

MasterClass
Module 0 « Immunologie de l'allergie »
16 décembre 2021

**Le système immunitaire en action
Induction et régulation
de l'inflammation cutanée**

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Team “Epidermal Immunity & Allergy”

Research activities



Allergic Contact Dermatitis Atopic Dermatitis (AD)
(ACD) **ECZEMAS**



Benign - Exanthema Severe – Bullous diseases
DRUG ALLERGY (DA)

Main Features

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

Allergens

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

Objectives

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

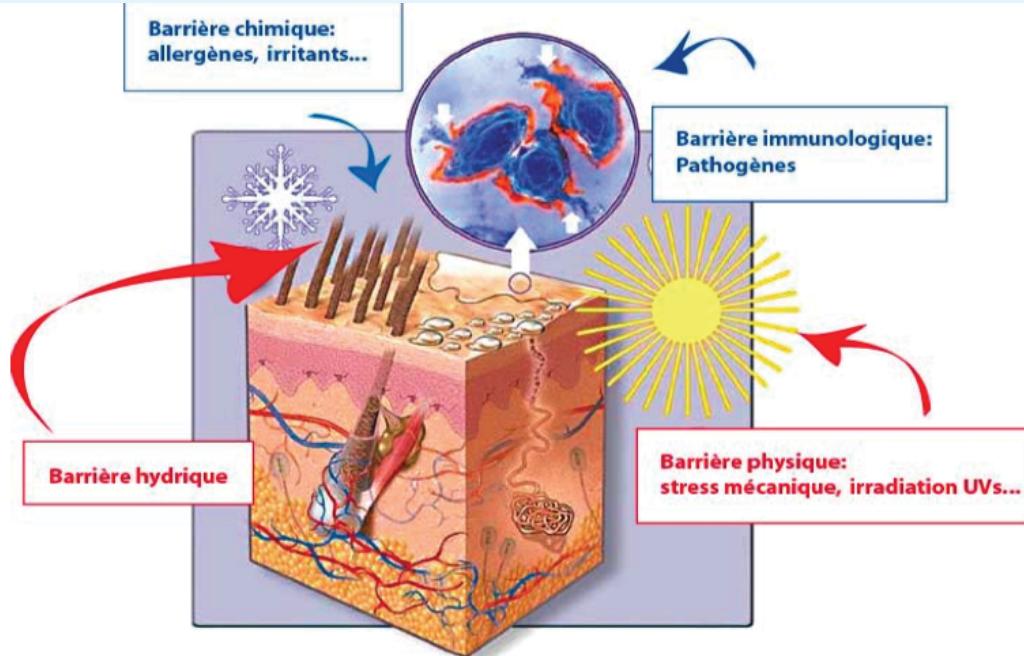
PLAN

- Bases immunologiques de la réponse à l'interface cutanée
- Induction & régulation de l'inflammation cutanée : *exemple de l'eczéma de contact*

PLAN

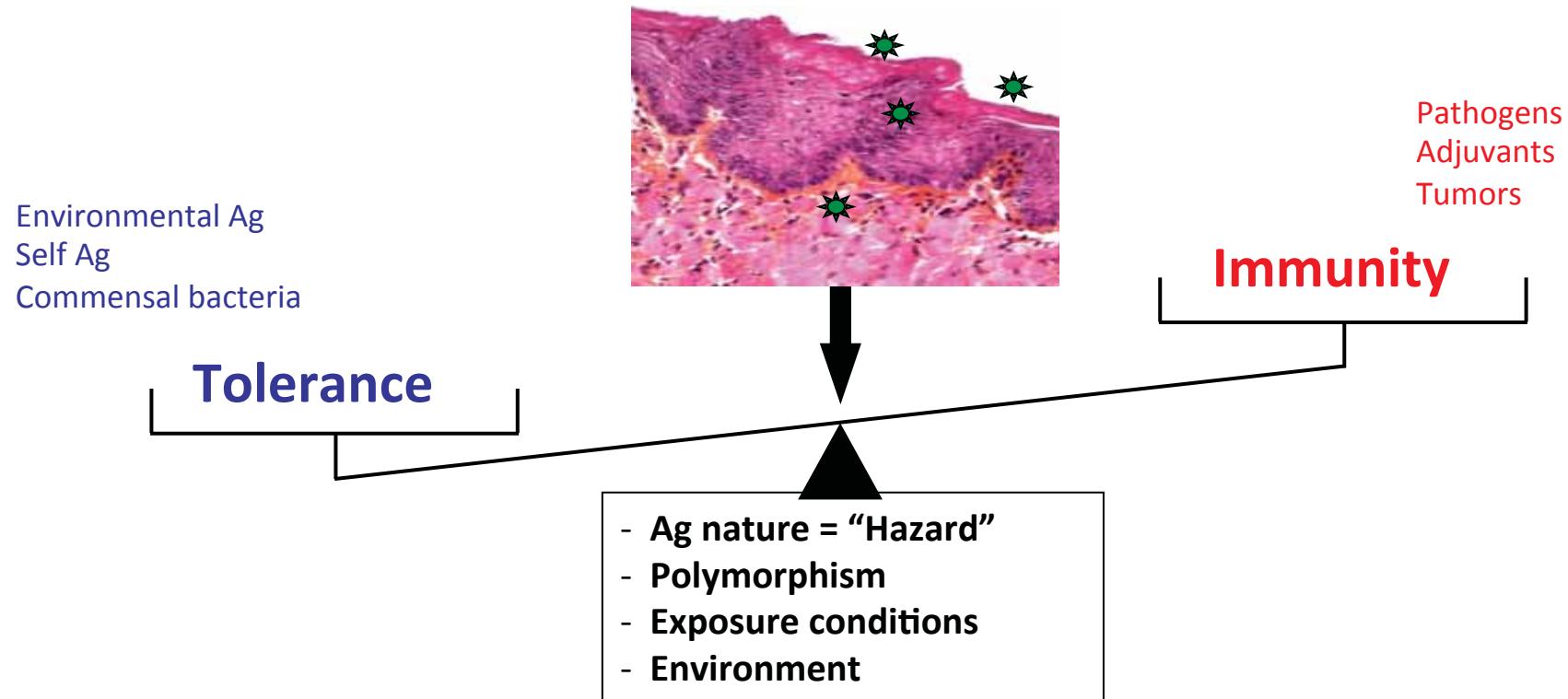
- Bases immunologiques de la réponse à l'interface cutanée
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The skin: the multitasking organ



- 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

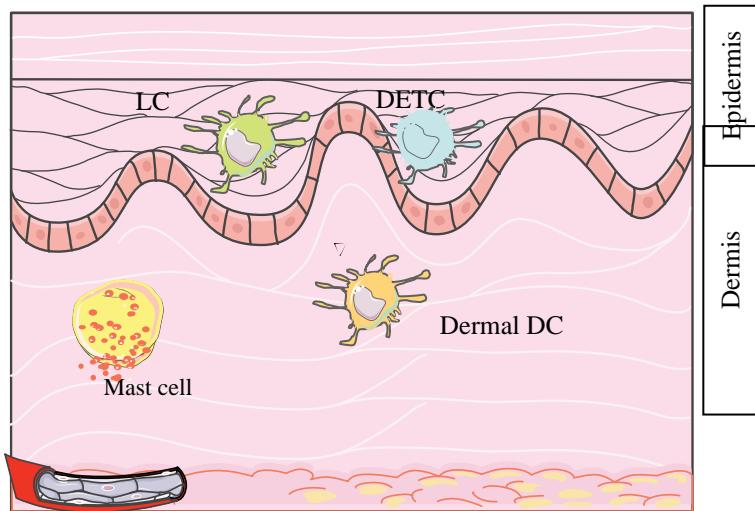
The skin: an immuno-protective organ



- 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

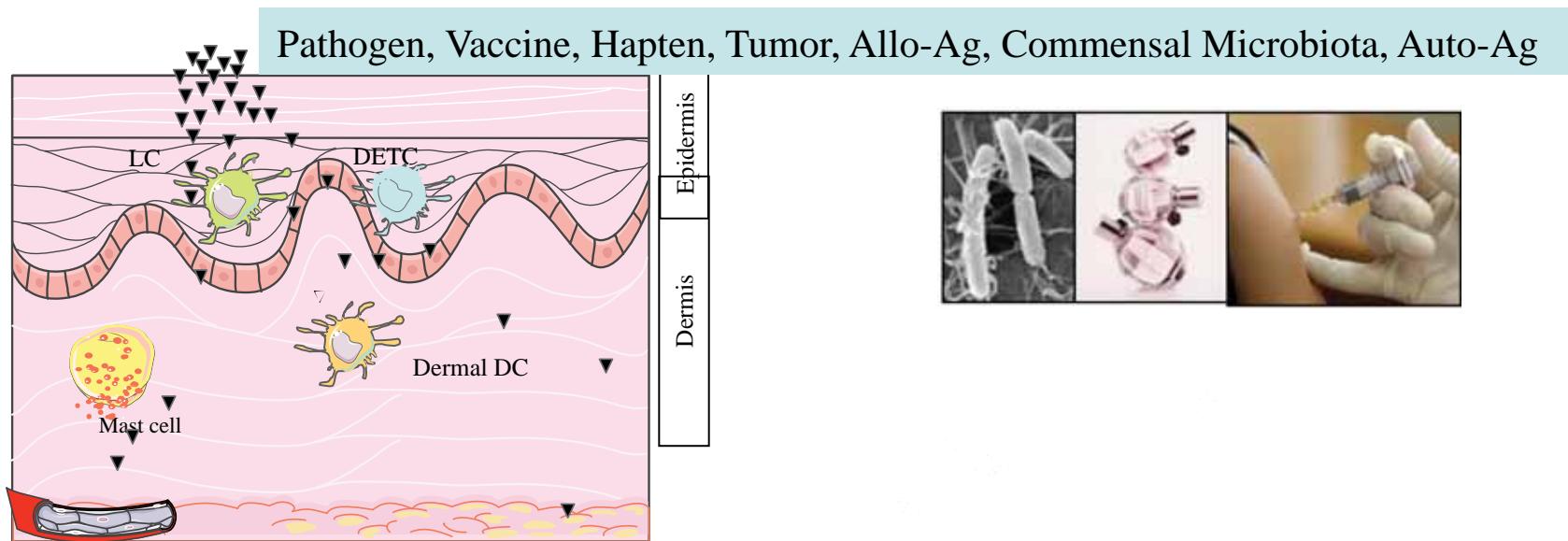
Induction of systemic immunity upon skin exposure/immunization

Skin exposure, immunization



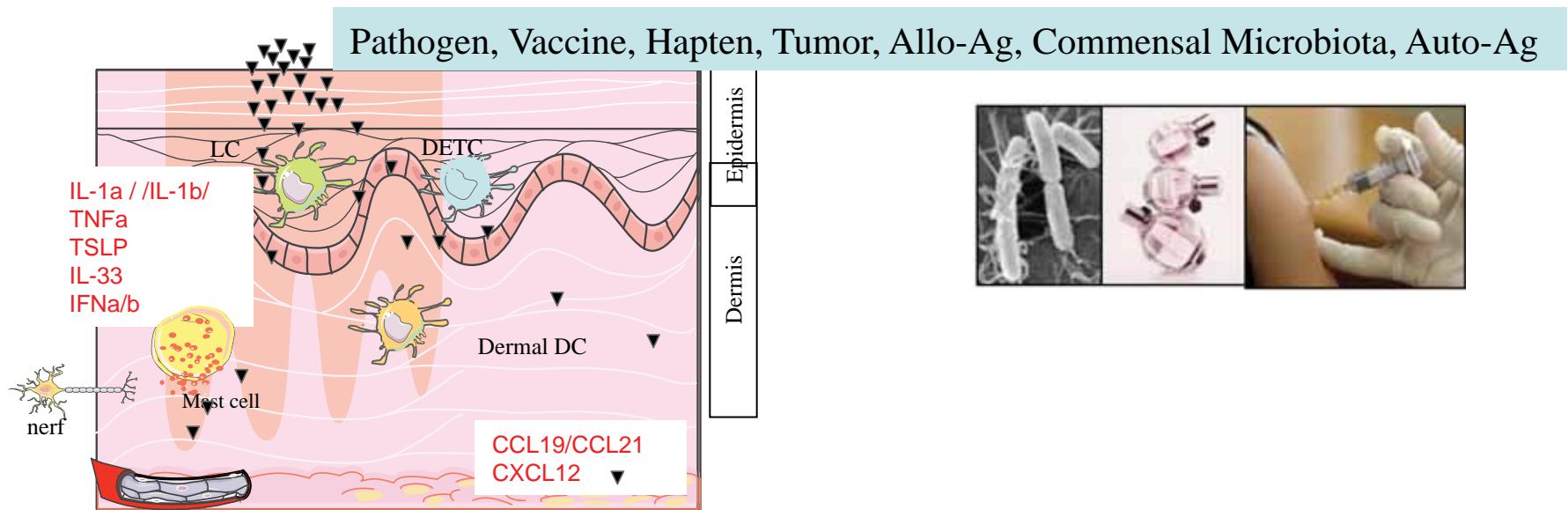
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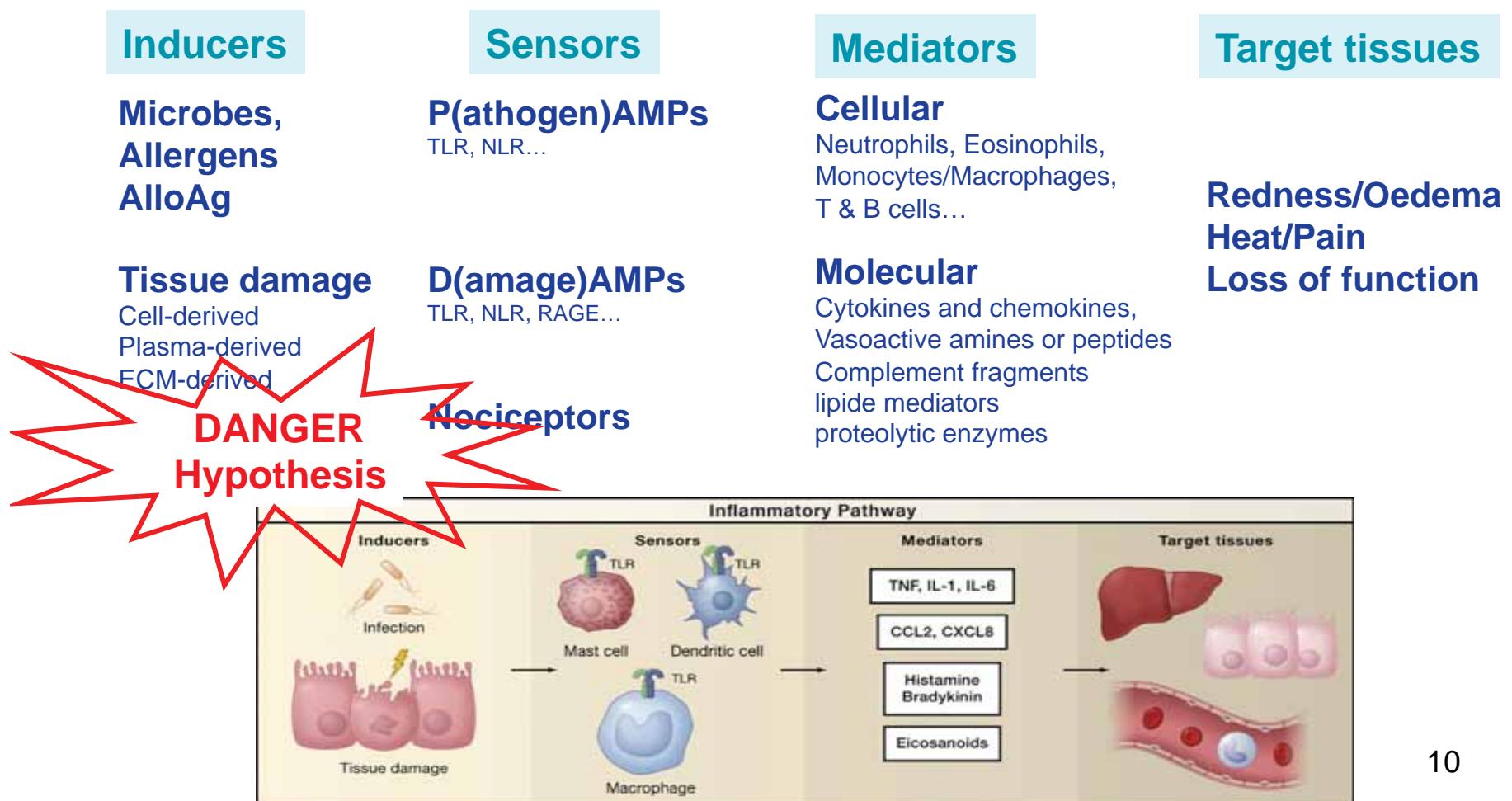
Innate immunity -> 1st line of defence

Release of inflammatory mediators

Inflammation

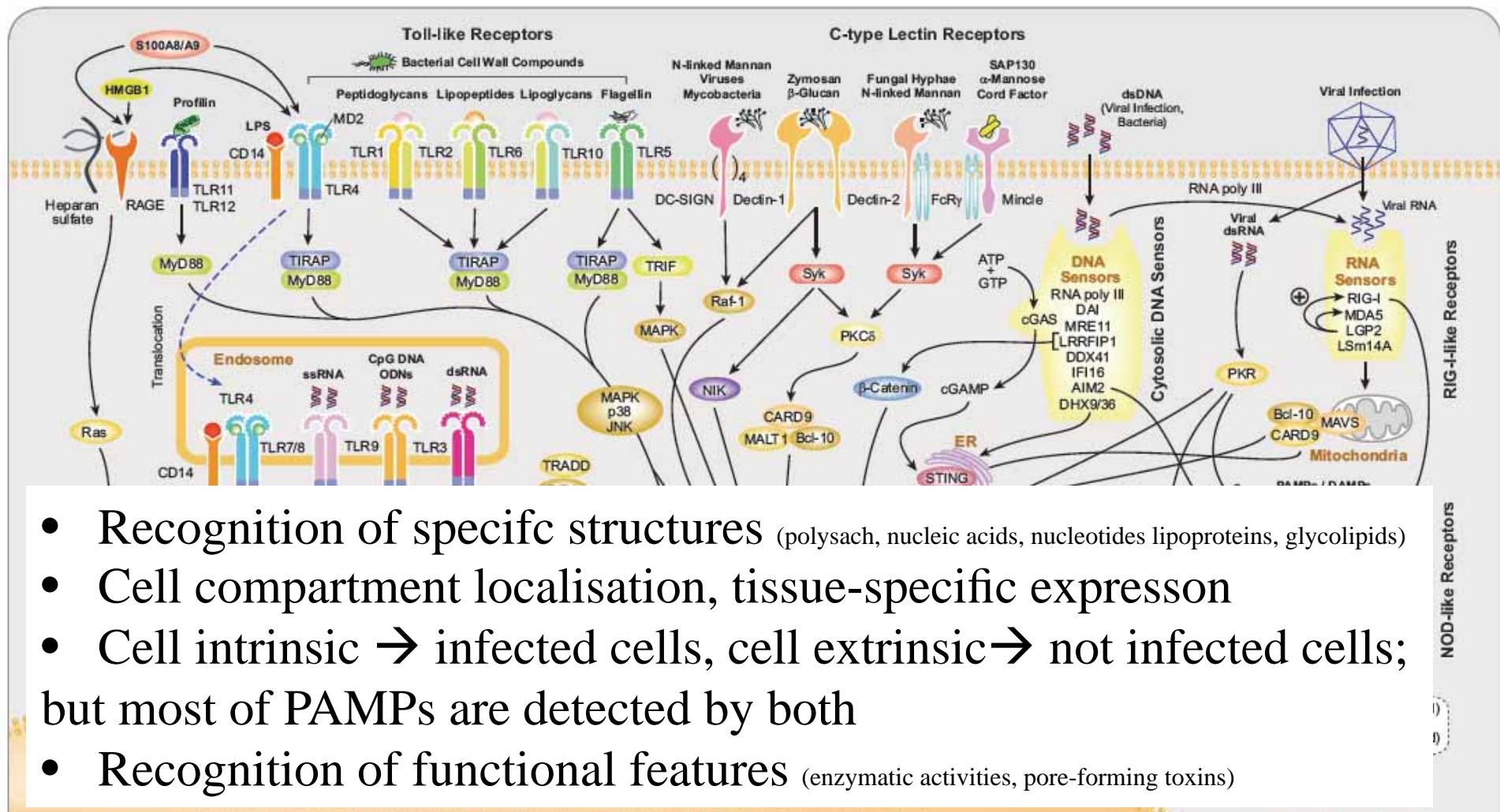
General scheme

4 major inflammatory components



Pathogen recognition receptors (PRRs)

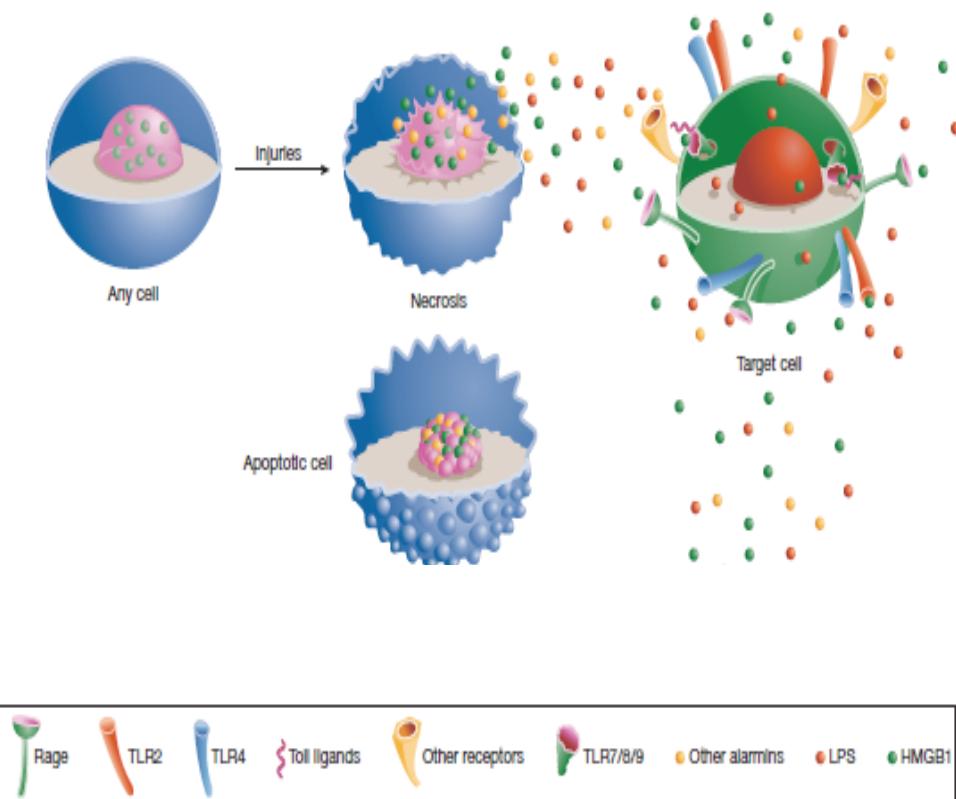
- Microbial Pattern Recognition Receptors: TLR, RLR, NLR, CLR signaling (examples)



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

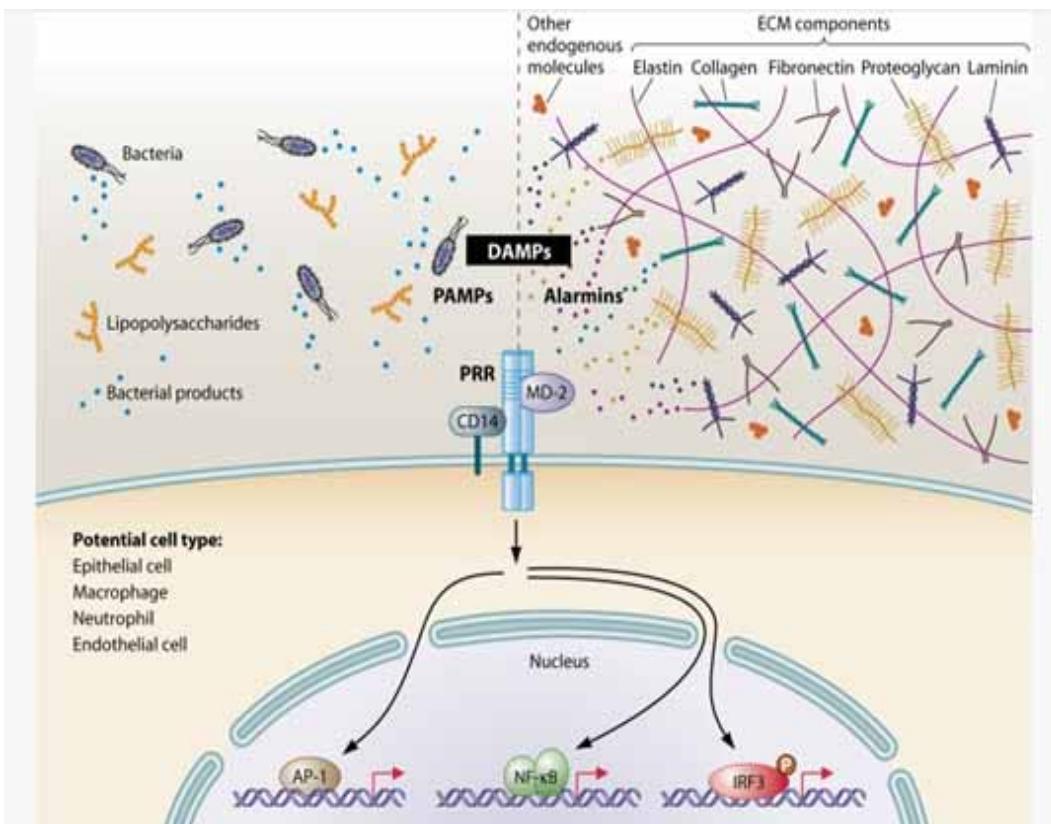
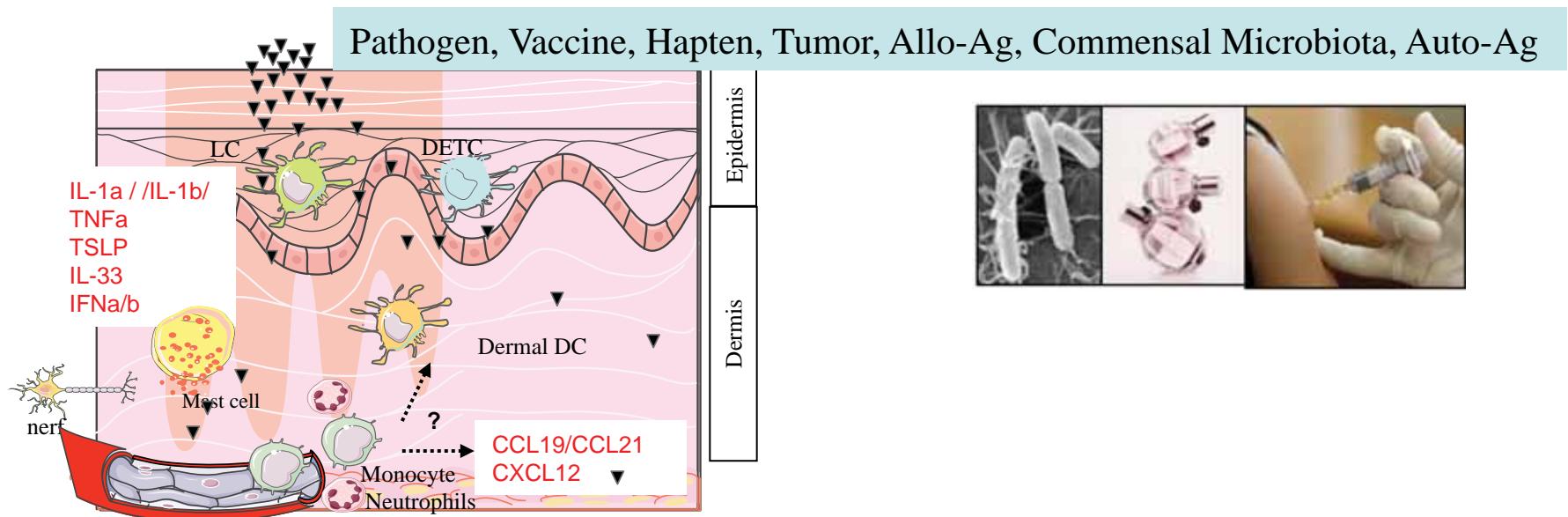


Table 2 | Adjuvant and pro-inflammatory activity of extracellular DAMPs

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

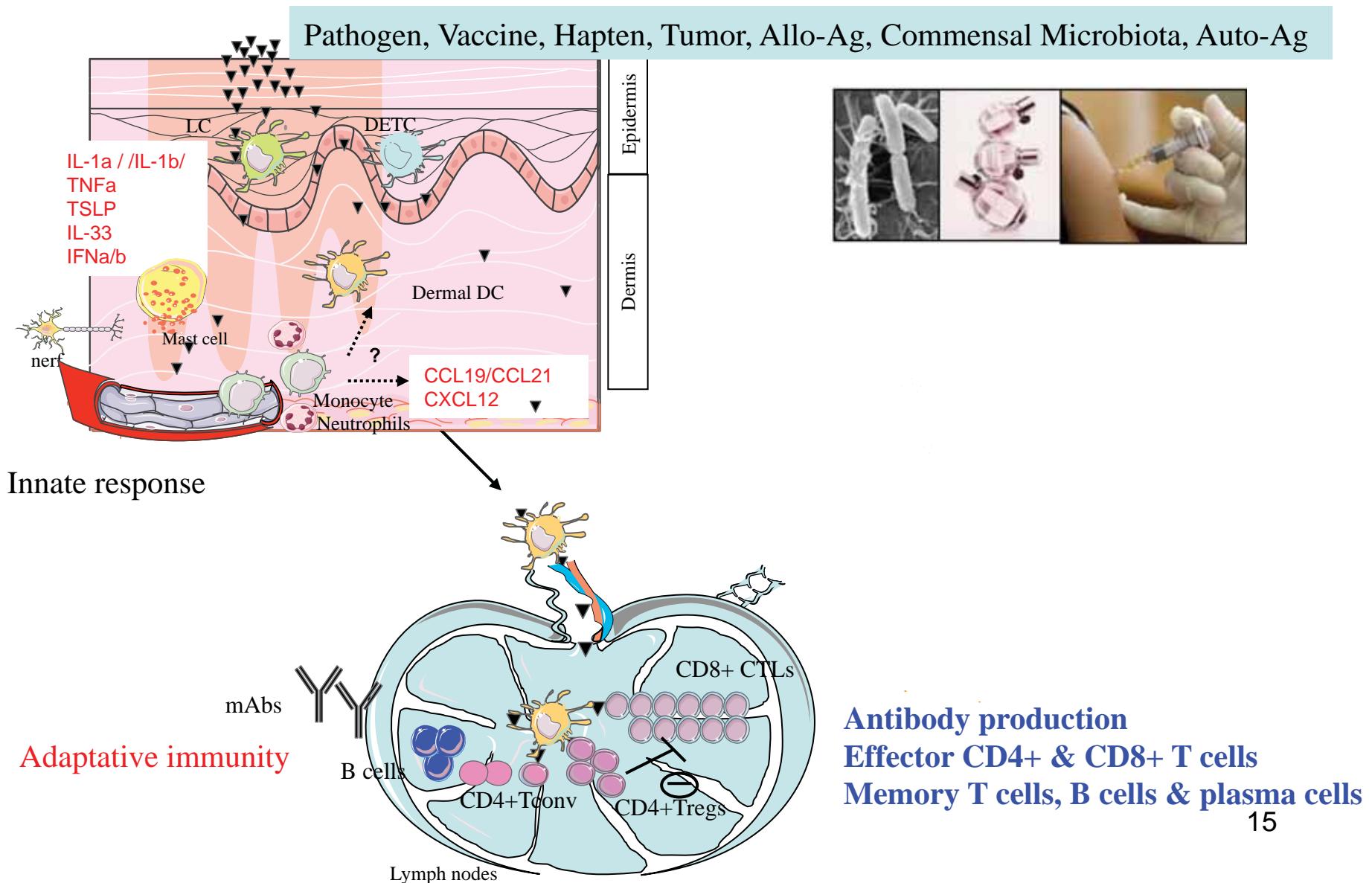
Release of inflammatory mediators

Coordinated cross-talk between epithelial and immune cells

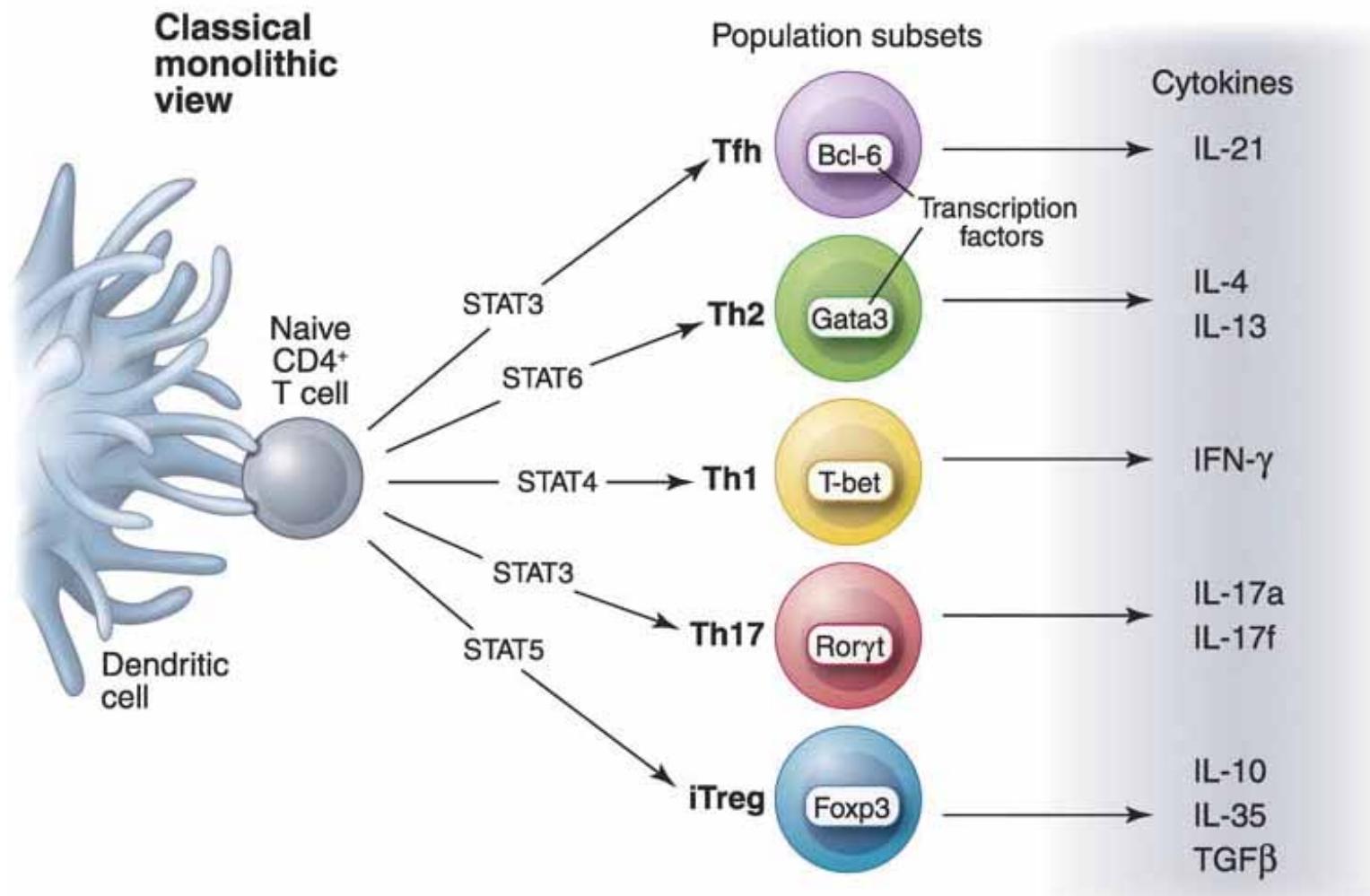
Infiltration of blood leucocytes

Induction of systemic immunity upon skin exposure/immunization

Skin exposure, immunization

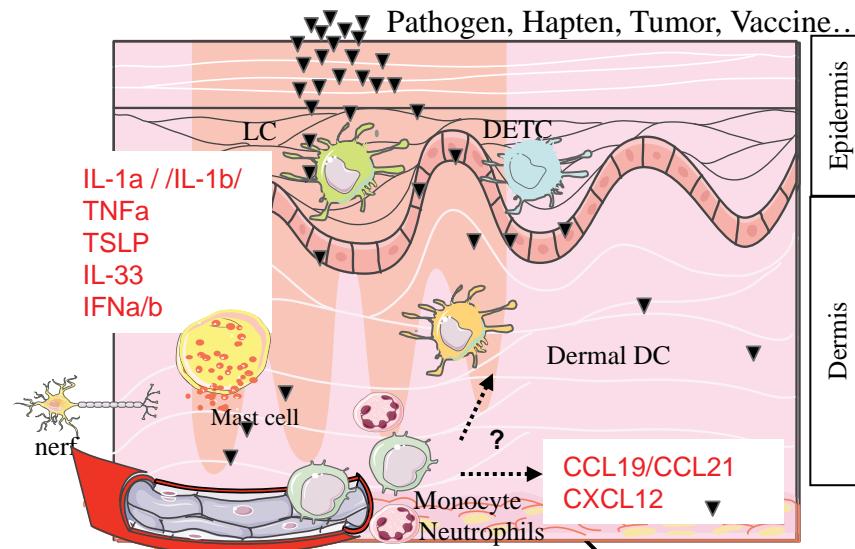


Distinct T cells

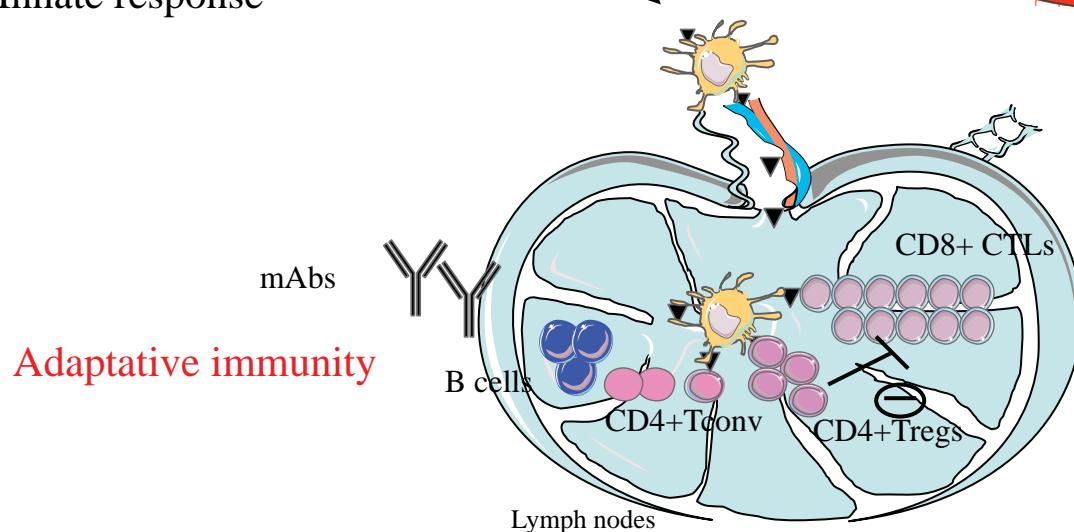


Induction of systemic immunity upon skin exposure/immunization

Skin exposure, immunization

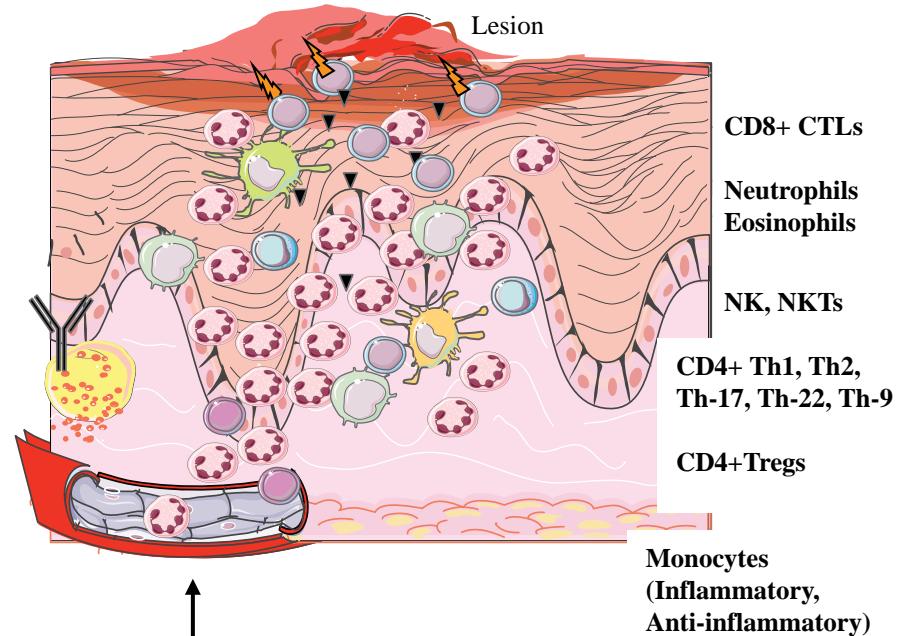


Innate response



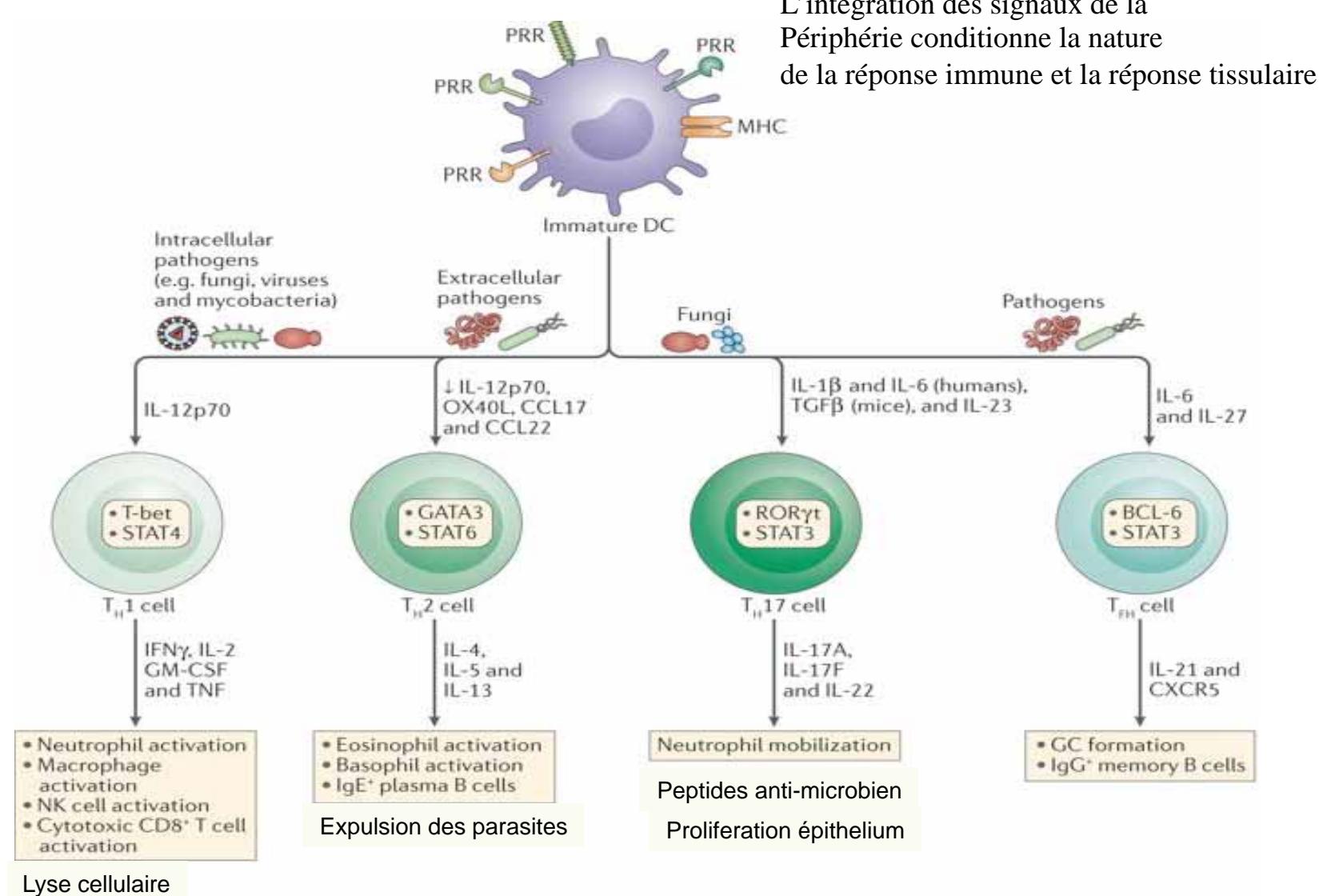
Adaptive immunity

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



**Effector & memory
response -> 2nd line of defence**

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



PLAN

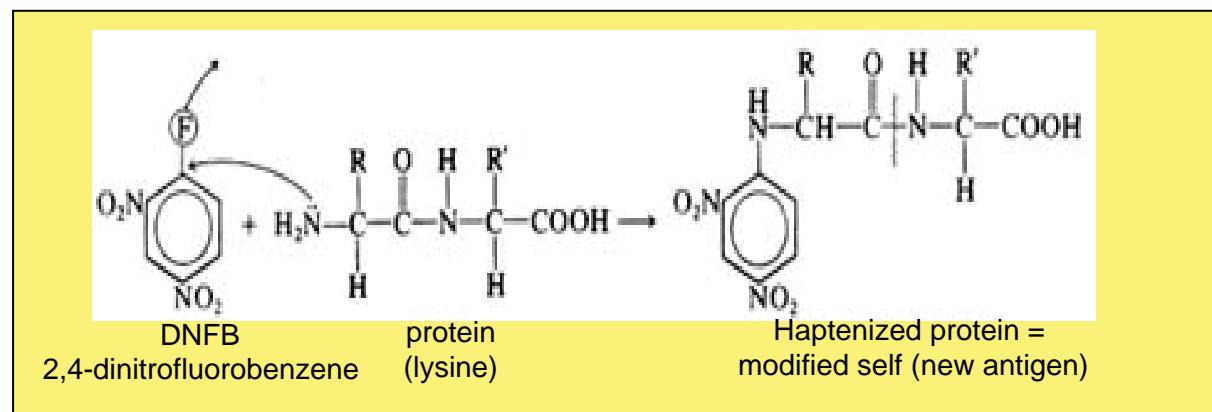
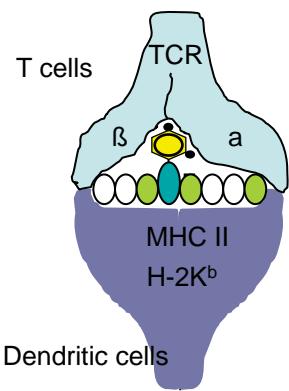
- Bases immunologiques de la réponse à l'interface cutanée
- Induction & régulation de l'inflammation cutanée : exemple de l'eczéma de contact

Allergic Contact Dermatitis (ACD): Generalities



Features

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

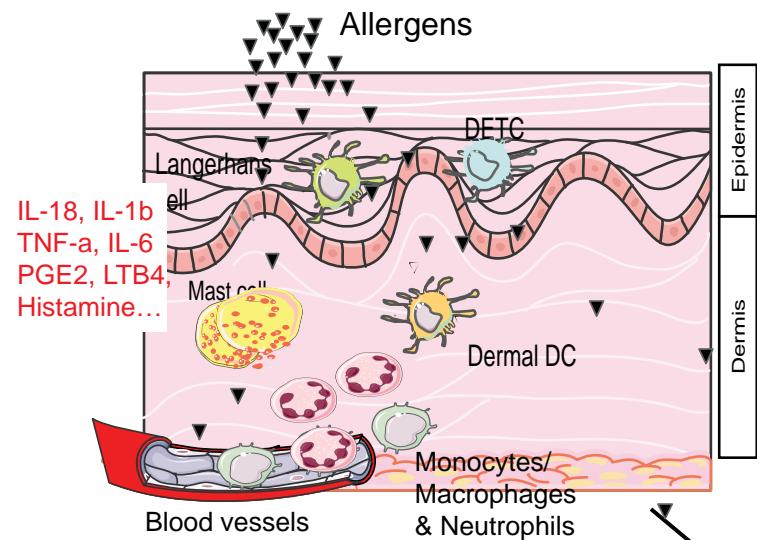


Presentation of haptenized peptides

Pathophysiology of skin allergy

1- Sensitization phase

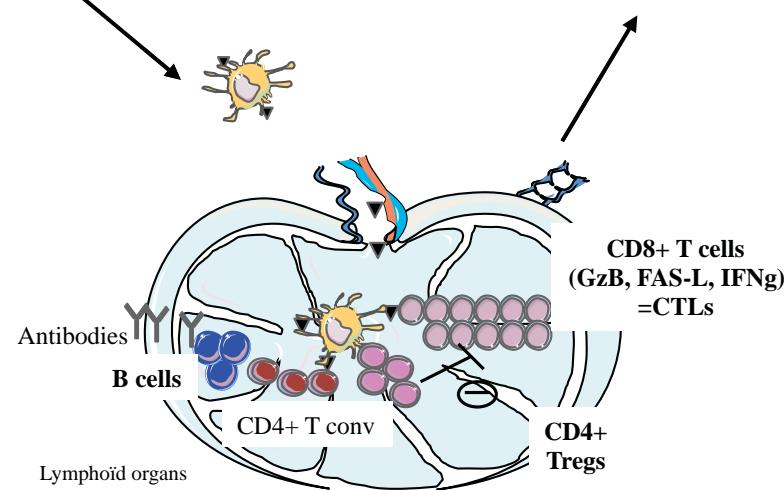
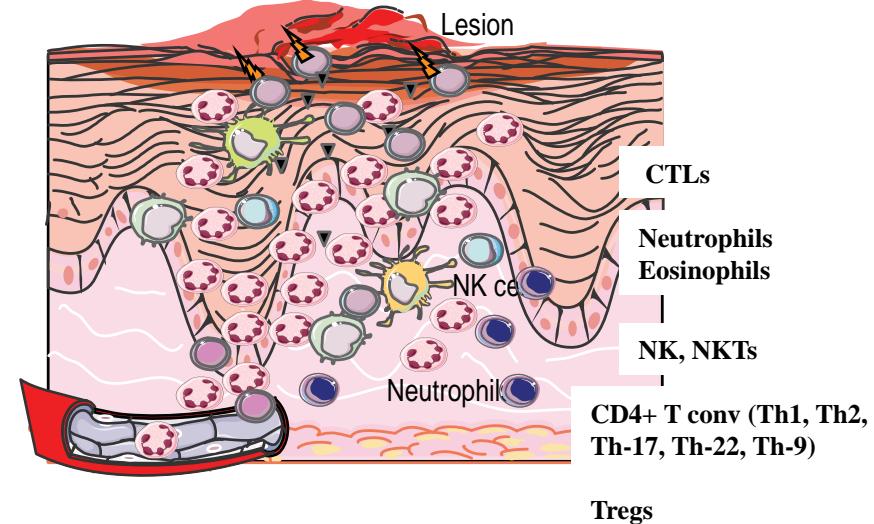
Innate immunity/ T cell priming



- 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
- GAMRADT *J Allergy Clin Immunol* 2019

2- Elicitation phase

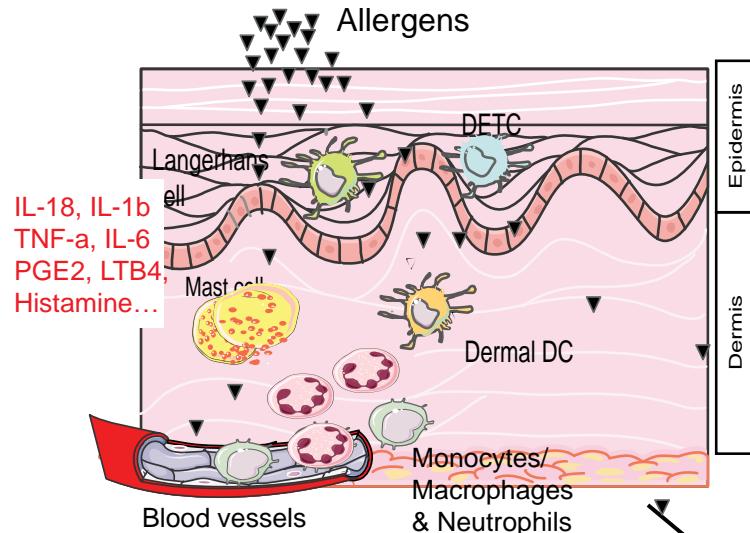
Effector response/ Polymorphic recruitment



Pathophysiology of skin allergy

1- Sensitization phase

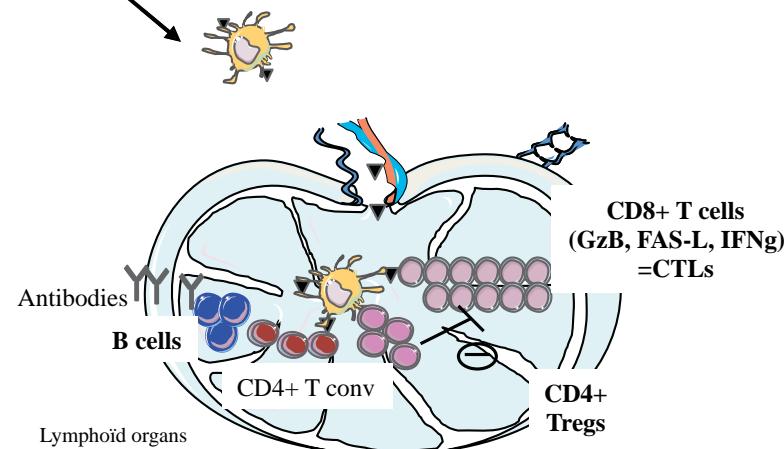
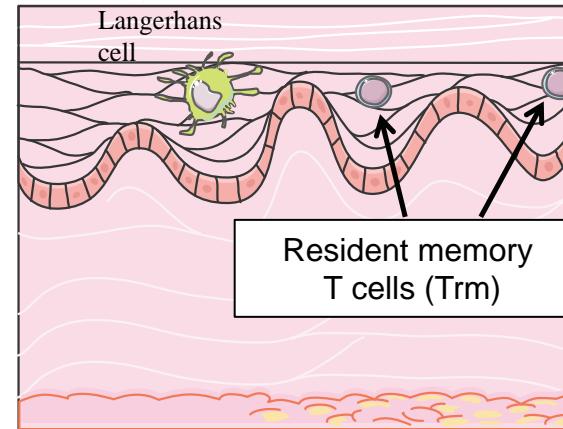
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- GOUBIER et al. *J Invest Dermatol*, 2013
- CORTIAL et al. *Nanomedicine*, 2015
- GAMRADT *J Allergy Clin Immunol* 2019

3- Resolution of skin inflammation

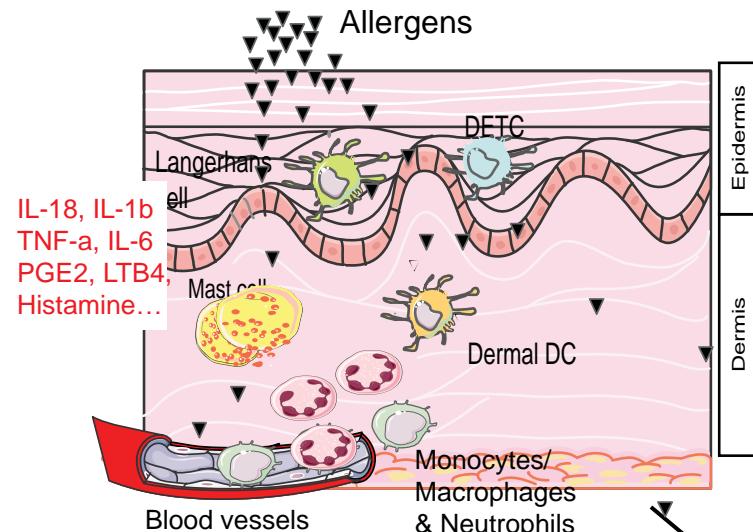
Healed lesion/ Persistence of skin Trm



Pathophysiology of skin allergy

1- Sensitization phase

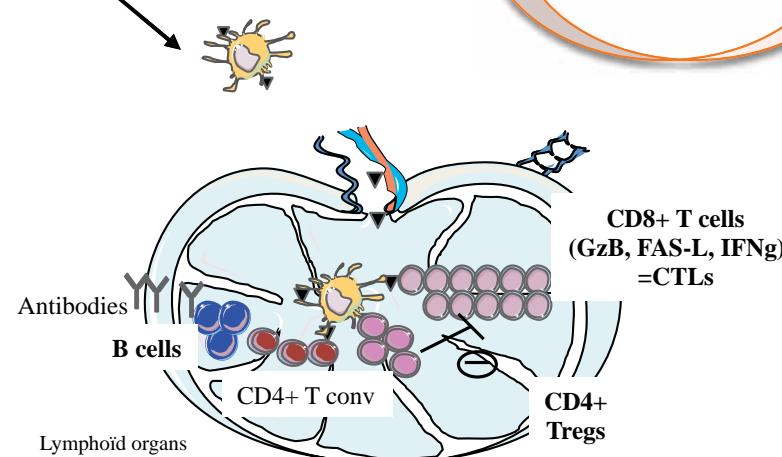
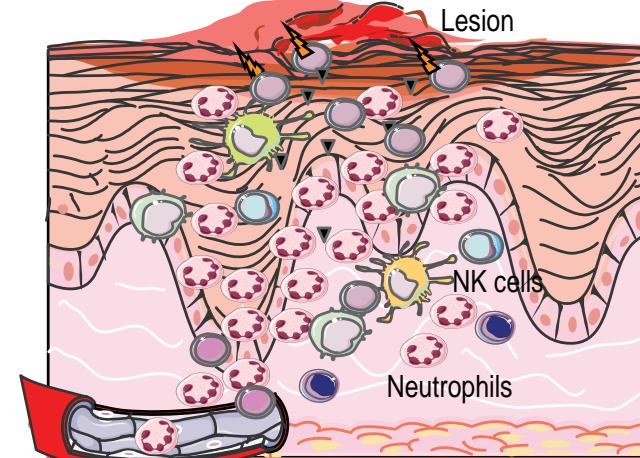
Innate immunity/ T cell priming



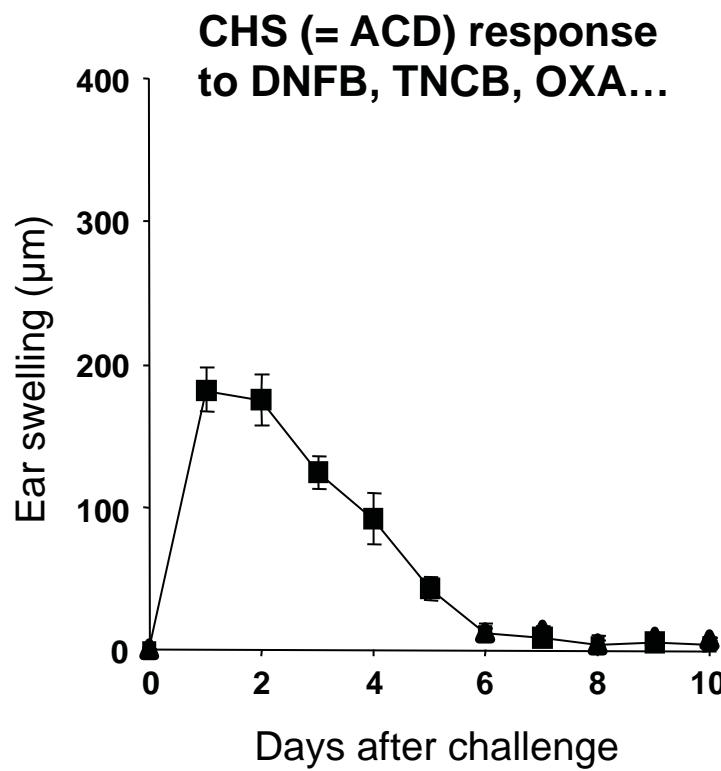
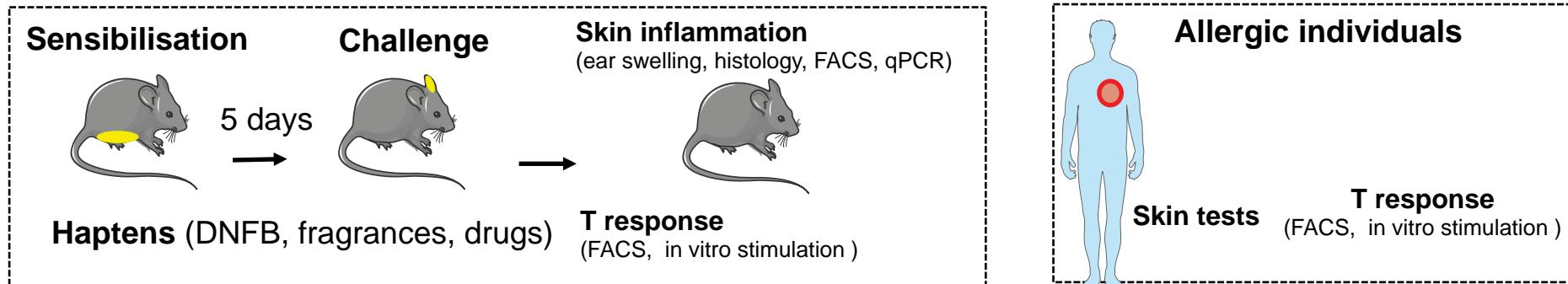
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- GOUBIER et al. *J Invest Dermatol*, 2013
- CORTIAL et al. *Nanomedicine*, 2015
- GAMRADT *J Allergy Clin Immunol* 2019

4- Recurrence / Severity / Chronicity

New exposure / Flares



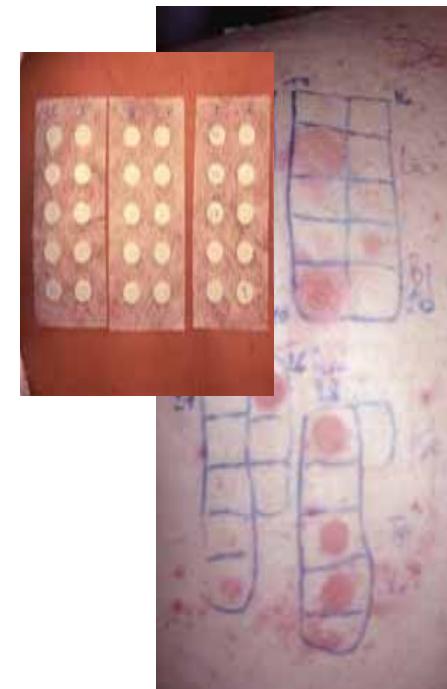
Experimental models of ACD in mouse, in human



ACD lesions



Positive patch-tests to reference allergens



Permeation of haptens into the skin

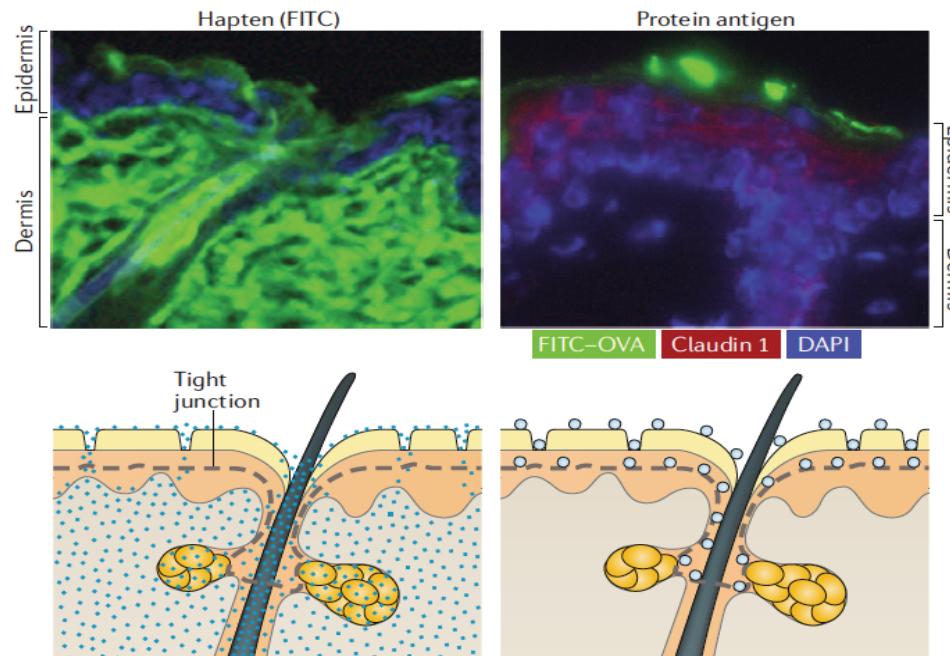
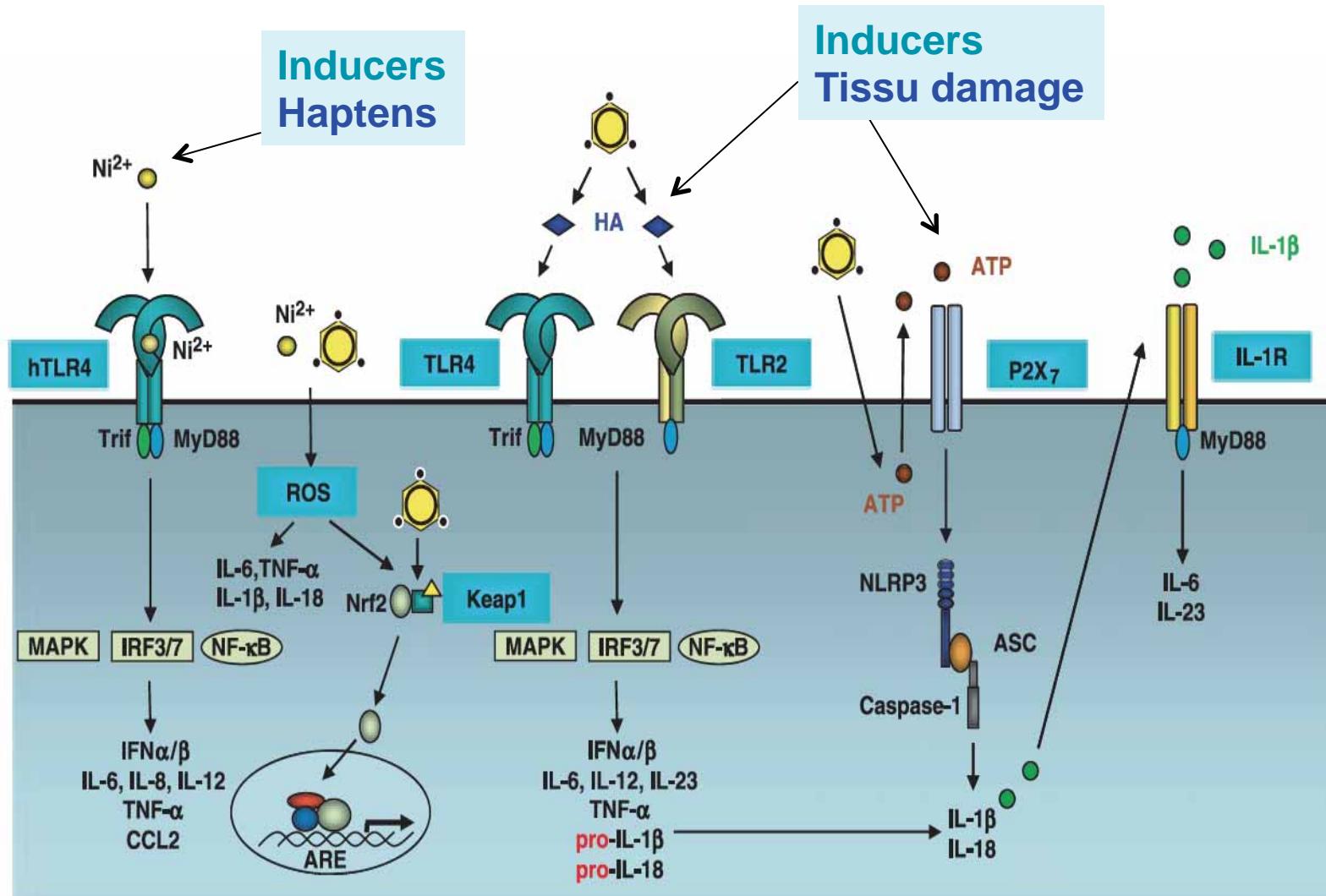


Fig. 4 | Penetration of hapten and proteins into the skin. A hapten (fluorescein isothiocyanate (FITC); molecular mass = 389; left) or FITC-conjugated ovalbumin (FITC-

- Les haptènes sont pour la plus part des substances hydrophobes
- Pénétration dépend de l'hydrophobicité (LogP), mais aussi de la présence de groupes chargés, la taille (poids moléculaire < 1000 Daltons), la forme moléculaire et du véhicule.
- Les peaux altérées (blessures physiques, chimiques ou anormalité génétique) favorisent l'apparition d'un eczéma de contact

Kabashima et al. *Nature Rev immunol* 2019

How haptens activate innate immunity?



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

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

Conserved histidines on human TLR4 as potential binding sites for nickel

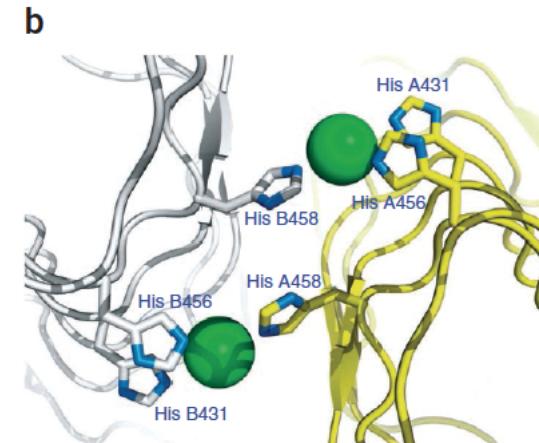
nature immunology

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

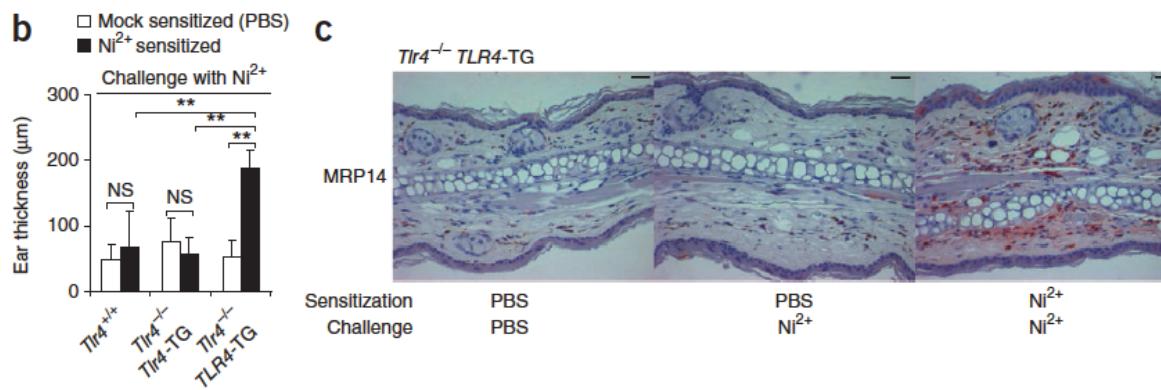
Marc Schmidt^{1,2}, Badrinarayanan Raghavan^{1,2}, Verena Müller^{1,2}, Thomas Vogl³, György Fejér⁴, Sandrine Tchaptchet⁴, Simone Keck⁴, Christoph Kalis⁴, Peter J Nielsen⁴, Chris Galanos⁴, Johannes Roth³, Arne Skerra⁵, Stefan F Martin⁶, Marina A Freudenberg⁴ & Matthias Goebeler^{1,2}

a

hTLR4 LRR14	DLPSLEFLDLSRNGLSFKGCCSQSDF	396
mTLR4 LRR14	ALEPSLYLDLSRNALSFSGCCSYSDL	394
hTLR4 LRR15	GTTSLKYLDDLSFNGVITMSSNFL	419
mTLR4 LRR15	GTNSLRLHLDLSFNQGAIIMSANFM	417
hTLR4 LRR16	GLEQLEHLDFQHGNLQCMSEFSVFL	444
mTLR4 LRR16	GLEELQHLDFOHQSTLKRVTEESAFL	442
hTLR4 LRR17	SLRNLIYLDISHTTRVAFNGIFN	468
mTLR4 LRR17	SLEKLLYLDISYTNTKIDFDGIFL	466
hTLR4 LRR18	GLSSLEVKKMAGNSFQENFLPDI	493
mTLR4 LRR18	GLTSINTLKMGNSFKDNNTLSNVFA	491
hTLR4 LRR19	ELRNLTFLDLSQCQ1EQLSPTAFN	517
mTLR4 LRR19	NTTNLTFLDLSKCQLEQISWKGVFD	515
hTLR4 LRR20	SLSSILQVLNNMSHNFFSLDTFPYK	541
mTLR4 LRR20	TLERLQLLNNMSHNNLFLDSSHYN	539
hTLR4 LRR21	CLNSILQVLDYSLNMTTSKKQELQH	566
mTLR4 LRR21	QLYSLSTLDCSFNQIETSKGI-LQH	563
hTLR4 LRR22	FPSSLAFLNLNTQNDFA	582
mTLR4 LRR22	FPKSIAFFNLNTNSVA	579
hTLR4 LRRCT	CTCEHQSFHQWIKDQRQLLVEVERM	607
mTLR4 LRRCT	CICEHQKFHQWVKEQRQFLVNVEQM	604

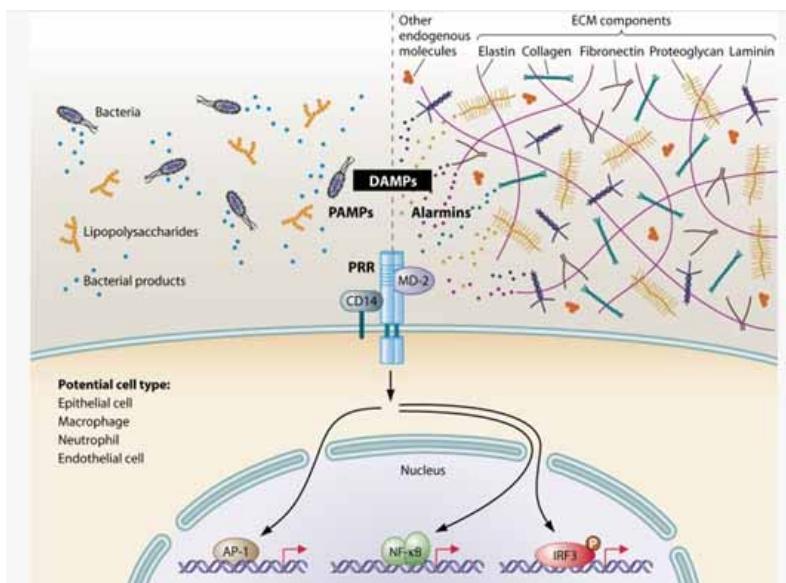


Transgenic expression of human TLR4 in mice confers reactivity toward nickel



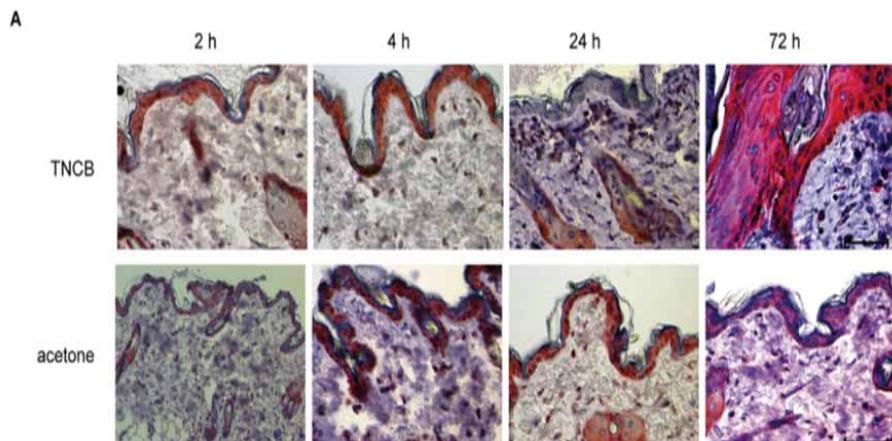
Les diverses étapes de la sensibilisation : activation de l'immunité innée

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

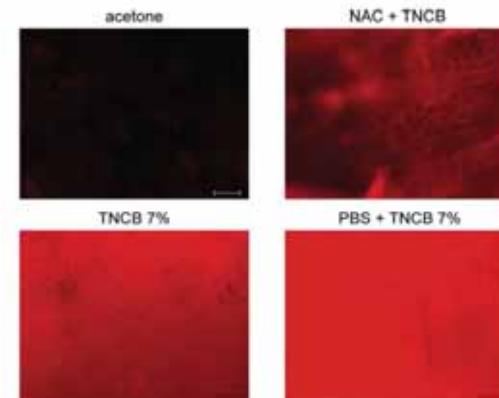


Esser P, Plos One 2012

Dégénération Acide Hyaluronique ht PW, 24h après application

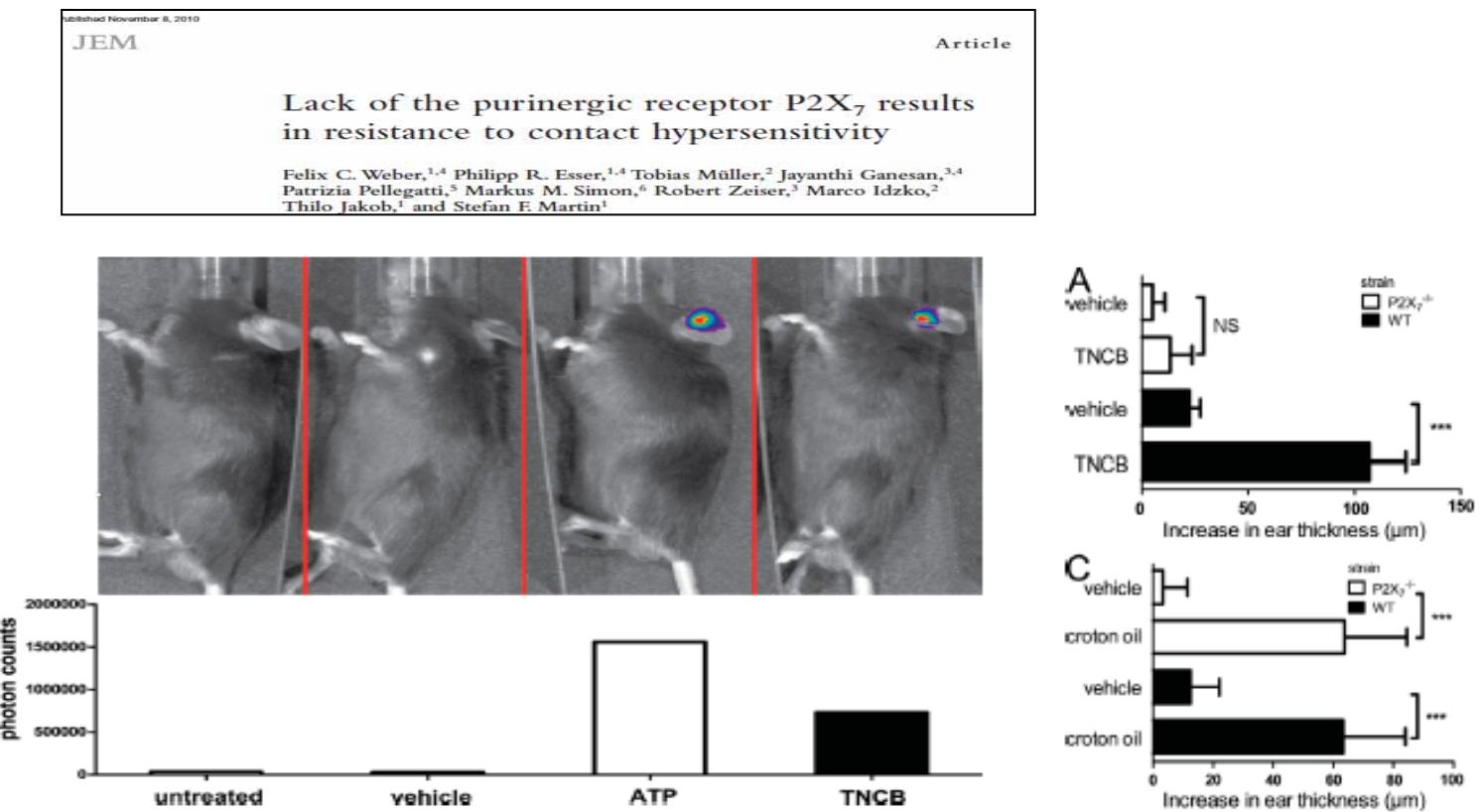


Production ROS, peau challengée



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

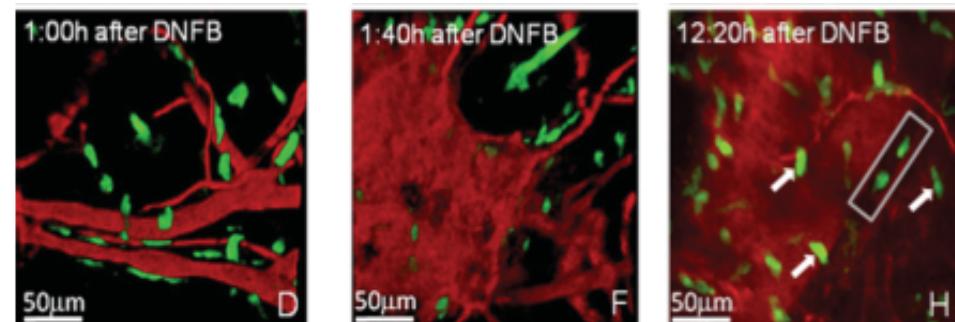
- Impact des médiateurs reconnus par les NLRs sur le développement de la réponse d'EAC



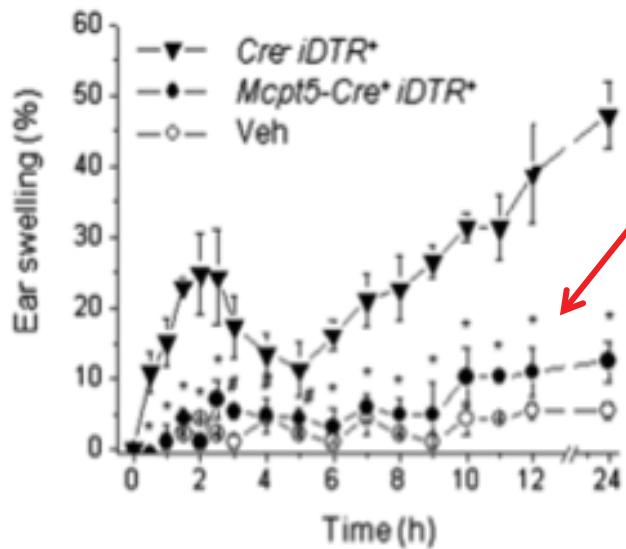
Contribution of innate cells? Mast cells



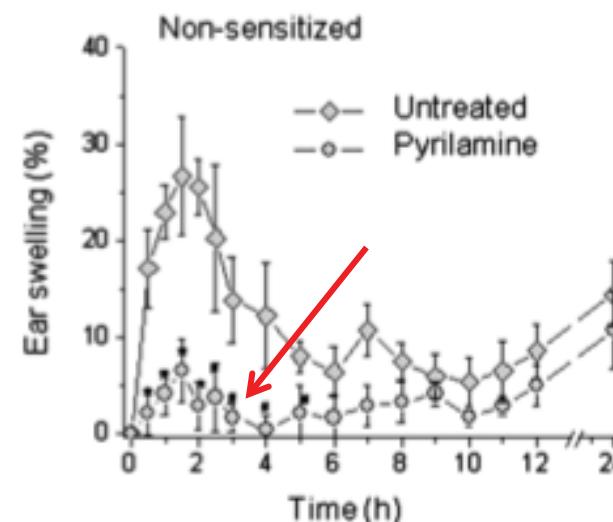
Ear skin mast cells and blood vessels respond to hapten



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

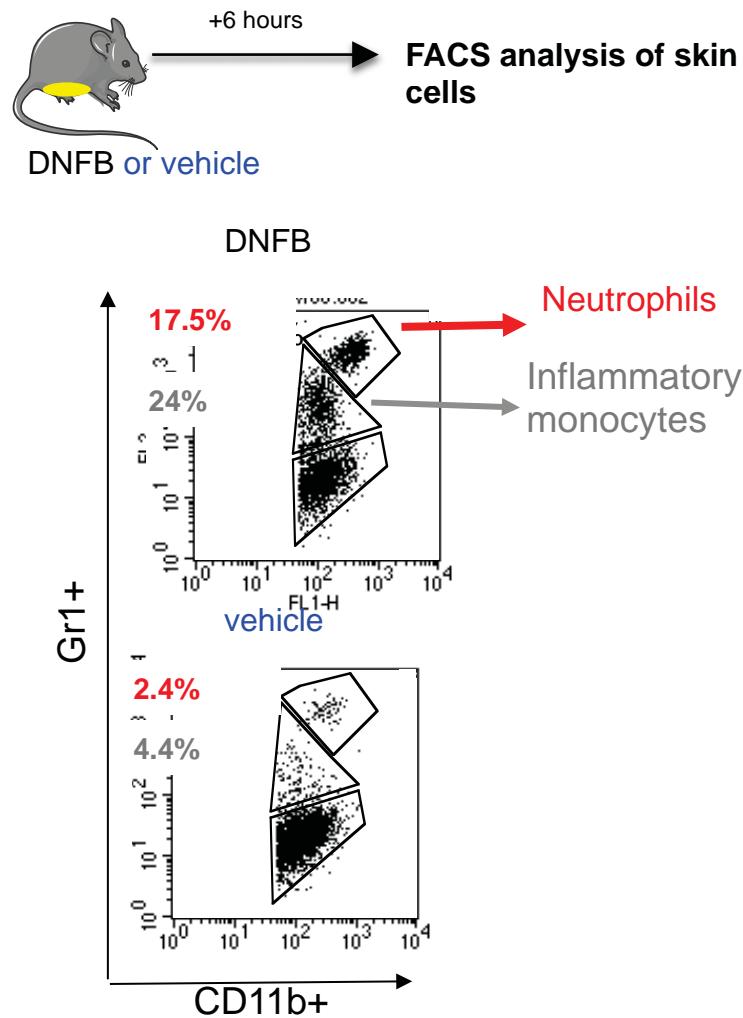


Skin inflammation is histamine-dependent

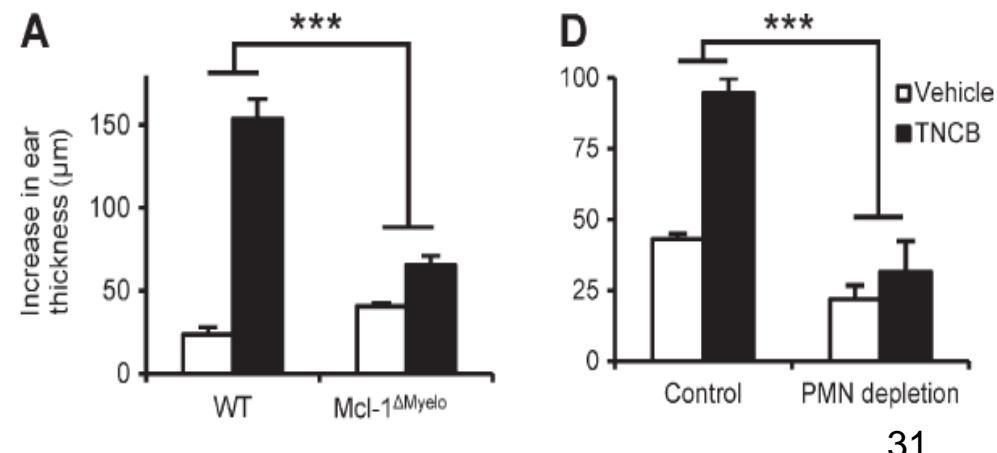
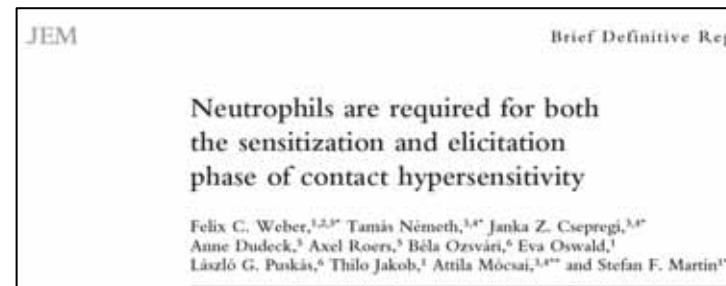


Contribution of innate cells? Neutrophils

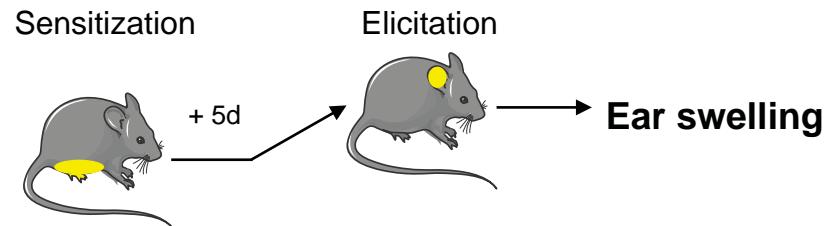
Large infiltration of neutrophils
in the hours following hapten application



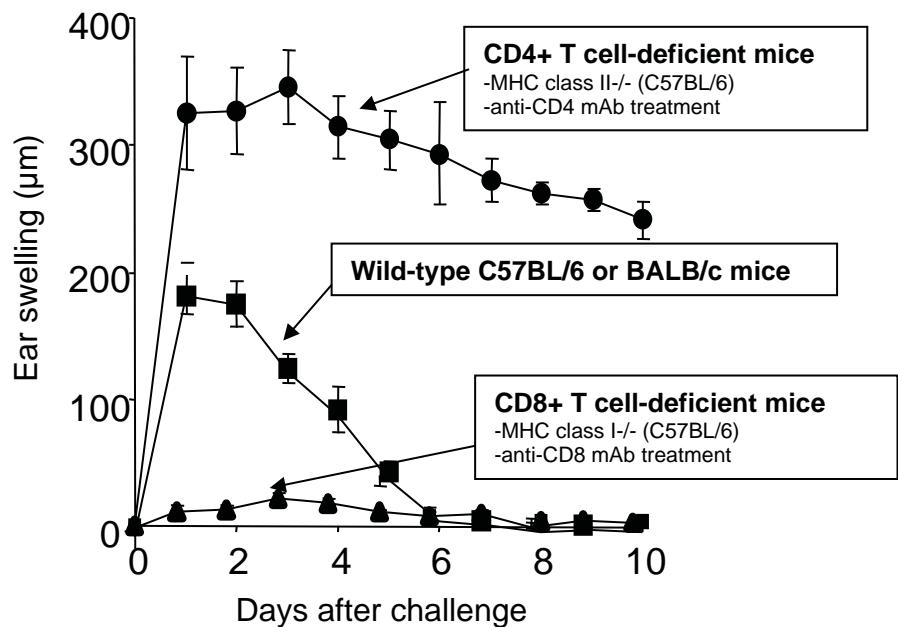
Lack of neutrophils (depletion, transgenic animals)
prevents T cell priming and development of skin inflammation



Main effectors? CD8+ CTLs

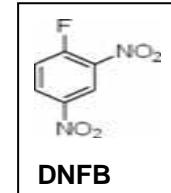
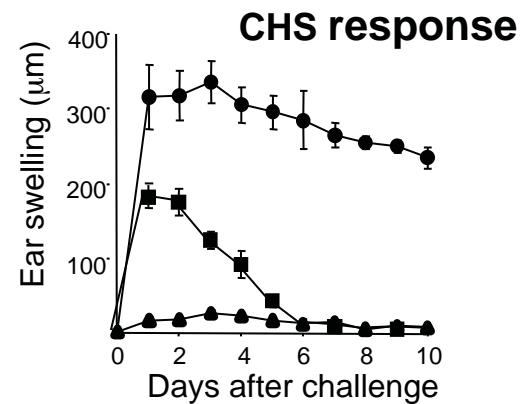
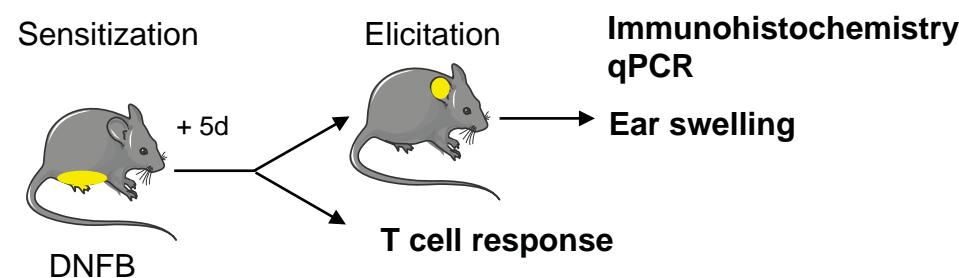


Strong haptens: DNFB, TNCB, OXAZOLONE...



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

Main effectors? CD8+ CTLs

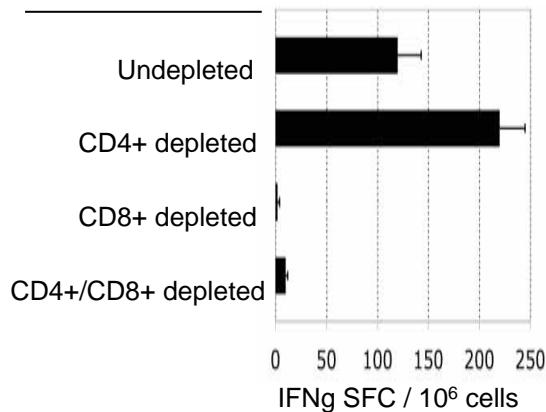


Priming of IFNg-producing CD8+ T cells

T cell response (draining lymph nodes)

Elispot assay

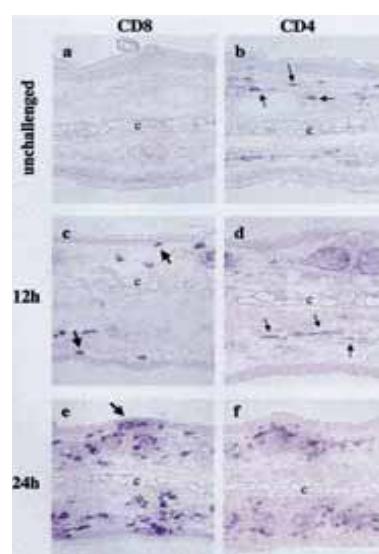
mAb Treatment



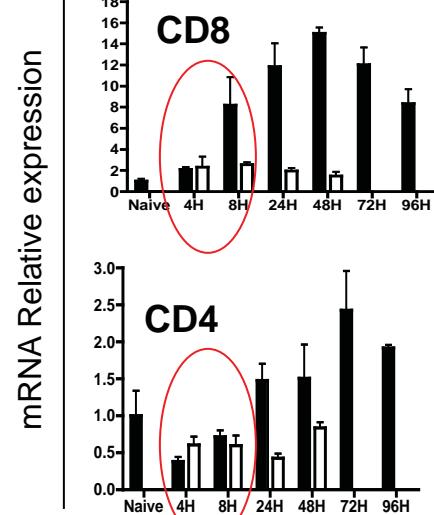
Early recruitment of CD8+ T cells initiates eczema

T cells recruitment (challenged ears)

Immunostaining

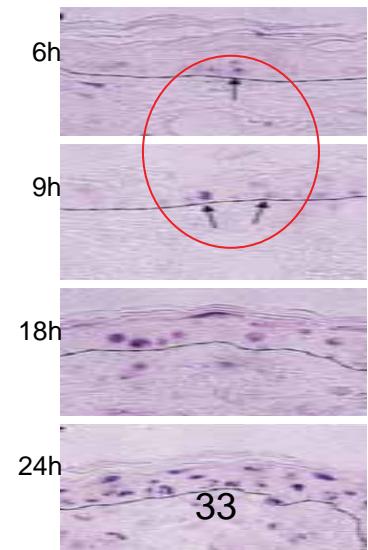


mRNA Relative expression ↑



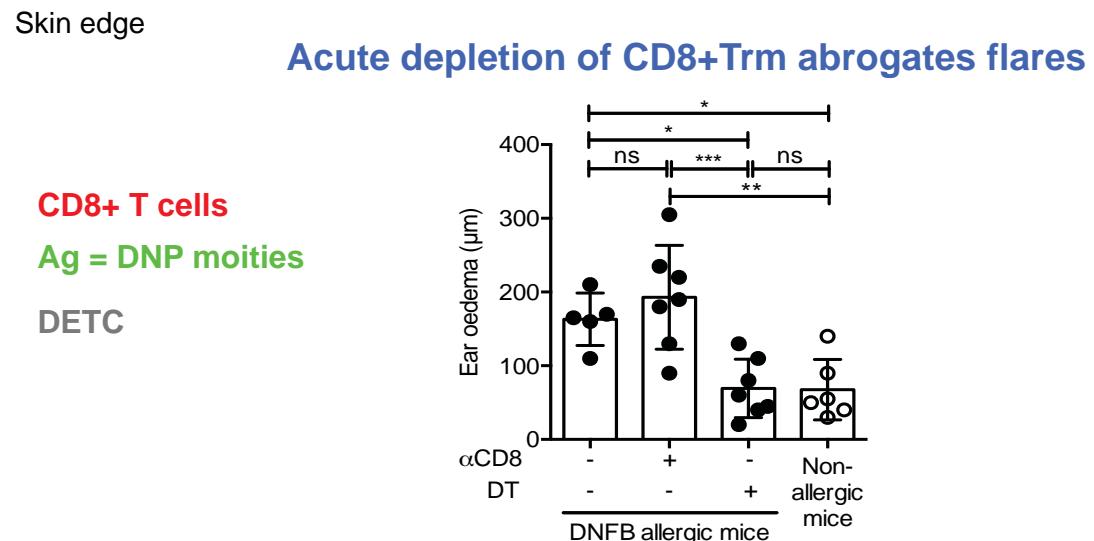
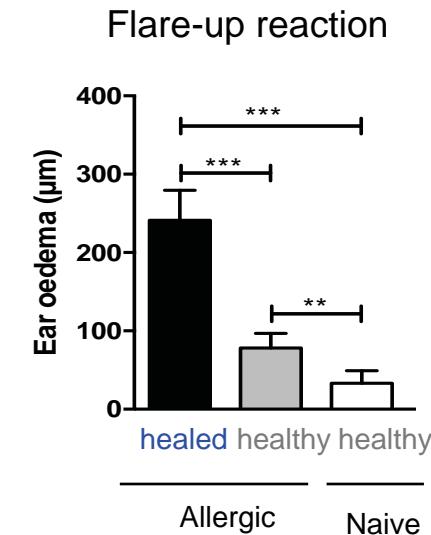
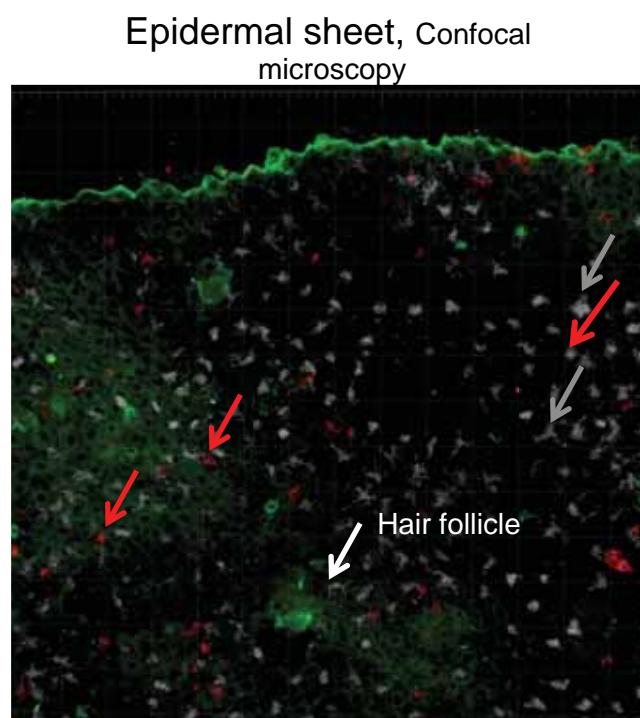
Keratinocytes: target of CTLs

TUNEL



Main effectors? CD8+ CTLs

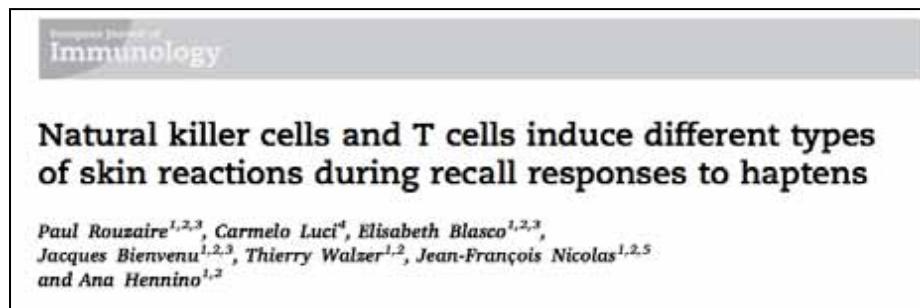
Recurrence, chronicity



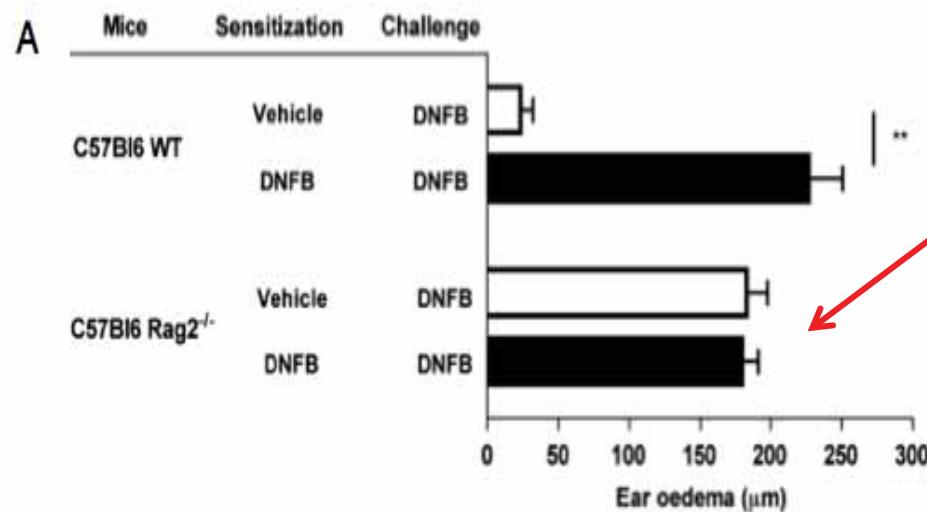
Injection of diphtheria toxin or anti-CD8+ mAbs
IDTR transgenic animals

Main effectors? NK cells

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



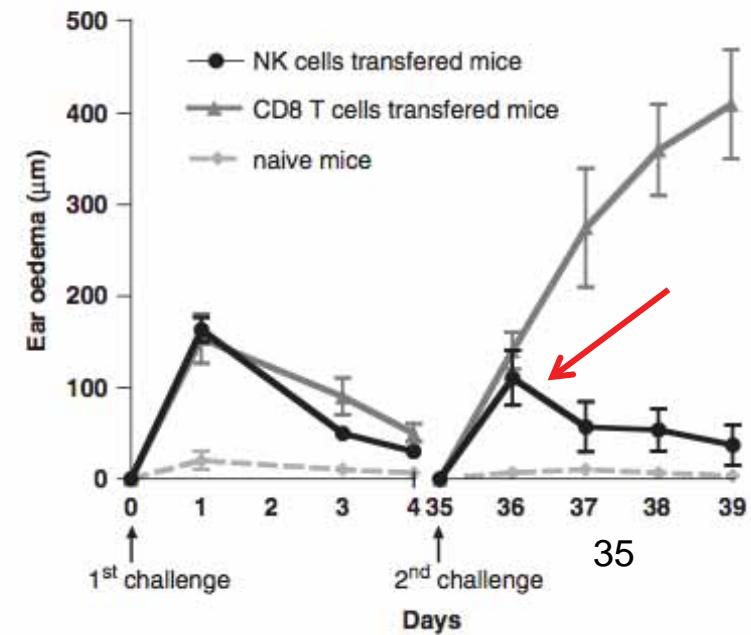
No CHS response in T cell-deficient strains



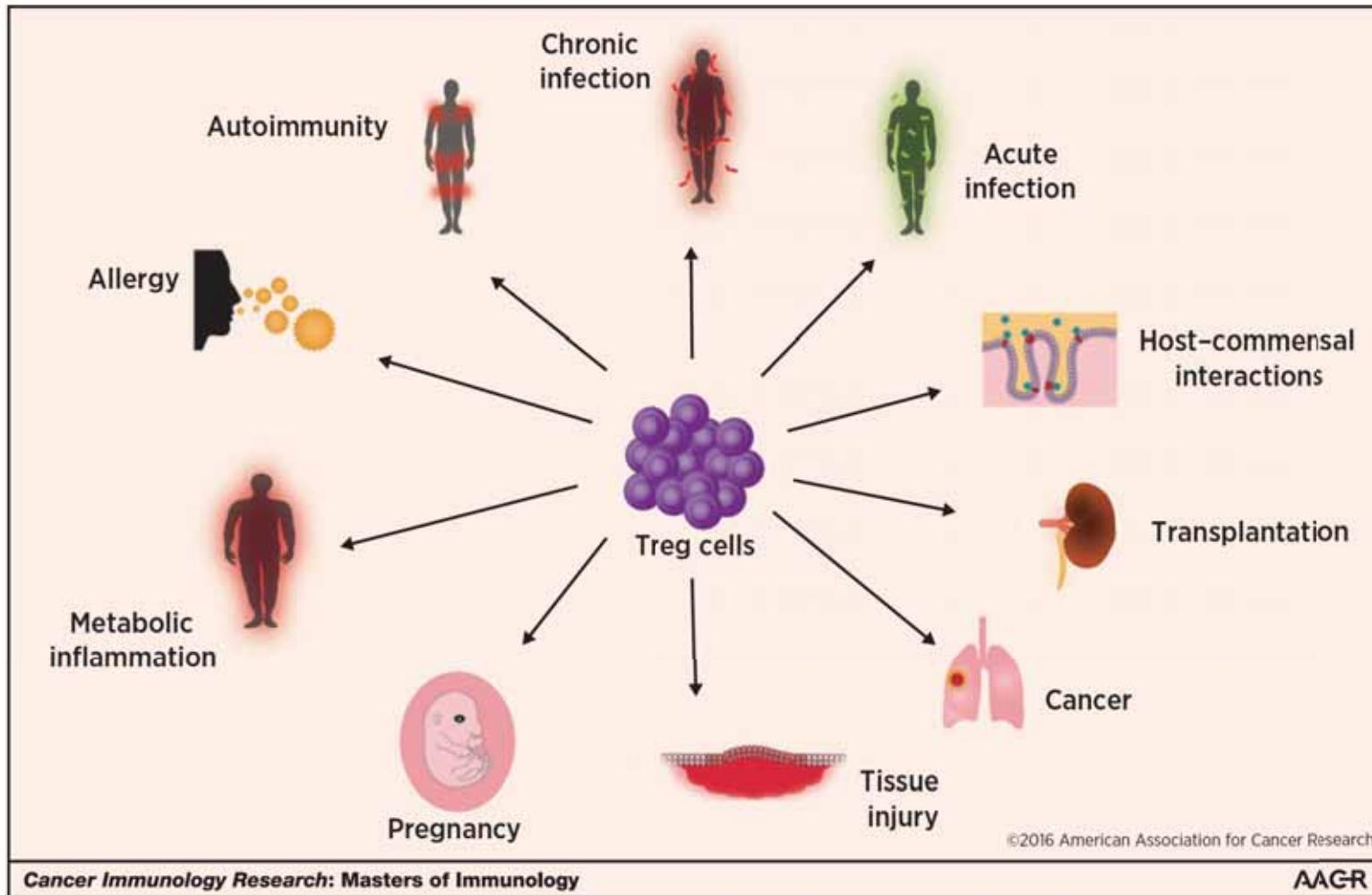
Paulst S. Nat Immunol 2011

NK cells confer CHS and recall responses, when extracted from liver and transferred into recipient animals

-> NK cell « memory »

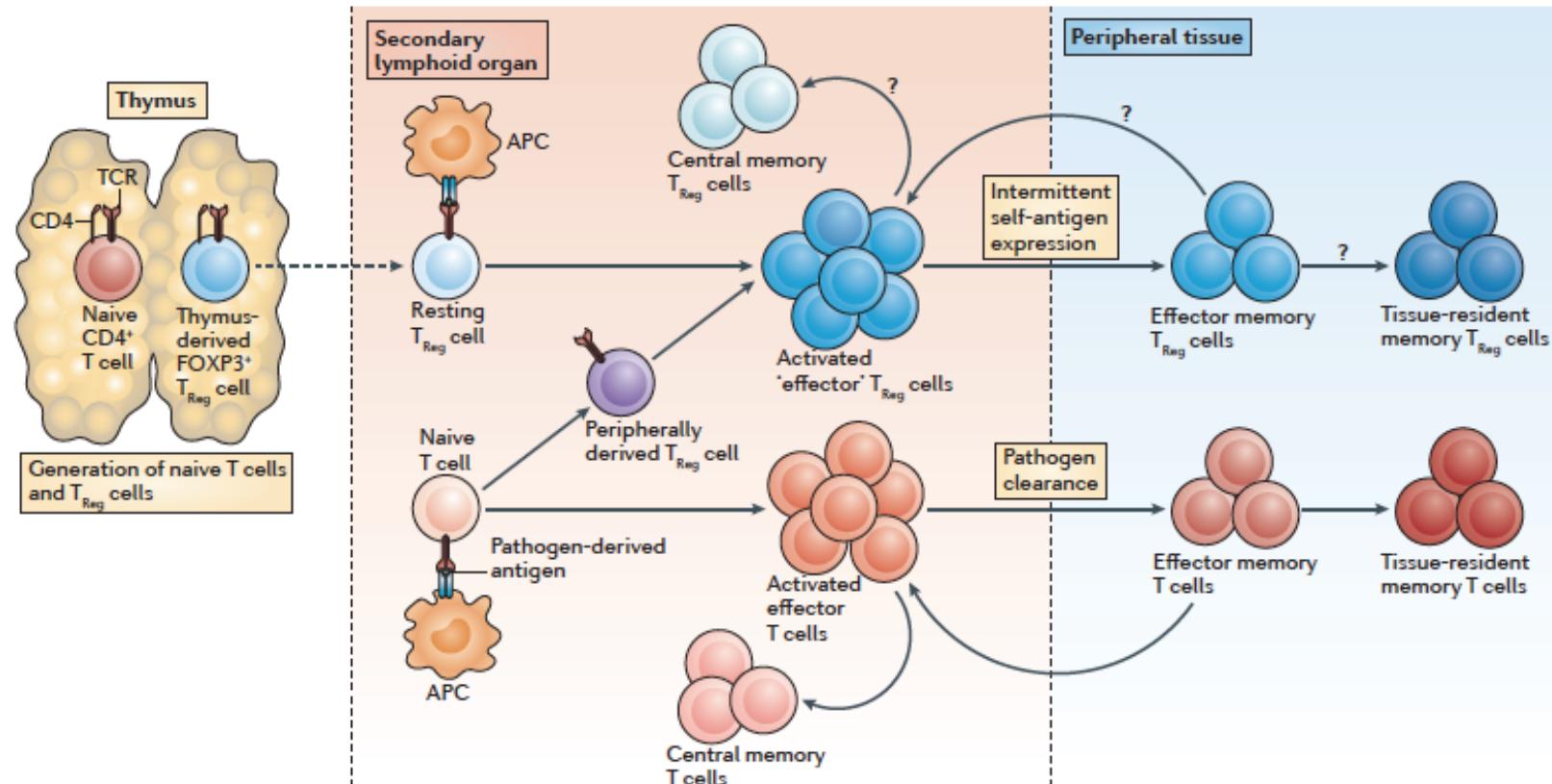


Les lymphocytes T régulateurs FoxP3+



Les lymphocytes T régulateurs FoxP3+

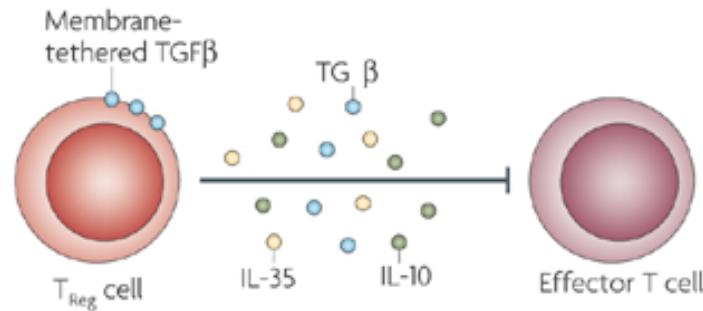
Ontogeny: Life Cycle of Regulatory and Conventional T cells



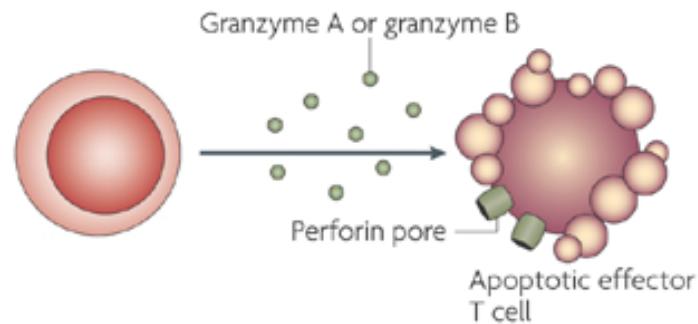
Les lymphocytes T régulateurs FoxP3+

Suppressive mechanisms used by Tregs

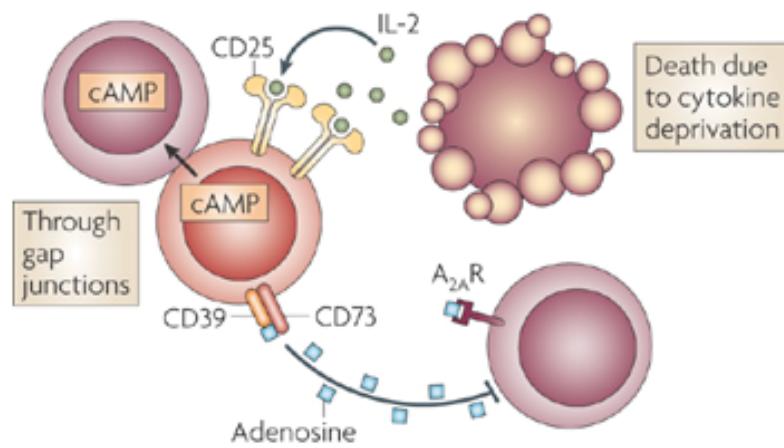
a Inhibitory cytokines



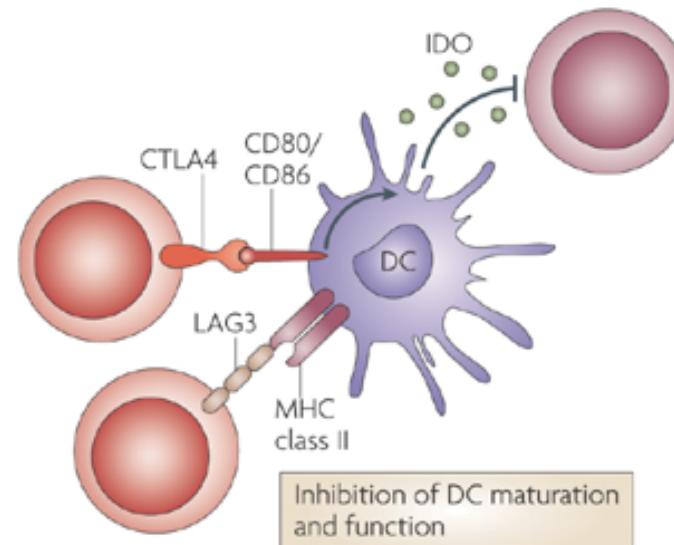
b Cytolysis



c Metabolic disruption

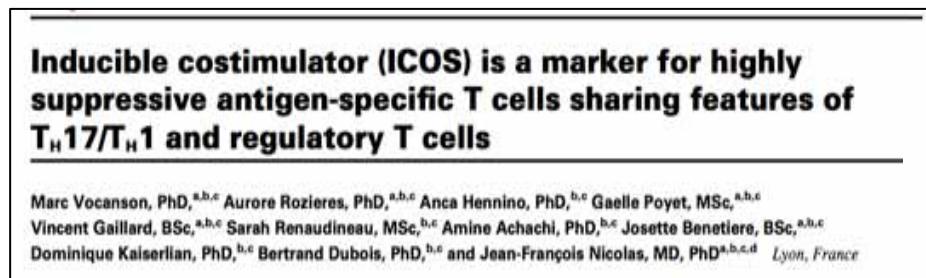


d Targeting dendritic cells



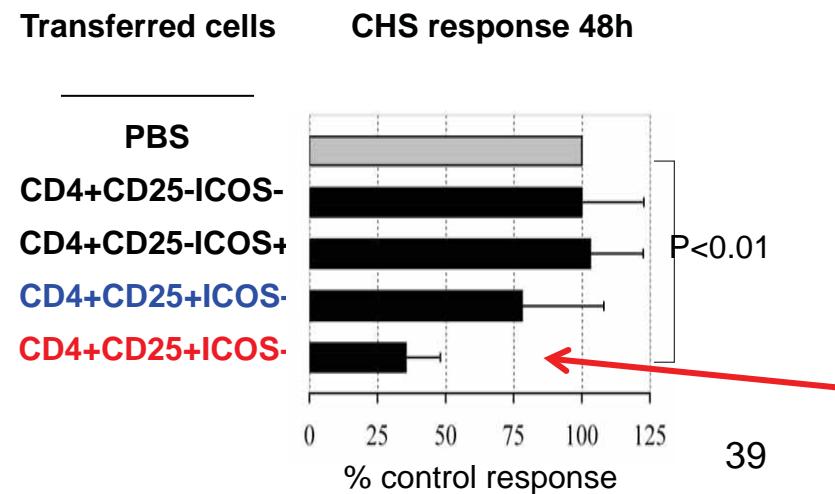
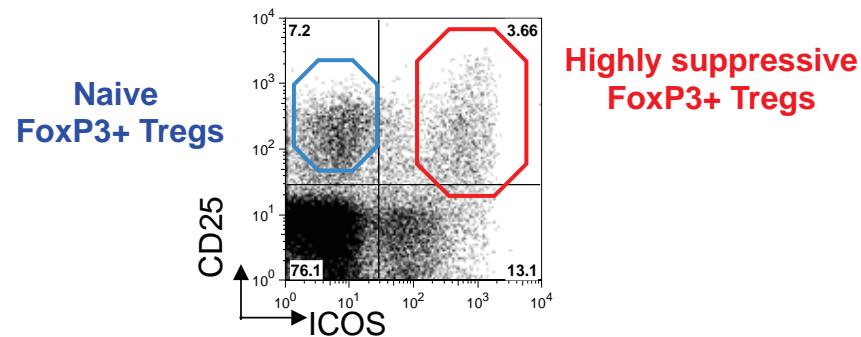
Main regulatory cells? FoxP3+Tregs

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

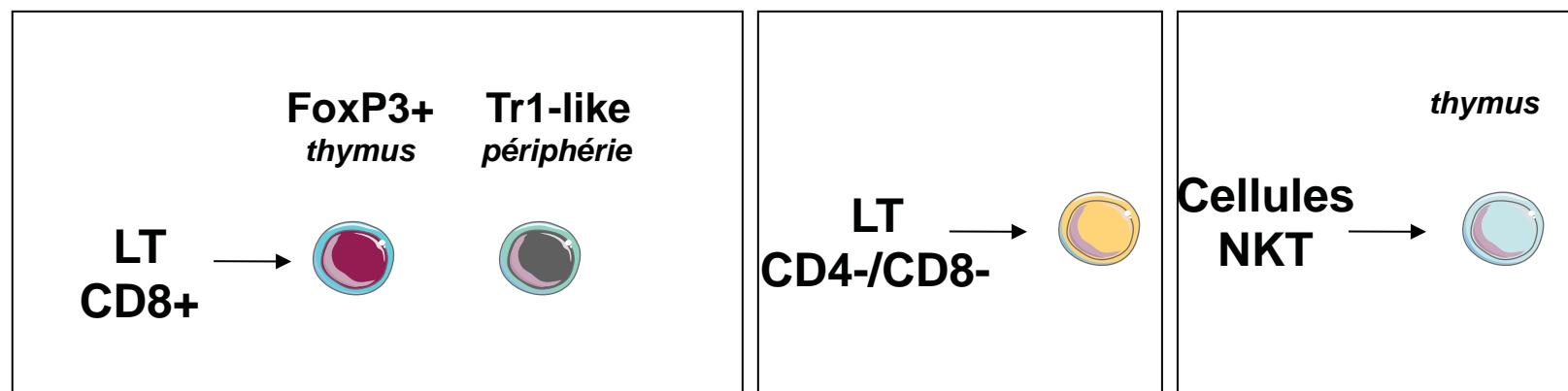
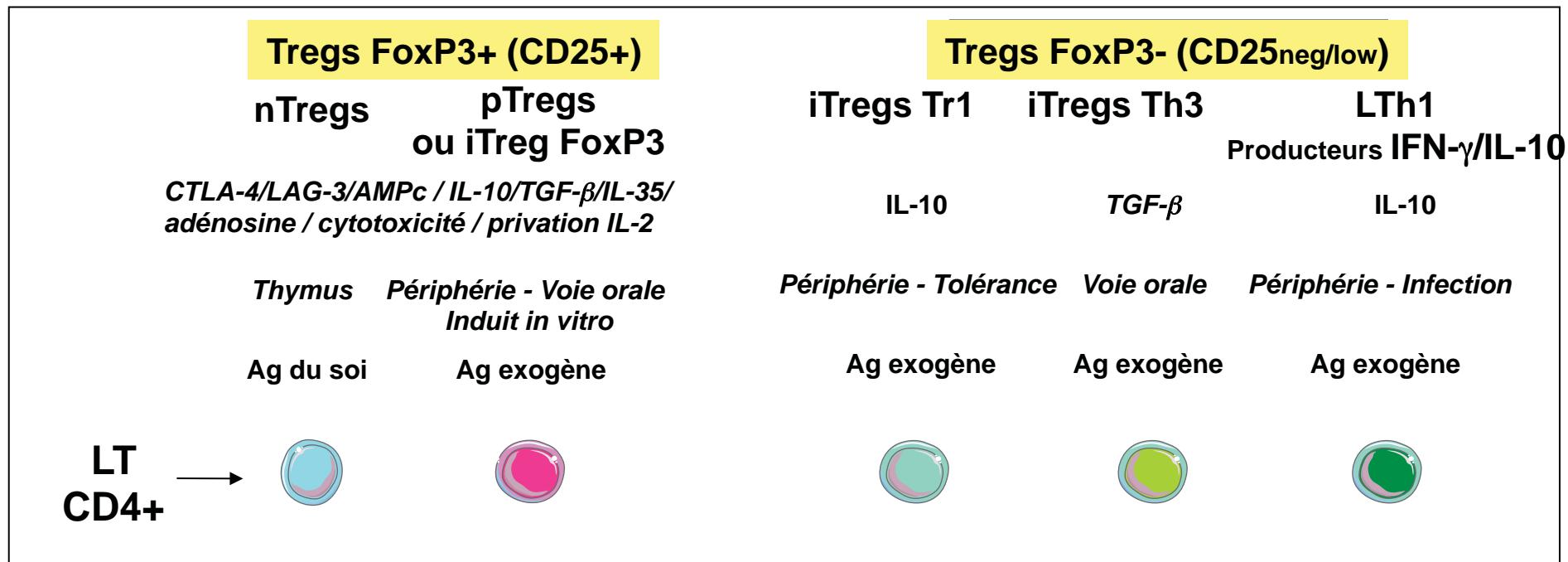


Activation of CD4+CD25+FoxP3+ICOS+ Tregs in the draining lymph nodes of hapten-sensitized mice

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

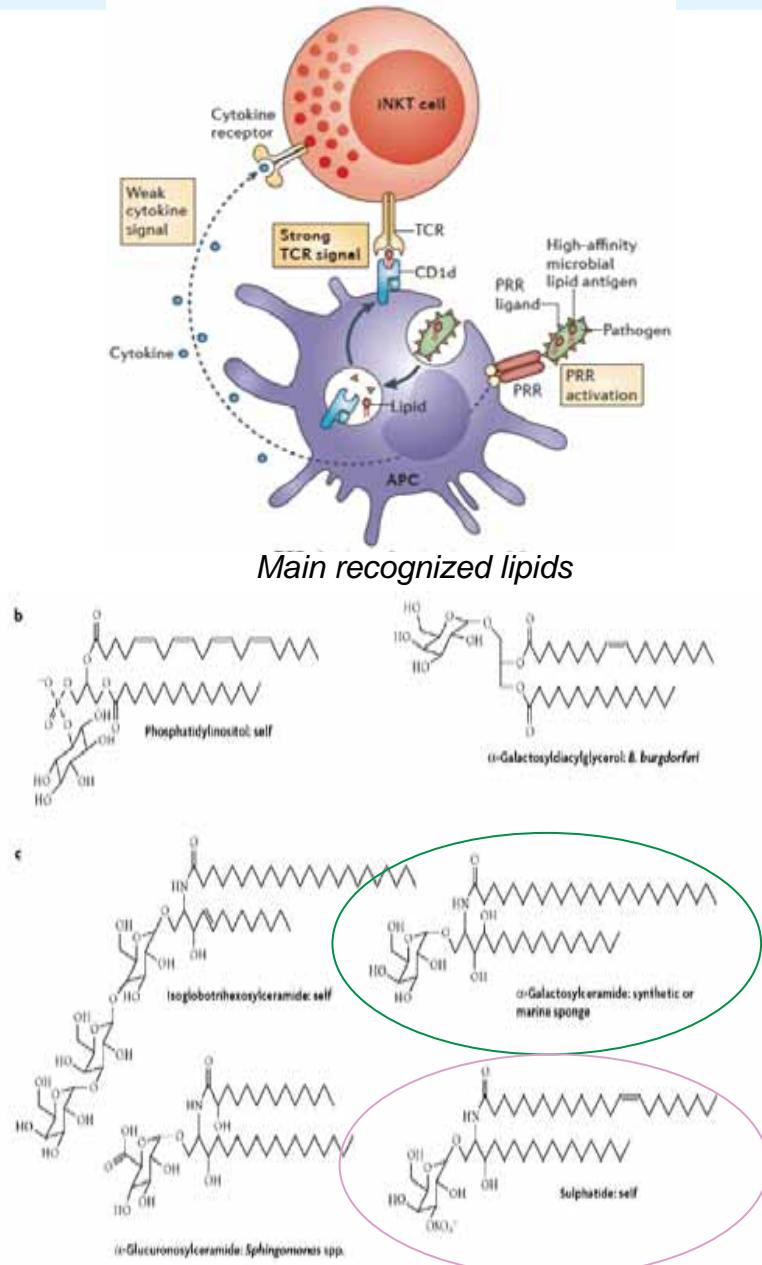


De nombreux lymphocytes régulateurs



Les lymphocytes non conventionnels : les cellules NKTs

TCR-driven activation



Main features

- 2 groups of NKT cells:
 - ✓ invariant NKT cells (iNKT cells) = TCR $V\alpha 24J\alpha 18$ and mainly $V\beta 11$
 - ✓ non-invariant NKT cells (oligoclonal)
- iNKT predominant in mice, few in humans
- NKT cells promote immunity against cancers and microbes but suppress autoimmunity
- Functional versatility → different subsets (NKT1, NKT2, NK17, NKT_{FH}...)
- iNKT cells respond to **self** and microbial lipids similar to the glycosphingolipid α -GalCer
- Non-invariant NKT cells respond to lipids similar to **sulfatide**
- CD1d-restriction

From Brennan et al. Nat Rev Immunol 2013

Other regulatory cells? iNKT cells

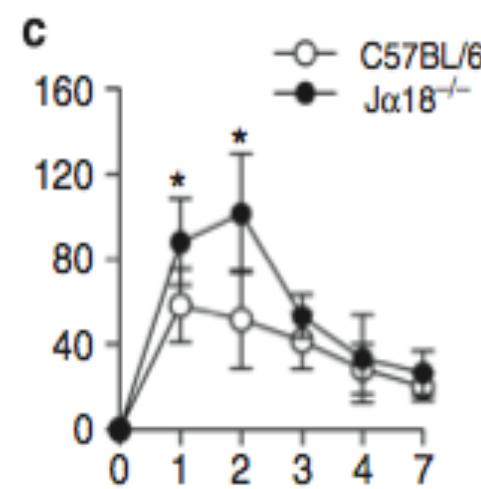
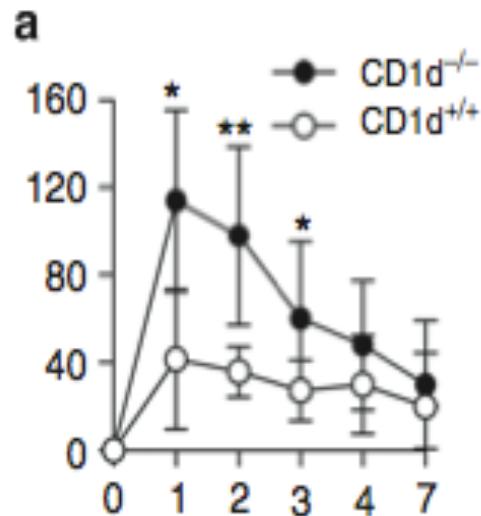
- iNKT cells are non-redundant downregulators of CTL-mediated CHS responses

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}

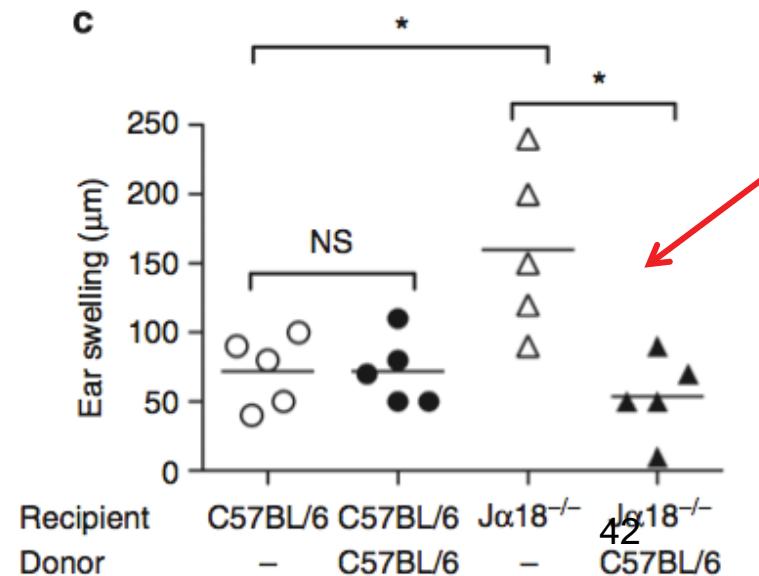
Journal of Investigative Dermatology (2013) 133, 980–987; doi:10.1038/jid.2012.404; published online 29 November 2012

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



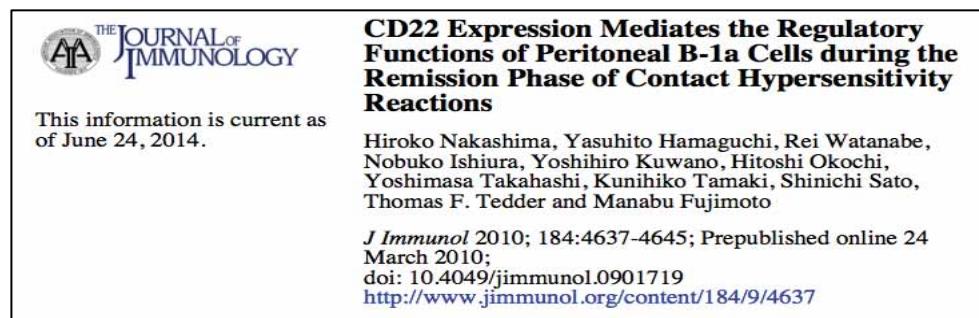
Other studies argues against the regulatory functions of iNKT cells and suggest stimulatory functions

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

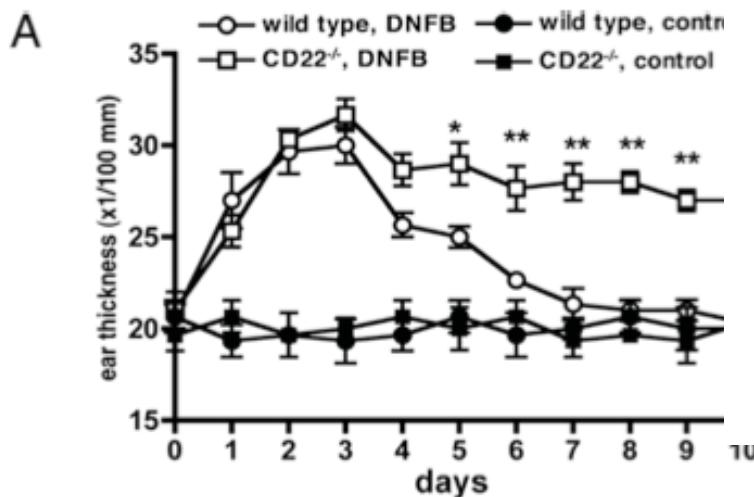


Other regulatory cells? B cell subsets

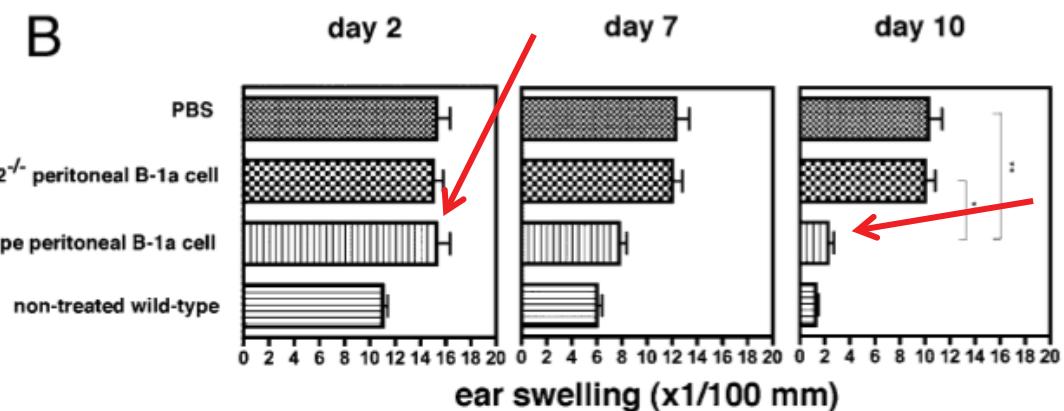
- Other regulatory cells (peritoneal B-1a cells) participate to the resolution of skin inflammation



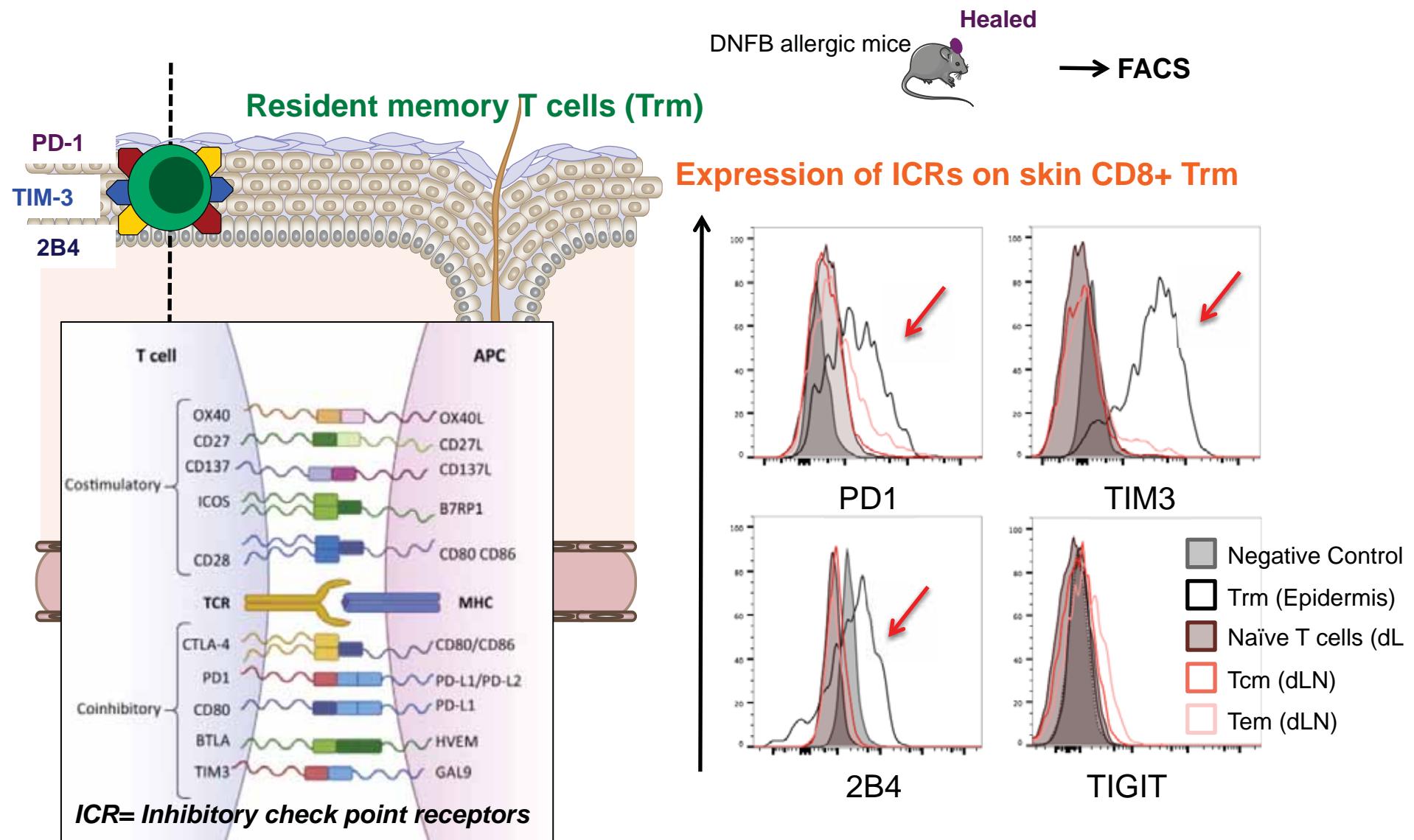
Absence of CHS resolution in CD22^{-/-} animals



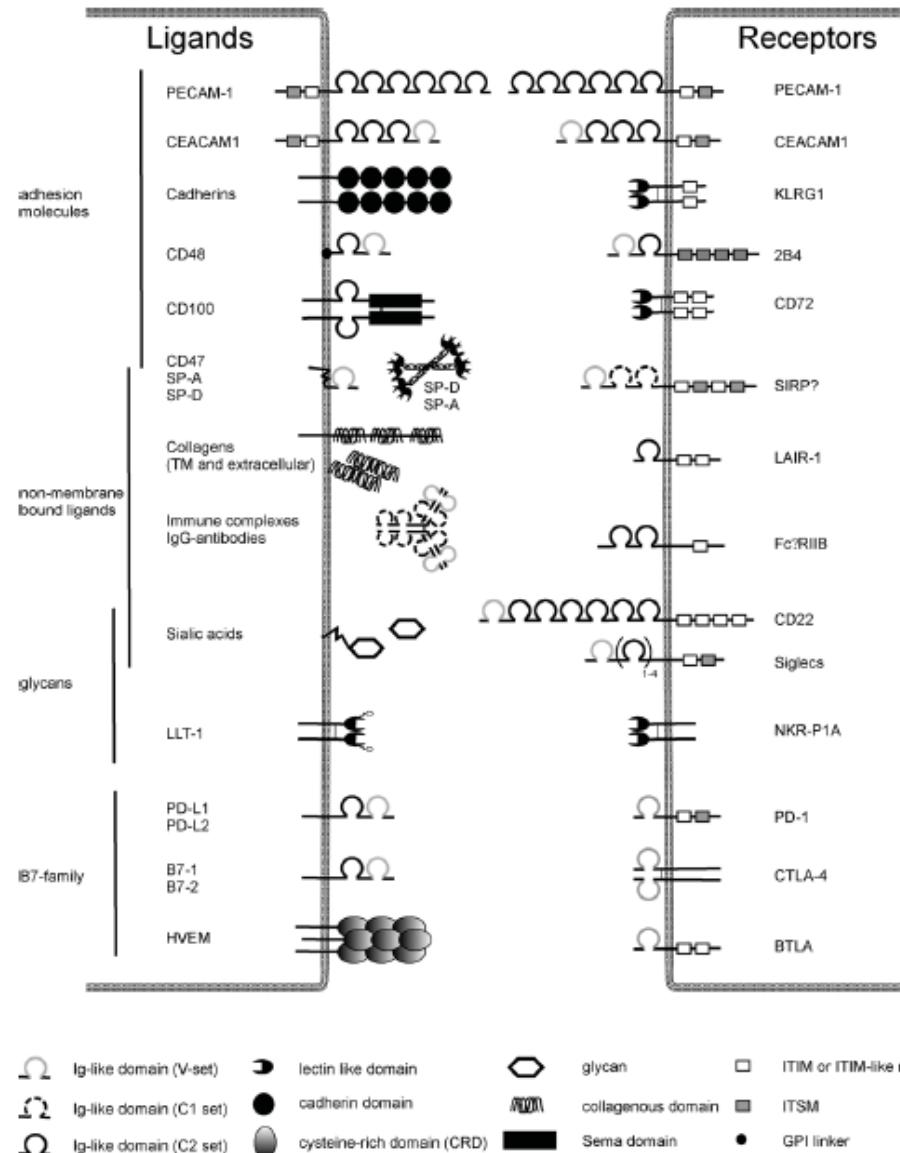
Adoptive transfer of B1-a cell promotes the resolution of skin inflammation in CD22^{-/-} animals



Les mécanismes de régulation intrinsèques: Les récepteurs inhibiteurs



D'autres mécanismes de régulation par le tissu?

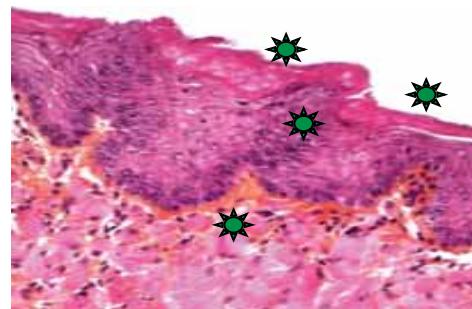


Eczéma allergique de contact : les facteurs de risques

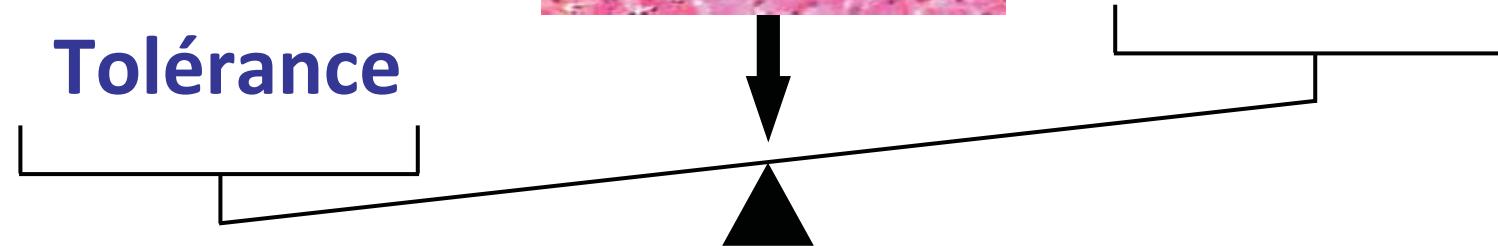
Ignorance?



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...)

Les facteurs génétiques

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

II Polymorphisms	III Results	
	E�osinophilic mutations (combined)	Results inconclusive
Cytokines: <i>ILB</i> – 511, <i>ILB</i> + 3953, <i>ILRA</i> , <i>IL6</i> – 174, <i>TNFA</i> – 238, <i>TNFA</i> – 308	<i>TNFA</i> – 308 (G → A): increased (in polysensitized individuals) <i>TNFA</i> – 308 G/G and <i>ILRA</i> polymorphism (77) increased in Turkish patients ($n = 50$)	tact dermatitis in controls: n/a
Cytokine: <i>IL-16</i>	<i>IL16</i> – 295 (T → C) increased (in polysensitized individuals)	tact dermatitis in patients to nickel
Cytokine <i>IL-4</i>	No difference between chromate allergics and controls with regard to <i>IL4</i> – 590 polymorphism	nickel in patients

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

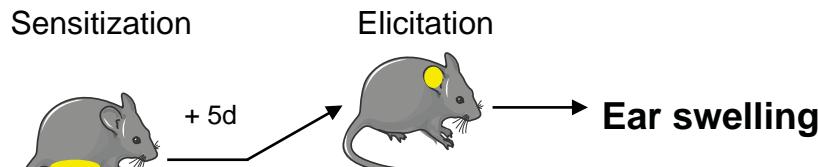
Chimique	Secteur	Pouvoir sensibilisant
Oxazolone	Chimie	Extreme
2,4-Dinitrofluorobenzene	Chimie	Extreme
2,4-Dinitrochlorobenzene	Chimie	Extreme
Glutaraldehyde	Conservateur, antiseptique	Fort
Formaldehyde	Cosmétique, Colorant	Fort
Cinnamaldehyde	Parfum, arôme	Modéré
Hexyl cinnamaldehyde	Cosmétique, Parfum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

Main effectors? CD8+ CTLs

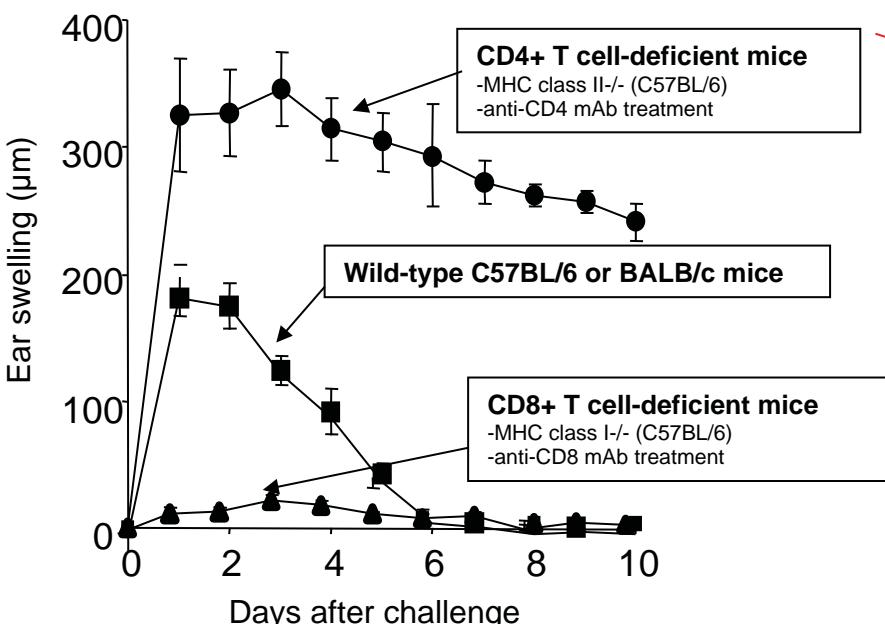
Journal of Investigative Dermatology (2006) 126, 815–820. doi:10.1016/j.jid.2005.11.014; published online 2 February 2006

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}

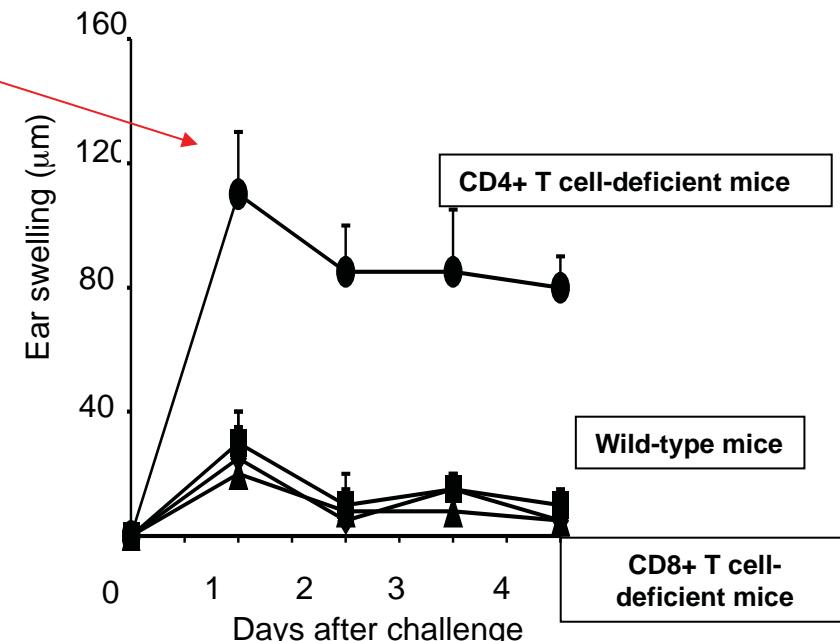


Strong haptens: DNFB, TNCB, OXAZOLONE...



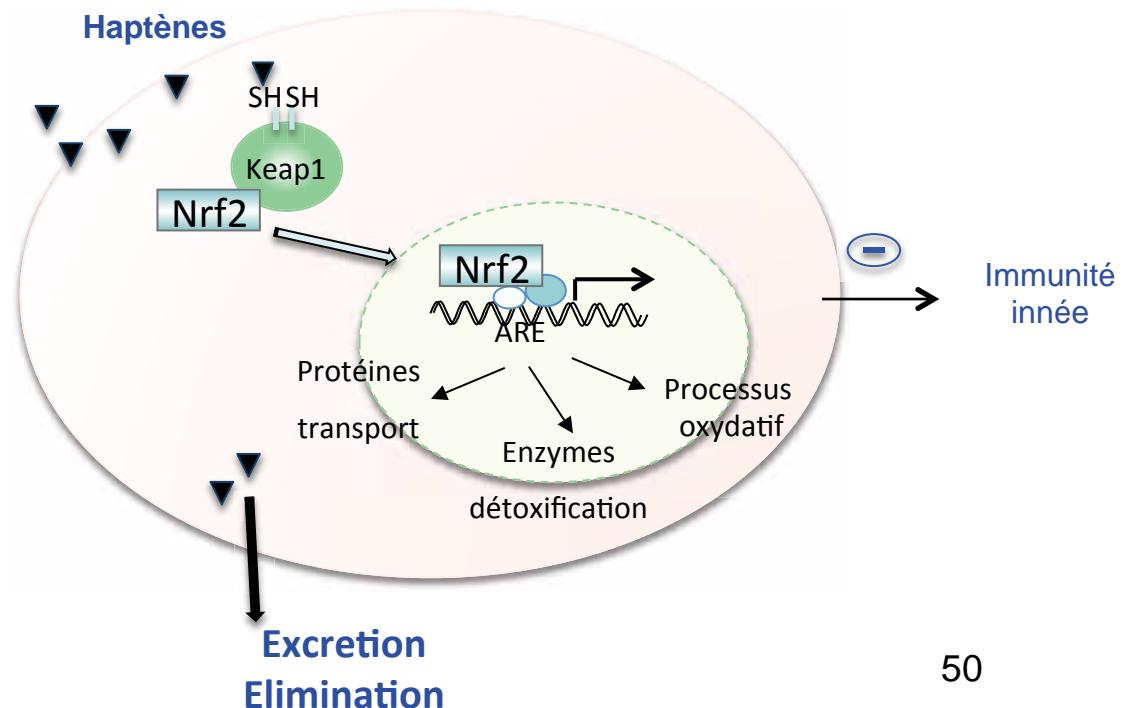
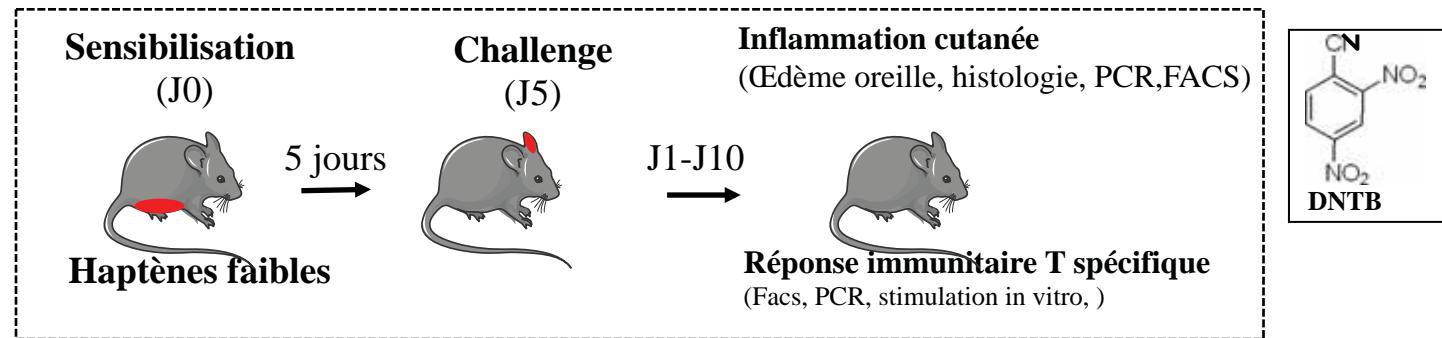
Weak haptens

- Fragrances (Hexylcinnamaldehyde, Hydroxycitronellal, Eugenol, Dihydrocoumarin, Isoeugenol),
- Dye (paraphenylenediamine)
- Drugs (Amoxicillin, Rosephén, Phenytoin, Sulfasalazin)

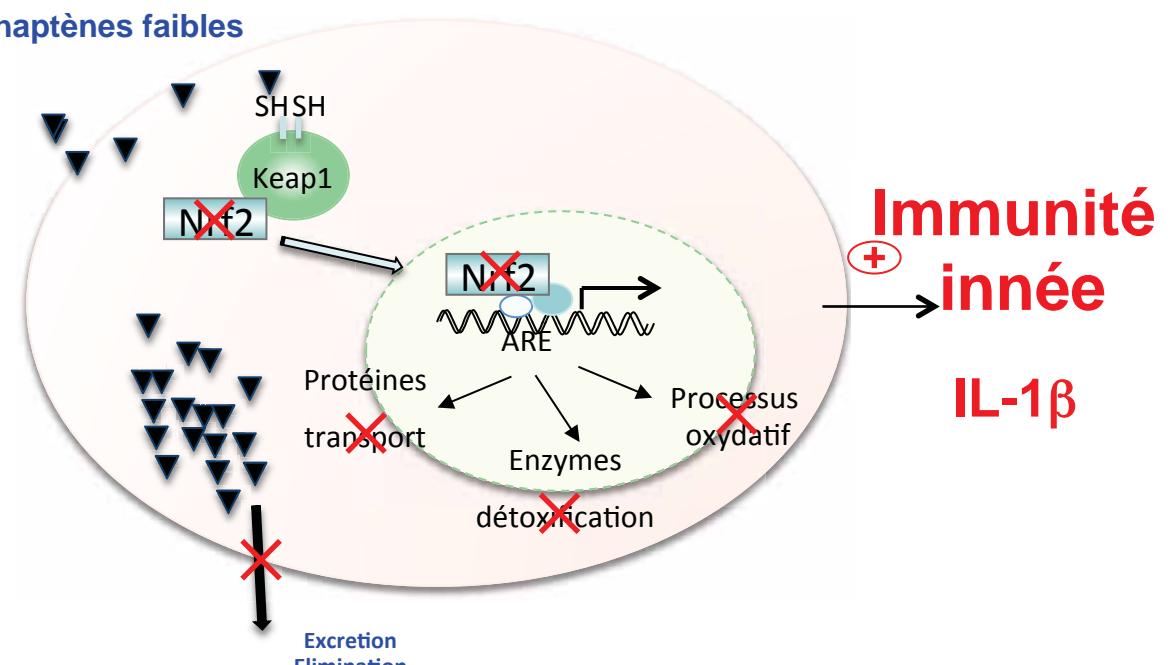
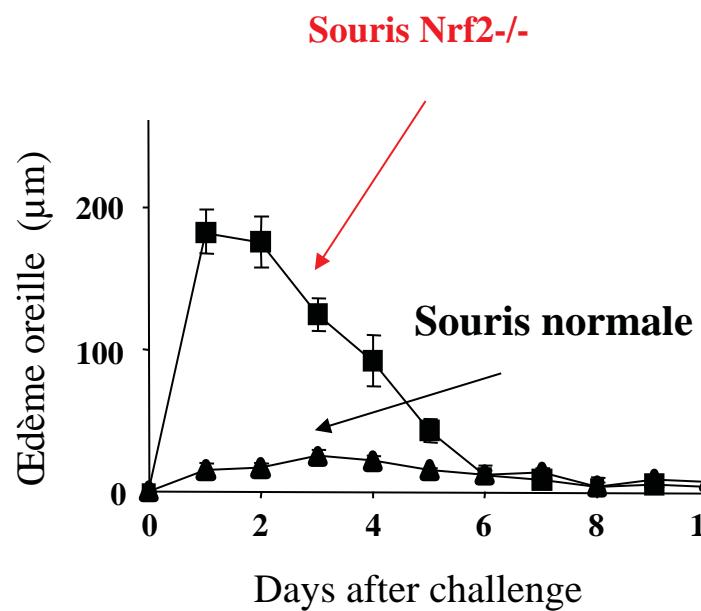
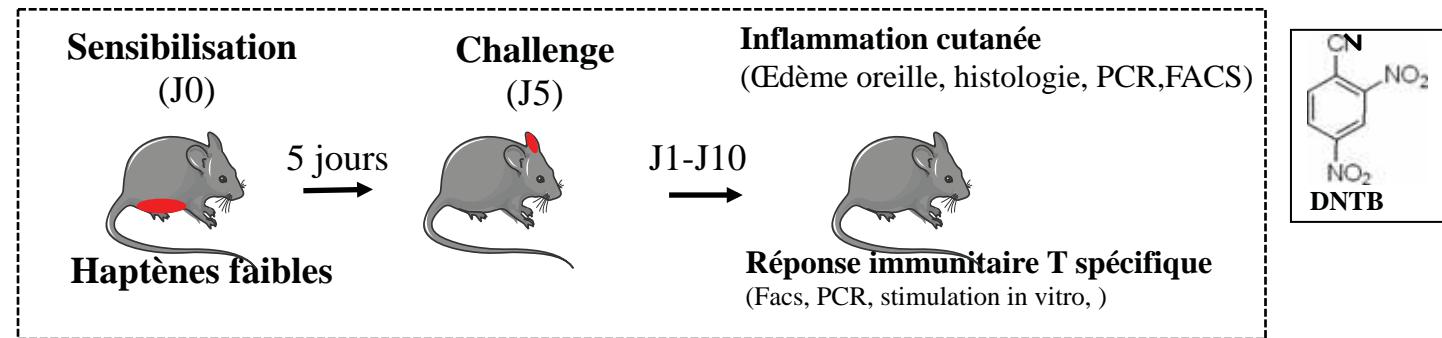


- CD8+ T cells are effector cells
- CD4+ T cells comprise regulatory T cells

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

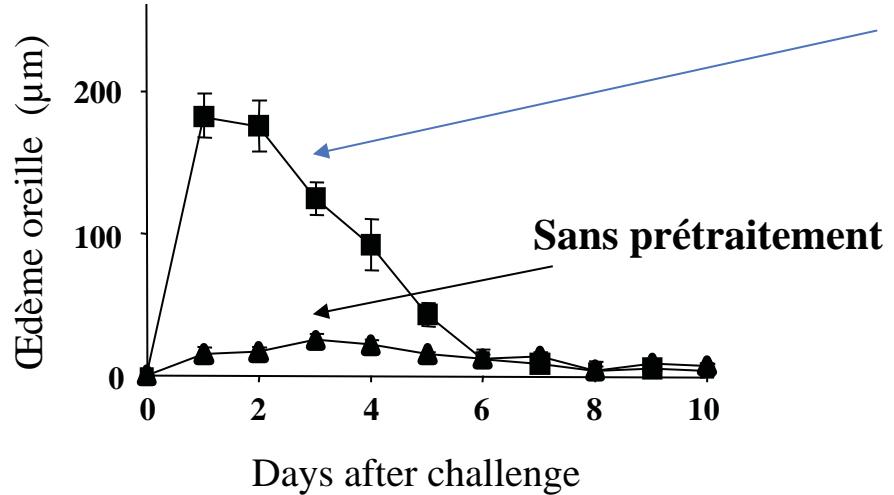
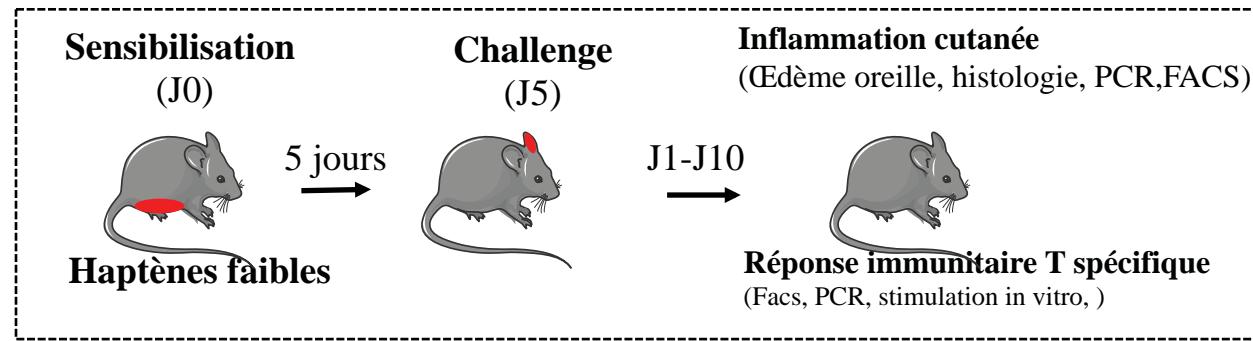
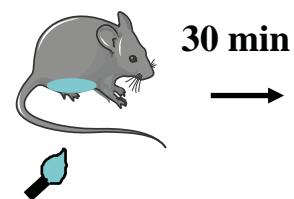


Un défaut de détoxification conduit à une rupture de tolérance vis-à-vis des haptènes faibles



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

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



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

L'irritation fait le lit de l'allergie



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

Département d'Immuno-Allergologie



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



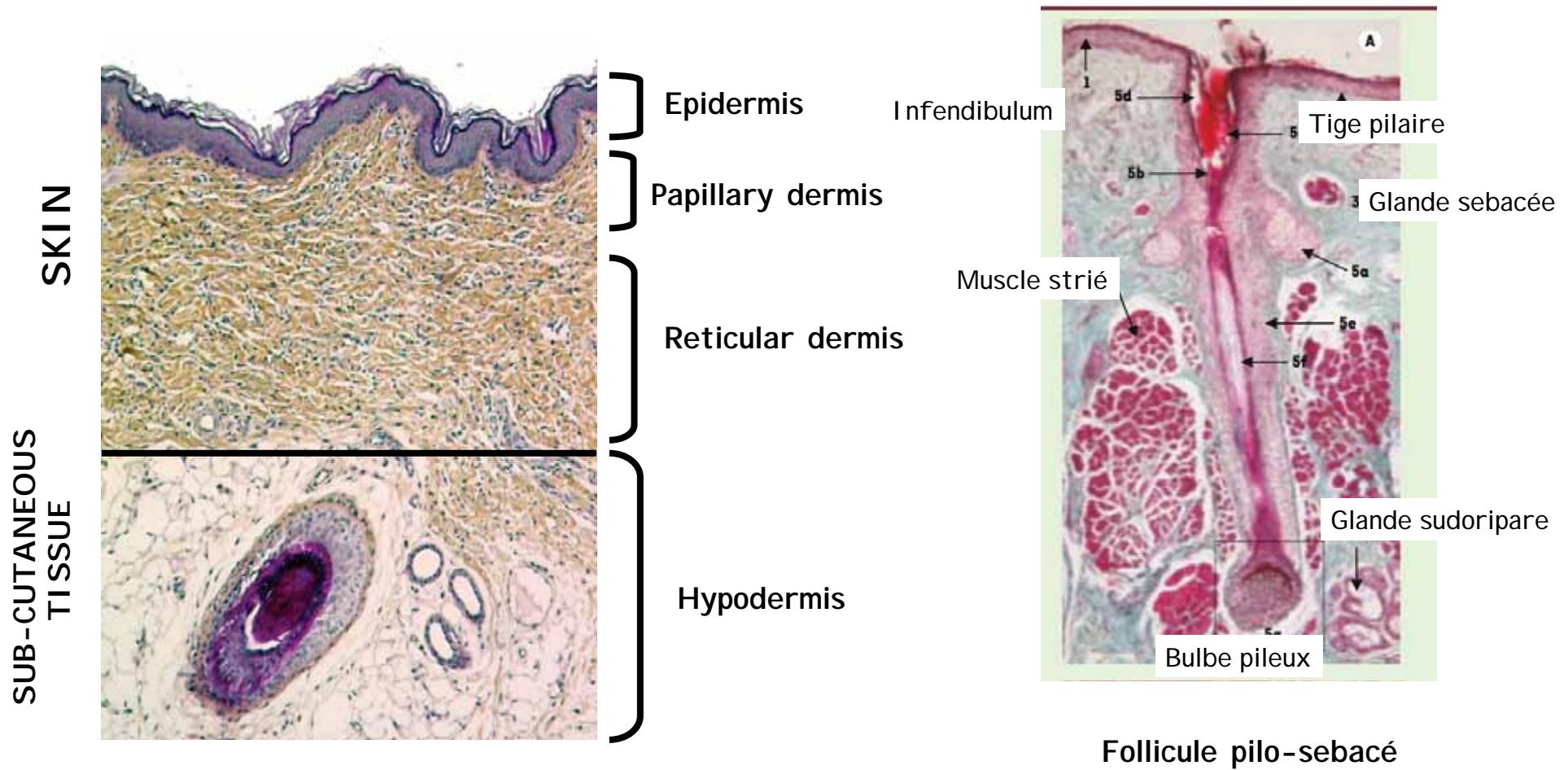
Equipe 20 – CIRI



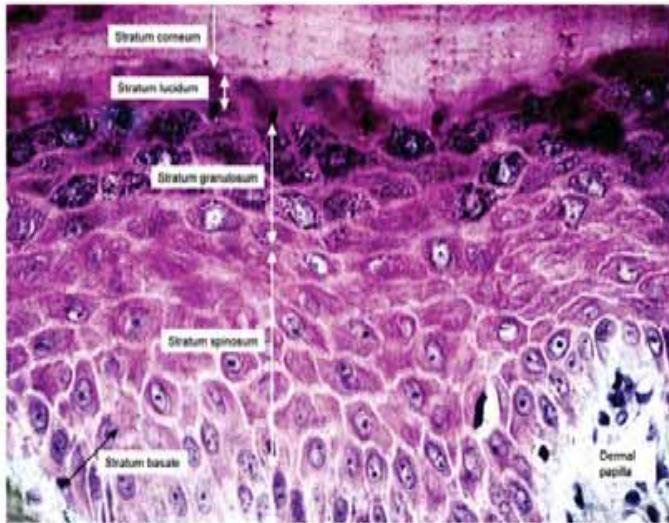
Unité de recherche Phase I, Lyrec- Lyon-Sud



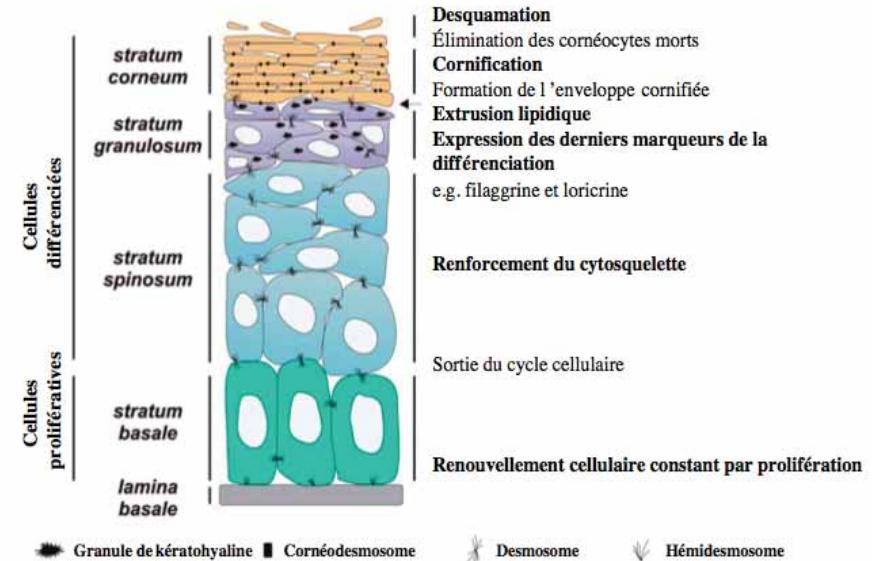
Anatomy of the skin



Anatomy of the epidermis



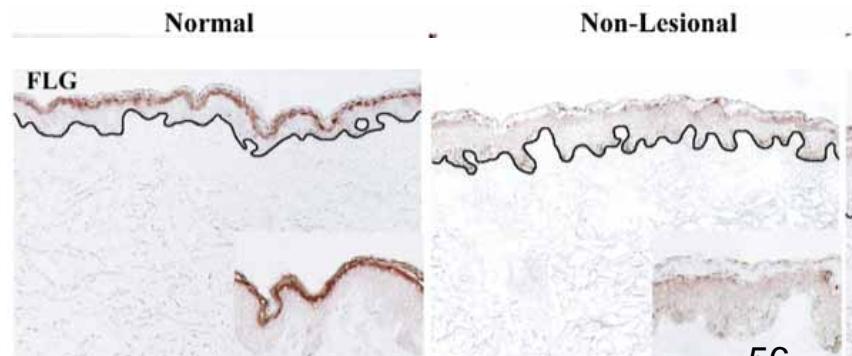
Epiderme - coloration Hematoxylline-Eosine



Différentiation épidermique - schéma

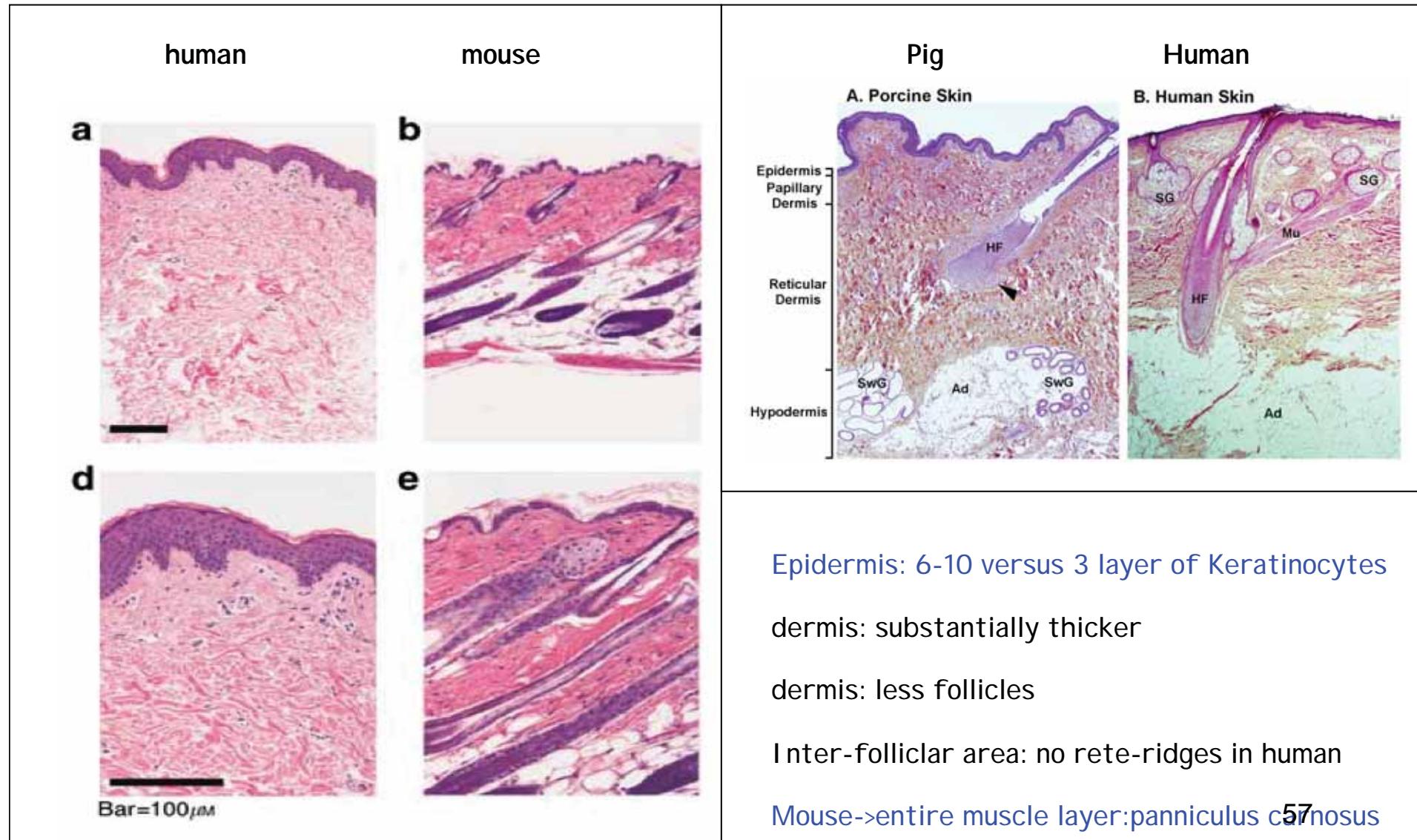


Atopic dermatitis

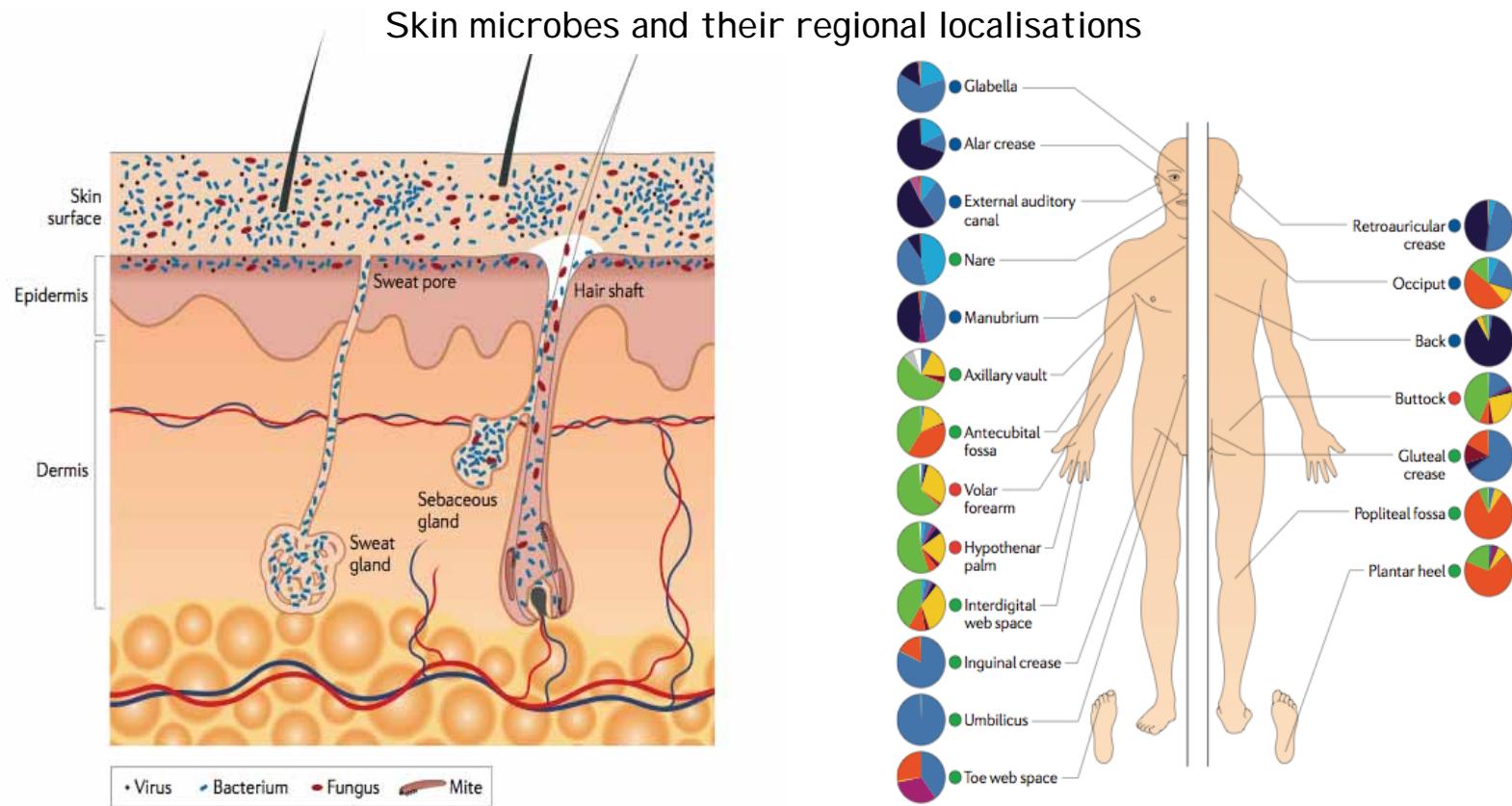


IHC staining of filagrin, Suarez-Farinas et al. JACI 2010

Anatomy of the skin - Comparison human / mouse / Pig



The skin microbiome



Grice et al. Nat rev microb 2011

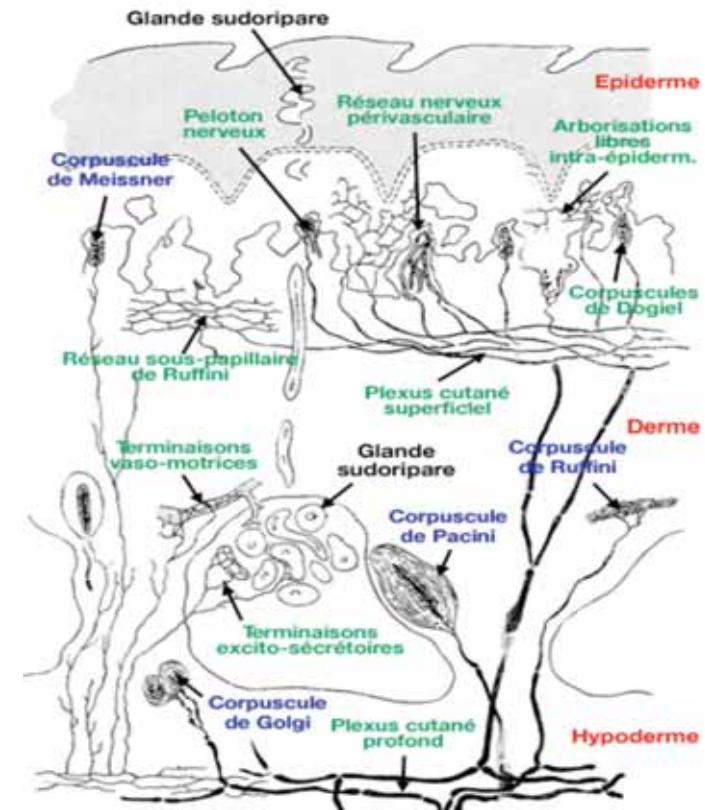
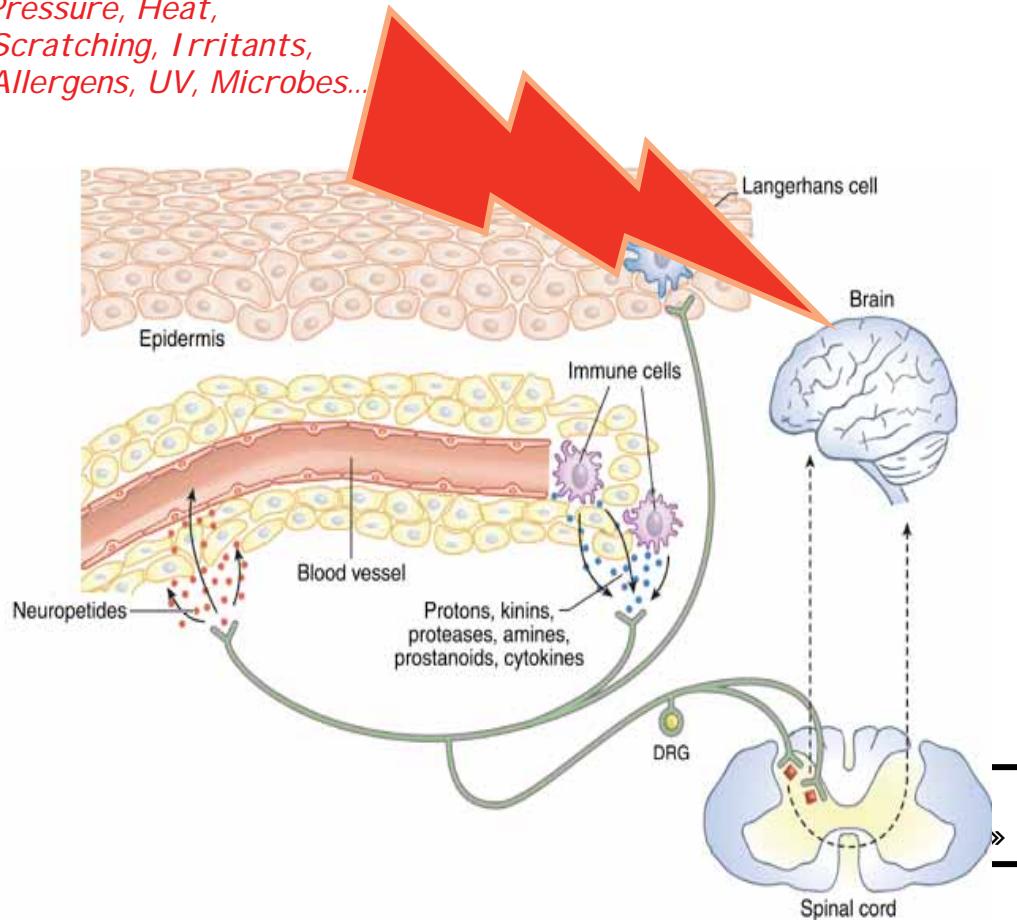
Up to 10^{12} resident bacteria/m²

3 species particularly well-adapted to the acidic PH environment and host AMPs: *Staphylococcus*, *Propionibacterium*, *Corynebacterium* 58

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