Therapeutic siRNAs: Small molecules with bigger function

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In the realm of molecular medicine, therapeutic small-interfering RNA (siRNA) is a promising class of molecules with exciting new opportunities in health care.[1,2] An essential component of RNA interference (RNAi) is siRNA.[3] In clinical setup, siRNA may be engineered to specifically target genes linked to certain diseases, providing a focused and accurate method of modulating gene expression. Many important factors characterize the use of therapeutic siRNA. Target gene expression is selectively silenced by therapeutic siRNA through the use of the RNAi pathway.[4] Guided by corresponding messenger RNA (mRNA) sequences, the double-stranded siRNA molecule is integrated into the RNA-induced silencing complex. This mechanism causes translational repression or mRNA cleavage, which in turn causes the relevant protein to be downregulated. Therapeutic siRNA is a promising avenue in several areas. siRNA can be used in oncology to target oncogenes or other important regulators, inhibiting cancer cell proliferation.[5] Furthermore, by modifying the expression of genes linked to disease, siRNA may be used to treat viral infections, neurological conditions, and other rare and hereditary diseases.[6-8] The selectivity of therapeutic siRNA is one of its main advantages. siRNA sequences can be engineered and customized to target specific genes linked to different diseases such as cancer or genetic disorders. This focused strategy improves the accuracy of the therapeutic intervention and reduces off-target effects. In a recent article by Nissen et al.,[9] siRNA targeting lipoprotein(a) (LP[a]) in a trial with 48 participants without cardiovascular disease and with LP(a) concentrations of 75 nmol/L or greater (or ≥30 mg/dL) was used to evaluate its tolerability and efficacy to reduce LP(a). Results showed that lepodisiran was found to be well tolerated and resulted in dose-dependent, long-lasting reduction in serum LP(a) concentrations in phase 1 trial with elevated LP(a) levels. Therapeutic siRNA-based diagnosis is rapidly advancing, and several siRNA-based medications are now entering clinical trials. These trials aim to assess the pharmacokinetics, safety, and effectiveness of siRNA therapeutics in human subjects, offering crucial new information about their potential as a treatment option. Despite the therapeutic potential of siRNA, clinical translation of siRNA faces a challenge in its effective delivery.[10-12] Naked siRNA molecules are more likely to degrade with a poor half-life and poor cellular uptake. Therefore, to increase the stability and delivery of therapeutic siRNA to target cells, a variety of delivery systems, such as lipid nanoparticles, viral vectors, and polymer-based carriers, are being investigated.

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