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## HUMAN T LYMPHOCYTE RESPONSES TO DENGUE VIRUSES: ROLE OF T LYMPHOCYTES IN THE PATHOGENESIS OF DENGUE HEMORRHAGIC FEVER

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Dengue virus infections are a serious cause of morbidity and mortality in many areas of the world: Southeast and South Asia, Central and South America and the Caribbean. The clinical manifestations of dengue virus infections range from asymptomatic infection to two forms of illness. Dengue fever (DF) is a self-limited febrile disease. Some patients with dengue virus infection develop a severe, life-threatening syndrome called dengue hemorrhagic fever (DHF). When plasma leakage is so profound that shock occurs, it is also referred to as dengue shock syndrome (DSS).

Following primary infection, life-long immunity develops against repeated infection by the homologous serotype of dengue viruses; however, protective immunity to the heterologous serotype is short-lived. It is known that antibodies to any of the four serotypes of dengue viruses augment dengue virus infection of Fc $\gamma$  receptor-positive cells such as monocytes. On the basis of the epidemiologic and laboratory studies, it has been hypothesized that antibodies to dengue viruses and other serotype-cross-reactive immune responses contribute to the pathogenesis of DHF.

Dengue virus-specific CD4<sup>+</sup>CD8<sup>-</sup> and CD4<sup>-</sup>CD8<sup>+</sup> memory T lymphocytes are present in individuals who were previously infected with dengue virus(1). These memory T lymphocytes include serotype-specific and cross-reactive T lymphocytes. Dengue virus-specific T lymphocytes have cytotoxic activity against dengue virus-infected cells and CD4<sup>+</sup> T lymphocytes produce IFN- $\gamma$  and IL-2 upon stimulation. The observation that CD4<sup>+</sup> and CD8<sup>+</sup> memory T cells induced by primary infection contain serotype-cross-reactive T lymphocytes supports the possibility that they will become activated during secondary infection by dengue virus of heterologous serotype. We also found that CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes are highly activated in vivo in patients with DHF (2).

The pathological mechanisms which increase permeability of vascular endothelial cells in DHF are not known. In secondary infection with dengue virus of a different serotype from that which caused primary infection, serotype-cross-reactive, non-neutralizing antibodies increase the number of dengue virus-infected monocytes by forming dengue virus-antibody complexes. Serotype-cross-reactive CD4<sup>+</sup> T lympho-

cytes are activated, and produce IFN- $\gamma$  and IL-2. Increase in the number of dengue virus-infected monocytes and augmented expression of HLA class I and class II by IFN- $\gamma$  facilitate the recognition of the epitopes on infected cells by virus-specific T lymphocytes, and results in very high levels of T cell activation. The marked T cell activation results in the production of much higher levels of lymphokines.

IFN- $\gamma$ -activated monocytes may release various kinds of cytokines upon infection with dengue viruses, or dengue virus-infected monocytes may release high levels of cytokines and chemical mediators in the result of lysis by dengue virus-specific CD8<sup>+</sup> and CD4<sup>+</sup> cytotoxic T lymphocytes and/or as a result of contact with virus-specific T lymphocytes. Once various cytokines are produced, the complex network of induction further increases the production of cytokines and chemical mediators. These cycles could result in high levels of cytokines and chemical mediators in a short period of time.

We hypothesize that rapid increase in the levels of cytokines and chemical mediators induces malfunctions of vascular endothelial cells, which lead to plasma leakage and shock. These processes appear to be initiated by antibody-dependent enhancement of dengue virus infection of monocytes, and triggered by serotype-cross-reactive T lymphocytes (3).

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