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Lysyl-tRNA Synthetase Pre-Transfer Editing Mechanism

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Aminoacyl-tRNA synthetases are presumably very ancient enzymes that are thought to play key roles in a diverse range of physiological processes including viral assembly, inflammation, cell death, and protein synthesis. Specifically, they catalyze the covalent attachment of their respective amino acids to the corresponding cognate tRNAs.\(^1\) This process occurs via two half-reactions. In the first, the amino acid is activated via reaction with ATP to give the aminoacyl-adenylate. The latter then is reacted with its cognate tRNA to give the desired aminoacyl-tRNA. Remarkably, despite their ancient nature, these enzymes are amongst some of the most accurate known. It is thought that they at least in part exploit pre- and post-transfer editing mechanisms to ensure no mis-acylation of the tRNA occurs. Unfortunately, how these mechanisms may occur is unknown. In addition to its obvious biological importance, a greater understanding of such processes could also lead to the development new catalysts or therapeutic agents.

We have used a multi-scale computational chemistry approach to investigate possible mechanism(s) of pre-transfer editing in lysyl-tRNA synthetase (LysRS). Specifically, the mechanisms by which it transfers its native substrate lysyl and the non-cognate amino acid ornithine onto its cognate tRNA has been examined using docking, molecular dynamics and QM/MM methods. The complementary application of such computational methods provides insights that no single method, or experimental study can provide. Some recent results and key findings from our studies will be presented.

References