Th17 cells and tissue remodeling in atopic and contact dermatitis

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# Recent concepts

<table>
<thead>
<tr>
<th>Atopic dermatitis</th>
<th>Allergic contact dermatitis</th>
<th>Irritant contact dermatitis</th>
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<tbody>
<tr>
<td><strong>AD</strong></td>
<td><strong>ACD</strong></td>
<td><strong>ICD</strong></td>
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<tr>
<td>• Type II reaction</td>
<td>• Type I reaction</td>
<td>• Type I reaction</td>
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<tr>
<td>• IgE receptor on epidermal DC</td>
<td>• 2 phases: sensitization, elicitation</td>
<td>• Skin barrier disruption, denaturation of keratins, cell membrane damage</td>
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<tr>
<td>• CD4&gt;CD8</td>
<td>• Haptens, bind to keratinocytes</td>
<td>• IL-1, IL-6, IL-8, IL-12, IL-18, TNF-α, GM-CSF, ICAM</td>
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<tr>
<td>• IL-4, IL-5, IL-13</td>
<td>• CD4, CD8: IFN-γ</td>
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<td>• also IFN-γ</td>
<td>• CD8&gt;CD4</td>
<td>• CD8&gt;CD4</td>
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<tr>
<td>• Sensitization via airways or gut</td>
<td>• IL-1, TNF-α</td>
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<td></td>
<td>• CD8: Perforin, granzyme, Fas/FasL</td>
<td>• GM-CSF, ICAM</td>
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IL-17 in ACD

• IL-17 deficient mice: impaired contact and delayed type hypersensitivity responses
• IL-17+ T cells near spongiosis

• IL-17 is produced by Ni-specific T cells
  • IL-17 augmented expression of adhesion molecules (ICAM) and proinflammatory cytokines (IL-8) by keratinocytes

• Subpopulations Th1/IL-17 >> Th1
  • induce ICAM-1 expression on keratinocytes
  • cytotoxic toward Ag-loaded target cells

Albanesi C et al.; J Immunol 1999;
IL-17 in AD

- IL-17 detected in acute AD lesions
- Number of peripheral blood IL-17+ CD4+ T cells correlated with disease severity
- Extracellular vesicles derived from Staph.aureus induce AD-like lesions and IL-17
- Staph.aureus toxin B (SEB) enhanced IL-17 production by Th17 cells isolated from APT to D.pter.
  - IL-17 induced production of HBD by keratinocytes

Hong SW et al. Allergy 2011; Eyrich K et al.; J Allergy Clin Immunol 2009
IL-22

- Produced by Th17 and Th22 cells
- IL-17 and IL-22 expression in ACD
- Upregulated in AD, independent Th22 cells

- IL-22 inhibited epidermal differentiation and induced proinflammatory cytokine expression
- Induced epidermal hyperplasia in chronic AD

IL-17, IL-22 and remodeling

- IL-17 stimulated eosinophils to produce profibrotic cytokines (TGF-β, IL-11)
- Eosinophils expressing TGF-β, MMP-9, CCL11 correlated with tenascin deposition and tenascin C⁺ cells in skin diseases

- IL-22 mediated dermal inflammation and acanthosis in psoriasis
  - IL-6 or IL-23 induce IL-22 production by T cells
  - TGF-β inhibited IL-22

Al-Muhsen et al. Respir Res 2013
Roth N et al. Allergy 2011
IL-17 in AD, ACD, ICD?

Diagram showing:
- Neutrophils
- DC
- TGF-β+IL-6
- Proliferation
  - IL-1
  - TNF-a
  - IL-6
  - IL-8
- HBD
- Remodeling
  - IL-4
  - IL-5
  - IL-13
  - Eosinophils
- Th1
- IL-17
- IL-23
- IL-21
- IL-22
- IFN-γ
- Th2
- Th22
Methods

• Punch biopsies from positive patch tests with
  – Aeroallergen (APT)
  – Contact allergen (CPT)
  – Irritant SLS (IPT)
    at days D2, D3 and D4
• Immunofluorescence staining with Ab against
  – IL-17, CD3
  – IL-21, IL-22, IL-23
  – IFN-gamma, IL-13
  – IL-1, IL-8, TGF-beta, IL-33
  – Tenascin C, procollagen-3, MMP-9
• Confocal microscopy
IL-13 dominates in APT, IFN-γ in CPT, IPT

Expression of IL-17, IL-21, IL-22 in APT, CPT, IPT

A

IL-17

B

IL-17+ CD3

C

IL-21+ CD3

D

IL-22+ CD3

E

IL-17

IL-17+CD3

Cytokines regulating Th17 differentiation and activation

Remodeling in APT, CPT, IPT

A

Procollagen-3

Cells per 10 fields

APT CPT IPT

B

MMP-9

Cells per 10 fields

APT CPT IPT

C

Tenascin C

Cells per 10 fields

APT CPT IPT

D

Tenascin C

Cells per 10 fields

IL-17^CD3^ cells

E

Tenascin C deposition

Score

D2D3 D4 D2D3 D4 D2D3 D4 D2D3 D4

IL-17^+CD3^+ correlate with MMP-9^+ eosinophils and tenascin C^+ cells
IL-22+ T cells correlate with eosinophil numbers

Summary

In AD, ACD, ICD:

• Expression of IL-17
  • APT (maximum D2) and CPT, IPT (maximum D4)
  • 30-50% of IL-17\(^+\) cells are Th17 cells

• Cytokines driving Th17 differentiation and activation (IL-1, IL-6, IL-23, IL-33, TNF-\(\alpha\), TGF-\(\beta\))

• Expression of IL-21 and IL-22

• Correlation of IL-22\(^+\)T cells and eosinophils

• Th17 cell numbers correlate with MMP-9\(^+\) eosinophils and tenascin C\(^+\) cells

Simon D et al. Allergy 2014