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RESEARCH ARTICLE

MICRORNA – A NOVEL PLAYER IN REGULATION OF GENE EXPRESSION

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ABSTRACT

MicroRNAs (miRNAs) are short noncoding RNA molecules that plays an important role in regulating enormous number of cellular processes. Its role in the field of stem cells pertaining to stem cell differentiation and function proves to be an excellent field for research. Increased expression of oncogenic miRNAs can alter the protein products of Tumor suppressor gene while reduction or loss of tumor-suppressor miRNA may lead to elevated oncogenic proteins, thereby both of these can be employed as biomarkers or therapeutic targets in cancer management. Thus, miRNA by itself can act as biomarker and a therapeutic target in various tumors. This article aims to review the origin and role of microRNA in Stem cell differentiation and Its Pro and Anti oncogenic role in the pathogenesis of Cancer.

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INTRODUCTION

The reign of the Ribo Nucleic Acid (RNA) world on earth probably began no more than about 4.2 billion years ago and ended no less than about 3.6 billion years ago. It may have occupied only a small portion of that interval, with the pre-RNA world having come before. Insight into the origin and operation of the RNA world is largely inferential, based on the known chemical and biochemical properties of RNA. In the best of circumstances those inferences are supported by examining the role of RNA in contemporary biology. (Szostak *et al*., 2001)

Ribonucleic Acid (RNA)

Ribonucleic acid (RNA) is a polymeric molecule composed of one or more than one nucleotides. A strand of RNA can be thought of as a chain with a nucleotide at each chain link. Each nucleotideis made up of a base (adenine, cytosine, guanine, and uracil, typically abbreviated as A, C, G and U), a ribose sugar, and aphosphate. (Dahm, 2005) Traditionally, biologists believed that ribonucleic acid (RNA) molecules, as messenger RNA (mRNA), simply carriedgenetic information from Deoxy-ribo nucleic acid (DNA) in the nucleus to the places in the cell where proteins are produced. The simple formula was believed to be DNA makes RNA, RNA produces protein, and proteins are major cellular machinery that carries out all the crucial tasks, as structural substances, enzymes, hormones, and so on. RNAs were also founded in the protein factory themselves. Two other molecules of the RNAs family are non-protein coding and are called ribosomal RNA(rRNA) and transfer (tRNA). With this idea, the major efforts ofgene hunter researchers were to discover new structural geneswhose products encode proteins. The role of RNA molecule is pervasive, in contemporary biology especially with regard to the most fundamental and highly conserved cellular processes. Despite containing only 4 different chemical subunits, it shows a remarkable structural versatility which is due to its ability to fold into a variety of complex tertiary structures, analogous to structured proteins, and catalyses a broad range of chemical transformations, aminosylation of transferred RNA and peptide bond formation. It plays a role as a primer in DNA replication, by carrying the genetic information to the translation machinery. RNA instructs the processing of precursor messenger RNAs during splicing and editing, and mediates numerous other transactions of RNA and proteins in the cell. Catalytic RNAs (ribozymes) helps in RNA processing events and the replication of viral genomes. Individual nucleotides serve as important signaling molecules and their coenzyme derivatives participate in most of the reactions of central metabolism. However, facts pertaining to the RNA originated and the degree of metabolic complexity pertaining to it, the role of it in DNA genomic properties and protein enzymes is still not completely resolved. It is as if a primitive civilization had existed prior to the start of recorded history, leaving its mark in the foundation of a modern civilization that followed.

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(Bahadori, 2008) In addition to the above, the recent studies indicated that nearly 97% of the human genome is composed of non-coding DNA, which varies from one species to another. Instead, many of them produce important on-coding regulatory products. The most recent among this non-protein-coding RNA (npcRNA) class are genes that encode small or short- length RNA molecules (approximately <40nucleotide in length). An important group of these are called micro RNAs. These molecules unlike messenger RNAs do not encode protein but inhibit mRNA gene production. (Joyce, 2002)

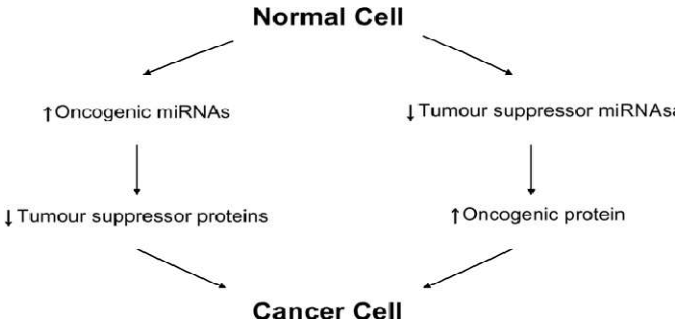
Micro RNA and stem cell concepts

The hallmark of a stem cell is its capability to self-renew and to produce differentiated cells. This property of these stem cells is controlled by active interplays between extrinsic signaling, epigenetics and transcriptional regulations. Recent research indicates that microRNAs (miRNAs) have an important role in regulating stem cell self-renewal and differentiation by repressing the translation of selected mRNAs in stem cells and differentiating daughter cells. Such a role has been shown in embryonic stem cells, germ line stem cells and various somatic tissue stem cells. These findings reveal a new dimension of gene regulation in controlling stem cell fate and behavior. (Yi and Fuchs, 2011) The concept of self-renewal holds good when a stem cell generated one (asymmetric division) or two (symmetric division) daughter cells that tends to have similar developmental potential as the parent cell. The property of stem cell to self-renew themselves depends upon various factors inclusive of epigenetic programs. The rate at which this happens depends upon the type of stem cell. Embryonic stem (ES) cells are cell lines derived from the inner cell mass of a developing blastocyst. These cells can self-renew and rapidly multiply thereby leading to production of large amount of tissue for tissue replacement. (Tiscornia and Izpisúa Belmonte, 2010) In addition to the roles of miRNAs in controlling stem cell differentiation, which have become increasingly well established, several new twists have emerged in the miRNA world. Among them is the notion that miRNAs function in injury or stress situations. Micro RNAs have also been implicated in the regulation of stem cell aging. In this regard, Hmga2, a key transcription factor for the self-renewal of neural stem cells, is highly expressed in fetal neural stem cells in mice, but its levels decline by more than 99% during their lifetime. The decreased level of Hmga2reduces the self-renewal capacity of neural stem cells and seems to be, in part, caused by an approximately 30-fold age-induced increase in the expression of let-7b, which is known to target and inhibit. The specific disruption of Hmga2 regulation usinglet-7b with a truncated 3'-UTR showed substantial rescue of the self-renewal capacity in an in vitro culture assay, supporting the causative role of let-7b in the down regulation of Hmga2. (Yi and Fuchs, 2011)

Micro RNA in cancerous disease

Cancerous disease

Cancer is a genetic and epigenetic disease that requires inactivation of tumour-suppressor genes and activation of protooncogenes. Mutated DNA sequences are transcribed to mRNA, which is finally translated into functionally aberrant proteins. However, RNA is not a 'passive intermediate product' between DNA and proteins. (Scholzová *et al*., 2007) The expression of genes is also dependent on RNA-based mechanisms, including nonsense-mediated decay, alternative splicing, RNA editing and miRNA. Functional regulation of these RNA based mechanisms could constitute one or more of the steps involved in cancer development. (Flow Chart.1) (Gomes and Gomez, 2008)



Flowchart 1. miRNA and cancer

Micro RNA alterations in OSCC miRNA expression profiles appear to be tumor- and tissue specific. Several miRNA expression profiling studies have identified aberrant miRNAexpression profiles in OSCC tissues and/or cell lines relative to the corresponding normal controls. A number of researches have also investigated common miRNAs abnormally expressed in head and neck squamous cell carcinoma (HNSCC), aheterogeneous disease that arises from the oral cavity, nasal cavity, pharynx and larynx. (Wu *et al*., 2011) In addition, there are some profiling studies that have shown that miRNA expression profiles correlate with and could explain the pathogenesis, metastasis, and chemo resistance ofOSCC. In considering the important effect of miRNAs on gene expression, it is not surprising that these small RNAs have been implicated in the pathogenesis of cancer. The expression profiles of miRNAs are usually altered in many cancers. A reduction in miRNAs accelerates oncogenic transformation thorough the deregulation of target oncogenes. For example, a reduction or loss of expression of the two clustered miRNAs, miR-15a andmiR-16-1, are found in chronic lymphocytic leukemia and in prostate cancer. (Fukumoto *et al*., 2015)

Role of miRNA in cancer pathogenesis

Micro RNAs discovery led to a wider research so conducted to establish their significant role in cancer pathogenesis. MiRNAs regulate molecular pathways in cancer by targeting various oncogenes and tumor suppressors, and have a role in cancer and stem cell biology, angiogenesis, the epithelial–mesenchymal transition, metastasis, and drug resistance. (Ahmad *et al*., 2013) Administration of miR-26a using adenoassociatedvirus (AAV) in an animal model in case of hepatocellularcarcinoma (HCC) tends to inhibits tumor progression without causing toxicity. Anti-miRNA oligonucleotides (AMOs) can block the combined effect of miRNA and its target through inhibition of base pairing. Administration of AMOs against few miR-16, miR-122, miR-192 and miR-194 in animals offer a long term quiescence of corresponding miRNAs. Non-small cell lung cancer (NSCLC) could be differentiated from healthy controls using a combination of differentially expressed miRNAs miR-15b and miR-27b, thereby pointing tothe potentials of serum miRNAs as biomarkers for early detection of NSCLC. Many cellular processes including cell proliferation, migration, invasion and

survival have been directly linked to over expression of miR-21, whereas, it's down regulation induces apoptosis. Over expression of miR155, another commonly deregulated miRNA, is also directly associated with tumorigenesis in lymphomas, breast, lung, colon, and pancreatic cancers. The ability of miRNAs to regulate cell growth and apoptosis has found its irreplaceable role in cancer pathogenesis which itself is a consequence of dysregulation of growth and apoptosis of cells. In order to identify the exact role of miRNAs in cancer pathogenesis, specific miRNAs over expression or misexpresion can be studied to determine their individual role in development of different types of tumor. Recognition of different variants of miRNAs that are variedly expressed among tumor and normal tissues may help to identify those specific miRNAs that are involved in human cancers and further confirm the role of miRNAs as biomarkers in cancer diagnostics. (Flow Chart.2) (Iorio *et al*., 2005)

MicroRNA as biomarker for cancer

Human micro RNA has been associated with cancer andcontrols the important processes such as cell proliferation, celladhesion, apoptosis and angiogenesis. Dysregulation of thesemiRNA, therefore play important roles in onset, progression andmetastasis of cancer. (Table 1 & 2)

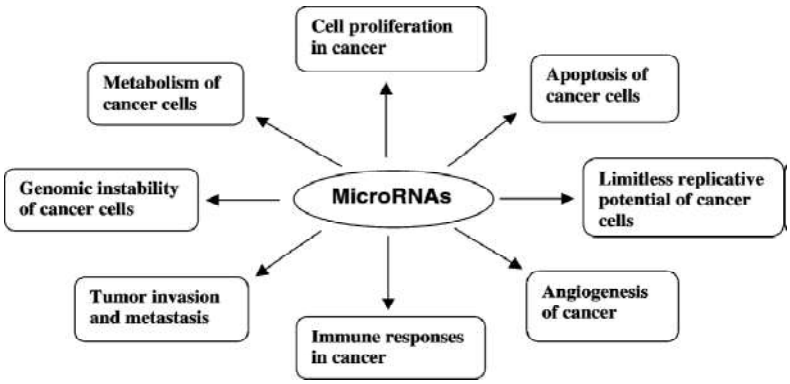
- miRNA-205, a specific marker for oral squamous cell
- carcinoma.
- miRNA-499c,a marker in hepato-cellular carcinoma. (George and Mittal, 2010)

Micro RNA – future perspectives

The discovery of small RNAs like miRNAs has revolutionized the concept of genes and gene regulation. It is clear that

Table 1. Cancer related micro RNAs

Cancer	Up-Regulated miRNAs	Down-Regulated miRNAs
Breast Cancer	miR-21, miR-155, miR-29b-2	miR-143, miR-145, miR-155, miR-200
Lung Cancer	miR-21, miR-189, miR-200b, miR-17-92 cluster	Let-7 family, miR-126, miR-30a, miR-143, miR-145, miR-188, miR-331, miR-34s
Colon Cancer	miR-223, miR-21, miR-17, miR-106m, miR-34s	miR-143, miR-145, miR-195, miR-130a, miR-331
Prostate Cancer	Let-7d, miR-195, miR-203, miR-125b, miR-20a, miR-221, miR-222	miR-143, miR-145, miR-128a, miR-146a, miR-126
Brain Cancer	miR-21, miR-221	miR-181
Hepatocellular Cancer	miR-34s, miR-224, miR-18, miR-21	miR-17-19bcluster, miR-200a, miR-125a, miR-199a, miR-195
Chronic Lymphocytic Leukemia	miR-15, miR-16	
Lung Cancer	miR-17-92	Let-7
Ovarian Cancer	miR-200a,b,c, miR-141	miR-199a, miR-140, miR-145, miR-125b
Pancreatic Cancer	miR-221, miR-181a, miR-21	miR-148a,b
Papillary Thyroid Cancer	miR-221, miR-222, miR-146, miR-181	
Stomach Cancer	miR-21, miR-103, miR-223	miR-218



Flow Chart. 2 Micro RNA in tumorogenesis

Table 2. Micro RNA and hallmark of cancer

Hall Marks of Cancer	Functions of miRNAs	miRNAs
Resistance from antiproliferation signals and independence from exogenous growth factor signals	Pro-Proliferation Anti-Proliferation	miR-21, miR-17 cluster, miR-221, miR-222, let-7, miR-519, miR-146a
Evasion of apoptosis	Pro-apoptosis Anti-Apoptosis	miR-34 cluster, miR-29, miR-15, miR-16, miR-17-92 cluster, miR-21
Limitless Replicative Potential	Regulation of immortalization and senescence	miR-290, miR-24, miR-34a
Induction of Angiogenesis	Pro- angiogenesis Anti-angiogenesis	miR-17-92 cluster, miR-378, miR-296, miR-27b,let-7f; miR-130, miR-126, miR-15, miR-16, miR-20a, miR-20b
Evasion of Immune system	Escape from immunosurveillance	miR-155, miR-17-92 cluster, miR-20a, miR-93, miR-106b, miR-372, miR-373, miR-520c, hmcv-miR-UL112
Tissue Invasion and Metastasis	Pro-metastasis Anti-metastasis	miR-10b, miR-21, miR-373, miR-520c, miR-155, let-7, miR-335, miR-206, miR-126, miR-146a, miR-101, miR-200
Genomic instability	Promote Genomic instability	Deletions or down-regulation of miRs, such as miR-17, miR-20a, miR-15, miR-16-1 or let-7

miRNAs play an important role in virtually all biological processes and that their dysregulation is associated with disease. In cancer, widespread changes in miRNAs levels have been observed in virtually all tumor types. Moreover, mouse studies have demonstrated that causal links exist between mi RNAs and cancer development, and miRNAs have been demonstrated to play crucial roles in the response to therapy. The ability to target multiple genes and their biological processes makes miRNAs one of the most unique target agent for cancer therapy. Initial evidence of the feasibility and efficacy of amiRNA-based therapy came from preclinical models aimed to understand the biological roles of a specific miRNA. Despite the fact that basic knowledge of miRNA biology is still providing new insights, miRNA is also has a discrete nature enabling easy manipulation of them pharmacologically enabling development of newer treatment strategies. To date, there are several tools available to selectively target miRNA pathways. One method is to increase miRNA levels by delivering chemically synthesizemi RNA mimics in vivo. miRNA mimics are synthetic RNA duplexes designed to mimic the endogenous functions of miRNA with chemical modifications for stability and cellular uptake. Synthetic miR-34a was recently shown to inhibit lung tumor growth in a mouse model. To target oncogenic miRNAs, the most widely used approach is to generate antimi Rs that are modified antisense oligonucleotides harboring the full or partial complementary reverse sequence of a mature miRNA of interest. Stability, specificity and binding affinity are the key requirements for an antimiR to achieve its efficacy in vivo. Two types of chemical modifications have been used for this purpose, including 2'-O-methyl-group modification and locked nucleic acid (LNA)-modification. (Lu and Wan, 2012) Micro RNA plays a pivotal role in stem cell regulation, differentiation of pluripotent stem cells, and in addition to the roles of miRNAs in controlling stem cell differentiation, which have become increasingly well established, several new twists have emerged in the miRNA world. Among them is the notion that miRNAs function in injury or stress situations, as alluded toearlier when discussing the roles of Pax7. (Yi and Fuchs, 2011) Furthermore, an approach involving the identification of miRNAs from the body fluids such as saliva, urine, and sweat, to establish them as biomarkers is necessary for relatively simple diagnosis, without the need for tissue or muscle biopsy. Further research involving the characterization of detailed mechanism in physiological and pathological changes in miRNA based on appropriate evaluation or assessment protocols were warranted. Nevertheless, the field of miRNA research is attractive and is expected to present a novel finding to researchers. Micro RNAs have wide spectrum of alternative translator applications that involve miRNAs ant their associated molecules and pathways. This includes tumor classification, diagnosis, prognosis, predilection of overall of survival for cancer patients and administration of effective therapeutic targets using miRNAs mimics and anti-miRs. Combinations of miRNAs along with current cancer therapeutic agents can lead to development of highly effective agents towards improving quality of life of cancer patients.

Conclusion

The discovery of the first micro RNA (lin-4, in *C. elegans*) in 1993, and the subsequent numerous scientific reports indicating that many more "RNA of this kind which do not encode protein" exist have announced a new world of RNA that subverts the traditional beliefs about RNA molecule. RNAi is becoming a new tool in the diagnosis and treatment of diseases and new advances to prediction of the disease outcome. Finally, now with the advances in new era of RNA activities and recent discoveries, it is likely to have changes in the people's point of view about how cells regulate themselves, how life becomes more complex, the features of creature developments, how a certain disease develops, how the diseases can be cured or prevented, and even how the process of evolution operates. Taking these and the additional issues outlined in this review into account, will allow for more accurate examination of a miRNA to guide one in understanding its biological significance. Further probing of miRNA biogenesis and functionality will enable the development of more specific and sensitive assays which can enable development of effective and efficient therapeutic agents.

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