Human riboswitch: are we close to predicting it?

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RNA molecules are essential cellular players for many fundamental biological processes. Distinct RNA classes present structural features with specific functional roles in prokaryotes and eukaryotes. Similar to proteins, the RNA structure may be subject to changes due to the interaction with various ligands, including proteins, other RNAs, and metabolites. Riboswitch is a molecular mechanism in which the RNA structure changes based on specific metabolite-RNA binding. A riboswitch can regulate gene expression in different aspects, such as the attenuation of transcription, translation initiation, mRNA splicing and mRNA processing. In many cases, they are involved in the regulation of key genes, which makes its control an essential part of cell survival. Most studies on riboswitches investigated their existence in prokaryotic organisms. In eukaryotes, TPP riboswitches have been found in fungi, algae, and plants. In animals, riboswitches have yet to be identified. The focus of this work is to determine potential riboswitches in the human genome. The study was conducted in three stages: (i) search for candidate riboswitch in the human genome, using the Infernal software that searches DNA sequence databases for RNA secondary structure and sequence similarities; (ii) modeling the three-dimensional structure of a candidate sequence using ModeRNA software; (iii) molecular dynamics simulations using package Gromacs to verify the stability of the modeled structure and compare it to the template. A sequence candidate TPP riboswitch in the mRNA transcript variant FBLN2 gene was identified. This sequence has 55% identity with the *Escherichia coli* TPP riboswitch (PDB Id: 2GDI:X) and 84% conserved residues for this type of riboswitch. As the TPP riboswitch has its conserved 3D structure, we performed comparative modeling using the structure 2GDI:X as a template. The model presented RMSD of 0.7Å with the template. Model and template were submitted to 1 μs of molecular dynamics simulations each. The template presented RMSD values of 0.36±0.02 while the model showed a higher value of 0.50±0.03 nm. Despite the conformational change, the model kept the base pairing and secondary structure without modifications in helix P1, P2, P5 and loop L5. Perspectives foresee a study on the candidate's affinity for the ligand, by molecular docking assays and new molecular dynamics simulations of RNA-ligand complex.

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