

Th17 cells and tissue remodeling in atopic and contact dermatitis

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Recent concepts

Atopic dermatitis

AD

- Type II reaction
- IgE receptor on epidermal DC
- CD4>CD8
- IL-4, IL-5, IL-13
- also IFN- γ
- Sensitization via airways or gut

Allergic contact dermatitis

ACD

- Type I reaction
- 2 phases: sensitization, elicitation
- Haptens, bind to keratinocytes
- CD4, CD8: IFN- γ
- CD8>CD4
- IL-1, TNF- α
- CD8: Perforin, granzyme, Fas/FasL

Irritant contact dermatitis

ICD

- Type I reaction
- Skin barrier disruption, denaturation of keratins, cell membrane damage
- IL-1, IL-6, IL-8, IL-12, IL-18, TNF- α , GM-CSF, ICAM

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;
Nakae S et al. Immunity 2002; Pennino D et al. J Immunol 2010

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

Koga C et al. J Invest Dermatol 2008; Toda M et al. J Allergy Clin Immunol 2003
Hong SW et al. Allergy 2011; Eyrich K et al.; J Allergy Clin Immunol 2009

IL-22

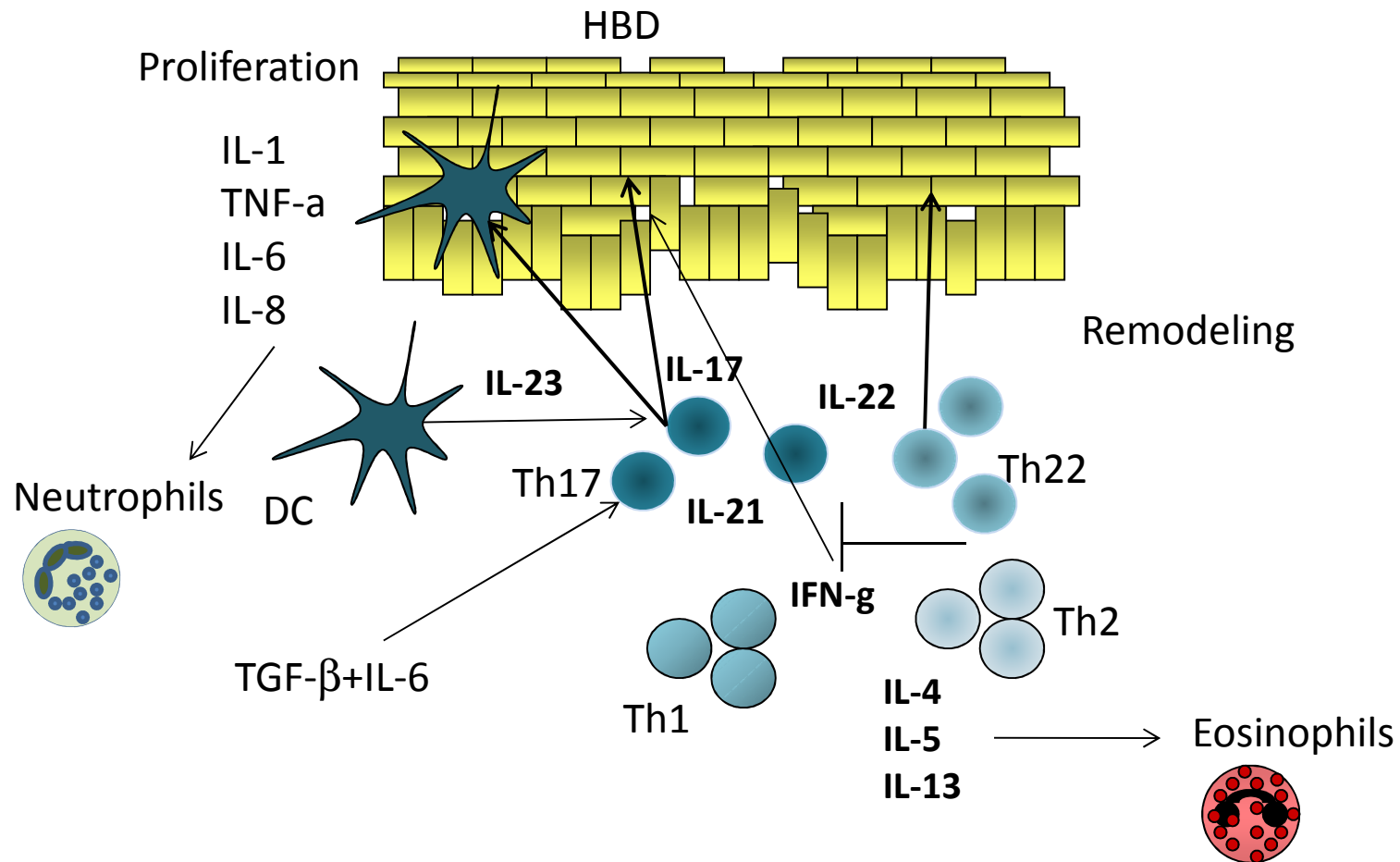
- Produced by Th17 and Th22 cells
- IL-17 and IL-22 expression in ACD
- Upregulated in AD, independent Th22 cells
- IL-22 inhibited epidermal differentiation and induced proinflammatory cytokine expression
- Induced epidermal hyperplasia in chronic AD

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
Zheng Y et al.; Nature 2007
Roth N et al. Allergy 2011

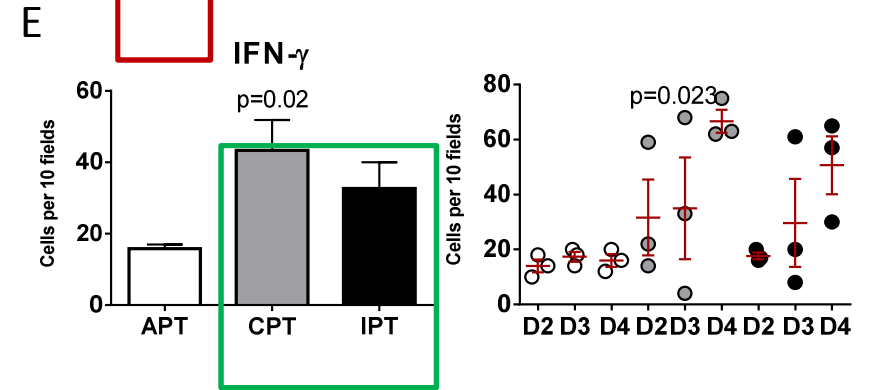
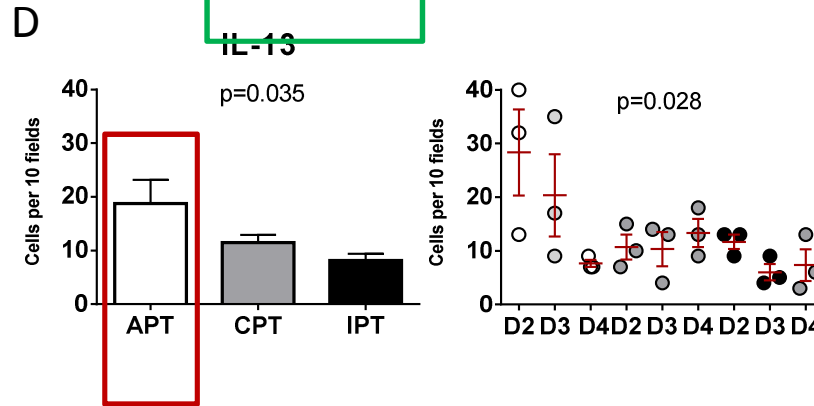
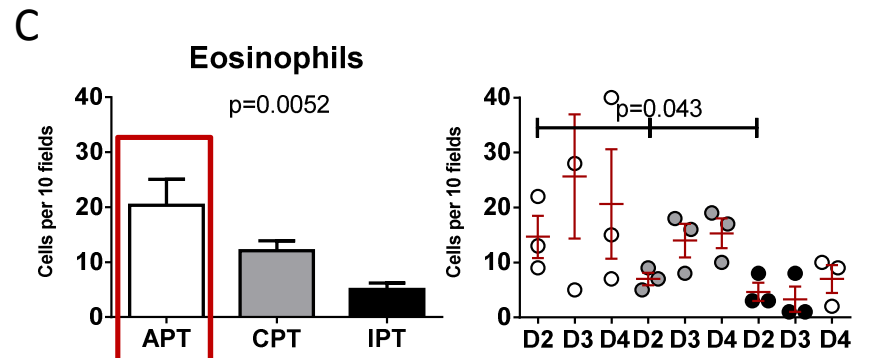
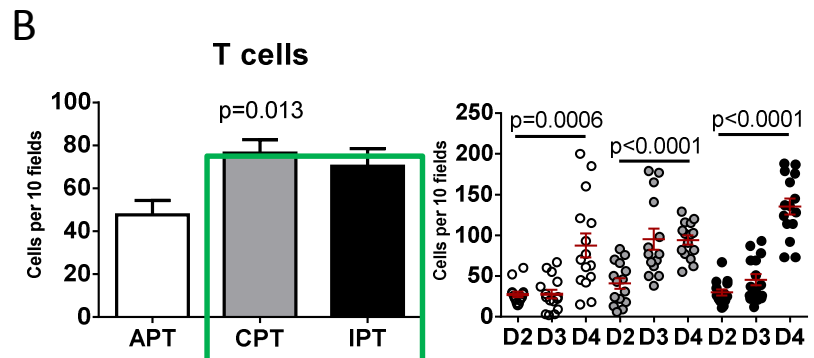
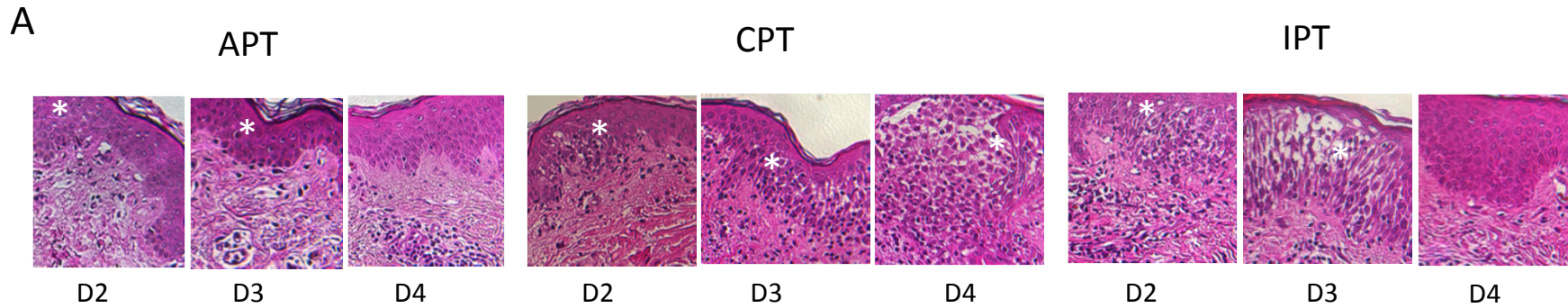
IL-17 in AD, ACD, ICD ?



Methods

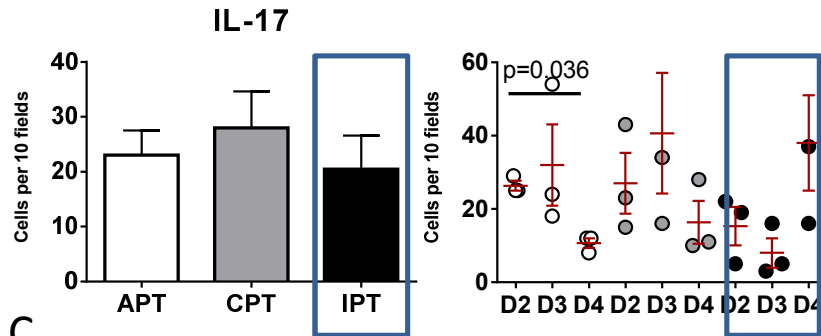
- Punch biopsies from positive patch tests with
 - Aeroallergen (APT)
 - Contact allergen (CPT)
 - Irritant SLS (IPT)at days D2, D3 and D4
- Immunofluorescence staining with Ab against
 - IL-17, CD3
 - IL-21, IL-22, IL-23
 - IFN-gamma, IL-13
 - IL-1, IL-8, TGF-beta, IL-33
 - Tenascin C, procollagen-3,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

IL-13 dominates in APT, IFN- γ in CPT, IPT

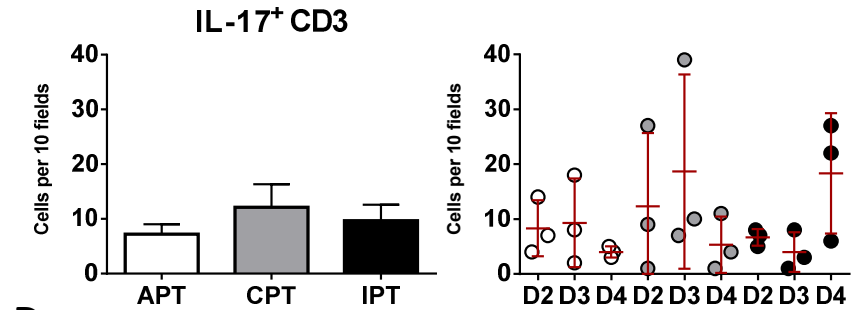


Expression of IL-17, IL-21, IL-22 in APT, CPT, IPT

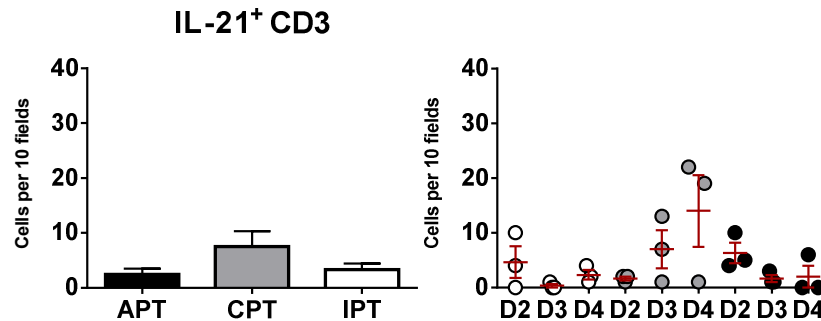
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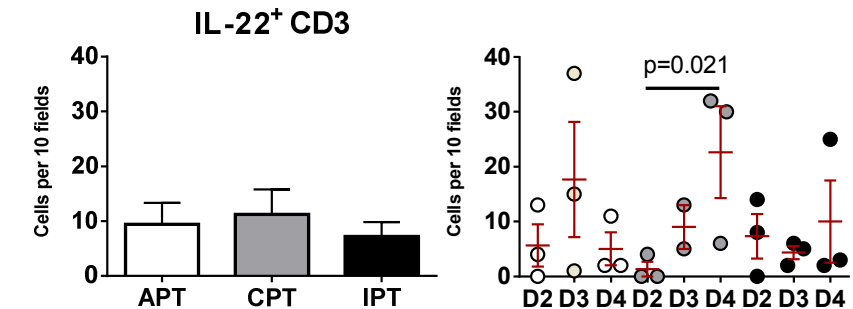
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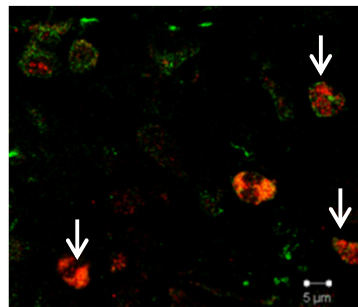
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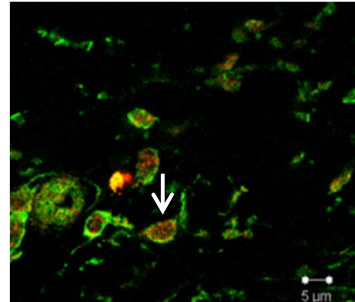
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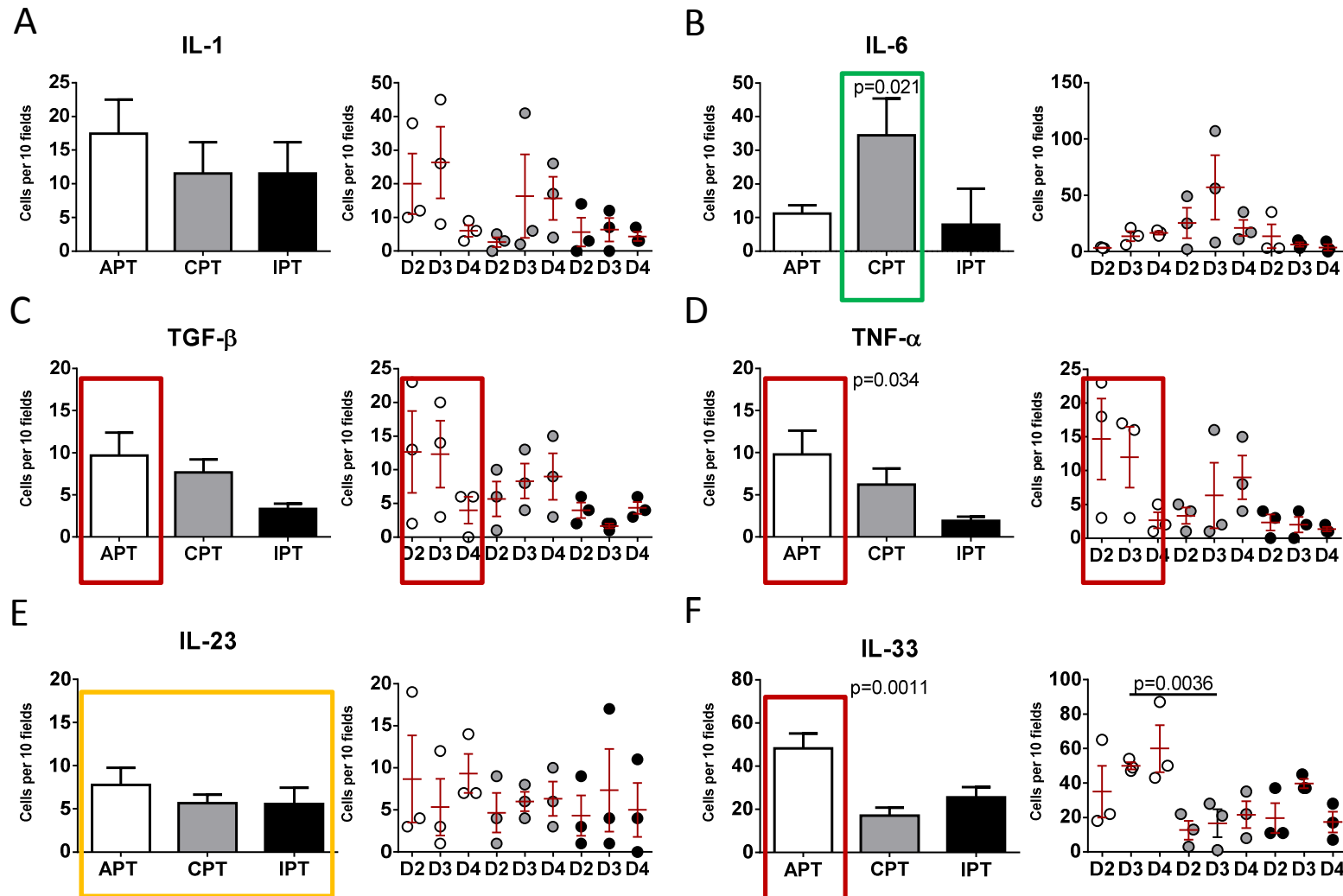


IL-17

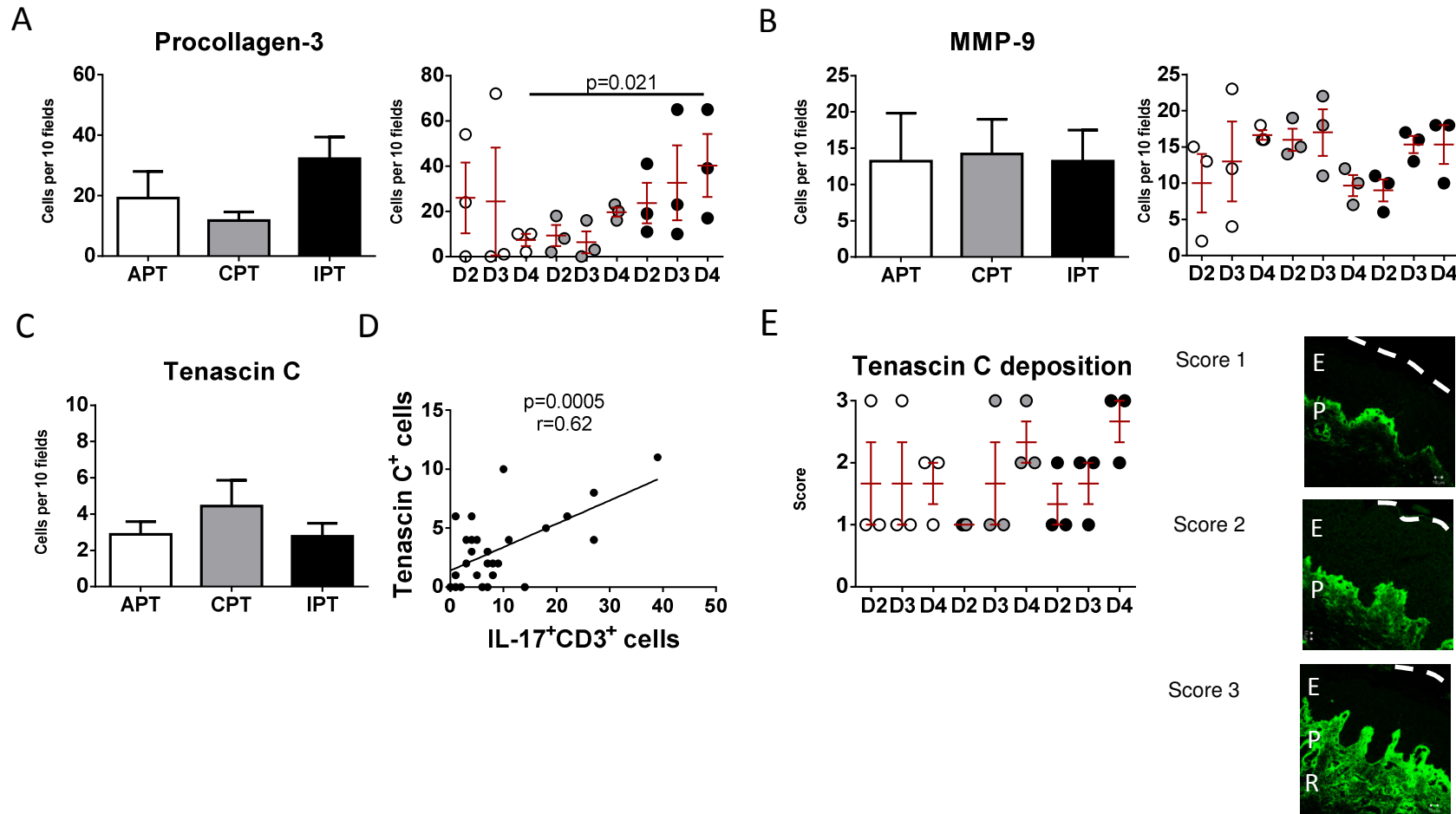


IL-17⁺CD3

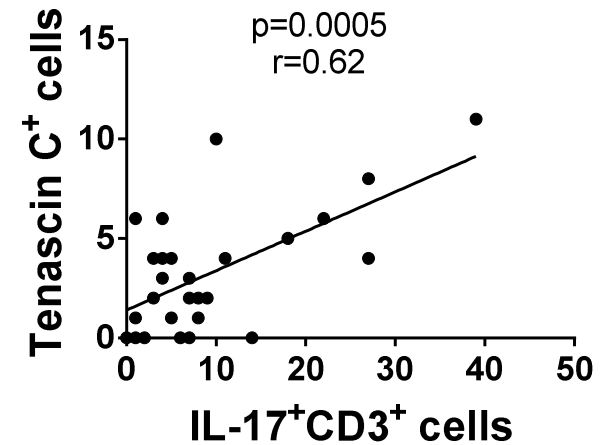
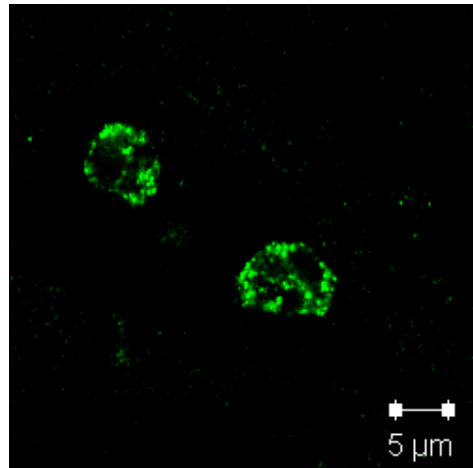
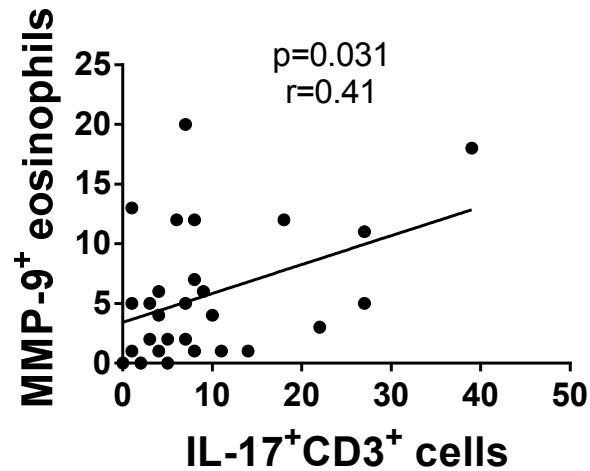
Cytokines regulating Th17 differentiation and activation



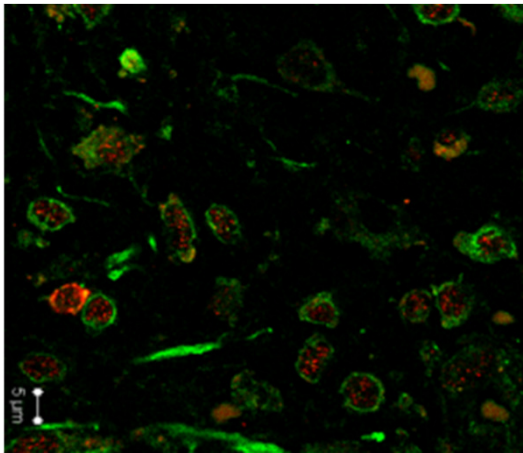
Remodeling in APT, CPT, IPT



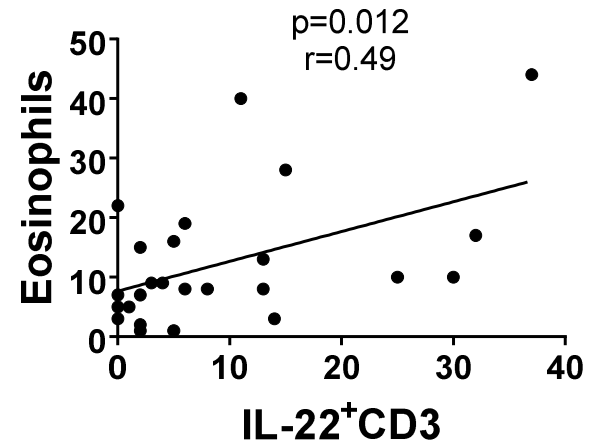
IL-17⁺CD3 correlate with MMP-9⁺ eosinophils and tenascin C⁺ cells



IL-22⁺ T cells correlate with eosinophil numbers



IL-22⁺CD3



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- α , TGF- β)
- 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