ImmunoTools *special* Award 2015

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Immune Response to Dengue Viral Infection

Dengue is the most significant mosquito-borne viral disease affecting mankind. It is an expanding public health problem in both Thailand and worldwide, especially in tropical and subtropical countries. An estimated 50 million people have dengue virus infection annually, and 2.5 billion people live in dengue epidemic countries. It causes significant morbidity, mortality and leads to hospitalization that consume numerous health care spending annually. Dengue infection has a wide spectrum of clinical outcomes from asymptomatic, uncomplicated dengue fever (DF), severe dengue fever (dengue hemorrhagic fever; DHF or dengue shock syndrome; DSS) to death. One to 5% of cases are symptomatic which can be severe with the development of plasma leakage and hemorrhage resulting in a mortality rate around 20% without appropriate treatment. However, with appropriate supportive care, the mortality rate can be reduced to below 1%. Currently, there is still no approved effective vaccine and specific treatment for these patients. This is partly because of the incomplete understanding of the disease pathogenesis.

Existing evidence shows that both viral and host factors could contribute to the severity of dengue infection. Particular viral genotypes and the high level of viral load were found to be associated with a more severe form of dengue infection. Host genetic background and immune responses were also shown to play a very critical role in the pathogenesis of dengue infection. Polymorphisms in host major histocompatibility complex (MHC) as well as DC-SIGN, among other genes, are found to link to the severity of dengue infection. Host immune response is important not only for viral clearance, but also contributes to immunopathology found in severe

disease in some circumstances. Several lines of investigation suggest detrimental immune reaction as the major cause of severe dengue hemorrhagic fever and dengue shock syndrome. First, clinical observation clearly showed that patients develop shock not during high viremia but after virus is cleared. Second, severe disease is associated with a peak of inflammatory cytokine production. Moreover, severe diseases are found more frequently in heterotypic secondary infection. The mechanisms by which immune responses caused severe disease are being actively investigated but not yet completely understood.

Both cross reactive B- and T-cells responses in secondary dengue virus infections have been implicated in immunopathogenesis of the severe disease. Both cross reactive B- and T-cells responses in secondary dengue virus infections have been implicated in immunopathogenesis of the severe disease. Antibody dependent enhancement (ADE) hypothesis suggests that antibodies specific to certain epitope of dengue virus serotype of prior infection are not protective against the subsequent infection with different dengue serotype. On the contrary, they enhanced dengue virus internalization into host cells and increased virus replication resulting in the development of severe disease. Moreover, the cross-reactivity of T-cells responses or T cell antigenic sin was also proposed to explain the role of the adaptive cell-mediated immune response in development of severity in heterologous secondary dengue infections. In secondary infection, memory T cells specific to primary serotype expand more rapidly in comparison to T cells specific to the current dengue serotype. The viral clearance mechanisms of these primary serotype specific T cells are suboptimal, while proinflammatory responses contribute to severe disease. However, the details of pathogenic role of adaptive T and B cell response and their cross talk with innate immune cells in dengue virus infection have much less been investigated. Therefore, a better understanding of this important arm of the immune response is crucial to decipher the complex immunopathogenesis of severe dengue disease.

The objective of our study is to investigate on the details of both innate and adaptive immune responses and immunopathogenesis in severe dengue disease in human by examining well-defined clinical samples from a cohort of dengue-infected patients. The ImmunoTools reagents will be useful for both *in vitro*

and *in vivo* studies. This study will lead to a better understanding of the intricate control of complex immune responses and immunopathogenesis in dengue infection. Altogether, the advancement in our knowledge will enable the development of novel preventive and therapeutic approaches in the future.

ImmunoTools *special* AWARD for **Ponpan Matangkasombut Choopong**

includes 25 reagents

FITC - conjugated anti-human CD4, CD14,

PE - conjugated anti-human CD3, CD56, IFN-gamma, TNFa, Control-IgG1,

PerCP - conjugated anti-human CD8,

APC - conjugated anti-human CD3, CD69, CD19, Annexin V,

human ELISA-set for 96 wells, human IFN-gamma, human IL-4, human IL-10 (each 3 reagents),

recombinant human cytokines: rh GM-CSF, rh IL-2, rh IL-4, rh TNFa

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