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Target-responsive DNA/RNA nanomaterials for microRNA sensing and inhibition: The jack-of-all-trades in cancer nanotheranostics?☆

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ABSTRACT

microRNAs (miRNAs) show high potential for cancer treatment, however one of the most significant bottlenecks in enabling miRNA effect is the need for an efficient vehicle capable of selective targeting to tumor cells without disrupting normal cells. Even more challenging is the ability to detect and silence multiple targets simultaneously with high sensitivity while precluding resistance to the therapeutic agents. Focusing on the pervasive role of miRNAs, herein we review the multiple nanomaterial-based systems that encapsulate DNA/RNA for miRNA sensing and inhibition in cancer therapy. Understanding the potential of miRNA detection and silencing while overcoming existing limitations will be critical to the optimization and clinical utilization of this technology.

Contents

1. Introduction

1.1. The history behind miRNAs: how, why, when and where?

In 1998, Fire and Mello observed for the first time that double-stranded RNA (dsRNA) was the main cause of sequence-specific

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inhibition of protein expression in *Caenorthabditis elegans*, which they called "RNA interference" (RNAi) pathway [1]. It became evident that RNAi is critical to the control of post-transcription gene silencing in widely dispersed eukaryotic forms from yeast, fungi, plants, and animals [2,3]. To date, four major types of noncoding RNAs have been identified as RNAi effectors: small interfering RNAs (siRNAs), microRNAs (miRNAs), piwi-interacting RNAs (piRNAs) and long intervening noncoding RNAs (lincRNAs) [4,5]. microRNAs are small endogenous noncoding RNA molecules (20–23 nucleotides) derived from imperfectly paired hairpin RNA structures naturally encoded in the genome [6] that act specifically as triggering molecules to control translational repression or mRNA degradation. They regulate 10–30% of all protein-coding genes, targeting amino acid coding sequences [7], as well as promoters of gene expression [8] and long-non-coding RNAs [9,10]. This remarkable machinery involved in gene regulation processes is evolutionarily conserved and involved in many biological processes such as cell proliferation, differentiation, apoptosis, metabolism, development, aging and cancer. Moreover, miRNAs are key players in reinforcing molecular networks, acting as "genetic buffers", minimizing the noise of floppy cellular transcription regulation [11,12].

miRNA biogenesis arises in the cell's nucleus and encompasses numerous RNA processing steps (Fig. 1). miRNA coding genes are generally transcribed by RNA polymerase II (Pol II) (from polycistronic transcripts, or introns of protein-coding genes) within the nucleus, producing large (several thousand bases in length) capped and polyadenylated pri-miRNA transcripts. These pri-miRNA transcripts are processed by the RNase III enzyme Drosha to generate ~70–90 nt long precursor miRNA (pre-miRNA). pre-miRNAs present an imperfect stem-loop hairpin structure and are transported from the nucleus into the cytoplasm by the exportin 5 enzyme. After Dicer processing the precursor miRNA is transformed into a transient 22 nt mature double stranded (ds) miRNA (miR:miR duplex). The Dicer also processed the unwinding of these miRNA duplexes and promotes the incorporation of one strand of the duplex into a miRNA-associated RNA-induced silencing complex (miRISC) and a multi-protein complex that includes Dicer and proteins from the Argonaute family. The mature miRNA guides RISC to target mRNAs and or proteins, promoting their degradation [13,14]. In animals, partial complementarity (in Mammalia, the miRNAs rarely have a perfect complementarity with their targets) between mature miRNA and mRNA leads to an endonucleolytic cleavage, catalyzed by the human Ago2 in the RISC. Translational repression occurs without endonucleolytic cleavage, contrary to their "close relative" siRNA.

The mechanism described above is the accepted pathway for miRNA biogenesis; however recent studies have reported several alternative pathways, which depends on cell type, organism and biological contexts [15,16].

1.2. miRNAs: the jack-of-all-trades or the master of none?

miRNAs' small size and lack of poly-A tails may have kept them out of the spotlight for decades, however it is thought that the human genome may contain up to one thousand miRNA genes, which could regulate one third of our protein-coding genes. Actually, there is more to miRNA than meets the eye. Almost 40 years after the discovery of RNA, there is a growing evidence that these small endogenous dsRNAs are just as potent as many transcription factors and can regulate the expression of a specific gene, and hence a protein. The concept is simple: miRNAs recognize a complementary sequence encoded in a specific messengerRNA (mRNA) and bind to it, interfering with the correct translation of the mRNA sequence, impairing protein production.

Of course ascribing the silencing of genes solely to the existence of miRNA is short-sighted. In reality, these major players need a battery of enzymes to meet their ends like Drosha and Dicer, whose major role is to recognize and cleave mRNA [17]. Contrary to plant miRNAs whose sequences match with a great precision to their complementary RNA targets, animal miRNAs are far more promiscuous. The binding procedure is far less accurate and demanding as miRNAs can bind to as many as one hundred different sequences. This may sound economical and cost-effective nature-wise, however their use in laboratory

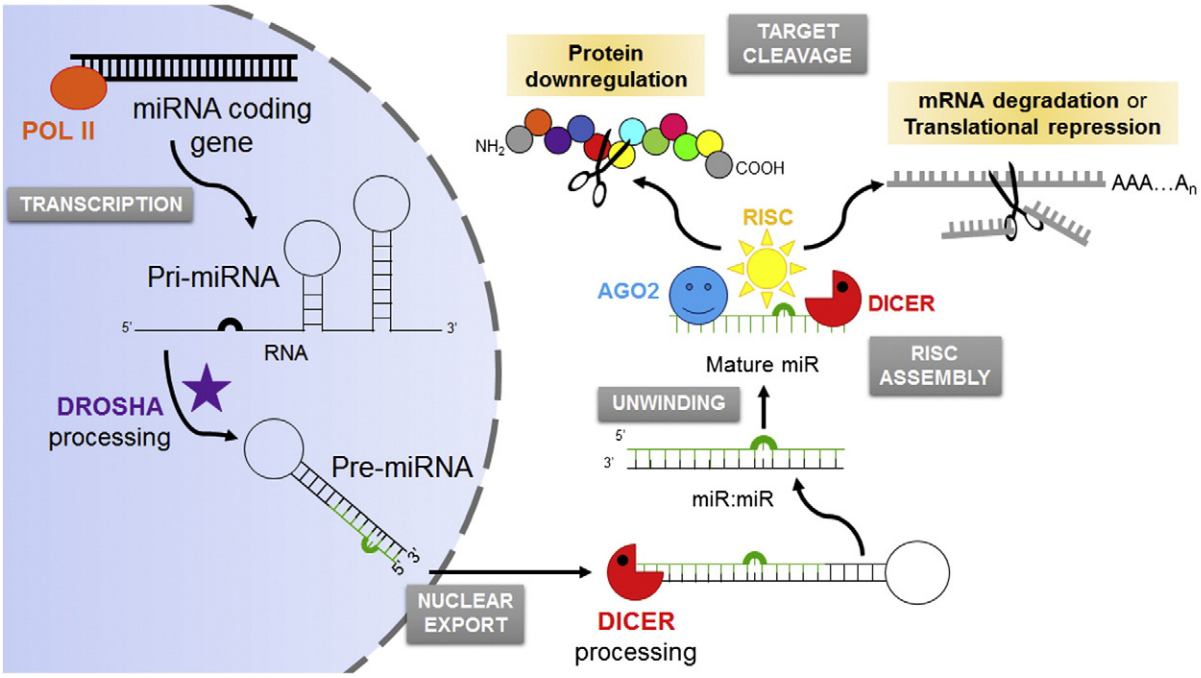

Fig. 1. miRNA biogenesis and mechanism of action. miRNA coding genes originate in the nucleus. RNA polymerase II (POL II) produces pri-miRs, transcribed from miRNA genes. Pri-miRNAs are then processed and catalyzed by DROSHA (RNase III type endonuclease) that processes pri-miRNAs to pre-miRNAs. After nuclear exportation (via Exportin5), DICER processes pre-miRNAs into 20-bp miR:miR duplexes. After miRNA duplex unwinding by the DICER, one strand is selected to function as mature miR and loaded into the RISC (RNA-induced silencing complex) and to the Argonaute family (specially, AGO2). The partner miR strand is degraded. The mature miR may lead to mRNA degradation or translational repression, as well as protein downregulation.