Activity of sarecycline in murine models of infection and inflammation

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Sarecycline (SAR) is a tetracycline-class antibiotic. FDA-approved for treatment of moderate-to-severe acne. In vitro studies demonstrated a narrow-spectrum antibacterial activity, targeting clinically relevant Gram-positive bacteria with reduced activity against Gram-negative bacteria commonly found in the human gastrointestinal tract. A murine systemic (intraperitoneal) infection model was used to assess the in vivo efficacies of SAR, doxycycline (DOX) and minocycline (MIN) against S. aureus and E. coli. At 48 hours after systemic infection with S. aureus, SAR, DOX, and MIN had a protective dose to achieve 50% survival (PD50) of 0.25, 0.3, and 0.03 mg/kg, respectively. In contrast, SAR did not demonstrate in vivo efficacy against E. coli at the doses dosed (≥ 20 mg/kg), while DOX and MIN had a PD50 of 5.72 and 6.95 mg/kg, respectively. A murine neutropenic thigh wound infection model was used to model tissue-based infection to assess efficacies of SAR and DOX against S. aureus. At 24 hours post infection, SAR achieved a 2-log reduction of thigh bacterial burden comparable to DOX, with 50% effective dose (ED50) values of 8.23 and 8.12 mg/kg, respectively. The anti-inflammatory effects of SAR, DOX, or MIN, were tested in male, Sprague-Dawley rats using a carrageenan-induced footpad edema model. Mean percent inflammation at a dose of 100 mg/kg was 53.1, 16.0, and 20.5, respectively. SAR demonstrated in vivo efficacy against S. aureus but not E. coli in animals model of infection, confirming the narrow-spectrum activity observed in vivo. SAR also showed an anti-inflammatory effect comparable to DOX and MIN.

A basophil-neuronal axis promotes itch

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Atopic dermatitis (AD) is a chronic and relapsing inflammatory skin disorder associated with severe, chronic itch. In addition to chronic itch, patients with AD often suffer from acute itch. Although recent seminal discoveries have unearthed the neuroimmune circuitry of itch, mechanisms underlying itch are largely unknown. Interestingly, imaging revealed basophil-sensory neuron interactions within the skin that was provoked by itch. Rather, we strikingly found that this form of itch was critically dependent on the presence of CysLTR2 on neurons, a receptor for cutaneous allergen exposure. Functionally, allergen-stimulated basophils exhibited enhanced histaminergic itch, in the context of AD-like disease, both mast cells and edema modeled a large proportion of patients with AD harbor allergen-specific IgE and exhibit a propensity for itch. Although there is an understanding of basophil-neuronal crosstalk, context of chronic skin inflammation to activate a non-canonical basophil-neuronal circuit. Our study demonstrates a previously unrecognized form of acute itch flare that emerges in the context of chronic skin inflammation to activate a non-canonical basophil-neuronal circuit.

Human papillomaviruses (HPVs), a group of non-enveloped small viruses with double-stranded circular DNA which lead to multiple skin diseases such as benign warts, are commonly seen in clinics. The current HPV detection systems aim mainly at mucosal HPVs, however, an efficient clinical approach for cutaneous HPVs detection is lacking. To establish a rapid detection system for cutaneous HPVs, we used a colorimetric loop-mediated isothermal amplification (LAMP) with hydroxynaphthol blue (HNB) dye in combination with microfluidic technology. The lower detection limit of the LAMP assay was 10^3 viral DNA copies/mL when tested on synthesized L1 DNA sequences, which was better than the conventional PCR. Compared to PCR sequencing, the sensitivity of HPV27, HPV2, HPV1, HPV57, HPV3, HPV4, HPV7 and HPV75 genotypes detections were 100%, whereas the specificity was 14.55%, 45.12%, 95.83%, 98.59% and 97.62% respectively, when tested on clinical samples. The new cutaneous type HPV detection system is characterized by both a good sensitivity and specificity compared to conventional methods.

Phenotypic heterogeneity of heterozygous dermatitis (DOCK8) mutations

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Background: Derivator of cytokinesis (DOCK8) deficiency leads to a combined immuno-deficiency characterized by cutaneous and systemic infections, atopy, and autoimmune. Inclusion of heterozygous mutation analysis may improve the collective understanding of DOCK8 genetic variants. Objective: The purpose of this review is to provide useful insights into the clinical features, genetic analysis and genetic variants of DOCK8 deficiency, with particular emphasis on heterozygous DOCK8 mutations. Methods: PubMed, NCBI, and Medline were searched for scientific articles that provide information on DOCK8 deficiency. The keywords queried included “DOCK8 deficiency”, “mutations”, “heterozygous”, and “genetics”. Results: Due to the vital role that DOCK8 plays in the immune system as well as the actin cytoskeleton, the clinical hallmarks of DOCK8 deficiency are recurrent upper respiratory tract, cutaneous infections and eczema. Although most symptomatic individuals have homozygous autosomal recessive mutations, this review revealed similar clinical findings in patients with heterozygous DOCK8 mutations. Conclusion: Although individuals with heterozygous DOCK8 mutations are generally asymptomatic, recent literature highlights the vast phenotypic heterogeneity of these individuals.

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