How To Effectively Construct Nanoscale RNA/Dendrimer Complexes

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RNA molecules have been emerging as important therapeutic agents for treating various diseases since the discovery of the catalytic RNA ribozymes and the small interfering RNA molecules (siRNA).1 However, the successful use of RNA for therapeutic purposes depends critically on efficient means of RNA delivery.We have been studying the use of polyamidoamine (PAMAM) dendrimers as self-assembling RNA delivery systems.2-4 We recently reported that the PAMAM dendrimers and the RNA molecules formed spontaneously self-assembled RNA/dendrimer complexes2-4 and established that higher generation PAMAM dendrimers are efficient siRNA delivery vectors.4

Although various aspects of the formation of nanometric DNA/dendrimer complexes have been described in the literature for DNA delivery, few efforts have been made so far with RNA/dendrimer complexes. We have therefore employed atomic force microscopy (AFM) to study various RNA/dendrimer complexes using PAMAM dendrimers, and various RNA molecules such as siRNA (21 bp), the *Candida* ribozyme (368 nt, a self-splicing group I intron of the fungal pathogen *Candida albicans*), and the poly(rU) (>2000 nt, an important component of the polyribonucleotide immunomodulators).

Our results indicate that effective construction of uniform, stable nanoscale RNA/dendrimer complexes depends strongly on the charge ratio between dendrimer and RNA, the size of the RNA molecules and the generation of the dendrimers.5 The charge ratio is one of the most important factors which need to be taken into account in the construction of RNA/dendrimer particles. At the high N/P ratio of 10, **G7** formed the most homogeneous spherical particles with various RNA molecules. With small RNA molecules such as siRNA (21 bp), only dendrimers of high generations can form stable, uniform and well-defined nanoscale siRNA/dednrimer particles; whereas with larger RNA molecules such as the ribozyme Ca.L-11 (368 nt) and poly(rU) (> 2000 nt), dendrimers from generations 1 to 7 readily form nanoparticles with RNA. All these findings provide useful information for designing appropriate dendrimers for use in the construction of stable nanoscale RNA/dendrimer complexes providing efficient delivery systems for RNA molecules of various sizes.

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