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Dengue infection: Cytokine profiles and modulation of the micro vascular endothelium

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Background: Dengue imposes serious healthcare, economic and social burden, with 390 million cases estimated annually, of which 75% are mild or asymptomatic cases. While many factors have been postulated in the pathogenesis of dengue, it has been traditionally believed to be an immune-mediated disease leading to endothelial dysfunctions. This study describes the cytokine levels of a dengue cohort in a Malaysia and investigates the protective immune correlates in clinically asymptomatic household members.

Methodology and results: Dengue-suspected patients and accompanying household members (no physical signs of illness) were recruited with informed consent. Clinical data information was obtained and dengue laboratory diagnostics (RT-PCR, MAC-ELISA, NS1 ELISA and HI) were conducted. Serum of patients (dengue positive or presumptive) was subjected to multiplex cytokine analyses while the dengue positive/presumptive household members were gene profiled to find protective immune correlates. Twelve cytokines namely IL-5, IL-10, IL-13, IFN-γ, MIF, IL-8, CCL11, CXCL10, IL-7, FGF-2, ICAM-1 and VCAM-1 were significantly differentially expressed at the different phases of illness in dengue patients. On the other hand, among 29 asymptomatic household members who were found to be dengue positive/ presumptive, cytokine-related genes including TNF-α, IL8, IL2, IL3, IL4, IL5, IL8, IL9, IL10 and IL13, IL18 were found to be down-regulated while CCL5, MIP-1α, MIP-1β, TGF-β were up-regulated. At the same time, a number of matrix metalloproteinase (MMP) members, such as MMP8, MMP10, MMP12, MMP15, MMP16, MMP24 and TIMP1 were significantly modulated. The involvement of these cytokine and MMPs indicate the endothelium as a major player in dengue pathogenesis. This was then demonstrated via in vitro infection of the brain and lung microvascular endothelial cells where both were found to be susceptible to dengue virus infections. Further investigations into the protein expression of dengue-infected microvascular cells reveal that various tight junctional proteins (ZO-1, Claudin-1, Occludin and ESAM) were modulated differentially.

Conclusion: Here, findings from other studies are re-iterated to show that cytokine storms are a significant component in dengue immunopathogenesis whereas subclinical infections reveal broad down-regulation many innate, adaptive cytokines and matrix Metalloproteinases. This led to the hypothesis where the endothelium is suggested to play an important role. In this study activation of the endothelial cells seemed to have occurred immediately upon dengue infection and is regulated differentially in different organs. This is postulated to trigger the various cascades of immune response as noted in dengue patients. As endothelium dysfunctions are often reversible, this may provide avenues for development potential pharmacologic agents to manage disease severity.

Biography

Shamala Devi Sekaran obtained her Bachelor's degree, Master's Degree and Doctorate in University of Malaya and has been working at the University of Malaya from 1976, as a Tutor, then as a Lecturer and currently a Professor in Microbiology and Immunology. Her initial duties centered on immunology but rapidly expanded to cover virology, bacteriology and diagnostic microbiology. There are 148 peer-reviewed publications in academic journals, 2 book chapters and holds the rights of 17 intellectual properties at both levels. In the field of dengue, she has published more than 40 papers and is currently involved in a number of projects which include epidemiological and immunological profiling of clinical dengue suspected patients, siRNA and synthetic AMPs for the development of anti-dengue viral peptides, development of diagnostics assays targeting the prM and envelope regions of dengue virus and probable mechanisms of vascular leakage.

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