Impact of microRNA in Different Diseases and Cancer

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Abstract

MicroRNAs (miRNA) are a group of short non- coding RNA molecules (≈ 22 bps) that are involved in post- transcriptional regulation of gene expression. Accumulated evidence of the vital role for miRNA in cell development and differentiation suggests a significant connection between miRNAs and human disease. In this mini review, some of the recent advances in studying the role of miRNA in disease development have been included.

Keywords: MicroRNA, Hematological malignancies, Cancer, Neurodegenerative diseases, Immune related diseases.

Abbreviations: MicroRNAs (miRNA), RNA-induced silencing complex (RISC), Non Small Cell carcinoma (NSCC), The Cancer Genome Atlas (TCGA), Migration and invasion enhancer 1 gene (MIENI).

Introduction

The latest release of miRBase database, (release 21) contains approximately 36000 mature miRNA products, in 223 species, with approximately 1900 in humans. The rapid increase in the number of new members of miRNA family is achieved through the utilization of high throughput sequencing and advances in bioinformatics. It is estimated that miRNA are involved in regulating more than 60% of protein- coding genes, which highlights the crucial role of these tiny molecules in disease development. [5] Part of the identified miRNAs exhibit tissue and developmental specific expression pattern and plays potential roles in cellular processes including cell proliferation and differentiation, apoptosis, and neural cells development. [16, 24] A large number of published reports are based on studies on the association between miRNA and human disease, the latest release of HMDD include 572 miRNA genes and 378 diseases from 3511 paper. According to these reports, miRNA are involved in various human diseases including neurological, cardiovascular, developmental diseases, autoimmune diseases, psychiatric diseases, skin diseases, asthma, infectious diseases, and cancer. [18]Based on the findings supporting miRNA – Disease association, the value of miRNA as therapeutic entities and as biomarkers for early disease detection, mainly cancer, is currently under investigation.

miRNAs and Human Diseases

miRNAs are small non- coding RNA molecules that are mainly negative regulators of gene expression in a sequence – dependent manner. After transcription, Pre-miRNAs are exported to the cytoplasm by exportin 5, to be cleaved near the terminal loop by the RNAseIII Dicer, releasing the ~22 it miRNA duplexes. After that, mature single- stranded miRNA incorporates into the RNA- induced silencing complex (RISC).This complex exerts its function through forming heteroduplex between the seed sequence (bases 2 to 8) of the 5′ end of the mature miRNA and the 3′ UTR of its target sequence. The RISC induced repression on gene expression depends on the degree of sequence complementarity between miRNA and its target mRNA. Whilst translation repression or target mRNA instability occurs in the case of partial complementarity; target mRNA destruction occurs in the case of perfect complementarity. [1]

Normal hematopoiesis (as demonstrated by several animal models) is coordinated by several miRNAs including: miR-17, miR-24, miR-146, miR-155, miR-128 and miR-181 which were found to prevent the differentiation of early stage progenitor cells, while miR-16, miR-103 and miR-107 act in later stages, and miR-221, miR-222 and miR-223 control the terminal stages of hematopoietic development. [2]

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Many of the miRNA that play an essential role in normal hematopoiesis are also key pathogenic factors in hematological malignancies. [2]

Hematological malignancies

Chronic Lymphocytic Leukemia: The first connection between miRNA and hematological malignancies came from the correlation of miR15a, and miR-16-1 deletions on chromosome 13 and CLL. Further studies suggested that these miRNA act partially through BCL2 antiapoptotic gene. Other miRNAs involved in CLL include miR-29 and miR-181b. [13]

Acute Lymphoid Leukemia (ALL): miR-128 and miR-16 were linked with ALL cases. [2] **Acute Myeloid Leukemia (AML):** A study on newly diagnosed AML samples identified 26 down-regulated miRNAs in AML samples compared with CD34 normal cells. [15] The role of aberrant miRNA in the development of AML was also demonstrated in various in vivo mouse models. Studies showed that the targeted deletion of murine HSC- encoded miR-145 and miR-146a caused mild neutropenia, megakaryocytic dysplasia, and eventual fatal myeloid malignancy. Over- expression of miR-125b resulted in the development of leukemia. Over-expression of miR-155 or miR-29a in mouse HSC results in myeloproliferative disorders that can progress to AML. [2]**Chronic Myeloid Leukemia (CML):** miR-150 and miR-146a in addition to miR-10a were found to be significantly decreased in CML patients. Their levels were significantly improved after treatment with imatinib. [9] De Leeuw et al. were able to define leukemias of ambiguous lineage to either AML or ALL by using the expression profiles of certain miRNAs including miR-23a, miR- 27a, miR-221, miR-223, and miR-199b. MiR-155 is considered the most common miRNA involved in hematological malignancies, including malignant Lymphoma, Acute Myeloid Leukemia, Multiple Myeloma, and Chronic Lymphocytic Leukemia. [6] **Cancer:** Expression profiling studies demonstrated the role of aberrant miRNAs in the development of cancer, either through acting as tumor suppressors or as oncogenes. As such, miR-15, miR-16 and let-7 act as tumor suppressors while miR-21 and miR-155 act as oncogenes. Nevertheless, some of the miRNAs may act as a tumor suppressor in some instances, and as an oncogene in others as in the case of mir-29 and Mir-26a. [11] The importance of miRNA regulatory system in normal physiology and tumorigenesis has been investigated through studying mouse strains overexpressing or lacking clusters or individual miRNAs. Many factors complicate studying the role of miRNA in cancer development, including the redundancy in their action; miRNAs act on multiple targets instead of a single target. Another complicating factor is the redundancy at the level of mRNA targets, in which one target might be regulated by miRNA with different seed sequences. Also, miRNAs that exist in families with similar seed sequences, or from different families are co- expressed in large clusters. [11] Lu J et al. used flow cytometric miRNA expression profiling to demonstrate that different tumors have different miRNA expression profile. Tumor profiling has the potential to classify tumors and predict patient's outcome, which might reflect on early diagnosis and better treatment. [11] **Lung Cancer:** Decreased level of tumor suppressive let-7 mirRNA family is associated with poor prognosis in lung cancer patients. Decreased level of tumor suppressor miRNA-16 in patients samples lead to the inhibition of tumor cell line growth. On the other hand, the increased expression of oncogenic miRNA-221/miRNA-222 leads to more aggressive NSCLC. [22]

Breast cancer

Down- regulated miRNAs include miR-31, 125b, 145, 200c and 342; up- regulated miRNAs include miR-10b, 21, 27a, 221 and 222. Li Guo et al. studied the correlation between expression of miRNA profile signature between tissue and serum samples. They found that the number of miRNAs expressed was similar with no significant difference detected between samples. Nevertheless, they found that serum samples contained a higher proportion of the abundant miRNA species. [10]

Ovarian cancer

Dicer expression in epithelial and serous ovarian cancer is associated with advanced tumor stage and low survival. Among the prognostic factors for ovarian cancer are the miR-200 family that predicted poor survival and low level of let-7i that was associated with shorter progression- free survival of end- stage patients. [5] In a later study, TCGA provided a comprehensive molecular classification of high- grade serous ovarian carcinomas in which four molecular subtypes of ovarian cancer were identified. A further classification was conducted according to miRNA expression, in which ovarian cancer was divided into three subtypes with overlap between these two classifications. miRNA subtype 1 was associated to worse survival outcome in comparison with other subtypes.

Colorectal cancer

Among the 160 miRNAs deregulated in CRC cases according to several studies compiled and analyzed by Xiaoya Luo et al, the most often reported miRNAs were miR-31 (upregulated) and miR-145 (downregulated). [19]In a study on a number of miRNAs deregulated in CRC, the expression levels of miR-18a, -20a, -21, -29a, -92a, -106b, -133a, -143, and -145 were found to be differentially expressed in CRC patients and controls. [18]

Prostate cancer

miRNAs' dysregulation in prostate cancer includes down- regulation of let-7, miR-145, miR-141, miR-125, miR-1, miR-133, miR- 106b, and miR-16, in addition to reduced levels of miR-15/16 cluster during the progression of cancer of the prostate. [5]Rajendiran et al. identified miRNA (miR-940) as a regulator of (MIEN1) gene, which enhances prostate cancer cell migration and invasion.[16] Rajendiran and his team demonstrated that miR-940 inhibited migratory and invasive potential of human prostate cells through its regulation of MIENI. [16]

Neurodegenerative diseases

Including Parkinson's disease (PK) and Alzheimer disease (AD), miRNAs display distinct expression pattern in AD; miR-9, miR-125b, and miR-146a are upregulated in the temporal lobe neocortex of AD patients, unlike other NDD. On the other hand, miR-29b and miR-107 were found to be down-regulated in AD patients. A study conducted systematic miRNA profiling in peripheral blood mononuclear cells from PD patients which showed the deregulation of miR-30b, miR-30c, and miR-26a expression to be associated with the susceptibility of the disease. Another study demonstrated that the deregulation of miR-133b expression may contribute to the pathogenesis of PD. [21]Leidinger et al. selected a panel of 12 miRNAs out of 140 miRNAs that changed expression levels in AD patients. Using this panel, the study group was able to distinguish between AD patients and healthy controls in addition to patients suffering from other neurological disorders. [14]

Immune related diseases

A study suggested a role for miR-326 in the pathogenesis of Multiple Sclerosis (MS) through its action on T helper 17 cells (Th17). Over expression of miR-326 promotes Th-17 differentiation through targeting Ets-1, a negative regulator of Th-17 differentiation. miRNA expression profiles in serum samples from different MS patients and healthy controls were analyzed, and it was revealed that miR-21 and miR- 106b were upregulated in all types of MS. Reduced expression of miR-146a correlated with increased risk for Systemic Lupus Erythematosus. miRNA expression profiling has also identified type 2 diabetes- related miRNAs including miR- 144, miR-146a, miR-150 and miR-182. miR-103 and miR-107 were also shown to down- regulate insulin sensitivity in type 2 diabetes. [25] The role of miRNA as a diagnostic tools and an effective therapeutics is of great potential mainly in cancer. One drawback in using miRNA based treatments is its low stability in vivo due to its degradation by RNases. Chemically modified oligonucleotides like LNA, PNA, FANA, and other chemical modifications were under investigation as an alternative for less stable miRNA. PNA with its enhanced stability and greater affinity to RNA has shown promising results targeting miRNA-221 in breast cancer. Short LNAs with a phosphorothioate backbone to enhance stability have also been developed. 7Efforts to use miRNAs as biomarkers for the early detection and prognosis of malignancies are undergoing to replace the less specific blood- based tumor markers, such as CEA, PSA or CA. miRNA expression profiles have been investigated in tissue samples and circulating body fluids for several types of malignancies. Nevertheless, due to redundancy in their action and mRNA targets, more work needs to be done to improve specificity before its use in clinical diagnosis. [4]

Conclusion

Recent studies provide clearer evidence on the involvement miRNA in the pathogenesis of many diseases. Using new technologies in sequencing and bioinformatics enabled scientists to establish panels of miRNA to identify certain diseases and types of cancer. These panels have the potential to be used as early biomarkers for disease detection. Nevertheless, factors like redundancy in miRNAs targets and function still complicates using miRNA as early biomarkers for disease detection.

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