LB1046
Keratinocyte metabolic reprogramming promotes self-RNA sensation by dendritic cells in psoriasis
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The maintenance of psoriasis as a skin-confined chronic inflammatory condition requires the abnormal activation of keratinocytes (KCs). Objectively, hyperproliferative epidermal keratinocytes and self-renewing immune cells. In this context, targeting metabolism of keratocytes is recently reported to be an approach for treating psoriasis, however whether and how the metabolic adaptations of keratinocytes introduce inflammatory cues are unknown. We report that in psoriatic lesions, Protein Phosphatase 6 (PP6) is diminished in the epidermis, and its levels negatively correlate with the disease severity. Mice with genetic deficiency of Pp6 in keratinocytes spontaneously develop psoriasis-like skin phenotype resembling psoriasis clinically, histologically, in its gene expression profile and in its response to therapy. Mechanistically, Pp6+ keratinocytes rely on inordinate urea cycle along with enhanced oxidative phosphorylation (OXPHOS) to hyper-polarize, mediated by increased Arginase-1 (Arg1) production resulting from the activation of CCAT/enhancer-binding protein beta (CEBPβ). Single-cell RNA-seq reveals the Arginine biosynthesis rate-limiting enzyme of PSK-complex contained in the pool of Arginase in psoriatic epidermis. Moreover, accumulated polyamines branched from urea cycle promote self-RNA-sensing by myeloid dendritic cells with the assistance of an RNA-binding peptide originated from heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1), a probable autoantigen in psoriasis, which directly links keratocyte hyper-proliferation to autoimmune responses. Targeting metabolic nodes of urea cycle in inqui-moD-injection may prime psoriasis-targeted metabolic inhibitors across the skin inflammation. Thus, our data reveal for the first time the molecular basis of an auto-inflammatory condition and the functional significance of target organ-intrinsic metabolic reprogramming in inflammation, bringing forth novel insights into the pathogenic and therapeutic strategies of chronic inflammatory disorders.

LB1048
TGF-β/Smad3 signaling pathway is required for epidermal Langerhans cells repopulation under inflammation condition but not for their homeostasis, maturation and migration in the steady state
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Langerhans cells (LCs) represent a subset of evolutionarily conserved dendritic cells (DCs) which are essential for induction of skin immunity and tolerance. They self-renew in the skin state at steady state, but could repopulate from peripheral blood Gr-1hi monocytes (DC) in skin, which are essential for induction of skin immunity and tolerance. They self-renew in the skin state at steady state, but could repopulate from peripheral blood Gr-1+ monocytes (DC). The role and mechanism of action for QRCSD in AD remained poorly understood. The study was designed to explore the underlying effects of the formula and identify the components accounting for the therapeutic effects in 2,4-Dinitrochlorobenzene (DNCB)-induced AD-like model of NC/Nga mice. Network pharmacological analysis first predicted the pharmacological and network pharmacological profile of QRCSD as well as UPLC-mass analysis identifying active components. QRCSD or prednisolone (positive control) was administered by gavage every other day over d14–d21. Dermatitis severity score and scratching behavior showed that oral administration of QRCSD markedly reduced the severity of dermatitis. The result was further confirmed that QRCSD treatment could relieve the manifestations of dermatitis, and pathology observation was designed to explore the therapeutic effects of QRCSD on AD. QRCSD markedly relieved the manifestations of dermatitis, and pathology observation was designed to explore the therapeutic effects of QRCSD on AD. QRCSD markedly reduced the severity of dermatitis. The result was further confirmed that QRCSD treatment could relieve the manifestations of dermatitis, and pathology observation was designed to explore the therapeutic effects of QRCSD on AD. BB

LB1047
Stat3 activation in epidermal keratinocytes induces Langerhans cells activation to form an essential circuit for psoriasis via IL-23 production

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Background: Psoriasis is an inflammatory disease associated with aberrant crosstalk between the epidermis and immune system. However, the role of Langerhans cells (LCs) in psoriasis remains controversial. Objectively, hyperproliferative epidermal keratinocytes and self-renewing immune cells. In this context, targeting metabolism of keratocytes is recently reported to be an approach for treating psoriasis, however whether and how the metabolic adaptations of keratinocytes introduce inflammatory cues are unknown. We report that in psoriatic lesions, Protein Phosphatase 6 (PP6) is diminished in the epidermis, and its levels negatively correlate with the disease severity. Mice with genetic deficiency of Pp6 in keratinocytes spontaneously develop psoriasis-like skin phenotype resembling psoriasis clinically, histologically, in its gene expression profile and in its response to therapy. Mechanistically, Pp6+ keratinocytes rely on inordinate urea cycle along with enhanced oxidative phosphorylation (OXPHOS) to hyper-polarize, mediated by increased Arginase-1 (Arg1) production resulting from the activation of CCAT/enhancer-binding protein beta (CEBPβ). Single-cell RNA-seq reveals the Arginine biosynthesis rate-limiting enzyme of PSK-complex contained in the pool of Arginase in psoriatic epidermis. Moreover, accumulated polyamines branched from urea cycle promote self-RNA-sensing by myeloid dendritic cells with the assistance of an RNA-binding peptide originated from heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1), a probable autoantigen in psoriasis, which directly links keratocyte hyper-proliferation to autoimmune responses. Targeting metabolic nodes of urea cycle in inqui-moD-injection may prime psoriasis-targeted metabolic inhibitors across the skin inflammation. Thus, our data reveal for the first time the molecular basis of an auto-inflammatory condition and the functional significance of target organ-intrinsic metabolic reprogramming in inflammation, bringing forth novel insights into the pathogenic and therapeutic strategies of chronic inflammatory disorders.

LB1049
Prolonged ex vivo exposure to the anti-p19 antibody tildrakizumab alters the profile of skin-resident T cells isolated from psoriatic skin
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Background: Psoriasis is an inflammatory disease associated with aberrant crosstalk between the epidermis and immune system. However, the role of Langerhans cells (LCs) in psoriasis remains controversial. Objectively, hyperproliferative epidermal keratinocytes and self-renewing immune cells. In this context, targeting metabolism of keratocytes is recently reported to be an approach for treating psoriasis, however whether and how the metabolic adaptations of keratinocytes introduce inflammatory cues are unknown. We report that in psoriatic lesions, Protein Phosphatase 6 (PP6) is diminished in the epidermis, and its levels negatively correlate with the disease severity. Mice with genetic deficiency of Pp6 in keratinocytes spontaneously develop psoriasis-like skin phenotype resembling psoriasis clinically, histologically, in its gene expression profile and in its response to therapy. Mechanistically, Pp6+ keratinocytes rely on inordinate urea cycle along with enhanced oxidative phosphorylation (OXPHOS) to hyper-polarize, mediated by increased Arginase-1 (Arg1) production resulting from the activation of CCAT/enhancer-binding protein beta (CEBPβ). Single-cell RNA-seq reveals the Arginine biosynthesis rate-limiting enzyme of PSK-complex contained in the pool of Arginase in psoriatic epidermis. Moreover, accumulated polyamines branched from urea cycle promote self-RNA-sensing by myeloid dendritic cells with the assistance of an RNA-binding peptide originated from heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1), a probable autoantigen in psoriasis, which directly links keratocyte hyper-proliferation to autoimmune responses. Targeting metabolic nodes of urea cycle in inqui-moD-injection may prime psoriasis-targeted metabolic inhibitors across the skin inflammation. Thus, our data reveal for the first time the molecular basis of an auto-inflammatory condition and the functional significance of target organ-intrinsic metabolic reprogramming in inflammation, bringing forth novel insights into the pathogenic and therapeutic strategies of chronic inflammatory disorders.

LB1050
Qing-Re Chu-Shi Decoction improves 2,4-dinitrochlorobenzene-induced Atopic Dermatitis-like Skin Lesions via Anti-inflammatory and Immune Regulation
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Atopic dermatitis (AD) is reported to be an allergic dermatitis characterized by eczematous lesions and pruritus. Qing-Re Chu-Shi Decoction (QRSCD) is the herbal formula long used as a complementary and alternative therapy for inflammatory skin diseases in China. However, the role and mechanism of action for QRSCD in AD remained poorly understood. The study was designed to explore the underlying effects of the formula and identify the components accounting for the therapeutic effects in 2,4-Dinitrochlorobenzene (DNCB)-induced AD-like model of NC/Nga mice. Network pharmacological analysis first predicted the pharmacological and network pharmacological profile of QRSCD as well as UPLC-mass analysis identifying active components. QRSCD or prednisolone (positive control) was administered by gavage every other day over d14–d21. Dermatitis severity score and scratching behavior showed that oral administration of QRSCD markedly reduced the severity of dermatitis. The result was further confirmed that QRSCD treatment could relieve the manifestations of dermatitis, and pathology observation was designed to explore the therapeutic effects of QRSCD on AD. BB

LB1051
A selective TYK2 inhibitor, BMS-986165, decreases the transcriptional signature of Th17, IL-12, and interferon pathways in skin of psoriasis: results from a Phase 2 trial
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Background: Psoriasis is a chronic, immune-mediated disease dependent upon the interleukin (IL)-23/Th17 pathway, thought to be initiated through plasmacytid dendritic cell activation and induction of Type I interferons (IFNs). BMS-986165 is a novel oral, selective tyrosine kinase 2 (TYK2) inhibitor that blocks signal transduction of IL-23, IL-12, and Type 1 IFNs in cellular assays. Its selectivity for TYK2 over Janus kinases 1–3 is driven by binding to the pseudokinase domain, rather than the conserved kinase domain. BMS-986165 was evaluated in a randomized, placebo-controlled, dose-ranging trial in 267 patients with moderate to severe plaque psoriasis over 3–4 weeks of culture, which were harvested for scRNA-seq or subjected to a 3.5-hour stimulation followed by CyTOF analysis with a 37-marker panel. Preliminary scRNA-seq data reveal multiple cell clusters exhibiting distinct gene expression patterns that vary by treatment condition. CyTOF profiling complemented these results, demonstrating unique tildrakizumab-induced T cell phenotypic divergence. We observe inter-individual variability, reiterating the heterogeneity of psoriasis and underscoring the importance of developing a robust computational approach for aggregating data across patients. Our current focus is interrogating the outputs of the two single-cell technologies to provide an unified profile highlighting T cell changes resulting from treatment with tildrakizumab.

B2 Journal of Investigative Dermatology (2019), Volume 139