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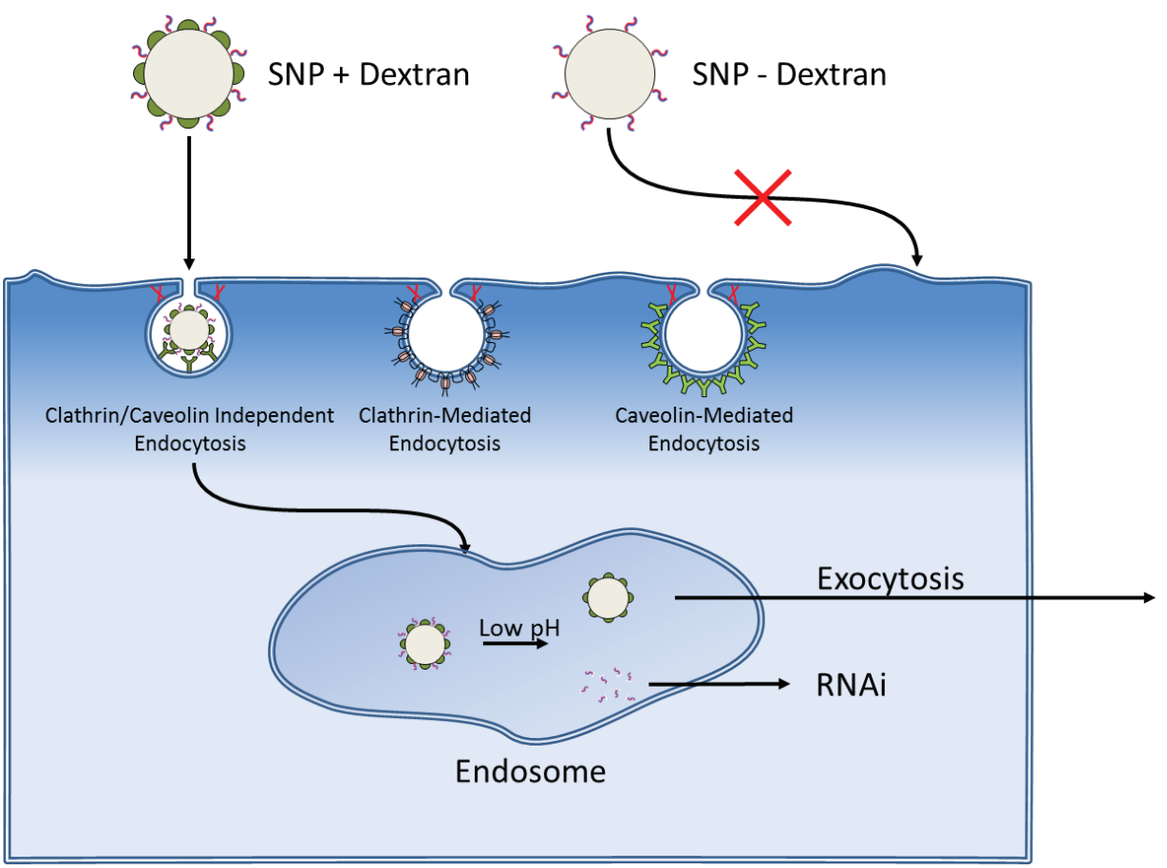
PRESS RELEASE

Silica nanoparticles deliver siRNAs through novel endocytosis pathway, resulting in efficient silencing without cytotoxicity

May 1, 2016 — Inclusion of dextran in the synthesis of silica nanoparticles yields siRNA delivery vehicles that are endocytosed via scavenger receptors in a clathrin/caveolin-independent manner.



Schematic of SNP-siRNA complex endocytosis. SNPs containing dextran (+) are endocytosed via a clathrin/caveolin-independent process and trafficked to the endosomes. The low pH environment of the endosome results in separation of the siRNAs from the complexes, at which point they can initiate RNAi. The partially-degraded SNPs are then trafficked out of the cell.

A team from Michigan State University (MSU) in East Lansing, MI have demonstrated the synthesis, characterization, and application of silica nanoparticle (SNP) delivery vehicles for short, interfering RNA (siRNA) therapeutics. The SNPs provide delivery efficiencies comparable to standard lipid-based reagents without the cytotoxicity often associated with lipid vehicles. Development of safe, effective delivery vehicles remains a central challenge in bringing therapeutics based on siRNAs to the clinic. The article appears in the March 2016 issue of the journal *TECHNOLOGY*.

"siRNA therapeutics have great potential that, as yet, has not been realized," says Professor S. Patrick Walton, Sc.D., principal investigator on the paper. "To achieve the activity and specificity that siRNA-based drugs could offer will require design of delivery vehicles that reach the target cells at sufficient concentration and are then taken up and processed by these cells via a pathway that allows the therapeutic cargo to be active."

siRNAs are rapidly degraded and filtered from circulation. Being hydrophilic and polyanionic, they also do not readily diffuse across non-polar cell membranes and can initiate an inflammatory response. Delivery vehicles must therefore be used to protect and conceal siRNAs while facilitating their transport to the cytoplasm of the targeted cells. Current siRNA delivery technologies are principally based on lipids (lipoplexes) or polymers (polyplexes), with many different chemistries tested. However, for lipid- and polymer-based vehicles, it is difficult to measure the changes in the structure and stoichiometry of the final complexes that result from changes in their chemistry. To address this challenge, the MSU team focused on using SNPs where changes in chemistry would not affect the spherical conformation of the delivery vehicles. The synthesis of SNPs allows easy manipulation of particle functionality, size, and charge density.

Using pharmacological inhibitors for endocytotic pathways, the MSU team determined that SNP complexes were endocytosed via a previously unreported mechanism for siRNA delivery in which dextran initiates scavenger receptor-mediated endocytosis through a clathrin/caveolin-independent process. Further, they identified acidic degradation of the particles as a possible mechanism for release of siRNAs from the SNP complexes, an important step in initiating silencing. The findings suggest that siRNA delivery efficiency could be enhanced by incorporating dextran into existing delivery platforms to activate scavenger receptor activity across a variety of target cell types.

Co-authors of the *TECHNOLOGY* paper are Daniel Vocelle, Olivia Chesniak, Amanda Malefyt, Ph.D., Georgina Comiskey, Ph.D., Kwasi Adu-Berchie, Milton Smith, Ph.D., and Christina Chan, Ph.D., from the Departments of Chemical Engineering and Materials Science and Chemistry at MSU.

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