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
Prevalence

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence world wide:</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>Prevalence Asthma world</td>
<td>4.5% - 14%</td>
</tr>
<tr>
<td>Prevalence Rheumatoid</td>
<td>0.4 – 1.3%</td>
</tr>
<tr>
<td>Arthritis world wide</td>
<td></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%** lifetime
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
The skin immune system

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

Danger signals

Self-DNA
LL-37

IFNα

pDC

mDC

IL-1α/β
TNFα
IL-6

IL-8

IL-17

IL-17

IL-12

IL-23

IL-22

Th17

Th1

Th17

Th17

Th22

Mph

IL-17

IFNγ

TNFα

IL-1

IL-6

IL-12

IL-17

IL-23

IL-12

Schlapbach, Semin Immunopathol, 2016
Trigger factors

- Trauma
  - Koebner phenomenon

- Infections
  - Streptococci
  - HIV

- Drugs

- Behavioural factors

- Occupational factors
Genetics of psoriasis

Population studies

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

Concordance rate in monoygotic 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>T&lt;sub&gt;H1&lt;/sub&gt;</td>
<td>IFN-γ, TNF-α</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>T&lt;sub&gt;H2&lt;/sub&gt;</td>
<td>IL-4, IL-13</td>
<td>Allergy</td>
</tr>
<tr>
<td>T&lt;sub&gt;H17&lt;/sub&gt;</td>
<td>IL-17</td>
<td>Psoriasis</td>
</tr>
</tbody>
</table>

- IL-12
- IL-23

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
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

Role of T cells in psoriasis
The 1 million dollar question in psoriasis

What is the antigen?
• β-haemolytic streptococci can trigger psoriasis

• T cells cross-react with epitopes 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, ...)

- CD80
- CD28
- LFA1
- ICAM1
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
Key cytokines in psoriasis: IFN-α

Xenotransplantation models:
- Psoriasis is inhibited by anti–BDCA-2
- Fully restored by addition of human 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
Infliximab (anti-TNF-α Antibody)

before Infliximab

on Infliximab since 3 years

Dept. of Dermatology, Inselspital, Bern University Hospital
Key cytokines in psoriasis: IL-12 and IL-23

T helper cell subsets

Polarization: naive, IL-12, IL-23

Defining properties:
- **T\textsubscript{H}1**: IFN-γ, TNF-α
- **T\textsubscript{H}2**: IL-4, IL-13
- **T\textsubscript{H}17**: IL-23R, IL-17

Pathology:
- Psoriasis
- Allergy

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

- IFNγ
- TNFα

- 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

Monocyte and neutrophil recruitment
Neovascularisation
Vasodilatation
T cell influx
Keratinocyte hyperplasia

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

IFNa

mDC

pDC

Th17

Th1

Th22

Mph

IL-22

IL-17

IL-1α/β

TNFα

IL-6

IL-8

IL-17

IFNγ

TNFα

IL-12

IL-23

IL-1α

IL-6

IL-23

IL-17

IL-12

IL-22

IL-17

IL-10

Lymph node

Schlapbach, Semin Immunopathol, 2016
Thank you for your attention