Eur Biophys J (2013) 42 (Suppl 1):S1–S236
DOI 10.1007/s00249-013-0917-x

9th European Biophysics Congress
Lisbon – Portugal – 13–17 July 2013

9th EBSA

European Biophysics Congress

July 13th – 17th 2013, Lisbon, Portugal

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EBSA Biophysics in Europe

This supplement was not sponsored by outside commercial interests. It was funded entirely by the publisher.

Acknowledgements

Sponsors:

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Abstracts

– Molecular Basis of Disease –

P-609

Dengue virus capsid protein interacts specifically with very low density lipoproteins

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Dengue virus (DENV) infects millions of people worldwide. With no specific treatment available, understanding its replication mechanisms is highly required to identify future therapeutic targets. In this study, using AFM-based force spectroscopy, DLS, NMR, and computational studies, we show that DENV capsid protein (C) binds specifically to very low density lipoproteins (VLDL) but not to low density lipoproteins (LDL). DENV C-VLDL binding is similar to DENV C interaction with lipid droplets (LDs), host intracellular structures essential for viral replication [1]. As on the DENV C-LDs binding, previously characterized by us [2-4], DENV C-VLDL interaction is K+-dependent, involves DENV C intrinsically disordered N-terminus, and is inhibited by pep14-23, a novel peptide drug lead against DENV [3,4]. As perilipin 3 (DENV C target on LDs [2]) is structurally similar to the VLDL protein ApoE, this protein may be the DENV C ligand on VLDL, enabling lipoviroparticles formation. The inhibition of this process may potentially be used as target on DENV life cycle inhibition.
References: [1] Samsa et al. (2009) PLoS Pathog 5:e1000632; [2] Carvalho et al. (2012) J Virol 86:2096; [3] Martins et al. (2012) Biochem J 444:405; [4] Patent no. WO2012159187

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Nucleosomal histones in neutrophils at patients with different types of COPD

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The purpose of research was studying of nucleosomal histones in neutrophils at patients with mixed (emphysematous and bronchial) and bronchial types of COLD. The composition of nucleosomal histones and histone H1 was examined in neutrophil's lyzats following the protocol of Markusheva L. et al. (2000). Patients were divided into 2 groups. 20 patients with mixed type of COLD (moderate severity, exacerbation, respiratory insufficiency of grade 2) were included in first group. Control group consisted of 20 subjects. 15 25 patients with bronchial type of COLD (moderate severity, exacerbation, respiratory insufficiency of grade 2) were included in second group. As compared to control ones the statistically significant change of the ratio of H1, H2A, H2B, H3 and H4 histones in neutrophils in patients with mixed type of COLD. The decreasing of histone H1 and sum fraction of histones Í2À, Í3 and Í4 was observed in neutrophils of patients with bronchial type of COLD as compared to control subjects and first group patients. Significant violations range nucleosomal histones and histone H1 in neutrophils of patients with bronchical type of COLD should be considered as a negative predictive setting, leading to a higher rate of progression of lung fibrosis.

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Concanavalin A fibrils formation from Coagulation of Long-lived "Crinkled" Intermediates

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Understanding the early events during the amyloid aggregation processes is crucial to single out the involved molecular mechanisms and for designing *ad hoc* strategies to prevent and reverse amyloidogenic disorders. Here, we show that, in conditions in which protein is positively charged and its conformational flexibility is enhanced, Concanavalin A leads to fibril formation *via* a non-conventional aggregation pathway. By different techniques (LS, CD, SAXS, Fluorescence and Confocal Microscopy) we highlight the formation of an on-pathway long-lived intermediate and a subsequent coagulation of such "crinkled" precursors into amyloid-like fibrils. In particular, the possibility to generate a long-lived intermediate open the way to new strategies to induce more stable *in vitro* on-pathway intermediate species depending by the initial conformational flexibility of the protein. This will allow isolating and experimentally studying such transient species, often indicated as relevant in neurodegenerative diseases, both in terms of structural and cyto-toxic properties.

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QM/MM study of HCV NS3/NS4A protease with its main substrates: from the structure to the kinetics

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We present a theoretical study of the reaction of the hepatitis C virus (HCV) NS3/NS4A protease with its main natural substrates (NS5A/5B, NS4B/5A, and NS4A/4B peptide junctions). This protease plays a key role in the HCV cycle because it is involved in the viral replication process inside the infected cell. The development of inhibitors of the NS3/NS4A protease has been and still is the main strategy in the fight against HCV. We applied a QM/MM technique which combines an accurate quantum method to describe the active site and a classical force field to take into account the effect environment where the reaction occurs.
The SCC-DFTB method with the CHARMM22 force field have been applied here as QM/MM method to describe:

- The ***potential energy surfaces*** and the ***minimum energy pathways***
- The ***free energy surfaces*** and ***potential mean force pathways,*** where T=300 K is considered
- The ***rate constants*** calculated by means of the TST adapted to be applied on enzymatic reactions

This study furnishes a satisfactory comparison with the experimental information available and suggests considering the barrier structures along minimum energy path as a useful starting point to guide the synthesis of a new type of inhibitors following a Transition State Analogues strategy.