

miRNA: An Overview of its Role in Cancer Research and Diagnosis



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Abstract

Despite of great advances in the spread of awareness, understanding and treatment of cancer, it still remains one of the leading causes of death worldwide. Several changes occur at the cellular and molecular levels viz. DNA, RNA, mRNA, miRNA and proteins of a patient suffering from cancer. Alteration in Protein expression due to genetic and epigenetic changes in the cell is one of the major causes of various types of cancers. These genetic and epigenetic changes in cells can be exploited as potential marker in detecting the cancer. MicroRNAs (miRNAs) act as negative regulators of gene expression and having the capacity to block the translation process. miRNAs are amongst the potential candidates, to be used as molecular prognostic markers in several tumor types. This mini review briefly describes the biogenesis of miRNA and its role in cancer diagnosis.

Keywords: Cancer; miRNA; Molecular diagnosis

Abbreviations: miRNA: Micro Ribonucleic Acid; ICMR: Indian Council of Medical Research; Nt: Nucleotide

Introduction

Cancer is a group of disease or malignancy in which there is abnormal or out-of control growth of the cell which possess tendency of spreading to other distant sites in the body. As per American Cancer Society there are more than 100 different types of Cancers and all these types of cancers can be classified into five different classes depending upon their source of origin. They are carcinomas, Sarcomas, Lymphoma & leukemia, Germ cell tumor and Blastomas.

According to the report published by World Cancer Research Fund International, there were an estimated 14.1 million cancer cases around the world in 2012, of these 7.4 million cases were in men and 6.7 million in women. This number is expected to increase to 24 million by 2035. Lung cancer was the most common cancer worldwide contributing to 13% of the total number of new cases diagnosed in 2012 [1].

In women, Breast cancer was the most common cancer worldwide in women contributing more than 25% of the total number of new cases diagnosed in 2012. The top three -breast, colorectal and lung cancers, contributed more than 43% of all cancers (excluding non-melanoma skin cancer). Cervical cancer also contributed nearly 8% of all cancers (excluding non-melanoma skin cancer) [1]. In men, Lung cancer was the most common cancer worldwide contributing nearly 17% of the total

number of new cases diagnosed in 2012. The top three - lung, prostate and colorectal cancers, contributed nearly 42% of all cancers (excluding non-melanoma skin cancer) [1]. In Indian scenario, as per the report published by ICMR, New Delhi in May 2016; India is likely to have over 17.3 lakh new cases of cancer and over 8.8 lakh deaths due to the disease by 2020 with cancers of breast, lung and cervix topping the list. Among females, breast cancer topped the list and among males mouth cancer (oral) as per the report published by ICMR. The ICMR depicted that in 2016 the total number of new cancer cases is expected to be around 14.5 lakh and the figure is likely to reach nearly 17.3 lakh new cases in 2020 [2].

The classification of cancer is done as per traditional parameters such as, histological type, grade, tumor size, lymph node involvement and vascular invasion, and biomarkers specific to different cancer types. With advancement in emerging imaging techniques such as digital mammography, tomosynthesis, ultrasonography, magnetic resonance imaging, nuclear medicine etc., diagnostics is going through a significant evolution [3].

Despite of the significant progress in the past three decades, cancer remains the second leading cause of death worldwide. In order to achieve the goal of decreasing mortality and morbidity

of cancer, it not only requires improvement in therapies but also need improved methods to assess an individual's risk of developing cancer at an early stages so that it can be treated more effectively, and it should also significantly distinguish between aggressive from nonaggressive type of cancers in order to monitor recurrence and therapeutic response [4].

Molecular diagnostics could be a promising area in early cancer detection and has considerably contributed in early diagnosis and treatment of cancer in last couple of decades. Molecular Techniques such as Qualitative PCR-ARMS and RFLP, real time PCR-TaqMan assays, nested PCR, FISH, capillary electrophoresis, sequencing/pyrosequencing, sequenom [5], targeted gene panel sequencing and microarrays [6] are some of

the new platforms available for cancer diagnosis.

Molecular biomarkers are the molecules indicating the presence of cancer in the body. They generally include genes and genetic variations, differences in messenger RNA (mRNA) and/or protein expression, posttranslational modifications of proteins, and metabolite levels in the body [7,8]. Molecular biomarkers have become routine diagnostic tool in several cancers at present. Apart from this, various small molecule inhibitors against these markers can be used for targeted therapies in cancer treatment. Since tumor progression is a very slow process and may take years to show its symptoms, a number of biomarkers - genomic, proteomic and metabolomic are the potential candidates in early detection, prognosis and monitoring of cancer [9-11] (Figure 1).

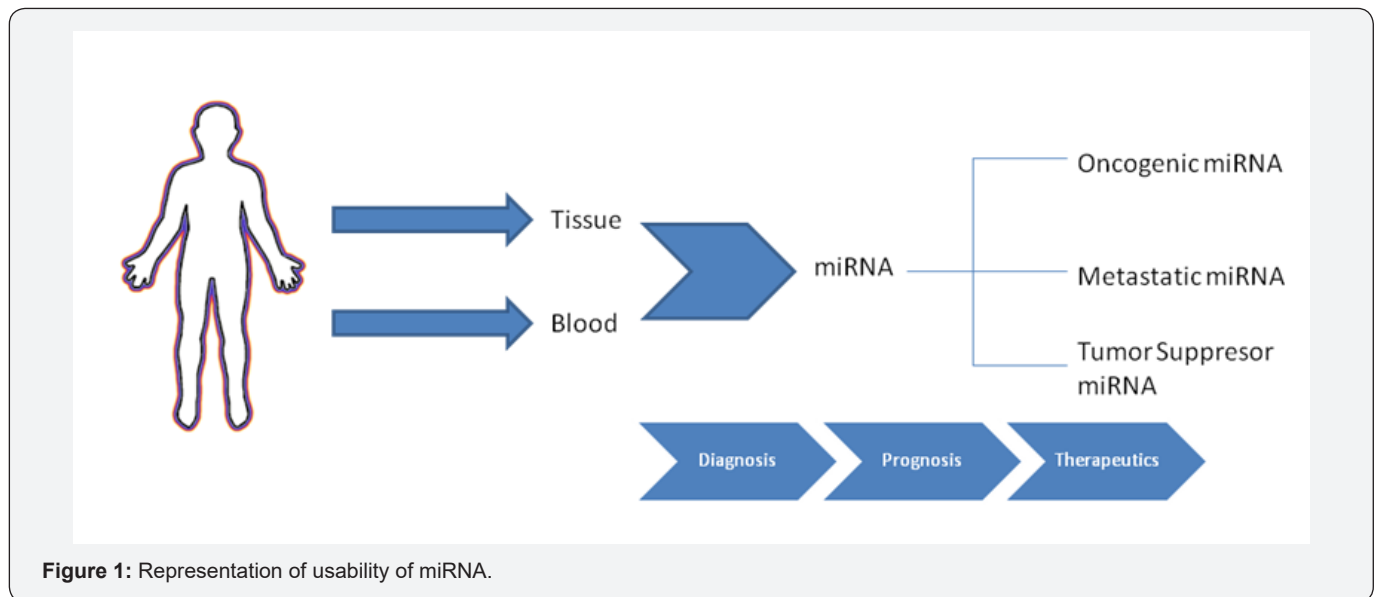


Figure 1: Representation of usability of miRNA.

miRNA and Cancer

MicroRNAs are short (20-22 nucleotides) sequences which are highly conserved during evolution and non-coding RNA molecules. They regulate gene expression by binding to the 3' -untranslated regions of a potential candidate mRNAs, and block the translation or degradation of target mRNAs which

regulates various pathophysiological courses [12]. In number of pathophysiological conditions, aberrant expression of miRNA has been reported, though it is also expressed in normal conditions [13-15]. This expression property of microRNAs makes it promising biomarkers in non-invasive liquid biopsies for cancer screening [16].

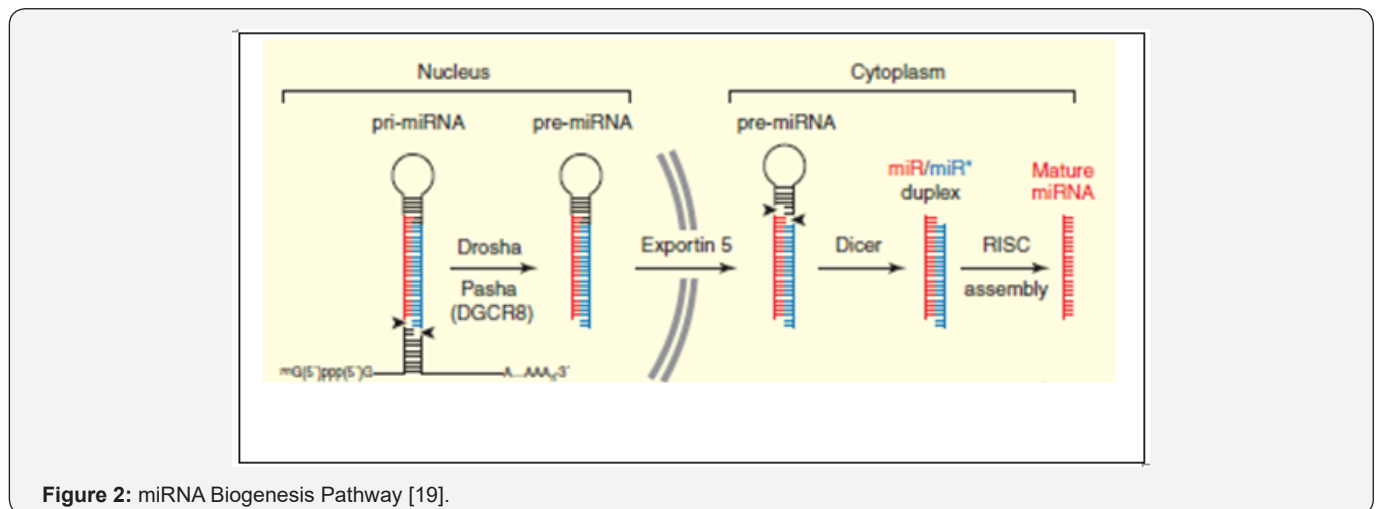


Figure 2: miRNA Biogenesis Pathway [19].

miRNA Biogenesis

Biogenesis of miRNA has been described in detail by Bartel [13]. Briefly, biogenesis of miRNA is initiated in nucleus and is a multistep complex process. Genes of miRNA are transcribed by RNA polymerase II into pri-miRNAs (primary miRNAs) which are cleaved into smaller structure- miRNA precursor (pre-miRNA) by RNase III (Drosha). This pre-miRNA is later exported to cytoplasm from nucleus by Exportin-5. Here, Dicer (a type of RNase III enzyme) and transactivator RNA-binding protein (TRBP) cleaves pre-miRNA to a 19 to 23 Nt RNA duplex. This RNA duplex have both mature miRNA strand and its complementary strand of which mature strand is incorporated into miRISC (microRNA-induced silencing complex) and the complementary strand is degraded. RISC guided by mature strand of miRNA causes repression of translation or degradation of target mRNAs [17,18] (Figure 2).

miRNA and Cancer diagnosis

Many research reports that hypothesize on onset and progression of different types of cancers are associated with changes in the expression levels of miRNA [17,19,20-31]. Downstream signal of gene or gene products can either up regulate or down regulate miRNA in cancers. Up regulated miRNA in cancers have an oncogenic potential whereas down regulated miRNA have a tumor suppressor effect. miR-155, miR-17-92 and miR-21 are the classical examples of miRNAs with an oncogenic potential. The let-7 family and miR-200 family are down-regulated in many types of cancers [32-36]. miRNAs released in the bloodstream has also been used in the early diagnosis of thyroid cancers [28]. In a recent study, miRNA-146b has been shown to act as oncogenic regulator which promotes cellular transformation and serve as an biomarker in Human Papillary Thyroid Cancer [37]. miRNA of let family and miR have been studied extensively as potential cancer therapeutic agents [38]. In an review paper from Madhavan et al. [39] they have summarized most recent findings in usability of circulating miRNAs related to cancer and also presented them in an tabular form, with individually focusing on prostate cancer, breast cancer, lung cancer, colorectal cancer and gastric cancer. They have also briefed about lymphomas and leukemia. It is an comprehensive summary about presence of different types of circulating miRNAs in plasma/serum which can be explored for diagnosis and/or prognosis of both primary and metastatic cancers [39].

Conclusion

Cancer diagnosis have undergone a paradigm shift in the last two decades and molecular alterations at DNA, mRNA, miRNA and proteome level is studies along with the traditional morphological parameters in cancer diagnosis. Pathogenesis of numerous cancers being exploited by the dysregulation of miRNAs makes it a promising candidate for clinical usage as therapeutic targets. The precise mechanism of miRNA function and its action in a diseased pathway needs to be elucidated at

molecular level in more detail using miRNA profiling data.

Conflict of Interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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