siRNA Delivery Systems in Cancer Therapy

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Recent Technology of siRNA Delivery System

Small interfering RNAs (siRNA) has been used extensively in blocking various genes and is presently being evaluated as a therapeutic for cancer and viral disease. RNA interference was first identified as a defence mechanism against the invasion of foreign genes in the nematode Caenorhabditis elegans and had subsequently been discovered in diverse eukaryotes such as fungi, insects, plants, and vertebrates. Researchers demonstrated that synthetic siRNAs were able to induce RNAi in mammalian cells. RNAi could affect gene silencing through chromatin remodeling, blocking protein synthesis and cleaving specifically targeted mRNA.

RNAi gene-silencing is dependent on the structure of the initiating RNA such as complete (siRNA) or incomplete (miRNA). These double stranded RNAs were processed by RNase III endonuclease enzyme called Dicer, which produces duplexes of approximately 21 nucleotides. After the action of Dicer, guide strand (one of the two strands of each fragment), were incorporated into the RNA induced silencing complex. Chemical modification of the phosphonothioate linkage had been used as a simple and effective method to increase the nuclease resistance of siRNA [1]. Other methods employed for the enhancement of siRNA stability in biological fluids including modification of the 2'-hydroxyl group of the pantone sugar, such as 2'-O-methyl or a methylene linkage between the 2' and 4' positions of the ribose [2].

It is becoming clear that due to its instability and degradability, naked siRNA is rarely applied in systemic delivery accordingly; this section will deal primarily with siRNA-loaded carriers, such as nanospheres, nanocapsules, liposomes, micelles, microemulsions, conjugates, and other nanoparticles. Polymeric biomaterials are classically biodegradable and positively charged (e.g., cationic cell penetrating peptides, cationic polymers, dendrimers, cationic lipids etc.) that are widely used as drug (gene, growth factor) carrier [3-20].

Conjugation of siRNA with a variety of small molecules (e.g., cholesterol, bile acids, and lipids), polymers, peptides, proteins (e.g., antibodies), as well as aptamers (e.g., RNAs), and encapsulating siRNA in nanoparticulate formulations improves the stability, cellular internalization, or cell-specific active targeted delivery synthetic polymers which have been widely investigated for siRNA delivery. These synthetic polymers may enhance intracellular delivery by facilitating endosomal escape and inducing lysosomal disruption, endosomal release, and siRNA protection from lysosomal degradation by way of buffering the endosomes [21-30]. Biodegradable polymers have been reported that they are enabling to undergo hydrolytic degradation, yielding non-toxic and neutral pH degradation products, thereby providing sustained gene delivery [31-45].

Therapies based on siRNA are entering clinics, especially for diseases requiring locoregional treatments, including age-related...
macular degeneration, diabetic macular edema, respiratory virus infection, pachyonychia congenital, hepatitis, human immunodeficiency virus infection, and cancer. There are several obstacles and concerns that should be overcome before RNAi will be used as a new therapeutic technique.

**Conclusion**

Although progress has been made in the field of siRNA delivery systems, there are several obstacles and concerns to be overcome before this new drug could be used as a new therapeutic agent. Several strategies need to minimize off-target effects, avoiding immune responses, increasing resistance to nuclease degradation and effective in delivery of siRNA to the appropriate cells or tissues by manipulating biphasiological properties.

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