Mini Review
Volume 16:7, 2022

Journal of Molecular and Genetic Medicine

ISSN: 1747-0862 Open Access

Review on Role of Mitochondrial RNA in Oncogenes

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Abstract

Endogenous tiny non-coding RNAs called microRNAs (miRNAs) control the expression of genes. Several mechanisms, including miRNA gene amplification or deletion, improper miRNA transcriptional control, dysregulated epigenetic alterations, and flaws in the miRNA biogenesis machinery, have been shown to contribute to the dysregulation of miRNA expression in human cancer. Under specific circumstances, miRNAs can act as tumour suppressors or oncogenes. The hallmarks of cancer, such as maintaining proliferative signalling, dodging growth inhibitors, resisting cell death, triggering invasion and metastasis, and generating angiogenesis, have been linked to the dysregulated miRNAs. MiRNAs have been implicated in an increasing number of studies as possible biomarkers for human cancer diagnosis, prognosis, and treatment targets or tools; nevertheless, further research and validation are required. In this review, we emphasise how miRNAs function as tumour suppressors or oncogenes to control the emergence of human cancers.

Keywords: Cancer cells • MiRNA • Cell Lysis • Oncogene

Introduction

Small non-coding RNAs known as microRNAs (miRNAs) control a variety of biological processes, including the development of cancer. MiRNAs have been discovered to be severely dysregulated in cancer cells. Ambros and colleagues found the first miRNA, lin-4, in Caenorhabditis elegans (C. elegans). It was discovered to be a short non-protein-coding RNA that controls the expression of the protein lin-14 to influence development. The subsequent discovery of miRNAs in 2001 by three separate groups suggested that miRNA-mediated post-transcriptional regulation serves as a universal regulatory mechanism across species. Some of the miRNAs were also shown to be highly conserved.

Description

The overall number of annotated human miRNA precursor genes is 1872, and these genes translate into 2578 mature miRNA sequences. However, the roles of many miRNAs are yet unknown. Dr. Croce's team discovered the first evidence of miRNA involvement in human cancer through research aimed at locating tumour suppressors in the 13q14 region of chromosomes in B-cell chronic lymphocytic leukaemia cells. Two miRNA genes, miR-15a and miR-16-1, were discovered to be present in this area, which is typically lost in B-cell chronic lymphocytic leukaemia. In the vast majority of instances of clinical chronic lymphocytic leukaemia, both genes are deleted or downregulated. Further research showed that miR-15 and miR-16-1 decrease Bcl-2, an anti-apoptotic protein overexpressed in malignant nondividing B cells and many solid malignancies, acting as tumour suppressors to promote apoptosis.

Most crucially, the ablation of the miR-15 and miR-16-1 cluster in mice reproduced the symptoms associated with chronic lymphocytic leukaemia seen in humans, conclusively demonstrating the crucial function of these two miRNAs in tumour suppression. In the years that followed, miRNA profiling and deep sequencing produced concrete proof that miRNA expression is dysregulated in cancer and that its fingerprints may be utilised to categorise, diagnose, and predict tumour outcomes. We briefly discussed miRNA biosynthesis and regulation in this review. In addition, we clarified the mechanisms through which dysregulation of miRNA expression occurs in human cancer. We examined the role of miRNAs as oncogenes or tumour suppressors in characteristics that characterise cancer. Finally, the promise of miRNAs as biomarkers for cancer detection, prognosis, and treatment as well as the difficulties in miRNA studies and uses are understood. The first step in miRNA synthesis is the transcription of a gene into a lengthy primary transcript (pri-miRNA), which has a 3′ polyadenylated structure and a 5′ cap. Although certain pre-miRNAs are produced by RNA polymerase III, RNA polymerase II mainly mediates transcription. RNA polymerase II typically transcribes the miRNA genes to create the huge main transcripts known as pri-miRNAs, which are then cut into an 85-nucleotide stem-loop structure known as pre-miRNA by a microprocessor complex made up of the RNA-binding protein DGCR8 and type III RNase Drosha.

The pre-miRNAs are transformed into a 20-22-nucleotide miRNA/miRNA* duplex by another RNase III enzyme, Dicer, after being transported from the nucleus to the cytoplasm by the Ran/GTP/Exportin 5 complex. The mature miRNA is integrated into the RISC protein complex once the duplex has been unravelled. Depending on the complementarity between the miRNA and the targeted mRNA transcript, a miRNA-loaded RISC mediates gene silencing via mRNA cleavage and destruction or translational repression. Furthermore, miRNAs might act as ligands for Toll-like receptors (TLR), activating downstream signalling cascades. Recent research has revealed that Methyltransferase-like 3 (METTL3) methylates pri-miRNAs to designate them for detection and processing by DGCR8 to produce mature miRNA. The seed region, a 6- to 8-nucleotide-long segment at the 5′ end of the miRNA that creates Watson-Crick pairs with the corresponding target, frequently mediates interactions between miRNA and target. No matter how intricate the connection, once miRNAs have bound to their target mRNAs, they either trigger target mRNA destruction in the event of incomplete complementarity or translational repression in the case of perfect complementarity. Recent research has revealed that miRNA also serves as a ligand to activate signalling pathways in addition to controlling gene expression via base pairing with cognate mRNA. MiRNA production is tightly regulated at a number of stages, including transcription, Drosha and Dicer processing, transportation, RISC binding, and miRNA decay. For instance, it has been suggested that Drosha-mediated miRNA maturation involves SMAD protein and DEAD-box RNA helicases. The loss of the miR-15a/16-1 cluster gene at chromosome 13q14, which is frequently seen in people with B-cell chronic lymphocytic leukaemia, is the earliest identification of a miRNA gene position alteration. The miR-143 and miR-145-containing 5q33 region is frequently deleted in lung cancer, which

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Date of submission: 04 July, 2022, Manuscript No: jmgm-22-72230; **Editor Assigned:** 05 July, 2022, Pre-QC No. P-72230; **Reviewed:** 12 July, 2022, QC No. Q-72230; **Revised:** 19 July, 2022 Manuscript No: R-72230; **Published:** 26 July, 2022, DOI: 10.37421/1747-0862.2022.16.562

lowers the expression of both miRNAs. In contrast, the miR-17-92 cluster gene was amplified in B-cell lymphomas and lung cancers24 and translocated in T-cell acute lymphoblastic leukaemia, which resulted in the overexpression of these miRNAs in these tumours.

High-resolution array-based comparative genomic hybridization on 227 specimens from human ovarian cancer, breast cancer, and melanoma confirmed the high frequency of genomic changes in miRNA loci. Additional genome-wide analyses showed that many miRNA genes are situated in genomic areas linked to cancer. A minimal zone of loss of heterozygosity, which may contain tumour suppressor genes, a minimal region of amplification, which may contain oncogenes, fragile sites, or common breakpoint regions are some examples of these regions. Overall, these results imply that particular genomic areas enclosing miRNA genes may be amplified or deleted, leading to aberrant miRNA expression in malignant cells. MicroRNAs (miRNAs) are short, non-coding RNAs with an average length of 19 to 25 nucleotides that have the ability to regulate a wide range of target genes. As a result, they play a role in the regulation of numerous biological and pathological processes, including the initiation and progression of cancer. One of the biggest challenges of treating this malignancy is drug resistance in chemotherapy. According to statistical data, medication resistance accounts for more than 90% of cancer patients' deaths. Cancer chemotherapy drug resistance can result from a variety of processes, including enhanced DNA damage repair, altered cell cycle checkpoints, altered drug targets, decreased anticancer drug uptake, and others.

Numerous studies in recent years have demonstrated that miRNAs play a role in the drug resistance of tumour cells by targeting genes associated with drug resistance or by affecting genes involved in cell proliferation, the cell cycle, and apoptosis. Multiple genes are frequently targeted by a single miRNA, and its regulatory impact is tissue-specific. A severe threat to human life and health, cancer has risen to the top of the list of fatal diseases in recent years. Statistics show that there were 14.1 million new instances of cancer worldwide in 2012, and 8.2 million people died from cancer overall. The incidence of cancer is rising as people are living longer and the global ecosystem is deteriorating. By 2030, it's anticipated that there will be 23.6 million new cases. Currently, the most popular cancer treatments include chemotherapy, radiation, and surgery. The initial line of treatment for diseases such lymphoma, leukaemia, and small cell lung cancer is chemotherapy. Chemotherapy can be used as a pre-local tumour treatment before surgery or radiotherapy or as an adjunctive treatment to remove postoperative residual nodules to prevent relapse for other solid tumours. Additionally, individuals who are unable to have radical surgery receive palliative care through chemotherapy. Chemotherapy medications have advanced significantly in recent years, however the establishment of tumour drug resistance frequently results in treatment failure. Drug resistance is a significant barrier to effective cancer treatment for patients with advanced cancer [1-5].

Conclusion

Statistics show that chemotherapeutic drug resistance is a factor in more than 90% of tumour patient deaths. Overall, there are two types of drug resistance: endogenous and acquired, and it is important to understand the underlying mechanisms. Drug resistance is currently thought to be correlated with an increase in drug efflux, target switching, cell cycle checkpoint alterations, apoptosis suppression, and DNA damage repair. Small non-coding RNAs called miRNAs, which regulate a variety of target genes, are about 19 to 25 nt in length. Numerous biological processes, including the cell cycle, differentiation, proliferation, apoptosis, stress tolerance, energy consumption, and immunological response, are regulated by miRNAs.

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How to cite this article: Angel, Mark. "Review on Role of Mitochondrial RNA in Oncogenes." J Mol Genet Med 16 (2022): 562