Proceedings of the 3rd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/69/2025.19747

Non-Coding RNAs in Tumor Biology: Exploring miRNAs, lncRNAs, and circRNAs Roles and Therapeutic Potentials

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Abstract: Tumorigenesis and progression are complex process with multifarious molecules and related mechanisms, while most of them are still elusive. Most research into the mechanisms of cancer today are focusing on encoding RNAs. However, for the past few years as the emergence and development of epigenetics, a kind of new molecule: non-coding RNAs (ncRNAs), RNAs without protein-coding function, have gained prominence in recent scientific discussions. Since the first ncRNA was discovered in 1990s, extensive research has shown that ncRNAs significantly influence processes such as cell growth, differentiation, metabolic regulation, and programmed cell death at both transcriptional and post-transcriptional stages. By means of acting as the tumor suppression and oncogenesis, research has identified several ncRNAs with abnormal expression patterns in cancer cells, marking them as primary oncogenic factors or valuable targets in cancer treatment. This review focus on three kinds of ncRNA, MicroRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), the molecule structure, generative mechanism, characteristic function and regulatory mechanism in tumor progression. In addition, we will discuss the application value and future expiration of the therapeutic that are focusing on ncRNA, that will open up a new idea and methods for the treatment of cancer for future investigation.

Keywords: Non-coding RNAs, cancer therapy, miRNA, lncRNA, circRNA

1. Introduction

While just 2% of human genome transcripts are protein-coding, the vast majority produce non-coding RNAs (ncRNAs) [1]. As non-coding RNAs, ncRNAs play essential regulatory roles within cells without encoding proteins. ncRNAs are grouped by size into microRNAs (miRNAs), which are shorter than 200 nucleotides, and long non-coding RNAs (lncRNAs), which extend beyond this threshold. Additionally, a distinct form of ncRNA, circular RNAs (circRNAs) form closed loops without the typical 3' and 5' ends [2].

The recognition of these ncRNA varieties has significantly altered perspectives in cancer biology. Research spanning several decades highlights ncRNAs as key regulators of cellular activities, impacting processes like cell growth, differentiation, apoptosis, and metabolic pathways by altering gene expression and genome structure [3]. Tumorigenesis, which occurs when the genome of normal cells undergoes mutations leading to genetic and epigenetic changes, is a complex process. Studies show that ncRNAs serve dual roles as oncogenic drivers and tumor suppressors in various cancers [4]. For instance, miRNAs may play roles as oncogenes or tumor suppressors by regulating mRNAs

DOI: 10.54254/2753-8818/69/2025.19747

that control the cell cycle, apoptosis, invasion, and tumor metastasis [5]. Through interactions with DNA, RNA, and proteins, lncRNAs modulate gene expression at multiple regulatory levels, thereby playing a role in cancer development [6]. The newly discovered circRNAs also play significant roles by acting as miRNA sponges or directly regulating transcription factors and signaling pathways, and misregulation of these molecules has been noted in numerous cancer cell types [7].

Furthermore, miRNAs, lncRNAs, and circRNAs form a complex regulatory network, interacting with each other and increasing the intricacy of their influence on tumors [8]. For instance, the inhibitory effect of miRNAs on mRNAs can be reduced by lncRNAs or circRNAs, which function as competing endogenous RNAs (ceRNAs) to absorb miRNAs [9]. A specific example of this is the lncRNA MALAT1, which can sponge miR-200c, thereby modulating ZEB1 and ZEB2 expression, two pivotal elements in EMT and cancer spread [10]. Conversely, some miRNAs can also regulate the stability and transcription of lncRNAs. Gaining insights into the diverse roles of ncRNAs in cancer could open new avenues for their application as diagnostic and prognostic markers, and as therapeutic targets.

This review summarizes the current understanding of the functions and molecular mechanisms of miRNA, lncRNA, and circRNA in tumorigenesis and cancer progression, discusses the key issues and challenges in this research field, and highlights some new methods of tumor diagnosis and therapies targeting ncRNA pathways. By elucidating the complex roles of ncRNAs in cancer, we strive to support the creation of effective diagnostic methods and targeted treatments, with the aim of improving outcomes for cancer patients.

2. Theoretical Research on Non-coding RNAs in Cancer

While cancer research has long concentrated on protein-coding genes, recent findings highlight ncRNAs as essential contributors to tumorigenesis and cancer advancement [4]. The exploration of ncRNAs has reshaped our view of cancer biology, exposing a new regulatory dimension that both complements and interacts with protein-coding genes. Uncovering ncRNA mechanisms is key to enhancing our grasp of cancer biology and developing diagnostics and therapies centered around ncRNAs.

2.1. MicroRNAs

The creation of microRNAs (miRNAs) involves several stages, beginning in the nucleus before further processing. Initially, RNA polymerase II (or occasionally RNA polymerase III) transcribes miRNA genes into primary miRNAs (pri-miRNAs). [11]. Pri-miRNAs are processed by the microprocessor complex, which includes DGCR8 and the RNase III enzyme Drosha, into hairpin-structured precursor miRNAs (pre-miRNAs).

After being transported to the cytoplasm through nuclear pore complexes, pre-miRNAs are processed by the RNase III enzyme Dicer into miRNA duplexes of 20-22 nucleotides. Finally, the mature miRNA strand from the duplex is selected and integrated into the RNA-induced silencing complex (RISC). By guiding RISC to specific mRNAs, the mature miRNA activates the complex's inhibitory function [12].

MiRNA expression is frequently dysregulated in tumor cells, and each miRNA has the potential to act as an oncogene or a tumor suppressor. For example, the let-7a3 locus is hypomethylated in lung and ovarian tumors compared to normal tissues, resulting in its upregulation in cancer [13]. Mechanistically, overexpression of let-7e can increase tumor invasiveness and proliferation by targeting ARID3a, which negatively correlates with pluripotency [14].

Interestingly, the let-7 family also demonstrates tumor-suppressive properties, highlighting the complex and context-dependent nature of miRNA function in cancer. Conversely, let-7 exhibits

DOI: 10.54254/2753-8818/69/2025.19747

tumor-suppressing activity by binding to and repressing particular oncogenes. Studies indicate a negative association between let-7 expression and the abundance of cancer stem cells. Under these circumstances, let-7 targets ARID3B and HMGA2, which are transcriptional activators of OCT-4 and SOX2, key regulators of pluripotency [15].

The contrasting roles of let-7 in cancer emphasize the intricate nature of miRNA functions and highlight the importance of additional research to clarify their role in tumor development. This complexity emphasizes the importance of considering cellular context, tissue type, and the broader regulatory network when studying miRNA function in cancer.

2.2. LncRNAs

lncRNAs are non-coding RNAs longer than 200 nucleotides, lacking protein-coding capacity. Similar to miRNAs, lncRNAs have also been discovered to serve as key factors in tumorigenesis. Several lncRNA mutations have been identified as the main factors in human malignancies [16]. The diversity and complexity of lncRNAs, including their varied lengths, structures, and cellular localizations, contribute to their wide range of functions in cancer onset and growth.

According to the location where lncRNAs function, they can be classified into two categories: nuclear lncRNAs and cytoplasmic lncRNAs. Nuclear lncRNAs function inside the nucleus and interact with chromatin, transcription factors, and RNA processing. Their effects can be cis, targeting adjacent chromosomal genes, or trans, engaging with distant genes across chromosomes [17]. Cytoplasmic lncRNAs function outside the nucleus and regulate translation or other cell signaling pathways by correlating with mRNA and signaling molecules [18].

2.2.1. Nuclear lncRNAs

Nuclear lncRNAs function in cis through chromatin modification, DNA methylation, and transcriptional regulation [16]. A representative example is the lncRNA Xist, which can bind to the proximal gene-rich region on the X chromosome and recruit regulatory factors to execute X chromosome inactivation, thus achieving X chromosome dosage balance in female mammals. Xist dysregulation is often associated with malignancies [19]. For instance, in breast cancer, loss of Xist expression has been linked to the reactivation of genes on the inactive X chromosome, contributing to cancer progression and poor prognosis.

Nuclear lncRNAs function in trans by regulating transcription factor recruitment, chromatin modification, and playing a role as a scaffold to assemble regulatory molecules at distant gene loci [16]. For instance, Through the recruitment of PRC2 and the LSD1/CoREST/REST complex, HOTAIR directs methylation at histone H3 lysine 27 and demethylation at lysine 4 at specific chromatin sites. Mechanistically, by linking PRC2 via its 5' domain and the LSD1/CoREST/REST complex through its 3' domain, HOTAIR acts as a scaffold for their chromatin interaction [20].

These mechanisms of nuclear lncRNAs significantly impact gene expression patterns and chromatin states, which are often dysregulated in cancer. The ability of lncRNAs to bind with diverse regulatory complexes and focus on specific genomic sites positions them as significant modulators in cancer, impacting cell growth, metastasis, and resistance to drugs.

2.2.2. Cytoplasmic lncRNAs

Cytoplasmic lncRNAs play multiple roles in post-transcriptional regulation, translation modulation, and signaling pathway regulation. These functions contribute significantly to cancer development and progression by affecting gene expression at various levels.

One key function of cytoplasmic lncRNAs is their interaction with mRNA, which affects post-transcriptional regulation [21]. In the cytoplasm, TINCR associates with Staufen 1 (STAU1) to target

DOI: 10.54254/2753-8818/69/2025.19747

and stabilize mRNAs containing the TINCR box motif. This reveals that lncRNAs can function as recognition molecules for the modulation of mRNA half-life [22]. TINCR dysregulation has been connected to various cancers, including gastric and breast cancer, influencing genes essential for cell growth and differentiation.

In addition, cytoplasmic lncRNAs can modulate the translation process and gene expression by targeting mRNA molecular constitution. Antisense Uchl1 lncRNA features a 5' sequence overlapping with sense mRNA and incorporates a SINEB2 repeat sequence [23]. The 5' antisense region is recognized as a specific binding site that binds to the target mRNA, while the repetitive element is recognized as the activation site that promotes mRNA translation. Once Antisense Uchl1 has matured in the nucleus, it is then transported to the cytoplasm, it binds with the target mRNA and swaps the overlapping sequence, thus facilitating protein encoding [23]. This mechanism demonstrates how lncRNAs can fine-tune protein expression, which is particularly relevant in cancer where precise control of oncogene or tumor suppressor expression is critical.

2.3. CircRNAs

As a novel form of ncRNA, circular RNA (circRNA) lacks a 5' cap and 3' polyadenylated tail, forming a continuous closed loop. While the exact mechanisms behind circRNA biogenesis are still unclear, it has been proven that the circular structure imparts high stability and RNase resistance [24]. Furthermore, the circRNA genome has high conservation during evolution, indicating many significant functions in various species. The stability and tissue-specific expression of circRNAs make them valuable candidates for use as cancer biomarkers and therapeutic targets.

Recently, a vast array of circRNAs, showing distinct cell-type and tissue-specific expression, has been identified through high-throughput sequencing, demonstrating that circRNAs are playing many significant roles in multiple tissues [25]. In cancer, one major role of circRNAs is their function as competing endogenous RNAs (ceRNAs), which adds another layer of complexity to the ncRNA regulatory network.

For instance, as a ceRNA, circRNA can absorb miRNAs and modulate biochemical activities involved in metabolism. The circRNA has_circRNA_001569 can sponge miR-145 and suppress its inhibition function to mRNA E2F5, BAG4 or FMNL2, subsequently facilitating the expansion and invasiveness of colorectal cancer cells [26]. Such a mechanism demonstrates how circRNAs can indirectly regulate gene expression by modulating miRNA activity, which is often dysregulated in cancer. Another example is circHIPK3, which has been found to sponge multiple miRNAs, including miR-124 and miR-558, affecting cell growth in various cancer types such as hepatocellular carcinoma and bladder cancer.

New research has uncovered an unexpected role for some circRNAs: they can produce small peptides sharing amino-acid sequences with corresponding proteins. Such a peptide can act as a decoy to enhance the corresponding protein by releasing them from inhibition and degradation [27]. circRNA circ-SHPRH produces SHPRH-146aa, a peptide aligned with the full-length SHPRH protein, which protects SHPRH from degradation by the ubiquitin-proteasome, lowering PCNA ubiquitination and, consequently, cell growth and tumor potential in glioblastoma [28].

Moreover, the peptide translated by circRNA can also function as an inhibiting factor by reducing the activity of the corresponding protein. The circRNA circ-AKT3 encoded peptide AKT3-174aa can competitively bind with the pyruvate dehydrogenase kinase isozyme 1 (PDK1), which is originally for the phosphorylation of the full-length protein AKT3, resulting in the reduction of the phosphorylation of thr-108 AKT3 and the depression of the signal intensity of PI3K/AKT3 signal pathway [29].

These discoveries of circRNA translation and the functional roles of circRNA-encoded peptides have opened up new avenues for understanding circRNA function in cancer. They suggest that

DOI: 10.54254/2753-8818/69/2025.19747

circRNAs can affect cellular processes not only through RNA-based mechanisms but also through the production of functional peptides. This dual functionality makes circRNAs particularly intriguing targets for cancer research and potential therapeutic interventions.

3. Conclusion

This article has summarized the molecule structure and regulate mechanisms of three types of ncRNAs: miRNAs, lncRNAs, and circRNAs, along with their roles in tumor formation and cell growth. By pairing with target mRNAs, miRNAs can function as tumor suppressors or oncogenes, carrying out either stimulatory or inhibitory roles. lncRNAs have a longer nucleotide chain than miRNA. It can play role both in nucleus by chromatin decoration, DNA methylation and transcription regulation, and in cytoplasmic by post-transcription and translation regulation, signal channel regulation. These actions allow lncRNA to impact the living processions of malignancy in various ways. Previously introduced as a special lncRNA subtype, circRNAs are circular and lack both the 5' cap and 3' polyadenylated tail. They can act as ceRNA to sponge target miRNA and influence these activities. In addition, circRNAs can be translated into peptides and affect other protein functions and stability.

Nowadays investigations have focused on the mechanisms of various ncRNAs. However, there is still a blank field that how these various ncRNA work together and impact tumorigenesis and apoptosis comprehensively. More investigations need to be research in order to elucidate the multiple functions of ncRNA and the utilization of the therapeutic effectiveness.

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