Dynamical structure changes of M. tuberculosis tyrosyl-tRNA synthetase revealed from molecular dynamics simulations using grid technologies

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Tyrosyl-tRNA synthetase from M. tuberculosis (MtTyrRS) is an enzyme of structural class I of aminoacyl-tRNA synthetases that catalyzes the attachment of tyrosine to the 3' end of cognate tRNA to form a tyrosyl-tRNATyr. MtTyrRS plays a key role in metabolism of M. tuberculosis cells and is not able to cross-recognition and aminoacylation of human cytoplasmic tRNATyr. Therefore this enzyme may be considered as a promising target for development of novel drugs against tuberculosis.

In order to study the enzyme conformational mobility and active site flexibility of MtTyrRS, we have performed 100 ns molecular dynamics (MD) simulations using computational grid technologies. Crystalline 3D structure of MtTyrRS dimer (PDB code 2JAN) was used to complete the missing amino acid residues at the A-subunit (M1-M4 and G424) and B-subunit (M1-M4 and P81-D93) by ModLoop server. In order to optimize 3D protein structure, the energy minimization was done using YASARA web server. All MD simulations of MtTyrRS dimer were performed under physiological conditions at 310 K using GROMACS program package with the AMBER99SB-ILDN force field. MD simulations were calculated at the Ukrainian National Grid clusters using the services of MolDynGrid virtual laboratory (http://moldyngrid.org).

It was found that after structure relaxation for 20 ns, the most flexible parts of MtTyrRS were the disordered KFGKS catalytic loop and C-terminal domain. Due to the high flexibility, the disordered KFGKS loop dynamically forms two β-strands at the active site. The movement of C-terminal modules can be described as deviations and closing-in to the N-terminal domains, that leads to loss of symmetrical form of the enzyme dimer. Our MD simulations data of enzyme active site flexibility are useful for virtual screening and docking of potential inhibitors of MtTyrRS as novel antituberculosis drugs.