Cooperative Roles of RNA 2' Sugar Modifications and Minor Groove Solvation on RNA Shape and Dynamics

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In the development of RNA aptamers and siRNA, the success of synthetic RNA for therapeutic purposes relies heavily on chemical modifications to enhance both functionality and degradative resistance. Chemical modification strategies have primarily been aimed at the nucleobase as well as the sugar–phosphate backbone. siRNA chemical alterations, such as those on the recently FDA approved therapies Patisiran and Givorsiran, are focussed on the decoration of multiple 2' ribose positions aimed at creating favourable pharmacokinetic properties without compromising intrinsic RNAi activity. The impacts of these various 2' modifications remain largely unexplored with respect to their synergistic effects on RNA secondary structure and the source of such changes. In this research, we investigate a number of commonly used as well as newly proposed 2' fluorinated nucleotides as single and multiple modified motifs on a 15-nucleotide hairpin model containing a GCAA tetraloop. Microsecond molecular dynamics simulations and subsequent detailed analysis of the modified models reveals sequence-dependent fingerprints of the structural influence of the 2' modifications on nucleobase orientations mediated through local solvation changes. As a result, this work introduces a set of potential guidelines concerning the structural stability and downstream effects when incorporating multiple chemical changes into the RNA duplex backbone.