001 Genome-wide association study of acne inversa in a multi-ethnic cohort
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Acne inversa, also known as hidradenitis suppurativa (HS), is a neglected, prevalent, chronic, stigmatizing, and debilitating inflammatory skin disease. HS patients suffer from deep, painful, recurrent abscesses that drain malodorous fluid and lead to disfiguring scars that can limit mobility of the arms and legs. People with African ancestry have a more than two-fold increased risk of HS. A lack of effective therapies and limited knowledge about HS pathogenesis contribute to unmet needs. Unlike other common inflammatory skin diseases, there has never been a genome-wide association study (GWAS) conducted for HS. We performed a GWAS of HS using data obtained from the electronic Medical Records & Genomics (eMERGE) network of electronic health record linked biorepositories. Cases were identified by the presence of at least one diagnosis code for HS (ICD-9 705.83). Controls were identified by the absence of any record of any immune mediated disease as defined by 28,419 ICD codes. Our final cohort consisted of 455 HS cases and 1,178 controls with comparable multi-ethnic ancestry.

Principal component analysis was used to estimate ancestry from a set of 40,156 SNPs. Our analysis showed the presence of at least one diagnosis code for HS (ICD-9 705.83). Controls were identified by the absence of any record of any immune mediated disease as defined by 28,419 ICD codes. Our final cohort consisted of 455 HS cases and 1,178 controls with comparable multi-ethnic ancestry."

002 The impact of Fc-binding proteins on IgG targeting BP180
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Pemphigus is a chronic autoimmune bullous diseases characterized by the production of antibodies against desmogleins (desmoglein 1 and 3). Antibody-producing cells are usually developed and activated in the germinal centers of secondary lymphoid organs such as lymph nodes and spleen. Ectopic lymphoid structures (ELSs) resembling the germinal centers have been recognized at inflamed tissues of various infectious or autoimmune diseases; however, the ELSs have been underdetected in the skin lesions of autoimmune bullous diseases including pemphigus. We firstly identified the skin ELSs in the chronic lesions of pemphigus with pemphigus. We found tight clusters of B and CD4+ T cells in the dermis of chronic blistering skin lasting at least 4 months from the patients with pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus. The clusters in the dermis contain perivascular node addressin’’’s vessels which are only observed in secondary lymphoid organs. Furthermore, lymphoid nodules targeted a type-2 response (IL-4, IgG), that is progressively balanced by an accumulation of Tregs and the production of counter-regulatory cytokines (IL-10, IL-17) and specific IgG1/IgG2a. Alternatively, we observed that skdCs target Langerhans cells, dermal conventional DC1 and DC2; retain their capacity to capture OVA in the skin and to migrate towards draining lymph nodes during EPIT. However, their activation status and stimulatory properties were progressively hampered, as shown by (i) weaker CD86 and CD40 expression in OVA+ DCs and (ii) the significant drop of OVA-specific T cells priming after 8 weeks of treatment. In conclusion, we recorded Tregs progression triggered by prime CD4+ T effector cells (Teffs) upon EPIT, but gained Treg stimulatory properties. We are currently investigating the mechanisms by which each skin DC subset subverts the contribution of pathogenic type-2 immunity to prevent the development of allergic symptoms. Taken together, our results open new avenues to better understand the complex mechanisms that lead to the efficacy of EPIT.

003 Aging alteration of skin T cells is different from that of blood T cells
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Aging alteration of skin T cells is different from that of blood T cells. Here, T cell density, diversity and function was assessed in 91 skin specimens and 97 blood samples from Japanese and Swedish subjects of different ages. Aging did not affect the density of T cells both in blood and skin but the frequency of epidermal T cells, particularly CD4+ CD8+ T cells, increased in elderly individuals. Furthermore, in CD8+ T cells, the ratio of n=0.062 in epidermis. To investigate the functional anti-pathogen activity of T cells in blood and skin, heat-killed Staphylococcus aureus and Candida albicans antigens were either co-cultured with PBMCs or injected to the resected skin specimens. Pro-inflammatory cytokine production from T cells were maintained in skin but declined in the blood of elderly individuals (e.g. IL-17A production in CD4+ T cells in blood: p=0.0154, in skin: p=0.3319). T-cell diversity was also evaluated by sequencing of genomic CDR3 in T cells. Over 60% of skin TCR clones were found as single copies and this ratio did not decline as individuals age (p=0.5756). The occupancy of top 10 most frequently-detected TCR clones in the total clones was high in blood, not in skin, of elder individuals (% occupancy of top 10 clones: 20-49 y.o. vs 50-79 y.o.; p=0.0299 in blood, p=0.1252 in skin), suggesting that T cells in blood, but not in skin, of elderly subjects become oligoconal with expansion of limited clones. Our findings demonstrate that skin T cells maintain diversity and protective cytokine production in elderly individuals despite reduced T-cell diversity and function in blood.

004 Ruxolitinib Cream Suppresses Inflammation in Adult Mild to Moderate Psoriasis Patients
MD Howell and H Liu Translational Research, Incyte Research Institute, Wilmington, DE A patient with psoriasis is considered to have mild to moderate disease if their skin disease characterized by significant cutaneous and systemic inflammation which negatively affects the quality of life. Specifically, psoriasis patients have elevated levels of Th1 associated cytokines and increased down-stream signaling in lesional skin and circulating blood. Ruxolitinib cream (Rux Cream) is a potent, topically applied, selective inhibitor of JAK1 and JAK2 of the JAK-STAT signaling pathway. Treatment with Rux Cream was associated with significant therapeutic benefit in mild to moderate psoriasis patients. This study investigated the effects of Rux Cream on inflammatory mediator expression in circulation. Sera from 22 subjects (n=5-0.5% BID, n=1-1.5% QD, and n=12-1.5% BID) in an open label Phase 2a study (NCT00617994) and 143 subjects (n=33 vehicle, n=16-0.5% QD, n=39-1.0% QD, and n=35-1.5% QD) in a dose range finding Phase 2b study (NCT010778700) were analyzed for a panel of pro-inflammatory cytokines and chemokines. The ratio of n=0.342 in skin, of elder individuals (% occupancy of top 10 clones: 20-49 y.o. vs 50-79 y.o.; p=0.0299 in blood, p=0.1252 in skin), suggesting that T cells in blood, but not in skin, of elderly subjects become oligoconal with expansion of limited clones. Our findings demonstrate that skin T cells maintain diversity and protective cytokine production in elderly individuals despite reduced T-cell diversity and function in blood.

005 Ectopic Lymphoid Structures Harbor Desmoglein-Specific B Cells in the Chronic Skin Lesions of Patients with Pemphigus
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Pemphigus is a chronic autoimmune bullous diseases characterized by the production of autoantibodies against desmogleins (desmoglein 1 and 3). Antibody-producing cells are usually developed and activated in the germinal centers of secondary lymphoid organs such as lymph nodes and spleen. Ectopic lymphoid structures (ELSs) resembling the germinal centers have been recognized at inflamed tissues of various infectious or autoimmune diseases; however, the ELSs have been underdetected in the skin lesions of autoimmune bullous diseases including pemphigus. We firstly identified the skin ELSs in the chronic lesions of pemphigus with pemphigus. We found tight clusters of B and CD4+ T cells in the dermis of chronic blistering skin lasting at least 4 months from the patients with pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus. The clusters in the dermis contain perivascular node addressin’’’s vessels which are only observed in secondary lymphoid organs. Furthermore, lymphoid nodules targeted a type-2 response (IL-4, IgG), that is progressively balanced by an accumulation of Tregs and the production of counter-regulatory cytokines (IL-10, IL-17) and specific IgG1/IgG2a. Alternatively, we observed that skdCs target Langerhans cells, dermal conventional DC1 and DC2; retain their capacity to capture OVA in the skin and to migrate towards draining lymph nodes during EPIT. However, their activation status and stimulatory properties were progressively hampered, as shown by (i) weaker CD86 and CD40 expression in OVA+ DCs and (ii) the significant drop of OVA-specific T cells priming after 8 weeks of treatment. In conclusion, we recorded Tregs progression triggered by prime CD4+ T effector cells (Teffs) upon EPIT, but gained Treg stimulatory properties. We are currently investigating the mechanisms by which each skin DC subset subverts the contribution of pathogenic type-2 immunity to prevent the development of allergic symptoms. Taken together, our results open new avenues to better understand the complex mechanisms that lead to the efficacy of EPIT.

006 Skin Dendritic Cells Progressively Subvert The Activation Of Pathogenic Type-2 Immunity Upon Epicutaneous Allergen Immunotherapy
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