037 CD4+CD103+ cutaneous TRM cells are found in the circulation of healthy humans
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Tissue-resident memory T cells (TRM) persist locally in non-lymphoid tissues where they provide
front-line defense against recurring insults. TRM at barrier surfaces express the markers CD103 and/or CD69 which function to retain them in epithelial tissues. In humans, neither the long-term migratory behavior of TRM nor their ability to re-enter the circulation and potentially migrate to distant tissue sites have been investigated. Using tissue explant cultures, we found that CD4+CD69+CD103+ TRM in human skin can downregulate CD69 and exit the tissue. Additionally, we identified a skin-tropic CD4+CD69+CD103+ population in human skin. This compartment is transcriptionally similar to the cutaneous CD4+CD103+ TRM population in the skin. Using a skin xenograft model, we confirmed that a fraction of the human cutaneous CD4+CD103+ TRM population can re-enter circulation, and migrate to secondary human skin sites where they re-assemble a TRM phenotype. Thus, our data challenge current concepts regarding the strict tissue compartmentalization of CD4+ T cell memory in humans.

038 A distinct Th17 cell subset producing IL-26 promotes expression of IL-17 in the skin through induction of TGFβ
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Chronic plaque-type psoriasis is a Th17 disease driven by IL-17. In addition to IL-17, Th17 cells also secrete IL-26, a member of IL-10 cytokines which induces TGFβ production. Here, we investigated whether IL-26-producing Th17 cells might be involved in IL-26-producing and IL-17-producing Th17 cells is unknown. By comparing the production of IL-26 and IL-17 in acute and chronic forms of psoriasis, we found a dichotomous expression of this cytokine by T cells. Immunofluorescence analysis of skin lesions showed increased numbers of IL-26-producing T cells with few IL-17-producing T cells in acute psoriasis, including erythrodermic and guttate psoriasis, whereas large numbers of IL-17-producing T cells and few IL-26-producing T cells characterized chronic plaque psoriasis. T cell receptor (TCR) analysis revealed a co-localized pool of Th17 cells that contained a subset of IL-26-producing T cells that was distinct from IL-17-producing T cells. Their differentiation from naive T cells was more rapid and did not require TGFβ contrary to IL-17-producing T cells, indicating that IL-26-producing T cells was a more efficient early differentiating subset of Th17 cells. Interestingly, IL-26 was able to induce TGFβ expression in keratinocytes, suggesting that IL-26-producing T cells drive the subsequent generation of IL-17-producing T cells via TGFβ induction in the skin. Together, our findings indicate that IL-26 producing T cells are an early differentiating subset of Th17 cells that promote induction of IL-17 producing T cells in the skin through TGFβ induction, providing new insights and potential therapeutic targets to block the pathogenic IL-17 pathway in psoriasis.

039 Transcriptome profiling of laminin α3 inhibited primary keratinocytes reveals the regulatory effect of laminin α3-binding on keratinocyte differentiation
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Primary keratinocytes were grown in serum free, low calcium media to subconfluence are then treated for 24 hours with a mouse monoclonal IgG1 antibody specific to human Lm α3 (laminin-α3, P3H-2, isotype controls in triplicate. Following treatment, RNA was extracted and sequenced via Illumina HiSeq 10120. A mean of 272,782 clean reads were attained, with mean percentage ≥20 of 94.2. Filtered clear reads were mapped to the reference genome using HISAT2, yielding a median of 52,145,921 (95%) mapped reads per sample. Reads were normalized to the number of mapped reads (Fractions Per Kilobase of transcript per Million mapped reads). We used DESeq to analyze differentially expressed genes, using a fold change ≥2 and false discovery rate < 0.01 as screening criteria. We also performed GO analysis to identify enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. Blockade of Lm α3 resulted in 3,394 differentially expressed genes. GO analysis demonstrated significant impact on epidermis and skin development, extracellular structure formation, extracellular matrix organization, keratinocyte differentiation, and cornification. RT-PCR was used to confirm several differentially expressed genes from RNA-seq experiments. We further investigated specific genes differentially expressed in various keratinocyte processes. We noted significant upregulation of desmosomal genes (DSP, DSC1, DSC3, DSG1, DSG3, KRT15, KRT17, KRT18, KRT19, and KRT20) and bullous pemphigoid pa-

040 Pathogenicity of anti-desmoglein 3 IgA1 autoantibodies is Fc-dependent in IgA pemphigus
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IgA pemphigus is an autoimmune blistering skin disease characterized by tissue-bound and circulating IgA, but not IgG, autoantibodies (autoAbs) against epidermal cadherins. Patients present with vesiculopustular skin eruptions, intradermal acantholysis and neutrophilic infiltrates. We cloned anti-DsG3 (Dsg3) monoclonal antibodies (mAbs) from an active IgA pemphigus vulgaris (IgA PV) patient, as confirmed by direct immunofluorescence (IF) microscopy. We analyzed serum anti-DsG3 IgA binding, isolated single-chain variable fragments (scFvs) bound to Dsg3 by ELISA and IF, and sera from the same patient and from unrelated active IgA/G/PV patients lacked binding to decreased binding of our scFvs, indicating binding to similar epitopes as polyclonal IgA/G serum autoAbs. In human skin organ culture, our mAbs showed dose-dependent pathogenicity, indicating that IgA PV anti-DsG3 IgA mAbs are necessary but insufficient for disease induction alone, because concurrent inactivation of Dsg3 was required in our models, but absent in the patient. Additional Fc-dependent mechanisms potentially involved were then studied in an in vivo model, using recombinant human full-Fc anti-DsG3 mAbs in the IgA1/IgA1a format: Incubation of skin cryosections with a full anti-DsG3-IgA1 mAb and peripheral polymorphonuclear cells led to intradermal acantholysis, whereas the same mAb in the IgA1 format was ineffective. We present compelling evidence demonstrating that interactions of the anti-DsG3 IgA1a-Fc part with its receptor is required and sufficient for pathogenicity in IgA pemphigus, without necessitating inactivation of compensatory Dsg3. Blocking this interaction may be a well suited therapeutic avenue for this difficult-to-treat skin disorder.

041 Simple and sensitive assays to detect autoantibodies against alpha 2 macroglobulin-like 1 in paraneoplastic pemphigus sera
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Paraneoplastic pemphigus (PNP) is a rare and severe variant of pemphigus associated with an underlying malignancy and poor therapeutic outcome. PNP is characterized by the presence of autoantibodies against a broad spectrum of desmoclonal components, additionally more than 50% of patients also have antibodies against the extracellular protease inhibitor alpha 2 macroglobulin-like 1 (A2ML1). A2ML1 expression in the epidermis is restricted to the granular layer and its biological function is still unknown. The detection of anti-A2ML1 anti-

042 MDAS+ dermatomysitis is associated with stronger skin type I interferon transcriptional signature with up-regulation of IFN-κ transcript
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MDAS+ dermatomyositis is an auto-immune disease that affects skin and muscles. The expression of interferons. Interestingly, IFIT2, CXCL10 and IFIH1 gene was the only interferon significantly elevated in MDAS+ DM, we showed using MxA immunohistochemistry that MDA5+ DM clustered independently according to the serology, indicating distinct molecular profiles. Herein, we assessed the global gene expression in the skin of 3 MDA5+ DM and 3 MDA5− DM samples expressed more MxA in inflammatory infiltrate than MDA5− skin samples. The transcriptionic signature of DM is characterized by a type I interferon (IFN) signature which has been shown to correlate with disease activity. Among autoantibodies, anti-Melanoma differentiation-associated gene 5 (MDAS+) antibodies are associated with a unique presenta-