

Exosomal miRNAs and Cancer

Abstract

MicroRNAs (miRNAs) represent a large family of small, nearly 20-22 nucleotide non-coding RNAs that modulate the expression of target genes, specially at the post-transcriptional level. Many studies suggest that miRNAs play a role in homeostatic preservation and that deviant expression of miRNAs is usually seen in several types of diseases, such as cancer. Exosomes are extracellular vesicles synthesized in the cells. They induce cell-cell communication and immunoregulatory functions. In cancer, exosome secretion is associated with primary tumor growth, regulation of local tumor microenvironment, and stimulation of distant metastatic niche formation during tumor spread. MiRNA expression is often dysregulated in tumour cells and can be reflected by distinct exosomal miRNA (ex-miRNA) profiles isolated from the cancer patients. In this minireview, we sum up the current understanding about exosomal miRNAs (ex-miRNAs) functions in cancer. We also review the possible clinical utilization of ex-miRNAs in cancer, for instance as diagnostic marker and therapeutic target.

Keywords: MicroRNA; Exosomes; Cancer; Marker

Mini Review

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Introduction

MicroRNAs (miRNAs) are non-coding RNAs with nearly 20-22-nucleotides. They modulate gene expression at the post-transcriptional level by binding to the 3'-untranslated regions (3'UTRs) of target genes or to imperfectly complementary sequences named miRNA response elements (MREs) [1]. The binding of miRNAs to target genes results in the degradation or translational inhibition. Numerous human protein-coding genes are regulated by miRNAs and growing data suggest that miRNAs constitute a key part in the complex regulatory networks regulating a wide range of cellular processes, such as the timing of developmental processes, cell proliferation/differentiation, apoptosis and organ development [2]. The comprehensive studies of the past years have shown that miRNAs are not only contained into cells, but are also found outside them, released in different body fluids (e.g. serum, plasma, saliva, urine) routinely tested in patients [3].

Although miRNA expression patterns are partially described in most cell types under normal conditions, aberrant expression of some miRNAs has been identified in various human diseases, implying that miRNAs can be beneficial as biomarkers for disease occurrence and as a possible target of treatment [4]. It has been reported that miRNA expression in tumor is up or down-regulated compared with normal tissue confirming their complex dual action either as oncogene (oncomir) or tumor suppressor gene [5]. Recently an amazing finding suggested that miRNAs are present in exosomes and these exosomal miRNAs (ex-miRNAs) can be functionally sent to target cells. In this minireview, we sum up latest advances in the exploration of ex-miRNAs in cancer. We also review the possible clinical utilizations of ex-miRNAs in cancer, e.g. as diagnostic markers and therapeutic targets.

Exosomes

Exosomes are small, measuring only 30–120 nm in diameter, cell-derived vesicles with an endosome origin that are secreted by cells into the extracellular space. They were first discovered in the mid-1980s as small vesicles that arise from reticulocytes during their maturation to eliminate some membrane bound proteins [6]. These vesicles are generated by a various cell types such as reticulocytes, epithelial cells, neurons, and tumor cells [7]. They transfer proteins, lipids, and nucleic acids to target cells, and change the biochemical composition, signaling pathways, and gene regulation of these cells [8]. Some reports have established that exosomes are involved in immune response, tumor progression, and neurodegenerative diseases.

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Similarly non-exosomal miRNA, ex-miRNAs have also been identified in bodily fluids [9,10]. Because of easy access and stability, ex-miRNA has been suggested as a new, minimally invasive tool for cancer diagnosis, with potential prognostic value. Ex-miRNA profiling of serum from cancer patients versus healthy individuals has shown significant differences with regard to tumor progression, highlighting a possible use of these miRNAs as disease prognostic biomarkers [11]. Exosomes are a reliable source of miR in bodily fluids, preventing breakdown of biological macromolecules under non-physiological conditions. It was reported that Ex-miR remains stable at -208 °C for 5 years and is resistant to freeze-thaw cycles [12].

Ex-miRNA can provide an understanding for the classification or subtype of the tumour. Besides, it was found that ex-miRNAs indicate tumour severity, progression and aggressiveness. The diverse range of information that might be obtained from ex-

miRNA, including progression of a tumour, identification of metastasis and possible drug resistance, could be used to affect clinical decisions and treatment strategies, thus promoting optimized treatments adjusted to meet the needs of the patient. These data could also have a prognostic value [13]. Furthermore, ex-miRNAs represent an encouraging new treatment approach due to their significant natural role in cellular processes along with high stability, tissue-specific expression and secretion into body fluids [14].

Conclusion

Extensive effort is spent for research to ascertain new cancer diagnostic and prognostic tools. Malignant progression is significantly affected by dynamic cross-talk between stromal and cancer cells. Exosomes regulate communication between both adjacent and distant cells, thus emerging as a new form of intercellular communication, as well as a delivery tool. As a noninvasive approach, measurement of extracellular miRNAs in bodily fluids might be a valuable strategy. Additionally, because dysregulation of miRNAs is essential to the pathogenesis of numerous cancers, they are promising candidates for clinical usage as therapeutic targets in both solid and hematological malignancies. The ex-miRNAs involved in the regulation of cancer metabolism may be possibly used for better diagnostics and treatment.

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