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Short-term exposure to Western diet (WD) predisposes mice to psoriasis-like skin and joint inflammation

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We have previously shown that long-term feeding (>3 month) with a high sugar, moderate fat diet (i.e., Western diet, WD) enhances susceptibility of mice to imiquimod-induced psoriasiform dermatitis (PsD), suggesting that specific components of diet increase susceptibility to PsD. Herein, we determined that short-term feeding (<1 month) with WD alone was sufficient to induce clinically and molecularly-detectable PsD. After weaning, C57BL/6 mice were fed a WD or an otherwise nutritionally matched, control diet (CD) for 1 month. WD-fed mice developed a subtle dermatitis that was characterized by skin edema, redness and mild scaling. Furthermore, we observed epidermal hyperplasia, parakeratosis, accumulation of IL-17A-producing γδ-low T cells, and elevated gene expression of characteristic Th17 cytokines (e.g. IL-17A by 300-fold) and Th1 cytokines. Notably, WD-induced skin inflammation was blocked by gut microbiota depletion with antibiotic treatment. Although no clinically visible inflammation was observed, WD-fed mice also exhibited higher levels of Th17 cytokines in joint tissue. In addition, a IL-23 minicircle DNA (IL-23 MC)-based murine model with features of PsD and psoriatic arthritis (PsA) was used to determine whether the WD exacerbated IL-23-mediated skin and joint inflammation. IL-23-MC-treated WD-fed mice had markedly enhanced skin inflammation versus CD-fed mice, as measured by increased ear thickness, epidermal thickness and mRNA levels of Th17 cytokines. Strikingly, joint inflammation was also exacerbated in WD-fed mice as evidenced by higher incidence of dactylitis and increased mRNA levels of cytokines such as TNF-α, IL-1β and Th17 cytokines (≥10-fold increase) in paw tissue. Furthermore, switching from a WD to CD after IL-23 MC delivery remarkably improved skin and joint inflammation. Taken together, diet influences inflammatory signaling in the skin and joint, supporting a critical role of dietary component in the pathogenesis of PsD and PsA.

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The sweat gland antimicrobial peptide dermcidin is downregulated in hidradenitis suppurativa and non-healing skin wounds but upregulated in healing-wounds

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Hidradenitis suppurativa (HS) presents with recurrent abscesses and sinus tracts leading to chronic non-healing wounds (NHW) in areas rich in hair follicles and sweat glands (SG). Given this clinical presentation, we used biocomputational approaches to study transcriptional similarities between HS and healing and non-healing wounds. We analyzed microarray gene expression of patient-matched HS lesional and non-lesional skin samples (Blok *et al.* 2016), defined differentially expressed genes (DEGs) in HS lesional vs. non-lesional and compared these to DEGs from punch-biopsy skin of healing wounds vs. normal skin (Iglesias-Bartolome *et al.* 2018) and to DEGs from diabetic foot ulcer (DFU) vs. diabetic foot skin (Ramirez *et al.* 2018). Several innate antimicrobial peptides and proteins and interferon (IFN)-stimulated antiviral genes were significantly upregulated in HS lesional and healing wounds. In contrast, the SG antimicrobial dermcidin (DCD) was among the most down-regulated genes in HS lesional (log_2FC=-4.90, $p<0.001$) and DFU (log_2FC=-5.16, $p<0.001$) but was up-regulated in healing wounds. Genes associated with SG function, such as secretoglobins, also showed statistically significant decreased expression in HS lesional skin and non-healing DFU, but increased expression in healing wounds. By calculating the Pearson correlation between DCD and all other genes in the HS dataset, we identified that type I IFN related genes were negatively correlated with DCD, such as STAT1 (correlation -0.88), IRF1(-0.83) and IFNAR2(-0.74). In agreement, we found that IFN-b(100U/ml), known to signal via STAT1, suppresses significantly DCD mRNA in human SG cells ($p<0.001$). Our finding that SG associated DCD was decreased in HS lesional and non-healing DFU, but not in healing wounded skin, suggests that impaired SG function and reduced DCD may play a key role in wound repair.

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Resident neuropeptide PACAP mediates potent cell-free infection defense in tissues

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The central nervous system (CNS) must defend itself against bacterial and fungal infection while also minimizing inflammatory infiltration and maintaining normal cognitive function. Since the CNS is an immune privileged site, inducible innate immune defense mechanisms endogenous to the CNS likely play a key role in this regard. Pituitary adenylate cyclase-activating polypeptide (PACAP) is a neuropeptide that regulates neurodevelopment, emotion, and stress responses via G-protein coupled receptors. While PACAP is known to interact with the immune system, its significance in host defense in the brain or in other tissues like the skin and the kidney is not known. Here, we use a machine learning classifier to identify PACAP as a tissue resident neuropeptide optimized for "clean" CNS defense against pathogens that traditionally require clearance by Th17 neutrophil-based responses. Synchrotron x-ray scattering, antimicrobial assays, and mechanistic fingerprinting enable us to profile precisely how PACAP exerts bactericidal activity against drug-resistant bacteria via multiple synergistic mechanisms including membrane permeabilization, disruption of cellular energetics, and activation of cell death pathways. Most importantly, we find that PACAP is strongly and selectively induced up to 50-fold in the brain and other tissues in mouse models of *S. aureus* and *Candida*infections. Interestingly, PACAP is also expressed by cutaneous peripheral neurons and likely plays a role in host defense of the skin. We are currently exploring how PACAP modulates the skin microbiome and cutaneous inflammation.

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Cutaneous group 2 innate lymphoid cells migrate to draining lymph nodes in mice with IL-33-induced atopic dermatitis-like inflammation

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We previously generated a transgenic mouse line expressing IL-33 driven by a keratin 14 promoter (IL33Tg) and showed that IL-33 elicits an atopic dermatitis (AD)-like itchy skin inflammation associated with group 2 innate lymphoid cell (ILC2) infiltration. ILC2s are believed to be tissue-resident cells under steady-state conditions, but the dynamics of ILC2 migration are not fully understood. In this study, we focused on the migration of ILC2s from skin to draining lymph nodes (dLN) in IL33Tg mice. We tracked ILC2 migration by crossing IL33Tg mice with Kikume Green-Red (KikGR) knock-in mice to generate KikGR IL33Tg mice. KikGR, a photoconvertible fluorescent protein, changes color from Kik-Green to Kik-Red upon exposure to violet light. Exposing the inflamed skin of KikGR IL33Tg mice to violet light allowed us to label ILC2s in the skin and track ILC2 migration from the skin to the dLN. The skin-derived Kik-Red ^{pos} ILC2s were an ST2 ^{low} and major histocompatibility complex (MHC) class II ^{high} population in the dLN ILC2s. ILC2s can also boost Th2 cell responses to antigens in an MHC class II-dependent manner; therefore, these results suggest that ILC2s are important for innate immunity as well as for the induction of adaptive immune responses.

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Tetrahydrocurcumin ameliorates skin inflammation and oxidative stress and induces autophagy in mice fed a high-fat diet

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Background: Curcumin has been known to have antioxidant and anti-inflammatory properties. Tetrahydrocurcumin (THC) is one of the major metabolites of curcumin. However, it is unclear whether administration of THC has beneficial effects on skin. In this study, we investigated skin inflammation, oxidative stress, and autophagy to assess beneficial effects of THC on cutaneous changes induced by high-fat diet in mice. Methods: Eight-week old C57BL/6J mice were divided into four groups and fed regular diet (RD), high fat diet (HFD, 60% of total calories from fat), HFD supplemented with THC 50mg/kg/day, and HFD supplemented with THC 100mg/kg/day orally for 12 weeks. Body weights, plasma glucose and lipid profiles were measured during the experimental periods. At the end of experiment, the skin samples of the mice were obtained. Western blot, real-time PCR and immunofluorescence analyses for inflammatory cytokines, oxidative stress markers, and autophagy markers were conducted. Results: Administration of THC decreased the expressions of inflammatory cytokines, such as tumor necrosis factor-alpha, interleukin (IL)-1 beta, and IL-6. Furthermore, THC significantly decreased NADPH oxidase 2 (NOX2) and NOX4 levels and activated the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. Also, administration of THC enhanced autophagy markers including LC 3-II, ATG5 and beclin-1. Also, immunofluorescence stainings with autophagy markers, LC 3-II showed that THC could induce autophagy. Conclusion: These findings reveal that the anti-inflammatory and antioxidant potential of THC in mice fed a high-fat diet through promoting autophagy in the skin. THC could be developed as a potential therapeutic agent against inflammatory skin diseases.

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***Staphylococcus epidermidis* protease EcpA is a deleterious component of the skin microbiome in atopic dermatitis**

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S. aureus (SA) and *S. epidermidis* (SE) are 80% genetically related and the two most abundant bacterial species found in atopic dermatitis (AD). Although both species are often overabundant, SA is considered to exacerbate AD while SE is thought to be a beneficial commensal. In this study, we hypothesized that the overabundance of SE might damage the epidermis by a proteolytic mechanism similar to SA. To test this, multiple strains of SE and other Coagulase-negative *Staphylococci* (CoNS) were screened for enzymatic activity. Several SE strains, but not other CoNS, had strong proteolytic activity. The enzyme responsible for activity was identified to be the cysteine protease EcpA by selective inhibitors and targeted gene deletion (ΔEcpA). Application of the WT strain to mouse skin disrupted the skin barrier (TEWL : 48.7 vs 13.2 g/h/m2, $p<0.001$) and induced inflammation (erythema; immune cell infiltration; IL6 mRNA: 40.1 vs 1.1, $p<0.01$) while the ΔEcpA strain had no effect. Application of purified EcpA alone also disrupted the epidermal barrier and induced inflammation (TEWL: 40.9 vs 8.8 g/h/m2, $p<0.05$; IL6 mRNA: 13.5 vs 1.13, $p<0.05$). Western blots showed EcpA degraded desmoglein-1 but not involucrin or corneodesmosin from human keratinocytes. EcpA also inactivated the antimicrobial activity of LL-37 against SA. qPCR analysis of *EcpA* mRNA on the skin of 14 healthy and 13 AD human subjects showed that EcpA expression was increased on subjects with AD and correlated with disease severity ($p<0.03$). EcpA expression is controlled by agr quorum sensing and could be inhibited by concomitant application of a *S. hominis* strain producing an SE inhibitory autoinducing peptide. These data change the current paradigm regarding the functions of microbes in the AD microbiome and show that SE can damage skin through the expression of EcpA.