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Extracellular/Circulating MicroRNAs: Release Mechanisms, Functions and Challenges

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ABSTRACT

MicroRNAs (miRNAs) are endogenously initiated, small non-coding RNAs and typically regulate the expression of mRNAs in post transcriptional level either via translational repression or mRNA degradation. Aberrant expression of miRNAs is observed in diverse disease and altered physiological states. Recently, it has been revealed that miRNAs are not only present in cells but also in extracellular milieu especially in different bio-fluids including blood plasma, follicular fluid and even in cell culture media. Such extracellular miRNAs (ECmiRNAs) are remarkably stable in the extracellular harsh environment with the presence of high RNAse activity. Although the precise mechanisms of release of cellular miRNAs to extracellular environment remain largely unknown, recent studies suggest that the expression of these ECmiRNAs can be associated with patho-physiological condition of an organism. Moreover, these ECmiRNAs may deliver to the recipient cells via certain pathways where they can regulate translational activity of target genes. This review will discuss the nature and stability of ECmiRNAs along with their release mechanisms. Furthermore, based on recent evidences, it also summarizes the possible function of these ECmiRNAs in distant cell-to-cell communication and the difficulties we may face during ECmiRNA research.

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MicroRNA (miRNA) and Their Biogenesis

miRNAs are mostly studied small non-coding RNAs, which are typically 18–24 nucleotides long and are considered as one of the major post-transcriptional regulators of gene expression. This process is accomplished through binding of miRNA to their target mRNAs by base-pairing and subsequently inducing either translational repression or mRNA destabilization. They are estimated to comprise 1–5% of animal genes, and thousands of miRNAs can be encoded by a genome at a time (Hossain et al., 2012). Bioinformatics analysis estimated that more than 60% of mRNAs in mammalian genome can be targeted by single miRNA. Because of their broader targeting characteristics, miRNAs are expected to be involved in most biological pathways and cellular processes including cell proliferation, apoptosis, cellular development and cellular signaling. Upon its discovery in *Caenorhabditis elegans* in the early 1990s (Lee et al., 1993), since then, miRNA has been identified in a wide range of biological pathways of different organisms, ranging from single-cell algae to multi-cellular mammalians, indicating their function is an ancient and critical cellular regulatory mechanism. According to miRbase (version) there are more than 2000 known human miRNAs that have been identified to influence gene expression and associated with pathological conditions.

The biogenesis of miRNAs is tightly regulated spatio-temporal process, and any deviation is associated with several diseases. The cellular process of miRNA biogenesis involves both nuclear and cytoplasmic processes (Lee et al., 2002). MiRNAs originate from large primary (pri) and precursor (pre) transcripts which undergo successive multi-steps of processing until they reach their mature and functional form (Fig. 1). All miRNAs are transcribed by RNA polymerase II from chromosomal DNA (intergenic

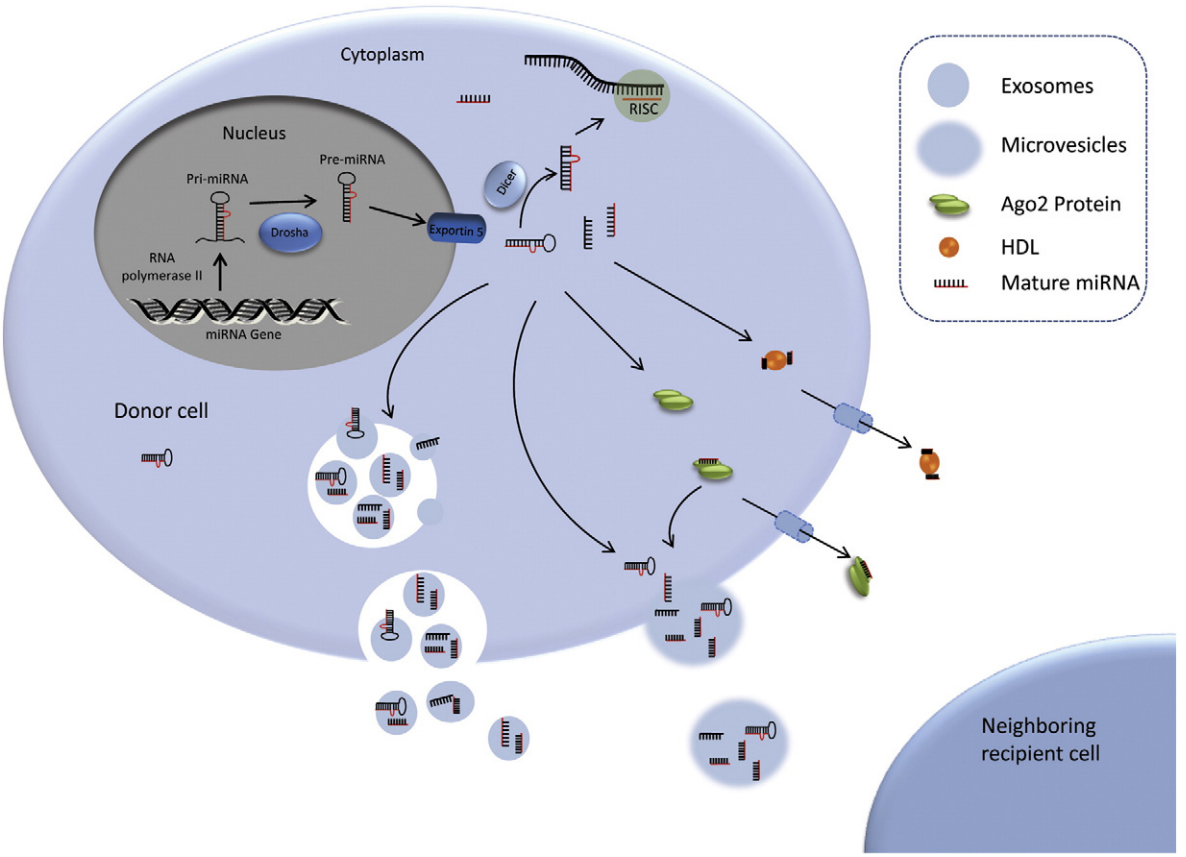

Fig. 1. miRNA biogenesis and release of miRNAs in the extracellular environment. Pri-miRNAs are transcribed by RNA polymerase II and later processed by Drosha to Pre-miRNA. Exportin5 transfer these Pre-miRNAs from nucleus to cytoplasm where Dicer processed them into mature miRNAs. Mature miRNAs can be selectively incorporated into the exosomes or coupled with Ago2 protein and released in to extracellular milieu. Alternatively, they can be enwrapped with microvesicles or attached to HDL and later released to extracellular environment.