ABSTRACT

Project code: BRG44-8-0004

Project title:
Identification and Characterisation of the Human Hepatocyte Receptor for Dengue Virus Infection.

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Over 2 billion people live in areas at risk of infections with the dengue virus, making the dengue virus a significant world public health issue. In Southeast Asia dengue virus infection is the leading cause of hospitalization amongst children, and it is predicted that the rate of infections will increase in the future. The dengue virus is transmitted by mosquitoes and replicates in the cells of the human host. The mechanism by which the virus enters into cells is of significant interest as it determines the tissue tropism of the virus, and ultimately the pathogenicity of the disease.

Our studies have focused on dissecting out the mechanism by which the virus enters into mammalian cells, and has primarily centered on the use of liver cells given that the liver is known to be a true target tissue for dengue virus replication. In addition we have undertaken studies that utilize strains of all four serotypes of the dengue virus. The times for the virus to internalize, replicate and be produced from the liver cells has been determined for each serotype, as well as the contribution of extracellular moieties such as glycosaminoglycans and proteins to the internalization process.

Using the technique of virus overlay protein binding assays, we have demonstrated that the proteins used to internalize the virus (the receptor proteins) are used in a manner that has a significant serotype specific element, and more over we have isolated and characterized a protein that acts as a receptor element for dengue virus serotype 2. This protein, GRP78 (BiP) normally functions as a molecular chaperonin, but its expression on the surface of a wide variety of cells has been well established. Blocking this protein on the surface of a cell with specific monoclonal antibodies reduces, but does not abolish entirely, the entry of dengue virus serotype 2 into liver cells. This protein does not seem to be involved with the entry of other serotypes into liver cells, suggesting that a wide variety of receptors can be use by the virus to enter into cells. Future work will involve isolating receptor proteins used by other serotypes to enter into liver cells.

Key words: BiP, dengue, hepatocyte, flavivirus, receptor.