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REVIEW

Recent advances in understanding the role of miRNAs in exosomes and their therapeutic potential

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Abstract

MicroRNAs (miRNAs) are small endogenous non-protein coding RNAs that range in size from 19–25 nucleotides. Thousands of miRNA genes have been identified in a variety of organisms, suggesting genetic exchange and distribution among species. miRNAs negatively regulate gene expression by binding to the 3´-untranslated regions (3´-UTRs) of their target genes and play an important role in growth, development and the occurrence of diseases. In this review, we summarize the recent advances in the understanding of the role of miRNAs in exosomes and their therapeutic potential, as well as provide an overview of the basic characteristics of miRNAs.

Keywords: miRNA, gene expression, gene regulation, gene transcription, exosomes, non-coding RNA

1. Introduction

The first small non-coding RNA, lin-4, was discovered in 1993 (Lee *et al*. 1993). Lin-4 controls the cell fate transitions through the early stages of larval development in *Caenorhabditis elegans* (Jagadeeswaran *et al.* 2010). In 2000, Rinhart *et al.* (2000) identified *let*-7, which is another heterochronic switch gene that regulates the timing of the developmental switch from larval to adult cell fate in *C. elegans*, and since then, thousands of miRNAs have been identified in many organisms. miRNAs play an important role in diverse cellular functions, including development, metabolism, cell fate and cell death (Elbashir *et al.* 2001; Carninci *et al.* 2005; Kozomara and Griffiths-Jones 2011). miRNAs are important regulators of gene expression, and the misregulation of miRNAs or mRNA mutations contributes to several diseases (Hannon and Rossi 2004). It is estimated that there are more than 2 000 identified mature miRNAs that are believed to target as many as 60% of mammalian mRNAs (Friedman *et al.* 2009). However, the biological function of most of these miRNAs remains to be uncovered (Mourelatos *et al.* 2002; Hannon and Rossi 2004; Kozomara and Griffiths-Jones 2011). This review summarizes the current understanding of the key characteristics of miRNAs and we highlight the role of miRNAs in exosomes and their therapeutic potential.

2. Characteristics of miRNAs

2.1. Structure of miRNA

miRNAs are endogenous non-coding single-strand RNA molecules that are about 19–25 nucleotides long (Pasquinelli and Ruvkun 2002; Bartel 2004). The 3´ terminus of a miR-

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NA molecules is flexible and usually has a 1–2 nucleotide overhang (Bartel 2004). A mature miRNA has 3′ hydroxyl and 5′ phosphate groups, which are important features that distinguish miRNAs from other small RNAs (Lee *et al.* 2002; Mourelatos *et al.* 2002; Pasquinelli and Ruvkun 2002; Carrington and Ambros 2003). The first nucleotide at the 5′ terminus has a strong bias toward U and is least likely to be a G. The second to fourth nucleotides are devoid of U and, in general, other positions (except the fourth) are not C. A mature miRNA pairs with its cognate target sites form a stem-loop structure within one strand (Lagos-Quintana *et al.* 2001, 2003; Kloosterman and Plasterk 2006). The stems of miRNA hairpins are highly conserved, and the loop regions are poorly conserved (Lagos-Quintana *et al.* 2001). About half of all of the miRNAs identified in vertebrates have homologous miRNA genes. Eighty-five percent of the miRNA genes in nematodes have well conserved homologs in *Caenorhabditis briggsae*, and about 12% of the miRNA genes in nematodes, fruit flies and plants are conserved. Some studies suggest that miRNA genes in one species may exist as orthologs or homologs in other species (Pasquinelli and Ruvkun 2002). An understanding of the variation of miRNAs between species is especially important for studying disease mechanisms in humans through the use of animal models.

2.2. Synthesis of miRNA

miRNA genes are transcribed into primary-miRNAs by RNA polymerase II or III and are cleaved by the protein Drosha into stem-loop miRNA precursors (pre-miRNAs) in the nucleus. The pre-miRNAs are transported into the cytoplasm by the protein exportin-5 and are further cleaved by Dicer into mature miRNAs, which are imperfect miRNA: miRNA* duplexes (Lund *et al.* 2004). Only one strand of the miRNA duplex (called the single strand guide) is subsequently incorporated into the effector RNA induced silencing complex (RISC) (Portnoy *et al.* 2011; Chen X *et al.* 2012). In animals, most miRNAs repress target gene expression primarily at the translational level by binding to the 3′-untranslated regions (3′-UTR) of the target mRNAs. A single miRNA molecule can thus regulate the translation of hundreds of proteins by inducing the degradation or inhibition of the translation of its mRNA targets (Diederichs and Haber 2007). Mature miRNAs interact with a member of the Argonaute (Ago) protein family members to form the RISC complex (Fig. 1). The modes of action of the RISC complex in silencing gene expression are a matter of debate, but several key mechanisms have been described over the years. These mechanisms and their controversies are discussed elsewhere (Morozova *et al.* 2012).

One difference between plant and animal miRNAs is that animals usually lack the complementary strands required for target mRNA cleavage by the RISC complex (Jinek and Doudna 2009). This fact indicates that, in animals, miRNAs function post-transcriptionally by regulating polypeptide chain initiation and elongation (through the promotion of ribosome separation) (Petersen *et al.* 2006). Moreover, mRNA repression correlates with poly(A) tail shortening, promoting mRNA deadenylation, decapping and leads to a more rapid degradation (Wu *et al.* 2006). miRNAs act as “rheotats” or “switches” to modulate mRNA levels and maintain the optimum protein synthesis activities. Studies confirmed that miRNAs inhibit translation by preventing the joining of the 60S and 40S subunits, which, thereby, inhibits the formation of the 80S ribosome (Wang *et al.* 2008) (Fig. 2).

2.3. miRNAs regulate gene transcription

To date, more than 9 500 miRNAs have been identified

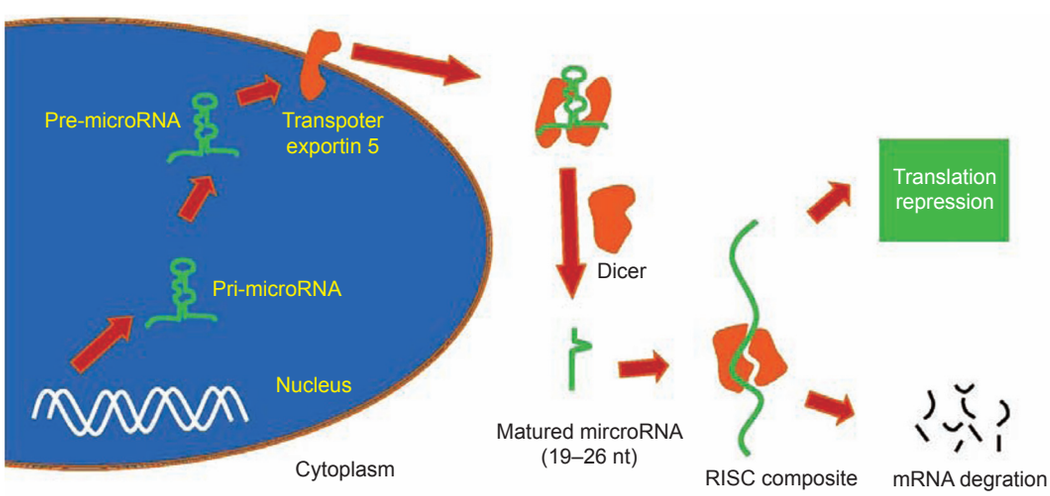

Fig. 1 MicroRNAs (miRNAs) biogenesis and mechanism of action. RISC, RNA induced silencing complex.