Sous populations lymphocytaires T CD4+ et CD8+ de type 1, type 2, type 17, type X …

CD4 Th1, Th2, Th17, ThX
CD8 Tc1, Tc2, Tc17, TcX

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T cell subset plasticity

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Outline

1. T cell subsets in humans
2. Psoriasis: a Th17-mediated disease through production of TNF-\(\alpha\) and IL-17
3. IL-17 and IL-17 targeting
4. Th17 and Th17 targeting
5. T cell plasticity
Many novel CD4+ T cell subtypes have been described in recent years

<table>
<thead>
<tr>
<th>Year</th>
<th>Subtype</th>
<th>Reference</th>
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"Suppressor cells" had been described in the late 1970s, but only identification of CD25+ enabled description.
Specific CD4+ T cell populations develop from naïve T cells

- Naïve T cell
  - IFN-γ, IL-12 → Th1
  - IL-4, IL-12 → Th2
  - TGF-β, IL-2 → Treg
  - TGF-β (IL-1), IL-6, IL-21, IL-23 → Th17
  - TGF-β, IL-4 → Th9
  - TNF-α, IL-6 → Th22

T cell populations are principally defined by their cytokine profiles

Naïve T cell

in the presence of

IFN-γ
IL-12

in the presence of

IL-4
IL-2

in the presence of

TGF-β
IL-2

in the presence of

TGF-β (IL-1)
IL-6, IL-21, IL-23

in the presence of

TGF-β
IL-4

in the presence of

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
IL-35

Th17

IL-17A
IL-17F
TNF-α
IL-21
IL-22
(IL-10)

Th9

IL-9
IL-10

Th22

IL-22

Each CD4+ T cell subtype has specific tasks in a normally functioning immune system.

- **Th1**
  - Promotes cell-mediated immunity and phagocyte-dependent protective responses
  - Promotes humoral immunity, e.g. immunoglobulin production

- **Th2**
  - Promotes humoral immunity
  - Regulation of immune responses

- **Treg**
  - In the presence of TGF-β (IL-1)
  - Promotes immune response to specific bacterial and fungal infections

- **Th17**
  - TGF-β (IL-1)
  - IL-6, IL-21, IL-23
  - Proposed to promote inflammation and immune cell proliferation

- **Th9**
  - TGF-β
  - IL-4
  - Context-dependent up- or down-modulation of tissue response to inflammation

- **Th22**
  - TNF-α
  - IL-6

**Promotes humoral immunity, e.g. immunoglobulin production**

**Regulation of immune responses**

**Proposed to promote inflammation and immune cell proliferation**

**Context-dependent up- or down-modulation of tissue response to inflammation**
CD4⁺ T cell populations have also been implicated in autoimmune or immune-mediated disorders

- **Th1**
  - IFN-γ, IL-12
  - Psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease

- **Th2**
  - IL-4, IL-2
  - Atopic disease, e.g. eczema, allergic rhinitis, asthma

- **Treg**
  - TGF-β, IL-2
  - Inappropriate balance or dysregulation associated with diseases, including autoimmunity, allergy and infection

- **Th17**
  - TGF-β (IL-1)
  - IL-6, IL-21, IL-23
  - Psoriasis, psoriatic arthritis, Crohn's disease

- **Th9**
  - TGF-β
  - IL-4
  - Proposed role in allergic disease

- **Th22**
  - TNF-α, IL-6
  - Proposed role in inflammatory and immune-mediated disease, including psoriasis, rheumatoid arthritis, Crohn's disease, atopic dermatitis
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Psoriasis : Dermatose Inflammatoire Chronique (érythémato-squameuse)

3 - 5% de la population

10% de formes graves
Psoriasis: 
= Dermatose Inflammatoire Chronique (érythémato-squameuse)

3-5% de la population
Patient avec poussées de psoriasis des coudes, des genoux et du cuir chevelu depuis 2 ans

Efficacité des traitements sur les poussées

Ne prend pas de médicaments par ailleurs
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 (auto-immune) = par activation dans la peau de LT spécifiques d’auto-Ag épidermique

anti-CD3
Pathophysiology of psoriasis

The vicious cycle of psoriasis

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

- **Adaptive immunity**
  - IL-12
  - TNF-α
  - IFN-γ

- **Innate immunity**
  - Antimicrobial peptides
    - IL-1β
    - IL-6
    - TNF-α
    - S100
    - CXCL8
    - CXCL9
    - CXCL10
    - CXCL11
    - CCL20
    - IL-17C

- **Keratinocyte**
  - IL-17A
  - IL-17F
  - IL-21
  - IL-22
  - TNF-α

- **Monocyte and neutrophil recruitment**
- **Neovascularisation**
- **Vasodilation**
- **T cell influx**
- **Keratinocyte hyperplasia**

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

Normal activity of IL-12 and IL-23
IL-12 and IL-23 neutralization

NK or T cell membrane

No signal
Effect of blocking IL-12 and IL-23 in psoriasis using anti-p40 antibody (ustekinumab)

Images courtesy of PHOENIX 2 Investigators.
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T cell plasticity
Can Treg cells convert to IL-17 effector cells?

Bovenschen HJ et al. Foxp3+ regulatory T cells of psoriasis patients easily differentiate into IL-17A-producing cells and are found in lesional skin. J Invest dermatol, 2011, 131:1853-1860
Key messages

• Psoriasis is a genetically based, auto-inflammatory disease

• Dendritic cells, T cells (Th1/Th17) and keratinocytes cross-talk to induce and maintain the disease

• DC produce IL-23 which activates Th17 cells leading to the production of IL-17 cytokines

• IL-17 activates keratinocytes which amplify the inflammatory response and initiate the vicious inflammatory circle. TNFa acts as a synergic cytokine

• Targeting Th17 and/or IL-17 results in dramatic improvement of psoriasis