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Tight junction changes associate with increased epidermal susceptibility to viruses

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Atopic dermatitis (AD) is characterized by skin barrier dysfunction, increased type 2 immunity, and an altered skin microbiota with high Staphylococcus aureus abundance. These factors contribute to enhanced susceptibility to viral skin infections. We hypothesized that both type 2 immunity (IL-4/13) and S. aureus colonization alter the epithelium to make it highly permissive to viral infections. Using human keratinocytes (KCs), we observed that the state of differentiation significantly affected susceptibility to vaccinia virus (VV). Similar trends were observed with herpes simplex virus. Undifferentiated KCs were relatively resistant to VV infection, whereas infection at the time of differentiation or up to 2 days later increased susceptibility by 1- and 6-fold, respectively (% area with plaques; n=5–9, p<0.001). This highlights a narrow window in which KCs are highly susceptible and implicates a role for tight junctions (TJ) in KC infectivity. We found that KCs exposed to S. aureus USA300 supernatant or IL-4/13 (50 ng/mL) had increased KC susceptibility to VV (7 & 8-fold increases in plaque number; p<0.01 & p<0.05 respectively) at day 2 post-differentiation. To further explore this observation of infectivity associated with changes in differentiation, we determined whether these stimuli had an effect on TJ function (Transcellular Electrical Resistance (TEER)). USA100 induced a decrease in TEER (>80%, p<0.02) and reduced accumulation of the TJ protein, occludin (p<0.02). The effect of IL-4/13 on TEER were highly variable. We are currently exploring whether IL-4/13 and USA100 alter the expression of KC differentiation markers and are using laser capture on full thickness human epidermal explants to identify strata that support viral replication. These findings will clarify which epidermal layers (differentiation states) are susceptible to viral infection and whether this is modified by exposure to S. aureus virulence factors and/or type 2 cytokines.

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Skin controls the gut immune response through innate ECM cross talk

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Inflammatory bowel diseases (IBD) associate with skin inflammatory diseases but why this occurs is unknown. Inflammation in the skin is a hallmark of the disease and the epidermis is the outermost layer of the body, reminiscent of the gut epithelium in its complex extracellular matrix (ECM) and production of HA fragments that have been shown to be recognized by TLR4. We hypothesized that such HA fragments may enable the skin to promote inflammation in the gut. To test this, mice expressing hyaluronidase in the skin (K14/Hyal1−/−) and control mice with skin wounds (Wd) were compared to their littermate controls. Both groups showed HA digestion in the demis but expression of Hyal1 did not induce skin inflammation. Remarkably, both skin interventions enhanced disease in the colon when mice were co-colonized with S. aureus and USA300. Using histology and DNA sequencing, in small intestine, the expression of genes related with apoptosis, protein digestion and absorption was significantly upregulated, whereas in the skin, that of NOD-like receptor pathway, and Th17 signaling pathway was markedly increased. With IBD-induced stimulation, IL-17 expression was significantly decreased while the expression of IL-1β, IL-6, TNF-α, and S100α was upregulated with decreased intestinal tissue integrity. The observation that inflammatory responses were differentially affected by TLR4 in skin and gut suggests that skin and gut compartments are differentially affected by TLR4, but we need to elucidate how these compartments are cross talk to maintain homeostasis of the skin and gut microenvironment.

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A multitargeted approach for soothing irritated skin

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Effective prevention and treatment of skin inflammation requires a multi-pronged approach targeting modulation of skin inflammation, protection from environmental aggressors and restoration of microbiome balance. This study evaluates the effectiveness of a novel soothing complex on the production of pro-inflammatory cytokines and the ability to protect from external stressors. Results indicate that the complex reduces the level of cytokines in cells following induction of an inflammatory state. The blend also decreases reactive oxygen species (ROS) in a DPPH assay and intracellular ROS in a DCFH assay following ROS propagation by urban dust and UV. Inclusion of an effective probiotic is shown to support growth of normal flora. Given these findings, this unique complex provides key benefits that are synergistic, resulting in soothing properties.

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Reactive adipogenesis in the perifollicular stroma is a component of the host immune response in acne

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Cathode ray tube (CRT) acne is a major cause of dermatological concern in acne patients. An inflammatory disease of the pilosebaceous gland, however the pathophysiology of acne is not well understood. Recent studies have shown that dermal fibroblasts actively contribute to innate cutaneous immunity but their function in acne pathogenesis has not been elucidated. In response to bacterial infection, dermal fibroblasts differentiate into adipocytes and acutely synthesize cathelicidin antimicrobial peptide (CAMP) in a process termed reactive adipogenesis. Analysis of human acne and marine acne-like skin by single-cell RNA-seq analysis identified increased reactive adipogenesis in the condition medium in MDO from PsA patients. The function of candidate WNTs in MDO was investigated using RNA sequencing, in small intestine, the expression of genes related with apoptosis, protein digestion and absorption was significantly upregulated, whereas in the skin, that of NOD-like receptor pathway, and Th17 signaling pathway was markedly increased. With IBD-induced stimulation, IL-17 expression was significantly decreased while the expression of IL-1β, IL-6, TNF-α, and S100α was upregulated with decreased intestinal tissue integrity. The observation that inflammatory responses were differentially affected by TLR4 in skin and gut suggests that skin and gut compartments are differentially affected by TLR4, but we need to elucidate how these compartments are cross talk to maintain homeostasis of the skin and gut microenvironment.

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TNF-α upregulates WNT5A that induces MCP-1 production in osteclasts, leading to recruitment of circulating monocytes in psoriatic arthritis

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Psoriatic arthritis (PsA) is a chronic inflammatory joint disease with bone erosions mediated by TNF-α and IL-17, a critical cytokine. MCP-1 is a potent monocyte chemoattractant and an important regulator of active osteolastogenesis. We aimed to investigate how TNF-α signal pathways regulate active osteoclastogenesis in PsA. The circulating CD14+ monocytes from 12 PsA patients (average age 45.2 years, M/F=8/4) and 2 healthy controls (HCs) (average age 47.4 years, M/F=7/5) were obtained and differentiated into monocyte derived osteoclasts (MDO) by TNF-α and RANKL in vitro. We profiled the transcriptional levels of 20 WNT ligands in MDO by PCR. The chemokine and cytokine levels in the MDO supernatants from PsA patients and HCs were measured by multiplex cytokine ELISA. The functional relevance of WNT5A in PsA was investigated using RNA interference. In PsA patients, WNT5A expression was increased in the skin wounds (Wd) as compared to that from HCs (n=12) as compared to that from HCs (n=12) as compared to that from HCs (n=12) as compared to that from HCs (n=12) as compared to that from HCs (n=12) as compared to that from HCs (n=12) as compared to that from HCs (n=12) as compared to that from HCs (n=12) as compared to that from HCs (n=12) as compared to that from HCs (n=12) as compared to that from HCs (n=12). WNT5A regulates MCP-1 expression, which is a systemic eosinophil deficiency. IMQ-treated mice showed significantly decreased weight and energy intake, while showing increased fecal protein and intestinal permeability. The composition of microbiota was also altered in PsA patients with increased Firmicutes and decreased Bacteroidetes. On host immunity in vivo. Together these in vivo results indicate that carefully selected skin soothing ingredients in an optimized combination may effectively mitigate stress-induced skin irritation while also protecting from external aggressors.