# CELLULAR RESPONSES TO DENGUE VIRUS REPLICATION IN HEPATOCYTES: IMPLICATIONS FOR PATHOGENESIS

Andrea T. Da Poian

Instituto de Bioquímica Médica, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil

Dengue virus (DV) replication in its target cells elicits a number of cellular responses that may result in a large spectrum of clinical manifestations ranging from a mild self-limited illness to severe and potentially life-threatening diseases. Since liver dysfunction is a characteristic sign of the severity of DV infection, we have been studying several aspects of the effects of DV infection in a hepatic cell model using different approaches. We observed that infection causes alterations on the cellular secretory function, including secreted proteins and cytokines. Using different proteomic approaches, we analyzed the secretome of infected cells, allowing the identification of a total of 119 proteins, among which 35 were found only in control and 25 only in infected cells samples. The results include proteins present in human plasma and proteins of interest for dengue pathogenesis, such as $\alpha$-enolase, superoxide dismutase, cyclophilins, tissue inhibitor of metalloproteinases and macrophage migration inhibitory factor (MIF). We also found an increase in MIF secretion in both hepatic cells and macrophages, confirming previous data obtained with patients with severe dengue. In addition to the effects on protein secretion, dysfunction of mitochondria was also observed in hepatic infected cells, including alterations on ultra-structure, respiratory and bioenergetics properties of this organelle. The disturbance in mitochondria physiology caused by DV infection seem to be of particular importance to the process of apoptosis and resulted in a significant decrease in the content of intracellular ATP. Taken together, these results provide clues for the progress in the understanding of the role of liver secretion and liver cell damage in the progression of the disease.

Keywords: dengue virus; hepatic cells, proteome, metabolism