INTERACTION OF THE DENGUE VIRUS FUSION PEPTIDE WITH MEMBRANES BY NMR: THE ESSENTIAL ROLE OF W101 OF THE E GLYCOPROTEIN FOR MEMBRANE FUSION

Manuel Nuno Melo[1,2,3], Francisco J. R. Sousa[1], Fabiana A. Carneiro[2], Miguel A. R. B. Castanho[3], Ana Paula Valente[2], Fabio C. L. Almeida[2], Andrea T. Da Poian[2], and Ronaldo Mohana-Borges[1]

[1]Instituto de Biofísica Carlos Chagas Filho, [2]Instituto de Bioquímica Médica, UFRJ, Brazil, and [3]Instituto de Medicina Molecular, Universidade de Lisboa, Portugal.

Dengue virus (DV) infection depends on a step of membrane fusion, which occurs at the acidic environment of the endosome. This process is mediated by virus surface glycoprotein E, in which the loop between residues D98-G112 is considered to be crucial, acting as a fusion peptide. We have characterized the interaction between the DV fusion peptide and different model membranes by fluorescence and NMR. Its interaction was strongest in dodecylphophocholine (DPC) micelles and in anionic PC:PG vesicles. The most striking result obtained from the solution structure of DV fusion peptide bound to DPC micelles was the hydrophobic triad formed by residues W101, L107 and F108, pointing toward to the same direction, keeping the segment between G102 and G106 in a loop conformation similar to observed in E glycoprotein structure solved by X-ray crystallography. The DV fusion peptide interaction with PG:PC vesicles was also mapped by transfer-NOE experiments, in which the NOE cross peaks were from the hydrophobic triad, corroborating the DPC-bound structure. Substitution of the residue W101 by an alanine residue completely abolished fusion mediated by the peptide. In conclusion, 15-residue DV fusion peptide has intrinsic ability to promote membrane fusion, probably due to the hydrophobic interaction among the residues W101, L107 and F108, which maintains its loop in the correct spatial conformation.

Keywords: dengue virus; fusion peptide; NMR