SUPPLEMENTARY MATERIALS & METHODS

Histology on psoriasis biopsies

Lesional and non-lesional biopsies were formalin fixed and paraffin-embedded for histological analysis. ISH and IHC were performed on 5 µm and 3 µm thick sections, respectively. Single ISH for *IL17RA* (401648, Bio-Techne), *IL17A* (310938, Bio-Techne), *IL17F* (310948, Bio-Techne), *IL17C* (422018, Bio-Techne) and *IL17E* (457818, Bio-Techne) was performed with RNAscope® (Bio-Techne) using fast red as detection while triple fluorescence ISH was performed with RNAscope® (Bio-Techne) multiplex fluorescent assay using TSA Plus-conjugated fluorophores: Cy5 (*CD3,* 586348-C3, Bio-Techne), Cy3 (*IL17F,* 310948-C2, Bio-Techne) and FITC (*IL17A,* 310938, Bio-Techne). IHC was performed with goat anti-human IL-17A (9 µg/mL, AF-317-NA, R&D Systems), goat anti-human IL-17C (3 µg/mL, AF1234, R&D Systems) and mouse anti-human neutrophil elastase (0.2 µg/mL clone NP57, M0752, Agilent). The primary antibodies for IL-17A and IL-17F were detected with BOND Polymer Refine Detection with rabbit anti-goat (P0449, Agilent) as secondary antibody and DAB as chromogen. Prior to incubation with primary antibodies HIER was performed by 20 min in BOND ER2 buffer (pH 9) at 99^{o}C for 20min. Neutrophil elastase was detected with BOND Polymer Refine RED Detection which has Fast red as chromogen without HIER. For single ISH and IHC, nuclei were stained blue with hematoxylin. In multiplex fluorescence, nuclei were visualized with DAPI. All stains were performed on a Leica BOND RX. Single ISH were scanned with a Nanozoomer 2.0 HT (Hamamatsu) and quantified by whole slide digital image analysis using Visiopharm Integrator Software (Visiopharm). The area of the fast red representing mRNA expression in epidermis was measured as percentage of the total area of the epidermis excluding stratum corneum and including papillary dermis. For image analysis, mean value ± SEM were calculated and statistical analysis was performed by two sided paired t tests.

Multiplex fluorescence slides were scanned confocally with an Operetta CLS (Perkin Elmer). For ISH *PPIB* (313908) and *DapB* (312038) were included as positive and negative controls, respectively. For IHC isotype controls were used as negative controls (goat IgG, LS-C351732, LSbio; Mouse IgG1, Ab18443, abcam).

Cytokine protein analysis on psoriasis biopsies

Lesional and non-lesional punch biopsies (n=8 patients, cohort II and n=8 patients, cohort IV) were snap-frozen in liquid nitrogen immediately after removal and stored at -80ºC until use. For protein extraction, tissue samples were suspended in cold 1× Cell lysis buffer (Cell Signaling Technology, Danvers, MA, USA) containing freshly added protease and phosphatase inhibitors, *e.g.* Complete Mini Protease Inhibitor Cocktail Tablet (Roche diagnostics, Mannheim, Germany), Halt™ phosphatase inhibitor cocktail (Thermo Fisher Scientific, Waltham, MA, USA) and Sodium Orthovanadate (New England Biolabs, Ipswich, MA, USA) and homogenized by using a Precellys® 24 bead-based homogenizer (Precellys® Bertin Technologies, France). After incubation on ice for 20 min to allow a complete lysis, the tissue lysates were cleared from cell and tissue debris by means of centrifugation at 15,000g for 15 min at 4ºC. Total protein concentration was measured by the BCA protein assay (Thermo Fisher Scientific) in the resulting supernatants. Subsequently, samples were normalized to a total protein concentration of 2 mg/mL, prior to assessment of the level of IL-17 cytokine family members. Protein levels of IL-17F were measured by ELISA, using the Human IL-17F DuoSet ELISA Kit (R&D Systems, Minneapolis, MN, USA). The MSD platform (Meso Scale Discovery, Rockville, MD, USA) was used for measurement of IL-17A/F and IL-17E (Human U-PLEX, individual assay for IL-17A/F and IL-17E) and IL-17A and IL-17C (Human U-PLEX, multiplex assay). All analyses were performed according to the manufacturer's instructions. Protein concentrations (unit: pg/mL) were quantified according to a standard

curve prepared using a similar skin matrix. Subsequently, protein levels in the skin biopsy were expressed as picograms per milligram of total tissue protein (pg/mg tissue protein) after total protein normalization, which is calculated as protein concentration (pg/mL) divided by the tissue total protein concentration (unit: mg protein/mL) of each protein sample. Finally, the protein levels were adjusted for each protein recovery efficiency. Limit of detection and protein recovery efficiencies for IL-17A, IL-17AF, IL-17C, IL-17E and IL-17F were estimated as: 7.5 pg/mL, 7 pg/mL, 10 pg/mL, 2.3 pg/mL and 8 pg/mL and 65%, 90%, 75%, 35% and 25%, respectively. Values are shown as means with lower and upper hinges corresponding to 25th and 75th percentiles. Statistical analysis was performed using a linear mixed-effects model.

Isolation of primary human epidermal keratinocytes

Human primary epidermal keratinocytes were isolated by enzymatic digestion of skin. In short, skin specimens were washed, trimmed for remaining subcutaneous fat and incubated with 2.4 U/mL dispase (Sigma, #d4693) overnight at 4°C to separate the epidermis from the dermis. The epidermis was collected and incubated with trypsin/EDTA at 37°C for 15 min to release keratinocytes into a single cell suspension. After addition of trypsin neutralizer, cells were collected by centrifugation and seeded in collagen-coated tissue culture plates (Thermo Fisher Scientific, #10408453) for expansion.

PBMC response to IL-17E stimulation

Peripheral blood mononuclear cells (PBMC) were isolated from buffy coat fractions by means of density gradient centrifugation using the density gradient medium Lymphoprep™ (STEMCELL Technologies, Vancouver, Canada) according to the manufacturer's instructions. Briefly, 20 mL of blood diluted in PBS (1:1 dilution) was layered in the upper chamber of a

Lymphoprep™ tube over the lower Ficoll-Paque-containing chamber. The filled Lymphoprep™ tube was centrifuged as per manufacturer's instructions. The PBMCs were then collected from the interface between Lymphoprep™ and plasma in the upper chamber, washed in fresh PBS and finally resuspended in RPMI 1640 media (Gibco, Life Technologies, Minneapolis, MN, USA), containing 2 mM L-glutamine (GlutaMAX, Gibco, Life Technologies), 10 ng/mL rhIL-2 and 100 µg/mL penicillin/streptomycin (Gibco, Life Technologies) at a concentration of $4x10^6$ cells/mL. Cells were seeded in 96-well round-bottom plates (50 µL of cell suspension for a final cell concentration of $2x10^5$ cells per well) and cultured at 37ºC in 5% CO_2 for 6 days in presence or absence of 1 ng/mL of IL-17E. At termination, supernatants from *in vitro* PBMC cultures were harvested and assessed for levels of IL-5 by using the MSD assay kit U-PLEX® Biomarker Group 1 (Human). The lowest limit of detection (LLOD) was determined as 1.7 pg/mL

Gene array & Statistical analyses

RNA was extracted from ex vivo cultured human skin biopsies using the mirVana kit (Life Technologies) according to the manufacturer's instructions and Precellys® 24 bead-based homogenizer (Precellys® Bertin Technologies, France) for the mechanical lysing of the tissue. Samples used for gene expression profiling passed the QC criteria of RNA integrity (RIN) >7.

Gene expression profiling of ex vivo cultured human skin biopsies was carried out on whole-transcript arrays (GeneChip™ Human Gene 2.1 ST Array, Thermo Fisher Scientific). Quality control of the raw CEL files was performed by visual inspection of pseudo images, and by using the R/arrayQualityMetrics package[1]. Summarization, background correction and normalization were performed using the packages R/oligo::rma[2], R/affy[3], R/preprocessCore[4]. Differential expression analysis was performed using the R/limma package[5], with annotations

based on the packages R/biomaRt[6,7], R/AnnotationDbi[8] and R/ hugene21sttranscriptcluster.db[9]. Downstream visualizations of the results were performed using R/ggplot2[10]. Further we applied R/stringr[11] and R/dplyr[12], for general data processing, and R/psych[13] and R/corrplot[14] for correlation analysis and plotting. All statistical data analyses were carried out in the statistical computing environment R (R Core Team 2019) in the RStudio IDE (RStudio Team 2015).

The DE analysis was performed with the respective contrasts stimulated versus unstimulated, using the moderated t-test of the R/limma package[5]. Correlation analysis of $\log_2$ transformed fold changes ($\log_2$FCH) was carried out using the Pearson correlation coefficients (r) of the R/psych[13] package.

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