IL-17E activates M2 macrophages to produce IL-8 in a p38 dependent manner and favors the recruitment of neutrophils in psoriatic skin

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Introduction

Psoriasis vulgaris is a common chronic recurrent immune-mediated skin disease. As of now, neutralization of Th17/IL-23 pathway via blockade of IL-17A or its receptor subunit IL-17RA, represents the most effective approach to treat the disease. In this study we investigated the biological effects of IL-17E, an isoform of the IL-17 family that also signals via the receptor subunit IL-17RA.

Results

Ex-vivo

A. Expression of IL-17E in normal, lesional and non lesional psoriatic skin. **B.** Expression of IL-17E (red), CD68, IL-17RB (IL-17E specific receptor subunit) and clathrin (green) in lesional skin. **C.** Correlation between the number of IL-17E+ cells and the number of MPO+ neutrophils or CD3+ T cells in lesional skin.

IL-17E is overexpressed in psoriasis and positively correlates with infiltrating neutrophils

In-vitro

A. IL-17RB expression assessed by qPCR in M0, M1 and M2 monocyte derived macrophages. **B.** M2 macrophages were stimulated with IL-17E. Cytokines/chemokines assessed by qPCR. **C.** Detection of signaling proteins in M2 macrophages stimulated with IL-17E for the indicated time points. **D.** IL-8 production by ELISA upon treatment with IL-17E alone or in presence of SB202190 or JSH 23. **E.** Neutrophil chemotaxis assessed in Transwell chamber using supernatants of M2 macrophages alone, in presence of anti-IL-8 antibody or SB 202190.

IL-17E activates M2 macrophages to produce IL-8 via p38 MAPK and recruit neutrophils

In-vivo

A. H&E and IF staining (Ly6G (green) and CD3 (red)) of back skin of BALB/c mice after two intradermal injections of IL-17E or saline in two consecutive days. **B.** Quantification of immune cells infiltrating in the skin by FACS. **C.** Anti-IL17E antibody and respective isotype control were injected i.p. 24h before applying tape-strapping on the back skin of mice. Quantification of immune cells infiltrating in the skin by FACS.

IL-17E induces skin inflammation and the recruitment of neutrophils in healthy WT mice and in tape stripping model

Conclusion

IL-17E induces the production of inflammatory cytokines and chemokines, in particular IL-8, in *in-vitro* M2 macrophages. IL-17E mediated-IL-8 production promotes neutrophil migration via p38 MAPK pathway. *In vivo*, IL-17E participates in skin inflammation and in the recruitment of innate immune cells, suggesting a pro-inflammatory role of this cytokine in psoriasis.