PATHOGENESIS AND IMMUNOGENESIS OF DENGUE VIRUS
TYPE-2 (DV2-16681)

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Dengue virus (DV) is a mosquito-borne flavivirus largely distributed among human intertropical populations and now considered as one of the major reemerging diseases. The hallmark of the pathology associated with Dengue virus is an etiological agent of a hemorrhagic fever, often leading to a fatal shock-like syndrome which is caused by the degradation of the endothelial extracellular matrix and an increase in the permeability of vascular endothelium. However, the molecular mechanism(s) underlying the changes in endothelial cell function remain, as yet, unclear. In the present study, it is shown that in vitro generated immature dendritic cells produce high levels of active matrix metalloproteinases (MMPs) MMP-2, MMP-9 and MMP-13, following infection with the Dengue viral strain DV2-16681. Culture supernatants derived from infected either primary immature dendritic cells or primary human umbilical vein endothelial cells were found to induce increased endothelial permeability, in an MMP-dependent manner, as measured on confluent layers of primary human umbilical vein endothelial cells. Moreover, these supernatants disrupted endothelial cell-cell interactions which were associated with a loss of expression of the junctional adhesion proteins PECAM-1 and VE-cadherin, as well as with a strong decrease in the number of F-actin stress fibers in these cells. Using either MMP-production or MMP-activity inhibitor the mentioned adhesion proteins and cell-cell junction structures were preserved. Altogether, the results provide potential mechanisms of the pathogenesis of DHF (Dengue Hemorrhagic Fever) critical therapeutic targets to overcome cytopathogenic mechanisms of Dengue virus and other viral hemorrhagic fever-inducing viruses.