BIOPHYSICAL CHEMISTRY: MEMBRANES, PROTEINS AND BEYOND.

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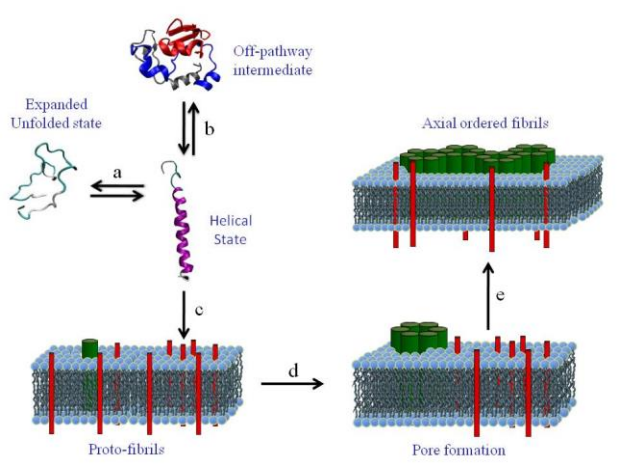

Fig. 1. Molecular model of pore and fibril formation consequently the interaction of human amylin and zwitterionic lipid membranes.

Our research is mainly addressed to clarify the molecular mechanism and driven forces involved in the folding-misfolding and aggregations of proteins. Moreover, since it was demonstrated the role played by membranes in this processes, our research also considers the interactions occurring between phospholipid bilayers and proteins. From knowledge fallout of this study will be possible to develop drug that prevent diseases as type II Diabetes, Alzheimer's, Parkinson's and Huntington's.

Keywords: Protein, Folding-Misfolding, Fibril, Membrane properties, Glycolipids, Theoretical models.

1. Interaction of phospholipid bilayers and proteins.

Pancreatic accumulation of islet amyloid polypeptide (IAPP, or amylin) into insoluble deposit is a common features of type II diabetic patient. IAPP in human, monkeys and cats form amyloid aggregates and these species are known to develop type II diabetes. Instead, rats and mice do not develop this pathology since rat and mice IAPP's do not show amyloidogenic features. Human IAPP (hIAPP) and rat IAPP (rIAPP) is a polypeptides containing 37 amino acid and differ only by six amino acid. In particular, rIAPP with respect to hIAPP contain three prolines which has some characteristic conformational restrains. The similarities between hIAPP and other amyloidogenic proteins also extend their ability to interact with lipid membranes, and several investigation have shown that such lipid-protein ineractions may play an important role in the pathogenesis of amyloid disease. Membranes have been implicated both as the targets of oligomer toxicity, via disruption of membrane integrity and as the catalyst that facilitates oligomer formation. By merging the available data and oour results emerge a scenarios where hIAPP in solution give rice to an equilibrium between random coil state, off-pathway intermediate not structured aggregates and a compact helical state. Moreover, in presence of zwitterionc bilayers, hIAPP quickly interact with the membrane in a first stage form pores followed by fibrils formation. Atomic Force Microscopy measurements show that pores are formed of amylin cluster (five or four) arranged a pentagonal or

square geometry. On the contrary, rIAPP in presence of zwitterionc bilayer do not form pores and fibrils. This results are summarized in the pictogram reported in fig 1.

2. Modelling of supra-molecular systems of biological relevance.

Analytical models, mainly based on statistical thermodynamics approaches, are currently developed in our group. Investigated topics include: Lipid Membranes structure and properties; Self-Assembling Systems; Physics of Macromolecules; Diffusion-Controlled Reactions; Chiral Systems; Chemical and Biochemical applications of the Fluctuation Theory.

Particularly active is the investigation of large aggregates (micelles, membranes) made-up of glycolipids, either isolated or mixed with other lipids. The bulky head of glycolipids introduces additional features to the chemico-physical properties of their aggregates in respect to those found in the case of common lipids. For instance, the conformational richness of the saccharidic heads, that may assume different spatial arrangements, gives rise to a variety of different phenomena such as: ultra-low bending energy, modulated spacing of the inter-lamellar distance in dense arrays of glycolipids bilayers, anomalous size behaviour of glycolipids micelles with micellar concentration, thermal hysteresis of the geometrical properties and so on. These studies are supported by Calorimetric and scattering measurements (Light (Milan), X-Rays (Trieste) and Neutron (Grenoble) scattering) performed in collaboration with several researchers of the University of Milan.

Recently, we are developing a model aimed at understanding the adhesion/fusion process between two lipid membranes. The model, based on a combination of viscoelasticity and electrostatic theories, investigates the nucleation and growth of a focal adhesion site induced by the bending fluctuations of two membranes brought at close contact. In most cases these focal contacts decay because of the unfavourable bending energy cost and electrostatic inter-membranes repulsion. However, when strong short-range adhesion forces are present, the contact site laterally expands, until complete short-range adhesion is reached. This intermediate structure further evolves because of the internal stresses of close adhering charged membranes, eventually leading to membrane destabilization and fusion between large lipid vesicles or cells.

This work, performed in collaboration with the Department of Mathematics of the Western Ontario University (Canada), has been implemented by extensive Molecular Dynamics simulations that basically confirm our conjectures based on the theoretical models.

Future developments will investigate the role of different parameters (ion concentration, membrane rigidity and viscosity, solvent properties, temperature, membranes surface charges, protein role and so on) on the adhesion/fusion rate.

Collaborations.

- Prof. A. Ramamoortly, University of Michigan, Ann Arbor, Michigan, USA.
- Prof. M. Kartunen, University of Western Ontario, Canada.
- Proff. M. Corti, L. Cantù, E. Del Bavero, University of Milano, Italy.
- Prof. G. Briganti, University La Sapienza, Rome, Italy.
- Dr. G. Zhavnerko, Belarus National Academy of Science, Belarus.

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Selected Publications

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