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Immature dengue virus: A veiled pathogen?

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Dengue virus (DENV) is a major emerging pathogen which causes disease symptoms ranging from febrile illness to devastating hemorhagic manifestations. Increased disease severity is associated with pre-existing DENV antibodies and high circulating virus titers, suggesting that antibodies directly influence the infectious properties of the virus. The molecular mechanism by which antibodies enhance DENV infection however remains elusive.

Cells infected with DENV release a high proportion of prM-containing, immature virions. It is generally believed that immature particles are irrelevant by-products of infected cells since numerous functional studies have demonstrated that fully immature particles lack the ability to infect cells. On the other hand, dengue-positive patients secrete substantial levels of prM antibodies, which suggest that immature particles are involved in disease pathogenesis. In attempt to unravel these contrasting paradigms, we investigated the infectious properties of anti-prM antibody-opsonized immature DENV in various FcR- expressing cell lines and human primary PBMC (peripheral blood mononuclear cells). We found that immature DENV particles become virtually as infectious as wild type virus in presence of antibodies. We demonstrate that prM antibodies facilitate efficient binding and cell entry of immature particles into Fc-receptor expressing cells. In addition, we observed that enzymatic activity of furin is critical to render the internalized immature virus infectious. Furthermore, we found that multiple E antibodies interact with immature particles and some of these antibodies were observed to stimulate the infectious properties of the virus. Not only monoclonal antibodies but also DENV immune sera was observed to trigger the infectivity of immature DENV. Altogether, our data suggests that in presence of antibodies, immature DENV particles have the potential to be highly infectious and hence may contribute to DENV pathogenesis. During the conference the critical determinants in immature DENV cell entry will be discussed.

Keywords: dengue, entry, pathogenesis, antibody-dependent enhancement