**Hyaluronic Acid/Chitosan Nanoparticles for Nucleic Acid Delivery**

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Abstract

Chitosan/hyaluronic acid (HA) nanoparticles combine the ability of polycation chitosan to encapsulate nucleic acids via electrostatic complexation with the CD44 targeting capabilities of hyaluronic acid, allowing selective gene delivery to malign cells over-expressing CD44 membrane receptor such as the HCT116 colorectal tumour cell line. When designing such drug delivery systems it is important to stablish correlations between macromolecular parameters (molecular weight; degree of deacetylation, i.e., charge density) and nanoparticle variables (complexation strength, i.e., stability; nucleic acid protection; internalization rate) on one hand, and transfection efficiency on the other hand. Here, we analysed the influence of these macromolecular/particle variables in the transfection efficiency of nanoparticles encapsulating either a short siRNA or a much larger mRNA. By analysing a small library of nanoparticles varying in complexation strength (avidity modulated by the molecular weight and degree of deacetylation chitosan, plus the molecular weight of the nucleic acid), we observed a strong correlation between the avidity of the complex and the easiness of nucleic acid cargo release. However, transfection efficiency did not follow the same tendency (higher transfection due to easier decomplexation of the nucleic acid in the cytosol); surprisingly, we observed a higher efficiency in those particles with the lowest propensity for RNA release. This seemingly contradictory result was ascribed to a higher ability of the more cationic chitosans (large molecular weight and degree of deacetylations) to escape endo/lysosomal compartments.