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Molecular Insights into The Role of Non-Coding Rnas in The Pathogenesis and Progression of Human Diseases: A Review Article

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ABSTRACT

The ncRNAs don't change the central dogma, but rather they tell us that non-protein coding parts of the genome are actually essential in controlling expression and functions of genes at the cellular level. The paper covers major classes of ncRNAs comprising housekeeping RNAs, microRNAs, small interfering RNAs, piwi-interacting RNAs, small nucleolar RNAs, small nuclear RNAs, long non-coding RNAs, and circular RNAs with diverse mechanisms of actions. More detailed descriptions are provided for ncRNA function in human health and disease: cancer; cardiovascular diseases; and neurological disorders. Herein they can be oncogenes and tumor suppressors or critical modulators in pathophysiological processes. This work highlights diagnostic as well as prognostic potentials based on circulating ncRNAs which are relatively novel non-invasive biomarkers that have gained much attention lately. Among therapeutic strategies discussed is one that includes direct miRNA replacement through synthetic miRNA mimics and antagomiRs plus antisense oligonucleotides as inhibitors of ncRNA function. The article also sets out current challenges and future directions for clinical application of research findings relating to ncRNAs even while underscoring their promise as key effectors in precision medicine.

KEYWORDS

ncRNA; microRNAs; long non-coding RNAs; circular RNAs.

Introduction

For many years, the central dogma of molecular biology served rather plainly as a mainstay to direct thought regarding where and how genetic information flows, positing a linear progression from DNA to RNA to protein. It has been greatly amplified by the existence of a large and sophisticated world of non-coding RNAs (ncRNAs). Previously considered transcriptional "noise" or the genome's "dark matter," ncRNAs are

nowAcknowledged pivotal regulators of everything you can imagine related to biology; from basic cellular function all the way up to elaborate mechanisms concerning human health and disease. This review discusses the varied landscape of ncRNAs and their complex roles in cell function as well as their deep effects on human health, mainly focusing on their link to cancer, heart diseases, and brain disorders. Also, we will talk about the promising potential of ncRNAs as new markers and treatment targets which gives us a look into the future of molecular medicine.

Types and Functions of Non-Coding RNAs

Non-coding RNA (ncRNA) molecules constitute a diverse population of RNAs that are transcribed from DNA but are not translated into proteins. In terms of their nature, the ncRNAs do not code for proteins; however, in reality, they are far more active and play important regulatory roles in different levels of gene expression resulting in various cellular activities leading to organism development and homeostasis. The ncRNAs may take place as constitutively expressed housekeeping ncRNAs necessary for the basic function of a cell and regulatory ncRNAs causing modulation of expression that is more dependent on the context.

A. Housekeeping ncRNAs

Housekeeping ncRNAs are essentially conserved because their roles are firmly tied to the fundamental cellular machinery. The most outstanding examples are transfer and ribosomal RNAs. Transfer RNAs are small RNA molecules normally about 76-90 nucleotides in length, essential as adaptors in protein synthesis. A specific amino acid is attached to each tRNA molecule, and an anticodon on it base pairs with the codon on the messenger RNA specifying the same amino acid. This ensures that the genetic code is accurately translated into a polypeptide chain [1]. Ribosomal RNAs represent the largest fraction of total cellular RNA and equally important are them as structural and catalytic components of ribosomes - the cell's protein-synthesizing machinery. Particulate ribonucleoproteins, ribosomes comprise several rRNA molecules along with many ribosomal proteins. It is the rRNAs of the ribosome that catalyze peptide bond formation between amino acids, thus accurately translating the nucleic acid sequence of mRNA into the amino acid sequence of a protein [1].

B. Regulatory ncRNAs

Regulatory ncRNAs comprise broad and wide classes of molecules in which they play some of the most thoughtful roles in regulating gene expression. They may further be divided according to their size and mode of action：

1．Small ncRNAs Small ncRNAs are less than 200 nucleotides in length and involve diversified gene regulatory mechanisms. In general, microRNAs are small, single-stranded ncRNAs of 19-25 nucleotides that further regulate gene expression at the post-transcriptional level. MiRNAs are transcribed as primary miRNAs (pri-miRNAs) processed by the nuclear Drosha-DGCR8 complex into precursor miRNAs (pre-miRNAs). These pre-miRNAs are exported to the cytoplasm where further Dicer enzyme processing results in mature miRNAs. The mature miRNA then gets incorporated into RNA-induced silencing complex (RISC) which guides miRNA to its target mRNA. This target puts forward the targets for the miRNA-RISC complex at the 3' untranslated region (UTR) of mRNA; either its translation is blocked or the mRNA is degraded hence downregulating gene expression. MiRNAs play numerous vital cellular biological functions from regulation during development to controlling cell proliferation and differentiation, even triggering programmed cell death. Short interfering RNAs are double-stranded RNA molecules of 20-25 nucleotides in length. They act through the RNA interference pathway and are typically derived from longer double-stranded RNA precursors, such as those from viruses or transposable elements, processed by Dicer. Like miRNAs, siRNAs get loaded into RISC which then mediates cleavage of target mRNA having complementary sequence thereby resulting in gene silencing. In this manner, short interfering RNAs play a fundamental role in antiviral responses and genome stability through suppression of transposable elements-in addition to their application for gene knockdown both as a research tool and potential therapeutic intervention [1]. Piwi-interacting RNAs are small ncRNAs 24-31 nt predominantly expressed in germline cells. PiRNAs bind to Piwi proteins, which are members of the Argonaute protein family and are essential for the repression of transposons as well as genomic stability in germ cells. In this way, they direct Piwi proteins toward RNA or DNA sequences that are their complements eliciting either transcriptional or post-transcriptional gene silencing

[1]. Small nucleolar RNAs (snoRNAs) belong to small non-coding RNAs and mainly guide chemical modification of other RNA molecules, mainly ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), and small nuclear RNAs (snRNAs). These modifications are important for the proper folding and functioning of the RNA molecules targeted. Small nuclear RNAs are members of the spliceosome, which is a large ribonucleoprotein complex involved in pre-mRNA splicing. A spliceosome precisely removes non-coding introns from pre-mRNA and joins coding exons together; this is a critical step for gene expression [1]. Extracellular RNAs are non-coding RNA species, including miRNAs, lncRNAs, circRNAs, located outside the cells generally encapsulated within extracellular vesicles such as exosomes, microvesicles, or apoptotic bodies. ExRNAs can be taken up by recipient cells where they may play some regulatory role hence mediating intercellular communication. Their stability in bodily fluids renders them potential candidates as biomarkers for diseases [3].

2. Long non-coding RNAs

Long non-coding RNAs are great and rapidly expanding groups of ncRNAs that are defined by their length which is greater than 200 nucleotides. Unlike small ncRNAs, lncRNAs may have a wide range of mechanisms of action and often their expression is restricted to certain cell types and tissues. Their functions can vary so radically that they could involve the regulation of gene expression at the epigenetic, transcriptional, or post-transcriptional level.

Some lncRNAs are able to act as competing endogenous RNAs (ceRNAs) which mean they bind and sequester miRNAs so that the miRNAs do not bind to their mRNA targets and thus the expressions of miRNA target genes are indirectly upregulated. This process further complicates gene regulation at the post-transcriptional level. LncRNAs also recruit chromatin-modifying complexes such as Polycomb Repressive Complex 2 (PRC2) to specific genomic sites. Alteration of chromatin structure, for instance through histone methylation can then affect transcription of certain genes. In this respect one well studied example is Xist PRC2 targeting the X chromosome It can provide molecular scaffolding thereby bringing several different proteins together into a functional ribonucleoprotein complex which in turn regulates numerous cellular activities including gene expression RNA processing and protein stability It may also bind and titrate out transcription factors or other regulatory protein preventing them from acting on their normal site of action. This system stops these proteins very well from doing their usual jobs and so controls gene expression. For example, the lncRNA GAS5 might trick the receptor for glucocorticoids and thus block its ability to help in transcription. LncRNAs may also attach to proteins right away and affect how they are shaped, how secure they are, or their enzyme-like action. This close binding can cause a change in what a protein does and then in the cell's activities.

3. Circular RNAs

Circular RNAs belong to a novel category of ncRNAs, which are formed as covalently closed circular molecules without 5′ caps and 3′ poly(A) tails. Because of this structural property, they become very much stable and resistant to degradation by exonucleases; therefore, their half-lives become much longer than those of linear RNA. Circular RNAs are expressed under mammalian cells prolifically and have relatively important roles in various biological activities and diseases [5].

A major way circRNAs act is by serving as competitors in which they bind to miRNAs and thus relieve the inhibition on target mRNAs of these miRNAs, resulting in increased gene expression. For instance, the circRNA CDR1as known as ciRS-7 can bind to miR-7, thereby increasing the expression of genes targeted by miR-7. CircRNAs can also bind and sequester RNA-binding proteins affecting where in the cell they are located their activity or how long they last This could influence a range of RNA-related activities such as splicing translation or RNA decay For example certain circRNAs might control the expression of the genes that created them by interacting with RNA polymerase II or other factors involved in transcription Just like it is less common for some circRNAs to directly interact with DNA or RNA polymerase and thus affect transcription of parental or other genes. Although circRNAs have traditionally been considered non-coding, it is now proven that some circRNAs can be translated into small peptides or proteins through a cap-independent mechanism. In turn, these circRNA-derived peptides may function in a wide array of cellular processes and diseases [6].

Role of non-coding RNAs in Human Health and Disease

Non-coding RNAs are recognized as increasingly important in the pathogenesis of human disease. As

precise regulators, small perturbations in their levels or activities necessarily have large downstream effects and so may contribute to disease initiation and progression as well as therapeutic resistance. Their implication is central for a huge range of conditions-from cancer to cardiovascular disease and neurological pathology. The aberrant expression of ncRNAs in these diseases can be through many mechanisms genetic alteration, epigenetic modification, abnormal processing. Genetic changes include mutations, deletions, or amplifications of ncRNA genes or their regulatory regions that alter expression and function. Among the epigenetic impacts on ncRNA transcription is DNA methylation and histone modification. Moreover, faults in the apparatus for ncRNA generation and handling (such as Dicer or Drosha) can lead to changed levels of mature ncRNAs. These misregulations may cause a lack of balance in gene expression systems, eventually adding to illness traits.

A. Role in Cancer

Cancer is a complicated disease resulting from abnormal growth and division of cells. The dysregulation of ncRNAs influences cancer very deeply. Depending on their specific targets and the cellular environment, ncRNAs may play the role of oncogenes or tumor suppressors. They are involved in all the hallmarks of cancer such as sustained proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality angiogenesis to be induced by these molecules and also invasion and metastasis to be activated.

MiRNAs are very put in cancer by either acting as oncogenes (oncomiRs) or tumor suppressors. A fine tuning of the gene expression makes miRNAs key regulators of cellular pathways related to tumorigenesis. Some are upregulated in cancer and promote tumors by repressing the gene of the tumor suppressor or genes involved in apoptosis and differentiation. An example is miR-21 which is overexpressed in most human cancers, breast, lung, colon, glioblastoma etc. MiR-21 promotes cell proliferation, invasion, and metastasis in these cancers through two different pathways targeting two different tumor suppressors PTEN(Phosphatase and Tensin Homolog) and PDCD4 (Programmed Cell Death 4). Its overexpression decreases apoptosis increases cell survival hence tumor progression. Other miRNAs are down-regulated in cancer that act as tumor suppressors by inhibiting oncogenes or genes promoting cell growth and survival. The miR-34 family (miR-34a, miR-34b, and miR-34c) is one of the most researched tumor suppressor miRNAs. In most cancers, miR-34a, a direct transcriptional target of the p53 tumor suppressor protein, is found to be downregulated. It inhibits cell proliferation and induces apoptosis as well as inhibits metastasis when expressed by targeting oncogenes such as BCL2 (B-cell lymphoma 2) and MYC (v-myc avian myelocytomatosis viral oncogene homolog) [8]. Restoration of miR-34a showed promising anti-tumor effects in preclinical studies.

LncRNAs play very diverse mechanisms in cancer. They may control gene expression at any level of epigenetic, transcriptional, or post-transcriptional regulation. Their dysregulation in the cell is a major contribution to carcinogenesis, progression, as well as metastasis of the disease. Many lncRNAs are expressed upregulated in cancer which promote oncogenic processes. In different cancers breast, liver, gastric among others HOTAIR (HOX Transcript Antisense RNA) is one of the highly expressed malignant lncRNAs.HOTAIR mediates metastatic and invasive carcinoma by altering recruitment of chromatin-modifying complexes to gene-specific loci resulting in tumor-suppressor gene silencing [9]. Its overexpression is also associated with a poor prognosis for most cancer patients. Some lncRNAs are underexpressed in cancer and act as tumor suppressors.GAS5 (Growth Arrest Specific 5) was seen as a tumor suppressor lncRNA.GAS5 was able to induce cell cycle arrest and apoptosis in multiple cancer cells. It thereby prevents the receptor from binding to its target genes and inhibiting cell proliferation. Therefore, GAS5 expression is typically lost in a majority of cancers that were reported to progress tumors. A stable circular formation under which they have attracted much attention about their regulation in cancer biology, CircRNAs can be either involved in oncogenesis and tumor suppression as well through several different novel mechanisms. Most identified circRNAs are upregulated relating to cancer; therefore, it facilitates tumorigenesis. For example, in gastric cancer cells, circ_0001649 was found sponged miR-143 to proliferate migration and invasion of these cells hence leading to the upregulation of targeted genes of miR-143., On the other hand, some Operate as tumor suppressors & are downregulated by cancer. _circ_Foxo3is one such Tumor suppressor circRNA It is considered to enhance apoptosis and suppress cell growth as well as metastasis in a variety of cancer types,

including breast cancer. Circ-Foxo3 can bind with proteins such as MDM2 and p53 thereby it can influence their stability and activities which in turn modulate cell cycle and apoptotic pathways [12].

B. Role in Cardiovascular Diseases

Cardiovascular diseases (CVDs) remain one of the principal leading causes of morbidity and mortality worldwide. NcRNAs, in particular miRNAs and lncRNAs are emerging modulators that substantially regulate the cardiac system under normal conditions and in disease pathogenesis of heart failure, myocardial infarction, or atherosclerosis. The miRNAs are involved in the genesis and development of CVD by controlling gene expression programs related to cardiac remodeling, angiogenesis, and inflammation. This miRNA is highly expressed in the heart. It has an influential role in cardiac hypertrophy as well as fibrosis. Its overexpression leads pathological cardiac remodeling to heart failure [13]. The miR-133a is expressed abundantly in both cardiac and skeletal muscle; it is negative regulation regarding cardiac hypertrophy and fibrosis. Commonly downregulated in heart failure restoring this might provide protection against dysfunction of the heart [14]. The lncRNAs got into much more roles actively involved with CVDs ranging from cardiomyocyte survival to vascular functionality plus inflammatory responses. LncRNA is involved in a cardiac outcome and a disease. The H19 lncRNA can absorb miR-196 thereby controlling the differentiation of cardiac progenitor cells and also aids cardiac repair post-injury [15-16].

Recent research has brought circRNAs to the limelight in CVDs. Their stable nature makes them attractive candidates for biomarkers and therapeutic targets. This particular circRNA is found to be upregulated in patients with acute myocardial infarction; it promotes cardiomyocyte apoptosis as well as inflammation, hence contributing to myocardial injury [17]. On the other hand, circRNA_ITCH has been demonstrated to play a protective role in the heart. It sponges miR-7 and miR-214 inhibiting cardiac hypertrophy and fibrosis [18].

C. Role in Neurological Disorders

Neurological disorders are diseases of the nervous system. They include neurodegenerative diseases characterized by progressive loss of neuronal function, such as Alzheimer's disease and Parkinson's disease. NcRNAs which are emerging key regulators in the central nervous system have roles affecting neuronal development and synaptic plasticity as well as neuroinflammation. MiRNAs seem to be very important for normal brain development and function, and their dysregulation appears to associate strongly with neurodegenerative diseases. For example, this miRNA is one of the most abundantly expressed in the mature brain and critical in the regulation of neuronal differentiation and maturation processes. Its dysregulation has been implicated in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [19]. Diseases related to altered synaptic plasticity, neuronal survival, and neuroinflammation show an abnormal expression of miR-132, like Alzheimer's disease.

LncRNAs are emerging as key players in the complex regulatory circuitry of the brain, and their abnormal expression is linked to a host of neurological maladies. For example, an lncRNA is antisense to the BACE1 gene encoding beta-secretase 1, which can enzymatically catalyze Alzheimer's disease. In that lncRNA- BACE1-AS, stabilization of BACE1 mRNA results in increased normal cellular protein levels for BACE1 and amyloid-beta production; hence it contributes to AD [21]. MEG3 (Maternally Expressed Gene 3) is involved in tumor suppression and also expressed in several neurological disorders. Dysregulation has been reported in neuronal apoptosis and neuroinflammation mediated by diseases like cerebral ischemia and AD [22].

The investigation of circRNAs in disease processes involving the nervous system is still nascent; however, data are emerging that will likely implicate them quite substantially. This circRNA has been abundantly expressed in neurons; it sponges multiple miRNAs, including miR-124, which plays a vital role in neuronal function. Dysregulation of circRNA_HIPK3 was proven to cause neuroinflammation and neuronal injury [23]. It contributes to neuronal apoptosis which is involved in neurodegenerative process. It is upregulated within AD models and hence might play a role within the progression of this disease. [24].

C. Role in Other Diseases

Beyond cancer, cardiovascular and neurological disorders, ncRNAs are also involved in many other human diseases. They are imprecisely implicated in conditions as diverse as metabolic disorders (e.g., diabetes), autoimmune diseases (e.g., lupus), infectious

diseases, and developmental disorders. Such a wide-ranging influence on the health and condition of humans makes research into them even more important. The unique properties of ncRNAs—robust stability in biofluids, disease-specific expression, and involvement in pathogenesis—make them one of the most attractive novel diagnostic biomarker candidates to be pursued for new and innovative treatment strategies. One such capability of ncRNAs that has been stably detected in all biofluids known to date—blood, urine, saliva, cerebrospinal fluid—is what has just recently revolutionized the field of liquid biopsies. An absolutely non-invasive approach that would be easily applicable to much earlier detection than is feasible with tissue biopsies; monitoring disease progression; and even monitoring response to treatment. Specific ncRNA patterns can be used to recognize disease initiation at very early time points well before clinical symptoms have manifested. For example, the levels of certain circulating miRNAs such as miR-21 or miR-155 are increased in the initial stages of a wide range of cancers and could therefore be exploited for non-invasive screening approaches. In addition to above, lncRNAs and circRNAs have also demonstrated diagnostic markers' potential for cardiovascular diseases and neurological disorders [25].

The expression of some ncRNAs may be associated with disease aggressiveness and survival as well as the response to therapy. For example, high levels of oncogenic lncRNAs such as HOTAIR are, unfortunately, most of the time related to a poor outcome of the patient; however, reestablishment of tumor suppressori miRNAs can signal that the treatment is going to be favorable. Circulating ncRNA level changes are monitored; hence, it gives one the ability to have real-time information on disease dynamics and personalized medicine approaches [26].

Role of ncRNAs Therapeutic strategies

The vital roles of ncRNAs in the pathogenesis of disease have created avenues for the design of ncRNA-based therapeutic strategies. The strategies involve either the inhibition of pathogenic ncRNAs or the restoration of normal functioning beneficial ncRNAs. These are synthetic RNA oligonucleotides antisense to miRNAs and are designed to inhibit the function of active miRNAs in disease. Restoring antimiRs (miRNA inhibitors) into diseased cells, therefore, reinstates suppressed cellular pathways and inhibits cancer growth. For instance, preclinical studies indicate that miR-34a mimics can be effective in suppressing tumor growth across a spectrum of malignancies [27]. The current ones are chemically modified antisense oligonucleotides whose sequence complementarily nucleotidically binds to excess oncogenic miRNAs thereby inhibiting their functions. Normalizing blocking pathologic miRNA activity under conditions where such miRNA activity is promoting disease could reverse such pathology. Miravirsen, an antagomiR targeting miR-122, was among the pioneer miRNA-based drugs to initiate clinical trials in the treatment of hepatitis C virus infection [28]. The therapeutic strategies oriented toward lncRNAs are still nascent; however, by their diversified mechanisms of action, lncRNAs present a very promising avenue. ASOs could be constructed with sequences complementary to specific lncRNAs and direct them towards degradation or inhibition of their functions. This approach can be exploited for the silencing of oncogenic lncRNAs as well. For instance, ASOs directed against MALAT1 have been proven useful in preclinical models for inhibiting proliferation and metastasis of cancer cells [29]. Gene editing tools such as CRISPR/Cas9 can apply precise alterations within genes coding for lncRNAs or regulatory elements associated with them which may further facilitate rather specific modes of lncRNA expression or function.

Although the potential of ncRNA is enormous, there are several challenges that need to be addressed before it can successfully be translated into clinical applications. Effective and targeted delivery of ncRNA therapeutics to the desired cells or tissues is still perceived as the biggest challenge. Nanoparticle-based systems, viral vectors, and chemical modifications are approaches being assayed to improve stability, bioavailability, and targeted delivery. Because some ncRNAs may have promiscuous roles in biology and unintended interactions could occur, design considerations must minimize these off-target effects for safety as well as efficacy. The development of therapeutic ncRNAs with high specificity for malignant cells will also be an important goal in reducing unexpected toxicities to normal cells [30].

Future trends will push toward even more advanced delivery systems for ncRNA therapeutics, highly selective and efficient modulators, and combination therapies using ncRNA-based strategies together with conventional treatments. As knowledge about biology

continues to grow and technologies related to RNA manipulation advance further, such progress will assuredly catalyze the emergence of novel treatments.

Conclusion

Non-coding RNAs (ncRNAs), once misunderstood, are now known to be key regulators of gene expression and essential for numerous cellular functions. They play vital roles in maintaining health and are deeply involved in the pathogenesis of diseases like cancer, cardiovascular, and neurological disorders. This review outlined the types and mechanisms of ncRNAs—such as miRNAs, lncRNAs, and circRNAs—and emphasized how their dysregulation contributes to disease. With their stability and tissue-specific expression, ncRNAs show strong potential as non-invasive biomarkers and therapeutic targets. Despite current challenges in delivery and specificity, ongoing advances are paving the way for their use in precision medicine.

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