Human Metabolome Technologies

HMT Exclusive: Interview with Dr. Chan Kuan Rong

Principal Research Scientist, Duke-NUS Medical School, Singapore

Dr. Chan is the lead author of the paper "Metabolic perturbations and cellular stress underpin susceptibility to symptomatic live-attenuated yellow fever infection", which includes key findings based on HMT's metabolome analysis, and was published in top biomedical journal Nature Medicine last August. Dr. Chan's team focused on the differences in blood profiles of symptomatic and asymptomatic individuals before and after inoculation with live yellow fever viral vaccine. Transcriptome analysis and metabolome analysis performed on blood specimens revealed that individuals with endoplasmic reticulum (ER) stress and reduced tricarboxylic acid (TCA) cycle activity have increased susceptibility to symptomatic outcomes after inoculation with the vaccine.

HMT had the opportunity to ask Dr. Chan via e-mail about examples of metabolome analysis in his research, and the significance and prospects of using metabolomics in infectious diseases research.

Q1. In the recent publication, you discovered that increased ER stress and altered metabolism in individuals resulted in adverse effects after yellow-fever vaccination. How do your findings contribute to infectious disease research worldwide?

Flavivirus infection can be asymptomatic or can result in a self-limiting febrile illness, that in some cases, progress into severe disease outcome that is life-threatening. Despite intensive research efforts to uncover the underlying molecular mechanisms behind disease pathogenesis, there is currently still no licensed therapeutics to relieve the burden of the disease. Hence, in this study, we leveraged on the live-attenuated yellow-fever vaccine, to explore the molecular underpinnings behind yellow fever-induced symptomatic outcome. The findings that increased ER stress and altered metabolism at baseline is associated with increased symptomatic rates or adverse event outcomes were based on two independent clinical trials. These results hint at the exciting possibility of modulating the ER stress response or the immunometabolic profile in humans before viral infection could influence symptomatic outcome, providing insights to the development of prophylactics against flaviviral diseases.

Q2. Why did you choose HMT's metabolomics for this study?

Our transcriptomic data analysis provided evidence that baseline metabolism, particularly the citric acid cycle genes, were expressed at lower abundance in the symptomatic subjects. At present, HMT is the sole provider for analysis of polar metabolites using CE-MS/MS with absolute concentration values, which is why we have approached HMT. In addition, we trusted their service as the staff was extremely helpful in explaining the CE-MS/MS technology and the coordination of sample preparation, transport, sample processing and data analyses.

Q3. How do you see metabolomics being applied to the field of infectious diseases today or in the future?

Viruses rely on host cells to provide ATP and macromolecules required for viral replication. Thus, viral infections could trigger energetic and metabolic stress that consequently lead to cell death. However, emerging evidence now support that different viruses may employ varied strategies to evade immune detection and cell death, or in some cases, even promote host metabolism to ensure that the host cell can support both virus and cell growth. Thus, I believe that uncovering these molecular mechanisms involved could potentially lead to the development of novel therapeutics against viral infections. In addition, the recent COVID-19 outbreak demonstrated that the elderly population, especially those with co-morbidities, have an increased susceptibility to severe disease outcome. As aging is closely associated with decreased bioenergetic capacity and mitochondrial functions, I anticipate that there will also be an increased interest in the understanding of how aging affects metabolomic profiles and viral infection outcomes.

Q4. What do you think are metabolomics' greatest strengths and weaknesses in infectious disease research?

The strength of metabolomics is that metabolites are the final products of transcriptomic and proteomic perturbations. They are thus potentially attractive for use as biomarkers for various diseases. However, as metabolism pathways are highly interconnected, it may be difficult to identify specific therapeutics that can only affect a particular pathway without affecting other metabolic pathways. Future research efforts into discovery of small molecules with greater substrate specificity could potentially circumvent this current limitation today.

Q5. What is the future of your research? (If possible, could you also provide some comments or advice for aspiring young researchers?)

With the collaboration between researchers, clinicians and industrial partners, I hope to examine further into the how immunometabolism impacts outcome of viral infections and vaccine responses.

Research is not a sprint but a marathon. There will be frequent cycles of successes and failures, so it is important to stay positive during times of failure. In my opinion, the best way is to build friendship with your colleagues, peers and even your mentor during your research career, as these are the people that will keep you motivated during downtime. On the other hand, when you are successful, help those who are in need. Over time, this will build a positive relationship that will keep your passion alive, in whatever you do.

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Reference: Chan KR, Gan ES, Chan CYY, Liang C, Low JZH, Zhang SL, Ong EZ, Bhatta A, Wijaya L, Lee YH, Low JG and Ooi EE (2019). Metabolic perturbations and cellular stress underpin susceptibility to symptomatic live attenuated yellow fever infection. Nature Medicine. DOI: 10.1038/s41591-019-0510-7.