Journal of Drug Delivery Science and Technology 37 (2017) 97–114

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Review article

Targeting nanocarriers containing antisense oligonucleotides to cancer cell

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ARTICLE INFO

Article history:
Received 14 September 2016
Received in revised form
1 December 2016
Accepted 6 December 2016
Available online 9 December 2016

Keywords:
Oncogene
Small interfering ribonucleic acid
Antisensing concept
Phagocyte
Nanoplex
Niosome
Immunostimulation
Bioimaging

ABSTRACT

Treatment of cancer is a furtive problem in the current era in spite of significant advancement in drug delivery systems and identification of new therapeutic molecules. The ration of lab to market translation of therapeutic research is quite low in anticancer therapy due to hidden and unnameable disease causing and disease progression mechanisms. Oncogene activation disturbs normal cell processes such as cell growth and apoptosis, which ultimately leads to cancer. Different ways, such as RNAi, antisense oligonucleotides, Translation suppressing oligonucleotide and external guide sequences which silences oncogenes are key techniques under investigation currently. The emerging way of formulating nanoparticles containing antisense oligonucleotides and the targeting approaches is illustrated with the brief information on key materials used for the same purpose. Gene targets identified and investigated by various companies and research groups are enumerated and reviewed for their potential to consider antisense gene therapy. Nanocarrier systems which have been reported to enhance feasibility of selective antisense oligonucleotides to treat the disease are assessed for their pros and cons.

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http://dx.doi.org/10.1016/j.jddst.2016.12.001
1773-2247/

1. Introduction

siRNA is the candidate who plays main role in the whole antisensing concept. RNAi or RNA interference is gene silencing approach and promising too. It is a single stranded molecule with 21 or 22 bases length. Firstly, binding of the siRNA with specific mRNA and secondly, activation of degradation enzyme because of double strand formation are the two main interesting steps in the RNAi concept [1,2]. There has been a huge advancement is reported in this method of treating cancer such as modification of oligonucleotides, specificity of siRNA and improvements in delivery by nanocarriers make this route more effectually and eternally useful [4,5,57]. Cancer is caused because of defective synthesis of key proteins from affected genes by carcinogens such as ultraviolet radiations, chemicals, hazardous metals ultraviolet radiations, chemicals and hazardous metals. There has been a lot of genes identified causing cancer and specific syndromes. Some of them are listed below in the first table. Various defective genes altogether create serious complications. Defective Genes are produced by damaging effect of carcinogens or might be inherited from parents.

Anticancer effects of oligonucleotides are operating in different ways, some of them are more prone to research such as RNA interference [5], antisense oligonucleotides (ASOs) strategy [11], translation suppression [19] and prevention of mRNA metabolism [22,25,27,32]. RNAi is one of the paths which contains tremendous benefits to knock down oncogenes by binding to its complementary sequences in specific mRNAs those are formed from the cancer causing genes. ASOs sequences work comparatively similar way as siRNA except prevent splicing of RNA. Translation suppression and interference in metabolism of mRNA are also good bypaths against cancer. Leading private and government organizations are currently working on these byways to cure cancers. They have done clinical trials on products of siRNAs and/or ASOs. There are many difficulties in safe and secure delivery of the gene based products including their degradation, instability, non-specificity and in-vivo inactivity which hinder successful delivery of the same. Various solutions are available but one of the highly investigated way is loading the genomic-based cargo into the nanocarriers [40,42,43]. Nanocarriers can overcome problems significantly and also provide benefits such as stability, targeting delivery, multifunctionality, Bioimaging and controlled release.

Now a day, lipid based systems [52], Polymeric and dendrimeric delivery systems [107], Inorganic nanoparticles [56], conjugation systems [58] are used for systemic delivery of ASOs. In addition, various strategies such as supramagnetic technology, ultrasound technology, and thermal ablation technology are mainly focused on local delivery [64–66] which facilitate our aim to minimize the drug resistance problem [82]. Different types of nanocarriers such as Liposomes [93], Lipoplexes [98], Micelles [102], Polymeric nanoparticles [110], Nanospheres [117], Nanocomposites [119], Solid Lipid Nanoparticles [122] and Niosomes [132] have been fabricated with this particular intentions. Various materials are used for preparation of nanocarriers for siRNA delivery include cationic polymers [139,144,151,154], neutral polymers [166,168], lipid like materials [170], carbon [178] and metal [188] nanoparticles.

Clinical trials on the ASOs product is the real step towards the utilization of research. The U.S. FDA has firstly approved an ASO marketed as VITRAVENE for treatment of cytomegalovirus retinitis. KYNAMRO is also approved by U.S. FDA in 2013, which is antiviral. There are around fifty ASOs for cancer treatment are under clinical trials, according to NCT website and nearly twenty have been passed through clinical phase one or two or both. Not even a single U.S. FDA approved anticancer ASO is reported till today.

2. Development in antisense oligonucleotides technology

An antisense RNA technology is defined as the process in which an ASO hybridizes to a target RNA to form a double strand. This double stranded molecules leads to the prevention of the target RNA from working properly and producing proteins. The first antisense technology developed in 1978 inhibits successfully the Rous sarcoma virus production [1]. Since then many modified RNA oligonucleotides with a length of 19–23 bases have been used for antisense technology. The most efficacious challenge for antisense based technology is not only to find the sequence that is perfectly complementary to ASO, but the modification of the oligonucleotide is also having similar importance for knockdown the specific gene [2]. Antisense RNA and RNAi technologies are most efficient genomically-based methods to knock down the specific gene targets. Antisense RNA is single stranded oligonucleotide which degrades complementary mRNA by activating RNase H and RNAi is a double stranded oligonucleotide degrades specific mRNA by using a Dicer enzyme.

2.1. Identified genes causing cancers

Oncogene activation disturbs normal cell processes such as cell growth and apoptosis. Oncogenes are altered form of genes from which defective proteins are synthesized and actively participating