058
[18F]FDG PET/CT-based imaging method to characterize the therapeutic effects of DMF in EAE
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Data from clinical and preclinical studies have shown that fumarates like dimethylfumarate (DMF) - by suppressing the Th17 response - improve psoriasis and multiple sclerosis in human and experimental autoimmune encephalomyelitis (EAE) in mice. In our previous studies, we analyzed the anti-inflammatory effects of DMF on the immune response by methodologies like intracellular cytokine staining and flow cytometry or by performing quantitative mRNA expression from isolated cells. Here we aimed to establish an in vivo method to follow T cell activation and cytokine production. For this purpose, we developed a PET/CT imaging data was analyzed by region of interest (ROI)-based methodology and validated by biodistribution studies and ex vivo mRNA expression analysis. Our findings show that the [18F]FDG and PET/CT-based imaging methodology can be used to characterize the effects of therapeutic compounds in the disease course of actively induced EAE in mice.

059
Characterization of a novel patient-derived antibody with sequence homology to antibodies directed against both desmosomal and non-desmosomal targets in pemphigus vulgaris
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Pemphigus is a primary autoantigenic targets in Pemphigus vulgaris (PV) have been considered to be the keratinocyte-associated adherens proteins desmoglein 3 (Dsg3) and Dsg1. We, and others have shown that PV patients additionally harbor autoantibodies to several non-Dsg antigens, including thyroid peroxidase (TPO). However, there remain major gaps in our current understanding of the specificity, efficiency, and functionality of non-Dsg autoantibodies present within and across individual PV patients. To investigate the broader repertoire of B-cell derived autoantibodies in PV we utilized Immune Repertoire Capture (IREC) technology to profile the B cell repertoire of undiluted PV sera against keratinocytes and elsewhere in vivo and to deliver fully human, recombinant monoclonal antibodies (mAb) isolated directly from patients. Utilizing plasmablasts from a PV patient in active disease, we identified and isolated a series of B cell receptor sequences that clustered in clonal antibody families. One of these, AB016313, was found to bear 74% heavy chain identity to the TPO antibodies and 86% light-chain homology to an anti-desmosome antibody as per BLAST alignment. This antibody did not bind to Dsg3 or Dsg1, did not stain intercellular regions on monkey esophagus by IFE, and did not bind TPO protein by Western Blot. However, AB016313 did bind a 55-kDa protein in HuCaT keratinocyte lysates. Moreover, immunofluorescence revealed a cytoplasmic target within HuCaT keratinocytes but no co-localization with the cell membrane or any component thereof (including Dsg1). While we have yet to identify the identity of this antigen, our data demonstrate the possibility of preventing sensitization and relapses of CD by an immune-suppressive method targeting a non-Dsg target within keratinocytes in an active PV patient. The availability of this renewable patient-derived mAb will be useful in future systematic studies of specificity and function of non-Dsg autoantibodies in PV.

060
Delivery of contact sensitizers and neurokinin 1 receptor antagonists by microneedle arrays targets different skin cells to abrogate contact dermatitis
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The development of contact dermatitis (CD) relies on innate and adaptive immunity that promote the activation of CD4 T helper 1 (Th1) and CD8 T cells, death of activated Th1 and Tc1 cells, decreased IFN-γ (polyclonal) or OVA OT1 and OT2 (monoclonal) models showed expansion of regulatory T cells, death of activated Th1 and Tc1 cells, decreased IFN-γ and, increased IL-10 in skin draining lymph nodes. Together these results established a significant diminished number of CD4 T cells homing in the skin after re-exposure to OVA or DNCB. Our data demonstrate the possibility of preventing sensitization and relapses of CD by an immune-suppressive method based on restraining neuroinflammation during skin Ag penetration.

061
Tissue DC antigen capture is selectively regulated by type II interferon
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DCs are specialized antigen-presenting cells that serve as essential mediators of immunity and tolerance. DCs mature from bone marrow precursors, that exit the bone marrow, circulate through the blood and secrete lymphoid organs, and non-lymphoid organs such as the skin, forming a network of poised sentinel. It remains unknown how maturation and the distribution of DCs across tissues and lymphoid organs occurs in vivo. We previously reported a highly conserved program of semi-maturation occurs during DC (and other myeloid) development from the bone marrow out to the tissue, and upon migration from the tissue to the draining LN. We identified IFNγ as a likely instructive cue. This study aimed to further understand the development and functional behavior of DCs during this developmental trajectory. Using 11-color multi-parametric flow cytometry to distinguish DC subsets and subsets, we found that IFNGR1 expression varies during the course of differentiation with IFNGR1 levels largely dictated by both location and DC maturation status in most sites. Because transcriptome analysis of IFNGR1 +/- vs WT might revealed differences in molecules associated with antigen processing and presentation, we tested antigen uptake ability in vivo by testing anti-DEC205 antigen capture. Fluorescent anti-DEC205 antibody capture in WT, IFNGR1-/-, IFNGR1-/-IFNAR1-/- and IFNAR1-/- mice was compared. We did not see significant differences in the in vivo antigen capture by miDCs derived from WT and IFNAR1-/- mice. However, we identified enhanced early capture of anti-DEC205 in IFNGR1-/- and IFNGR1-/-IFNAR1-/- mice, suggesting the specific regulation of antigen capture by type II IFN (IFNγ) signaling. Future studies in our lab will further interrogate the molecular mechanisms involved in how IFNγ/IFNGR1 signaling conditions DC development and function in tissues.

062
Therapeutic effects of Smad7-based protein on imiquimod-induced psoriatic lesions
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Smad7 structurally consists of N- and C- terminal domains linked with a PY motif. Its shuttles between the cytoplasm and nucleus. This domain contains different biological functions. Smad7 is overexpressed in epidermis of clinical psoriatic lesions, which was thought to contribute to epidermal hyperplasia in psoriasis. To address if this is the case, we assessed the role of Smad7 in its functional domains in IMQ-induced psoriatic pathogenesis using genetic and pharmacological approaches. K5.Smad7 mice, which express Smad7 in epidermis of clinical psoriatic lesions, which was thought to contribute to epidermal hyperplasia in psoriasis. To address if this is the case, we assessed the role of Smad7 in its functional domains in IMQ-induced psoriatic pathogenesis using genetic and pharmacological approaches. K5.Smad7 mice, which express Smad7 in epidermis of clinical psoriatic lesions, which was thought to contribute to epidermal hyperplasia in psoriasis. To address if this is the case, we assessed the role of Smad7 in its functional domains in IMQ-induced psoriatic pathogenesis using genetic and pharmacological approaches. K5.Smad7 mice, which express Smad7 in epidermis of clinical psoriatic lesions, which was thought to contribute to epidermal hyperplasia in psoriasis. To address if this is the case, we assessed the role of Smad7 in its functional domains in IMQ-induced psoriatic pathogenesis using genetic and pharmacological approaches.