REVIEW ARTICLE

MicroRNAs - Biology and clinical applications

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ABSTRACT
MicroRNAs are a highly conserved group of small, non-coding RNA molecules, which are 19-25 nucleotides in size. Previously thought to be evolutionary debris with no evident function, these small RNAs have been found to control gene expression primarily by silencing the gene. MicroRNAs are critical to cell physiology and development. They are also implicated in pathological processes such as autoimmune diseases, viral infections and carcinogenesis.
Key words: Gene silencing, MicroRNAs, non-coding RNAs

INTRODUCTION

Molecular biology's central dogma explains life using 3 macromolecules: Deoxyribonucleic acid (DNA)-the genetic material of almost all living organisms, -which is transcribed to Ribonucleic acid (RNA), which transmits genetic information from DNA to the cytoplasm to be translated to amino acids and forms protein which is a sequence of amino acids that forms the structural and functional basis of every cell.[1]

For decades, RNA was thought to play a very minor role in gene expression by converting genetic information from DNA into functional proteins upon receiving an appropriate signal. In the late 1960s, a subset of RNAs was found to control gene expression by stating which genes should turn on and which should turn off.[2] These non-coding RNAs, rightly named because they do not code for a protein, are of distinct classes distinguished based on their function and origin. These include microRNA (miRNA), small temporal RNA (stRNA), short interfering RNA (siRNA), short hairpin RNA (shRNA), small nuclear RNAs (snRNA), small nucleolar RNAs (snoRNA), transfer RNAs (tRNA) and ribosomal RNAs (rRNA).[3]

MiRNAs and siRNAs are currently among the most studied small non-coding RNAs. Following completion of the Human Genome Project, it was found that there are about 1000 genes in humans that encode miRNAs, which account for approximately 3% of the human genome.[4-6]miRNAs are critical in determining cellular fate as they regulate development, maturation, differentiation and apoptosis of the cell, cell signaling, cellular interactions and homeostasis. Alternatively, they also assume central importance in our understanding of many pathologic conditions such as carcinogenesis.[7,8] Small non-coding RNAs are thus at the forefront of modern biology, heralding in an era of RNomics (the study of small non-messenger RNA) and challenging a central dogma proposed by Francis Crick more than half a century ago.

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HISTORY

Living cells arose on Earth around 3.5 billion years ago when spontaneous reactions occurred between molecules of which RNA (Ribonucleic acid) molecules were the prime players. With time, protein catalysts accumulated, thereby resulting in the evolution of more complex and efficient cells and eventually the DNA double helix molecule, being more stable, replaced RNA in order to store the larger amounts of genetic information needed by these cells. The RNA molecule remained an intermediary, connecting the DNA, having the genetic function, with the proteins, having the catalytic function.[9]

Coding RNAs

Based on their function, RNA molecules can be broadly classified into coding RNAs and non-coding RNAs. Coding RNAs are molecules that code for a particular protein. They are key players in protein transcription and translation. The gene that codes for the protein of interest is unwound and transcribed into a single-stranded RNA molecule, the messenger RNA (mRNA), so called because it carries the genetic information from the nucleus into the cytoplasm, where it is translated into a sequence of amino acids forming a polypeptide chain. However, it remained unclear as to what made the genes to be transcribed into a particular protein and

how the process was turned on and off in each cell.[1] Human genome analysis has revealed that a very small portion of the human genome is translated into functional proteins while the majority (approximately 65%) of the genome is transcribed into RNAs, whose function is still not determined.[10]

Non-coding RNAs

Non-coding RNAs, unlike mRNAs, do not encode protein but control various levels of gene expression.[11,12]Based on their function, non-coding RNAs can be categorized into housekeeping RNAssuch as tRNAs, rRNAs, snRNAs and snoRNAs and regulatory RNAs. Housekeeping RNAs are usually constitutively expressed whereas regulatory non-coding RNAs are produced only at certain stages of cellular development and differentiation or in response to external stimuli. Among the small regulatory RNAs, miRNAs are the most phylogenetically conserved and function post-transcriptionally to regulate physiological processes by silencing the gene.[13-15]

Gene regulation

Genetic regulation is essential to development and is the process that controls the differentiation of a single totipotent cell into a functional, complex multicellular organism. An interspecies variation, or more simply, what makes us human, is not only the difference in the genetic makeup but also the differences in gene regulation.[16] It is also the cause of phenotypic variations among individuals of the same species as well as the reason for disease processes when the regulation is aberrant.

Both RNA and protein can be regulated to control the amount of active gene product formed by epigenetic control, chromatin remodeling through DNA modifications and regulating the transcript. This can occur at the transcriptional level, when the gene is transcribed to an RNA transcript; at the translational level, when the gene encodes a protein; or the post-transcription and post-translational level, after the gene product is synthesized. Small non-coding regulatory RNAs regulate post-transcriptional gene expression.[17]

Gene regulation can result in up-regulation or down-regulation of the gene product. Down-regulating the formation of active gene products or "turning off" the gene is called gene silencing. RNA interference (RNAi) is a method of sequence specific post-transcriptional gene silencing.[18]RNAi was first discovered in 1998 in *Ceanorhabditiselegans* and plays an important role in regulating eukaryotic gene expression, causing repression through various methods including mRNA degradation, inhibition of its translation or chromatin remodeling.[3,18,19]

RNAi (in mammals) and post-transcriptional gene silencing (PTGS) (in plants) has been thought to represent an evolutionarily conserved mechanism developed to protect against viruses and mobile genetic elements such as *transposons*, which causes genomic instability.[20,21]Central to the mechanism of RNA interference are two small non-coding regulatory RNAs-miRNAs and small interfering RNAs.

THE MIRNA AND SIRNA GENE FAMILY

miRNAs are highly conserved class of small (19-25 nucleotides), non-coding RNAs, which regulate post-transcriptional gene expression by binding to target mRNAs and result in gene silencing.[22,23] In the genome, miRNAs can be found situated in the exons of non-coding genes, introns of coding and non-coding genes and the intragenic regions.[24] Small interfering RNAs (siRNAs) are approximately 22 nucleotides in length and mediate RNA interference (RNAi). Both miRNAs and siRNAs mediate the down-regulation of gene expression; however, their biogenesis and method of gene silencing differs significantly.[25,26]

The first miRNA, lin-4 (abnormal cell LINeage) was discovered by Ambros and coworkers (1993) in *C. elegans* as an endogenous regulator of genes that regulate developmental timing.[10] The second miRNA, let-7 (LEThal), was discovered 7 years later and found to function similar to lin-4. Eventually, two categories of small RNAs were established that regulated gene expression: miRNAs, which regulate endogenous genes and siRNAs, which defend genome integrity in response to foreign or invasive nucleic acids such as viruses, transgenes and transposons.[27,28]

Following the discovery of *lin-4* and *let-7,* several hundreds of miRNAs have been identified. Some miRNAs, such as *let-7,* are highly conserved through evolution and are essential to many biological processes, while the individuality of an organism can be ascribed to lineage- and species-specific miRNAs.[29,30] There are currently 1872 precursor and 2578 mature human miRNA sequences listed in the miRNA registry (Sanger miRBase release 20; http://www.mirbase.org/). Almost 60% of mammalian mRNAs are predicted targets of a relatively small number of miRNAs, suggesting that a given miRNA can silence many target genes. This is thought to be because miRNA does not require perfect sequence complementarity with its target mRNA.[31]

BIOGENESIS OF MIRNAs

miRNAs are produced through transcription of miRNA genes in the nucleus known as miRNAs precursor genes (mir-gene). The miRNA transcripts are then spliced and capped similar to protein coding mRNA transcripts. These primary miRNAs form a hairpin-shaped stem loop, prior to being processed into pre-miRNAs. This processing is carried out by a microprocessor complex that consists of Drosha (RNase III endonuclease) and DiGeorge syndrome critical region 8 (DGCR8) or Pasha, which is an essential cofactor. This

complex processes the primary mircoRNAs into pre-miRNAs, which are 60- to 70-nucleotide long and contain a 5′ phosphate and a 3′ nucleotide overhang. The pre-miRNA is then transported to the cytoplasm by exportin 5 of the Ran transport receptor family.[3,32]

In the cytoplasm, the pre-miRNA is further processed to a short double strand miRNA by partner proteins Dicer (second RNase III endonuclease) and trans-activator RNA binding protein (TRBP). The duplex is then unwound by a helicase and the final mature miRNA is generated. Dicer also initiates the formation of the RNA-induced silencing complex (RISC). The mature miRNA product is a single-stranded, non-coding, regulatory RNA molecule 22 nucleotides long, which is guided to the target mRNA after it is incorporated into an RNA-induced silencing complex (RISC).[33]

The Argonaute (Ago) family of proteins is a major component of RISC and functions as a protector, protecting the RISC-loaded mature miRNA from degradation. After its function is complete, however, the mature miRNA is degraded.[34]

miRNAs have also been shown to be produced by two Drosha independent, non-canonical or alternative pathways. In the first pathway, early processing is carried out by spliceosome and a debranching enzyme to produce the short hairpin structure. These miRNAs have been called *mirtrons*. In the other non-canonical pathway, short hairpin RNAs (shRNAs) undergo processing by unknown nucleases into pre-miRNAs, which then follow the regular sequence of being processed into miRNAs by Dicer. These miRNAs are therefore called *shRNA-derived miRNAs*.[35]

The level of complementarities between the target mRNA and miRNA determines the method of binding and silencing.[36] miRNAs and siRNAs involved in RNAi use the same RISC to direct silencing. After that, the mechanism diverges-miRNAs attach imperfectly to mRNA and form a bulge that prevent mRNA from producing protein while siRNA binds perfectly with the target mRNA and destroy the mRNA.[3]

ROLE IN PHYSIOLOGY

miRNAs have been found to regulate almost all cellular functions including cell proliferation, growth, differentiation and apoptosis. They are thought to play a role in specifying tissue identity since they are involved in the process of differentiation into specific tissue. Thus, the expression of miRNA in a specific cell type can be a useful marker for identifying the particular cell type.[37]

Tooth development

Specific codes of miRNAs have been identified which regulate cell differentiation and are required for tooth patterning; size, shape and number determination.[38]

Stem cells and miRNAs

miRNAs have been implicated in controlling the fate and behavior of stem cells. Down-regulation of miR-21, targets *Nanog*, *SOX2* and *OCT4*, which are essential for stem cell self-renewal. Self-renewal is also promoted by the miR-290-295 cluster, which epigenetically silences *OCT4*. Embryonic stem cell differentiation is promoted by miR-296 and inhibited by miR-22.[39]

Stem cells divide to produce an undifferentiated stem cell and a daughter cell that may differentiate. This division is a carefully regulated process since excess divisions may result in cancer while too few divisions may lead to a loss of tissue homeostasis.[40]miR-138 has been found to negatively regulate osteogenic differentiation of human Mesenchymal Stem Cells (hMSCs). Thus, to increase bone formation *in vivo,* osteogenic differentiation of hMSCs can be accelerated by inhibiting miR-138. Another miRNA, miR-125b, has been shown to inhibit osteoblastic differentiation. The miRNA, miR-26a modulates osteogenic differentiation of stem cells derived from human adipose tissue by targeting the SMAD1 transcription factor.[39,41]

Induced pluripotent stem (iPS) cells were first created by introducing reprogramming factors (So×2, Oct3/4, c-Myc and Klf4) into fibroblasts. The factor, c-Myc represses miRNAs, such as let-7a, miR-21 and miR-29a, during reprogramming. Cell types from different tissues are capable of being reprogrammed to iPS cells but the reprogramming efficacy is very low (0.01-0.2%). It has been found that miR-93 and miR-106b enhance reprogramming efficacy.[42]

ROLE IN PATHOLOGY

The involvement of miRNAs in human diseases was identified from two observations. The first was that humans with mutations in fragile (a RISC cofactor) or DGCR8 (a Drosha cofactor) suffer from mental retardation and DiGeorge syndrome, respectively. Second, almost 50% of human miRNA genes are present at genetic loci which are implicated in cancers.[33]

MiRNA and cancer

In humans, the balance between apoptosis and proliferation is vital for homeostasis maintenance. Some miRNAs are oncogenes (oncomiRs) and some are tumor suppressor miRNAs. miRNAs play a vital role in evaluating the development, progression, prognosis, diagnosis and treatment response in cancer patients.[37]

miRNAs target apoptotic genes, thereby mediating tumorigenesis. The capability of cancer stem cells to evade the G1/S checkpoint is partly due to miRNAs. Calin *et al.* reported a unique pattern of miRNA expression signatures

that were capable of differentiating aggressive from indolent chronic lymphocytic leukemia (CLL).[43]

Recent evidence indicates that miRNAs play an important role in p53 tumor suppressor pathways. He *et al*. found miR-34a, miR-34b and miR-34c to be closely linked to p53 status and oncogenic stress and DNA damage induced their expression.[44,45]

Oral cancer

miRNA profiling in head and neck squamous cell carcinomas (HNSCCs) revealed miR-451 to be a potential prognostic marker. miR-375 and miR-106b-25 cluster to be mediate the development and progression of HNSCC.[46]Kozaki *et al.* showed that miR-137 and miR-193a function as tumor suppressors and are silenced in oral carcinogenesis.[47]Wong *et al*. studied the expression patterns of miRNAs in squamous cell carcinoma of the tongue and found an over expression of miR-184 which was thought to have an oncogenic role by inducing proliferative and anti-apoptotic processes.[48,49]

Henson *et al.* found that the development and/or progression of oral squamous cell carcinoma are associated with the down-regulation of miR-100 and miR-125b and these miRNAs may be the reason for the low sensitivity to ionizing radiation.[50] Li *et al.* found that miR-21 was an independent prognostic indicator for tongue squamous cell carcinoma and played a role in its development by inhibiting apoptosis of cancer cells.[51]

Metastasis is a significant event in the progression of HNSCC and Liu *et al.* found miR-138 to acts as a tumor suppressor which could be a potential target for therapy in patients with a risk of metastasis.[52]

Cervigne *et al.* found miRNA signatures that could potentially identify leukoplakias which are at a risk of malignant transformation. The expression of miR-21, miR-181b and miR-345 were found to be consistently increased and associated with increase in the severity of the lesion. Overexpression of these miRNAs was thought to play a major role in malignant transformation.[53]

miRNAs and viruses

RNA interference and gene silencing is an innate host cell mechanism to protect against viruses. Viruses, on the other hand, have evolved to bypass host interference by various mechanisms which include altering miRNA expression in the host cell in a way that promotes viral replication. Nef and rev are viral genes in the human immunodeficiency virus that suppress host silencing mechanisms.[54-56]

miRNAs in autoimmune diseases

miRNAs are found to regulate immune response, immune cell development and prevention of autoimmunity. A possible role has been suggested for miRNA in the development of autoimmune diseases such as Rheumatoid Arthritis (RA), Sjögren'ssyndrome and Systemic Lupus Erythematosus (SLE). Distinctive miRNA expression patterns have been linked to salivary gland dysfunction in patients with Sjögren's syndrome and these miRNAs can serve as potential biomarkers for the disease. Proteins such as Ago2, involved in the biogenesis of miRNAs, have been found to be targets of these autoantibodies.[57,58]

Periodontal disease

miRNAs have been shown to play a major role in regulating the immuno-inflammatory response. Xie *et al.* compared the miRNA profiles of inflamed and healthy gingival tissue and found 91 miRNAs up-regulated and 34miRNAs down-regulated in the inflamed gingival tissue indicating a plausible relationship between periodontal inflammation and miRNAs. miRNAs may be involved in regulating toll-like receptors (TLRs) in periodontal inflammation.[59]

THE CLINICAL POTENTIAL OF MIRNAS: DIAGNOSTIC, PROGNOSTIC AND THERAPEUTIC IMPLICATIONS

The majority of miRNA are intracellular, but some miRNA exists in the extracellular compartment and are seen to be mediators of cell-cell communication. Extracellular miRNAs can be isolated from body fluids such as serum, plasma and saliva. They can act as potential biomarkers for the detection of various diseases.[60] Salivary miRNAs can be used clinically to detect oral cancer. Healthy saliva contains approximately 50 miRNAs. Two miRNAs in particular, miR-125a and miR-200a have been found exclusively in the saliva of oral cancer patients and are diagnostic markers of the disease.[61-63]

The presence of RNAases in body fluids precludes the existence of any intact RNA. Thus, it has been theorized and proven that miRNA exist extracellularly within small, cell-secreted vesicles called "exosomes".[64]These vesicles can regulate intercellular communication and facilitate certain processes such as antigen presentation. Exosomes are present in body fluids that include plasma, blood, breast milk, saliva and urine and can have a potential role in immunotherapy and vaccination modalities and as a potential vector for gene therapy. Salivary exosomal miRNAs may be important not only as a diagnostic tool but can also provide information regarding the role of miRNAs in the pathophysiology of various salivary gland diseases.[64]

QUANTIFICATION

Microarrays and quantitative PCR (qPCR)-based methods are the major modalities used to profile miRNAs. Quantitative PCR methods are widely available, relatively inexpensive and allow for the measurements of minute quantities of

miRNAs. However, the primer design can influence the results. With microarray-based methods, it is difficult to detect different miRNAs at one time. Northern blotting, direct sequencing and ligation-based measurement can also be used.[62] *In situ* hybridization is a reliable method to localize and detect miRNAs in both frozen tissue and paraffin-embedded sections. To confirm the function of a specific miRNA, loss-of-function and gain-of-function approaches can be applied *in vivo* in mammals as well as *in vitro* in cultured cells.[37]

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