siRNA and mRNA Delivery with Chitosans

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RNA delivery can be acheived by packaging in lipid or polymeric nanoparticles or by chemical modification and conjugation with targeting entities. The cationic natural-derived glucosamine-based polymer chitosan has been used for two decades, intially to deliver plasmid DNA, and subsequently siRNA and mRNA. Our previous studies of polyelectrolyte complexes of chitosan with these different nucleic acids has revealed significant differences in bioactivity that depend on the molecular weight (MW) of chitosan and its degree of deacetylation (DDA) which determines charge density and degradability. We found that particular combinations of low MW and high DDA were required for plasmid and were different from those where siRNA is most active that included high MW chitosans in the presence of high serum content. Physicochemical measurements of binding affinity and FRET-based imaging in cells showed that the binding affinity of chitosan to the nucleic acid was a main factor in controlling bioactivity through balanced protection against nuclease activity and effective release of payload intracellularly[1]. In vivo studies of siRNA knockdown in mice using tail-vein injections showed high targeting and knockdown of a reporter in proximal tubule epithelial cells in the kidney cortex, most likely through a process involving receptor mediated uptake of chitosan bound to siRNA by these cell types[2]. In the most recent study with mRNA we found that complexes of chitosan and an mRNA Luciferase reporter could express the mRNA in vitro most effectively when chitosan MW was lowest (5kDa) but only at slightly acidic medium pH which was not a requirement for siRNA activity. Coating these binary polyelectrolyte complexes with low molecular weight hyaluronic acid that was also sulfated increased expression and this expression was further increased when complexes were formed in the presence of trehalose, but again only at slightly acidic pH since expression at pH 7.3 was still very low for these systems. The main conclusion of this sequence of studies using chitosans to deliver RNA is that careful selection of chitosan molecular weight and DDA is needed for each type of nucleic acid and that siRNA/chitosan complexes can be directly bioactive in vivo while mRNA/chitosan activity needs to be acheived through further optimisation and modification of these systems.

1. Thibault M et al., Biomaterials 32 : 4639-4646, 2011
2. Alameh MG et al., Biomacromolecules,19 (1), 112–131, 2018
3. Soliman OY et al., submitted 2018.