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Abstracts

– Molecular Basis of Disease –

P-617

Local beta-sheet formation in 153-156delVKQV mutant of human TyrRS associated with CMT disease

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Certain mutations in human TyrRS (*Hs*TyrRS) lead to Charcot-Marie-Tooth disease (CMT) – a group of heterogeneous inherited disorders that are characterized by degeneration of peripheral nerve fibers. Currently, three heterozygous missense mutations (G41R, E196K, K265N) and one *de novo* deletion (153-156delVKQV) in *Hs*TyrRS were identified in patients with CMT disease.
Since 3D structures of all 4 CMT *Hs*TyrRS mutants are still unknown, we performed computational modeling of mutant proteins structures using Modeller v9.7 software. Molecular dynamics (MD) simulations were carried out using GROMACS 4.0.7 (FF G53A6). All MD simulations and analysis of trajectories were performed using the MolDynGrid virtual laboratory services (*http://moldyngrid.org*).
In general, structures of *Hs*TyrRS mutants revealed less relaxed states with higher values of RMSD and higher values of gyration radii. The melting of H9 helix (T141-A148) and subsequent partial melting of H11 helix were observed in 153-156delVKQV mutant TyrRS. A novel beta-sheet formation was observed in S145-V152 region for 5-65 ns time interval.
Hence, the CMT-causing mutations in *Hs*TyrRS could be understood in terms of long-range structural effects on the dimer interface and local beta-sheet formation in CP1 region.

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Divalent Cations dependence of the fibrinogen binding to its receptor on human erythrocytes

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The glycoprotein $\alpha_{IIb}\beta_3$ is the platelets integrin receptor for fibrinogen. Its activation is Ca^{2+}-dependent. Our previous studies showed that fibrinogen binding to its receptor on human erythrocytes is also impaired when calcium ions are removed from the medium [1]. From this point, we intended to study the influence of two additional divalent cations, $Mg^{2+}$and Mn^{2+}, and EGTA (a calcium chelator) on the interaction of fibrinogen with erythrocytes. By atomic force microscopy (AFM) based force spectroscopy, we determined the force necessary to break the bond between fibrinogen and erythrocytes, at the single-molecule level, as well as the binding frequency of this process. For the sake of comparison, similar measurements were done in parallel with platelets. Our results revealed that erythrocytes are more prone to bind fibrinogen in the presence of Mg^{2+} than with Ca^{2+} or Mn^{2+}. A higher binding with Mg^{2+} relative to Mn^{2+} was also observed for the fibrinogen-platelet interaction, but both with a lower strength than in the presence of Ca^{2+}. Therefore, the presence of magnesium ions seems to be the most relevant for the activation of the poorly characterized erythrocytes receptor for fibrinogen.
[1] Carvalho *et al.* (2010) *ACS Nano*, 4, 4609

P-619

FTIR and Resonance Raman studies on the coordination of Aβ16 with Cu(II) and Zinc (II)

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There is a broad interest in protein/peptide aggregation, since they represent a common feature of several degenerative diseases. An example is the amyloid beta (Aβ) peptide that plays a crucial role in Alzheimer's disease (AD); Cu-ions have been proposed to be linked to the aggregation cascade of the Aβ peptide and to be involved in the generation of ROS. Zn ions are eventually able to prevent this generation. The strongest binding sites for these metal ions are found in the N-terminal portion; that is why the truncated Aβ portion (1-16) is a valuable model for the study of the molecular basis of this disease.
For the coordination of Cu(I) and Cu(II) we studied the reorganization of the Aβ16-Cu-peptide upon redox reaction with electrochemically induced FTIR difference spectroscopy. For the Zn(II) we examined the coordination through FTIR and Resonance Raman. Different labeled samples and small model compounds have been analyzed. The complexes were prepared at different pH (6.8 and 8.9) simulating the two major complexes found at physiological pH. The data reveals that Cu binding involves Asp1, His6, His13 and His14. Changes in coordination upon reduction are found. The comparison between the Cu (II)-Aβ and the Zn(II) Aβ points towards different coordinations of the histidines.