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A new tRNA-assisted mechanism of post-transfer editing by aminoacyl-tRNA synthetases

National Academy of Sciences of Ukraine, Ukraine

S a f P b : Aminoacyl-tRNA synthetases (aaRSs) maintain delity during protein synthesis by attaching amino acids to their cognate tRNAs. For many aaRSs, the required level of amino-acid speci city is achieved either by speci c hydrolysis of misactivated aminoacyl-adenylate intermediate (pre-transfer editing) or by hydrolysis of the mischarged aminoacyl-tRNA (post-transfer editing). Both reactions are depend on a tRNA cofactor and required translocation to the editing site located in the separate domain. In this work we have studied molecular mechanisms of editing by synthetases from two di erent classes: ermus thermophilus leucyl-tRNA synthetase (LeuRSTT) from class I and Enterococcus faecalis prolyl-tRNA synthetase (ProRSEF) from class II.

M & ca O a : To investigate the mechanism of post-transfer editing of norvaline by LeuRSTT and alanine by ProRSEF, we used molecular modeling, molecular dynamic (MD) simulations, quantum mechanical (QM) calculations, site-directed mutagenesis of the enzymes and tRNA modi cation. e transition states of the reactions were identi ed.

F : e results support a new tRNA-assisted mechanism of hydrolysis of misacylated tRNA which directly involves two water molecules. e most important functional element of this catalytic mechanism is the 2' or 3'-OH group of the terminal adenosine 76 of aminoacyl-tRNA, which forms an intra-molecular hydrogen bond with the carbonyl group of the misacylated residue. Bonding increases the electrophilic character of the carbon atom and strongly facilitates the subsequent nucleophilic attack by water molecule.

C & S ca : Class I LeuRS and class II ProRS with a di erent architecture of editing site have both tRNA-assisted mechanism of post-transfer editing in which free 2' or 3'-OH group of the substrate plays a key role in hydrolysis by forming an intra-molecular hydrogen bond with the substrate amino-acid carbonyl group. Proposed editing mechanism is signi cantly di erent from those described in the literature for class-I and class-II aaRSs.

mtukalo@imbg.org.ua

Advances in recent enzymology

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