



CHEMISTRY

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SEMINAR SERIES

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Experimental and Theoretical Investigations of Modified Nucleotides in RNA

RNA modifications are known for their importance in mediating cellular activities and are often located in functionally important regions. There are over 100 naturally occurring nucleobase modifications having distinct impacts on RNA function. Despite their high abundance, many properties and roles of RNA modifications are still poorly understood. Our laboratory employs various experimental and theoretical methods to increase our understanding of modified nucleotides. Examination of pseudouridine sequencing data by the region in which the modification occurs on the mRNA reveals certain trends. Pseudouridylated mRNAs have favored sequences surrounding the site of modification and display higher enrichment in sequences that have specific cellular functions; with differences in RNA structural effects of pseudouridylation.

One important physical property of a modified nucleotide is its pKa value. To determine the effects of modifications on the pKa values of pyrimidines and purines, ab initio quantum mechanical calculations in conjunction with an implicit-explicit solvation system were used. This method provides insight into how modifications affect the pKa values at protonatable positions.

The ribosome contains numerous RNA modifications located in important regions involved in ribosome assembly and function. One functionally important RNA hairpin, helix 69, located on the large ribosomal subunit, has three pseudouridine modifications that promote base flipping required for association with the small subunit. By examining small molecules and peptides that target helix 69 in varying conformation states, we can gain a better understanding of the binding preferences of these antimicrobial compounds. Performing experimental and theoretical studies of modifications leads to knowledge of their roles in mediating RNA structure and reactivity.