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CONFORMATIONAL CHANGES IN HUMAN TYROSYL-tRNA SYNTHETASE STUDIED IN THE MOLDYNGRID VIRTUAL LABORATORY

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MolDynGrid (http://moldyngrid.org) is one of the first web-oriented virtual laboratories (VL) in Ukrainian National Grid infrastructure (UNG, http://ung.in.ua/) dedicated to computational structural biology and bioinformatics, particularly to molecular dynamics (MD) simulations of biological macromolecules and their complexes [1]. The project goal is providing efficient infrastructure for automation of MD simulations and trajectories analysis in Grid computing environment NorduGrid ARC as well as EGI-based. In addition to standard MD analysis techniques provided by the GROMACS package (http://www.gromacs.org/), MolDynGrid VL features advanced analysis tools such as Pteros molecular modeling library (http://pteros.sourceforge.net/) and Distributed Analyzer Script (DAS) [1].

Currently MolDynGrid VL is used for MD simulations of various proteins with an emphasis on tyrosyl-tRNA synthetases (TyrRS). Human TyrRS is the key enzyme of protein biosynthesis, which catalyzes the aminoacylation of $tRNA^{Tyr}$. The 3D structure of this protein is still unknown. The full-length *Hs*TyrRS does not reveal cytokine activity, but its proteolytic cleavage reveals IL8-like activity of the N-terminal catalytic module and EMAP II-like activity of non-catalytic C-terminal domain. It was shown that the ELR-motif (E91, L92, R93) in TyrRS is responsible for IL8-like cytokine activity [2].

In this work we constructed the model of the full-length *Hs*TyrRS structure and studied its putative compactization by all-atom MD simulations [3]. All computations were performed using grid services of the MolDynGrid virtual laboratory. Three-dimension structure of *Hs*TyrRS was constructed in Modeller 9.7 using structure templates (1N3L, 1NTG and 1OPL for interdomain linker). Six independent 100 ns MD trajectories of *Hs*TyrRS were computed using GROMACS 4.0.5 software in G43a1 force field. The Contacts Analyzer Script (CAS) and the tRMSF tool of the Pteros molecular modeling library were used for analysis. The Distributed Analyzer Script was used for analytical tools automation.

The strongest binding energy of ~1000 kJ/mol is observed for the second C-module of *Hs*TyrRS. Antiparallel β-sheet formation in Ala 355 – Val 363 region was revealed for 3-100 ns time interval (~ 85 % of time). Extensive MD simulations, which were possible in the ARC-based UNG infrastructure, allowed us observing the hydrogen bonding between the residue R93 of the ELR motif and the residues A340 and E479 in C-module and finding local conformational changes (antiparallel β-sheet formation) in Ala 355 – Val 363 region. These findings support the idea that the full-length TyrRS lacks its cytokine activity because of the interactions between N-terminal and the C-terminal modules, which protect the ELR cytokine motif [4].

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