The Journal of Immunology

ABSTRACT | MAY 01 2023

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J Immunol (2023) 210 (1_Supplement): 59.16.
https://doi.org/10.4049/jimmunol.210.Supp.59.16

Evaluation of cutaneous immune response in a controlled human in vivo model of mosquito bites

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Mosquito-borne viruses are a growing global threat. Initial viral inoculation occurs in the skin via the mosquito 'bite', eliciting immune responses that shape the establishment of infection and pathogenesis. Here we assess the cutaneous innate and adaptive immune responses to controlled Aedes aegypti feedings in humans living in Aedes-endemic areas. In this single-arm, cross- sectional interventional study (trial registration #NCT04350905), we enroll 30 healthy adult participants aged 18 to 45 years of age from Cambodia between October 2020 and January 2021. We perform 3-mm skin biopsies at baseline as well as 30 min, 4 h, and 48 h after a controlled feeding by uninfected Aedes aegypti mosquitos. The primary endpoints are measurement of changes in early and late innate responses in bitten vs unbitten skin by gene expression profiling, immunophenotyping, and cytokine profiling. The results reveal induction of neutrophil degranulation and recruitment of skin-resident den- dritic cells and M2 macrophages. As the immune reaction progresses T cell priming and regulatory pathways are upregulated along with a shift to Th2-driven responses and CD8+ T cell activation. Stimulation of participants' bitten skin cells with Aedes aegypti salivary gland extract results in reduced pro-inflammatory cytokine production. These results identify key immune genes, cell types, and pathways in the human response to mosquito bites and can be leveraged to inform and develop novel therapeutics and vector- targeted vaccine candidates to interfere with vector-mediated disease.