RNA molecular recognition and self-assembly into nanoparticles

(Article submitted for presentation only)

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1. INTRODUCTION

Biomolecular nanostructures hold a tremendous promise for effective use in such applications as drug delivery, nanoelectromechanical systems, molecular sensors, and molecular lithography. Nucleic acids are especially appealing molecules for nanodesign due to versatility in function and structure. RNA, for example, can carry genetic information, posses catalytic properties and can naturally fold or can be programmed to self-assemble into complex structures. Complex RNA molecules can be engineered into novel nanostructutures using the straightforward molecular recognition properties of base pairing. RNA molecules can make up effective 2D and 3D nanoparticles, nanotubes and scaffolds for the assembly of molecules or electronic components. Moreover, protein-free RNA nanoparticles do not induce a detectable immune response which makes them an attractive material for use in medical applications and drug delivery. However, the 3D structures are not determined by base pairing alone and unpaired residues play a critical role in nanodesign and super-assembly. At the present time there is a limited understanding of the rules of formation of RNA superstructures. Techniques for a scalable nanoassembly suffer from errors that are due to inherent limitations in the specification of contacting motifs and the control over hybridization kinetics. For successful design we need to understand and control the intermolecular associations, base on natural tendency and favorability and various physical components. Fundamental advance in understanding of the complex assembly of RNA molecules may further advance use of RNA building blocks for nanotechnology.

Computational techniques are used to elucidate dynamical processes in materials and can assist and accelerate nanodesign. We use molecular modeling to provide critical information on self-assembly processes of natural and synthetic RNA. This information is used for *in silico* design of novel RNA nanomaterials. The computational analyses are done at different levels of details. An accurate atomistic modeling is used for modeling of biopolymers, nanoparticles and interactions between sets of complex biomolecules and interfaces. Complex large-scale model is being developed for simulations of macromolecules, multi-level molecular complexes, and RNA nanomaterials.

2. RESULTS

The most common motifs found in nature and used in bionanotechnology are hairpin loops which consist of a helical part and a loop with unpaired residues. The unpaired residues in these elements can lead to further super-assembly of RNA structures via formation of the “kissing loops” motifs. These kissing loops motifs regulate gene expression in different viruses and organisms and are also actively used in bionanotechnology for self-assembly of RNA building blocks into novel nanostructures.

It has been observed that the super-assembly of RNA directly depends on the presence and specific concentration of ions.

In order to understand the role of ions in kissing loops formation and stability, we conducted a series of explicit solvent atomistic molecular dynamics simulations of ten distinct kissing loops elements taken from various organisms. The RNAs starting coordinates were taken from solved NMR and crystal structures. In our simulations we varied the concentration of different ions (such as Na^{+}, K^{+}, Mg^{2+}, and Cl^{-}) from zero to 1M solution and examined known destabilizing mutations. We found that loop-loop assembly process depends heavily on the presence of specific electronegative and hydration channel located directly inside the kissing loops part of the motif. We observed that the size of this channel directly relates to the stability and sequence of the RNA motif. Moreover, different types of ions play distinct role in stability. The sequence also determines the way loop and loop motifs participate in hydrogen bonding interactions and the angle of the distinct kink between stems. The angle of these kinks ranges from 30^{o} to 180^{o} degrees. Using the diversity of these angles we engineer the assembly of simple RNA building blocks via kissing loops motifs into nanostructures of a predefined geometry, such as RNA triangles, RNA rings, and RNA cubes. The primarily goal of this project is to provide fundamental understanding of the mechanism of self-assembly of RNA molecules and building blocks into functional nanodevices. Controlling these processes is necessary to build nanodevices for efficient drug delivery devices and bioscaffolds. Such novel biosensoring nanoparticles and nanomaterials will lead to new diagnostic and therapeutic approaches to human disease. Moreover, further investigation of molecular mechanisms should help elucidate the roles of RNA in bacterial genetic circuitry and allow us to build a more complete picture of the structures and functions of complex RNAs.