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A Review of MicroRNA in Carcinogenesis

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Abstract

MicroRNAs (miRNAs) are small RNAs involved in regulation of several cellular processes which are involved in the silencing of cell's message in various processes. They are class of 21- to 24-nucleotides (nt), non-coding, regulatory RNA molecules, was first discovered in developing nematode. After the discovery of the first miRNA in the roundworm *C. elegans*, these short regulatory RNAs have been found to be an abundant class of RNAs in plants, animals, and DNA viruses. About 3% of human genes encode for miRNAs, and upto 30% of human protein coding genes may be regulated by miRNAs. MicroRNAs play a key role in diverse biological processes, including development, cell proliferation, differentiation and apoptosis. Accordingly, altered miRNA expression is likely to contribute to human disease, including cancer. Recent findings indicate that carcinogenic processes are associated with alteration in the expression of several microRNAs. Furthermore finding suggested that some microRNAs have got cancer promoting role (as oncogene) and the others act as tumour suppressor genes. In this review we illustrate the specific role and relationship of microRNA in a wide variety of cancer and also the application of microRNA in cancer detection as biomarker as well as therapeutic potential.

Key words: Cancer, Carcinogenesis, MicroRNA, oncogene.

Introduction

A microRNA (miRNA) is a short ribonucleic acid (RNA) molecule found in eukaryotic cells and first discovered in 1993 by Victor Ambros, Rosalind Lee and Rhonda Feinbrium during a study of the gene lin-14 in *C. elegans* development (Lee et al., 1993) They found that LIN-14 protein abundance was regulated by a short RNA product encoded by lin-4 gene. A 61-nucletide precursor from the lin-4 gene matured to a 22-nucleotide RNA that contained sequences partially complementary to multiple sequences in the 3' UTR of the lin-14 miRNA. This complementarily was both necessary and sufficient to inhibit the translation of the lin-14 miRNA into the LIN-14 protein. Retrospectively, the lin-4 small RNA was the first microRNA to be identified, though at the time, it was thought to be a nematode idiosyncrasy. In the year 2000 a second RNA was characterized: let-7, which repressed lin-41, lin-14, tin-28, lin-42, and daf-12 expression during developmental stage

transitions in *C. elegans*. let-7 was soon found to be conserved in many species (Reinhart et al., 2000) indicating the existence of a wider phenomenon. Animal miRNA genes are clustered within the genome and co-transcribed as polycistronic RNAs (Ahmada et al., 2013). miRNAs can target messenger RNA but as well as DNA (MiR-373) and proteins like as MiR-328 interacts with a heterogeneous ribonucleoprotein, hnRNP-E2, to regulate RNA-binding protein function (Melo and Esteller, 2011). Many cellular pathways are affected by the regulatory function of miRNAs like pathways that control developmental and oncogenic process (Winter et al., 2009). MiRNA genes involved in regulating cancer-related pathways are silenced in association with CpG island hyper-methylation. Aberrant DNA methylation of miRNA genes is a potentially useful biomarker for detecting cancer and predicting its outcome (Suzuki et al., 2012).

Biogenesis

The majority of the miRNA genes are oriented antisense to neighboring genes and are therefore suspected to be transcribed as independent unit. 40% of miRNA genes may lie in the introns of protein and non-protein coding genes or even in exons of long non-protein-coding transcripts, are usually found in a sense orientation and are regulated together with their host genes. The miRNA genes showing a common promoter include the 42-48% of all miRNAs originating from polycistronic units containing multiple discrete loops from which mature miRNA are processed. The promoters shown to have some similarities in their motifs to promoters of other genes transcribed by RNA polymerase II such as protein coding genes (Lee et al., 2005). The DNA template is not the final word on mature miRNA production: 6% of human miRNAs show RNA editing (IsomiRs), the site-specific modification of RNA sequences to yield products different from those encoded by their DNA. This increases the diversity and scope of miRNA action beyond that implicated from the genome. Transcription is a major point of regulation in miRNA biogenesis (Melo and Esteller, 2011). MiRNA genes are usually transcribed by RNA polymerase II (Pol II).

A single pri-miRNA may contain from one to six miRNA precursors. These hairpin loop structures are composed of about 70 nucleotides each. Each hairpin is flanked by sequences necessary for efficient processing. The double-stranded RNA structure of the hairpins in a pri-miRNA is recognized by a protein named as DiGeorge Syndrome Critical Region 8 (DGCR8 or “Pasha” in invertebrates). Pre-miRNAs that are spliced directly out of introns, bypassing the “Microprocessor” complex, are known as “Mirtrons”, have been discovered in several species including mammals, *D. melanogaster* and *C. elegans* (Winter et al., 2009). Pre-miRNA hairpins are exported from the nucleus in a process involving the nucleo-cytoplasmic shuttle Expotin-5. This protein, a member of the *karyopher* in family, recognizes a two-nucleotide overhang left by the RNase III enzyme Dorsha at the 3’ end of the pre-miRNA hairpin. Exportin-5 mediated transport to the cytoplasm is energy-dependent, using GTP bound to the Ran protein (ref).

In cytoplasm, the pre-miRNA hairpin is cleaved by the RNase III enzyme DICER I. DICER1 is a highly conserved protein with one homologue in the yeast *Schizosaccharomyces pombe* (Dcr), one in human, one in nematode worm (DCR-1), two in *Drosophila* (DCR-1 and DCR-2), and four in *Arabidopsis* (DCL1, DCL2, DCL3, DCL4) (Melo and Esteller, 2011).

MiRNA as novel biomarkers in cancer

MiRNA directly or indirectly regulate many molecular pathways(genetic or epigenetic), which trigger cancer by targeting many

oncogenes and tumour suppressor genes. They also help in cancer diagnosis, prognosis and therapy. Genetic mechanisms are usually chromosomal abnormalities that can lead to the deletion, amplification, or translocation of miRNAs. In addition, approximately 50% of all annotated human miRNA genes are located at fragile sites or areas of the genome that are associated with cancer which are prone to breakage and rearrangement in cancer cells (Melo and Esteller, 2011). The miR-15a and miR-16-1 genes located in chromosome region 13q14, deleted in chronic lymphocytic leukemia. As miRNA regulate the expression of their target genes, so over or under expression can change the amount of protein product of the mRNA gene. For example, mir-15 and miR-16 are down-regulated chronic lymphocytic leukemia (CLL) and induce apoptosis by targeting anti apoptotic gene B cell lymphoma 2 (BCL2) mRNA (Melo and Esteller,2011).The let-7 family was the first identified microRNA in humans (Inamura and Ishikawa, 2016). Johnson et al., (2005) discovered that lung tumor tissues contain reduced levels of let-7 and increased levels of RAS protein relative to normal lung tissue, suggesting that let-7 miRNA directly regulates ras and myc oncogenes due to let-7a-3 hypomethylation (Melo and Esteller, 2011). As miRNA regulate the expression of their target genes, so over or under expression can change the amount of protein product of the miRNA gene, like, mir-15 and mir-16 are severely down regulated in chronic lympholytic leukemia (CLL) and induce apoptosis by targeting anti-apoptotic gene B cell lymphoma 2 (Bcl2 mRNA) (Melo and Esteller,2011). Although the let-7 family is globally down regulated in lung cancer (Takamizawa et al., 2004; Yanihara et al., 2006), there is evidence of let-7a-3 hypomethylation (Brueckner et al., 2007).

MicroRNA-21 an oncomiR is among the first few identified miRNAs. Transgenic mice that over-express or lack specific miRNAs have provided insight into the role of small RNAs in various malignancies. A study of transgenic mice which produce excess c-Myc, a protein with mutated forms involved in the developmental form of several cancers shows that miRNA has an effect on the process of carcinogenesis. Mice that were engineered to produce a surplus of types of miRNA found in lymphoma cells developed the disease within 50 days and died two weeks later, while, mice without lived over 100 days (Melo and Esteller, 2011). While over expression of miR-21 is found in a number of haematological malignancies such as acute myeloid leukemia (AML), chronic myeloid leukemia (CLL), and solid tumors including glioblastoma, cancers of the liver, pancreas, prostate, stomach, colon, lung, breast; MiR-29 family genes are down regulated in CLL, lung cancer, invasive breast cancer, AML, and cholangiocarcinoma. MiR-34a is a potential tumour suppressor in brain tumors'. The miR-17-92 cluster which contains six miRNAs (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92-1) is trans-activated by *c-myc* oncogene and reported to be frequently over expressed in follicular lymphoma and diffuse large B cell lymphoma, in cancers of the breast, colon, lung, pancreas, prostate, and stomach (Vishwanathan et al., 2009). Over expression of Circulating miR-141 in the serum of Prostate cancer patients indicate that circulating miRNA levels may be used as a biomarker in Prostate cancer diagnosis. (MicroRNA expression and function in prostate (Kumar and Lupold, 2016). Likewise the level of miR-26 expression was also associated with hepato-cellular carcinoma Expression of this miRNA in liver cancer cells in vitro induces cell cycle arrest associated with direct targeting of cyclins D1 and D2 (Melo and Esteller, 2011). MiR-155 a tumour oncogene is highly expressed in paediatric Burkitt lymphoma, Hodgkin disease, primary

mediastinal non-Hodgkin lymphoma, CLL, AML, lung cancer, and breast cancer (Ahmad et al., 2013) and is found to be responsible to accelerate tumour development during its ectopic expression (Melo and Esteller, 2011). Expression of miR-145 and miR-143 is reduced at different forms of colorectal neoplasia due to post-transcriptional control which reduces mature miRNA levels (Melo and Esteller, 2011). The miR-200 family (miR-200a, miR-200b, miR-200c, and miR-429), which are epithelial to mesenchymal cell transiters, plays an important role in the progression of lung cancer (Inamura and Ishikawa, 2016). MiR-203 encodes a candidate tumour suppressor and is epigenetically silenced in oral cancer (Kozaki et al., 2008), haematopoietic malignancies, (Bueno et al., 2008) and HCC. It was found that the expression levels of miR-16, miR-21, miR-155, miR-181a, miR-181b, miR-196a and miR-210 were significantly increased in plasma from pancreatic cancer patients (Li et al., 2016). In human testicular germ cell tumors two miRNAs were re-ported to be oncogenic, miR-372 and miR-373 , both of them inhibit p53-mediated CDK inhibition through direct inhibition of the Large Tumor Suppressor Homolog 2 (LATS2), and promote tumorigenesis of primary human cells which have oncogenic RAS and active wild-type p53 (Melo and Esteller,2011). Expression levels of miRs-21, −34b, −130b, −135b, −146b, −151, −181b, −199b-5p, −221, −222, −451, −623, −1271, −2861, and let-7e showed significant association with at least one aggressive feature, such as large tumor size, extra-thyroidal extension, multifocality, lymphovascular invasion, lymph node metastases, distant metastasis in thyroid cancer (Patricia et al., 2015). In breast cancer, dysregulation of miR-145 and miR-121 has been associated with tumour progression. The miRNAs miR-21 and miR-155 are associated with non-small cell lung cancer (Blenkiron et al., 2007). Colorectal neoplasia (colon cancer) is also associated with alteration in miRNA expression. Some miRNAs also play an important role in drug resistance, such as miR-19, miR-21, and the miR-221/miR-222 cluster were unregulated several fold in association with this phenomenon (Garofalo, 2009; Shi, 2010; Liang, 2011). MiRNAs regulate many cell cycle proteins including Cdk6, Cdc25A, Ccnd2 (cyclin D2), Cdk4, a Rb-family protein, and p180 subunit of DNA polymerase A and pRB itself is abnormally down-regulated by the over expression of the miR-106a in different human oncogenic miR-17-92 clusters (Melo and Esteller, 2011). The miR-34 family of miRNAs are directly induced by p53 and can down regulate protein levels of cyclin D1 and CDK 6. CDK6 is also targeted by miR-124 or miR-137. The let-7 family may control multiple regulators of cell proliferation such as cyclin A2, cyclin B1, cyclin E2 and CDK8 .Therefore, functional abnormalities of miRNA which control many cell cycle regulatory proteins, can give rise to the malignant phenotype in human tumors (Melo and Esteller, 2011).

MicroRNA in cancer therapy

recent advances in micro-array and sequencing technologies have enabled comprehensive analysis of the epigenome and miRNA expression in cancer cells, and as a result the list of miRNA genes silenced by methylation in cancer is rapidly growing (Lopez-Serra and Esteller, 2012). Saito et al., (2006) analyzed the expression profiles of miRNA in a T24 bladder cancer cell line treated with or without the DNA methyl transferase inhibitor 5-aza-2'-deoxycitidine(5-aza-de) and the histone deacetylase inhibitor 4-phenyl butyric acid (4-PBA)(Suzuki et al, 2012). Combined effect of methylated CpG island amplification along with CpG island microarray analysis, the

methylation of miR-9-1 was identified in pancreatic cancer (Omura et al., 2008). MiRNA genes are tightly associated with histone modifications, among which trimethylation of histone H_3 lysine 4 is a hall mark of active transcription, which can be used as a marker of active miRNA genes (Suzuki et al., 2012). Three main epigenetic events regulate tumor-associated genes: the aberrant hyper-methylation of tumor suppressor genes, global DNA hypomethylation and post-translational modifications of his-tone]. An extensive analysis of genomic sequences of microRNA genes has shown that approximately half of them are associated with CpG island (Melo and Esteller, 2011). MiRNA over expression or inhibition could also have some therapeutic value in different cancer cell types; for example , miR-9, a pro-metastatic miRNA in breast cancer, when suppressed can reduce highly metastatic 4T1 mouse mammary cell line growth by 50% (Melo and Esteller, 2011). There are many chemical compounds which could change the expression pattern of certain miRNA, leading to change the malignant forms of certain tumour tissues to its normal form. One of such chemical is fluoroquinolones that have significant growth inhibitory effect on transitional cell carcinoma of bladder, colorectal carcinoma and prostate cancer cells (Melo and Esteller, 2011). NSAID modulate miRNAs in both cell culture and animal models (Kunte et al., 2011). MiRNA also allow to discriminate between metastatic and non-metastatic tumors, so they can be very useful as different types of biomarkers in different tumour types (Malumbres, 2013). Functional analysis of miRNA might be also important for the development of diagnostic miRNAs. For example, miRNA-451 has been linked to controlling expression of P-glycoprotein, a critical protein for multi drug resistance in cancer cells.

Conclusion

MiRNA research can be used as important biomarkers in therapeutics of different cancer cells. They help in post transcriptional control of different target genes, thus help to modulate the epigenetic control of different proteins at gene level. Some serum circulating miRNAs found in different cancer tissues can also help to discriminate between carcinogenic and benign tumors. Moreover, modulation of different enzymes and genes in microRNA biosynthesis pathway can also lead to cell transformation. Thus understanding the miRNA biology completely will help to understand and elucidate different possible mechanism that can control transformation of cancer cells.

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