Virus-mimic DNA nanoparticles have hollow shell architecture

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ABSTRACT

DNA, an extended negatively-charged polymer, condenses into compact nanoparticles in the presence of polymeric cations. We report the detailed organization of DNA within nanoparticles condensed with mannose-modified polyethyleneimine. Mannose-modified DNA nanoparticles have been used in gene therapy for targeting the dendritic cells of the immune system. Dendritic cells endocytose the nanoparticles via surface receptors for mannose, a mechanism exploited by viruses to enter these cells. Mannose-modified nanoparticles are currently in clinical trials as a DNA-based vaccine against HIV. We probed the three-dimensional arrangement of DNA within the mannose-modified nanoparticles by nano-indenting them in fluid with Atomic Force Microscopy (AFM). At small indentations, the nanoparticles behaved like a rubbery elastic material. At larger indentations, however, they exhibited a classic buckling-like response, which was reversible and not due to particle damage. The rate of buckling decreased with indentation. Such poroelastic mechanics can be explained by high fluid content in the particle core. We confirmed the relative absence of DNA in the particle core by imaging with Transmission Electron Microscopy. We also estimated the fluid content of each nanoparticle by correlating their volumes in solution against that in dried state. The volumes were measured with Dynamic Light Scattering and AFM. The water content varied with nanoparticle size in a manner expected for hollow shells with wall thickness of 2 - 3 DNA. The water content was ~95% for nanoparticles in the 50 – 300 nm diameter range (virus-like dimensions effective for gene therapy). We probed the DNA arrangement in the wall of the nanoparticles by using 1 kb DNA to slow down nanoparticle assembly and imaging the intermediate stages with AFM. Extended DNA initially folded into rod-like structures. The rods assembled into interwoven networks, which compacted around condensation loci to form nanoparticles. The interwoven network arrangement could be visualized on the surface of fully formed nanoparticles with AFM phase imaging. The study showed that the mannose-modified DNA nanoparticles are hollow, with a water-filled core and woven-DNA shell. The implication of this architecture for gene therapy needs to be studied. Our study also presents new

strategies for improving the gene-therapy efficacy by entrapping drugs and biomolecules in the nanoparticles for co-transport along with the DNA vaccine.