**Quantitative microscopy approaches for the study of the interactions between Influenza matrix protein and host plasma membrane**

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Influenza is a prominent cause of mortality in modern society and a major burden on health systems globally. The Matrix Protein 1 (M1) is an essential component involved in the structural stability of the Influenza A virus (IAV) and in the budding of new virions from infected cells. During virus assembly, M1 is recruited to the host plasma membrane (PM) where it interacts with specific lipids and other viral proteins. The structure of M1 is only partially characterized and the molecular mechanisms determining how the protein interacts with the PM, as well as those governing protein-protein interaction and multimerization, have not been yet clarified. We quantitatively investigated M1 multimerization and its interaction with lipids, both in model membranes and in living cells. To this aim, we used a combination of biophysical techniques including FRET, confocal microscopy imaging, raster image correlation spectroscopy, CD spectroscopy, surface plasmon resonance and Number and Brightness (N&B) analysis. Our results show that M1 forms multimers upon interaction with phosphatidylserine (PS)-rich domains in the PM. Protein-lipid interactions are mediated by specific residues in the N-terminal domain of M1 and cause alterations in protein structure and intra-molecular dynamics. Our experimental findings are supported by molecular dynamics simulations as monomer in solution or bound to a negatively-charged lipid bilayer. Taken together, our results provide novel quantitative information regarding the molecular interactions between IAV and host cellular membranes.

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