Nanotechnologies for targeted delivery of nucleic acid

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Hyaluronic acid (HA) is a glycosaminoglycan, the main constituent of the extracellular matrix and the natural ligand of CD44 receptor. The association of HA with nanotechnology allow to target the cancer stem cells through the CD44 receptor overexpressed on the surface of these cells. Lipoplexes containing a HA-dioleoyl phosphatidylethanolamine conjugate (HA-DOPE) were designed for this purpose. They were prepared from cationic liposomes and used to complex small interfering RNA (siRNAi). Targeting the CD44 receptor on lung cancer cells was shown to improve the inhibition effect of siRNA using the luciferase gene as a target. The internalization mechanism of the lipoplexes was shown to be mediated by both the CD44 receptor and caveolae. This approach has been applied successfully to deliver the same siRNA anti-luciferase in a mouse model of lung metastases demonstrating a higher inhibition than the non-targeted formulation. We have also associated an aptamer antiCD44 to the surface of liposomes. These vectors have also shown great potential for siRNA delivery in vitro and in vivo to cells overexpressing CD44 avoiding the toxicity problems related to lipoplexes. These data validates the relevance of CD44 as a target for the delivery of macromolecular drugs by nanotechnology. Finally, we have designed inhaled formulation for siRNA delivery in the treatment of lung injury disease, to reduce inflammation. Dendriplexes delivery of an antiTNF siRNA have shown, after intratracheal administration, a potent inhibition of this cytokine demonstrating the potential of nanotechnologies to also deliver locally the siRNA.