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Structural landscape of base pairs containing post-transcriptional modifications in RNA

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Base pairs involving post-transcriptionally modified nucleobases are believed to play important roles in a wide variety of functional RNAs. Here we present our attempts toward understanding the structural and functional role of naturally occurring modified base pairs using a combination of X-ray crystal structure database analysis, sequence analysis, and advanced quantum chemical methods. Our bioinformatics analysis reveals that despite their presence in all major secondary structural elements, modified base pairs are most prevalent in tRNA crystal structures and most commonly involve guanine or uridine modifications. Further, analysis of tRNA sequences reveals additional examples of modified base pairs at structurally conserved tRNA regions and highlights the conservation patterns of these base pairs in three domains of life. Comparison of structures and binding energies of modified base pairs with their unmodified counterparts, using quantum chemical methods, allowed us to classify the base modifications in terms of the nature of their electronic structure effects on base-pairing. Analysis of specific structural contexts of modified base pairs in RNA crystal structures revealed several interesting scenarios, including those at the tRNA:rRNA interface, antibiotic-binding sites on the ribosome, and the three-way junctions within tRNA. These scenarios, when analyzed in the context of available experimental data, allowed us to correlate the occurrence and strength of modified base pairs with their specific functional roles. Overall, our study highlights the structural importance of modified base pairs in RNA and points toward the need for greater appreciation of the role of modified bases and their interactions, in the context of many biological processes involving RNA.

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