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Tight junction changes associate with increased epidermal susceptibility to viruses

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Abnormal epidermal barrier formation in psoriasis leads to increased susceptibility to viral infections. The skin is an important barrier to viral entry, and is compromised in psoriasis. Changes in tight junction (TJ) proteins are associated with psoriasis, but their role in virus entry is not well understood. We investigated the role of TJ proteins in viral entry using murine and human skin models. Using an in vitro model of human skin, we found that the TJ protein, occludin (p<0.0001), was significantly increased in HC infected skin compared to infected skin from patients with psoriasis (PsA). Additionally, overexpression of occludin in an immortalized epidermal cell line (HaCaT) reduced the susceptibility to viral infection. These findings suggest that increased occludin expression may contribute to increased susceptibility to viral infection in psoriasis.

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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 of the skin is a key component of the mucosal immune response in the intestinal mucous layer (EMM) and production of HA fragments that have been shown to be recognized by TRAL. 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/C6-Hyal1) or wild-type (Wd) were compared to their littermate controls. Both groups showed HA digestion in the demes but expression of Hyal1 did not induce skin inflammation. Remarkably, both skin interventions enhanced disease in the colon when mice were challenged with DSS. In these histological changes, loss of weight was lower only in the colon (Control 100% survived, K14/Hyal1: 20%, Wd; 80%), and FACS. Even in the absence of DSS challenge, scRNA Seq of colons from K14/Hyal1 revealed large changes in the abundance of stromal fibroblast subsets; cluster 5 increased from 2.12 to 42.23, clusters 0, 2 and 7 increased from 1.03 to 15.16, 18.39 to 97.8, respectively. Best differential analysis distinguished three lineages within these populations with HA-induced shift from Cluster 2 toward 5 in lineage 3 most associated with fat cell differentiation. Genes altered in these subsets were validated by whole tissue RNA Seq and qRT-PCR. Colon fibroblasts from K14/C6 mice failed to respond to HA fragments. DSS challenge in mice further induced genes related to adenosine. Reanalysis of scRNA-Seq data from healthy human subjects and patients with newly diagnosed IBD was consistent with our observations in mice of increased fat cell differentiation. Taken together, these results show that fibroblasts and reactive adipogenesis in tissue inflammation and directly demonstrate how the skin can control intestinal inflammation.

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A multitrailored 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 the microbiome balance. This study evaluated 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 induction murine model of psoriasis, using Aβ1-42 mice, which have a systemic encephalitis deficiency. IMQ-treated mice showed significantly decreased weight and energy intake, while showing increased feral protein and intestinal permeability. The composition of microbiota was also altered post treatment. Fecal microbiota sequencing, in small intestine, the expression of genes related to 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 IMQ-induced stimulation, IL-17-producing T cells were significantly increased in the skin, but not in the small intestine. In small intestine, IL-17 expression was significantly decreased while the expression of IL-1β, IL-6, TNF, and ST10a was upregulated with decreased intestinal tight junction molecules. These changes were not observed in large intestine. Interestingly, the small intestine of IMQ-treated mice showed markedly increased expression of genes, with a significant upregulation of the encephalitis degranulation markers. The underlying pathologic role of degraded small intestinal encephalitis in psoriasis inflammation was further substantiated by a significantly upregulated tight junction and mucus molecules in the small intestine of IMQ-treated Aβ1-42 mice. These collective data suggest that degradation of small intestinal encephalitis accelerates pathogenesis of psoriatic inflammation by damaging barrier integrity.

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Inflammatory changes of the small intestinal microenvironment in the murine model of psoriasis

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Psoriatic arthritis (PsA) is a chronic inflammatory joint disease with bone erosions mediated by Th17. The WNT signaling pathway is an important regulator of active osteolastogenesis. We aimed to investigate how WNT signal pathways regulate active osteolastogenesis 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 condition medium in MDO from PsA patients (n=12) was compared to that from HCs (n=12) (9.6 ± 2.8 and 1.0 ± 0.53, p<0.01). MCP-1 expression is selectively increased among 31 chemokines and 36 cytokines in the condition medium in MDO from PsA patients. Interestingly, the increased MCP-1 level in MDO from PsA was abrogated when these cells were transfected with WNT5A siRNA. The ratio of CD14+ monocytes migration in the MDO supernatants from PsA and HCs patients was 1 ± 0.0 and 2.4 ± 0.0 (p<0.01). Furthermore, WNT5A expression and MCP-1 production in MDO from PsA patients were significantly decreased by TNF-α blockers for treatment. We concluded that TNF-α upregulates WNT5A that induces MCP-1 production in osteoclasts, leading to recruitment of circulating monocytes in psoriatic arthritis.