Title:
Inhibition of Dengue Virus Infection by Targeting on Macrophage Migration Inhibitory Factor-induced Autophagy

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Innate immunity and infection

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Abstract:
Dengue virus (DENV) infection is the most prevalent mosquito-borne viral infection, of which satisfactory therapeutic drugs are still in need. Previous studies have shown that DENV infection can induce autophagy, which facilitates DENV replication. In addition, the amount of a pro-inflammatory cytokine, macrophage migration inhibitory factor (MIF) in dengue patients’ sera is correlated with the severity of the disease. Since MIF is able to induce autophagy, we propose and test the hypothesis that inhibition of MIF-induced autophagy can inhibit DENV replication. We first showed that DENV infection induced MIF secretion and autophagy flux in HuH-7 cells. Either suppression of endogenous MIF by short hairpin RNA (shRNA) or inhibition of MIF activity by MIF inhibitor, ISO-1, attenuated DENV infection. On the other hand, co-culture with recombinant MIF or conditioned medium containing native MIF enhanced DENV infection and increased viral load. In addition, we found antibiotics such as minocycline and azithromycin could attenuated DENV infection by blocking DENV-induced MIF secretion and autophagy. Taken together, these results support our hypothesis that MIF is a potential therapeutic target and inhibition of MIF by minocycline and azithromycin may represent an alternative therapy approach against DENV infection.