Genome-wide association study of acne inversa in a multi-ethnic cohort

A Khan1, MG Hayes2, J Connolly3, 4, F Mench1, F Pelean1, 5, H Hakanson6, 7, J Denny1, GM Hrivnak1, 4, J Potthoff1, 4 and 5, Northwestern University, New York, NY, 2 Northwestern University, Chicago, IL, 3 Children’s Hospital of Philadelphia, Philadelphia, PA, 4 University of Pennsylvania, Philadelphia, PA and 5 Vanderbilt University, Nashville, TN

Acne inversa, also known as hidradenitis suppurativa (HS), is a neglected, prevalent, chronic, inflammatory skin disease of the skin. 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 as having no record of any immune mediated disease as defined by 28,419 ICD codes.

Principal component analysis was used to estimate ancestry from a set of 40,156 SNPs. Our approach for genome-wide significance (p < 5x10^-8). The p-values were compared with thresholds for five principle components and run using PLINK (v1.9). Six loci approached the threshold for genome-wide significance (p < 5x10^-8), with p-values that ranged between 2.0x10^-5 and 9.9x10^-7, and effect estimates (2.36-OR:1.41) that suggest a moderate expansion in sample size will allow us to exceed genome-wide significance. There was no evidence for HLA association supporting classification of HS as inflammatory rather than autoimmune. Our group is constructing multi-ethnic replication cohorts that will allow us to expand this study in the near future.

The impact of Fc-binding proteins on IgG targeting BP180

H Iwata1, M Kamaguchi2, H Ujije1, K Natsuga1, W Nishie1 and H Shimizu1
1 Dermatology, 2 Oral Diagnosis and Medicine, Hokkaido University Graduate School of Dental Medicine, Sapporo, Japan

Ectopic Lymphoid Structures Harbor Desmoglein-Specific B Cells in the Chronic Skin Lesions of Patients with Pemphigus

H Koguchi-Yoshida1, 2, E Hoffer3, S Cheuk1, Y Matsumura1, S Vu1, Y Fujisawa2, M Fujimoto1, L Libon1, R Clark4 and R Watanabe2
1 Dermatology, University of Tsukuba, Tsukuba, Japan, 2 Dermatology, Brigham and Women’s Hospital, Boston, MA

Human skin contains a large number of T cells many of which display markers associated with resident memory T cells (Tres). TRes can stay in the same site for long periods and are superior to recirculating T cells in their ability to initiate local barrier protection against pathogens. The skin barrier is challenged through life and T cell functionality may change with time. Here, T cell density, diversity and function was assessed in 91 skin specimens and 79 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+ TCRdupTres, increased in elderly individuals. In CD8+ T cells, CD28p0.0062 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 oligo-oligonal 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.

Ruxolitinib Cream Suppresses Inflammation in Adult Mild to Moderate Psoriasis Patients

MD Howell and H Liu Translational Research, Incyte Research Institute, Wilmington, DE

Ruxolitinib cream (Rux Cream) is a potent, topically applied, selective inhibitor of JAK1 and JAK2 of the Jak-STAT 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=5.05% BID, n=5.1% BID, and n=12.15% BID) in an open label Phase 2a study (NCT00617994) and 143 subjects (n=33 Vehicle, n=15.0% QD, n=39.1% QD, and n=15.1% QD) in a dose range finding Phase 2b study (NCT00778700) were analyzed for broad proteomic changes following treatment. Paired t-tests were used to establish significant changes within treatment groups at a cutoff of p<0.05. Expression of 1010 proteins was evaluated for each subject. In the Phase 2a study, 99 proteins were significantly modulated between baseline and week 4 (from all 22 subjects). In the Phase 2b study, 19 proteins were modulated between baseline and week 4 in the 0.5% QD, 65 proteins in 1.0% QD, and 34 proteins in 1.5% QD compared with 9 proteins in the vehicle cohort. Interestingly, peptidase inhibitor 1 (P3), elafin, skin-derived antitryptase antitryptase [SKALP], a potential inflammatory marker in psoriasis, was significantly down-regulated in all Rux Cream treated cohorts across both Phase 2 studies. Additionally, IL-17A and kallikrein related peptide 8 (KLK8) levels were significantly reduced in all subjects from the Phase 2a study and those treated with 1.5% QD in the Phase 2b. The results from these studies suggest that topical treatment with Rux Cream has the potential to modulate disease pathogenesis by reducing the circulating levels of disease-related inflammatory markers during the course of treatment.

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

L Lasch1, 2, H Sanders1, 2, MC Monsieur1, 2, J Nicolas1, 2, V Drezek1, 2 and M Vocomson1
1 CIRM - INSERM U1111, ENS de Lyon, UCB1, CNRS UMR 5308, Lyon, France and 2 DBV Technologies, Montreuil, France

Dendritic cells (DCs) play a critical role in the activation of inflammatory cells via Fc-receptors. However, little is known about the impact of Fc-binding proteins, other than Fc-receptors, on the pathogenicity of skin diseases characterized by significant cutaneous and systemic inflammation which negatively affects the quality of life. Specifically, psoriasis patients have elevated levels of Th17 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 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=5.05% BID, n=5.1% BID, and n=12.15% BID) in an open label Phase 2a study (NCT00617994) and 143 subjects (n=33 Vehicle, n=15.0% QD, n=39.1% QD, and n=15.1% QD) in a dose range finding Phase 2b study (NCT00778700) were analyzed for broad proteomic changes following treatment. Paired t-tests were used to establish significant changes within treatment groups at a cutoff of p<0.05. Expression of 1010 proteins was evaluated for each subject. In the Phase 2a study, 99 proteins were significantly modulated between baseline and week 4 (from all 22 subjects). In the Phase 2b study, 19 proteins were modulated between baseline and week 4 in the 0.5% QD, 65 proteins in 1.0% QD, and 34 proteins in 1.5% QD compared with 9 proteins in the vehicle cohort. Interestingly, peptidase inhibitor 1 (P3), elafin, skin-derived antitryptase antitryptase [SKALP], a potential inflammatory marker in psoriasis, was significantly down-regulated in all Rux Cream treated cohorts across both Phase 2 studies. Additionally, IL-17A and kallikrein related peptide 8 (KLK8) levels were significantly reduced in all subjects from the Phase 2a study and those treated with 1.5% QD in the Phase 2b. The results from these studies suggest that topical treatment with Rux Cream has the potential to modulate disease pathogenesis by reducing the circulating levels of disease-related inflammatory markers during the course of treatment.

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