ROLE OF CA^{2+} IN ROTAVIRUS ENTRY AND ASSEMBLY IN CULTURED CELLS

Marie Christine Ruiz, Yuleima Díaz, Franshelle Peña, Olga Carolina Aristimuño, Maria Elena Chemello, Fabian Michelangeli.
Laboratorio de Fisiología Gastrointestinal, Centro de Biofísica y Bioquímica, Instituto Venezolano de Investigaciones Científicas (IVIC), Apartado 20632, Caracas 1020A, Venezuela;

Ca^{2+} plays a key role in many pathological processes, including viral infections. Rotavirus, the major etiological agent of viral gastroenteritis in children and young animals, provides a useful model to study a number of Ca^{2+} dependent virus-cell interactions. Rotavirus entry, activation of transcription, morphogenesis, cell lysis and particle release are Ca^{2+}-dependent processes. In the extracellular medium, Ca^{2+} stabilizes the structure of the viral capsid formed by three concentric protein layers. The mechanism by which rotavirus and other nonenveloped viruses enter the cell is still not clear. We have proposed an endocytosis model where the critical step for virus uncoating and membrane permeabilization is the decrease in Ca^{2+}concentration in the endosome. During entry into the cell the low cytoplasmic Ca^{2+} concentration induced the solubilization of the outer protein layer of the capsid constituted by VP4 and VP7. Ca^{2+} decreases in the endosome from 1.8 mM to a low concentration (nM) by diffusion. The positive potential generated by the vesicular H+/ATPase would further force Ca^{2+} out of the endosome. Low Ca^{2+} in the endosome would induce solubilization of VP4 (VP5*+VP8*) and VP7 and permeabilization of the vesicle to release double layer particles (DLP) in the cytoplasm and activate transcriptase. Newly form DLP bud into the ER for the acquisition of the capsid outer layer and requires a high Ca^{2+} concentration inside this compartment. Infection modifies Ca^{2+} homeostasis of the cell, increasing ER Ca^{2+} content, which may be advantageous to virus replication. The non-structural viral protein, NSP4, modifies Ca^{2+} homeostasis, which, in turn, favors viral morphogenesis and induces cell death.