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MicroRNAs as Early Detection Biomarker in Cancer

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MicroRNAs are 20–24-nucleotide-long noncoding RNAs that bind to the target mRNAs at the 3′ UTR (untranslated region) and regulate the expression of various oncogenes or tumor suppressor genes. Under various physiological conditions the ability of miRNAs to control gene expression has widely focused and gained their attention. It has also been reported that there is a link between deregulated expression of miRNAs to different disease states. In the last few years there has a great trend to know the biological role of mircoRNA (miRNA) in normal cellular as well as in disease processes. The expression profiling of miRNAs has clearly assessed their role as diagnostic and prognostic biomarkers which will help clinicians to assess tumor initiation, progression and response to treatment in cancer patients. In the development of various stages of cancer, the role and involvement of miRNAs has been revealed. This review focuses on the association of miRNAs with that of cancer and highlights the role of miRNAs in clinical practice, such as diagnosis, prognosis and detection.

Introduction

MiRNAs are a highly conserved class of small non coding RNA molecules with a length of 19-24 nucleotides. More than 1,000 members of small-regulatory RNAs are found in the mammalian genome. Several hundred of miRNA molecules have been found due to the discovery of lin-4 in Caenorhabditis elegans by Victor Ambros, Rosalind Lee and Rhonda Feinbaum in 1993 during their studies on development in the nematode *Caenorhabditis elegans* (*C. elegans*). miRNAs do play an important role in the gene regulation and are found in eukaroytes including the genome of humans. In humans 30% of protein coding genes are regulated by mi RNA and also it accounts 1- 5% of the human genome [1-5]. Till now in the human genome about 940 distinct miRNAs molecules have been identified [6-9]. Presently a little knowledge is known about

the function and targets of miRNA but it is clear that they do exhibit a role in regulation of gene expression. In addition to this, miRNAs in a cell do exhibit their control on cellular and metabolic pathways. In specific tumors the alteration in expression of miRNAs does indicate that they have a possible role in development of cancer and other diseases [10-16].

MicroRNAs act as post-transcriptional regulators and bind to complementary sequences in the 3' UTR of multiple target mRNAs, usually resulting in their silencing.

MicroRNA – in the genome

In the human genome there is a variety of small RNA molecules such as small transfer RNA (tRNA), ribosomal RNA (rRNA), small nucleolar RNA (snoRNA), small interfering RNA (siRNA) and microRNA (miRNA). Out of these, miRNA and siRNA are the only RNA molecules which are biochemically and functionally indistinguishable. Both these molecules have 5'-phosphate, 3'-hydroxyl ends and are 19-25 nucleotides long. They are involved in gene silencing and assemble into RISC [17-19].

On the basis of their respective origins these molecules are easily distinguished. From a double-stranded region of a 60 -70nt RNA hairpin precursor miRNA is formed. In the different regions of the genome whether intergenic regions or introns of protein coding genes, the precursors of miRNA are found in clusters. Previously the functions of these regions was not known and were referred to as junk DNA. But the discovery of miRNA genes has changed the whole scenario and has made it clear that 'junk DNA' is not useless as originally thought. In the antisense transcripts and exons of transcripts the precursors of MiRNA are less commonly found [20, 21].

Biogenesis of mi RNA

Mi-RNAs are universally conserved in different species and help to regulate 50% of the genome. MiRNAs do regulate innate as well as adaptive immunity and act as regulators of post transcription (22). The control of gene expression by MiRNAs post transcriptionally occurs by protein translational repression or by promoting mRNA degradation.

In a variety of organisms that involves plants and animals Mi RNA has been reported and their role in developmental and cellular processes in plants and vertebrates has been reported (23). Various types of cells do synthesize Mi-RNAs and finally it is released into extracellular spaces and fluids. From the primary miRNA the synthesis of miRNAs occurs and these events occur in nucleus. By the catalytic activities of Drosha-DGCR8 enzyme the cleavage of larger hairpin to pre miRNA occurs. After the process of trimming Exportin -5 helps to transport short structures of RNA to the cytoplasm. (24). The synthesis of mature mi-RNA takes place inside the cytosol with the help of Dicer and TRBP (Tar RNA binding protein) proteins. The duplexes of mi-RNA loaded into Argonaute protein (Ago2) form effector complexes, also known as, RNA-induced silencing complex (RISC) (25). Out of the two strands, one of the strands at the 5' end of the duplex which is thermodynamically less stable will become the mature mi-RNA. This form of mature miRNA is finally retained in RISC and forms miRISCs complex resulting in their inhibition (26).

MicroRNAs in cancer

Cancer is a metabolic dysregulation characterized by abnormal growth of cells, genetic alterations, and series of processes that transform the cancer cells from benign

state to malignancy. multistep process in which normal cells experience genetic changes that progress them through a series of pre-malignant states (initiation) into invasive cancer (progression) that can spread throughout the body (metastasis). Several distinct features are observed in the resulting transformed cellular phenotype that enables cells to multiply excessively in an autonomous manner. The capability of cancerous cells to proliferate is not dependent on growth signals, probably it is unresponsive to the inhibitory signals of growth and further it evades the apoptotic pathways, overcomes the limits of intrinsic cell replication, induces angiogenesis and forms new colonies that bare discontinuous with the primary limits[27]. The progression and initiation of cancer is related with the dysregulation of genes that are involved in proliferation of cells, differentiation and apoptosis. The genes that are associated with the development of cancer are categorized as oncogenes and tumor suppressors. Based on the functions the products of oncogenes are divided into six groups and these include transcription factors, growth factors, growth factor receptors, chromatin remodelers, apoptosis regulators or signal transducers [28]. Genetic alterations activate oncogenes that in turn amplify the genes which in due course of time act on the promoters/enhancers to increase the expression of genes or interfere with the structure of protein to a permanent active state [29-30]. In biological pathways the products of tumor suppressor genes have regulatory roles. Dysregulation that is associated with cancer is due to the loss of functions of tumor suppressor genes [31]. Various pathways whether metabolic or cellular that control cell proliferation, differentiation and survival, mi-RNA do play a significant role in all of these [32-34]. In most tumors that have been examined dysregulation of miRNAs has been demonstrated [35]. Due to the intricate pattern of expression of miRNAs it has became very difficult to classify miRNAs as either oncogenes or tumor suppressors. It is not well understood that whether the altered patterns of miRNA expression are the direct cause of cancer or not. It has also been studied and reported that multiple targets can be regulated by a single miRNA [36].

MiRNAs biomarkers

Recently, microRNAs (miRNAs) have emerged as a new type of specific and potential biomarker in cancer. In the body cells secrete miRNAs and a variety of body fluids including blood, saliva and urine where miRNA is also found and these are the areas where miRNAs are quantifiable and extremely stable. Therefore in any potential human disease including cancer miRNAs are becoming ideal candidates as non-invasive biomarkers. The potential utility of miRNAs can be used in the diagnosis and prognosis in cancers. In tumors the alteration in the expression of miRNAs does clearly suggest that they have got a role in the diagnosis and prognosis of cancers. To assess the correlation between the expression of miRNAs and cancer diagnosis/prognosis numerous clinical trials are going on from the past few years. It has been found that the miRNAs derived from the expression profile of tumor patients is useful in the diagnosis and prognosis of the disease. For example, the studies which were carried out by Lu *et al.*, reported that to classify various types of cancers the expression profile of miRNA can be precisely used. Due to the advances in the technological areas, refinement and enrichment of existing miRNA families has resulted in the increased discovery of new micro RNAs. It has been reported on the studies carried out in 193 species that the central repository for miRNA research, miRBase (release 19, dated August 2012), contains 21,264 validated miRNA genes expressing 25,141 mature miRNA. Based on the sequence and structural

properties, about 73% (15,554) of the miRNA genes at miRBase have been assigned into 1,543 miRNA families based. In cytogenetically normal and abnormal acute myeloid leukemia patients, an independent prognostic assessment cold be provided by the MiR-181(37-40). In a study carried out by Yang *et al.,* in the serum of patients with advanced stage (grade IIeIV) astrocytomas, the levels of seven different miRNAs, miR-15b*, miR-23a, miR- 133a, miR-150*, miR-197, miR-497 and miR-548b-5p significantly decreased(41). In the human serum or plasma several studies has reported different miRNAs that are highly stable and further the expression patterns of these miRNAs are distinctive.(42-45). The miRNAs in the circulation could also serve as diagnostic/prognostic indicators. In recent years it has been reported that in patients of many types of cancers including multiple myeloma, nasopharyngeal carcinoma, gastric cancer, prostate cancer, breast cancer, colon cancer, pancreatic cancer, diffuse large B-cell lymphoma, squamous cell carcinoma, lung cancer, ovarian cancer and several others differential expression of circulating miRNAs has been seen. The miRNAs in the circulation have got a great potential for the diagnosis of cancers where there is an unmet need to be able to diagnose cancers at an early stage or distinguish between cancer types. Due to the presence of miRNAs in the circulation fluids, it provides a path of non-invasive ways of establishing early prognosis, predicting treatment response and ascertaining progression risk.

Till now significant scientific developments have taken place that ultimate describe the utility of miRNAs as biomarkers for prediction, diagnosis and prognosis. Recent studies also suggest that in order to develop novel treatment strategies, substitution of tumor suppressive miRNAs could also be a possible alternative. Additional studies needs to be carried out on dysregulation of miRNAs in tumors as well as in cancers. Also in future the development of such novel techniques or methods needs to be carried out that could predict whether the increase or decrease in the expression of miRNAs could directly be linked to rise in the development of tumors or cancers. Besides this it is also essential to develop such reliable and cost-effective miRNA-based technologies to collect blood, saliva and urine that could easily predict cancer diagnosis/detection and therapeutic assessment/prognosis.

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