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**Title: Dengue virus-mosquito-host interactions: assessing type I interferon mediated immune processes and immunological effects of mosquito salivary glands on Dengue infection**

**Acronym: DeSiReS: Dengue Severe Immune Response Studies**

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Annual Report

Dengue virus is an arthropod-transmitted viral disease of the genus Flavivirus (family *Flaviviridae*). The virus is endemic in more than 100 countries, and currently half of the world population is at risk of infection. The clinical presentation of dengue virus (DENV) infection is variable. Severe complications mainly result from exacerbated immune responses. Type I interferons (IFN-I) are important in antiviral responses and form a crucial link between innate and adaptive immunity. IFN-I responses are mainly triggered through the binding of viral RNA to RIG-I-like receptors (RLRs), RIG-I, and MDA5, along with endosomal Toll-like receptor 3 (TLR3) and TLR7. IFN regulatory factor (IRF) 3 and 7 are primary transcriptional factors downstream of RLRs/TLRs signaling, and promote IFN-I response induction during DENV infection, albeit IRF7 plays a more important role than IRF3 in stimulating the early production of IFN-I. In order to balance IFN-I defense with inflammatory damage, FOXO3, a member of the forkhead family of transcription factors, has been recently identified as a negative regulator of IRF7 transcription. DENV evasion strategies interfering with IFN-I production have been identified from in vitro studies. Indeed, DENV overcomes IFN-I-defense mechanisms in primary human immune cells, which appear to have a key role in modulating pathogenesis. However, the *in vivo* direct implications of the IFN-I evasion mechanisms adopted by DENV have, so far, been poorly explored, mainly due to the technical challenges to detect low circulating levels of different IFN-I proteins. Here, we aimed to perform a comprehensive evaluation of type I IFN responses during the earliest phase of disease, within 96h of fever onset in a cohort of Cambodian children. We conducted an integrated analysis of expressed genes related to IFN-I signaling in PBMCs, determination of plasma IFNα/β by ultrasensitive digital ELISA and extensive DC subset phenotyping in patients stratified for infection history and disease severity. Blood samples were obtained from hospitalized children (≥ 2 years) who presented with dengue-like symptoms at the Kanta Bopha Hospital in Phnom Penh, Cambodia. The time-point for collection of blood samples was within 96 h of fever onset at hospital admittance. Patients were classified according to the WHO 1997 criteria upon hospital discharge as dengue fever (DF) or dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS). In addition, age and sex-matched healthy donors were recruited from a cluster-based investigation in Kampong Cham province. Higher concentrations of type I IFN proteins were observed in blood of DENV patients, compared to healthy donors, and correlated with viral load. Stratifying patients for disease severity, we found a decreased expression of IFN-I in patients with a more severe clinical outcome, such as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). This was seen in parallel to a correlation between low IFNα protein concentrations and decreased platelet counts. Type I IFNs concentrations were correlated to frequencies of plasmacytoid DCs, not DENV-infected myloid DCs and correlated inversely with neutralizing anti-DENV antibody titers. Overall, our study indicates that IFN-I produced in the acute phase of infection is associated with less severe outcome of dengue disease. Novel detection methods for IFN-I might help in the stratification of patients at hospital admittance.

Publications

Vinit Upasani\*, Carolina Scagnolari\*, Federica Frasca, Nikaïa Smith, Vincent Bondet, Axelle Vanderlinden, Sokchea Lay, Heidi Auerswald, Sothy Heng, Denis Laurent, Sowath Ly, Veasna Duong, Guido Antonelli, Philippe Dussart, Darragh Duffy, Tineke Cantaert. Decreased Type I Interferon Production by Plasmacytoid Dendritic Cells Contributes to Severe Dengue. Front Immunol. 2020 Dec 17;11:605087. doi: 10.3389/fimmu.2020.605087. eCollection 2020 \*These authors have contributed

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