Advanced Drug Delivery Reviews 87 (2015) 108–119

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

Preclinical and clinical development of siRNA-based therapeutics☆,☆☆

Gulnihal Ozcan [a], Bulent Ozpolat [a], Robert L. Coleman [b], Anil K. Sood [b,c,d], Gabriel Lopez-Berestein [a,d,*]

[a] Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[b] Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[c] Department of Cancer Biology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[d] Center for RNA Interference and Non-Coding RNA, The University of Texas MD Anderson Cancer Center, Houston, TX, 77030, USA

ARTICLE INFO

Available online 7 February 2015

Keywords:
siRNA
Gene silencing
Therapeutic use
Nanocarriers
Ovarian cancer
EphA2
Nanoliposomes

ABSTRACT

The discovery of RNA interference, first in plants and *Caenorhabditis elegans* and later in mammalian cells, led to the emergence of a transformative view in biomedical research. Knowledge of the multiple actions of non-coding RNAs has truly allowed viewing DNA, RNA and proteins in novel ways. Small interfering RNAs (siRNAs) can be used as tools to study single gene function both in vitro and in vivo and are an attractive new class of therapeutics, especially against undruggable targets for the treatment of cancer and other diseases. Despite the potential of siRNAs in cancer therapy, many challenges remain, including rapid degradation, poor cellular uptake and off-target effects. Rational design strategies, selection algorithms, chemical modifications and nanocarriers offer significant opportunities to overcome these challenges. Here, we review the development of siRNAs as therapeutic agents from early design to clinical trial, with special emphasis on the development of EphA2-targeting siRNAs for ovarian cancer treatment.

© 2015 Elsevier B.V. All rights reserved.

Contents

Abbreviations: 2′-OMe, 2′-*O*-methyl; 2′-F, 2′-fluoro; CH/TA, chitosan/thioaptamer; DOPC, 1,2-dioleoyl-*sn*-glycero-3-phosphatidylcholine; DOTAP, 1,2-dioleoyl-3-trimethylammonium-propane; DOTMA, *N*-[1-(2,3-dioleoyloxy)propyl]-*N*,*N*,*N*-trimethylammonium methyl sulfate; EA5, EphA2 agonistic antibody; EphA2, ephrin type-A receptor 2; GalNAc, *N*-acetylgalactosamine; IVT, intravitreal; LNAs, locked nucleic acids; MSV, multistage vector; OC, ovarian cancer; PEG, polyethylene glycol; PLA, polylactic acid; PLGA, poly(lactic-co-glycolic) acid; PS, phosphorothioate; SLN, solid-lipid nanoparticles; SNALPs, stable nucleic acid-lipid particles; TTR, transthyretin.

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Oligonucleotide Therapeutics".

☆☆ The authors have no conflicts to report.

* Corresponding author at: Division of Cancer Medicine, Unit 1950, P.O. Box 301429, Houston, TX 77230, USA.
E-mail address: glopez@mdanderson.org (G. Lopez-Berestein).

http://dx.doi.org/10.1016/j.addr.2015.01.007
0169-409X/© 2015 Elsevier B.V. All rights reserved.

1. Introduction

1.1. RNA interference

RNA interference (RNAi) is an evolutionary conserved mechanism in which double-stranded RNA (dsRNA) molecules silence the post-transcriptional expression of homologous target genes. This phenomenon was first discovered in plants in the late 1980s [1] and then in *Caenorhabditis elegans* in 1998 by Fire et al. [2]. Demonstration of similar processes in mammalian cells in 2001 [3] led to the emergence of new tools to study gene function.

Small interfering RNA (siRNA) is a member of a family of non-coding RNAs (ncRNAs) that affect and regulate gene, RNA and protein function. ncRNAs can be classified into infrastructural ncRNAs that involve ribosomal, transfer, small nuclear and small nucleolar RNAs with well-known functions and regulatory ncRNAs that can be further classified into long ncRNAs (lncRNAs) and small ncRNAs based on transcript size. lncRNAs are transcripts ranging in length from 200 nucleotides (nt) to approximately 100 kilobases and are mostly involved in trafficking of protein complexes, genes and chromosomes to appropriate locations. They have been proposed to mediate epigenetic changes in a cell type-specific manner, by recruiting chromatin-remodeling complexes to specific genomic loci. Many different classes of small ncRNAs have been defined with distinct functions. Piwi-interacting RNAs (piRNAs) are small ncRNAs (24–31 nt in size) that can form complexes with Piwi proteins of the Argonaute family and play a role in suppression of transposon activity during germline development. Recently, promoter-associated RNAs (PARs) and enhancer RNAs (eRNAs) have been described as novel classes functioning in transcriptional regulation [4,5]. In addition to these, pyknons, which are nonrandom patterns of repeated elements found more frequently in 3′ UTR regions of genes, are being classified under small ncRNAs with their possible involvement in posttranscriptional silencing of genes, mainly related to cell communication, regulation of transcription, signaling and transport [6]. Most well-known classes of small ncRNAs, namely micro-RNAs (miRNAs) and siRNAs, are the major mediators of RNAi and will be discussed in detail in the following sections.

1.2. Gene silencing by micro-RNAs

miRNAs are small non-coding dsRNAs transcribed by genomes. Initially they were found as complex stem-loop or short hairpin structures called pri-miRNAs (Fig. 1). pri-miRNAs are processed by Drosha into pre-miRNAs in the nucleus, followed by transport of pre-miRNAs to the cytoplasm via exportin-5. A cytoplasmic RNAse III enzyme called Dicer cleaves the pre-miRNAs into shorter double-stranded miRNAs with imperfect complementarity. These short fragments are recognized by Argonaute 2 (AGO2) and RNA-induced silencing complex (RISC), where one of the strands is degraded and the other strand guides the AGO2–RISC complex to bind and block translation of target mRNAs having partial complementary sites typically located in the 3′UTR [7,8].

1.3. Gene silencing by small interfering RNAs

siRNAs are synthetic mediators of RNAi that are dsRNA molecules of 21 to 23 base pairs (bp) in length designed specifically to silence expression of target genes. They can be introduced exogenously into the cell or organism in short (21–23 bp) form or in the form of long dsRNA molecules. These dsRNAs are processed by endogenous RNAi machinery after introduction into the cell (Fig. 1). First, the cytosolic enzyme Dicer cleaves long dsRNAs into shorter fragments (siRNAs), leaving two nucleotide (2-nt) 3′ overhangs and 5′ phosphate groups [9,10]. siRNAs are recognized by the AGO2–RISC enzyme complex, where one of the strands is degraded and the other (mostly antisense) strand is left as a guide to find target mRNA sequences. Unlike miRNAs, siRNAs bind sequences with perfect or nearly perfect complementarity and cause cleavage of targets instead of translational suppression [11,12]. Because they can efficiently silence target gene expression in a sequence-specific manner, siRNAs became indispensable tools to study the function of single genes [11,13].

1.4. Challenges with siRNA-based therapeutics

1.4.1. Off-target effects

siRNAs are designed to knock down specific targets. However, recent studies have shown that they may also silence an unknown number of unintended genes. There are two mechanisms suggested to explain this off-target effect. First, siRNAs can tolerate several mismatches at the mRNA target and retain their ability to silence those targets with imperfect complementarity [14]. The second mechanism involves promiscuous entry of siRNAs into endogenous miRNA machinery [15]. miRNAs recognize targets with perfect complementarity to their ‘seed regions’ composed of nucleotides 2–8. Complementarity of remaining nucleotides has less importance for recognition. Because siRNAs are very nearly identical to the related class of miRNAs, they can recognize mRNAs with their seed region and lead to degradation of an unpredictable number of mRNAs [16].

1.4.2. Efficacy

During the past few years, a number of siRNAs and other ncRNAs, such as miRNAs, have been successfully used in experimental models. Data from preclinical models are now giving rise to translation of new siRNA (Table 1) and miRNA-based therapies into clinical trials. In the case of siRNAs, the target selection process is extensional, requiring a thorough mining of databases and pathways [17]. Different siRNAs targeting different parts of the same mRNA sequence have varying RNAi efficacies, and only a limited fraction of siRNAs has been shown to be functional in mammalian cells [18]. Among randomly selected siRNAs, 58–78% were observed to induce silencing with greater than 50% efficiency and only 11–18% induced 90–95% silencing [19]. Some of the principles to design siRNAs are discussed in Section 2.1.

1.4.3. Delivery

Delivery of siRNAs to target tissues is impeded by many barriers at different levels. siRNAs are easily filtered from the glomerulus

Download English Version:

https://daneshyari.com/en/article/8403053

Download Persian Version:

https://daneshyari.com/article/8403053

Daneshyari.com