Psoriasis
- Immunology and Pathogenesis

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Definition of Psoriasis

- Genetics
- Immune system
  - Innate IS
  - Adaptive IS
- Environmental factors
- Skin manifestations
- Joint manifestations
- Comorbidity
  - Quality of life
  - Metabol. disease

- Chronic - relapsing
- Common disease

Boehncke, Lancet, 2015 / Nestle, NEJM, 2009
## Prevalence

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence world wide</strong></td>
<td>2%</td>
</tr>
<tr>
<td>North America / Europe</td>
<td>up to 4%</td>
</tr>
<tr>
<td>Lapps/Africa/Asia</td>
<td>0.4 – 0.7%</td>
</tr>
<tr>
<td><strong>Prevalence Asthma world wide</strong></td>
<td>4.5% - 14%</td>
</tr>
<tr>
<td><strong>Prevalence Rheumatoid Arthritis world wide</strong></td>
<td>0.4 – 1.3%</td>
</tr>
</tbody>
</table>

Ethnicity?  
Climate?  
Sun exposure?
Epidemiology: Good and bad news

- **80% mild psoriasis** (topical treatment only)
- **5 - 20% psoriasis arthritis**

- **75% onset before 40 years of age**
- **80% psoriasis of the scalp** (most frequent localisation)
- **nail changes: 50% at diagnosis, 70% life time**

Clinical face of psoriasis
Clinical face of psoriasis
Clinical face of psoriasis
Clinical face of psoriasis
Pathological hallmarks of psoriasis

Abnormal differentiation and hyperproliferation of keratinocytes

Infiltration of inflammatory cells
Increased dermal blood vessels
Normal & psoriatic skin
The skin immune system

Nestle, Nat Rev Immunol, 2009
Immuno-pathogenesis of psoriasis

Danger signals

Self-DNA
LL-37

IL-1α/β
TNFα
IL-6

pDC

IFNα

mDC

IL-8

IL-17

IL-17

mDC

IL-12

IL-23

Lymph node

Th17

IL-1
IL-6
IL-23

mDC

Th1

IL-17

Th17

Th17

Th1

Th22

IFNγ

TNFα

Mph

IL-12

IL-22

IL-17

IL-17
Trigger factors

- **Trauma**
  - Koebner phenomenon

- **Drugs**

- **Infections**
  - Streptococci
  - HIV

- **Behavioural factors**

- **Occupational factors**
Genetics & Pathogenesis

Genetics

Immune system
- Innate IS
- Adaptive IS

Environmental factors

Skin manifestations

Joint manifestations

Comorbidity
- Quality of life
- Metabol. disease
Genetics of psoriasis

Population studies

1\textsuperscript{st}/2\textsuperscript{nd} degree relatives: Higher incidence of psoriasis

Concordance rate in monocygotic twins = 3-times higher than in discordant twins

Type I: positive family history – more severe course
Type II: negative family history – milder course
Genetics of psoriasis

Genetic studies

>40 susceptibility loci are associated with psoriasis

Candidate genes suggest key role for
- adaptive immunity
- innate immunity
- skin barrier functions
Genetics of psoriasis

PSORS1

HLA-Cw6
## Genetics of psoriasis

<table>
<thead>
<tr>
<th>Gene / locus</th>
<th>Chromosomal location</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSORS1</td>
<td>6p</td>
<td>6.4</td>
</tr>
<tr>
<td>PSORS2</td>
<td>17q</td>
<td>-</td>
</tr>
<tr>
<td>IL12B</td>
<td>5q</td>
<td>1.4</td>
</tr>
<tr>
<td>IL23R</td>
<td>1p</td>
<td>2.0</td>
</tr>
</tbody>
</table>
T helper (T_H) cells

<table>
<thead>
<tr>
<th>Polarization</th>
<th>Cytokine profile</th>
<th>Target</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>naive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T_H1</td>
<td>IFN-γ</td>
<td>macrophages</td>
<td>Intracellular pathogens</td>
</tr>
<tr>
<td></td>
<td>TNF-α</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T_H2</td>
<td>IL-4</td>
<td>eosinophils</td>
<td>parasites</td>
</tr>
<tr>
<td></td>
<td>IL-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IL-13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T_H17</td>
<td>IL-17</td>
<td>neutrophils</td>
<td>Extracellular pathogens</td>
</tr>
</tbody>
</table>

Sallusto, Eur J Immunol, 2009
T helper cell subsets

<table>
<thead>
<tr>
<th>Polarization</th>
<th>Defining properties</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>naive</td>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td>IL-23</td>
<td>IL-4, IL-13</td>
<td>Allergy</td>
</tr>
<tr>
<td>IL-12</td>
<td>IFN-γ, TNF-α</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>IL-23R</td>
<td>IL-17</td>
<td></td>
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</table>
Role of T cells in psoriasis

Xenotransplantation models

1. Non-lesional human skin from healthy or psoriasis donor
2. Engrafted onto immuno-compromised mice
3. Spontaneous development of psoriatic phenotype (psoriasis donors but not healthy donors)
4. Blocking of T cells lead to inhibition of psoriasis development

Day 0

Day 56

anti-human CD3 mAb
Infiltrate:

- memory-effector T cells
  CD4 ↔ DC, macrophages
  CD8 ↔ keratinocytes

T cells are activated
- CD69, CD25, HLA-DR

clonal T cell expansions
- antigen-specific stimulation
What is the antigen?
Putative antigen(s)?

- β-haemolytic streptococci can trigger psoriasis
  - T cells cross-react with epitops which are common to streptococcal M protein and keratins

Innate immunity is critical for T cell activation

Signal 1: Antigen

Signal 2:
- Co-stimulatory molecules
- Adhesion molecules

Signal 3:
- Cytokines (IL-2, IL-12, IL-23,...)
Psoriatic skin is highly infiltrated by dendritic cells (DC)

- plasmacytoid DC (BDCA-2)

- myeloid DC (CD11c, BDCA-1)
Activation of DC and production of cytokines

Schlapbach, Semin Immunopathol, 2016
Xenotransplantation models:
- Psoriasis is inhibited by anti–BDCA-2
- Fully restored by addition of human IFN-α

Key cytokines in psoriasis: IFN-α

Boyman, J Exp Med, 2004
Key cytokines in psoriasis: TNF-α

- **Enhanced expression in**
  - skin
  - joints
  - serum (correlates with activity)

- **Produced by multiple cells**
  - DC, macrophages
  - T cells
  - mast cells
  - keratinocytes, endothelial cells
Key cytokines in psoriasis: TNF-α

- Keratinocyte activation
- Recruitment of further leucocytes
- Stimulation of cytokines/chemokines
- Adhesion molecules
- Neovascularisation
Modulation of key cytokines

TNF Antagonists

Etanercept

Adalimumab

Infliximab
before Infliximab

on Infliximab since 3 years
Key cytokines in psoriasis: IL-12 and IL-23

# T helper cell subsets

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<tr>
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<th>Pathology</th>
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<tbody>
<tr>
<td>naive</td>
<td>Th1</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>IL-12</td>
<td>IFN-γ, TNF-α</td>
<td></td>
</tr>
<tr>
<td>IL-23</td>
<td>Th2</td>
<td>Allergy</td>
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Sallusto, Eur J Immunol, 2009
IL-12 & IL-23: heterodimers with common p40 subunit

- IL-12 and IL-23 bind to specific receptors on T cells and natural killer cells
- Strongly influence T cell differentiation and activation
Th1 cytokines: inflammatory processes in psoriasis

- IFN\(\gamma\)
- TNF\(\alpha\)
- iNOS (NO)
- IL-8
- MIG, IP-10
- VEGF
- MHC Class II
- ICAM-1
- VCAM-1

- Vasodilation
- Neutrophil influx
- T cell influx
- Neovascularisation
- Keratinocyte and endothelial cell activation
Th17 cytokines: inflammation and keratinocyte hyperplasia

- Th17
- IL-17
- IL-22
- TNFα

- MCP-1
- Gro-α
- IL-8
- G-CSF
- GM-CSF
- IL-6
- PGE2
- ICAM-1
- VCAM-1

- Monocyte and neutrophil recruitment
- Neovascularisation
- Vasodilatation
- T cell influx
- Keratinocyte hyperplasia
Modulation of key cytokines

- Anti-IL-12/Il-23 p40

Ustekinumab
Ustekinumab (anti-p40-Ab)

Before Ustekinumab

week 12

week 52
Summary: Key steps in the immunopathogenesis

- Activation of DC and T cells
- Stimulation of keratinocytes
- Neovascularisation
- Recruitment of further leucocytes
- Perpetuation of inflammation
Immunogenetics of psoriasis

Danger signals

Self-DNA LL-37

mDC

pDC

IFNα

IL-1α/β TNFα IL-6

IL-8

IL-17

mDC

Th17

Lymph node

Th1

IL-17

Th17

IL-12

Th17

IL-23

Th1

IL-12

Th17

IL-22

IFNγ TNFα

Mph

Th22

IL-17

IL-1α β TNFα IL-6

IL-8

IL-17
Thank you for your attention