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“Dynamics of the immune responses to Scrub typhus in non-human primate (Rhesus macaque) model and in human study”

Monday, 6 December 2021
5.15 – 6.00 pm
Zoom link: https://swisstph.zoom.us/j/86216228559?pwd=STYrMUYza3pSYVBUMmd0ZEpoTG1oQT09

Background: Scrub typhus is a mite-borne rickettsiosis which is treatable but potentially severe if untreated or diagnosis is delayed/missed. This disease is largely prevalent in southeastern and eastern parts of Asia including Thailand. In endemic areas, the presence of infected vectors harboring diverse strains of Orientia tsutsugamushi, the causative agent of scrub typhus, has been observed. Pre-existing immunity to scrub typhus in people living in endemic areas may affect the immune response dynamics and clinical disease severity. However, how strain-specific immune responses and previous exposure contribute to the course of infection remains unclear and the high genetic diversity of Orientiae necessitates evaluation of the strain specific immunopathophysiology. The animal models that replicate human disease is essential in the study of immunopathogenic study, assessment of the safety and efficacy of candidate vaccines and new therapeutics.

Methods: In this study we performed a comparative analysis between a pediatric clinical perspective study at Chiangrai Prachanukroh hospital in Chiangrai province endemic area of scrub typhus in Thailand and Rhesus macaques scrub typhus model at AFRIMS, Bangkok Thailand. We investigated the longitudinal dynamics of the immune responses over 1 year in pediatric scrub typhus patients (n=60) compared to exposed controls (n=80 included both child and adult) and healthy controls (n=30). The comparative analysis of the immune responses (cellular-, humoral- and cytokine-mediated immune responses) along with the clinical presentation in pediatric scrub typhus patients was further compared to our characterised scrub typhus non-human primate (NHP) model via intradermal infection with O. tsutsugamushi strain Karp (n=4) and Gilliam (n=4).

Results: The comparative analysis demonstrated that the NHP model resemble the clinical presentations in human scrub typhus. Clinical signs and immune responses with strain-specific characteristics were noticed in both Human and NHP studies. Of 35 confirmed positive scrub typhus were found 40% of the confirmed cases (14/35) belonging to UT76 (Karp-like, local Thai strain), 20% (7/35) Ikeda, 6% (2/35) Kato and 6% (2/35) TA716 strain while 28% (10 of 35) of the confirmed scrub typhus patients were found undetectable bacteremia based on genotype classification (Type Specific Antigen (TSA) 56 gene). Kinetics of the specific humoral-, cellular- and cytokine-mediated immune responses have revealed a similar pattern of the responses in the UT76-infected human and Karp-infected macaques while the other strains induced differences in the dynamic of the immune response pattern over a period of the observation.

Conclusion: The antigenic heterogeneity of O. tsutsugamushi has been a serious obstacle for developing effective diagnosis and a universal scrub typhus vaccine. Results in this study suggest a strain specific immune response presentation. More in-depth analysis could be enable to identify a critical Immunological markers correlate with the protective mechanism against Scrub typhus. Exploration of the conservative immunological markers between the NHP model and humans will be used to predict desired benefit for vaccine safety and immunogenicity study. Moreover, this is beneficial to find protection/appropriate clinical marker or endpoint in animal challenge studies and extrapolate to humans.

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