I14 Involvenc deficiency results in decreased D receptor-mediated inflammation and Cerke isoform bias
AD Schrader, P. Smith, L. Gavrilova, C. Dunn, M. Goldman and C. De Guzman Strong Dermatology, Washington University in St Louis School of Medicine, St Louis, Missouri, United States
We previously identified increased involvenc (IVL) expression for human skin barrier evolution. The IVL is known to reduce the function of involucrin in adult and newborn IVL- mice. We investigated the inflammatory responses in adult mice using the MC903 (vitamin D agonist) inducible model for atopic dermatitis. Unexpectedly, IVL- mice exhibited reduced ear thickness compared to WT mice (p<0.01). Underlying this decrease ear inflammation was a comprehensive decrease in thymic stromal lymphopoietin (TSLP) expression in IVL- treated ears. Flow cytometry analysis to determine innate and adaptive immune cell phenotypes identified a notable decrease in CD4+ T cell infiltrate in IVL- mice. We investigated the role of involucrin in a mechanistic evaluation of the high MC903-induced inflammation and identified reduced vitamin D receptor (VDR) expression in IVL- versus WT skin. Thus far, we have identified a new phenotype for IVL- mice with reduced VDR-mediated inflammation and decreased adaptive CD4+ T cell response as a result of decreased VD. We further examined the impact of involucrin on epidermal metabolic processes using a comprehensive multi-omics approach (ATAC-seq, RNA-seq, and LC/MS proteomics) to determine chromatin accessibility, transcriptomic, and protein changes in IVL- and WT newborn epidermis (p<0.05). Invovlenc was identified at the intersection of all three datasets, thus demonstrating the validity and rigor of the approach. Five potential targets at the intersect of ADAC-seq differentially accessible regions and LCMS differentially expressed proteins were determined. Of most interest, Cerke, known to regulate circadian clock, was found to have less accessible chromatin and reduced protein expression. DESeq analysis identified a bias for Cerke isoform transcripts in IVL- mice. Together our findings reveal a functional role for the evolutionarily selected involucrin to regulate VDR-mediated inflammation and potentially for the circadian response in the skin.

I16 SDR9C7 catalyzes the critical dehydrogenation of acylceramides for skin barrier formation
T Takeuchi, T Hirahayashi, Y Miyasaka, A Kawamoto, Y Yokono, S Taguchi, T Tanaka, T Sakata, T Roeglinger, D Watkinson, M Kono, M Mori, T Ishikawa, T Ohno, AR Brash and M Akiyama
1 Muro1, J Ishikawa3, T Ohno1, AR Brash6 and M Akiyama1, 2 Shi1, C Murase1, H Takama5, K Tanaka3, W Boeglin6, M Calcutt6, D Watanabe5, M Kono1, Y Gutman-Yassky1
The corneocyte lipid envelope, composed of covalently bound ceramides and fatty acids, is protective against dehydration. It is important for the integrity of the permeability barrier and its absence is a prime structural defect in various skin diseases associated with defective skin barrier function. SDR9C7 encodes short-chain dehydrogenase/reductase family 9C member 7 (SDR9C7). The gene Ivl is known to be associated with barrier function via its role in the synthesis of acyl-ceramides and lipid biosynthesis. In a patient with SDR9C7 mutation and in a mouse Sdr9c7-knockout model, we show that the loss of covalent binding of epidermal ceramides to protein appears as a structural fault in the barrier. For quantitative liquid chromatography epoxy-11 SDR9C7 Muro1, J Ishikawa3, T Ohno1, AR Brash6 and M Akiyama1, 2 Shi1, C Murase1, H Takama5, K Tanaka3, W Boeglin6, M Calcutt6, D Watanabe5, M Kono1, Y Gutman-Yassky1

I17 Ichthyosis transcriptome revealed increased atherosclerosis markers and immune and barrier differences amongst subtypes
M Kim1, D Mikhaylov1, M Sun1, K Malik1, HH e1, Y Renert-Yuval1, AB Pavel1, A Paller2 and E AD Schmidt, M Mathyer, E Brettmann and C de Guzman Strong Dermatology, Washington University in St Louis School of Medicine, St Louis, Missouri, United States
We previously identified increased involvenc (IVL) expression for human skin barrier evolution. The IVL is known to reduce the function of involucrin in adult and newborn IVL- mice. We investigated the inflammatory responses in adult mice using the MC903 (vitamin D agonist) inducible model for atopic dermatitis. Unexpectedly, IVL- mice exhibited reduced ear thickness compared to WT mice (p<0.01). Underlying this decrease ear inflammation was a comprehensive decrease in thymic stromal lymphopoietin (TSLP) expression in IVL- treated ears. Flow cytometry analysis to determine innate and adaptive immune cell phenotypes identified a notable decrease in CD4+ T cell infiltrate in IVL- mice. We investigated the role of involucrin in a mechanistic evaluation of the high MC903-induced inflammation and identified reduced vitamin D receptor (VDR) expression in IVL- versus WT skin. Thus far, we have identified a new phenotype for IVL- mice with reduced VDR-mediated inflammation and decreased adaptive CD4+ T cell response as a result of decreased VD. We further examined the impact of involucrin on epidermal metabolic processes using a comprehensive multi-omics approach (ATAC-seq, RNA-seq, and LC/MS proteomics) to determine chromatin accessibility, transcriptomic, and protein changes in IVL- and WT newborn epidermis (p<0.05). Invovlenc was identified at the intersection of all three datasets, thus demonstrating the validity and rigor of the approach. Five potential targets at the intersect of ADAC-seq differentially accessible regions and LCMS differentially expressed proteins were determined. Of most interest, Cerke, known to regulate circadian clock, was found to have less accessible chromatin and reduced protein expression. DESeq analysis identified a bias for Cerke isoform transcripts in IVL- mice. Together our findings reveal a functional role for the evolutionarily selected involucrin to regulate VDR-mediated inflammation and potentially for the circadian response in the skin.

I18 Effect of the antimicrobial peptide derived from insulin-like growth factor binding protein 5 on skin barrier regulation
H. Nguyen2, J. Vu Trujillo1, G. Peng2, H. Yue1, M. Takahashi1, R. Rautama1, Y. Umehara1, H. Ogawa1, S. Ikeda2, F. Nishiyama1, 2 Neeta (Allergy) Research Center, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan, 5 Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan and 3 Faculty of International Liberal Arts, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan
Background: A novel antimicrobial peptide derived from insulin-like growth factor binding protein 5 (AP-IBP5) displays both antimicrobial and immunomodulatory properties. AP-IBP5 is involved in the regulation of cutaneous immunity through cytokine/chemokine production and promotion of keratinocyte migration and proliferation. However, the role of AP-IBP5 in the associated with inflammatory disorders, including atopic dermatitis. The differentially expressed genes play roles in barrier function, adhesion, cytokine-receptor interactions, and cancer-associated pathways. Surprisingly, genes associated with AP-IBP5 showed variable regulation with age: NODAD and MIAF had weak negative correlations, whereas PINT and PVTL, components of the p53/Myc pathway, were enriched with age. Comparison to publicly available skin suction blister and dermal fibroblast aging datasets revealed a core set of genes. We conclude that skin aging is associated with the layer or embryonic origin on the cell. In contrast, AP-IBP5s were notably lineage specific and may represent a modality for cell-type specific targeting of the aging process. Given the finding of altered barrier function in aged human keratinocytes, these findings will be compared to psoriasis, atopic dermatitis, and ichthyosis, diseases in which barrier dysfunction contributes to pathogenesis.

I19 Proteomics and lipids indicate the protective mechanism of dietary n-3 PUFA supplementation for photaging
P. Wang, G. Yan, H. Xue, Y. Yao, C. Zhang and X. Wang
Institute of Photomedicine, Shanghai Skin Disease Hospital, Tongji University School of Medicine, Shanghai, China
The anti-photoaging effects of dietary n-3 polyunsaturated fatty acid (n-3 PUFA) supplementation have been well demonstrated in a variety of in-vivo and in-vitro models, and the underlying mechanism has been suggested to be related to the modulation of mitochondrial function, antioxidant activity, and the suppression of inflammatory responses. However, the precise mechanisms of action of dietary n-3 PUFA supplementation in counteracting skin photaging has become a new prime target in fighting photoaging. We previously identified increased involvenc (IVL) expression for human skin barrier evolution. The IVL is known to reduce the function of involucrin in adult and newborn IVL- mice. We investigated the inflammatory responses in adult mice using the MC903 (vitamin D agonist) inducible model for atopic dermatitis. Unexpectedly, IVL- mice exhibited reduced ear thickness compared to WT mice (p<0.01). Underlying this decrease ear inflammation was a comprehensive decrease in thymic stromal lymphopoietin (TSLP) expression in IVL- treated ears. Flow cytometry analysis to determine innate and adaptive immune cell phenotypes identified a notable decrease in CD4+ T cell infiltrate in IVL- mice. We investigated the role of involucrin in a mechanistic evaluation of the high MC903-induced inflammation and identified reduced vitamin D receptor (VDR) expression in IVL- versus WT skin. Thus far, we have identified a new phenotype for IVL- mice with reduced VDR-mediated inflammation and decreased adaptive CD4+ T cell response as a result of decreased VD. We further examined the impact of involucrin on epidermal metabolic processes using a comprehensive multi-omics approach (ATAC-seq, RNA-seq, and LC/MS proteomics) to determine chromatin accessibility, transcriptomic, and protein changes in IVL- and WT newborn epidermis (p<0.05). Invovlenc was identified at the intersection of all three datasets, thus demonstrating the validity and rigor of the approach. Five potential targets at the intersect of ADAC-seq differentially accessible regions and LCMS differentially expressed proteins were determined. Of most interest, Cerke, known to regulate circadian clock, was found to have less accessible chromatin and reduced protein expression. DESeq analysis identified a bias for Cerke isoform transcripts in IVL- mice. Together our findings reveal a functional role for the evolutionarily selected involucrin to regulate VDR-mediated inflammation and potentially for the circadian response in the skin.