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205 Evaluation of SARS-CoV-2 spike protein response on PI3K agonist-mediated IL-8 release
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A novel coronavirus related to a condition known as a severe acute respiratory syndrome (SARS-CoV-2 or COVID-19), which has caused an unprecedented global pandemic. While the mode of COVID-19 infection, its structural configuration, and multiple mechanisms of action including the critical roles of spike protein have been substantially explored, elucidation of signaling pathways regulating its cellular responses is yet to be fully determined. Among major signaling cascades, phosphoinositide 3-kinases (PI3K) and its downstream pathways have been exploited as potential therapeutic targets for COVID-19, and its activation induces the release of cytokines such as interleukin-8 (IL-8). We recently demonstrated that SARS-CoV-2 spike S1 subunit protein (referred to as COVID-19) on PI3K agonist, phorbol myristate acetate (PMA)-mediated IL-8 release. Given that multiple cell types including epithelial lining of the nasal, bronchial and alveolar cells have been found to be primarily affected by COVID-19, we used nasonov phage Trojan, human KBP and non-small cell lung cancer, A549 cell lines. We observed that treatments with only PMA but not COVID-19 were able to induce dose-dependent IL-8 release from both KBP and A549 cell lines. Our next studies determined the effects of COVID-19 pretreatment with PMA and vice versa to evaluate if any of these combinations would exert synergistic effect on IL-8 release. We observed no significant differences in IL-8 release with either of these combinations when compared with PMA-alone group. However, significantly increased IL-8 release was noticed by PMA + COVID-19 combination when compared with COVID-19-alone group. Overall, these studies indicate that PI3K signaling does not directly mediate COVID-19-induced IL-8 release in these cellular models.

207 Targeting of HDAC8 and HDAC9 in keratinocytes to enhance skin immune defense
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We recently reported that short-chain fatty acids (SCFA) promote an inflammatory response in keratinocytes by suppression of HDAC8 or HDAC9, specific histone deacetylases whose activity increases tolerance of the skin to inflammatory signals. Upon silencing of HDAC8 or 9 in keratinocytes, subsequent exposure to TLR2/6, TLR4, or TLR7 ligands activates inflammatory cytokine production in keratinocytes, but this effect does not occur in bone marrow derived cells, thus demonstrating epidermal specificity of this mechanism. Chip-Seq and signal pathway analysis by RNA-Seq identified MAP2K1 as a key intermediate in this process, with increased acetylation at H3K9 and H3K27 in the MAP2K1 promoter after silencing HDAC8 and HDAC9 or inhibition of HDAC activity by SCFA butyrate. Antibody pull-down and mass spectrometric analysis showed that H3K9 and H3K27 were acetylated in vitro by SCFA, indicating that SCFA are directly involved in the regulation of MAP2K1 expression. Treatment of keratinocytes with SCFA caused a dose-dependent increase in the expression of the TLR2/6, TLR4, and TLR7 ligands. We also showed that SCFA treatment of keratinocytes increased the expression of IFN-α and IFN-β as well as the IFN-α/β receptor and the IFN-induced genes. These results are consistent with a role for SCFA in the immune response of keratinocytes to inflammatory signals, potentially providing a novel therapeutic strategy for the treatment of skin diseases.

209 Epidermal interferon expression is positively regulated by Staphylococcus aureus in SLE and involves the STING pathway
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Cutaneous inflammation is exhibited by many systemic lupus erythematosus (SLE) patients. Keratinocytes are an important source of type I interferons (IFN-I) in the epidermis of SLE patients, which can induce a range of skin manifestations. We recently demonstrated that SLE lesional skin is highly colonized by Staphylococcus aureus (S. aureus), and that S. aureus expression is increased in SLE patients compared to healthy controls. In this study, we investigated the role of S. aureus in the regulation of IFN-I expression in keratinocytes. S. aureus was isolated from lesional skin biopsy samples from SLE patients and used to infect keratinocytes. We used a panel of microorganisms that reflect the diversity of the gut microbiome to evaluate the impact of S. aureus on IFN-I expression. We found that S. aureus significantly increased the expression of IFN-I in keratinocytes, suggesting a role for S. aureus in the regulation of IFN-I expression in keratinocytes. These results have important implications for the treatment of SLE and other skin disorders associated with S. aureus infection.

206 The distinct skin microbiota of congenital ichthyoses
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The ichthyoses are genetic keratinization disorders with an impaired epidermal barrier and increased risk of microbial infections. Congenital forms have recently been found to have a Th17 immune signature with increased antimicrobial peptides, but the skin microbiota is largely unexplored. We analyzed the metagenome profile of the skin microbiome for major congenital ichthyosis subtypes. Body site matched skin surface samples were collected from the scalp, upper arm, and lower back of 23 adult patients with ichthyosis and 16 healthy controls for whole metagenomics sequencing analysis. Taxonomic profiling showed changes in bacteria, fungi, and virus abundance across the subtypes. Cutibacterium and Malassezia were significantly reduced on ichthyotic skin, while Malassezia, Staphylococcus aureus, and Candida were increased on ichthyotic skin compared to controls. Compared with ichthyosis subtypes, S. aureus was enriched on ichthyotic skin, which is consistent with previous studies. This study highlights the importance of understanding the skin microbiome in ichthyosis and suggests potential therapeutic targets for targeted treatments.

208 Sarecycline demonstrates reduced activity against representative fungal and bacterial species commonly found in the human gastrointestinal tract
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Use of broad-spectrum antibiotics (e.g., doxycycline, minocycline) significantly alter the gut microbiome leading to dysbiosis, resulting in microbial imbalance and has been associated with exacerbation of infection. Sarecycline was developed as the first narrow-spectrum tetracycline-class antibiotic to treat acne. Narrow-spectrum antibiotics are hypothesized to cause minimal interference with endogenous gastrointestinal (GI) tract microbiota, thereby maintaining innate microbial diversity. To examine the breadth of this effect, a panel of microorganisms that reflect the diversity of the gut microbiome were evaluated with sarecycline compared to the broad-spectrum minocycline using in vitro susceptibility testing and time-kill assays. Sarecycline had a lower minimum inhibitory concentration (MIC) against 3 out of 4 isolates of Actinobacteria phylum, 10 out of 12 isolates from Bacteroidetes, and 5 out of 7 isolates from the Firmicutes. Furthermore, sarecycline was less active against E. coli, and significantly less active against P. fluorescens when compared to minocycline. Against fungi, sarecycline showed less activity against 4 representative Candida species. Time-kill curves for E. coli and C. tropicalis showed significantly less activity against E. coli for sarecycline compared to minocycline at all points in time (p-values <0.05). Similarly, sarecycline was significantly less effective in inhibiting C. tropicalis compared to minocycline at 20 and 22 hours exposure. Overall, sarecycline showed reduced antimicrobial activity against 79% of gut microflora tested compared to minocycline, suggesting that it has less potential to cause dysbiosis. Further in vivo testing is warranted.