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Review article

Biodegradable nano-polymers as delivery vehicles for therapeutic small non-coding ribonucleic acids

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ABSTRACT

Nowadays, small non-coding Ribo Nucleic Acids (sncRNAs) such as siRNA, miRNA and shRNA are extremely serving to gene regulation. They are involved in many biological processes and in an increasing number of studies regarding a variety of application of sncRNAs toward human health and relieving diseases ranging from metabolic disorders to those involving various organ systems as well as different types of cancer. One of the most severe limitations for applying RNA interference technology is the absence of safe and effective carriers for in vivo delivery, including localizing the molecules to a specific site of interest and sustaining the presentation of the payloads for a controlled period of time. In this review, we focus on the sncRNA functions and recent advances on the delivery of these molecules by biodegradable, biocompatible and nontoxic biopolymers including chitosan, cyclodextrins, poly-L-lysine, dextran, poly (lactic co-glycolic acid), polyglutamic acid, hyaluronic acid and gelatin.

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1. Introduction

1.1. sncRNAs, structure and mechanism of function

Non-coding RNAs (ncRNAs) comprise a great number of cellular transcripts. There are different classifications of non-coding RNAs, based on their function and their length which put them into separate categories. Non-coding RNAs can be divided into housekeeping or infrastructural ncRNAs and regulatory ones, which the expression of the former is constitutive and their function is vital for the cell, but the latter express in some certain developmental stages. Housekeeping non-coding RNAs include rRNAs, tRNAs, snoRNAs, snRNAs, and scaRNAs. Regulatory non-coding RNAs include examples such as miRNAs, siRNAs, and piRNAs. Non-coding RNAs also can be classified based on size, which divide them into small non-coding RNAs (sncRNAs), shorter

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than 200 nucleotides, and long non-coding RNAs (lncRNAs) which their size are longer than 200 nucleotides [1–3]. The sncRNAs that participate in RNA interference pathway are shortly described in Table 1.

MicroRNAs are endogenous regulatory single strand sncRNAs consisting of approximately 20–24 nucleotides. These sncRNAs mediate gene silencing via binding to 3′un-translated regions (UTRs) of mRNA molecules thereby either induction of mRNA degradation or inhibition of mRNA translation through incomplete coupling with target. The primary precursor of miRNAs (pri-miRNA) is transcribed by RNA Poly II in nucleus. Then, processed in nucleus by DGCR8 and a DROSHA (a type of RNase III enzyme which especially cleavage double-stranded RNA molecules) and produce a hairpin-shaped precursor structure with about 60–70-nucleotide which is named pre-miRNA. Following nuclear processing by Drosha, pre-miRNAs are exported to cytoplasm by the karyopherin exportin-5 and its cofactor Ran. In cytosol pre-miRNAs processed through a cytoplasmic RNase III called Dicer to about 22 nucleotide (nt)double-stranded miRNA with 2 nt in 3′ overhangs. In the next step, the double-stranded miRNA (dsmiRNA) are assembled together with argonaute (Ago) into miRNA-induced silencing complex (miRISC) [4,5]. In miRISC complex, the passenger strand of dsmiRNA is released and then degraded while mature strand (the guide strand) of miRNA retained in the complex. The mature strand could be identified and bound to target mRNAs by sequence complementary to 3′ UTRs of mRNA leading to translation repression or degradation of target mRNA in processing body components (P-bodies). Perfect complementation between miRNA and mRNA leads to cleavage or degradation of the mRNA by miRISC complex, and imperfect complementation of miRNA and mRNA leads to suppression of mRNA translation in P-bodies [6,7].

siRNA is a group of dsRNAs, 21–23 nucleotides in length, which is able to cleave RNA by mediated RISC complex, leading to the silencing of their target genes and the disruption of translation. In comparison with siRNA, after the delivery of the shRNA-expressing vectors into the cytosol, the vector must be imported to the cell nucleus for transcription by RNA PolyIII or II through their specific promoters on the expression cassette. The primary transcripts (pre-shRNA) which contain a hairpin like stem-loop structure follow a similar way as microRNA and are processed by Drosha/DGCR8 complex and form pre-shRNAs. This creates pre-shRNAs containing a 2 nt 3′ overhang and transports to the cytoplasm by exportin-5 for further processing by Dicer/TRBP/PACT complex to produce mature shRNA. Mature shRNAs in the Dicer/TRBP/PACT ternary complex are connected with argonaute protein containing RISC which provides RNA interference function. After loading onto RISC complex, the passenger strand departs; and similar to siRNA or miRNA, leading either to the mRNA degradation, or through translational suppression in P-bodies. Studies showed that inhibition of gene expression by shRNAs is more durable and effective than siRNA in gene silencing with the same targeting sequences [8,9].

Table 1
Characterization of small non-coding RNAs (sncRNAs).

Type	Long name	Function	Length (nt)	Structure	Species	Processing proteins	Derived from	Over expression	Delivery
miRNA	MicroRNA	Repress the translation or cleavage of target mRNAs	19–25	Single-stranded RNA	223 species	Drosha and Dicer	Short hairpins RNA transcripts(pri and pre miRNA)	Chemically synthesized microRNA (miRNA) mimics, expression from plasmid or viral vectors	Viral vectors Nonviral miRNA delivery systems: Lipid-based delivery system, polyethylenimine (PEI)-based delivery system, dendrimers, poly(lactide-co-glycolide) (PLGA) particles, naturally occurring polymers such as chitosan, protamine, atelocollagen, inorganic nanomaterials
siRNA	Small interfering RNA	Cleavage of target RNAs	20–25	Double-stranded RNA with dinucleotide 3′ overhangs	Animals, plants, algae, fungi, protists	Dicer	Double-stranded RNA	Chemical synthesis expression from plasmid or viral vectors	Electroporation, lipid-based delivery system, polyethylenimine (PEI)-based delivery system, poly(lactide-co-glycolide) (PLGA) particles, naturally occurring polymers such as chitosan, protamine, atelocollagen, Inorganic nanomaterials, spherical nucleic acid nanoparticle conjugates (SNA-NCs),
shRNA	Short hairpin RNA	Cleavage of target RNAs	A 19–29 (bp) stem a 4 (nt) loop and a dinucleotide overhang at the 3′ end.	Stem loop structure	Animals, plants, fungi, protists	Dicer	Stem loop structures	Expression from DNA-based vectors	Infection of viral base vector Transfection of plasmids
piRNA	PIWI-interacting RNA	Germline silencing of repeat transcripts and transposable elements	24–32	Precursor ssRNA, which is modified to contain 3′-terminal 2′-*O*-methyl	Drosophila, mammalian, Metazoans	Dicer-independent methyltransferase PIWI and PIWI-like proteins	Single-stranded RNA precursors	Chemically synthesized piRNAs (consists of a 2′-*O*-methyl group at the 3′ end a phosphate at the 5′ end)	Lipofectamine transfection Nanoparticles