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Review Article

Unravelling The Connection: The Role of Micro- RNAs in Bridging T-RNA And M-RNA Interactions

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ABSTRACT

MicroRNAs, commonly known as miRNAs, are short-stranded non-coding RNA sequences that are of extreme importance in the regulation of gene expression since they are involved in the stability and the translational efficiency of the mRNAs. MiRNAs were almost exclusively studied in relation to their target mRNA molecules, however recently some studies imply that miRNAs may have an ability to control the position of tRNA relative to the mRNA providing another layer of regulation to various functioning processes in a cell such as protein production synthesis, stress, and diseases. In this paper, we consequently shed light on the contribution of miRNAs on tRNA and mRNA interface translation as in ensuring the accuracy and efficiency of translation. For a long time, this duo of tRNA – an adapter RNA, that carries amino acids, and mRNA – the RNA that is encoded with the code, was considered as two distinct components. But it is coming into light that miRNA's help these two types of RNA to communicate. This is achieved through the ability of miRNAs to recognize perfectly matched regions in both mRNA and tRNA allowing them to control the supply and activity of the equipment needed for translation and consequently the level of proteins produced within the cellular environment. In this article, we focus on the molecular mechanisms of interaction mediated by miRNAs, including regulation of tRNA modifications and ribosome dynamics, and where possible, their biological and pathological significance, including stress response, metabolic processes, diseases like cancer and neurodegeneration. tRNA, mRNA and miRNA do not exist in isolation; miRNAs are integral to RNA interactions within a cell, reiterating the functional significance of

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miRNAs. By resolving these intricate webs of interactions, one is able to appreciate the cellular processes that have to do with eukaryotic cell regulation and disease processes that are associated with erratic behaviour of RNA.

INTRODUCTION

MicroRNA (miRNA) can be defined as a small non-coding RNA molecule approximately 20– 22 nucleotides in length that regulates gene expression in cells. [1] In contrast to protein coding, miRNAs regulate protein synthesis by binding to messenger RNAs (mRNAs) in part or full base sequence inhibition leading to either translation repression or mRNA cleaving that alters the concentration of particular proteins in the cell. They are present in plants and animals as well as in certain types of viruses. [2] MiRNAs in turn regulate the levels of different proteins, and thus they also regulate a variety of cellular activities such as cell growth and differentiation, programmed cell death, and metabolism. Since they were first discovered, miRNAs have become known as important modulators of gene expression, affecting multiple biological processes and many diseases, most notably cancers, heart diseases and neurological disorders biogenesis and function of miRNAs. [3] The biosynthesis of miRNAs comprises several processes:

- **Transcription:** The production of miRNA begins when an RNA polymerase II synthesizes primary miRNA (primiRNA) transcripts.
- **Processing:** In the nucleus of the cell, pri-miRNAs are modified by the Drosha nuclease into pre-miRNAs. [4]
- **Export and Maturation:** The intermediates are transported into the cytoplasm where they undergo further cleaving by Dicer to produce the active form of miRNAs - mature miRNAs.
- **Function:** Inhibition of specific translation is achieved when mature miRNA is incorporated into a complex called the RNA-induced silencing complex (RISC), which directs each to specific mRNA bearing complementary sequences for either translation suppression or degradation of the mRNA. [5]

History And Discovery Of Microrna:

The history of microRNAs (miRNAs) can be traced back to the early 1990s with their first identification and characterization in a nematode, Caenorhabditis elegans. [6] The understanding of miRNAs initially was limited and it took them several years to accept this class of regulatory agents in controlling gene expression.

Bright Spots in the Timeline of miRNAs Discovery and Development: -

First Understanding Concept (1993): First working on the identification of C. elegans microRNA lin-4, then a team of Victor Ambros, Rosalind Lee, and Rhonda Feinbaum, all from the University of Massachusetts, USA, identified the first published miRNA – it was in Caenorhabditis. [7] It was established lin-4 produces a small RNA that binds to the mRNA of the lin-14 gene, consequently inhibiting its expression. Although this was the first example of gene expression regulation by a small RNA, it was thought to be an exception at first rather than a mechanism that all small RNA molecules employ to regulate genes at large.

NA Discovery (2000): Later on, the laboratories of Gary Ruvkun and Frank Slack also discovered a second microrna, known as len-7 in C. elegans, which further attenuated the scope of the understanding of micrornas. It was shown that let-7 controls the timing of development by inhibitory action on several genes. [8] Notable let-7 was also found in other related species and even in human beings that limited the idea of evolution of these mir- nanes only in certain few organisms.

Establish as a New Class of RNAs (2001): By this time (i.e. 2001) a few more miRNAs had been discovered in different species and therefore led to the establishment of a classification of small ringicular rnas specific to these types of small rnas called mi rnas. [9] The year 2001 was remarkable

for the research of Tuschl, Bartel, and Ambros and others, as they expounded on the number of miRNAs in humans and other animals and their function, proposing that such regulation was essential.

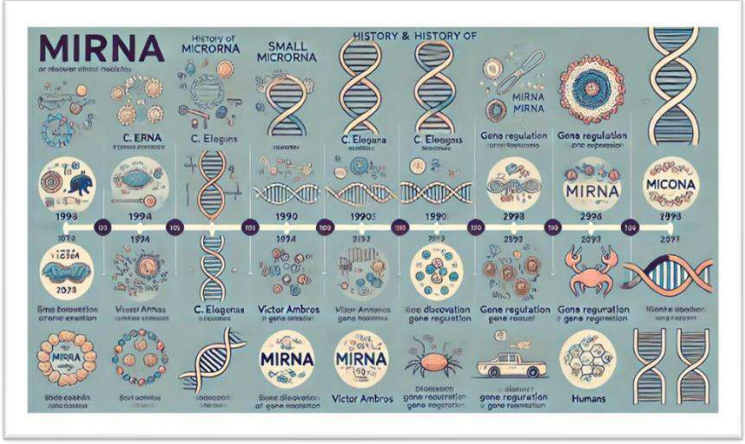

Figure:1 History And Discovery Of Microrna

Importance of Studies on Disease Target MicroRNAs: With the discovery of more and more miRNAs, research was subsequently focused on their biological importance and the understanding of the diseases in which they occur. [10] By the mid-2000s, investigations commenced showing the association of miRNA deregulation with neoplasms, ischemic heart disease, and many other pathological conditions, providing evidence that miRNAs are important for human health and illness.

Advancement of miRNA Profiling and Its Suggested Use in Therapy: Since the start of the 2010's, novel sequencing approaches became a very useful tool for a deep understanding of miRNA expression profiles allowing to know more about their functions in a number of biological processes. [11] Moreover, the studies on the treatment of diseases utilizing miRNAs turned to the development of approaches that include miRNA mimics and inhibitors and intracellular delivery devices due to the therapeutic potential of miRNAs.

Biogenesis Of MicroRNAs:

The biogenesis of microRNAs (miRNAs) is comprised of different stages that begin inside the nucleus and end in the cytoplasm and processes that mature them for further use in gene regulations. [12] There are also several enzymes and protein-processing machines that meticulously process the miRNA so that it works as intended and is able to interact with mRNA.

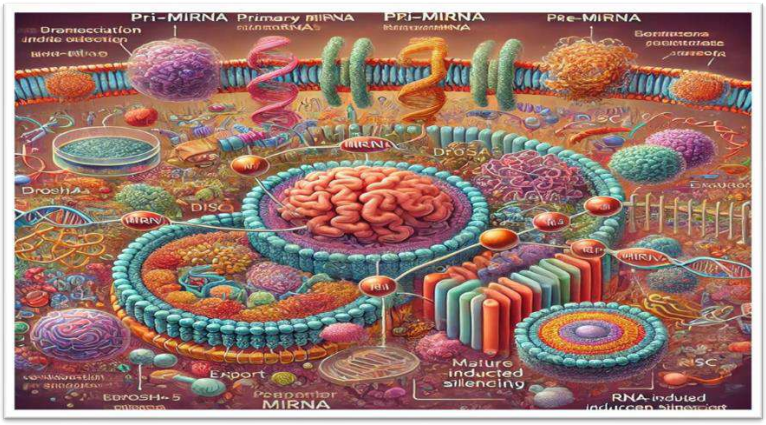

Figure:2 Biogenesis Of MicroRNAs

Stages of miRNA Processing: -

Transcription: The synthesis of miRNA genes is conducted predominantly by RNA polymerase II (occasionally there can be RNA polymerase III), where a long primary transcript is produced and called primary miRNA (pri-miRNA) in typical alignment. This also contains a 5' cap and 3' Poly A tail like that of mRNAs.

Nuclear Processing (Drosha-DGCR8 Complex): Within the cell nucleus, transforming pri- miRNA into its functionally active form is accomplished by a microprocessor complex composed of an RNase III type enzyme known as Drosha and the protein DGCR8 (DiGeorge Syndrome Critical Region 8), which acts as its auxiliary element. [13] This complex also cuts out the section of pri-mRNA to make the pre-miRNA and unlike pri-mRNA, pre-miRNA is about seventy nucleotides long with a typical hairpin appearance.

Nuclear Export and Exportin-5: The transport of pre-miRNA occurs after the action of Exportin- 5; a nuclear transport protein that possesses the ability to embrace the unique shape of pre-miRNA hairpin structure and performs the task of translocation of such structures across the nuclear envelope. [14] This process requires energy in the form of Ran-GTP.

Cytoplasmic Processing (Dicer): In the course of migrating to the cytoplasm, following the point of synthesis, Dicer, which is also an RNase III enzyme cleaves the pre-miRNA for the second time to make way for the resulting hairpin wherein it cuts through the loop of pre-miRNA. This gives rise to a double-stranded RNA that is about 20-22 nucleotides long, which has the processed strand of the mature miRNA and its counterpart 'passenger' strand. [15]

Formation of RISC (RNA-Induced Silencing Complex): The RNA-induced silencing complex is then charged with the mature strand of the miRNA. The complex then uses the strand to locate specific mRNA targets. The other strand, passenger strand, is destroyed. Inside RISC, the target mRNAs are hybridized with the mature miRNA at specific regions on the mRNA (usually in the 3' UTR). [16] This mainly results in repression of translation or degradation of the mRNA depending on the extent of base complementarity.

Mechanism Of Action Of MicroRNA:

The working principle of microRNA or miRNA relies mostly on its binding to particular messenger RNAs or mRNAs in a tissue where it modulates the expression of genes by inhibiting production of proteins or destroy the mRNA components. [17] Here is the overview:

miRNA-Mediated Targeting: After the formation of the mature miRNA, the next step is the incorporation of the miRNA into a complex known as the RNA-induced silencing complex (RISC). This binding of a miRNA in RISC is to one of the target mRNAs which usually RISC contain complementary sequence which is found predisposed in the 3-UTR region of the target mRNA. [18]

Blocking Translation or Degrading mRNA: When a miRNA interacts with an mRNA, the mRNA deviation from the perfect sequence match with the miRNA and the potential outcomes can be:

- **Incomplete Complementarity:** In such cases where the matching is said to be partial, binding of miRNA often inhibits the process of translation thus preventing the corresponding mRNA from being utilized in the synthesis of a protein.
- **Complete or High Complementarity:** Where the match is of very high sequence identity, the RISC complex is able to shear the target mRNA leading to its degradation thus lowering its intracellular levels and consequently abolishing protein synthesis.

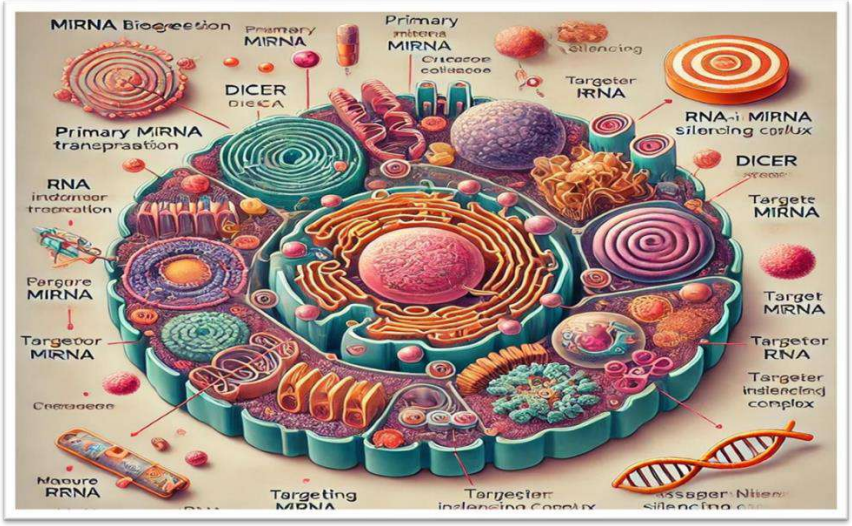

Figure:3 Mechanism Of Action Of MicroRNA

Outcome: Hence, through such processes, the levels of proteins present in the cells are regulated by miRNAs, influencing different cell activities, including growth, development and responding to external stimuli. [19]

Techniques For MicroRNA Identification And Analysis:

It is crucial to identify and experimentally study microRNAs (miRNAs), given their gene regulatory roles and pathophysiological relevance. There are several approaches that are either conventional or high-throughput for exploring miRNA and conducting quantification and functional studies. Following is some of the frequently used techniques:

1. Next Generation Sequencing (NGS): NGS profiles microRNAs by deep sequencing of small RNA fractions of a sample. It can help to discover expression of both known and novel micrornas and much more on the levels and variety of microrna sequences in the studied sample.

Applications: NGS is very frequently applied in budding studies, particularly to include in the analysis along with other factors, miRNAs types from a variety of tissues, stages of development, or diseases. [20]

2. Microarray Analysis: Microarrays are also high throughput techniques in which probes for a large number of micrornas are printed onto a chip. The RNA Sample is hybridized onto the chip and the amount of fluorescent signal produced indicates the level of miRNA expression.

Applications: Microarrays are advantageous for analysing changes in miRNA expression across several populations of specimens and so have found the greatest use in research with cancer and other diseases. [21]

3. Quantitative Real-Time PCR (qRT-PCR): qRT-PCR is a powerful technique used to measure the levels of specific miRNAs. In order to increase specificity for the target miRNA, stem-loop primers or locked nucleic acid (LNA) probes are commonly used.

Applications: qRT-PCR is often employed for the validation of miRNA expression differential in small sample sizes or patients as well as for the confirmation of data obtained through high-throughput analyses. [22]

4. Northern Blotting: Northern blotting measures size and the amount of miRNA. It is time- consuming, but it has been able to provide some information on miRNA maturation and helps to separate pri- and mature miRNAs.

Applications: Commonly employed to support the levels of miRNAs expression that have been observed using other techniques and to assess the

level of certain miRNAs expression in a sample. [23]

5. In situ hybridisation (ISH): ISH allows the use of labelled probes to find where specific miRNAs are located in tissue sections or cells, thus providing a location for corresponding miRNA expression.

Applications: This technique comes in handy in developmental biology where one can study the expression patterns of miRNAs in particular cell types or tissues. [24]

6. Luciferase Reporter Assays Overview: Luciferase assays serve the purpose of analysing the interactions of miRNA targets. A luciferase reporter gene is linked to the 3' UTR of the target mRNA. miRNA-dependent regulation of a target results in a decrease in luciferase activity.

Applications: Mostly used to confirm the miRNA-mRNA interactions that have been computationally predicted or which have been profiled. [25]

7. Bioinformatics Analysis Overview: The expression analysis data and the computational tools to predict the miRNA targets. an analysis with TargetScan, miRanda and miRBase, which identify these sites and allow insight into the potential regulatory networks.

Applications: Such tools are useful for the amount of data produced in NGS or Microarray studies and these are usually used alongside with experiments validation techniques. [26]

These techniques, applied alone and in conjunction, provide clues of the regulatory roles of miRNAs and also the influence of miRNAs on the expression of genes, normal cellular processes, and disease states.

MicroRNA And Disease:

Dysregulation of microRNAs (miRNAs) is involved in the pathogenesis and progression of numerous diseases including but not limited to malignancies, cardiovascular disorders, neurodegenerative diseases, autoimmune derangements, and metabolic syndromes. [27] Since miRNAs are molecules in charge of regulating gene expression, their abnormal levels can cause disturbances in normal functions of cells which enhance disease development.

1. Cancer: -

MicroRNAs can be classified as oncogenes (oncomiRs) or tumor suppressor genes, and their deregulation tends to be common in cancer diseases.

OncomiRs: This class of miRNAs aid in cancer progression by inhibiting the expression of tumor suppressor genes. [28] For instance:

miR-21: Highly expressed in a range of cancers including breast cancer, lung cancer, and colon cancer. It also acts on tumor suppressors such as PTEN and PDCD4, enhancing cell growth and survivalmiR-155. [29] This miRNA, which is often overexpressed in many forms of cancer, targets SOCS1, a tumor suppressor, and assists in cell proliferation and invasiveness.

Ppressor miRNAs: Endogenous oncomiR inhibitory function is often lost in cancer:

miR-34: A classic example of a tumor suppressor which targets BCL2 and MET. Invasive lobular breast cancer and lung cancer have been correlated with the overexpression of this particular miRNA due to treatment with inhibitors of CDK4/6. [30]

miR-15a/: In the case of chronic lymphocytic leukemia (CLL), these anti-apoptotic miRNAs are deleted or downregulated leading to an enhanced expression of BCL2 and other survival– promoting factors.

2. Cardiovascular Diseases: -

MicroRNAs are key players in heart formation, blood vessel's function and the mechanisms of hearts responding to damage. [31] However, weaknesses in control of the miRNAs can cause pathological conditions such as heart failure, heart attack and atherosclerosis.

miR-1: A critical miRNA in the heart that is responsible for its proper functioning. Its

downregulation is found to lead to cardiac hypertrophy, arrhythmias and even heart failure.

miR-133: This is essential in the proliferation and differentiation of the muscle cells of the heart. Its down expression is found to result in heart failure and ischemic damage of the heart. [32]

miR-155: High levels of this miRNA have been seen in atherosclerosis, as it causes the inflammation of the blood vessels and the proliferation of smooth muscle cells. [33]

miR-21: This is a miRNA that is present in excess with the cardiac fibroblasts resulting in fibrosis as well as cardiac restructuring in heart failure. [34]

3. Neurological Disorders: -

MicroRNAs are responsible for the control of some brain functions, the differentiation of neurons, and plasticity of synapses. [35] Change of the normal level of any particular miRNA expression occurs in numerous diseases of the nervous system.

Alzheimer's disease (AD): MiR-9 and MiR-124 are both microRNAs found to be downregulated in Alzheimer's disease resulting in an upregulation of inflammatory and degenerative genes. [36]

- **MiR-34:** Is overexpressed in the Alzheimer's condition and it relates to apoptotic processes of neurons and aggregation of tau proteins.

Parkinson's Disease: MiR-133b Found to be downregulated in Parkinson's disease which contributes to the loss of dopaminergic neurons.

- **MiR-146a:** Found to be overexpressed in neurodegeneration, including in Parkinson's disease, promoting inflammation. [37]

Autism Spectrum Disorders: There are many dysregulated micrornas in the context of autism, including mir-132, mir-181, and mir-137. [38] Changes in the levels of activity of these micrornas can lead to abnormal development of neurons, building and remodelling of synapses, and signalling between neurons.

MicroRNA Role In Oncogenesis and Tumor Suppression:

MicroRNAs (miRNAs) are significant in gene expression regulation and take part in many cellular activities including proliferation, apoptosis, differentiation, and stress response. Their relationship with oncogenesis (cancer development) as well as with 'innate' tumor suppression has been actively researched. [39] On the one hand, miRNAs can act as oncomiRs (oncogenic miRNAs) and on the other, as tumor suppressor miRNAs, and it is their dysregulation that has been linked to the initiation, advancement, and spread of numerous cancers.

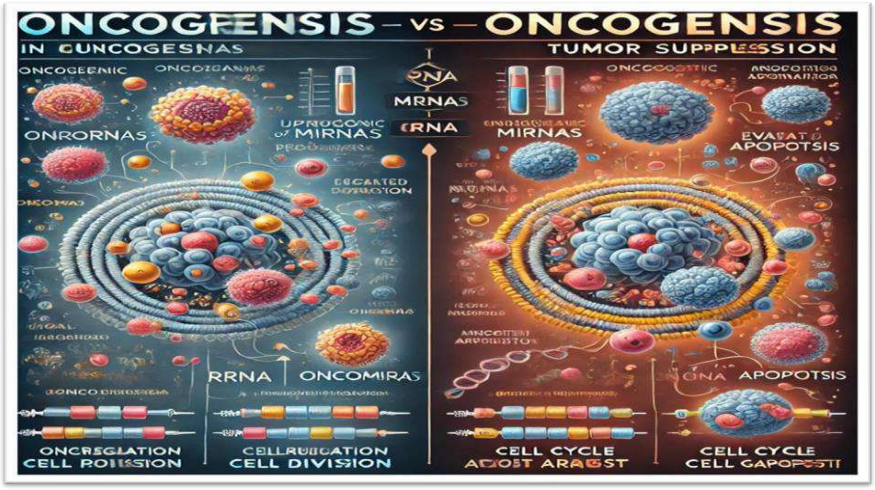

Figure:4 Microrna Role In Oncogenesis And Tumor Suppression

1. miRNAs as OncomiRs (Oncogenic miRNAs):

OncomiRs are known as the miRNAs that help cancer by enhancing the expression of the prosurvival factors or by downregulating certain cancer protective genes.

- **miR-21:** Probably one of the most researched oncomiRs, miR-21 is frequently found in elevated levels in several cancers such as breast, lung, and colon as well as liver cancer.

Oncogenesis is promoted by miR-21 through degradation of tumor suppressors like PTEN, PDCD4, and TIMP3. This involves apoptosis, modulation of cell cycle and inhibition of metastases, augmented by the action of miR-21, enhances not only cell survival but cell growth and invasion as well.

- **miR-155:** In the case of breast cancer, gastric cancer, and lymphoma, there have also been reported instances of an elevation in the levels of miR-155. [40] Target genes of miR-155 include SOCS1, PTEN, and IRF1, which are critical for regulation of immune response, apoptosis, and tumor suppression respectively, thus making it oncomiR. Its upregulation leads to the promotion of inflammation along with immune tolerance, which further supports tumor formation.
- **miR-10b:** This miRNA has been implicated in breast cancer as well as other solid tumors in the promotion of metastatic spread. It inhibits HOXD10 – a metastasis suppressor gene- thereby promoting the migratory and invasive capabilities of cells, which are essential factors contributing to the metastatic spread of tumors.

2. Inhibiting Cancers with MiRNAs: Tumor Suppressors:

Oncogene-Silencing miRNA's (oncomirs) function as tumor suppressors; they prevent cancer from developing and facilitate cell cycle arrest, apoptosis, and differentiation. The overall anti-cancer activity of these suppressor miRNAs is reduced or lost over the course of development of cancer.

- **miR-34:** As one of the most studied tumor-suppressing miRNAs, miR-34 is responsive to the activation of the transcriptional regulator p53 upon DNA damage. Outside of this fairly narrow function, it also targets a number of genes related to cell cycle and apoptosis regulation such as BCL2, CDK6, NOTCH1 and SIRT1. [41] Decreased expression of tumor suppressor microRNA-34 is linked to numerous types of cancers, including liver, colon and lung tumors, and its downregulation facilitates aberrant cell proliferation and apoptosis resistance.
- **miR-15a and miR-16-1:** Similar deletions or downregulation of these two miRNAs have been observed in a significant proportion of patients suffering from chronic lymphocytic leukemia (CLL). [42] This allows the anti-apoptotic protein BCL2 to be expressed at high levels. Subsequent loss of such tumor-protective miRNAs causes disruption of apoptosis allowing malignant B cells to persist hence CLL disease progression.
- **let-7 family:** The let-7 miRNAs are known to function as tumor suppressor by targeting several oncogenes such as RAS, MYC, HMGA2. Let -7 is known to regulate cell proliferation, differentiation and apoptosis and its expression is downregulated in many cancers, for instance lung cancer and glioblastoma.

3. The Role of Micro RNA in the Development and Spread of Cancer:

MicroRNAs is a word that is broadly understood and recognized, even outside the oncological context. In addition, the roles of these small noncoding RNAs are actually way beyond contribution to cancer initiation and rather more concerned with the activity and spread of the tumor as a whole.

[43] In this way, ability of cancer cells to disseminate and establish metastases is regulated by means of miRNAs dependent on the level of

expression of genes connected with epithelial-mesenchymal transition (EMT), cell migration and invasion.

- **miR-200 family:** Siblings miR-200b, miR-200c and miR-141 are members of the class of miRNAs that play a role in controlling the processes of epithelial-mesenchymal transition and cancer spread. The reduced activity of the let-7a family of miRNAs facilitates the processes of epithelial-mesenchymal transition (EMT) which includes the loss of epithelial characteristics, like E-cadherin, and the gain of more motile mesenchymal features, like N- cadherin, resulting in enhanced invasion potential. [44] This is important for the spread of disease in breast and ovarian cancer and other tumors.
- **miR-31:** Advances in various cancers such as colon cancer and breast cancer have identified upregulation of mir-31 as a promoter of malignancy. miR-31 allows cell migration and invasion by silencing of genes integral to cell adhesion such as TLN1 or members of the small GTPase family like RhoA which are vital for actin cytoskeleton organization.

4. Medical applications of miRNAs:

Because of their importance in initiation and progression of cancer, miRNAs have been considered as possible drugs and biomarker development in fighting cancer. [45]

- **miRNA replacement therapy:** Administering tumor suppressive miRNAs into malignant cells e.g. miR-34, let-7, miR-15a/16-1 could restore normal expression of genes inhibiting the processes that promote tumorigenesis. On the other hand, employing antagomirs or other inhibitors to suppress oncomiRs for instance miR-21, miR-155 has also been helpful in preclinical cancer studies.
- **miRNA-based diagnostics:** Altered levels of expression of miRNA can be used as cancerous diseases + prospects assessment indicators. For example, patients with breast cancer and high levels of miR-21 have poor survival rates when compared to patients without the miRNA. [46] Lowering of levels of miR-34 was also reported to correlate with poor prognosis in liver cancer.

Computational Tools For MicroRNA Research:

Computational approaches underpin a variety of tasks by using microRNAs (miRNA) for instance, in identification of the microRNAs, and predicting their targets and functional analyses among others. These approaches utilize bioinformatics algorithms to interpret genomic, transcriptomic, and proteomic data, thereby elucidating on the biology of the microRNAs in gene regulation, as well as in pathogenesis. Here is a summary of some of the widely explored computational approaches in the context of MicroRNA studies, with appropriate citations.

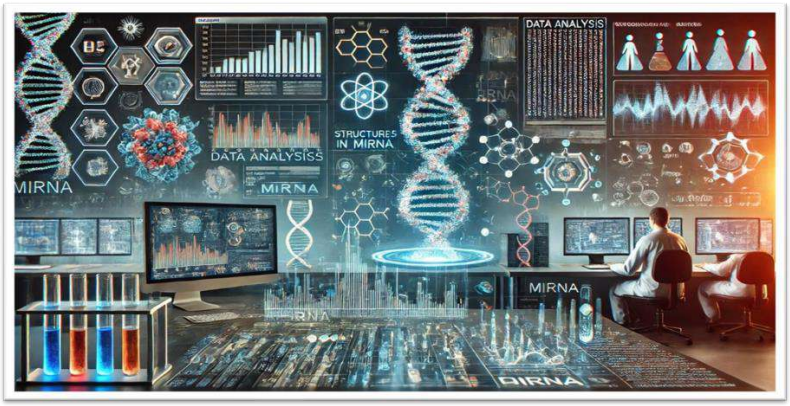

Figure:5 Computational Tools For Microrna Research

1. MicroRNA Identification Tools:

These tools are used to identify novel miRNAs from genomic or transcriptomic data.

- **miRDeep:** It is an algorithm that helps find new miRNAs in deep sequencing data. It employs a statistical model that is able to separate real microRNA precursors from 'noise' allowing very reliable predictions of the presence of microRNA in the sample without sequencing. [47]
- **miRBase:** MiRBase is an integral database and reference for known sequences and annotations of microRNAs. Its annotations detail the genes of miRNAs, their sequences and the location within the genome. It is also a widely recognized 'go to' database in studies which deal with miRNA. [48]
- **MirGeneDB:** The purpose of this database is to deliver a confidence-enhanced set of conserved and novel microRNA genes within and across species. Its focus on detail in curation and annotation makes it an important database for studies on microRNA. [49]

2. MicroRNA Target Prediction Tools:

MicroRNA target prediction tools infer the targets of mRNA by measuring parameters such as sequence complementarity, conservation, and additional features.

- **TargetScan:** TargetScan is the most preferable software application in predicting the targets of miRNAs. It uses the presence of conserved 7-8 nucleotide seed matches in the 3' untranslated regions (UTRs) of mRNAs, and adds context scores for the efficacy of targeting the mRNA. [50]
- **miRanda:** This algorithm recognizes the target miRNAs through sequence matching and the free energy of binding of the two sequences. miRanda is characterized by its high specificity, so it is often employed in studies where many targets need to be identified. [51]
- **PITA (Probability of Interaction by Target Accessibility):** PITA employs an analysis of both sequence base pairing and target site accessibility to predict miRNA targets which in turn enhances the prediction of biologically relevant combinations. [52]

3. MicroRNA Functional Analysis Tools:

Tools of functional analysis enable researchers to understand the biological roles and effects of miRNAs on the underlying pathways.

- **DIANA-miRPath:** DIANA-miRPath is a tool for pathway analysis concerned with the identification of the pathways regulated by a certain set of miRNAs. It combines target predication with functional annotation, so allowing the understanding of the miRNA-driven pathways in relation to certain disorders. [53]
- **miRSystem:** This tool is an integration of several target prediction tools and pathway databases for specific miRNAs-enabled pathways identification. This tool is very efficient in investigation of the multi-miRNA involved function in a particular biological event. [54]
- **Gene Set Enrichment Analysis (GSEA):** Sets of predicted target genes for miRNAs can be analysed for their enrichment in particular pathways or functions using GSEA, thus this method can be incorporated into the research of miRNAs. GSEA is very beneficial when used together with expression of miRNAs, to assess the functional relevance of the findings. [55]

4. MicroRNA Expression Profiling and Analysis Tools:

Routine Expression understanding of miRNA analysis between various tissues, formation stages and diseased states.

- **miRDeep2:** Mirdwelling is an expanding field and the second iteration of Mirdwelling is miRDeep2 whose functions within the scope as far as interpreting the expression of miRNA and finding new ones from the data generated by novel sequencing technology is concerned improved. [56]

- **miRExpress:** miRExpress is a more into attempting to define quantitatively the levels of the expression of miRNA in the data obtained through high through sequenced puts. It is intended for the precise and high-throughput analysis of the miRNA profile across various samples and experiments. [57]
- **Partek Genomic Illustrative Suite:** The package allows a thorough analysis of the obtained data containing information on the expression levels of both miRNA and mRNA Eurasian configuration. It also enables the combination of the miRNA and mRNA expression data to we examine the gene regulatory networks of interest. [58]

5. MicroRNA -Disease Association Tools:

Tools in this category identify which I the role of miRNAs in the context of pathogenesis and their likelihood of being used as biomarkers or targets for therapy.

- **HMDD (Human MicroRNA Disease Database):** It includes data on miRNA/disease interactions, ranked and summarized by evidence type from the literature. It is possible for users to search for miRNA that are associated with a disease and the other way round as well. [59]
- **miR2Disease:** miR2Disease is a database of clinically annotated information on predicted, validated and known associations between human diseases and distinct miRNA families, including those related to obesity, cancers, cardiovascular and neurological diseases, and immune system disorders. [60]
- **Pharmaco-miR:** This database associates miRNAs with pharmacogenomics information, depicting the role of miRNAs in drug actions and metabolism across different disease states. [61]

DISCUSSION:

MicroRNAs (miRNAs) are key elements of gene regulation as they often bind to complementing regions of mRNA and either block translation and/ or lead to degradation of the mRNA product by enzymes. These processes are crucial in many cellular functions such as growth, differentiation, apoptosis and metabolism. The first microRNAs were identified in organisms like *C. elegans* (e.g. lin-4 and let-7). Afterwards, micro molecules were found in other species including humans which indicates their evolutionary importance and the purpose they serve. The production of miRNA can be viewed as an elaborate sequence of events that consists of transcription, nuclear processing, export and cytoplasmic maturation before 'full' miRNAs, which are incorporated into RISC, target their mRNA. The revolution in molecular diagnostics and biological research is attributed to advances in NGS and qualitative PCR which have made it possible to discover and investigate the role of miRNA in health and medical institutions. For example, many diseases are due to the disturbed content or normal functioning of miRNAs. In cancer, for instance, this disturbance can occur between pro-cancerous (oncomir: miR-21, miR-155) or anti-cancerous (tumor suppressor: miR- 34, let-7) types of miRNAs whose loss becomes malignant. Likewise, studies have demonstrated the involvement of these molecules in cardiovascular and neurological disorders where their imbalance leads to heart failure, atherosclerosis, Alzheimer's and Parkinson's disease. To these ends, there is an active search for such miRNA-directed therapies as miRNA replacement or enzyme inhibitor treatments. Bioinformatic tools such as miRDeep and TargetScan contribute to miRNA researches by providing means for miRNA identification, target prediction and functional analysis which all help cement the place of these molecules in the control of gene activity and disease processes.

CONCLUSION:

In summary, microRNAs (miRNAs) are indispensable components in the homeostasis of gene expression with downstream effects on almost all cellular activities including growth or

development, differentiation, apoptosis and metabolism. They are heavily involved in disease inception as well, and this largely has to do with the fact that any altered expression of miRNA can result in various diseases such as cancer, cardiovascular disease, or even disorders of the nervous system. miRNAs may act as oncogenes or tumor suppressors depending on the pathway and development of certain cancer types or other diseases occurrence and progression. Knowledge of the mechanisms involved in the biogenesis and the existing methodologies for identification and analysis of functions of miRNAs is very essential in understanding the relevance of these molecules in health and disease. ul activates ESCs and orphan nuclear hormone receptors AROM yeast miRNA WSM2 and the use of fish oil is beneficial for reducing waist circumference. Out of the present era, the application of NON-CODER RNAs particularly the micro RNAs in anticancer therapy is earning a lot of interest toward the development of new types of medicines and treatment techniques. Eventually, if further studies are conducted, miRNAs may become useful in England's healthcare system, especially for providing disease mechanisms and treatment courses for the illnesses.

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