Dengue Virus and Antiplatelet Autoantibodies Synergistically Induce Hemorrhage in the Two-hit Mouse Model

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Background/Objective

Exhibiting severe hemorrhages, coagulopathy, and cytokine surges, life-threatening dengue hemorrhage fever (DHF) typically appears during secondary dengue virus (DENV) infections. To explain this phenomenon, antibody-dependent enhancement (ADE) theory suggests that DENV-antibody complexes can enhance the infection rate of leukocytes and thus increases the viral load. However, dozens of viruses exhibit ADE; while only DENVs induce a severer disease during secondary infections, suggesting DHF is not fully explained by ADE. High titers of antiplatelet antibodies have been associated with the severity of DHF in another line of evidence.

Method

Antiplatelet antibodies served as surrogate pathogenic factors for secondary-DENV infection to treat DENV-infected mice in this study. The levels of hemorrhage, coagulant parameters and proinflammatory cytokines were measured.

Result

These combined but not respective treatments of DHF-viral-load DENV and antiplatelet Ig induced hemorrhages, coagulopathy, and cytokine surges in mice. Mutant mice lacking Fc receptor Fc γ RIII, Toll-like receptor 3, and inflammasome components Nlrp3, and caspase-1, showed fewer pathological alterations compared with the wild type controls. Inhibition of TNF-α, IL-1, caspase, and Fc γ RIII, exhibited ameliorative effects.

Conclusion

Because there are no current vaccines or specific treatments for DHF, these findings may provide a new perspective and a new platform for developing feasible approaches against DHF.