Immunology of psoriasis

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Aetiopathogenesis of psoriasis

Genetic factors

Defects in epidermal function, innate/acquired immunity

Environmental factors

e.g. streptococci
Pathological hallmarks of psoriasis

Abnormal differentiation and hyperproliferation of keratinocytes

Infiltration of inflammatory cells
Increased dermal blood vessels
Where is the primary defect?

Previous hypothesis (pre 1990)
- Primary activation of keratinocytes
- Subsequent release of cytokines and antigen-independent activation of T cells

Current understanding (post 1990)
- Persistent T-cell stimulation (antigen?) which drives abnormal keratinocyte proliferation
- Exaggerated innate immune response
  (DC, macrophages, IFNs, TNFα, IL-12/IL-23)
- Alteration of transcription factors in keratinocytes
Role of T cells in psoriasis

Xenotransplantation models:

AGR-/- xenograft model\(^1\)

→ non-lesional human skin engrafted onto AGR129 mice
→ spontaneous development of psoriatic phenotype
Role of T cells in psoriasis

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

Krueger JG. J Am Acad Dermatol 2002; 46: 1
Putative antigen(s) ?

• β-haemolytic streptococci can trigger psoriasis

• Superantigens stimulate a skin-homing molecule (CLA) on T cells

• T cells cross-react with epitops which are common to streptococcal M protein and keratins \(^{1,2}\)

Innate immunity is critical for T cell activation

Signal 2:
- Co-stimulatory molecules
- Adhesion molecules

Signal 3:
- Cytokines (IL-2, IL-12, IL-23,…)
Innate immunity in psoriasis

- Psoriatic skin is highly infiltrated by dendritic cells (DC)
  - plasmacytoid DC (BDCA-2)
  - myeloid DC (CD11c, BDCA-1)

Lowes et al. PNAS. 2005; 102: 19057
Activation of DC and production of cytokines

- plasmacytoid DC (BDCA-2)
  \[ \rightarrow \text{IFN-}\alpha \]

- myeloid DC (CD11c)
  \[ \rightarrow \text{TNF-}\alpha, \text{IL-12, IL-23} \]
Key cytokines in psoriasis: IFN-α

Xenotransplantation models:

AGR-/- xenograft model

- Psoriasis is inhibited by anti–BDCA-2
- Fully restored by the addition of recombinant human IFN-α

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 $\alpha$

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

- **TNF Antagonists**
  - Etanercept, ENBREL
  - Adalimumab, HUMIRA
  - Infliximab, REMICADE
TNF Antagonists

before Remicade

on Remicade since 3 years
Key cytokines in psoriasis: IL-12 and IL-23
IL-12 and IL-23 are heterodimers with a 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
IL-12 and IL-23 drive development of Th1 and Th17 cells
Th1 cytokines drive inflammatory processes in the psoriatic plaque

Th17 cytokines drive inflammation and keratinocyte hyperplasia in the psoriatic plaque

- 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

Aggarwal S, Gurney AL. J Leukoc Biol. 2002; 71:1
Modulation of key cytokines

• Anti-IL-12/Il-23 p40
  Ustekinumab, STELARA®
  Briakinumab, ABT-874
Ustekinumab, STELARA
Summary:
Key steps in the immunopathogenesis

- Activation of DC and T cells

  - Stimulation of keratinocytes

  - Neovascularisation

  - Recruitment of further leucocytes

Perpetuation of inflammation