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Different Roles of Mosquito and Human Derived Phenotypes of Dengue Virus Causing Human Disease

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ABSTRACT

Plasma membrane of mid gut epithelial cells of the mosquito differs from that of human dendritic cells in its lipid content and post translational modifications like glycosylation of proteins. Unlike mammalian cells, glycosylations in insect cells are less complex, because of fewer processing enzymes and usually contain high mannose. 'Viral envelope' is acquired by virions while budding out from their respective host cells, flaunting structural idiosyncrasies of plasma membrane of that cell type. Envelopes of virions produced in mosquito cells thus differ from those budding out from human cells, Richly 'mannosylated' envelope proteins (e.g. E1) of 'mosquito derived' DENV serve as ligand for putative 'attachment sites' on immature dendritic cells (DC-SIGN) macrophages and Monocyte derived DCs (Mannose receptors) or CLEC5A, all which are C type Lectins, sensing 'mannose'. E proteins of virions of 'human origin' that lack in mannose are not so recognized. Virions that initiate primary infection in man thus are 'mosquito derived'; the daughter virions released by the dendritic cells take over from then on, multiplying and spreading within the body, responsible for disease progression. It may be noted however, that they are of 'human cell origin' - with envelopes deficient in mannose content! Alternative modes exist, that allow cell entry of virus belonging to both phenotypes which require participation of antibody.

Fc alpha/mu Receptors' present on macrophages (and platelets) allow cell entry of virions bound to 'non-neutralizing' IgM antibody, that may occur during primary infection (non-neutralizing antibodies may be produced against immature virions with un-cleaved precursor envelope protein (PrM), that form ~30-40% of the virion population. Post zone phenomenon with sub threshold level of antibody is another reason cited for Fc entry) Fc gamma receptors allow virions to be carried in into Dendritic cells and M2 type macrophages as immune complexes formed with non-neutralizing class switched IgG. This happens during 'secondary infection' with a heterologous serotype which may lead to ADE.

Other putative attachment sites involved in DENV cell entry, include CD14 - HSP70/HSP90 complex in monocytes, Heparan sulfate (HS), Glucose regulated protein (GRP-78), Neolactotetraacyl ceramide in liver (targeted during DHF/DSS) and TIM and TAM trans membrane receptors (involved in phagocytosis of apoptotic cells).

Direct translocation of the genome into neighboring cells also has been described.

Significance: Mediation of the biological vector mosquito is required in natural cycle of transmission of DNV from man to man. This emphasizes the importance of vector control in dengue control.

The possibility of transmission of Dengue through blood transfusion/organ transplant or mother to child - involving the 'human phenotype', is discussed, however which is restricted by concomitant requirement of 'non-neutralizing antibody'

Differences between mosquito derived and human derived virions and their modes of cell entry, may be capitalized, in formulating drugs to treat primary infection (say, with mannose analogues? or soluble AsNs?) Similarly non neutralizing antibodies that purport ADE may be targeted (for instance, by competitive inhibition of 'PreM' binding).

So even in designing a vaccine that prevented natural infection with all the four serotypes of virus e.g. targeting a common site for glycosylation on CDIII (viz., AsN67).

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