

Biomarkers detected for Chikungunya fever

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Three specific biomarkers provide an accurate indication of the severity of Chikungunya fever (CHIKF), which is emerging as a threat in South-East Asia, the Pacific and Europe, according to research conducted in Singapore.

Since the biomarkers can be easily detected and measured in blood, this finding could expedite identification and monitoring of patients.

The study, the first comprehensive investigation of the many biological factors such as cytokines and chemokines produced in the human body in response to Chikungunya virus infection, was conducted by researchers at A*STAR's Singapore Immunology Network (SIgN) and the Communicable Disease Centre (CDC) at Singapore's Tan Tock Seng Hospital (TTSH).

Cytokines are proteins, peptides or glycoproteins that belong to a category of signaling molecules that, like hormones and neurotransmitters, are used extensively in cellular communication. Chemokines are small cytokines of relatively low molecular weight that are released by a variety of cells.

The Singapore scientists found that levels of three specific biological factors, interleukin-1, beta, (IL-1 β), interleukin-6 (IL-6) and RANTES, distinguished patients with the severe form of the disease from those in whom the infection was mild.

The findings of the study, conducted on blood samples obtained from 10

patients who developed the disease during Singapore's CHIKF outbreak in Jan. 2008, were published online one year later (Jan. 2009) by the *PLoS ONE*.

Lisa Ng, Ph.D., principal investigator of the Chikungunya research team at SIgN and co-author of the PLoS ONE article, said, "This first comprehensive report, which examines the cellular signals produced as part of the human immune response to Chikungunya virus infection, enables us to understand the changes in molecular signals in the body when infection sets in. These biomarkers can potentially lead to the development of therapeutics to reduce the severity of the disease and halt its progression."

Dr. Ng and her colleagues discovered that an increase in the levels of IL-1 β and IL-6, with a concomitant decrease in RANTES, was an indication of a severe form of CHIKF. This finding would allow for quicker and more accurate prognosis of infected patients.

The scientists also determined that the level of RANTES was lower in patients with severe CHIKF, as compared to those with dengue. This result could potentially enable physicians and scientists to distinguish quickly between CHIKF and dengue fever - two diseases that present clinically similar symptoms.

SIgN Chairman Philippe Kourilsky, Ph.D., said, "This is indeed a significant breakthrough in the research on Chikungunya fever, which is emerging as a threat in South-East Asia, the Pacific and Europe. The landmark findings are a testament to the successful collaboration between a basic research institute and a hospital, where both parties combine their resources and expertise to achieve clinical relevance. SIgN will continue to work with our partners in the hospitals to better understand the disease and translate such findings into relevant clinical outcomes." In addition to TTSH, SIgN has clinical collaborations with

Alexandra Hospital, Singapore General Hospital and National University Hospital, in research areas such as immunology and cancer studies.

Associate Professor Leo Yee Sin, M.D., Clinical Director of CDC at TTSH, said, "This study proves that cytokines could be used as biomarkers in predicting the severity of the disease. They provide immunological information for us to understand the causal effect of Chikungunya in the human host. Further research along a similar vein is ongoing with a larger number of cases from later Chikungunya outbreaks that had occurred in Singapore."

Research is now underway in Singapore to ascertain the immune and pathogenic mechanisms behind CHIKF, which could guide the development of future therapeutic applications.

This research is being conducted through a follow-up on more than 100 cases of CHIKF, to further refine the understanding of CHIKF clinical manifestation over a prolonged period of time.

Prof. Leo added, "We are hopeful that our research endeavor can further our understanding of Chikungunya and enable us to apply the knowledge gained to better manage the disease".

With outbreaks in the Pacific region in recent years, CHIKF has emerged as a potentially serious international health threat. However, little is known about the disease progression and the immune response in patients. In late 2007, SIgN initiated clinical immunology research on Chikungunya led by Dr. Lisa Ng to study the immunological process of CHIKF.

During the 2008 outbreak of CHIKF in Singapore, the CDC team led by Associate Professor Leo Yee Sin, Clinical Director of the CDC, TTSH, responded swiftly to contain it and set up outbreak research through the

support of National Healthcare Group Domain-Specific Review Boards. CDC's swift action enabled prospective sample collection at a very early stage of the outbreak, which allowed the research team to study early cytokine response.

More information: The research findings were reported in the article, "IL-1 β , IL-6 and RANTES as biomarkers of Chikungunya Severity," in the Jan. 21, 2009 issue of PLoS ONE. The paper is available online at dx.plos.org/10.1371/journal.pone.0004261

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