The Role of Plasmacytoid Dendritic Cells in Psoriasis

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Psoriasis: Clinical Spectrum
Histology – Keratinocyte or Immune Defect?

- Epidermal Hyperproliferation
- Inflammation
- Angiogenesis
Psoriasis

Uniquely human disease
AGR Mouse Model

New mouse model with **spontaneous** development of psoriasis

AGR Mouse Model

Uninvolved skin from a psoriasis patient.

A = Type I IFN receptor deficiency
G = Type II IFN receptor deficiency
R = Rag⁻⁻
Spontaneous Conversion

Uninvolved skin on AGR

Macroscopic

Day 0

Day 56

CD3

AGR Mouse Model - Pathogenesis

PN day 0

AGR Mouse Model - Pathogenesis

PN day 7

AGR Mouse Model - Pathogenesis

PN day 21

AGR Mouse Model - Pathogenesis

PN day 35

AGR Mouse Model - Pathogenesis

AGR Mouse Model - Pathogenesis

AGR Mouse Model - Pathogenesis

Chronic Plaque Psoriasis

Chronic phase

psoriasis

IFN-γ

IL-17
IL-22

Th1/Tc1 cells

Th17/Tc17 cells

TNF

IL-23

Chronic phase
**Immunopathogenesis**

**Koebner Phenomenon**
(skin wounding)

**Triggers of acute phase?**

**psoriasis**

- Th1/Tc1 cells
- IFN-γ
- IL-17
- IL-22

- Th17/Tc17 cells
- IL-23

- TNF

**Chronic phase**
Aldara (Imiquimod) Induces Psoriasis

M. Bowen?

Psoriasis!

Week 0

Week 6

Week 10
pDCs in Antiviral Immunity

DNA and ssRNA Viruses

plasmaytoid DC (pDC)

Cellular resistance to viral infection

IFN-α/β

Immature cDC

Activated cDC

Antibodies

Cytotoxicity
pDCs in Psoriasis

Psoriasis Skin Lesion  pre-psoriatic skin

BDCA-2

IFNα Induces Psoriasis

pDC-derived IFN\(\alpha\) Induces Psoriasis

Pathophysiology of Psoriasis

**Koebner phenomenon**
*(wounding, mechanical stress)*

- *plasmacytoid DC*
- IFN-α

**Acute phase**

- Th1/Tc1 cells
- IL-17
- IL-22
- IL-23
- TNF

**Chronic phase**

- Th17/Tc17 cells
- IFN-γ
AMP LL37 - Key Trigger of pDC Activation

HPLC of psoriatic skin

Lande et al. Nature. 2007
Cationic Antimicrobial Peptides (AMP)

- evolutionary ancient antimicrobial defense mechanism
- highly cationic, amphipathic peptides
- 2 main classes in humans:

**DEFENSINS** (beta-sheet peptides)
- $\alpha$-defensins
- $\beta$-defensins

**CATHELICIDINS** (alpha-helical peptides)
- LL37 is the only human member
Discrimination between viral and self-DNA

VIRAL INFECTION

DNA virus

HOST CELL DEATH

human DNA

plasmacytoid DC

IFN-α/β
LL37 Converts Otherwise Inert self-DNA into a Trigger of IFNα

Lande et al. Nature. 2007
LL37 controls ability of pDCs to sense self-nucleic acids

HOST CELL DEATH

Self-DNA/RNA

LL37

Self-DNA/RNA-LL37 complexes

1- PROTECTION
2- INTERNALIZATION
3- ENDOSOMAL RETENTION

pDC

TLR9/7

IFN-α/β

Lande et al. Nature. 2007
Psoriasis: Pathogenesis

Psoriasis: Pathogenesis

Th1/Tc1 cells

Th17/Tc17 cells

IL-17
IL-22
IFN-γ

TNF

IL-23
# Biologics for Psoriasis Therapy

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Humira (Adalimumab)</th>
<th>Enbrel (Etanercept)</th>
<th>Remicade (Infliximab)</th>
<th>Stelara (Ustekinumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecule</td>
<td>Human monoclonal antibody</td>
<td>Fusion protein</td>
<td>Chimeric monoclonal antibody</td>
<td>Human monoclonal antibody</td>
</tr>
<tr>
<td>Therapeutic approach</td>
<td>TNF-α</td>
<td>TNF-α</td>
<td>TNF-α</td>
<td>IL12/23</td>
</tr>
<tr>
<td>Indications</td>
<td>RP, Pso, PsoA, SA, CD</td>
<td>RP, Pso, PsoA, CD, JIA</td>
<td>PR, Pso, PsoA, SA, CD, UC</td>
<td>Pso</td>
</tr>
<tr>
<td>Dosage for psoriasis</td>
<td>40 mg every 2 weeks</td>
<td>50 mg per week or 25 mg twice weekly</td>
<td>5 mg/kg every 8 weeks</td>
<td>45 mg/90 mg* every 12 weeks</td>
</tr>
</tbody>
</table>

* For patients >100 kg

RP = Rheumatoid polyarthritis
Pso = Psoriasis
PsoA = Psoriatic arthritis
SA = Ankylosing spondylarthritis
CD = Crohn’s disease
UC = Ulcerative colitis
Case Report

- Patient S.C., 18.04.1987
- Crohn’s disease, first diagnosed 2007
  - steroid-refractory
  - started with azathioprine (Imurek®)
  - reactivation of Crohn’s disease
- Adalimumab (Humira®)
Cutaneous Eruptions Under anti-TNF Therapy

Crohn’s disease, under adalimumab
Cutaneous Eruptions Under anti-TNF Therapy

Crohn’s disease, under adalimumab
Case Report

- Patient C.M., 1953

- Spondylarthritis

- 2 months after starting anti-TNF therapy (infliximab, Remicade®)
Cutaneous Eruptions Under anti-TNF Therapy

Spondylarthritis, under infliximab
Cutaneous Eruptions Under anti-TNF Therapy
Cutaneous Side Effects of anti-TNF Therapy

- **Immediate adverse events**
  - Acute infusion reaction (frequent)
  - Immune-mediated hypersensitivity reaction (rare)
- **Delayed cutaneous eruptions**
- **Psoriasis**
  - Worsening of pre-existing psoriasis
  - Onset of a psoriasiform eruption
  - Pustular psoriasis
- **Lupus erythematosus**
  - Discoid lupus erythematosus
  - Systemic-lupus-erythematosus-like syndromes
- **Interface dermatitis**
  - Erythema multiforme
  - Lichenoid eruption
- **Bullous eruption**
- **Vascular lesions**
  - a Leucocytoclastic vasculitis
  - b Serum sickness
  - c Eczematid-like purpura
  - d Perniosis
- **Eczematous eruption: atopic-dermatitis-like eruption**
- **Granuloma annulare**
- **Infections**
  - a Acute bacterial folliculitis
  - b Dermatophytosis
  - c Molluscum contagiosum
  - d Herpes
- **Cutaneous lymphomas: CD30 T-cell lymphoma**
- **Non-melanoma skin cancer**
  - a Kerato-acanthomas
  - b Squamous cell carcinoma
Cutaneous Side Effects of anti-TNF Therapy

- Psoriatic skin lesions induced by anti-TNF therapy
  « paradoxic psoriasis »

  - Histologically confirmed
Paradoxic Psoriasis Induced by TNF-Inhibitors

- Well known side effect of anti-TNF therapy
- Numerous cases reported in the literature
- 2% of patients receiving anti-TNF treatment
# Paradoxic Psoriasis Induced by TNF-Inhibitors

<table>
<thead>
<tr>
<th>Indication for anti-TNF</th>
<th>Type of anti-TNF</th>
<th>PA psoriasis</th>
<th>FA psoriasis</th>
<th>Delay after therapy start</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. C.M. 1953 SA</td>
<td>Infliximab</td>
<td>-</td>
<td>-</td>
<td>2 months</td>
</tr>
<tr>
<td>2. C.I. 1978 Crohn</td>
<td>Infliximab</td>
<td>-</td>
<td>+</td>
<td>2 months</td>
</tr>
<tr>
<td>3. M.V. 1987 Crohn</td>
<td>Infliximab</td>
<td>-</td>
<td>-</td>
<td>6 months</td>
</tr>
<tr>
<td>4. R.G. 1941 SA</td>
<td>Adalimumab</td>
<td>-</td>
<td>-</td>
<td>28 months</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
<td></td>
<td></td>
<td>2 months</td>
</tr>
<tr>
<td>5. C.C.1952 SAPHO/PsoA</td>
<td>Adalimumab</td>
<td>-</td>
<td>-</td>
<td>3 weeks</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. J.R. 1939 RP</td>
<td>Adalimumab</td>
<td>-</td>
<td>-</td>
<td>5 months immediatly</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. R.C. 1945 Crohn</td>
<td>Infliximab</td>
<td>-</td>
<td>-</td>
<td>2 months</td>
</tr>
<tr>
<td>8. R.Y. 1945 PsoA</td>
<td>Adalimumab</td>
<td>+</td>
<td>-</td>
<td>2 months</td>
</tr>
</tbody>
</table>
TNF-Inhibitors for Chronic Psoriasis

week 0

week 2

week 10

Remicade (infliximab 5mg/kg)
Paradoxic Psoriasis Induced by TNF-Inhibitors

Pathogenesis unknown
Yin-yang of TNF and IFN-α

Immunity as a dynamic system driven by sets of opposite vectors (TNF/IFN-α)

adapted from: Banchereau et al. Immunity 2004
Dysregulation by TNF-Inhibitors

Acute/paradoxic psoriasis

Anti-TNF-α
Clinical Relevance

• Class effect of TNF-inhibitors

→ no switch to another TNF-inhibitor

- topical steroids
- MTX, cyclosporine, short-term systemic steroids, retinoids
- switch to another class:
  anti-IL12/23, anti-IL17 (psoriasis)
  anti-CTLA4, anti-CD20, anti-IL6 (arthritis)
- anti-IFN-α?
Clinical Relevance

Immunity as a dynamic system driven by sets of opposite vectors (TNF/IFN-α)

TNF prevailing: TNF-mediated autoimmunity (arthritis)

IFN-α: IFN autoimmunity (SLE, thyroiditis, diabetes)

adapted from: Banchereau et al. Immunity 2004
Dysregulation by TNF-Inhibitors

- Lupus erythematosus
- Acute/paradoxic psoriasis
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