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EDITORIAL

New insight on dengue virus-induced thrombocytopenia

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Dengue virus (DENV) is a mosquito-borne flavivirus that is endemic in over 100 countries around the globe. There are four serotypes that each produce similar clinical presentations. The clinical spectrum of DENV is wide and varies from asymptomatic infection to an acute flu-like illness with or without warning signs of shock.[1] Approximately half of infections are asymptomatic even though these individuals have a sufficiently high enough viral load to transmit virus back to the mosquito population.[2] Symptomatic infection generally leads to high fever, headache, retroorbital pain, myalgias, arthralgias, and a diffuse erythematous maculopapular rash.[3] Hemorrhage may also be evident in the form of petechiae, skin bruising, or subconjunctival hemorrhage.[1,3] Severe dengue with shock is the most serious manifestation of DENV infection, and it can be life threatening.[1] Warning signs include abdominal pain, abdominal tenderness, persistent vomiting, ascites, pleural effusion, mucosal bleeding, lethargy, restlessness, hepatomegaly, increase in hematocrit and a rapid decrease in platelet count.[3] Hemorrhage and third spacing of fluids can occur rapidly leading to shock and death.[3]

At the heart of severe dengue is the development of thrombocytopenia and clotting abnormalities. The reduction in thrombocytes that occurs during infection likely prevents repair of damaged tissue and contributes to hemorrhage and third-spacing of fluids.[3] It is not clear how DENV infection leads to a decrease in thrombocyte numbers, although a number of studies have investigated this phenomenon.[4]

Studies suggest that DENV-induced thrombocytopenia is a complex phenomenon. Thrombocytes are targeted at multiple levels. The strongest data suggests that DENV infection leads to bone marrow suppression and peripheral destruction of thrombocytes.[5,6] Bone marrow suppression likely occurs due to aberrations in differentiation or inducing cell death of thrombocyte progenitors.[4,6] Research also suggests that DENV is present in mature thrombocytes, which may lead to their clearance by phagocytic cells.[4,7,8] Additionally, DENV-exposed thrombocytes from human subjects exhibit markers of apoptosis, including increased phosphatidylserine exposure, mitochondrial depolarization, and caspase activation.[9] Thrombocytes are dysfunctional at multiple levels of differentiation during DENV infection. Further, NS1 contributes to thrombocytopenia because anti-NS1 antibodies cross-react with platelets and inhibit their function. Other viral proteins may also raise cross-reactive antibodies that contribute to thrombocytopenia.[4,10] Interestingly, mice exposed to antiplatelet or anti-NS1 antibodies showed similar degrees of hemorrhage, coagulopathy, and cytokine expression, suggesting that anti-NS1 antibodies are key drivers of thrombocytopenia.[10] Anti-thrombocyte IgM titers are also increased in patients with severe dengue.[4] Finally, DENV infects endothelial cells and promotes vascular permeability, which may contribute to thrombocytopenia by localizing thrombocytes to DENV infected endothelial cells.[11] A number of other events may occur that contribute to the reduction in thrombocyte numbers seen during severe dengue. These data reveal a complex interplay involving thrombocyte differentiation, phagocytosis, apoptosis, cross-reactive antibodies, and coagulation that leads to the inhibition of thrombocyte development, their destruction, and consumption.

In the current study, Lin et al. (2017) suggest that DENV-envelope protein domain III (DENV-EIII) is sufficient to suppress differentiation of megakaryocytes to thrombocytes and that replication within haematopoietic precursors is not required.[12] The investigators hypothesized that engagement of DENV-EIII with the cell surface

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would be sufficient to perturb cell signaling and the differentiation of the thrombocyte progenitors.[12] Previous research has shown that DENV antigens are present on the surface of thrombocytes and that virions can enter into these cells through engagement with DC-SIGN.[4,9] To test their hypothesis, the investigators confirmed that DENV-EIII could bind to megakaryocytes, and then administered DENV-EIII to a mouse model and progenitor cells from both murine bone marrow and human cord blood. Treatment with DENV-EIII reduced megakaryocyte numbers in each of these model systems.[12] In order to understand how DENV-EIII suppressed megakaryopoiesis, megakaryocytic differentiation was performed using human cord blood-derived $CD34^+$ cells. Cells treated with DENV-EIII had altered autophagy profiles and increased markers associated with apoptosis.[12] Previous studies have demonstrated that altered autophagy profiles can lead to cell death of megakaryocytes.[13] These data suggest that DENV-EIII alone can modulate autophagy and induce apoptosis in progenitor and mature megakaryocytes.

This manuscript reveals additional mechanistic detail about the pathogenesis of severe dengue and identifies a new therapeutic target to limit thrombocytopenia and the development of shock. Specifically, these data suggest that DENV-EIII is a virulence factor that contributes to pathogenesis, and that inhibiting its interaction with megakaryocytes through antibody-mediated engagement would limit the severity of disease. Current dengue vaccine candidates already include envelope protein and antibodies are typically raised against specific epitopes in DENV-EIII. Future research will be important to determine if antibodies that target DENV-EIII can prevent thrombocytopenia and vascular leak in an *in vivo* model.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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