RNA Knot: Topological-Based Prediction of Proviral DNA Expression

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The m6a methylation of the TAR region promotes neuroinflammation in HIV-1 neurocognitive disorders. This is facilitated by the RBM15 protein recognizing and binding U-rich bulges to act as a site marker for methyltransferase. Therefore, RNA deformation agents like microRNA are promising drug candidates. RNA Knot is designed to predict the tertiary structure of functional RNA and identify optimal sites for microRNA attachment. However, current RNA structure prediction softwares rely on free energy minimization, which does not address intermediary states that emerge during accessory protein interactions. The software presented instead converts an oligonucleotide atomic coordinate map to a spherical planar knot, where the weights of each node are defined by the nucleic acid base. Sequences of Reidemeister moves are iterated to optimize the Laplacian of the knot so that multiple primer binding sites can be simultaneously expressed while preserving stability. An energy heat map is then generated, from which high binding-affinity sites are extracted. This approach identified a region of methylome Peak 12 in the HIV-1 genome (base 8450-8480, concordant with the TAR region) as a target for microRNA-mediated inhibition. The model showed an 88.2% accuracy rate and an 83% sequence validity. Furthermore, RNA Knot simulates the effects of sequence-specific ligand binding by inducing downstream stem loop formations to stabilize docking via inverse folding. An RNA molecule was synthesized to match the modified TAR region modeled by RNA Knot. Binding of RBM15 to this molecule was measured using gel electrophoresis, finding significant inhibition of SAM-domain attachment to complementary binding sites.

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