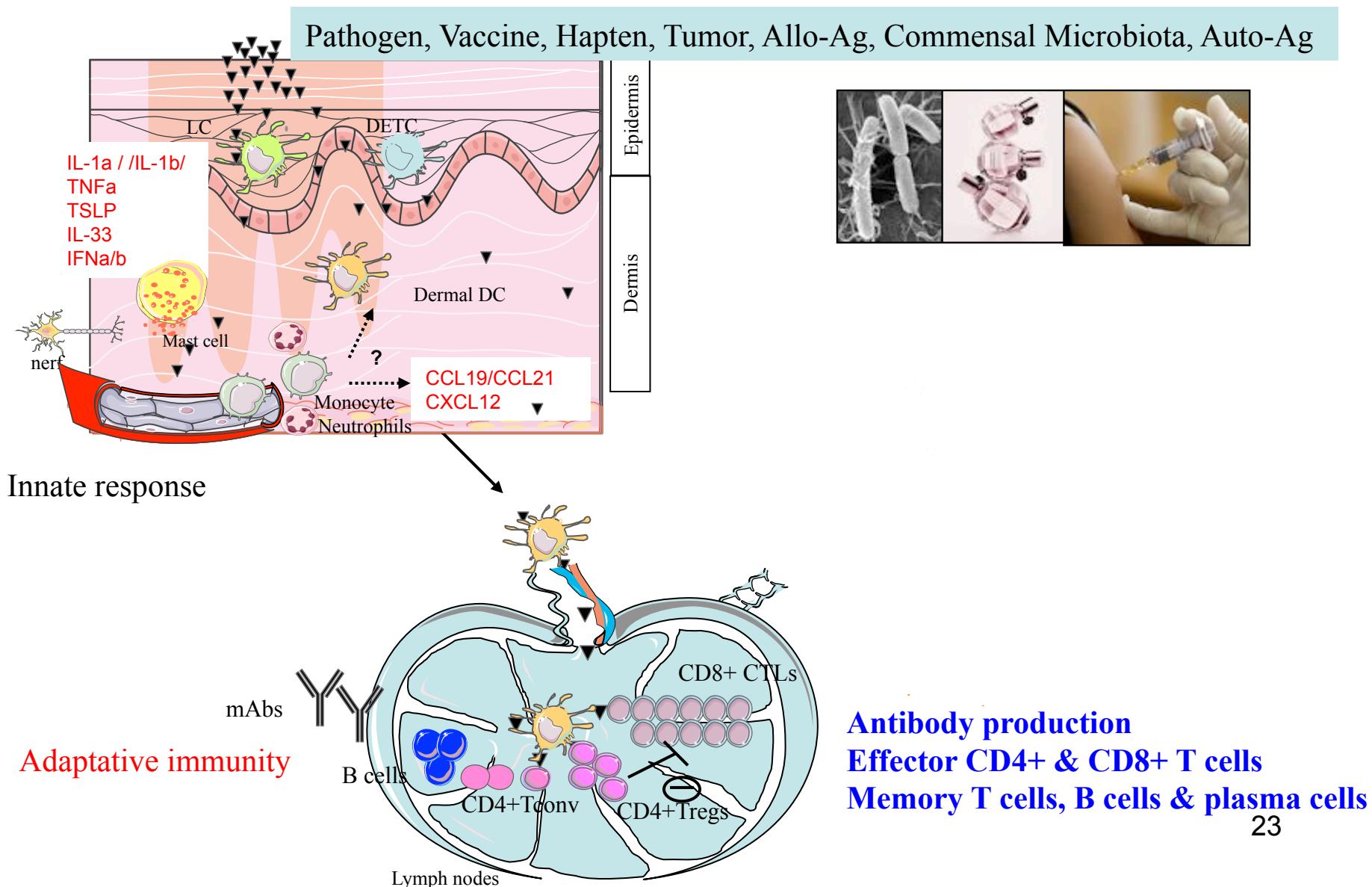
Release of inflammatory mediators

Coordinated cross-talk between epithelial and immune cells

Infiltration of blood leucocytes

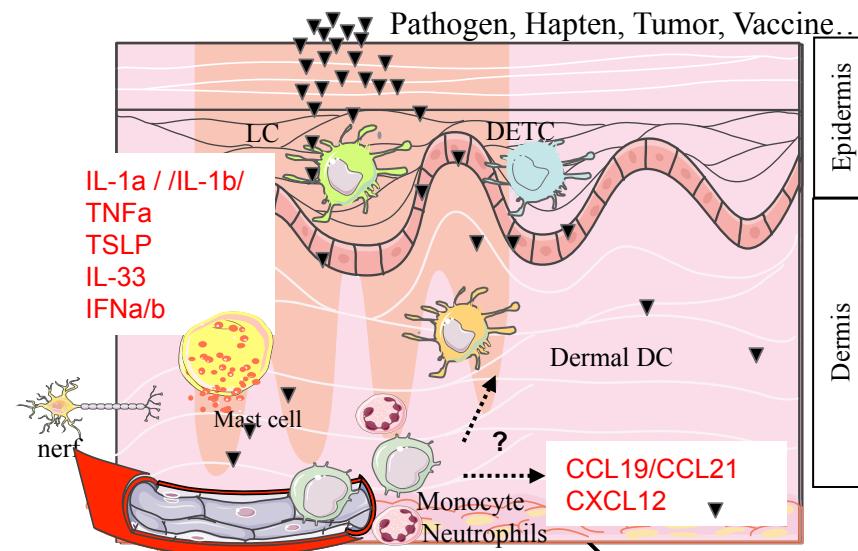
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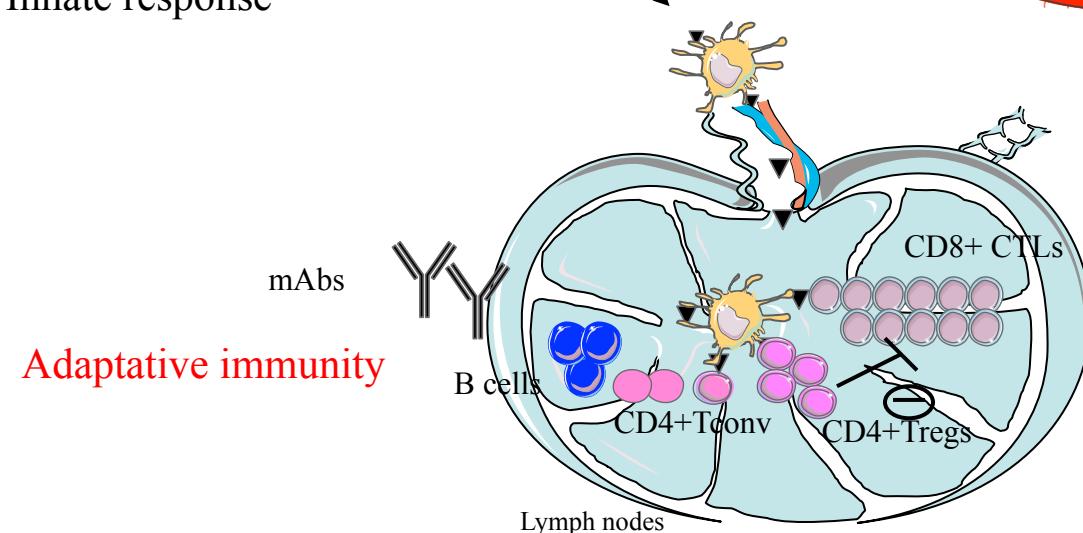


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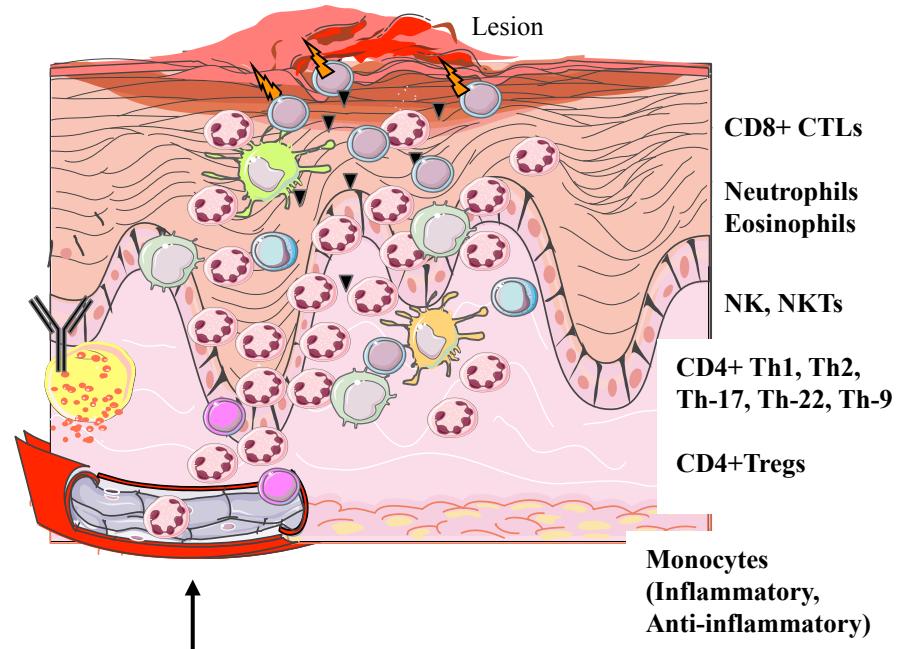


Innate response



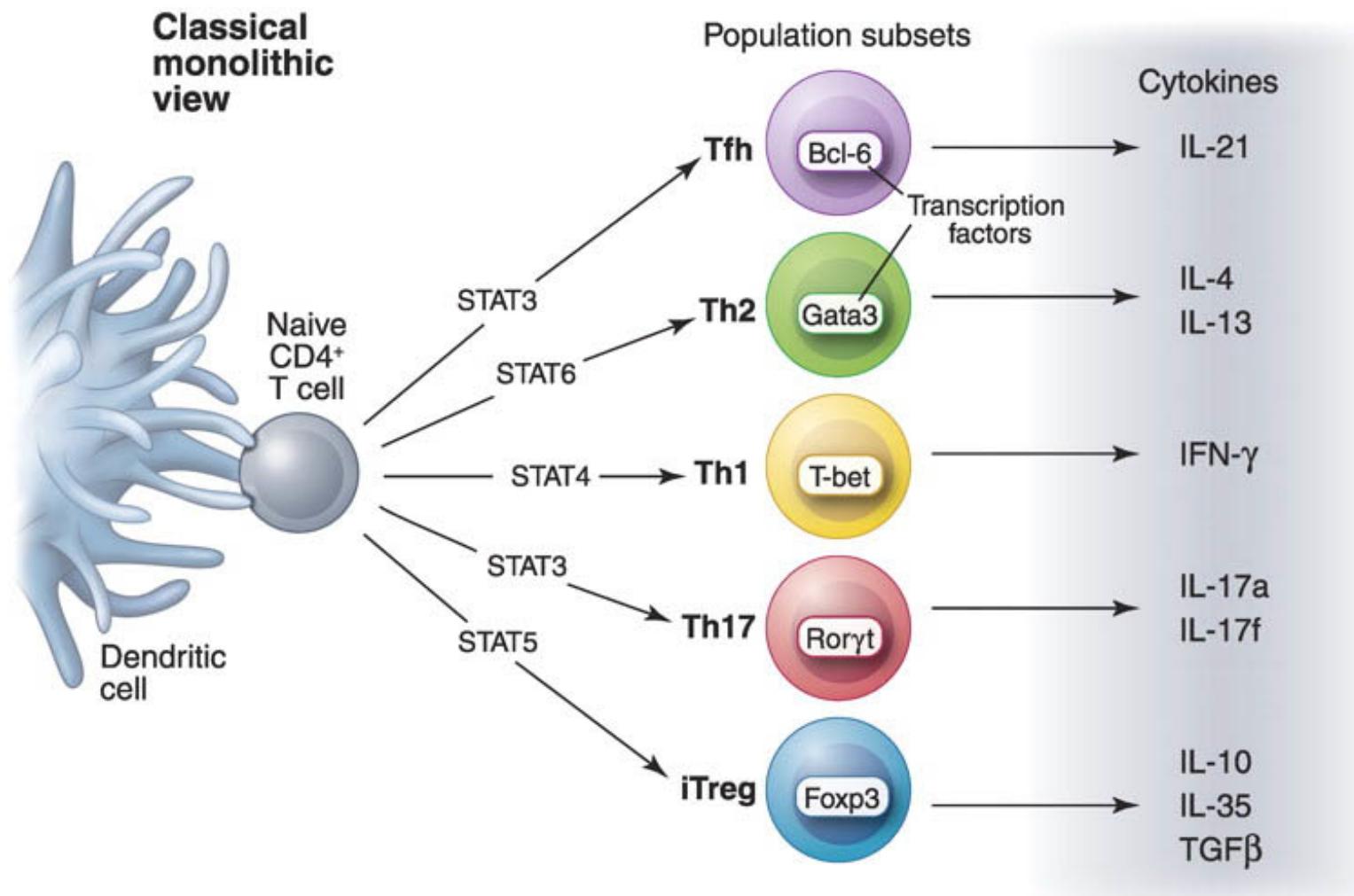
Adaptive immunity

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

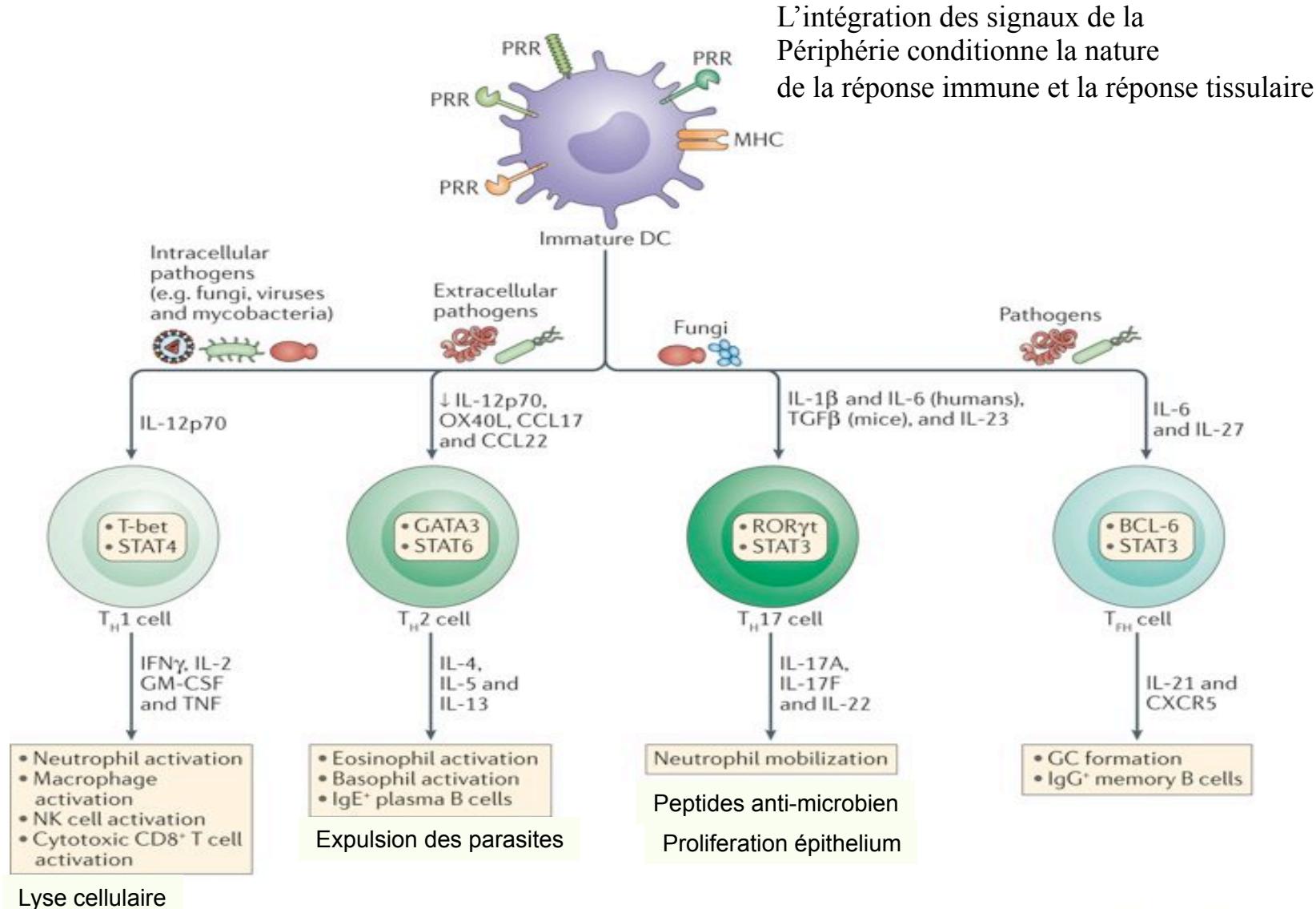


Effector & memory response -> 2nd line of defence

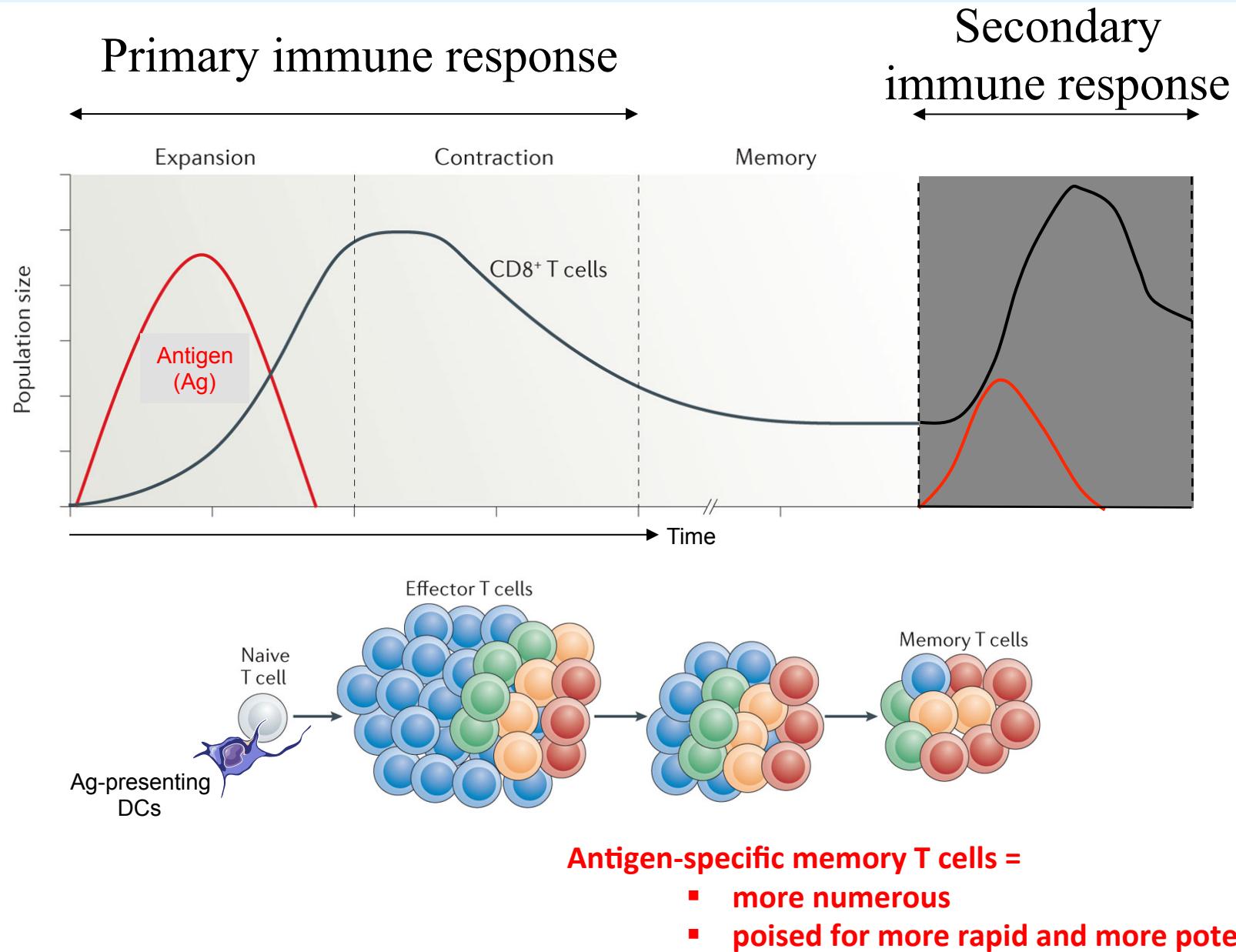
Distinct T cells



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



The development of T cell memory



PLAN

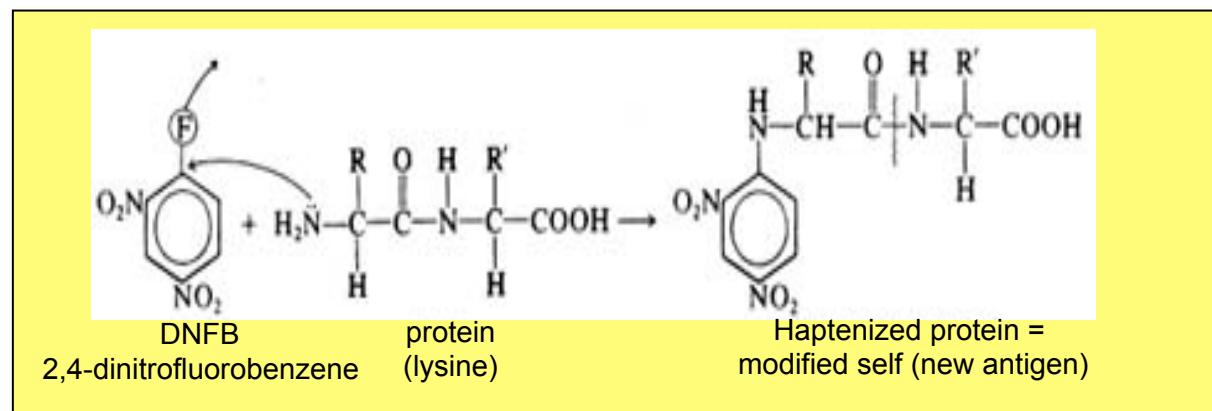
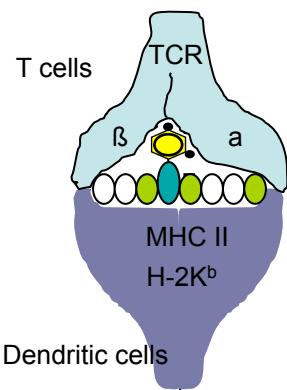
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Allergic Contact Dermatitis (ACD): Generalities



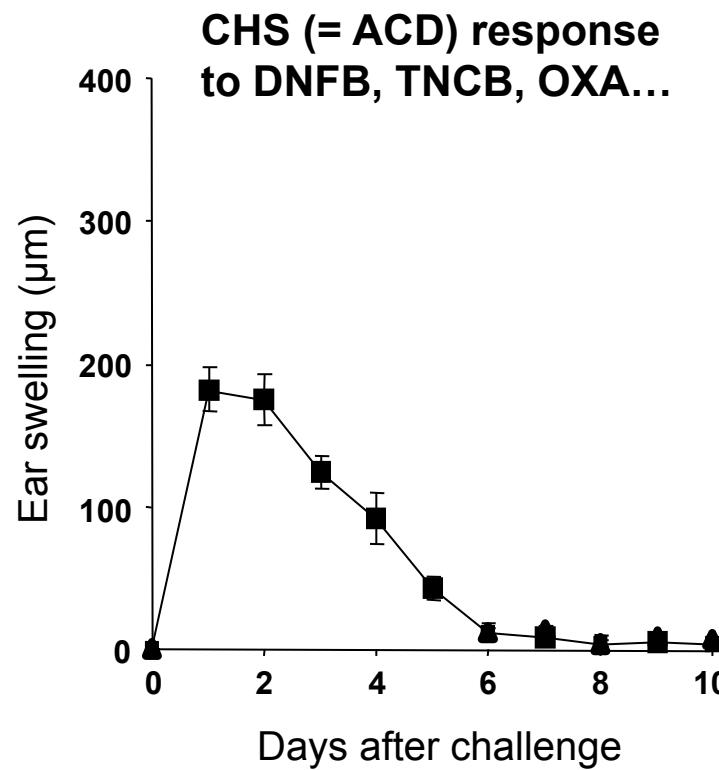
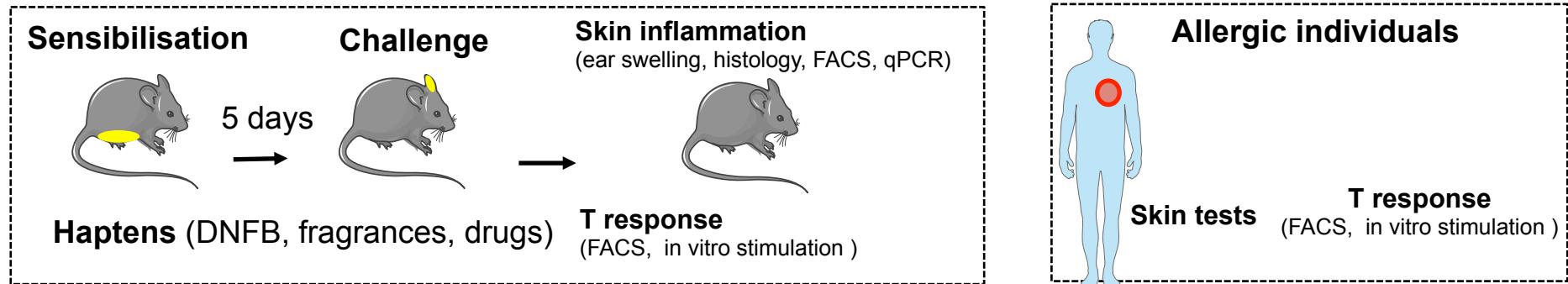
Features

- 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

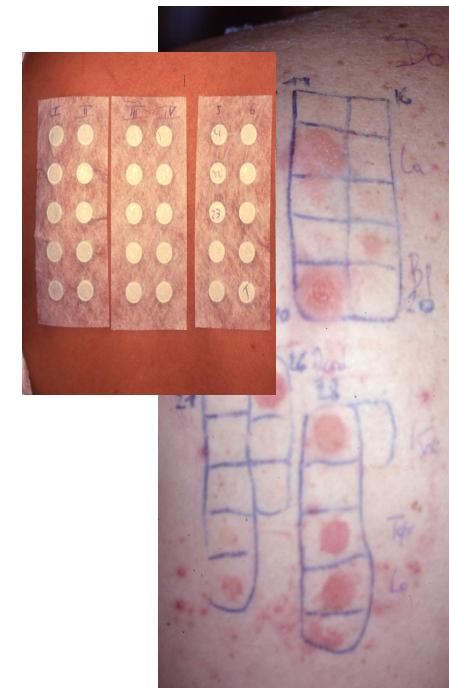
Experimental models of ACD in mouse, in human



ACD lesions



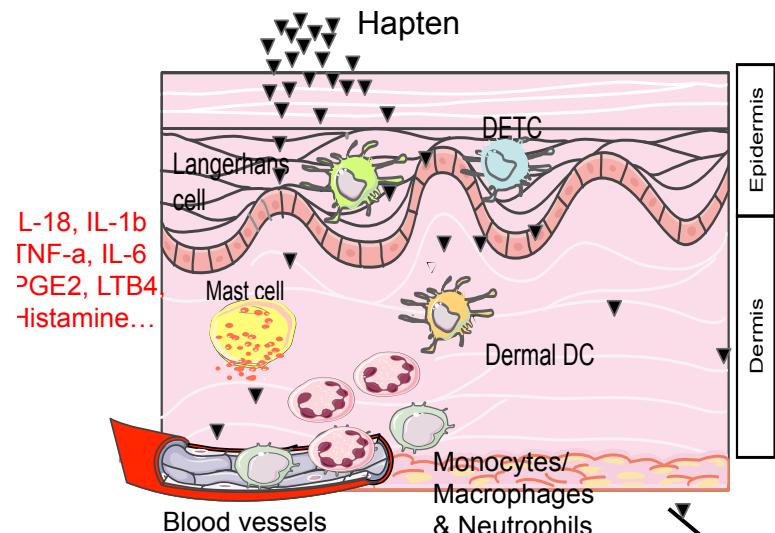
Positive patch-tests to reference allergens



Pathophysiology of Allergic Contact Dermatitis (ACD)

1- Sensitization phase

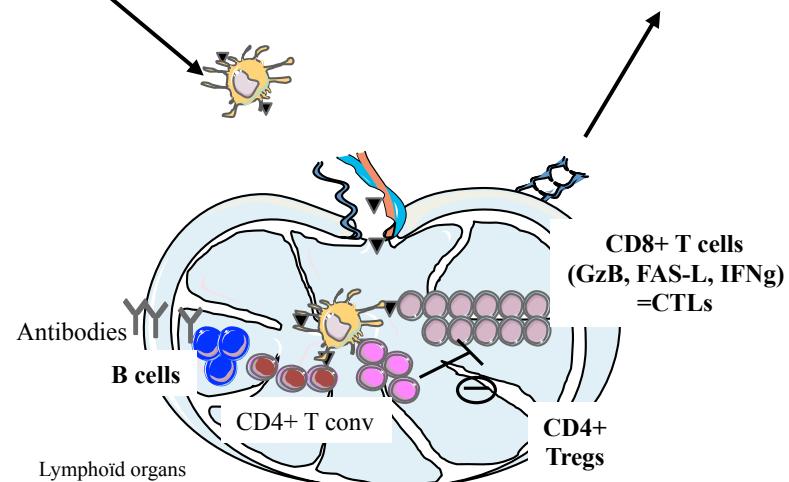
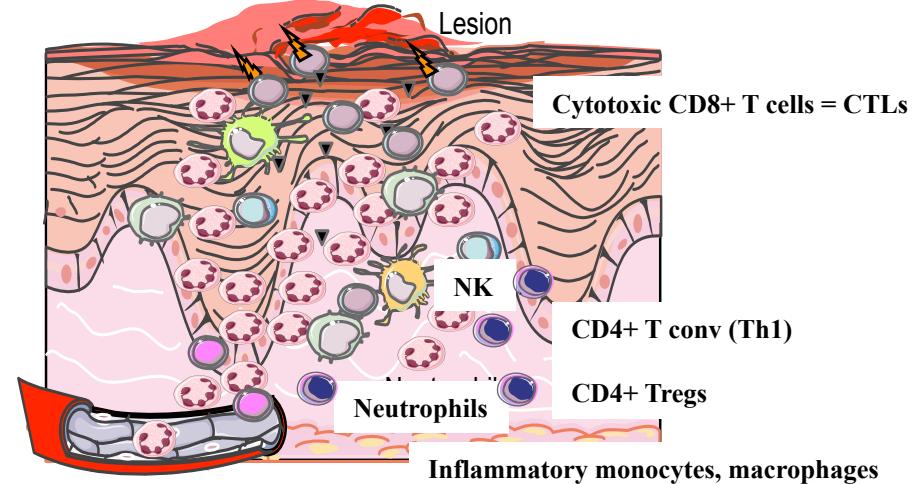
Innate immunity/ T cell priming



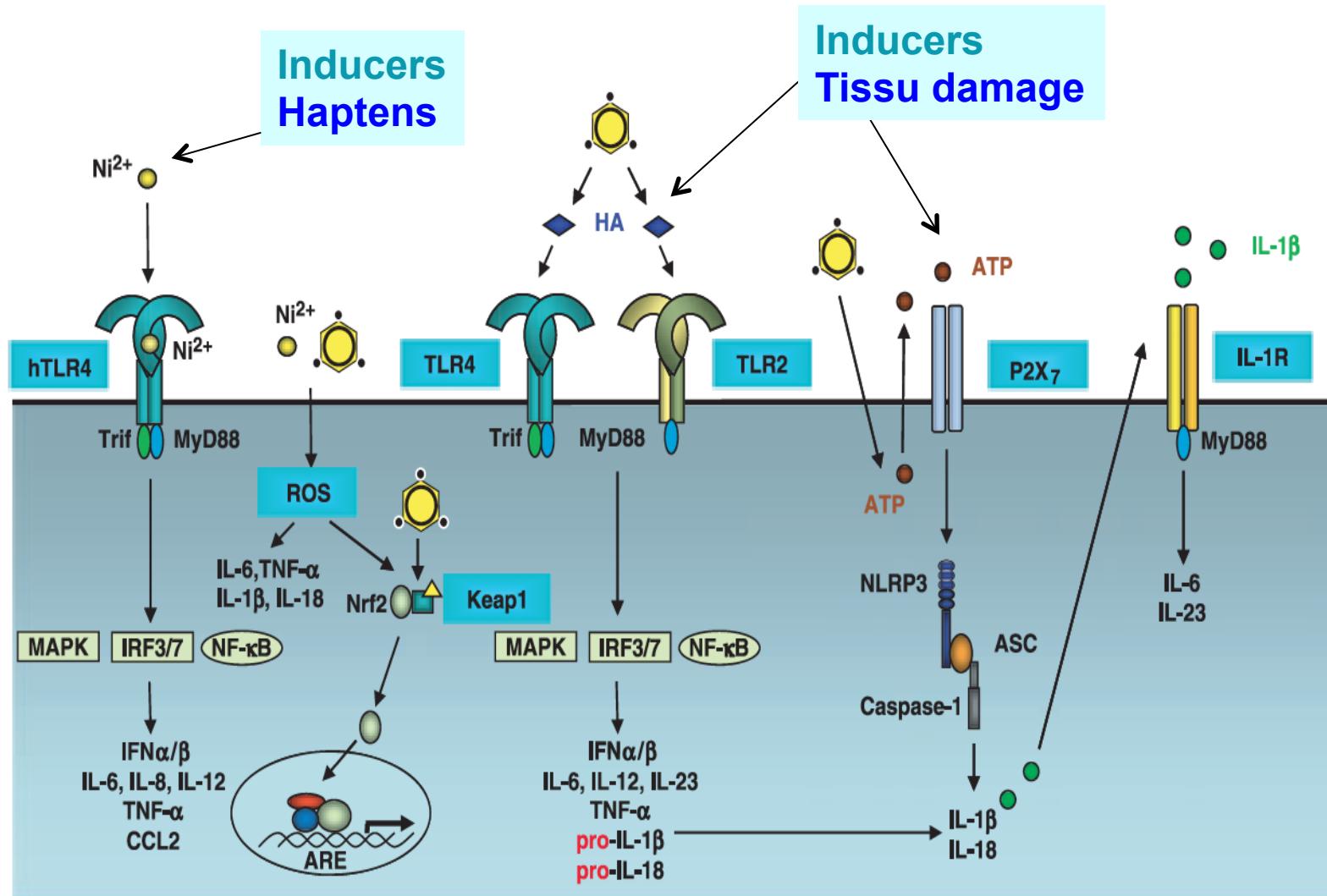
- BOUR et al. *Eur J Immunol*, 1995
- KRASTEVA et al. *J Immunol*, 1998
- KEHREN et al. *J Exp Med*, 1999
- AKIBA et al. *J Immunol*, 2002
- SAINT-MEZARD et al. *J Immunol*, 2003
- AKIBA et al. *J Invest Dermatol*, 2004
- SAINT-MEZARD et al. *J Invest Dermatol*, 2005
- VOCANSON et al. *J Invest Dermatol*, 2006
- BONNEVILLE et al. *J Invest Dermatol*, 2007
- HENNINO et al. *J Immunol*, 2007
- VOCANSON et al. *J Invest Dermatol*, 2009
- VOCANSON et al., *Allergy*, 2009
- VOCANSON et al. *J Allergy Clin Immunol*, 2010
- ROZIERES et al., *Allergy*, 2010
- VANBERVLIET et al. *J Allergy Clin Immunol*, 2011
- ROUZAIRE et al. *Eur J Immunol*, 2012
- GOUBIER et al. *J Invest Dermatol*, 2013
- CORTIAL et al. *Nanomedicine*, 2015

2- Elicitation phase

Effector response/ Polymorphic recruitment

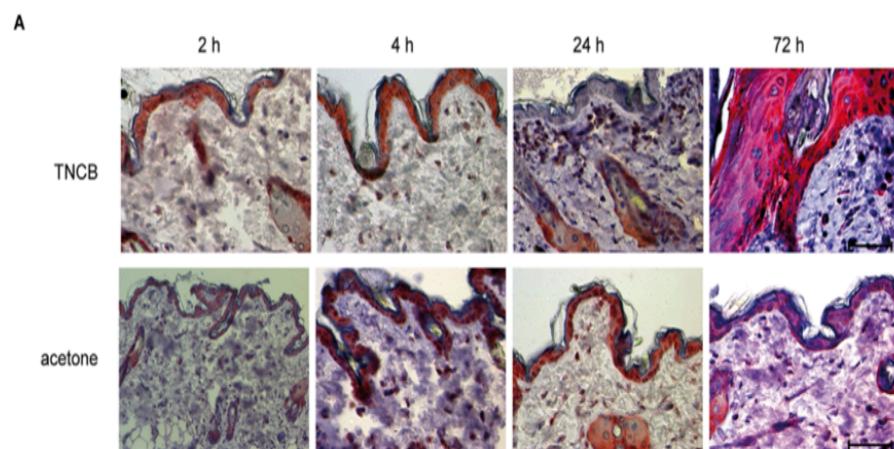
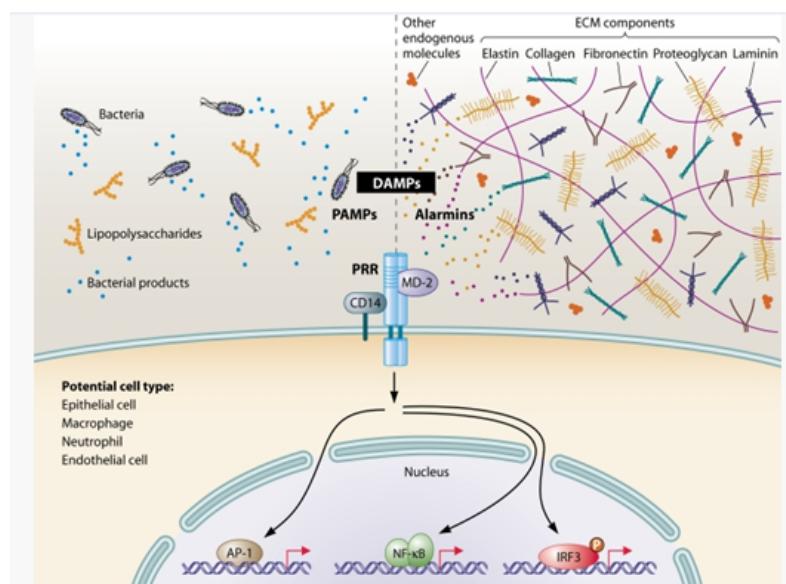


How haptens activate innate immunity?

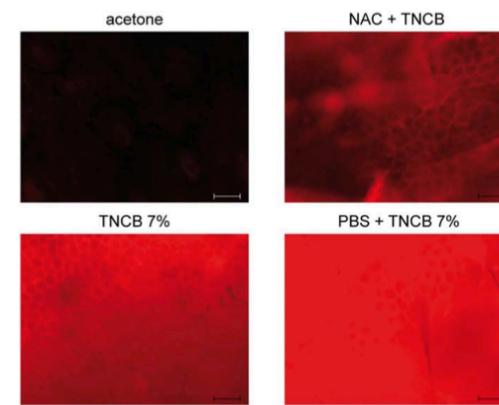


Les diverses étapes de la sensibilisation : activation de l'immunité innée

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

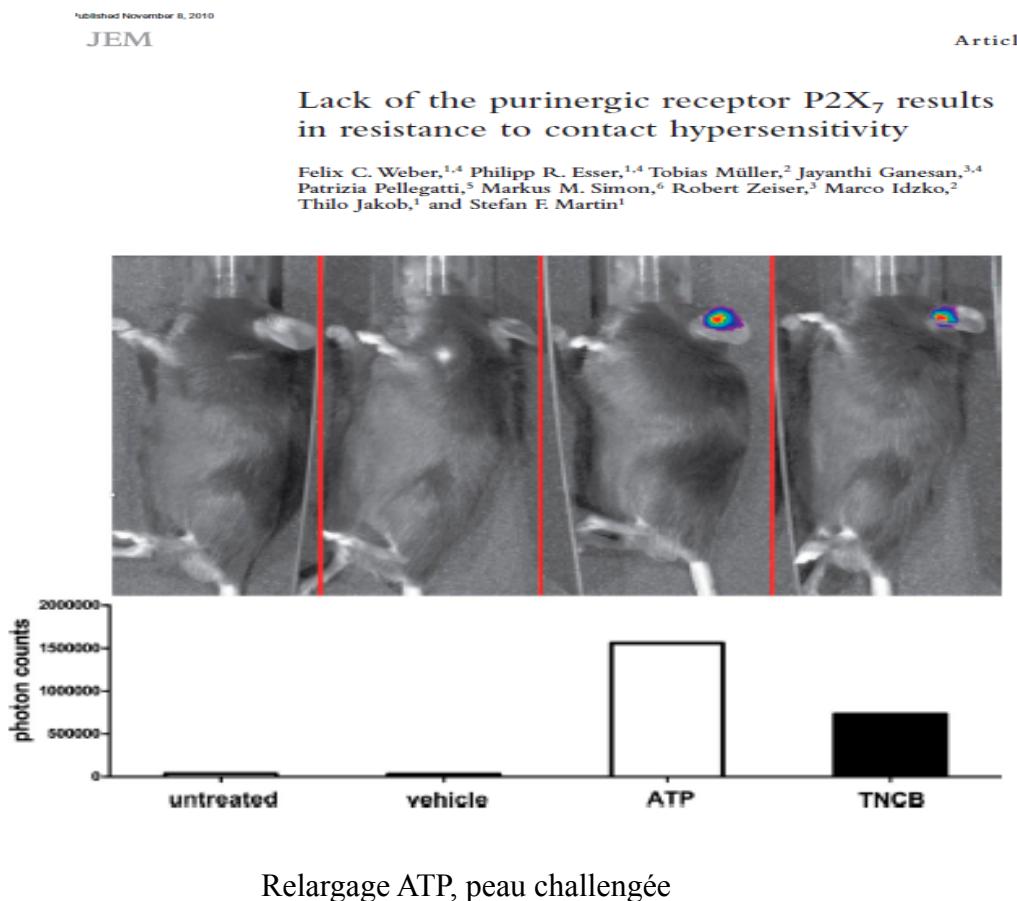


Dégredation Acide Hyaluronique ht PW, 24h après application

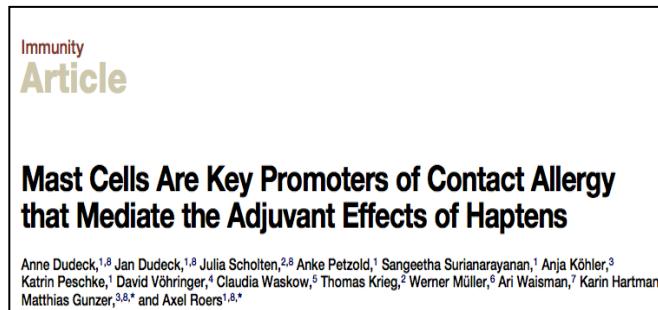


Les diverses étapes de la sensibilisation : activation de l'immunité innée

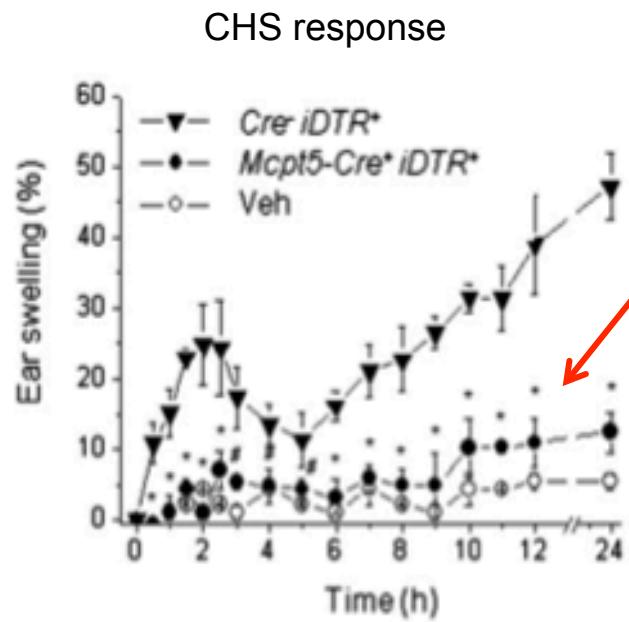
- Impact des médiateurs reconnus par les NLRs sur le développement de la réponse d'EAC



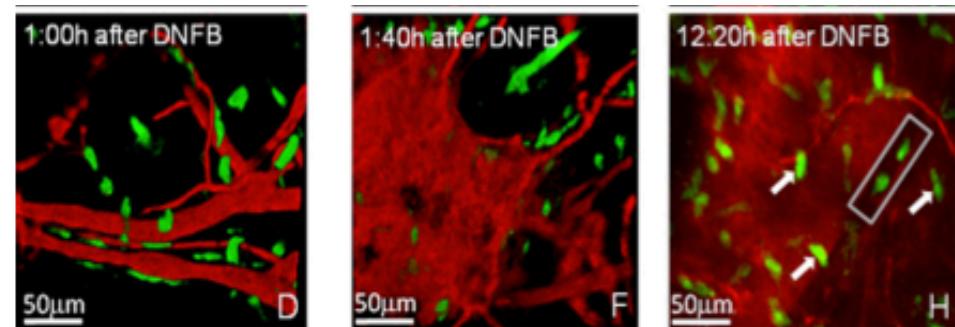
Contribution of innate cells? Mast cells



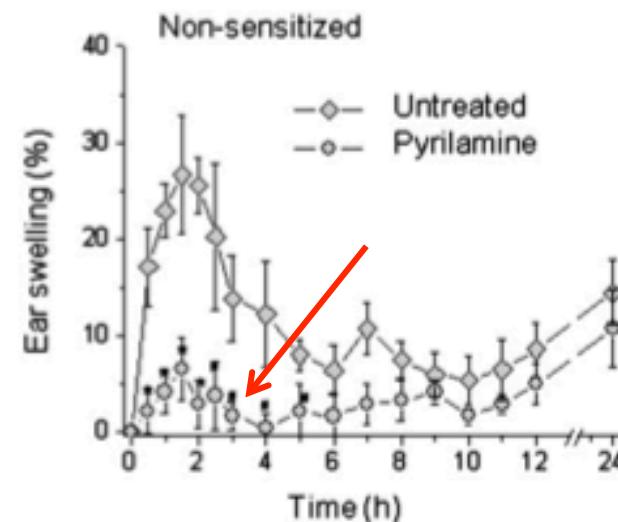
Dramatic decrease of CHS response in animals conditionally depleted in mast cells



Ear skin mast cells and blood vessels respond to hapten

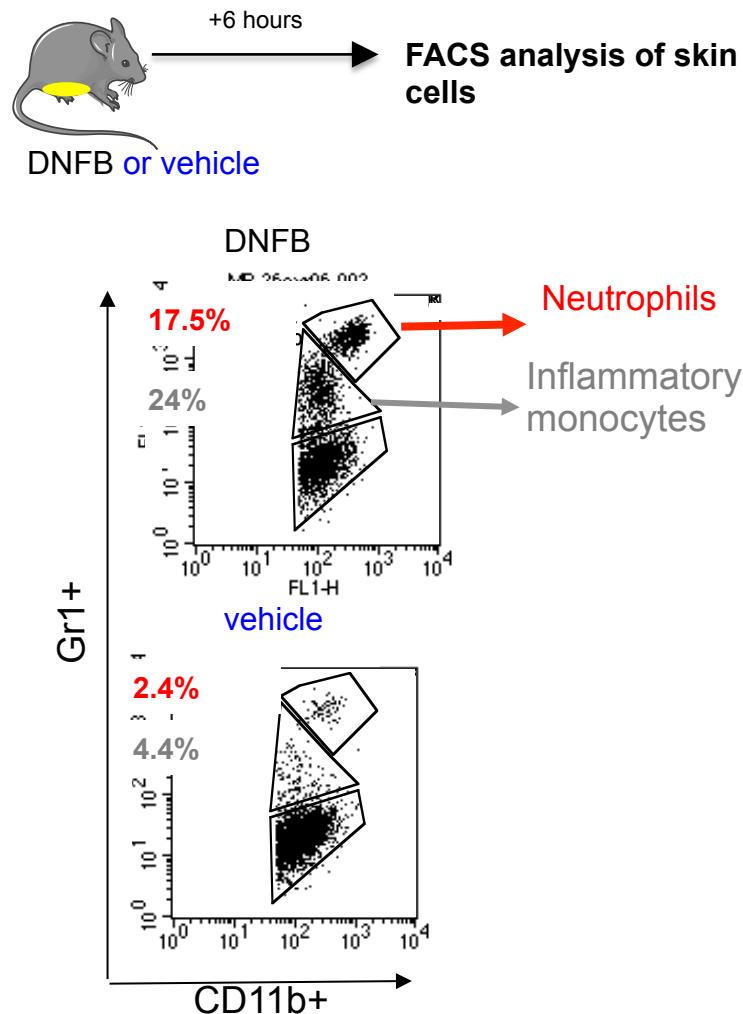


Skin inflammation is histamine-dependent

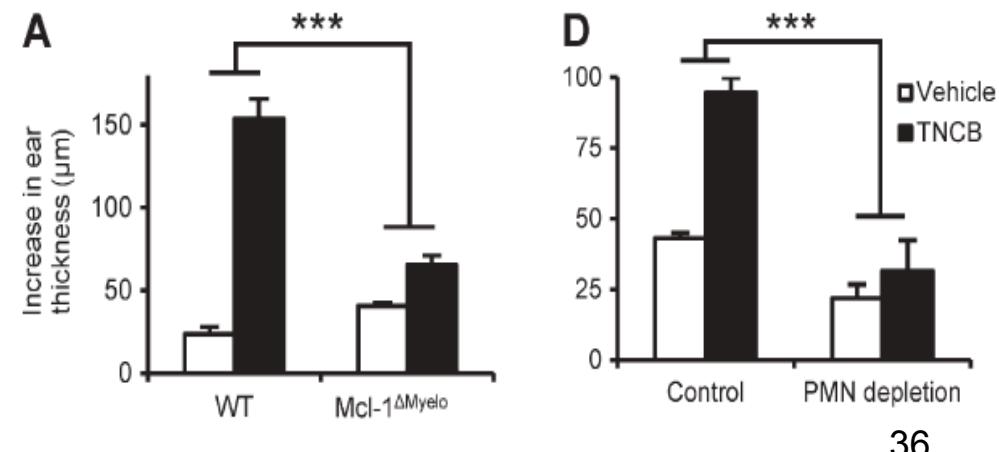
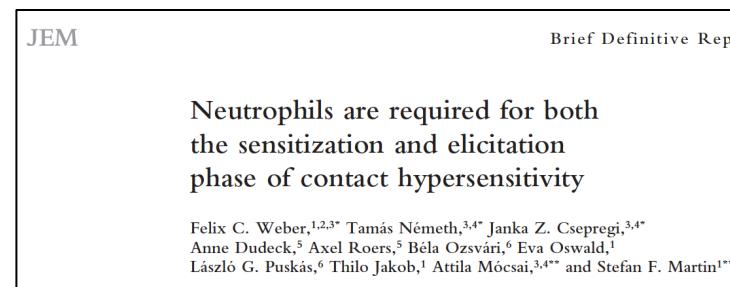


Contribution of innate cells? Neutrophils

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

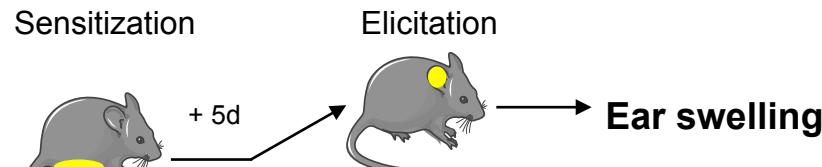


Main effectors? CD8+ CTLs

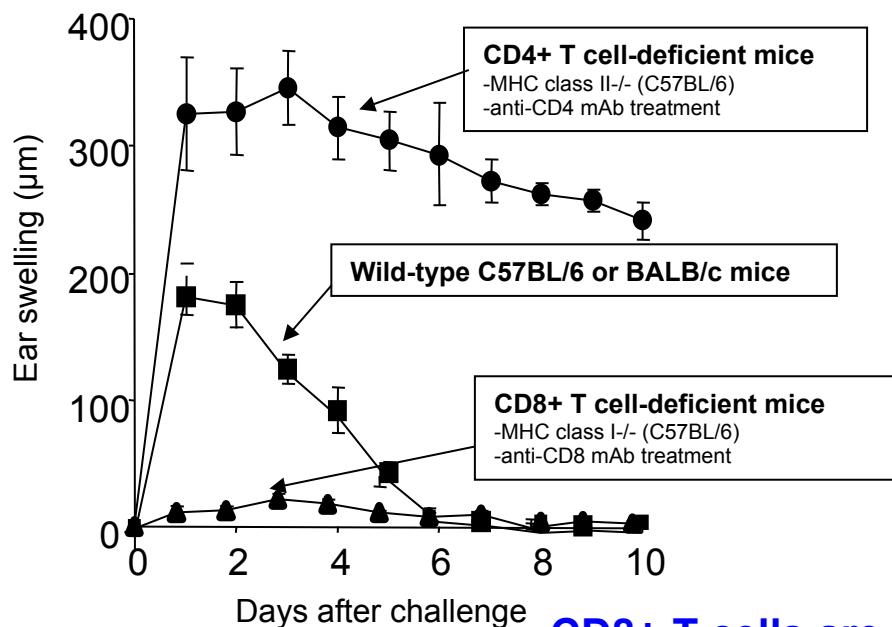
Journal of Investigative Dermatology (2006) 126, 815-820. doi:10.1038/sj.jid.5700174; published online 2 February 2006

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

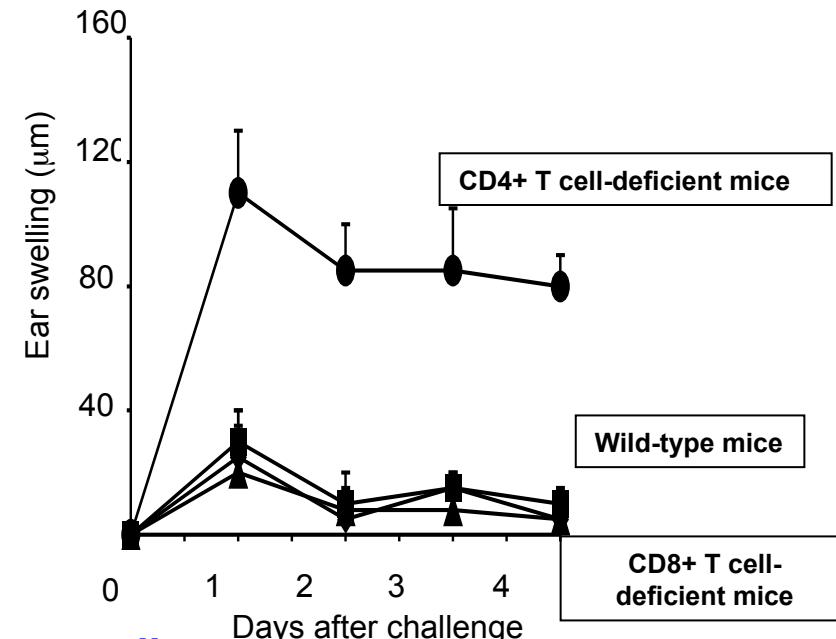
Marc Vocanson¹, Anca Hennino¹, Magalie Cluzel-Tailhardat¹, Pierre Saint-Mezard¹, Josette Benetiere¹, Cyril Chavagnac¹, Frederic Berard^{1,2}, Dominique Kaiserlian³ and Jean-François Nicolas^{1,2}



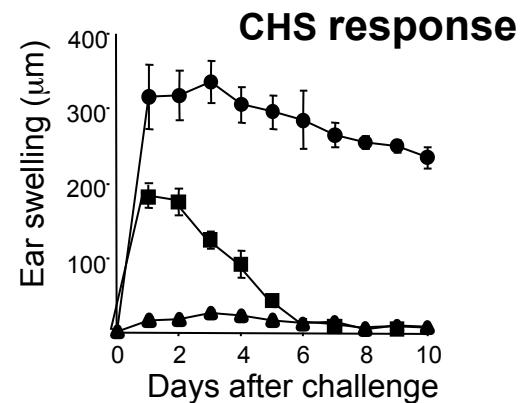
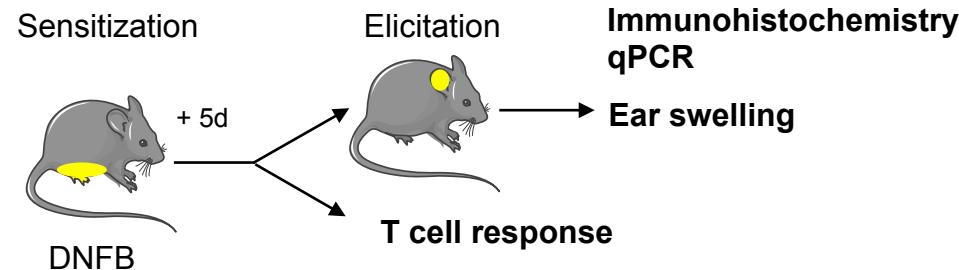
Strong haptens: DNFB, OXA...



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



Main effectors? CD8+ CTLs

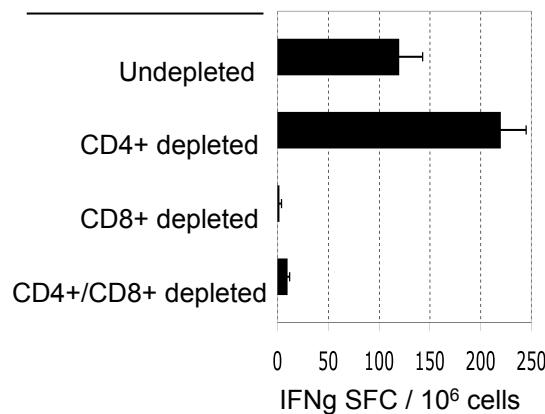


Priming of IFNg-producing CD8+ T cells

T cell response
(draining lymph nodes)

Elispot assay

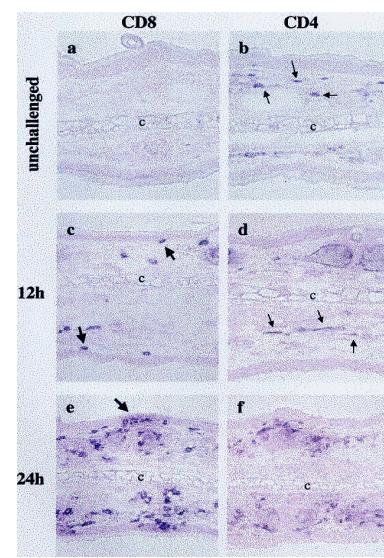
mAb Treatment



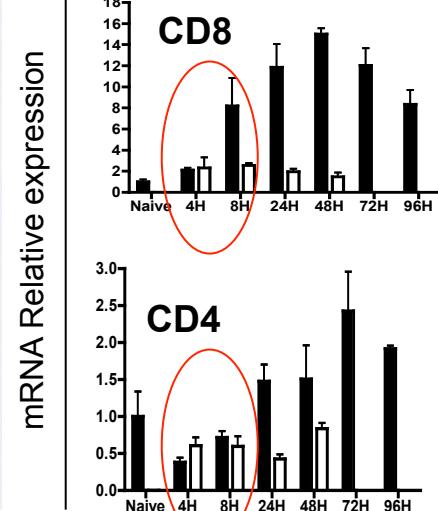
Early recruitment of CD8+ T cells initiates eczema

T cells recruitment
(challenged ears)

Immunostaining

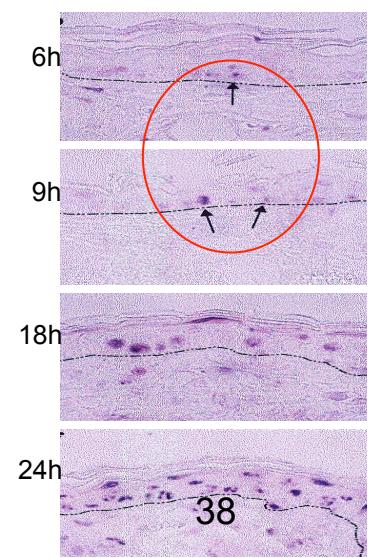


mRNA Relative expression ↑

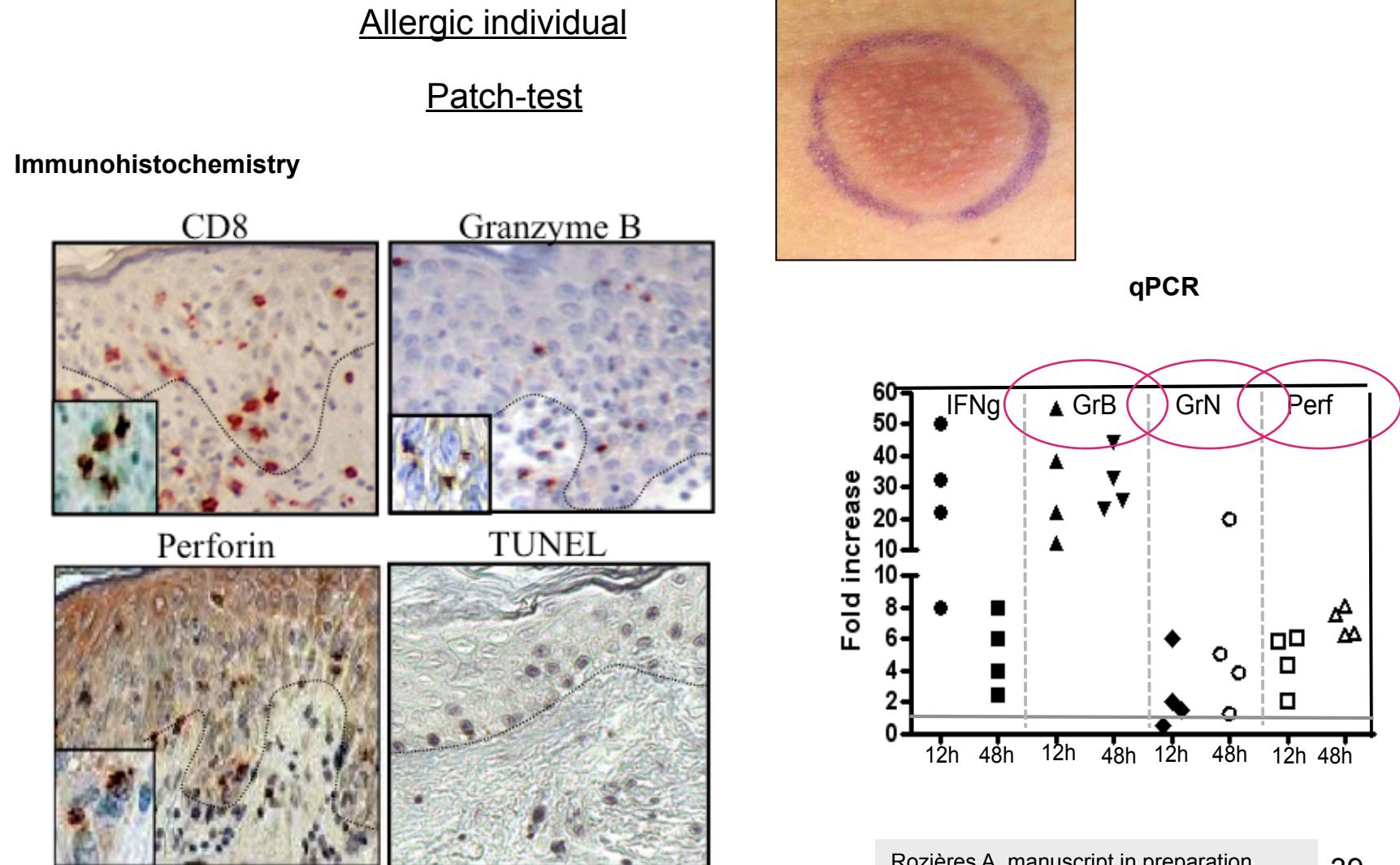


Keratinocytes:
target of CTLs

TUNEL

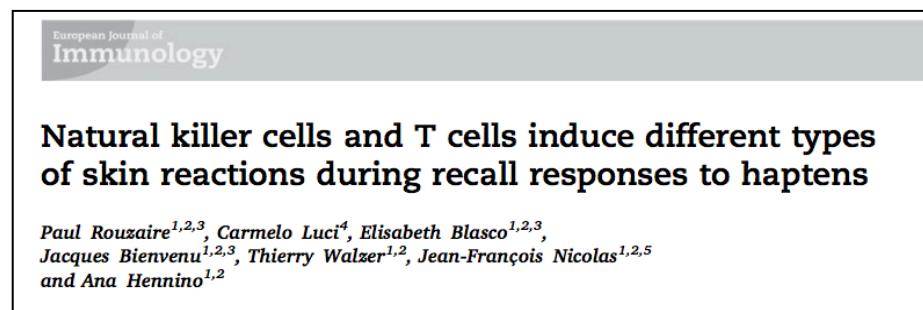


Main effectors? CD8+ CTLs



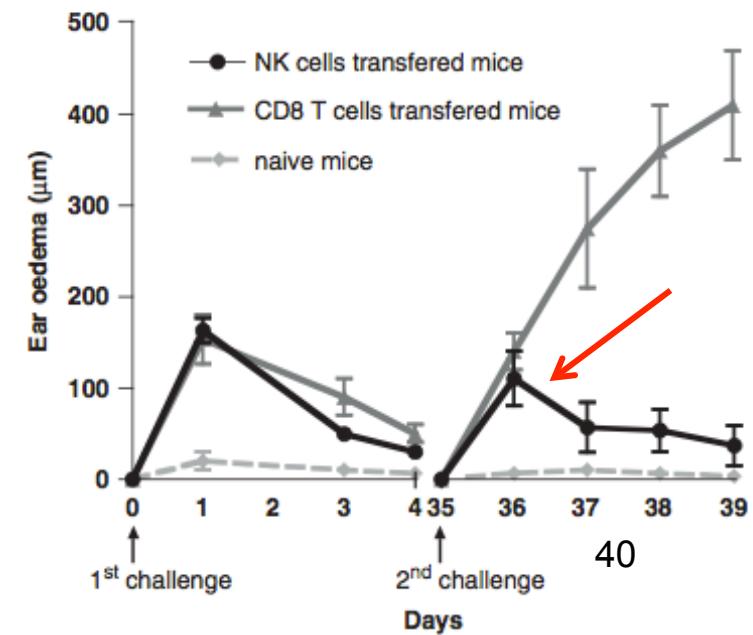
Main effectors? NK cells

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



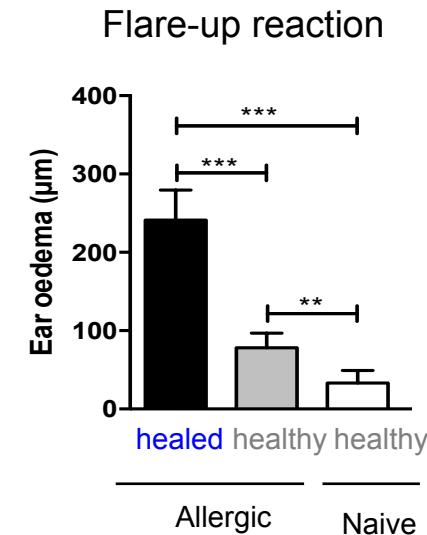
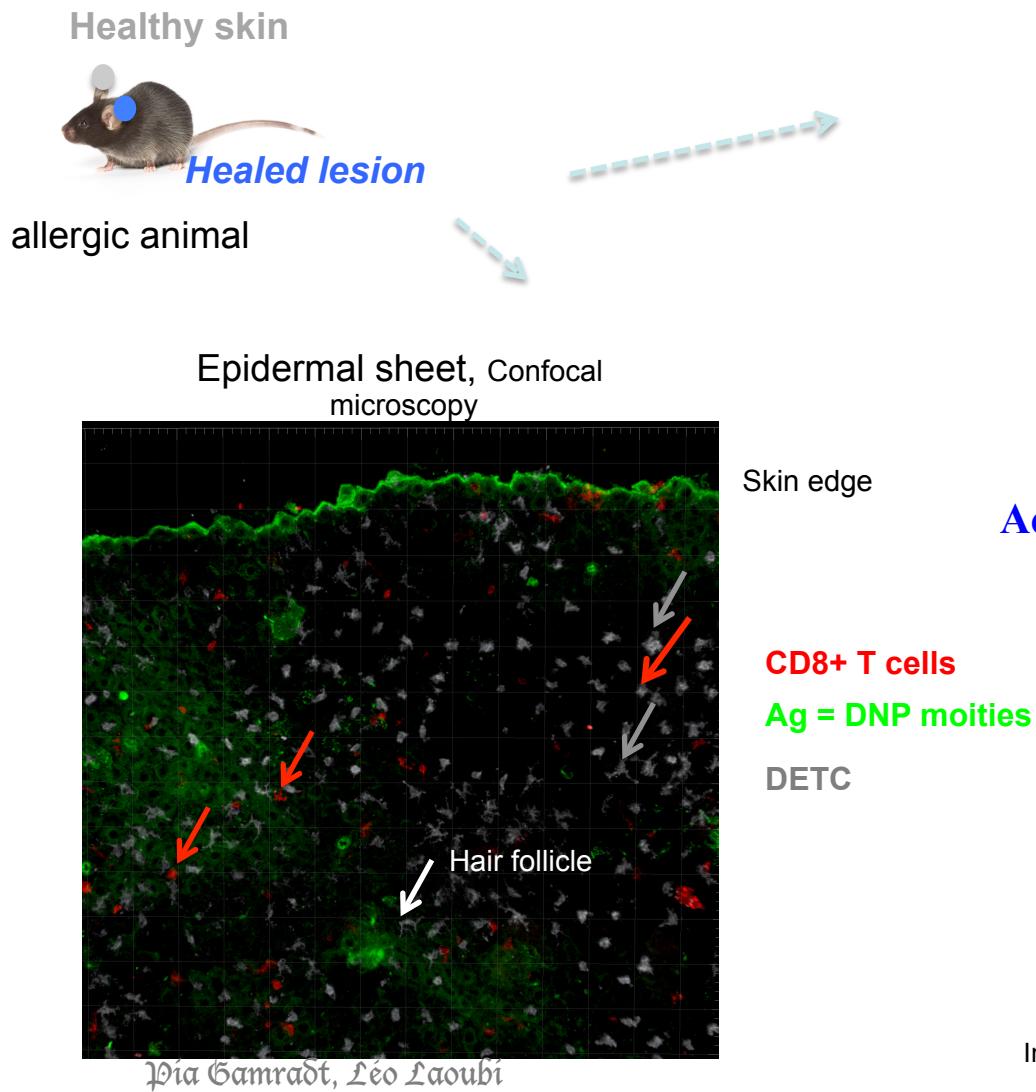
- Paulst S. Nat Immunol 2011

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

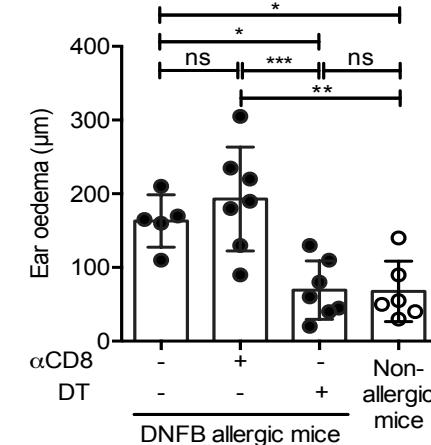


Main effectors? CD8+ CTLs

Recurrence, chronicity



Acute depletion of CD8+Trm abrogates flares



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

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

PERSPECTIVE

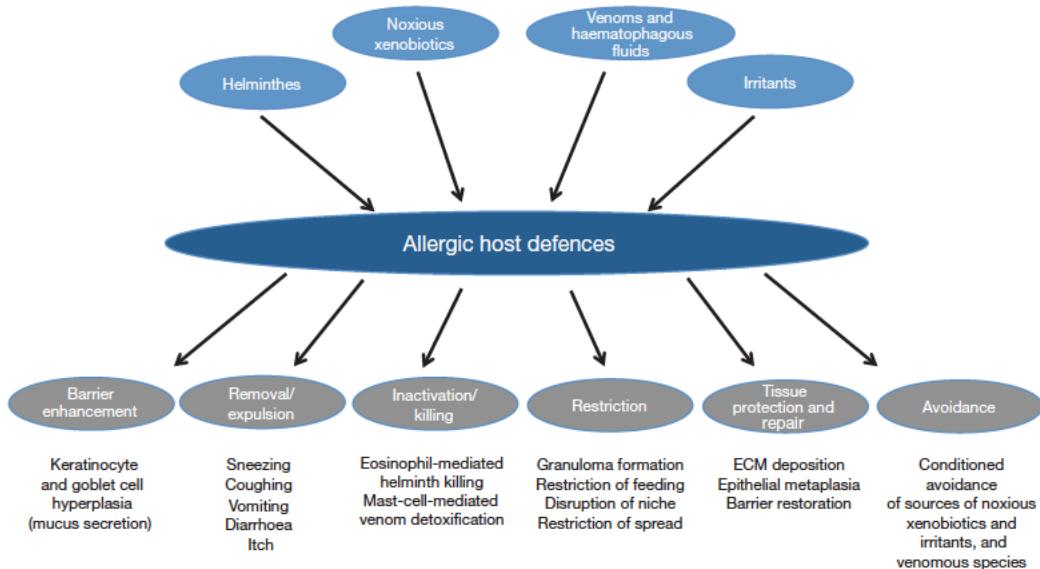
doi:10.1038/nature11047

Allergic host defences

Noah W. Palm^{1*}, Rachel K. Rosenstein^{1*} & Ruslan Medzhitov¹

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.

RESEARCH PERSPECTIVE



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

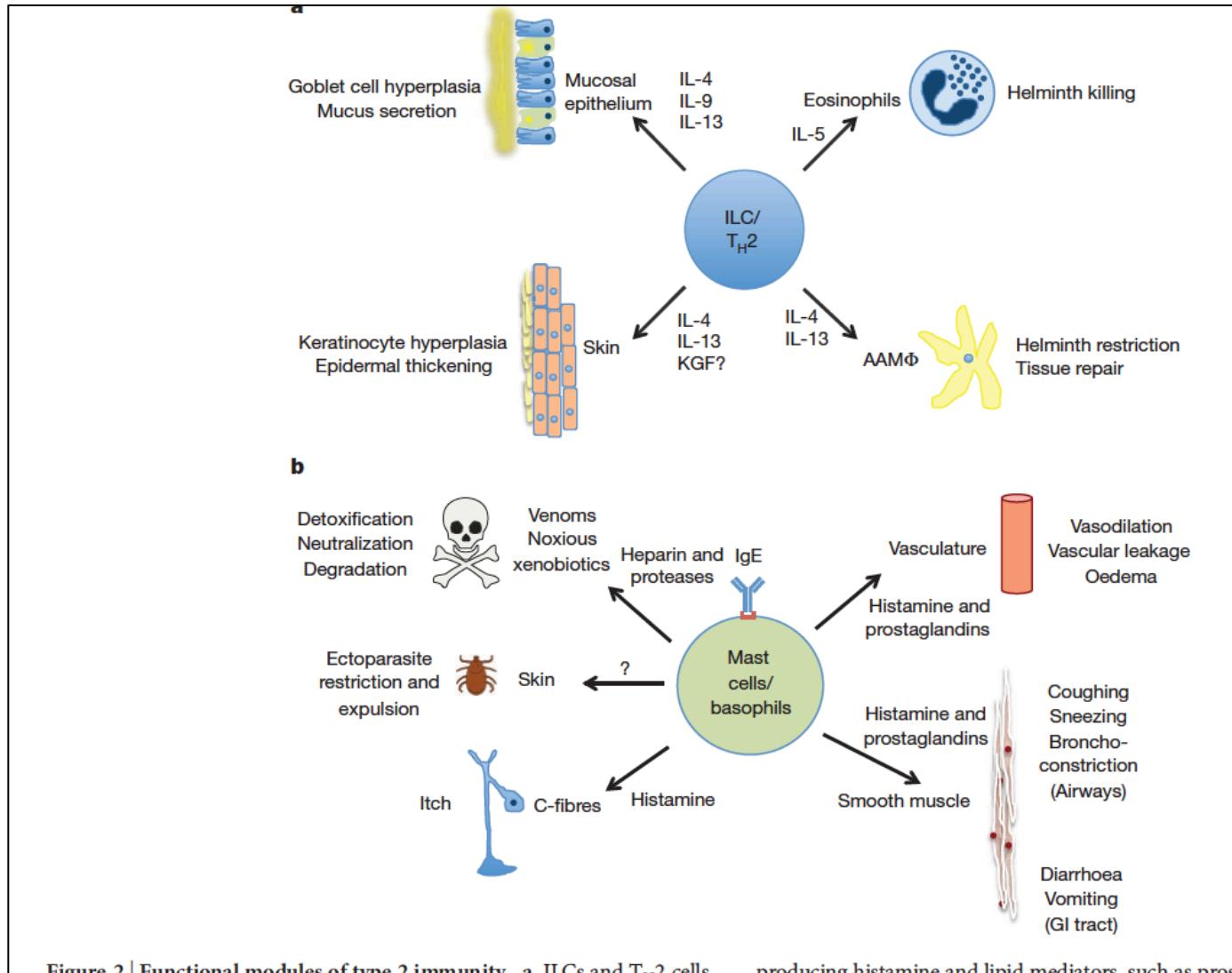


Figure 2 | Functional modules of type 2 immunity. a, ILCs and T_H2 cells producing histamine and lipid mediators, such as prostaglandins, and other molecules, such as KGF, that act on epithelial cells to induce hyperplasia and thickening. b, Mast cells and basophils produce histamine and lipid mediators, such as prostaglandins, and other molecules, such as IgE, that act on various tissues to induce diverse physiological responses.

PLAN

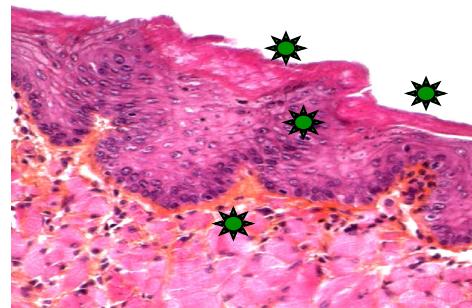
- La peau
- Bases immunologiques de la réponse inflammatoire cutanée
- Allergie cutanée : l'exemple de l'eczéma de contact
- Principes généraux / Mécanismes de tolérance/régulation de la réponse d'eczéma

Eczéma allergique de contact : les facteurs de risques

Ignorance?



Tolérance



Sensibilisation
Eczéma

- > 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

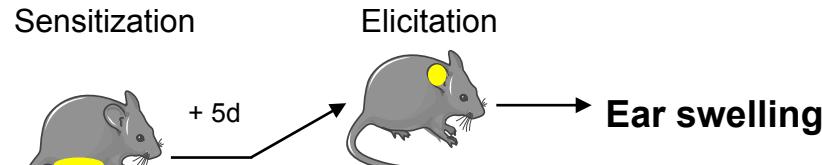
Chemical	Field	Sensitizing potency
Oxazolone	Chemistry	Extreme
2,4-Dinitrofluorobenzene	Chemistry	Extreme
2,4-Dinitrochlorobenzene	Chemistry	Extreme
Glutaraldehyde	Preservative, antiseptic	Strong
Formaldehyde	Cosmetic, Dye	Strong
Cinnamaldehyde	Perfum, Flavour	Moderate
Hexyl cinnamaldehyde	Cosmetic (fragrance)	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

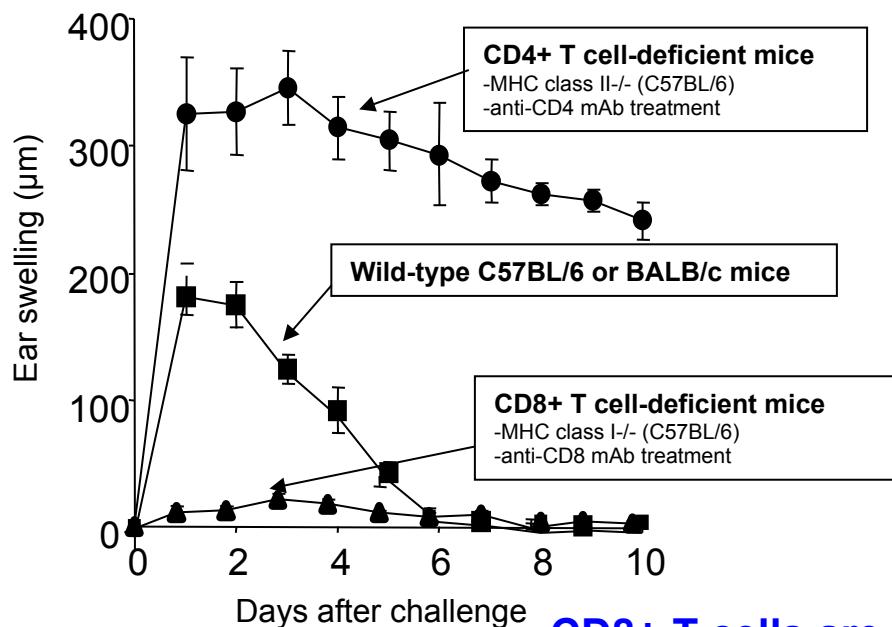
Journal of Investigative Dermatology (2006) 126, 815-820. doi:10.1038/sj.jid.5700174; published online 2 February 2006

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

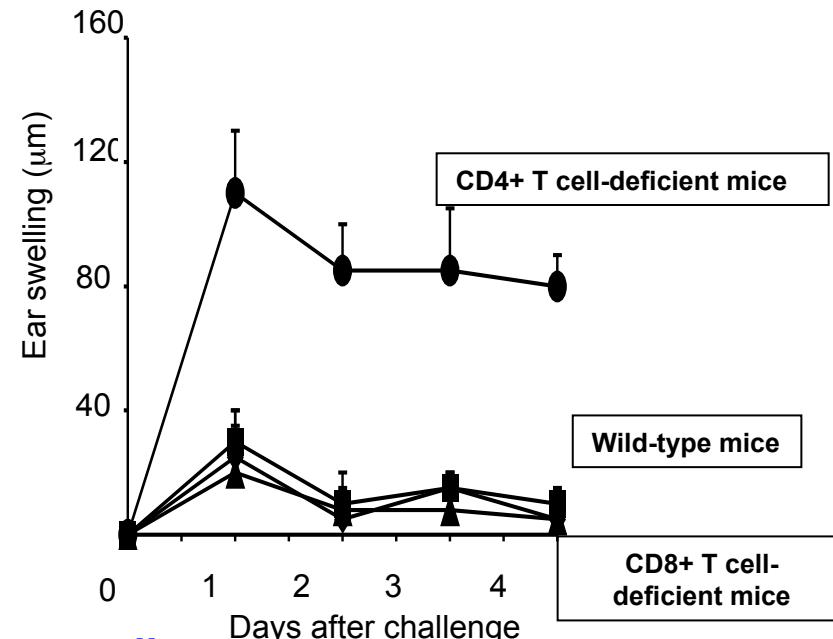
Marc Vocanson¹, Anca Hennino¹, Magalie Cluzel-Tailhardat¹, Pierre Saint-Mezard¹, Josette Benetiere¹, Cyril Chavagnac¹, Frederic Berard^{1,2}, Dominique Kaiserlian³ and Jean-François Nicolas^{1,2}



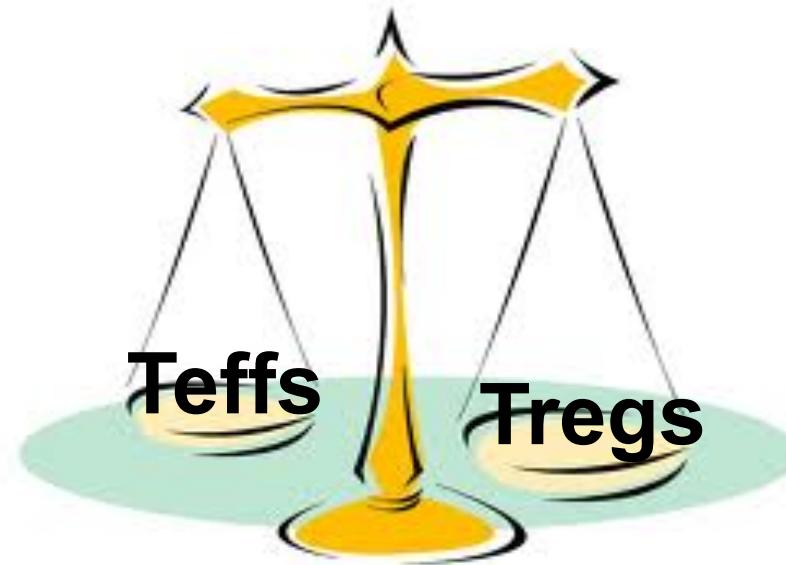
Strong haptens: DNFB, OXA...



- 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

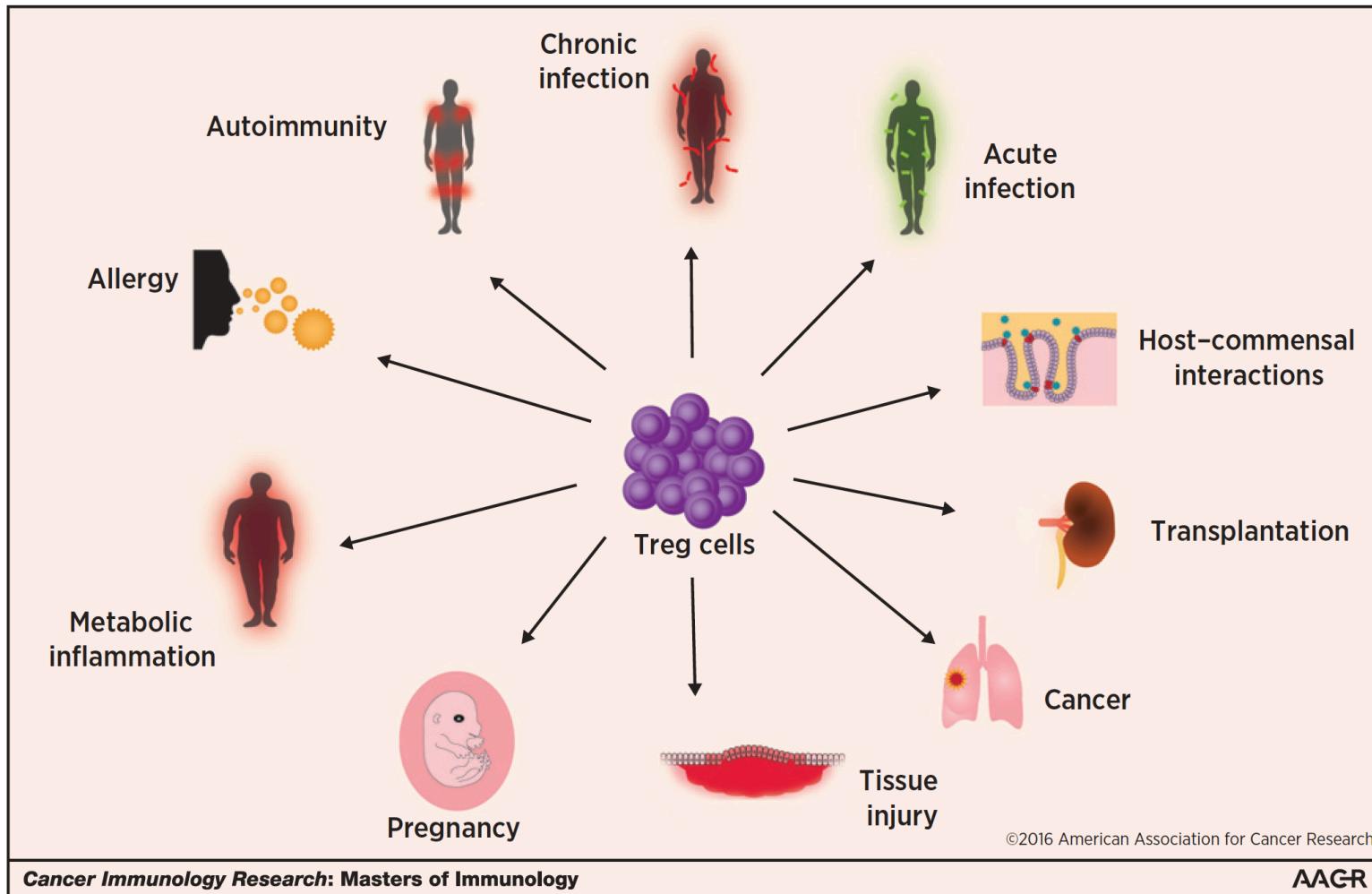
Tolérance
LT régulateurs

Normale: réactions contre les pathogènes

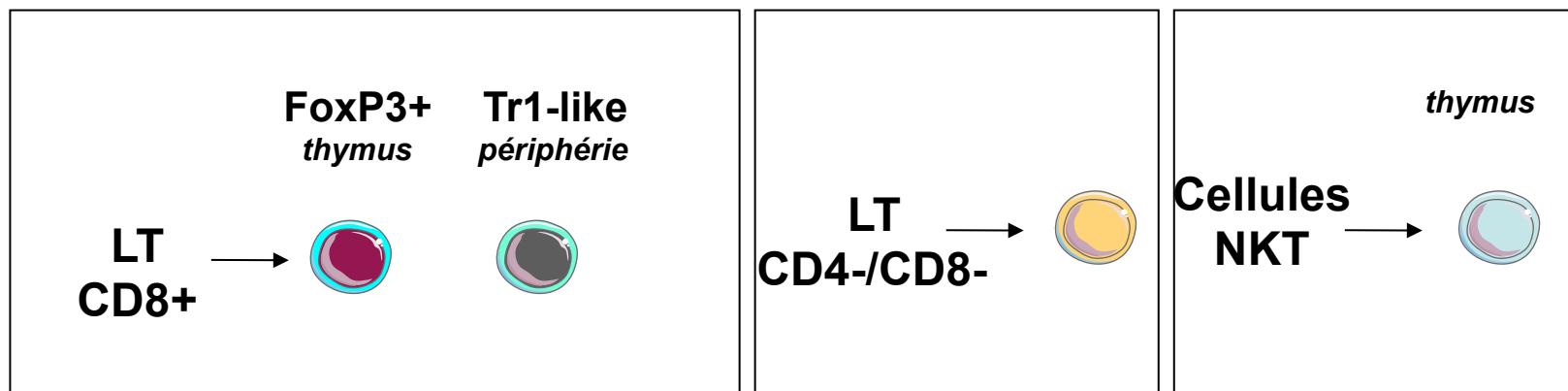
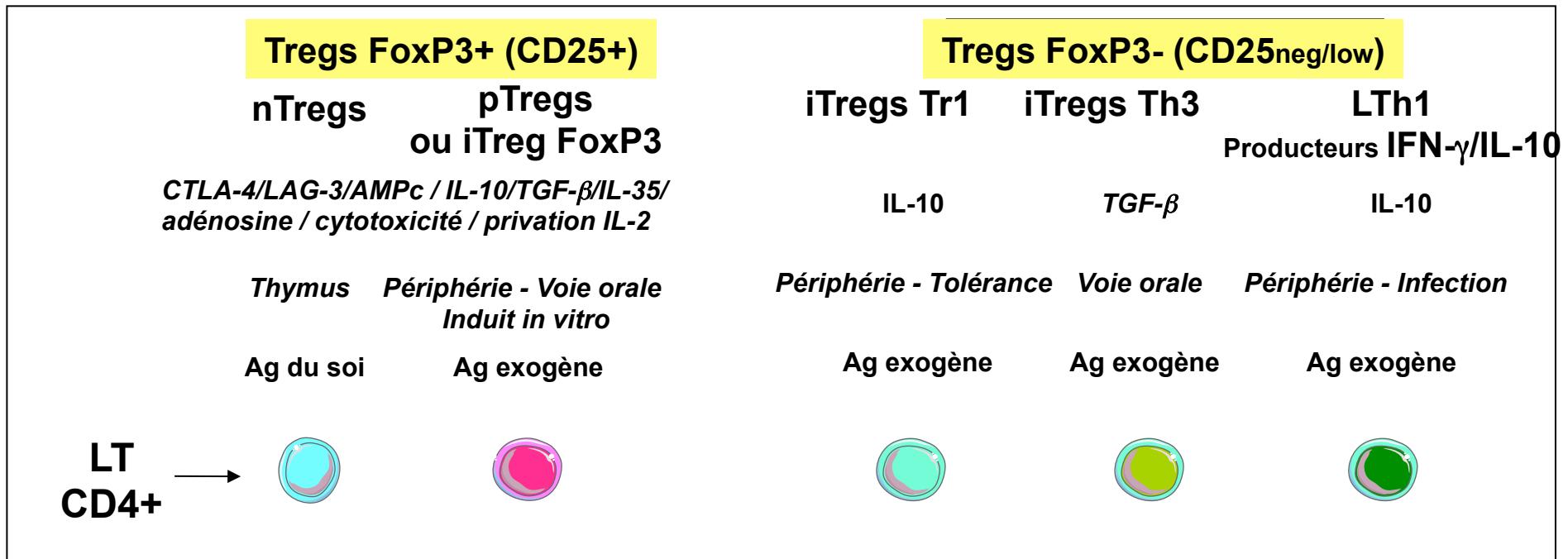
Pathologique: maladies inflammatoires: allergiques, autoimmunes

Pas de réponse contre le soi
Réponses contrôlées contre les pathogènes

Regulatory T Cells (Tregs)

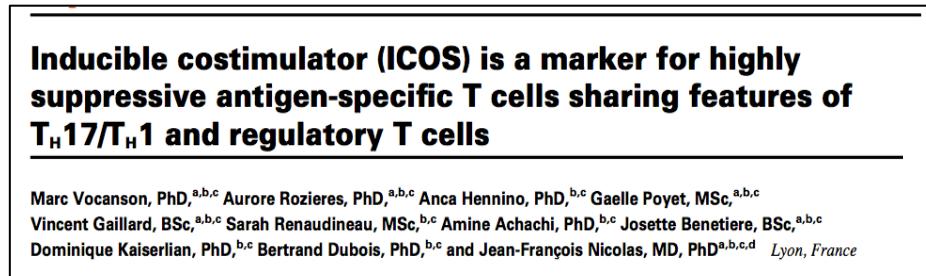


De nombreux lymphocytes T régulateurs



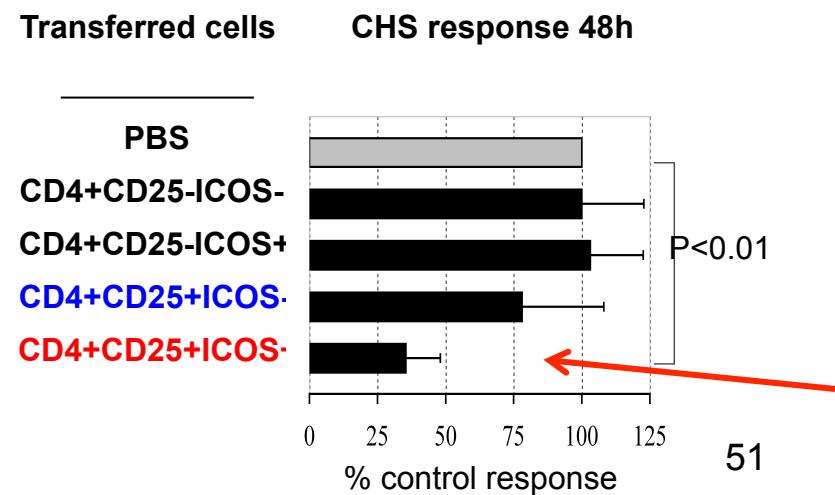
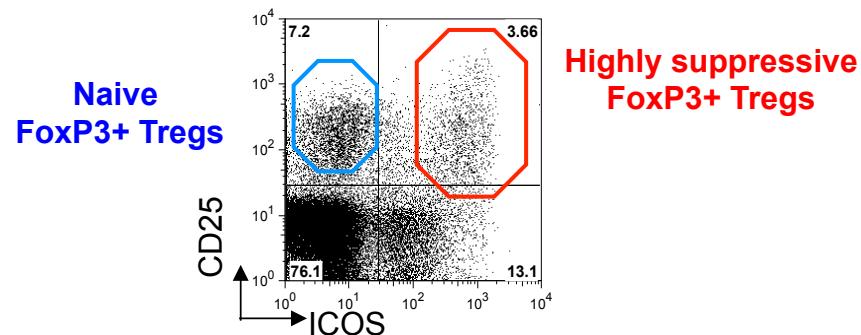
Main regulatory cells? FoxP3+Tregs

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



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 development of skin inflammation in an antigen-dependant manner

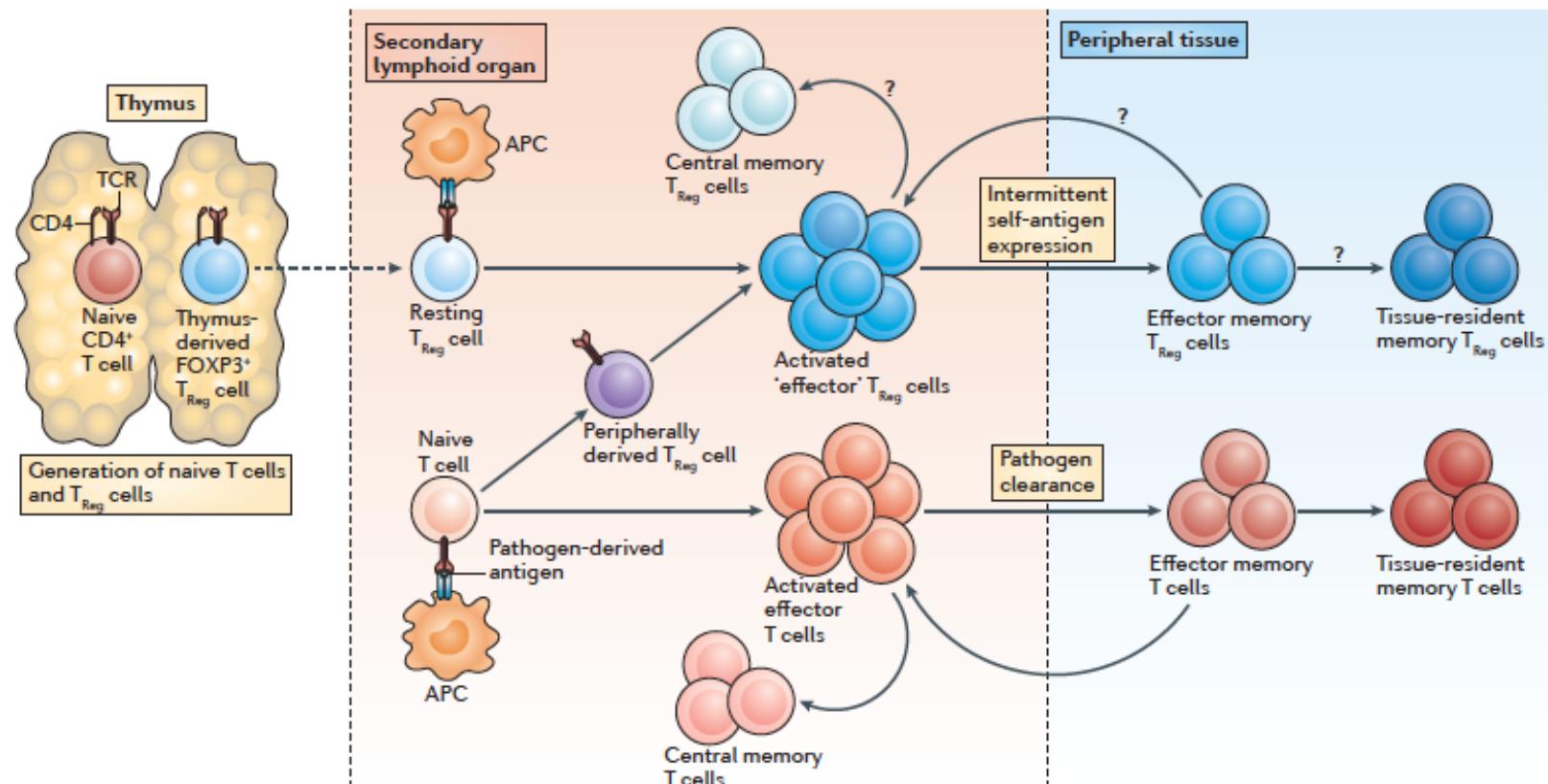


Regulatory T Cells (Tregs)

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



Foxp3-expressing Treg Subsets

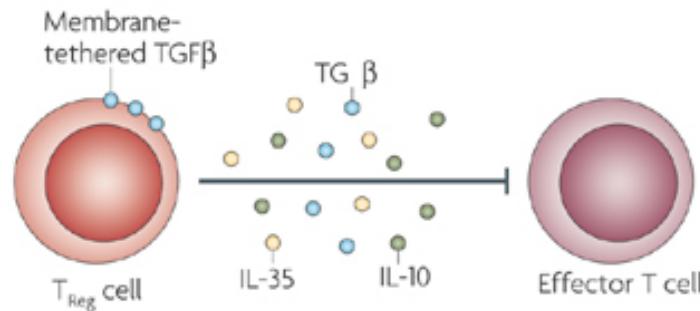
- Several subsets on the basis of
 - **The sites in which they are generated**
 - Thymus-derived Treg cells (tTregs)
 - Peripherally-derived Treg cells (pTregs)
 - In vitro induced (iTregs) also called Tr1
 - No reliable marker to differentiate these subsets in the skin
 - **Their relative differentiation 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

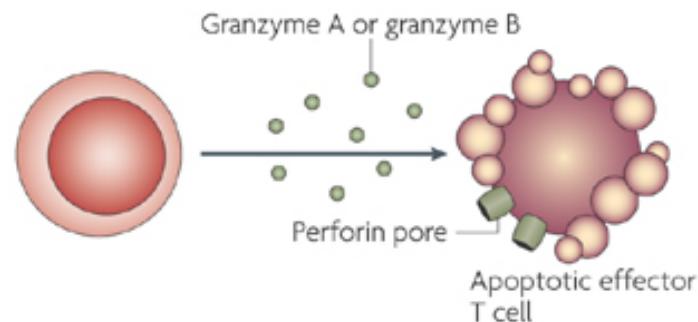
	Conventional T cells			Regulatory T cells		
	Resting	Activated effector	Memory	Resting	Activated effector	Memory
Selected phenotypic markers	CD25 ^{low}	CD25 ^{hi}	CD25 ^{low}	CD25 ^N	CD25 expression variable	CD25 ^{hi}
	CD44 ^{low}	CD44 ^{hi}	CD44 ^{hi}	CD44 ^N	CD44 ^{hi}	CD44 ^{hi}
	CD45RA ^{hi†}	CD45RA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

Suppressive mechanisms used by Tregs

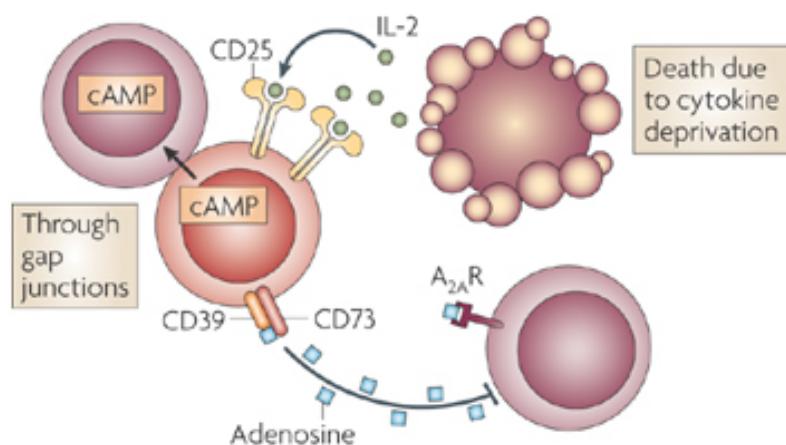
a Inhibitory cytokines



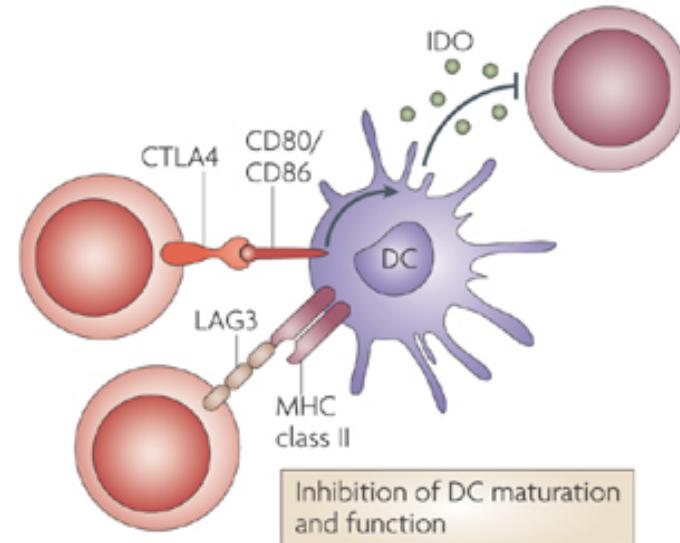
b Cytolysis



c Metabolic disruption



d Targeting dendritic cells

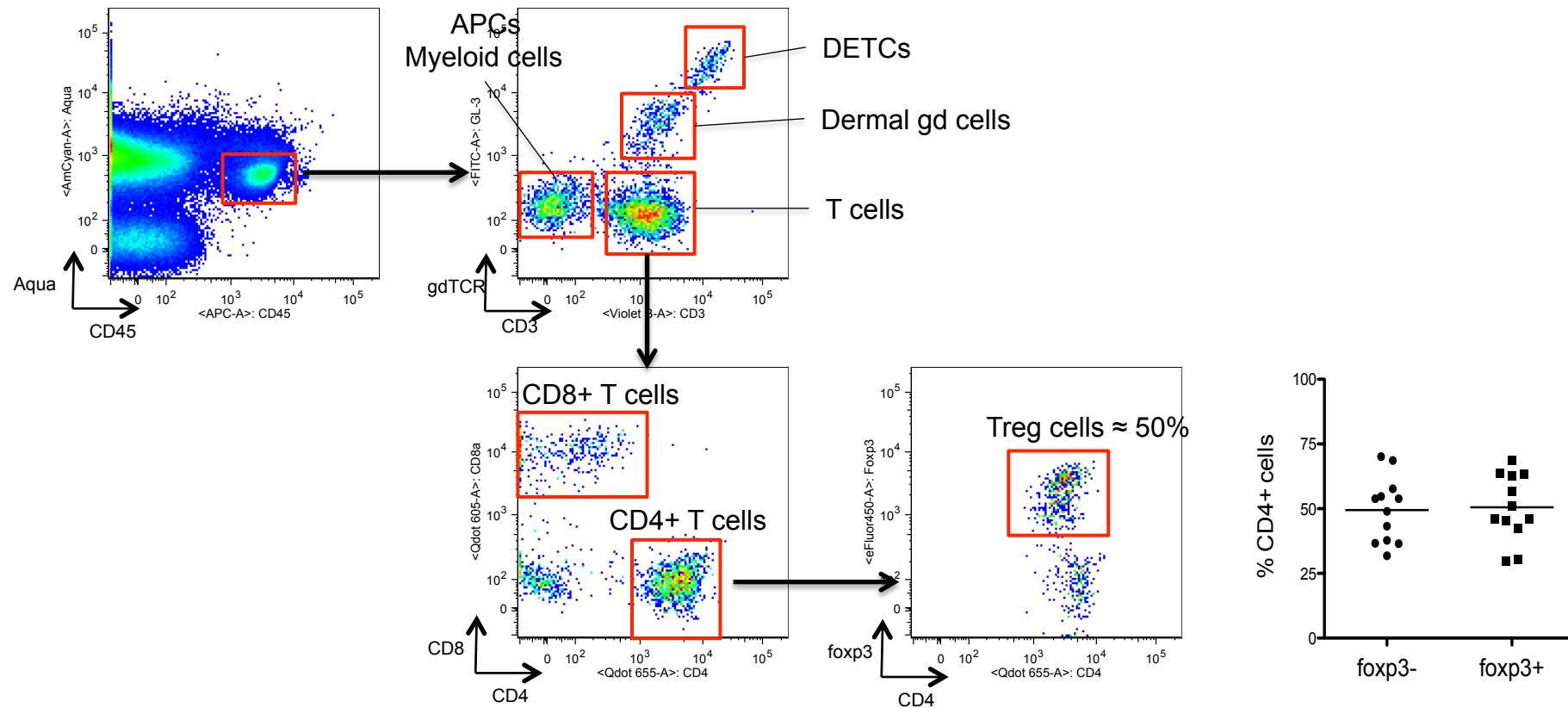


Fonctions « non immunologiques » des Tregs dans les tissus

- 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

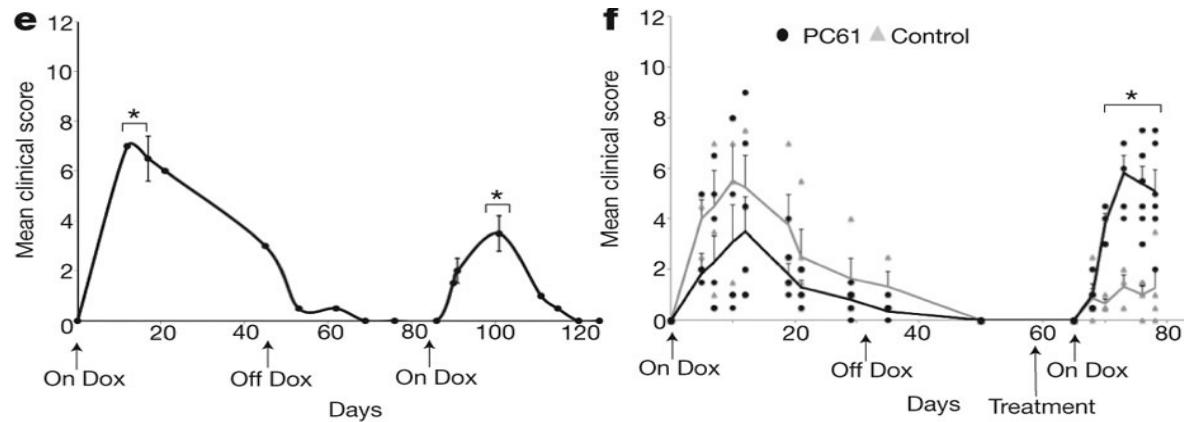
Mouse Skin Gating strategy in Flow Cytometry



- Could be considered as tissue resident cells

Treg Functions in Skin (1/4)

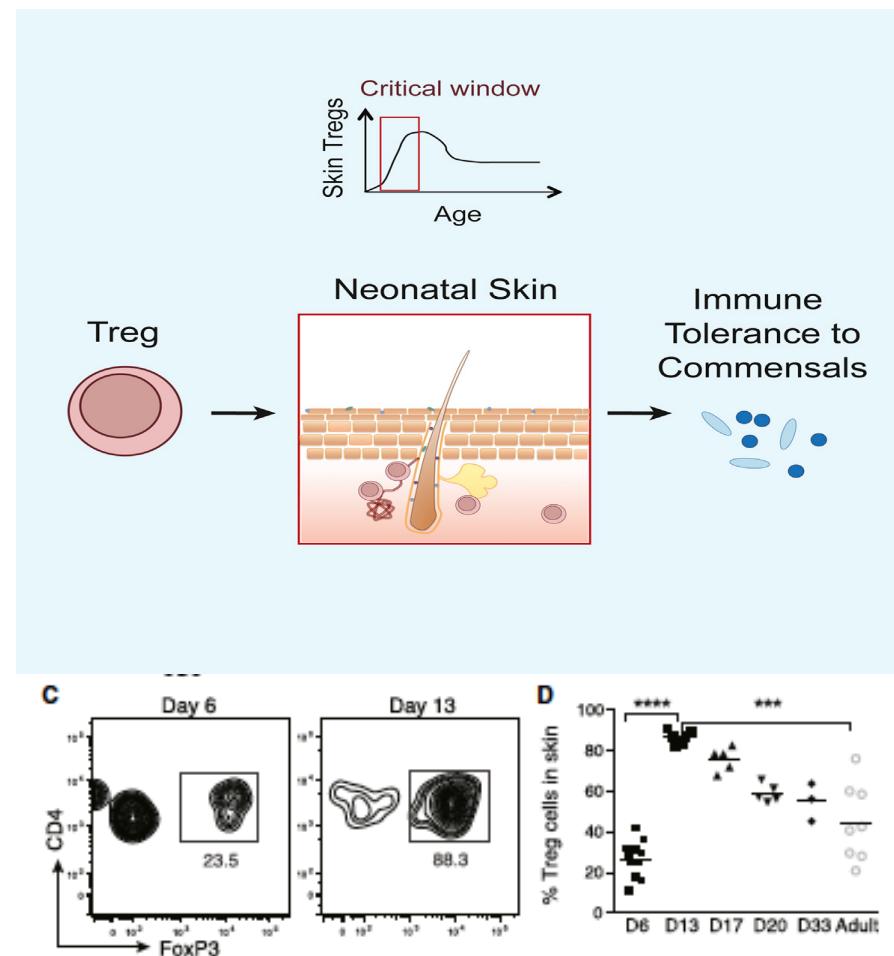
- To limiting skin auto-immunity
 - Memory T_{reg} cells attenuate skin disease upon re-expression of tissue antigen.



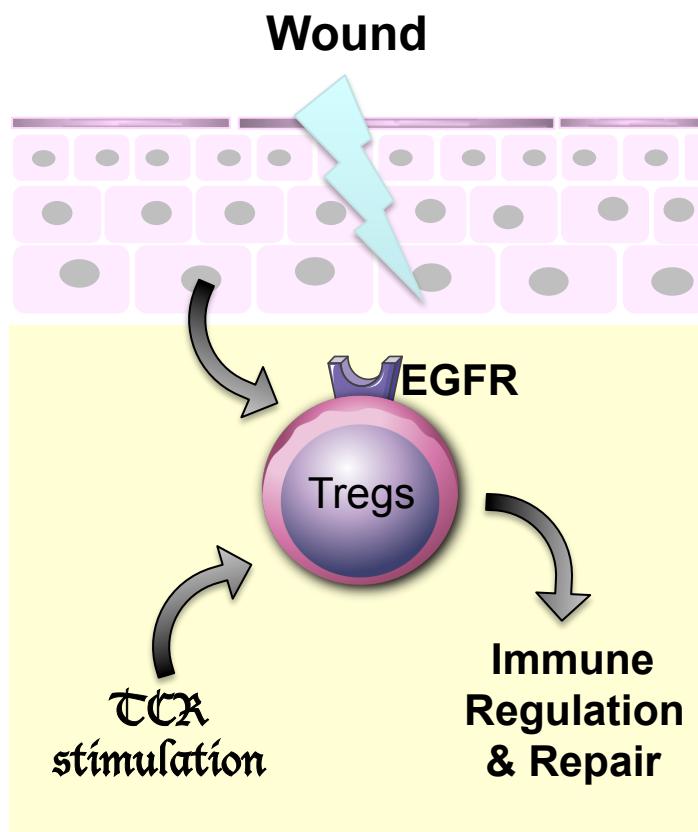
- Exposure to tissue autoantigens leads to the activation of self-reactive Treg cells
- Those Tregs are generated by self-antigen expression in the thymus.
- Activated Treg cells persist in the target tissue and suppress autoimmune responses upon repeated or chronic encounters with tissue autoantigen

Treg Functions in Skin (2/4)

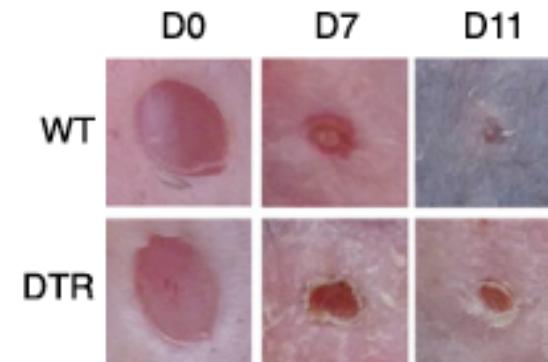
- **Promoting tolerance to commensal bacteria**
 - Skin bacteria activate antigen-specific T cells across an intact skin barrier
 - Tolerance to skin commensal bacteria is preferentially established in neonatal life
 - A unique wave of activated regulatory T cells enters skin in this critical window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



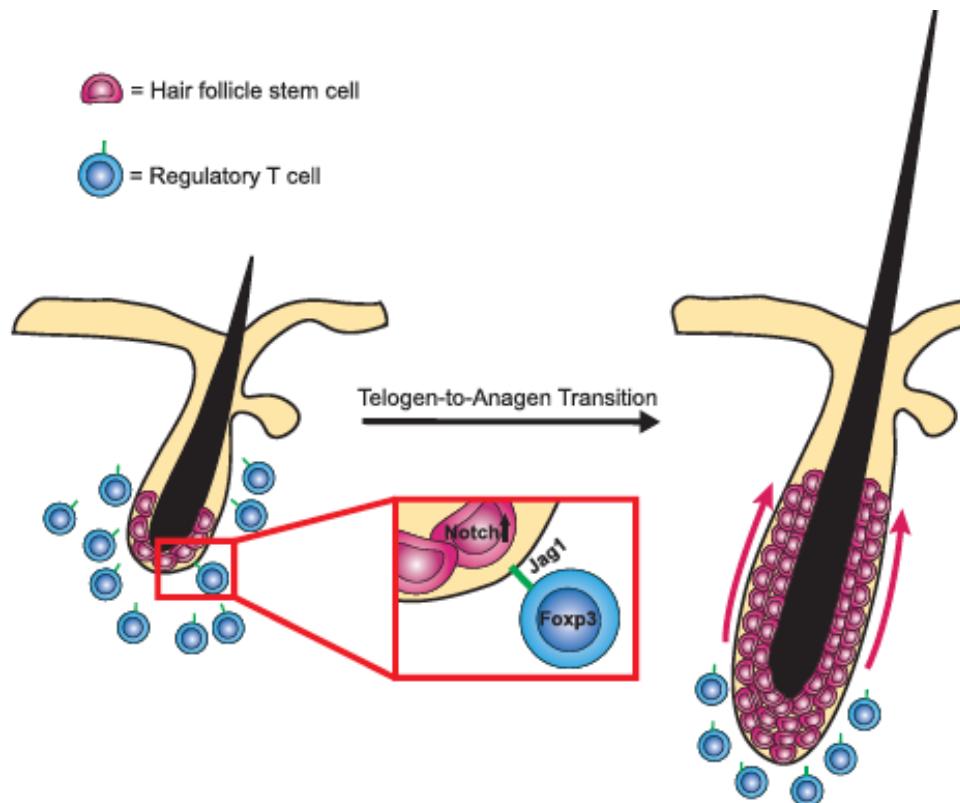
Treg Functions in Skin (3/4)



- **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



Treg Functions in Skin (4/4)



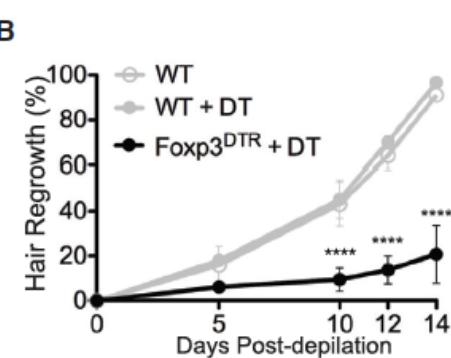
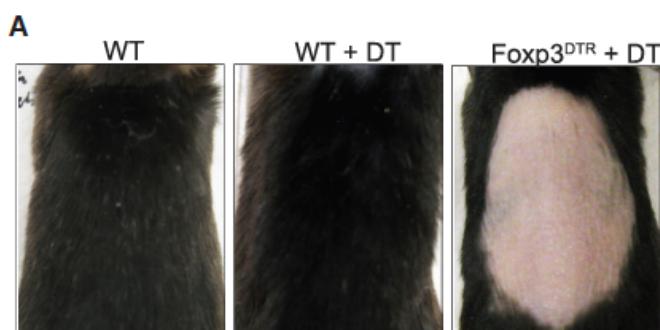
- **Facilitating epithelial stem cell differentiation**

Treg activation in skin closely correlates with the HF cycle

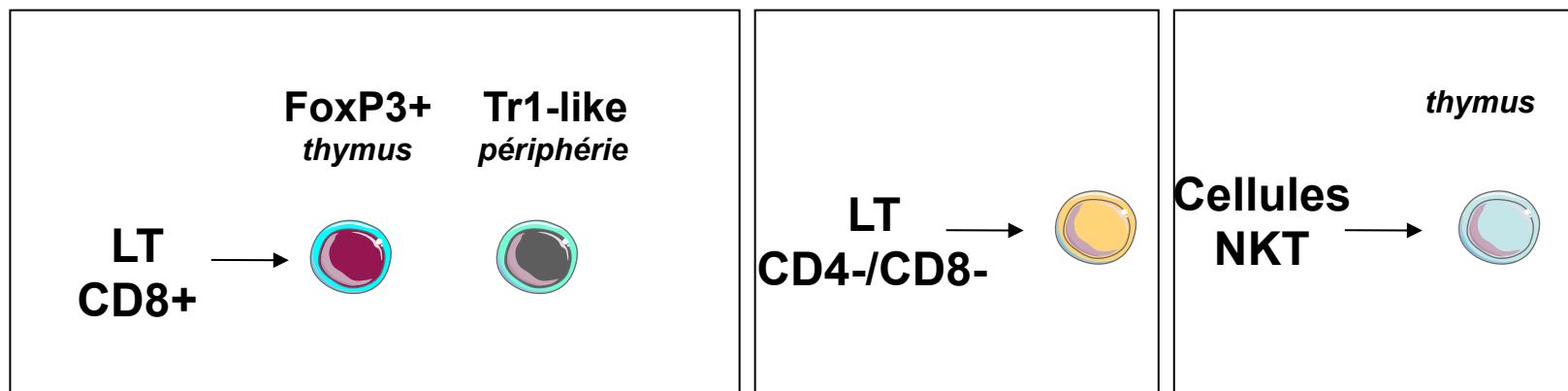
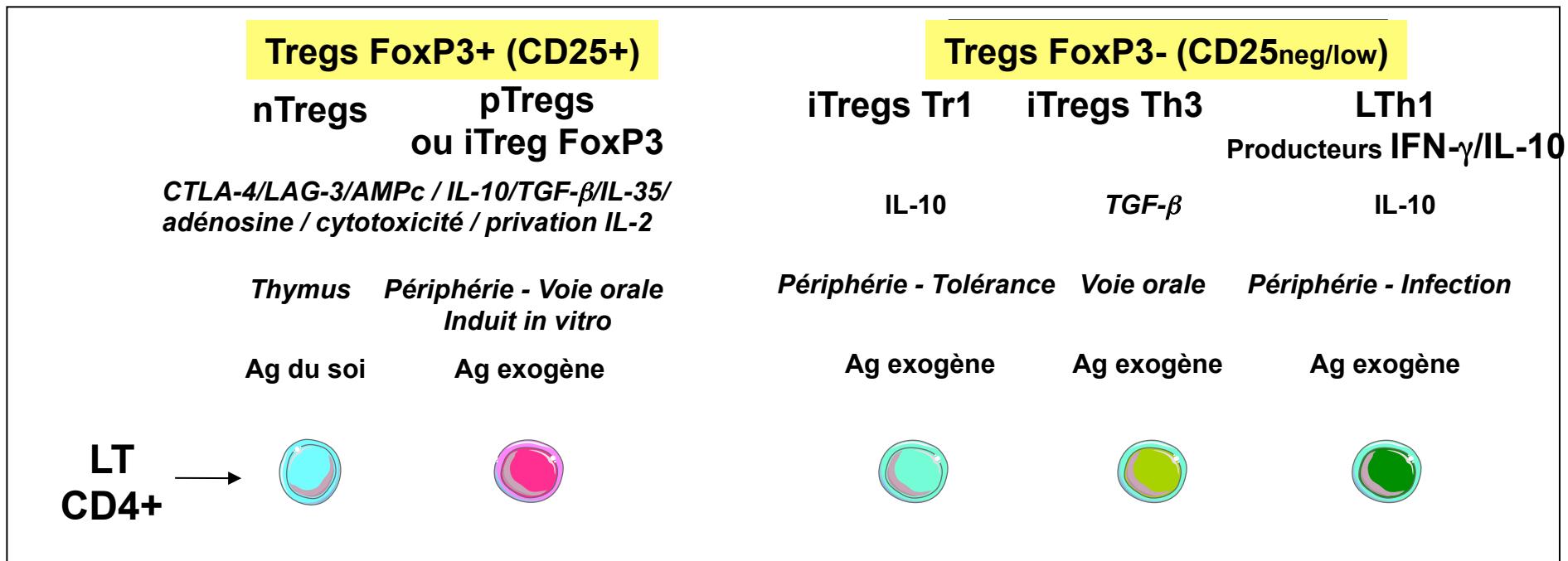
Tregs localize to HFSCs and play a major role in HF regeneration

Tregs facilitate HFSC proliferation and differentiation to initiate HF cycling

Treg expression of Jagged 1 is required for efficient hair regeneration



De nombreux lymphocytes T régulateurs



Other regulatory cells? iNKT cells

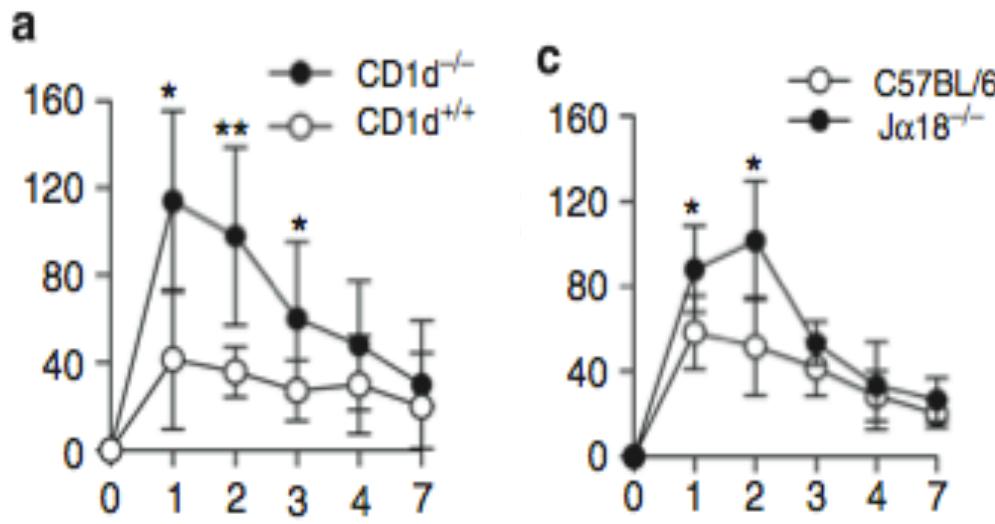
- iNKT cells are non-redundant downregulators of CTL-mediated CHS responses

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}

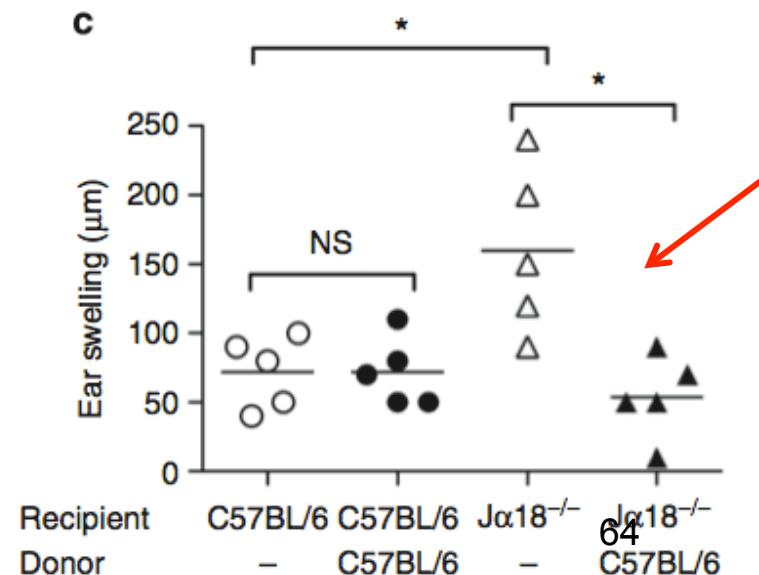
Journal of Investigative Dermatology (2013) 133, 980–987; doi:10.1038/jid.2012.404; published online 29 November 2012

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



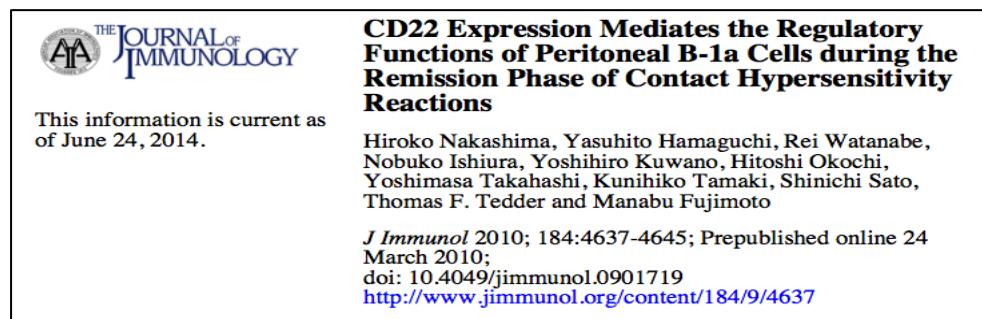
Other studies argues against the regulatory functions of iNKT cells and suggest stimulatory functions

Adoptive transfer of iNKT in Jα18^{-/-} mice normalises CHS response

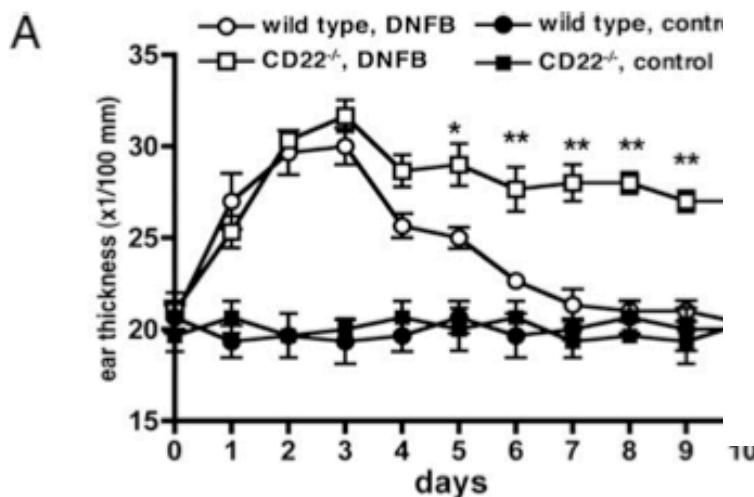


Other regulatory cells? B cell subsets

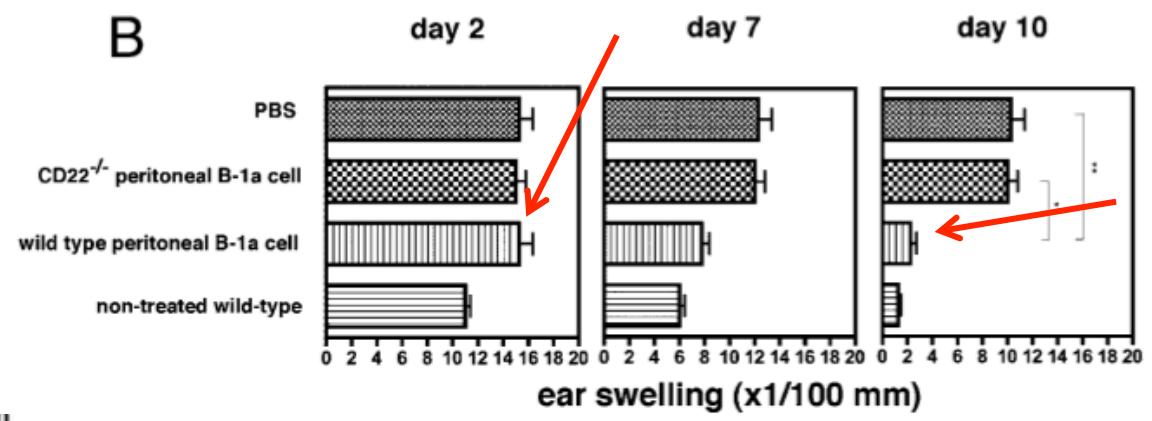
- Other regulatory cells (peritoneal B-1a cells) participate to the resolution of skin inflammation



Absence of CHS resolution in CD22^{-/-} animals



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

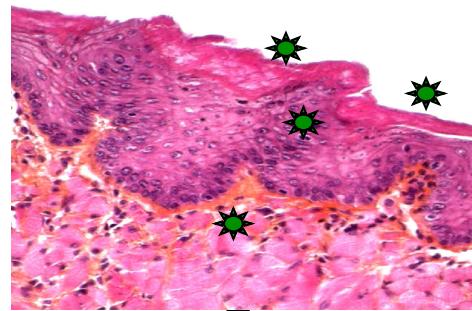


Eczéma allergique de contact : les facteurs de risques

Ignorance?



Tolérance

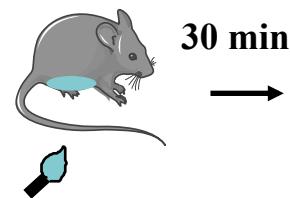


Sensibilisation
Eczéma

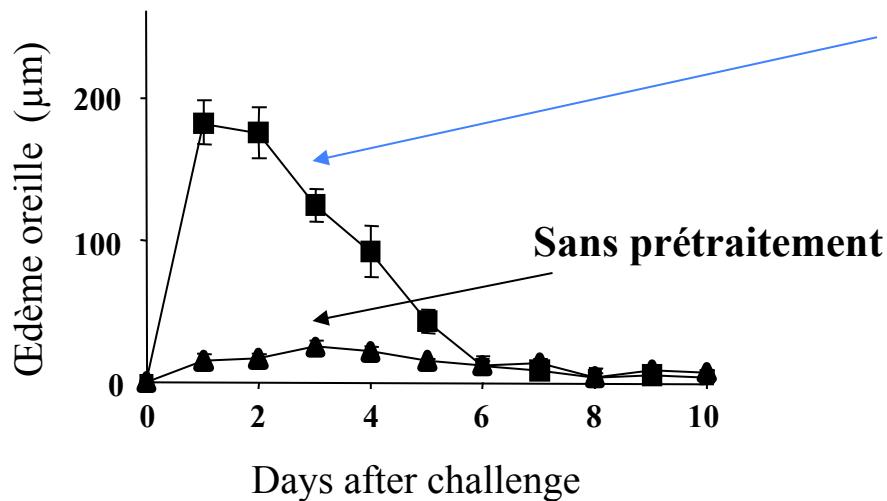
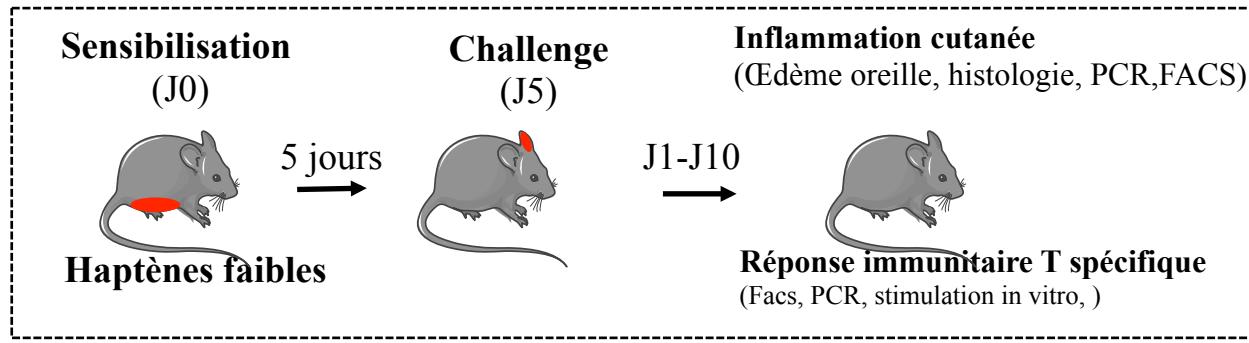
- > la nature de l'antigène = “le danger”
- > les conditions d'exposition (dose, fréquence, durée, route)
- > le polymorphisme génétique (barrière cutanée, enzymes de détoxification...), âge, sexe
- > l'environnement (maladie sous-jacente, stress, pollution...)

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

Prétraitement
Irritant (SLS)
Véhicule DMF
Injection d' IL-1 β



30 min

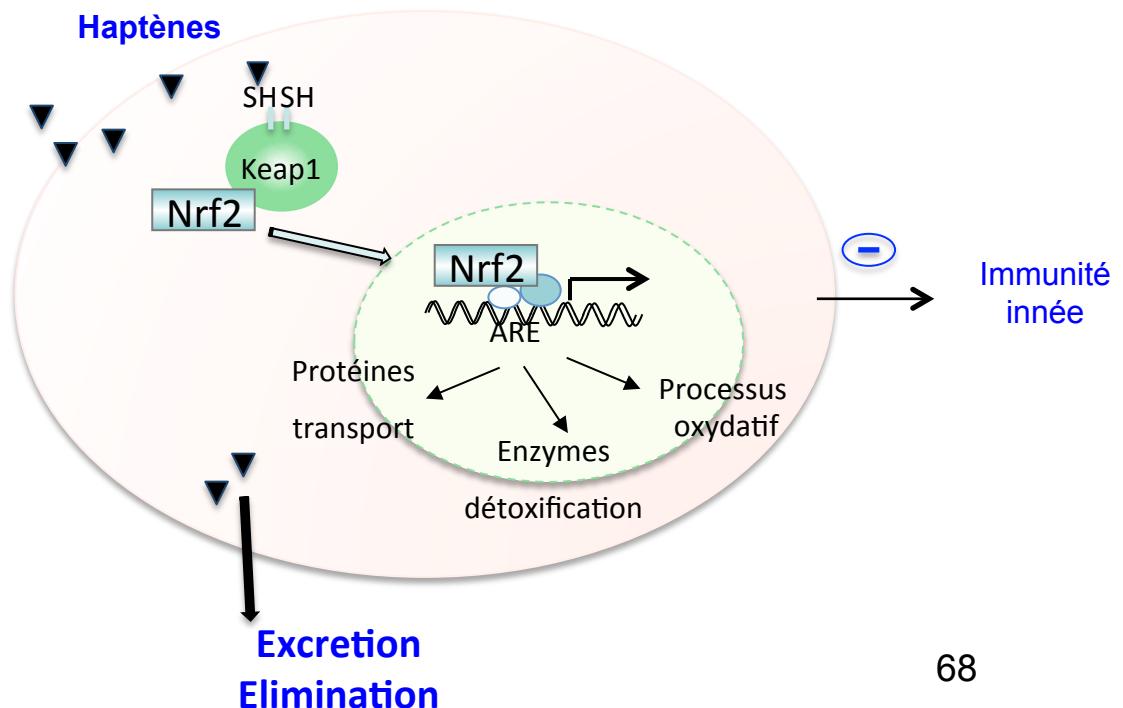
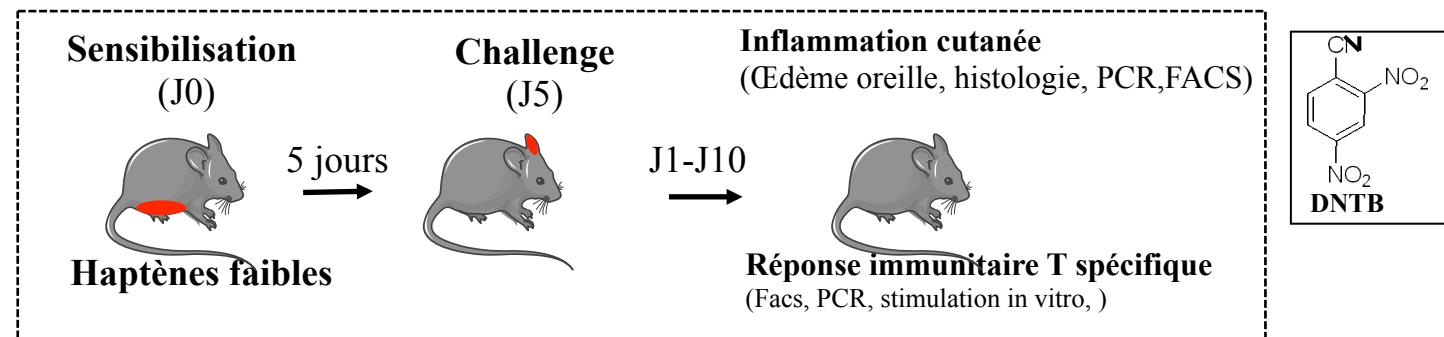


L'application d'un irritant SDS / un véhicule différent (DMF) / l'injection d'une cytokine proinflammatoire comme IL-1 β avant la sensibilisation induit une réponse d'eczéma vis-à-vis d'un allergène faible

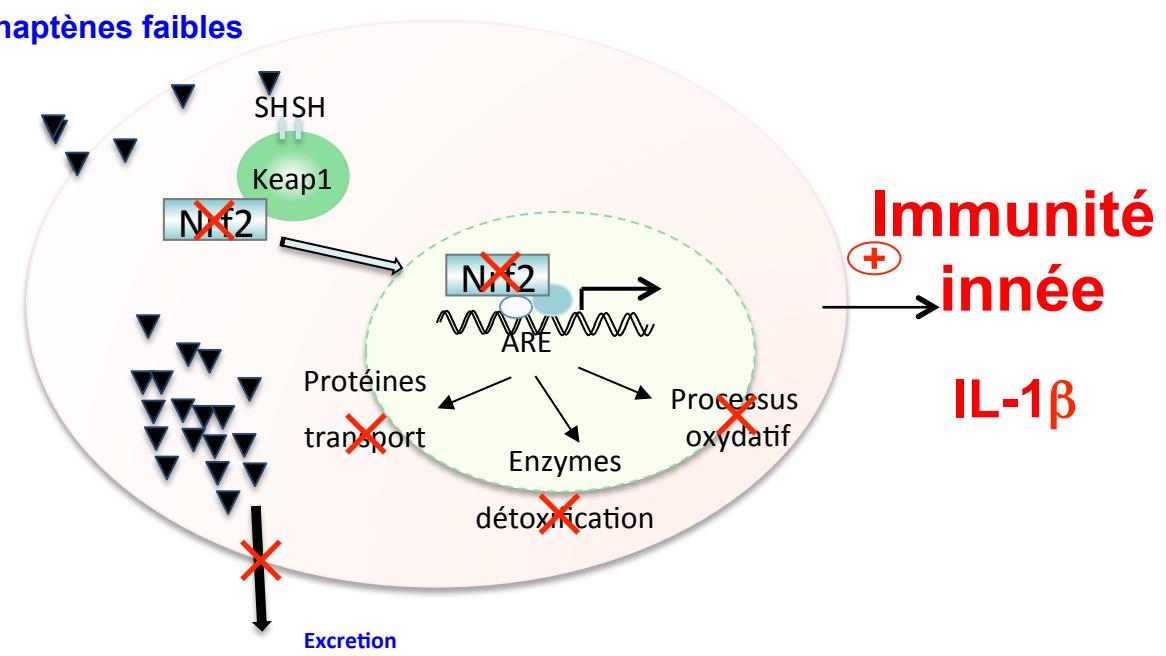
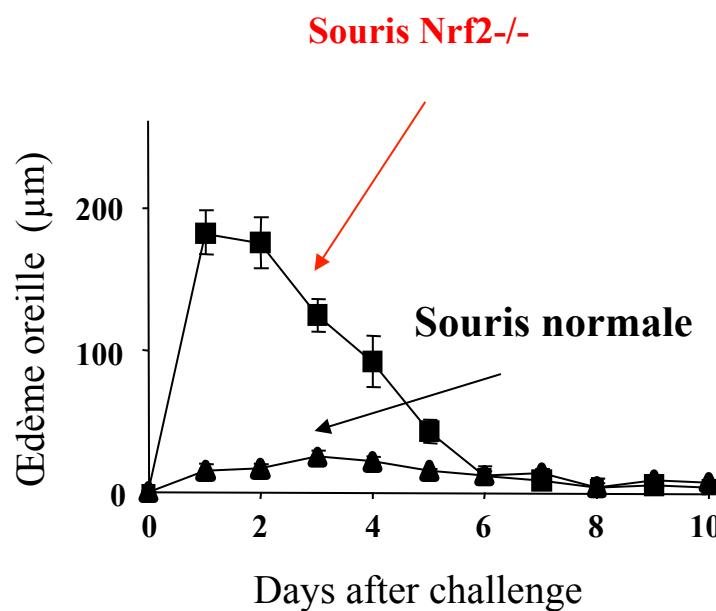
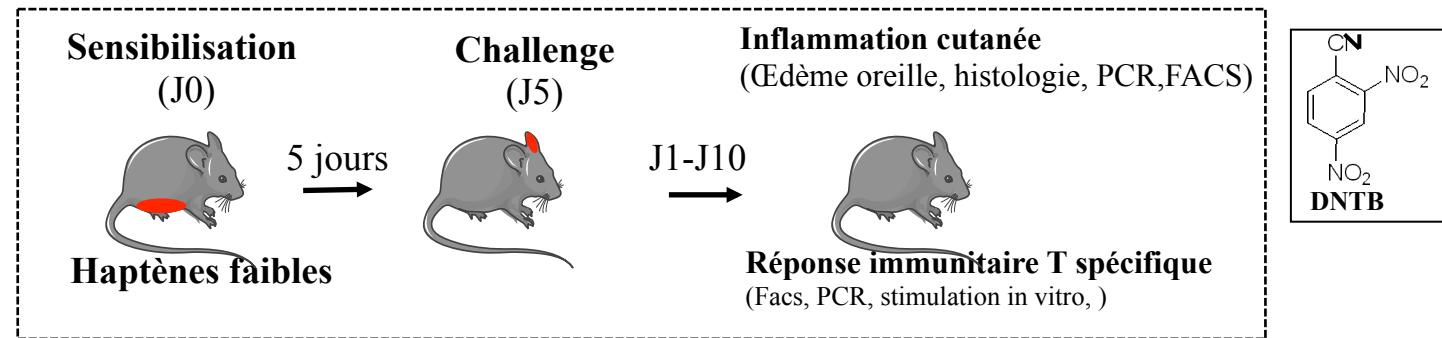
L'inverse est vrai pour un haptène fort : bloquer la production d'IL-1 β prévient la sensibilisation et favorise la tolérance

67

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



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