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Going beyond the liver: Progress and challenges of targeted delivery of siRNA therapeutics

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Abstract

Therapeutic gene silencing promises significant progress in pharmacotherapy, including considerable expansion of the druggable target space and the possibility for treating orphan diseases. Technological hurdles have complicated the efficient use of therapeutic oligonucleotides, and siRNA agents suffer particularly from insufficient pharmacokinetic properties and poor cellular uptake. Intense development and evolution of delivery systems have resulted in preclinically active uptake predominantly in liver tissue, in which practically all nanoparticulate and liposomal delivery systems show the highest accumulation. The most efficacious strategies include liposomes and bioconjugations with N-acetylgalactosamine. Both are in early clinical evaluation stages for treatment of liver-associated diseases.

Approaches for achieving knockdown in other tissues and tumors have been proven to be more complicated. Selective targeting to tumors may be enabled through careful modulation of physical properties, such as particle size, or by taking advantage of specific targeting ligands. Significant barriers stand between sufficient accumulation in other organs, including endothelial barriers, cellular membranes, and the endosome. The brain, which is shielded by the blood-brain barrier, is of particular interest to facilitate efficient oligonucleotide therapy of neurological diseases. Transcytosis of the blood-brain barrier through receptor-specific docking is investigated to increase accumulation in the central nervous system.

In this review, the current clinical status of siRNA therapeutics is summarized, as well as innovative and promising preclinical concepts employing tissue- and tumor-targeted ligands. The requirements and the respective advantages and drawbacks of bioconjugates and ligand-decorated lipid or polymeric particles are discussed.

Keywords

RNA Interference, siRNA, delivery systems, liposomes, bioconjugates, targeting

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