IMMUNITÉ CUTANÉE

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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
• La peau
• Bases immunologiques de la réponse inflammatoire cutanée
• Dermatoses inflammatoires : 2 exemples:
  – Le psoriasis
  – L’eczéma de contact
• La peau
• Bases immunologiques de la réponse inflammatoire cutanée
• Dermatoses inflammatoires : 2 exemples:
  – Le psoriasis
  – L’eczéma de contact
The skin: the multitasking organ

- Skin area=1.8 m²
- Being constantly exposed to potential hazards -> maintain homeostasis
- Examples of the non-immune functions of the skin:
  - Physical and biochemical barrier
  - Sensory-receptive area
  - Ensures 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 autoimmunity.
Anatomy of the skin

SKIN

SUB-CUTANEOUS TISSUE

Epidermis

Papillary dermis

Reticular dermis

Hypodermis

Infendibulum

Muscle strié

Glande sudoripare

Bulbe pileux

Glande sebacée

Follicule pilo-sebacé
Anatomy of the epidermis

Epiderme - coloration Hematoxylline-Eosine

Différenciation épidermique - schéma

Atopic dermatitis

IHC staining of filagrin, 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

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

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

Grice et al. Nat rev microb 2011
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

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 $\gamma5+$ cells into the mouse epidermis (DETC, about 90% of T cells)

Phenotypic differences in DC subsets
Recent studies identify subsets with functional homologies
• La peau
• **Bases immunologiques de la réponse inflammatoire cutanée**
• Dermatoses inflammatoires : 2 exemples:
  – Le psoriasis
  – L’eczéma de contact
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
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
4 major inflammatory components

**Inducers**
- Microbes, Allergens
- AlloAg

**Sensors**
- P(pathogen)AMPs
  - TLR, NLR...
- D(amage)AMPs
  - TLR, NLR, RAGE...

**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

**Nociceptors**

**DANGER Hypothesis**

Inflammation
General scheme

**Inflammatory Pathway**

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Sensors</th>
<th>Mediators</th>
<th>Target tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Tissue damage</td>
<td>Mast cell, Dendritic cell</td>
<td>TNF, IL-1, IL-6</td>
</tr>
<tr>
<td>Cell-derived, Plasma-derived, ECM-derived</td>
<td>TLR</td>
<td>CCL2, CXCL8</td>
<td></td>
</tr>
<tr>
<td>Tissue damage</td>
<td>TLR</td>
<td>Histamine, Bradykinin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eicosanoids</td>
<td></td>
</tr>
</tbody>
</table>

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

PAMPs – DAMPs and their sensors

Intracellular DAMPs

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

PAMPs – DAMPs and their sensors

Extracellular DAMPs

<table>
<thead>
<tr>
<th>DAMP</th>
<th>Adjuvant activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronic acid</td>
<td><em>In vivo</em>: inhibition of Langerhans-cell maturation by blocking peptide; adjuvant activity by administration of purified molecule</td>
</tr>
<tr>
<td></td>
<td><em>In vitro</em>: DC maturation</td>
</tr>
<tr>
<td>Heparan sulphate</td>
<td><em>In vitro</em>: DC maturation</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td><em>In vitro</em>: DC maturation</td>
</tr>
<tr>
<td>Collagen-derived peptides</td>
<td><em>In vivo</em>: ND</td>
</tr>
<tr>
<td></td>
<td><em>In vitro</em>: DC maturation</td>
</tr>
<tr>
<td>Fibronectin</td>
<td><em>In vitro</em>: DC maturation</td>
</tr>
<tr>
<td>Elastin-derived peptides</td>
<td><em>In vivo</em>: ND</td>
</tr>
<tr>
<td></td>
<td><em>In vitro</em>: ND</td>
</tr>
<tr>
<td>Laminin</td>
<td><em>In vivo</em>: ND</td>
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<tr>
<td></td>
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</table>
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
Induction of systemic immunity upon skin exposure/immunization

Skin exposure, immunization

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

Dermis
Epidermis

IL-1α / IL-1β/TNFα
TSLP
IL-33
IFNα/β

CCL19/CCL21
CXCL12

Mast cell
Dermal DC

Monocyte
Neutrophils

nerve

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

Innate response

Adaptative immunity
Induction of systemic immunity upon skin exposure/immunization

Skin exposure, immunization

Persistance / Re-exposure ->
Skin inflammation, elimination of infected cells
Tissue response/repair

Effector & memory response -> 2nd line of defence

Adaptative immunity

Innate response
Induction of systemic immunity upon skin exposure/immunization

Skin exposure, immunization

Commensals
(S. epidermidis microcopié electronique)

IL-1a / IL-1b/TNFα
TSLP
IL-33
IFNα/β

CD4+ Th1, Th2,
Th-17, Th-22, Th-9

CD4+ Tregs

Monocytes
(Inflammatory,
Anti-inflammatory)

CCL19/CCL21
CXCL12

Monocyte
Neutrophils

Dermal DC

Mast cell

nerve

Effector & memory
Immune response

CD8+ CTLs

B cells

CD4+ Tconv

CD4+ Tregs

Lymph nodes

Innate response

CD8+ CTLs

Monocytes

Neutrophils

Eosinophils

CD4+ Tconv

CD4+ Tregs

B cells

CD4+ Tconv

Effector & memory
Immune response

CD8+ CTLs

B cells

CD4+ Tconv

CD4+ Tregs

Lymph nodes

Innate response

Abstract
Intestinal commensal bacteria induce protective and regulatory responses that maintain host-microbial mutualism. However, the contribution of tissue-resident commensals to immunity and inflammation at other barrier sites has not been addressed. We found that in mice, the skin microbiota have an autonomous role in controlling the local inflammatory milieu and tuning resident T lymphocyte function. Protective immunity to a cutaneous pathogen was found to be critically dependent on the skin microbiota but not the gut microbiota. Furthermore, skin commensals tune the function of local T cells in a manner dependent on signalling downstream of the interleukin-1 receptor. These findings underscore the importance of the microbiota as a distinctive feature of tissue compartmentalization, and provide insight into mechanisms of immune system regulation by resident commensal niches in health and disease.
Mechanosensors to protect against pressure ulcers

**Innate response**

**Adaptative response**

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*Asic3 is a neuronal mechanosensor for pressure-induced vasodilation that protects against pressure ulcers.*

Frony R¹, Linguella F, Signaud-Roussel D, Saumet JL, Lazdunski M.

**Abstract**

Pressure-induced vasodilation (PIV) delays the decrease in cutaneous blood flow produced by local application of low pressure to the skin, a physiologically appropriate adjustment of local vasomotor function. Individuals without a normal PIV response have a high risk of ulceration. Here we demonstrate that acid-sensing ion channel 3 (Asic3) is an essential neuronal sensor for the vasodilation response to direct pressure in both humans and rodents and for protecting against pressure ulcers in mice.
• La peau
• Bases immunologiques de la réponse inflammatoire cutanée
• Dermatoses inflammatoires : 2 exemples :
  – Le psoriasis
  – L’eczéma de contact
Eczéma allergique de contact (EAC)

Eczéma à la pPD

Erythème / Œdème / Vésicules

Diagnostic

Aspect histologique

- Couche cornée
- Épiderme
- JDE
- Derme
- Infiltrat cellulaire
- Vésicules
- Exocytose
- Acanthose
- Spongiose
- Apoptose kératinocyte

Étapes de la procédure:

- Préparation des patchs tests
- Pose des patchs
- Lecture des patchs

Étiquettes:

- Eczéma interdigital (coiffeuse)
- 48 à 72 heures
Allergic Contact Dermatitis (ACD): Generalities

Health problem

- Occupationnal disease (hairdressers, nurses…)
- About 4000 molecules endowed with sensitizing potency = (haptens)

ACD = Delayed-type hypersensitivity reaction

Key role exerted by hapten-specific T lymphocytes infiltrating the skin
- Breakdown of cutaneous tolerance

Hapten sources: Cosmetics (perfums), drugs (penicillin), jewels (nickel), clothes (dyes)…

Hapten properties: Low molecular weight
- Electrophilic properties: binding to self-protein --> new T cell epitope
- Adjuvant properties: delivery of inflammatory signals

Sensitizing potency:
- Strong haptens: 90% of individuals are sensitized after single exposure (DNFB)
- Weak haptens: <1% of individuals are sensitized after repeated exposures (perfums)
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Key role exerted by hapten-specific T lymphocytes infiltrating the skin

- Breakdown of cutaneous tolerance

**Haptenized protein = modified self (new antigen)**

**DNFB**
2,4-dinitrofluorobenzene (hapten)

**protein** (lysine)

**Haptenized protein** = modified self (new antigen)
Irritant Contact Dermatitis (ACD): Generalities

**Health problem**
- Occupationnal disease (hairdressers, metal workers, florists, chemical industry workers…)
- accounts for 80% of all Contact Dermatitis

**ICD =** Toxic/proinflammatory reaction - Corrosion=most severe form
Key role exerted by innate immunity

**Irritant sources**: Soaps, solvents, acids, alkalis

**Irritant properties**
- Damage to cell membrane, via disorganisation of barrier lipids, protein denaturation
- Cytotoxicity
  - delivery of inflammatory signals
Chemical

- Irritancy
- Allergenicity

Contact dermatitis

- Irritant contact dermatitis
- Allergic contact dermatitis

Non-allergic Innate immunity

Adaptive immunity (T cells)
ACD pathophysiology

1- Sensitization phase
Innate immunity / T cell priming

- Chemicals (haptens)
  - Langerhans cell
  - Mast cell
  - Dermal DC
  - Monocytes/Macrophages
  - Neutrophils

2- Elicitation phase
T cell effector response / polymorphic lesion

- Lesion
  - Neutrophils
  - NK cells
  - Effector CD8+ T cells
  - CD4+ T regulatory cells
  - Detached Langerhans cells
  - Neutrophils
  - Blood vessel
  - Draining lymph nodes

Chemicals (haptens) induce immune response:
- IL-18, IL-1β
- TNF-α, IL-6
- PGE2, LTB4, Histamine...

Draining lymph nodes activate:
- Effector CD8+ T cells
- CD4+ T regulatory cells

T cell priming occurs via:
- Innate immunity
- T cell priming
ICD pathophysiology

Innate immunity

Chemicals (non-sensitizing irritants)

Langerhans cell

DETC

Mast cell

Dermal DC

Monocytes/
Macrophages

&

Neutrophils

Blood vessel

Effector CD8+ T cells

Draining lymph nodes

CD4+ T regulatory cells

IL-18, IL-1b

TNF-a, IL-6

PGE2, LTB4, Histamine…
EAC : les facteurs de risques

- la nature du produit chimique = “le danger”
- les conditions d’exposition (dose, fréquence, durée, route)
- le polymorphisme génétique, âge, sexe
- l’environnement (maladie sous-jacente, stress, pollution...)

Tolérance

Sensibilisation

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

<table>
<thead>
<tr>
<th>Status of parents</th>
<th>Percentage of children sensitized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitized</td>
<td>65 DNCB 51 NDMA</td>
</tr>
<tr>
<td>Not sensitized</td>
<td>52 DNCB 29 NDMA</td>
</tr>
<tr>
<td></td>
<td>( p &lt; 0.10 ) ( p &lt; 0.01 )</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Polymorphisms</th>
<th>Results in conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filaggrin null mutations</td>
<td>(a) not associated with allergic contact dermatitis</td>
</tr>
<tr>
<td>combined genotypes for R501X and 2282del4</td>
<td>(b) when (a) as compared with other controls: risk increased</td>
</tr>
<tr>
<td>Genotype and phenotype of NAT2</td>
<td>(c) not associated with allergic contact dermatitis</td>
</tr>
<tr>
<td>NAT1 and NAT2 in patients allergic to ‘para-compounds’</td>
<td>(d) associated with relevant sensitization to nickel only</td>
</tr>
<tr>
<td>GSTM1 and GSTT1</td>
<td>(e) only association in women with nickel dermatitis and without ear piercing</td>
</tr>
<tr>
<td>MnSOD</td>
<td>Genotype and phenotype of ‘rapid acetylators’ increased</td>
</tr>
<tr>
<td>ACE (insertion/deletion polymorphism)</td>
<td>( NAT2^*4 ) allele (rapid acetylators) increased; ( NAT2^*5b/2^*6a ) (slow acetylators) decreased. Genetic linkage of ( NAT1^*10 ) with ( NAT2^*4 )</td>
</tr>
<tr>
<td>Cytokines: ( ILB – 511 ), ( ILB +3953 ), ( ILRA ), ( IL6 – 174 ), ( TNFA – 238 ), ( TNFA – 308 )</td>
<td>Combined deletion (GSTM1/GSTM1) in patients allergic to organic mercury compounds as compared with controls and para group allergic</td>
</tr>
<tr>
<td>Cytokine: ( IL-16 )</td>
<td>Valine (Val) to alanine (Ala) at amino acid – 9 (Val9→Ala) polymorphism. No difference between allergics and controls</td>
</tr>
<tr>
<td>Cytokine ( IL-4 )</td>
<td>Insertion (I) or deletion (D) of 287 base pairs in intron 16/1 polymorphism (low ACE activity) increased</td>
</tr>
<tr>
<td>Cytokine ( IL-16 )</td>
<td>TNF( \alpha ) – 308 (G→A): increased (in polysensitized individuals)</td>
</tr>
<tr>
<td>Cytokine ( IL-4 )</td>
<td>TNF( \alpha ) – 308 G/G and ILRA polymorphism (77) increased in Turkish patients ( n = 50 )</td>
</tr>
<tr>
<td>Cytokine ( IL-295 ) (T→C) increased (in polysensitized individuals)</td>
<td>No difference between chromate allergies and controls with regard to ( IL4-590 ) polymorphism</td>
</tr>
</tbody>
</table>

Schnuch A, Contact Dermatitis 2010
Les diverses étapes de la sensibilisation : la pénétration

Skin exposure, immunization

Les haptènes sont des substances hydrophobes : meilleure pénétration de la peau

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

Rhodamine B isothiocyanante (en rouge) 1H après exposition ; Simonsson et al. 2012
Les diverses étapes de la sensibilisation : la réactivité chimique

Skin exposure, immunization

Hapten, Mast cell

Tableau 3. Principales fonctions chimiques électrophiles rencontrées dans les molécules allergisantes et mécanismes de réaction avec un nucléophile

(D’après Lepoittevin et Benezra 1991)
Les diverses étapes de la sensibilisation : la réactivité chimique

Skin exposure, immunization

Structure

Reactivity with thiols

Bromobimane; Simonsson et al. 2012
How haptens activate innate immunity

Inducers

Haptens

Ni^{2+} → hTLR4 → MyD88 → Trif → MAPK, IRF3/7, NF-κB → IFNα/β, IL-6, IL-8, IL-12, TNF-α, CCL2

Ni^{2+} → TLR4 → MyD88 → Trif → MAPK, IRF3/7, NF-κB → IFNα/β, IL-6, IL-12, IL-18, TNF-α

Inducers

Tissu damage

HA → SYK, CARD9/BCL10 → MAPK, IRF3/7, NF-κB → IFNα/β, IL-1β, IL-18

ATP → P2X7 → IL-1β, IL-6, IL-23

NRF2 → Keap1 → ROS

SF Martin et al, Allergy, 2011

Yasukawa et al, Nat Comm, 2014
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

Dégradation Acide Hyaluronique ht PW, 24h après application

Esser P, Plos One 2012
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
L’activation des lymphocytes T spécifiques d’haptènes
Mode de reconnaissance des déterminants antigéniques

Modèle du TNP-VSV8
(RGY\text{K}YQGL)

Vue de face

Vue de coté


L’activation des lymphocytes T spécifiques d’haptènes
Mode de reconnaissance des déterminants antigéniques

- Présentation de peptide hapténisé
- Activation de type Superantigène-like (Nickel)
- Interaction non covalente entre le CMH et le récepteur T (sulfamethoxazole, lidocain)
- Présentation de peptide cryptique
Skin allergic diseases - Pathophysiology (ACD model)

1- Sensitization phase
Innate response / T cell activation

3- Regulation phase
Tregs

Elicitation (challenge) phase
- T effector response / Skin inflammation
- Perf/Granz
- Fas/FasL
- IFNg/IL17?
- CXCL9/CXCL10
- TNFa/CXCL8
- Neutrophiles
- Cellules NK

Regulation phase
- Tregs
- DC dermique
- Mastocyte
- Dermis
- Epidermis
- Stratum corneum
- Kératinocytes
- Cellule de Langerhans

Afferente / Efferente
- CD8+ T effector cells
- CD4+ T regulatory cells
- Lymph nodes
Weak sensitizers are unable to trigger an ACD response in normal mice

mAb Treatment:
- Anti-CD4 mAb (GK1.5)
- Anti-CD8 mAb (H35)

Strong haptens
- DNFB, TNCB, OXA...

Weak haptens
- HCA, Eugenol, Paraphenylenediamine, Amoxicillin

Ear swelling measurements:
- Skin inflammation 24-120 h

Sensitization
- 3 consecutive applications

Challenge
- 5 days

CD4+ T cell-deficient mice

CD8+ T cell-deficient mice

Normal mice

Marc VOCANSON et al., J Invest Dermatol, 2006

Ear swelling (µm)

Days after challenge
La peau
Bases immunologiques de la réponse inflammatoire cutanée
Dermatoses inflammatoires : 2 exemples:
– Le psoriasis
– L’eczéma de contact
Psoriasis: Dermatose Inflammatoire Chronique (érythémato-squameuse)

2% de la population européenne
Psoriasis = 2 anomalies majeures...

Prolifération accrue des kératinocytes et différenciation altérée (squames)

Inflammation cutanée (érythème) dermique et épidermique

... points d’impacts des traitements
Psoriasis
= Dermatose Inflammatoire Chronique

The disease usually occurs in individuals with genetic susceptibility in conjunction with environmental stimuli, and may involve an immune response to autoantigens.

Evidence supports a central role for T cells in establishing and maintaining of psoriatic plaque development.
Pathophysiology of psoriasis


Les kératinoocytes sont la source de l’inflammation psoriasique

Activation des pDCs par des complexes LL37-self DNA dans les lésions

Le peptide anti-microbien LL-37 est un auto-Ag

Les pDC jouent un rôle initiateur clé dans la pathologie

Activation de LT producteurs de cytokines de type-1 et de type-17
Physiopathologie du psoriasis

The vicious cycle of psoriasis

Les sous-populations de lymphocytes T sont définies par les cytokines qu’elles produisent.

- **Naive T cell**
  - IFN-γ
  - IL-12
  - IL-4
  - IL-2
  - TGF-β
  - IL-2
  - TGF-β (IL-1)
  - IL-6, IL-21, IL-23
  - TGF-β
  - IL-4
  - TNF-α
  - IL-6

  - **Th1**: TNF-α, IFN-γ, IL-2 (IL-10)
  - **Th2**: IL-4, IL-5, IL-13, IL-25, IL-10
  - **Treg**: IL-10, TGF-β
  - **Th17**: IL-17A, IL-17F, TNF-α, IL-21, IL-22 (IL-10)
  - **Th9**: IL-9, IL-10
  - **Th22**: IL-22

Les sous-populations de lymphocytes T
Sont responsables de pathologies inflammatoires

- **Th1**
  - Psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease
  - Atopic disease, e.g. eczema, allergic rhinitis, asthma

- **Th2**
  - Inappropriate balance or dysregulation associated with diseases, including autoimmunity, allergy and infection

- **Treg**

- **Th17**
  - IL-17A, IL-17F, TNF-α, IL-21, IL-22 (IL-10)
  - Psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease

- **Th9**

- **Th22**
  - Proposed role in inflammatory and immune-mediated disease, including psoriasis, rheumatoid arthritis, Crohn's disease, atopic dermatitis

- **Naïve T cell**

IFN-γ, IL-12

IL-4, IL-2

TGF-β, IL-2

TGF-β (IL-1), IL-6, IL-21, IL-23

IL-4

TNF-α, IL-6, IL-21, IL-23


IL-17A has effector activity on cells of multiple lineages

**Target-Cell Type**

- Macrophage, dendritic cell
- Endothelial cell
- Fibroblast
- Osteoblast*
- Osteoclast*
- Chondrocyte
- Keratinocytes

**Products**

- IL-17A
- IL-1β
- TNF-α
- IL-6
- IL-8
- CRP
- MMP9
- IL-6
- IL-8
- CCL20
- G-CSF
- GM-CSF
- MMP1,3,13
- RANKL
- Chemokines
- Osteoclastogenesis
- RANKL
- MMP1,2,3, and 9
- IL-1
- IL-6
- iNOS
- Chemokines
- IL-6
- Chemokines
- Anti-microbial peptides
- Ki67 (proliferation)

**Immunity**

- Immunity anti-fongique,
- anti-bactérienne
- Réparation des barrières épithéliales

**Autoimmunity**
IFNg has effector activity on cells of multiple lineages

- Surveillance immunitaire contre certains pathogènes (bactéries intracellulaires, virus)
  - Immunité anti-cancéreuse
- Nombreuses redondances avec IL-17
- Autoimmunité

- Chemokines
- Anti-microbial peptides
- Influx of T cells
- Influx of IL-23+ TNFα+ NO+ DC
DC-T cell-keratinocyte interactions drive the disease process and maintenance

- Antimicrobial peptides: IL-1b, IL-6, TNF-a, S100, CXCL8, CXCL9, CXCL10, CXCL11, CCL20, IL-17C
- Inflammatory cytokines: IFN-g, IL-1b, IL-6, TNF-a

- Innate immunity: Monocyte and neutrophil recruitment, Neovascularisation, Vasodilation, T cell influx, Keratinocyte hyperplasia

DC-T cell-keratinocyte interactions drive the disease process and maintenance

Principaux médicaments biologiques approuvés et en développement dans le psoriasis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trade name</th>
<th>Target</th>
<th>Drug</th>
<th>Phase</th>
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<td>TNF</td>
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<td>Stelara</td>
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<td>Anti-p40 mAb</td>
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<td>Otezla</td>
<td>PDE4</td>
<td>Oral small molecule</td>
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Les anticorps anti-IL-12/IL-23p40 et anti-IL-17 sont très efficaces dans le psoriasis

- Amélioration > 75% du score clinique chez 75% des patients
- 4 injections sous-cutanée / an pour l’anti-IL-23 ustekinumab