Is Paramyxovirus Hemagglutinin Transmembrane Domain involved in Virus-Cell Fusion? Computational Studies of Hydrophobic Profile and Membrane Orientation Depict Similarities with F Protein Fusion Peptide

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Membrane Fusion is the crucial process for cell life and it is adopted by enveloped viruses to enter into the cell. The virus-cell fusion process at acid pH induced by influenza virus HA is described at molecular level while fusion at neutral pH is poorly understood. Nevertheless the viral envelope glycoproteins, involved in fusion, share common features. The most important is that almost all viral systems seem to possess a fusion peptide (FP), which inserts obliquely into the membrane because of its peculiar hydrophobic gradient. The oblique insertion is thought to be the trigger of membrane fusion. Even if the molecular event, bringing the FP into the lipids, is still puzzling, it is known that the paramyxovirus-cell fusion requires the cooperative interaction between the hemagglutinin neuraminidase (HN) and the fusion (F) glycoprotein. The interaction seems to be very specific, in fact viral envelopes formed by HN or F derived from not homologous strains do not fuse. A study based on the Recurrence Quantitative Analysis (RQA) shown that the hydrophobic profiles of the homologous F and HN glycoproteins are correlated (1). However it was undefined which regions are responsible for the correlation.

Here we report an analysis of HN and F glycoproteins performed by an algorithm that is able to make the best local and global alignment of their hydropathy patterns. The algorithm can be run using different scales, different embeddings and hydropathy profile smoothness. Surprisingly the results, obtained for Sendai virus (SV) using Goldman-Engelman-Steiz hydropathy scale without smoothness, show that the best alignment occurs between the region containing the transmembrane domain (TMD) of HN and the region (as mirror image) of the F protein FP. Similar result has been obtained in the NDV case. These data prompted that, like FP, also the HN TMD might have a tilted orientation. Therefore the SV and NDV HN TMD were submitted to analysis with IMPALA algorithm, which was developed by Brasseur et al. (2) for predicting the membrane orientation of hydrophobic peptides. This method recognizes two segments in SV HN TMD and one in the NDV case, having high potentiality to be obliquely orientated in the viral membrane.

We are currently engaged to experimentally confirm these findings and particularly to understand whether or not an oblique orientation of HN TMD plays a role in virus-cell fusion.

1. Giuliani A, Tomasi M.(2002) Proteins. 46,171-176
2. Ducarme, P., Rahman, M., Brasseur, R. (1998)) Proteins 30, 357-371