00028 Metabolomic Determinants of Symptomatic Flaviviral Infections

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Aims: Primary and secondary flaviviral infections are often self-limiting, ranging from asymptomatic to a wide range of clincial manifestations including fever, myalgia, headache and malaise. Most flaviviral infections are asymptomatic, and uncovering the determinants of asymptomatic infections presents a unique opportunity to understand the host responses that control inflammation and infection. However, without effective therapeutics against flaviviruses, conducting human challenge studies to understand these processes can be ethically challenging.

Methodology: We used a recently completed clinical trial where subjects were either immunised with the Yellow Fever live-attenuated vaccine (YFLAV) or with sequential vaccination of Japanese Encephalitis vaccine and YFLAV. All subjects had detectable viremia, and 63.2% of the subjects reported adverse events (AE) that resemble symptoms of an acute febrile illness, including fever, myalgia, headache and malaise. We integrated transcriptional and metabolomic profiling approaches to compare host responses in subjects with or without AE.

Result: Although subjects with AE (AE+) and without AE (AE-) had similar levels of viremia, distinct metabolomic signatures were observed between the AE+ and AE- subjects. Specifically, the baseline citric acid cycle (CAC) intermediates were significantly downregulated in the AE+ compared to AE- subjects. In the AE+ subjects, the increased demand for energy after YFLAV infection led to reduction of alternating sources of energy, including lipids and branched chain amino acids. This metabolic shift resulted in an elevated reactive oxygen species (ROS) production in the AE+ subjects. Consistent with the clinical observations, reducing CAC intermediate flux in vitro resulted in augmented superoxide production and proinflammatory responses.

Conclusion: Herein, we uncover the underlying metabolomic basis behind occurrence of AE, where we show that the levels of baseline CAC intermediates play a crucial role. Further studies are now underway to examine the genetic and environmental factors that contribute to different baseline CAC intermediates.