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Mini Review

SiRNA Delivery for Cancer Therapy: Challenges and Future Perspective

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Abstract

Cancer is one of the leading causes of death across the globe. Despite advancement of conventional treatments, the safety and efficacy of various chemotherapeutic drugs remained questionable. Recent advances in biotechnology and discovery of siRNA and RNA interference mechanism has brought a new light in more specific and targeted treatment of malignant tissue. Important advantage of siRNA-based therapy is its target specificity and safety, but disadvantage is to build an appropriate vehicle for its delivery into target site. Various phase I and II clinical trials are under way to test the efficacy of this new modality of treatment.

Keywords: SiRNA; RNA interference; Cancer therapy

Abbreviations: SiRNA: Small Interfering Ribonucleic Acid; WHO: World Health Organization; RNA: Ribonucleic Acid; DNA: Deoxyribonucleic Acid; RISC: RNA Induced Silencing Complex; Mrna: Messenger Ribonucleic Acid; VEGF: Vascular Endothelial Growth Factor; KSP: Kinesin Spindle Protein; PKN3: Protein Kinase N3; BCL-2: B-Cell Lymphoma 2; Kda: Kilo Dalton

Introduction

Cancer is a global public health problem. Global estimation from WHO fact sheet revealed that nearly 1 in 6 deaths occur due to cancer [1]. There are various aspects of treatment of cancers. The three arms of cancer treatment are chemotherapy, radiotherapy and surgical resection. Although, in last few decades, we have witnessed discovery of various new chemotherapeutic drugs and surgical advancements, the three major disadvantages of all this treatment modalities remained to be their side effects, expenses, sub-optimal and sometime dismal effects. siRNA nanotherapeutics is one of the new recent advancement in this field. In current review we will discuss various advantages and potential role of siRNA in cancer therapy.

SiRNA and Post Transcriptional Gene Silencing

RNA interference is a cellular process where the undesired gene expression can be silenced by degrading of that undesired mRNA. siRNA is small double stranded RNA about 21 nucleotides long with 3' overhang at each end that regulates gene or genome. Three mechanisms were investigated that leads the overall RNA interference,

A. changes in heterochromatin formation

B. Inhibition of translation of target mRNA

C. Degradation of the target mRNA.

Second and third phenomena are mostly explored [2]. After entering to the cells, the double stranded RNA cleaved by an enzyme known as DICER and 20 to 22 nucleotide long siRNA formed. The source of the double stranded RNA can be viral genome, bacterial DNA or synthetic RNA. Later, the double strand of the siRNA is separated by helicase enzyme and the antisense strand binds to the RNA induced silencing complex (RISC). RISC carries the siRNA to the target mRNA site and degrades the mRNA. Degradation of mRNA inhibits the gene expression.

Advantages of SiRNA Therapeutics in Cancer Treatment

Anticancer chemotherapeutic agents mainly exert their affect either by impeding DNA or RNA synthesis, or by inducing their destruction or arresting cell cycle at particular stage. This leads to programmed cell death known as apoptosis. The major disadvantage of this treatment is that, the drugs do not differentiate between the healthy and cancer cells and thus affects non -cancerous cells also, which leads to their side effect. siRNA on the other hand has several potential advantages in this respect. Firstly, siRNA causes target specific gene silencing through RNA interference system. The risk of teratogenicity and mutation is less as it inhibits post transcriptional gene expression and does not interact with DNA [3]. Another important advantage of siRNA is its high efficacy. Several copies of siRNA can suppress the gene expression in a single cancer cell. siRNA binds by complementary base pairing that restricts the

damage of healthy cells compared to the conventional anticancer drugs. Thirdly, synthesis of siRNA is easy and low cost as compared to other proteins or antibiotics [4]. Besides the sequence can be highly specific for their target organ of interest.

Clinical Trials with siRNA for Cancer Therapy

Mutations in proto-oncogene or in tumor suppressor gene lead to cancer. This ontogenesis is potential target for gene silencing by RNA interference mechanism. siRNA based therapy has been used in many cancers like thyroid, prostatic, pancreatic, lung, liver, colon, renal, non-Hodgkin lymphoma and breast cancer [5]. Alnylam Pharmaceuticals has completed phase 1 extension study with lipid nano-particle (molecule named ALN-VSP)[6] that targets two gens VEGF and KSP that are responsible for primary liver cancer. Another pharmaceutical company is conducting human phase1 study with siRNA with lipoplex delivery system (Atu-027) [7] that targets PKN3 gene responsible for cancer metastasis that may have potential role in advanced solid tumor. Santaris Pharma has completed a phase II trial with siRNA-based therapy (molecule named SPC2996)that targets BCL-2 gene responsible for chronic lymphocytic leukemia.

Barriers of SiRNA Delivery and Future Perspective

There are still some disadvantages which restricts the clinical trials of siRNA delivery for cancer therapy.

A. siRNA molecules are large molecule (13kDA) and negatively charged and hydrophilic [3] and hence cannot diffuse cell membrane alone.

B. Stability of siRNA is another important issue for siRNA. It is easily degraded in the physiological condition by the nuclease enzyme plasma and tissue. Half-life of unmodified siRNA [8] in serum ranges from few minutes to 1hr. kidney is another barrier that plays an important role in clearing the siRNA from the body. Apart from kidney and nuclease, siRNA is taken up by reticuloendothelial system with the help phagocytic cells [9], including circulating monocytes and tissue macrophages.

C. Another problem of siRNA is off targeting [9] that can lead to the silencing of gene expression of non-pathogenic genes which, in results hinder the cellular normal function.

D. Activation of immune response [10] by high levels of siRNA is another important challenge that restricts its therapeutic efficacy.

E. To overcome the barriers, siRNA therapy requires suitable drug delivery system that requires a carrier to deliver siRNA to its targeted place. The carrier should be biologically inert, non-immunogenic, and able to evade RE phagocytosis, prevent renal clearance, facilitate cell entry to RNAi mechanism and most importantly have low toxicity. Currently researches on liposomal and various nanoparticle-based siRNA delivery systems are underway.

Conclusion

siRNA based treatment holds a promising future in treatment of various cancers of our body. Delivery of siRNA to its main concern is the area of interest in research of biotechnology [11]. Various nano-particles based and liposomal delivery systems are being tried in various clinical studies. It can be a safe, non-toxic treatment option compared to conventional therapies in cancer treatment.

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