Best Practice & Research Clinical Endocrinology & Metabolism xxx (2016) 1–14

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

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

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MicroRNAs as paracrine signaling mediators in cancers and metabolic diseases

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
miRNAs
extracellular vesicles
cell–cell communication
cancer microenvironment
metabolic disorders

The contribution of microRNAs to the regulation of mRNA expression during physiological and developmental processes are well-recognized. These roles are being expanded by recent observations that emphasize the capability of miRNA to participate in inter-cellular signaling and communication. Several factors support a functional role for miRNA as mediators of cell-to-cell signaling. miRNA are able to exist within the extracellular milieu or circulation, and their stability and integrity maintained through association with binding proteins or lipoproteins, or through encapsulation within cell-derived membrane vesicles. Furthermore, miRNA can retain functionality and regulate target gene expression following their uptake by recipient cells. In this overview, we review specific examples that will highlight the potential of miRNA to serve as paracrine signaling mediators in metabolic diseases and cancers. Elucidating the mechanisms involved in inter-cellular communication involving miRNA will provide new insights into disease pathogenesis and potential therapeutic opportunities.

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http://dx.doi.org/10.1016/j.beem.2016.07.005
1521-690X/

The functions of miRNAs

MicroRNAs (miRNAs) are small non-coding RNA of 18–25 nucleotides (nt) that can negatively regulate gene expression through either post-transcriptional degradation or translational repression. A single miRNA can target a broad range of mRNAs with nearly complementary sequences, and thereby has the capacity to have a broad impact on gene expression [1]. In humans, the miRBase database identifies 2588 mature miRNAs (http://www.mirbase.org/) [2]. Many of these miRNA are also highly conserved across many species [3]. MiRNAs are initially transcribed as primary-miRNA (pri-miRNA) with a characteristic stem-loop structure. The stem-loop structure of pri-miRNAs is cleaved by the enzyme Drosha within the nucleus and results in precursor miRNA (pre-miRNA). Pre-miRNAs are then exported from nucleus into the cytoplasm by exportin 5 and processed by Dicer, an RNase III enzyme, to generate mature strands. The mature miRNA strand is incorporated into an Argonaute-containing RNA-induced silencing complex (RISC). The RISC can bind to a perfect or a nearly perfect complementary sequence within a target mRNA and the sequence is cleaved by the miRNA-RISC complex. In addition, miRNA can also induce protein translational repression of the target genes [4] (Fig. 1).

MiRNAs can contribute to diverse physiological roles and developmental processes and can also contribute to the pathobiology of diseases such as cancer [5] or metabolic disease [6]. The extent of their combinatorial impact is emphasized by the ability of each miRNA to bind several target sequences

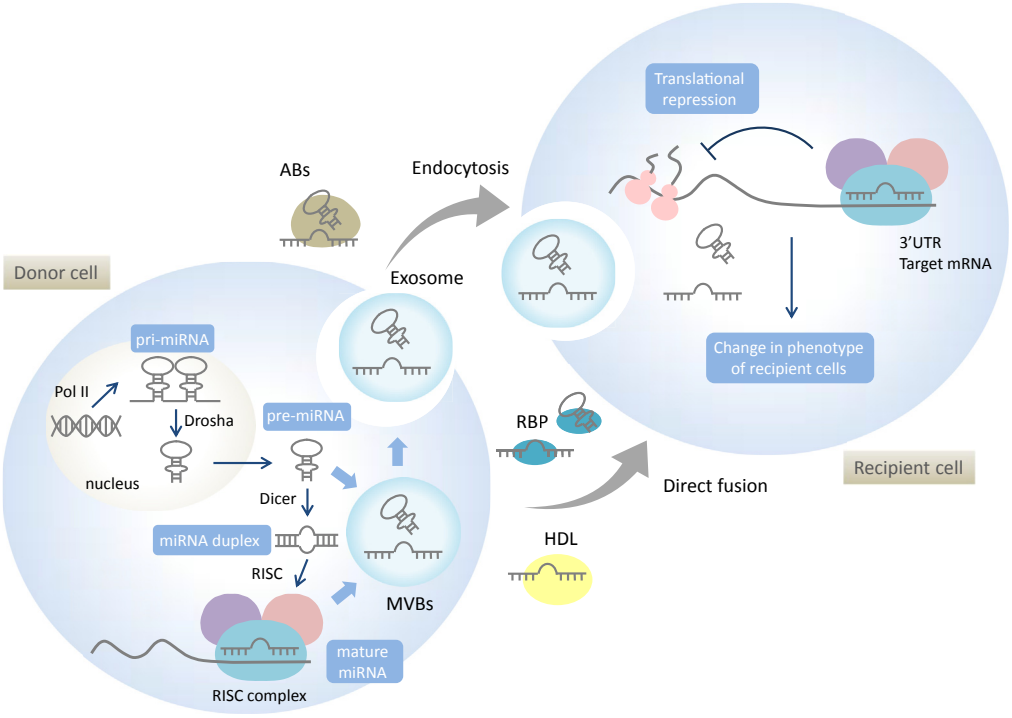

Fig. 1. miRNA biogenesis, cellular release and paracrine cell-to-cell communication. MiRNAs are typically transcribed by polymerase II (Pol II) as primary miRNA (pri-miRNA). Pri-miRNAs are cleaved by RNase III-type enzyme Drosha to produce hairpin-structured precursors (pre-miRNAs). Pre-miRNAs are transported to cytoplasm, the Dicer complex removes the loop region from pre-miRNAs to generate an imperfect duplex miRNA. Mature miRNA is bound by Argonaute to form a RNA-induced silencing complex (RISC). In the cytoplasm, pre-miRNAs or mature miRNAs can also incorporate into multivesicular bodies (MVBs). miRNA can be released from cells through release of exosomes derived from MVB's, microvesicles derived from plasma membranes or within apoptotic bodies. They can also be associated and released with RNA-binding protein complexes (RBP) or high density lipoproteins (HDL). Extracellular miRNAs can be transferred to recipient cells and bind to their target messenger RNAs (mRNAs) to repress their translation or induce their degradation.

Please cite this article in press as: Matsuda A, et al., MicroRNAs as paracrine signaling mediators in cancers and metabolic diseases, Best Practice & Research Clinical Endocrinology & Metabolism (2016), http://dx.doi.org/10.1016/j.beem.2016.07.005