Dengue Virus Nonstructural Protein 1 Induced Vascular Leakage through Macrophage Migration Inhibitory Factor Secretion

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Background/Objective

Dengue virus (DENV) is a member of flaviviridae and it causes the most common mosquito-borne disease, including the life-threatening dengue hemorrhagic fever (DHF) and shock syndrome (DSS). Vascular leakage is the major characteristic feature of DHF/DSS, However, the mechanisms to cause vascular leakage during DENV infection remain unclear. DENV non-structural protein 1 (NS1) is a highly conserved protein and its serum level is positively-correlated with the severity of the disease. On the other hand, macrophage migration inhibitory factor (MIF) is a cytokine which serum levels in dengue patients is also correlated with disease severity. In this study we test the hypothesis that NS1 can stimulate endothelial cells to secrete MIF to cause vascular leakage.

Method

Recombinant NS1 (rNS1) generated in E. coli was used. The expression and secretion of MIF in human microvascular endothelial cell line (HMEC-1) were determined by RT-PCR and ELISA. Endothelial permeability was determined by real-time cellular analysis and transwell permeability assay. The distribution of junctional proteins VE-cadherin and ZO-1 in HMEC-1 was determined by immunofluorescent antibodies and confocal microscopy. In vivo permeability assay was demonstrated by Evans blue permeability assay and abdominal lavage in mice.

Result

We first demonstrated that rNS1 induced vascular leakage in vitro and the distribution of VE-cadherin and ZO-1 in HMEC-1 was disarrayed. The effects of rNS1 on HMEC-1 cells were abolished when rNS1 was heat-denatured or co-treated with rNS1 neutralizing antibodies. Furthermore, rNS1 induced MIF secretion both in vitro and in vivo and the vascular leakage induced by rNS1 was blocked by MIF inhibitor.

Conclusion

Taken together, these results suggest that DENV NS1 induces vascular leakage through MIF secretion, which may contribute to the pathogenesis of DHF/DSS.