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Role of conformational equilibrium in molecular recognition and capsid assembly: The case of flavivirus capsid proteins

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Proteins are dynamic entities able to move in a wide range of timescales that goes from picoseconds to seconds. Motions that occur in microseconds to seconds define biologically relevant events that are frequently involved in binding, allostery and catalysis. In our laboratory, we used relaxation parameter, relaxation dispersion experiments and molecular dynamic simulation to correlate conformational equilibrium with molecular recognition and catalysis. Dengue and Zika are major arthropod-borne human viral disease, for which no specific treatment is available. The flavivirus capsid protein is the trigger of virus assembly. Capsid proteins are located at the cytoplasm bound to lipid droplets (LD). Binding to LDs are essential for virus assembly. We previously showed that the positively charged N-terminal region of Dengue virus capsid protein prompts the interaction with negatively charged LDs, after which a conformational rearrangement enables the access of the central hydrophobic patch to the LD surface. We also showed the participation of the intrinsically disordered region in binding and possible regulation of capsid assembly. We probed the structure and dynamics of Dengue virus and Zika virus capsid proteins (DENVC and ZkC) by nuclear magnetic resonance. They bind lipid droplets (LD) in the cytoplasm, which mediates virus assembly in an unknown way. We showed that the dynamics of the capsid protein is intrinsically involved in the mechanism of LD and RNA binding and virus assembly. We also measured binding to nucleic acids and probed the assembly using small angle x-ray scattering and negative staining electron microscopy. The understanding and the participation of the intrinsically disordered N-terminal region and its dynamics helped us propose a mechanism for Dengue and Zika virus assembly and to develop a peptide with the potential to block virus assembly.

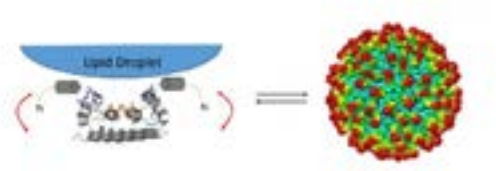

Figure1: *The role of conformational equilibrium in lipid droplets recognition and capsid assembly.*

Biography

Fabio C L Almeida has his expertise in protein structure and dynamics by nuclear magnetic resonance (NMR). He solved the structure of several proteins by NMR. He has important contribution in the structure and dynamics of plant defensins. He and his group showed that despite the conserved folding, defensins display a wide variation in dynamics, which enabled the mapping of binding regions and description of the mechanism of membrane recognition. The group also showed that dynamics are also the key for understanding the mechanism of membrane recognition of antimicrobial peptides. Pre-existent order in flexible peptides permits discrimination between the regions of specific and non-specific binding. His group has also described the structure and dynamics of the water cavity of thioredoxin, which is an essential structural element for catalysis. He is the Director of the National Center of NMR (CNRMN) and President of the Brazilian NMR Association (AUREMN).

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