

The Mechanisms of Non-coding RNAs in Tumorigenesis and Cancer Progression

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Abstract. Non-coding RNAs (ncRNAs) represent approximately 98% of the human genome and serve as critical regulators in cancer biology. This comprehensive review examines the multifaceted roles of ncRNAs, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), in orchestrating key oncological processes such as immune system evasion, metastatic progression, and tumor angiogenesis. We analyze their paradoxical functions as both tumor promoters and suppressors, highlighting mechanistic insights from studies of HOTAIR, miR-21, and circRNA_0084043 across diverse malignancies. The review further evaluates their clinical utility as diagnostic biomarkers and therapeutic targets, while critically addressing implementation challenges including delivery limitations, off-target interactions, and regulatory network complexity. We discuss innovative solutions such as bioengineered exosomal delivery platforms and targeted chemical modifications that show promise for clinical translation. This analysis synthesizes current understanding of ncRNA-mediated cancer regulation and outlines strategic directions for therapeutic development.

Keywords: non-coding RNA, cancer, microRNA, lncRNA, tumor microenvironment, ferroptosis, exosomes

1. Introduction

Cancer remains one of the most devastating diseases globally, representing a major threat to human health and survival. According to the World Health Organization's International Agency for Research on Cancer (IARC), millions of new cancer cases are diagnosed annually worldwide, with high mortality rates primarily attributed to tumor metastasis and therapeutic resistance. Traditional cancer treatments, including chemotherapy, surgery, and radiotherapy, have significantly improved patient survival rates; however, their efficacy remains limited due to drug resistance and tumor recurrence. These persistent challenges underscore the urgent need to explore novel therapeutic pathways, particularly focusing on non-coding RNAs as emerging targets for cancer intervention.

Cancer is fundamentally characterized by the uncontrolled proliferation and survival of abnormal cells. Cancer cells can activate oncogenes or inactivate tumor suppressor genes to evade normal growth-suppressive signals, allowing them to bypass inhibitory mechanisms that prevent excessive cell proliferation. Moreover, tumors acquire enhanced mobility through epithelial-mesenchymal transition (EMT), enabling metastatic spread to distant organs [1]. Additionally, tumors promote

angiogenesis by secreting vascular endothelial growth factor (VEGF) to induce blood vessel formation, ensuring adequate nutrient supply for sustained growth.

Standard cancer therapeutics primarily focus on rapidly proliferating cellular populations but face significant limitations due to tumor heterogeneity and adaptive resistance mechanisms. Cytotoxic chemotherapy relies on agents that preferentially target dividing cells, yet this approach lacks precision, potentially affecting healthy proliferating tissues and fostering resistance through selective pressure. Radiation therapy employs high-energy particles to induce DNA damage in malignant cells but may cause collateral damage to adjacent normal tissues. Surgical resection, while effective for localized disease, may be insufficient when microscopic tumor deposits remain undetected, leading to disease recurrence.

In contrast, non-coding RNAs—regulatory molecules that lack protein-coding capacity—present novel opportunities for cancer intervention through their fundamental roles in gene expression control and cellular process regulation [2,3]. These molecules function as master regulators of cancer initiation and progression, operating through sophisticated epigenetic, transcriptional, and post-transcriptional mechanisms. The ncRNA family encompasses diverse subtypes including microRNAs (miRNAs), small interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs), enhancer RNAs (eRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), each possessing distinct regulatory capabilities [2].

Non-coding RNAs have been reported to participate in multiple aspects of tumor biology [3]. They may function as either oncogenes or tumor suppressors, depending on the specific ncRNA type and cellular context. For instance, certain miRNAs act as tumor suppressors by targeting oncogenes, while others function as oncomiRs by targeting tumor suppressor genes. LncRNAs also exert diverse effects on cancer development and metastasis, potentially interacting with chromatin-modifying complexes to alter the epigenetic landscape of cancer cells or binding to transcription factors to regulate cancer-critical gene expression [4]. The involvement of ncRNAs in cancer biology has introduced unprecedented complexity to our understanding of cancer mechanisms while establishing them as promising biomarkers and therapeutic targets.

Research on ncRNAs has profound clinical implications. First, their abnormal expression patterns in tumors and body fluids (such as blood and saliva) make them valuable non-invasive diagnostic and prognostic tools [5]. Second, ncRNAs can serve as therapeutic targets or agents [6,7]. Additionally, combining ncRNA-based approaches with conventional therapies could help overcome drug resistance and enhance treatment efficacy, representing a paradigm shift in cancer therapeutics [8,9].

2. Theoretical background

2.1. Classification and functional mechanisms of non-coding RNAs

The ncRNA landscape encompasses a sophisticated array of regulatory molecules that orchestrate gene expression through diverse mechanisms [2]. Structural and functional characteristics define distinct ncRNA categories. MicroRNAs constitute compact regulatory elements of 20-22 nucleotides that execute post-transcriptional gene silencing through sequence-specific interactions with target messenger RNAs. Long non-coding RNAs, characterized by lengths exceeding 200 nucleotides, demonstrate extraordinary structural complexity and mediate gene regulation through chromatin remodeling, transcriptional modulation, and RNA processing mechanisms. Circular RNAs adopt unique closed-loop conformations via back-splicing processes, conferring remarkable molecular stability and specialized regulatory properties [3].

NcRNA regulatory mechanisms demonstrate remarkable sophistication and diversity. Epigenetic regulation involves ncRNA-mediated recruitment of chromatin-modifying enzymes to specific genomic regions, resulting in histone modifications and DNA methylation alterations that reshape gene expression landscapes. Post-transcriptional regulation represents a major regulatory paradigm wherein ncRNAs influence messenger RNA stability, translational efficiency, and subcellular distribution. The competing endogenous RNA (ceRNA) hypothesis describes complex regulatory networks where ncRNAs function as molecular sponges, sequestering microRNAs and thereby modulating target gene expression in interconnected regulatory circuits.

2.2. Roles of ncRNAs in key tumor biological processes

Non-coding RNAs serve as master orchestrators of fundamental cancer characteristics through sophisticated regulatory networks [3]. Cellular proliferation control involves ncRNA modulation of cell cycle checkpoints and growth signaling cascades. The lncRNA HOTAIR exemplifies this regulation by epigenetically suppressing cell cycle inhibitors, while miR-21 promotes proliferative signaling through targeted suppression of tumor suppressor genes including PTEN and PDCD4. Apoptosis resistance, another cornerstone of malignant behavior, depends on ncRNA-mediated balance between pro-survival and pro-death signaling pathways.

The malignant processes of invasion and metastasis, which account for cancer mortality, are extensively controlled by ncRNA regulatory systems [1]. CircRNA_0084043 demonstrates this regulation by influencing epithelial-mesenchymal transition transcription factors and extracellular matrix degradation enzymes that facilitate tumor cell dissemination. Cancer stem cell characteristics, which contribute to tumor heterogeneity and treatment resistance, are maintained through ncRNA-dependent regulatory networks. Furthermore, metabolic reprogramming—an increasingly recognized cancer hallmark—is directed by ncRNAs that target critical metabolic enzymes and transcriptional regulators controlling glycolytic flux, mitochondrial respiration, and lipid biosynthesis.

3. Current problems and research gaps

3.1. Abnormal expression and unclear mechanisms of ncRNAs in cancer

Contemporary ncRNA research faces significant gaps in mechanistic understanding despite substantial investigative progress. Current studies lack comprehensive integration of multi-layered regulatory networks, particularly regarding inter-ncRNA communication patterns and their collective influence on malignant progression. The temporal dynamics and spatial distribution patterns of ncRNA expression throughout cancer evolution remain inadequately characterized, constraining our capacity to predict therapeutic responses and develop precision oncology strategies.

Representative examples demonstrate these mechanistic gaps. The lncRNA HOTAIR, originally characterized as a breast cancer oncogene, exhibits context-dependent functionality across different malignancy types, with regulatory mechanisms varying substantially between primary lesions and metastatic sites [4]. Similarly, miR-21, among the most extensively studied oncogenic microRNAs, displays tissue-specific targeting preferences and regulatory networks that remain incompletely mapped. CircRNA_0084043 represents an emerging regulatory element with significant therapeutic promise, yet its complete interactome and downstream effector cascades require comprehensive elucidation [10].

The heterogeneity of ncRNA expression within individual tumors presents additional challenges. Single-cell RNA sequencing studies have revealed remarkable cell-to-cell variability in ncRNA expression, suggesting that bulk tumor analyses may mask critical regulatory mechanisms operative in specific cellular subpopulations. Furthermore, the influence of tumor microenvironment factors, including immune cell infiltration, hypoxia, and metabolic stress, on ncRNA expression patterns remains poorly understood.

3.2. Limitations of ncRNA-based cancer therapeutics

Clinical translation of ncRNA research encounters substantial implementation barriers that restrict widespread therapeutic adoption. Delivery challenges constitute the primary obstacle, as ncRNAs must navigate multiple biological barriers including enzymatic degradation, immune surveillance, and cellular internalization limitations. Existing delivery platforms, while showing promise, frequently exhibit inadequate tissue selectivity, restricted cellular penetration capacity, and potential safety concerns.

Molecular stability issues compound therapeutic development challenges. Many ncRNAs demonstrate inherent instability in physiological environments, necessitating chemical modifications or protective delivery vehicles that may compromise their biological functionality. Developing chemically modified ncRNAs with enhanced stability while preserving regulatory activity requires sophisticated medicinal chemistry approaches that significantly extend development timelines.

Specificity challenges emerge from the complex regulatory networks mediated by ncRNAs. Unintended interactions with off-target molecules can occur when therapeutic ncRNAs engage with unintended binding partners, potentially causing adverse clinical consequences. Predicting and preventing such off-target effects demands comprehensive computational modeling and extensive preclinical validation that substantially increases development costs and regulatory complexity.

4. Problem-solving methodologies and technological advances

4.1. Advanced techniques for ncRNA functional analysis

Contemporary technological innovations have transformed our capabilities for investigating ncRNA functions and mechanisms. RNA sequencing methodologies, particularly single-cell RNA sequencing approaches, facilitate comprehensive characterization of ncRNA expression profiles with exceptional resolution [5]. These technological advances have uncovered previously unrecognized ncRNA diversity and provided insights into cell-type-specific regulatory architectures. Chromatin immunoprecipitation coupled with sequencing enables direct characterization of ncRNA-chromatin associations, illuminating epigenetic regulatory mechanisms.

CRISPR-based methodologies have emerged as transformative tools for ncRNA functional investigation. CRISPR interference (CRISPRi) and CRISPR activation (CRISPRa) platforms enable precise ncRNA expression modulation without permanent genomic alterations. These approaches prove particularly valuable for investigating lncRNAs and circRNAs, whose functions often resist assessment through conventional knockout strategies.

Cross-linking and immunoprecipitation (CLIP) methodologies, including PAR-CLIP and eCLIP variants, generate comprehensive maps of RNA-protein associations, elucidating molecular mechanisms underlying ncRNA regulatory activities. These techniques have proven instrumental in identifying RNA-binding proteins that mediate ncRNA functions and characterizing the dynamic properties of ribonucleoprotein assemblies.

4.2. Innovative delivery systems for ncRNA therapeutics

Sophisticated delivery system development has addressed numerous limitations associated with ncRNA-based therapeutics. Bioengineered exosomes represent a particularly promising strategy, providing multiple advantages compared to synthetic delivery platforms [6,7]. These naturally derived extracellular vesicles demonstrate capacity to traverse biological barriers, including the blood-brain barrier, while maintaining biocompatibility and minimizing immunogenic responses. Contemporary studies have established successful therapeutic miRNA and siRNA delivery using engineered exosomes, demonstrating encouraging outcomes in preclinical cancer models [11].

Lipid nanoparticle (LNP) systems have developed as versatile platforms for ncRNA therapeutic delivery. Advanced LNP formulations incorporate targeting moieties, pH-responsive elements, and biodegradable components to optimize delivery efficiency while minimizing off-target effects. The successful clinical implementation of siRNA therapeutics utilizing LNP delivery systems establishes a precedent for additional ncRNA-based therapeutic modalities.

Chemical modifications of ncRNAs have substantially enhanced their therapeutic potential. Modifications including 2'-O-methyl, 2'-fluoro, and phosphorothioate substitutions improve nuclease resistance while maintaining biological activity. Advanced modification approaches, including bridged nucleic acids (BNAs) and peptide nucleic acids (PNAs), provide additional improvements in stability and targeting specificity.

4.3. Preclinical and clinical translation examples

Multiple ncRNA-based therapeutic approaches have progressed to clinical evaluation, demonstrating the feasibility of translating fundamental research discoveries into potential treatments. Anti-miRNA therapeutics targeting miR-122 in hepatitis C virus infection have achieved clinical efficacy, validating the therapeutic potential of miRNA modulation strategies. Similarly, siRNA therapeutics for hereditary transthyretin amyloidosis have obtained FDA approval, establishing regulatory precedent for RNA-based pharmaceutical interventions.

In oncology, numerous ncRNA-targeted therapeutic approaches are under active development. Preclinical animal studies have demonstrated tumor growth suppression and metastasis inhibition following treatment with anti-miR-21 oligonucleotides delivered through engineered exosomal systems [12]. LncRNA-targeting approaches utilizing antisense oligonucleotides have demonstrated promising efficacy in preclinical models of diverse cancer types, including prostate carcinoma and acute myeloid leukemia [13].

The integration of ncRNA biomarkers with therapeutic interventions represents an emerging paradigm in precision cancer medicine. Circulating miRNA profiles are being developed as companion diagnostics to guide treatment selection and monitor therapeutic responses. These approaches promise to personalize cancer treatment based on individual ncRNA expression patterns and predicted therapeutic vulnerabilities.

5. Future perspectives and clinical applications

5.1. Emerging therapeutic strategies

The future trajectory of ncRNA-based cancer therapeutics centers on developing combination strategies that simultaneously target multiple pathways. Contemporary studies have established synergistic effects when integrating ncRNA therapeutics with conventional treatments including

chemotherapy and radiation therapy. For instance, miR-34a replacement therapy combined with standard chemotherapy has demonstrated enhanced tumor suppression compared to monotherapy approaches.

The evolving relationship between ncRNAs and ferroptosis, a recently characterized form of regulated cell death, creates novel therapeutic opportunities [8,9]. Ferroptosis-related circRNAs have demonstrated regulatory roles in tumor metastasis through intricate mechanisms involving iron homeostasis and lipid peroxidation [1]. CircRNAs such as circRNA_0084043 can modulate ferroptosis susceptibility in cancer cells, potentially circumventing resistance to conventional apoptosis-inducing therapies [4,14].

Immunotherapy combinations represent another promising therapeutic frontier. NcRNAs regulate diverse aspects of immune function, including T cell activation, immune checkpoint expression, and tumor antigen presentation [15]. Therapeutic modulation of immune-regulatory ncRNAs could enhance the efficacy of immune checkpoint inhibitors and adoptive cell therapies.

5.2. Technological integration and precision medicine

The integration of artificial intelligence and machine learning approaches is accelerating ncRNA research and therapeutic development. Computational algorithms can now predict ncRNA-target interactions, identify potential off-target effects, and design optimized therapeutic sequences. These tools are particularly valuable for lncRNA and circRNA research, where experimental validation of all potential interactions is practically impossible.

Single-cell technologies are revealing unprecedented insights into ncRNA functions in cancer. Single-cell RNA sequencing studies have identified cancer cell subpopulations with distinct ncRNA expression profiles that correlate with treatment resistance and metastatic potential. These findings suggest that ncRNA-based therapies may need to target multiple cell populations within tumors to achieve optimal therapeutic outcomes.

The development of real-time monitoring systems for ncRNA expression and activity will enable dynamic treatment adjustments based on therapeutic responses. Liquid biopsy approaches using circulating ncRNAs are being developed as minimally invasive methods to monitor treatment efficacy and detect early signs of resistance or recurrence.

5.3. Regulatory and clinical implementation challenges

The clinical translation of ncRNA therapeutics faces unique regulatory challenges that require careful consideration. Regulatory agencies are developing specific guidelines for RNA-based medicines, addressing issues such as manufacturing standards, quality control measures, and safety assessment protocols. The establishment of standardized analytical methods for ncRNA characterization and quantification is essential for regulatory approval processes.

Manufacturing scalability represents a significant challenge for complex ncRNA therapeutics, particularly those involving engineered exosomes or sophisticated delivery systems. The development of robust, cost-effective production methods is crucial for widespread clinical implementation. Academic-industry partnerships are fostering innovation in manufacturing technologies and accelerating the translation of promising research findings.

Patient stratification based on ncRNA profiles requires the development of companion diagnostic tests that can reliably predict therapeutic responses. The validation of these biomarkers in large clinical cohorts is essential for regulatory approval and clinical adoption. Collaborative efforts

between researchers, clinicians, and regulatory agencies are necessary to establish appropriate validation standards and implementation guidelines.

6. Conclusion

Non-coding RNAs represent a paradigm shift in our understanding of cancer biology and therapeutic intervention. Their diverse regulatory mechanisms, spanning epigenetic modifications, transcriptional control, and post-transcriptional regulation, position them as central orchestrators of cancer hallmarks. The documented roles of specific ncRNAs such as HOTAIR, miR-21, and circRNA_0084043 across multiple cancer types demonstrate both the complexity and therapeutic potential of these molecules.

The emergence of ncRNAs as promising biomarkers for early diagnosis and prognosis prediction offers opportunities for improving cancer detection and patient stratification. Their stability in biological fluids and tissue-specific expression patterns make them ideal candidates for non-invasive diagnostic applications. Furthermore, the potential for ncRNAs to serve as therapeutic targets or agents provides novel avenues for cancer treatment, particularly in combination with existing therapies.

However, significant challenges remain in translating ncRNA research into clinical applications. Off-target effects, delivery obstacles, and complex regulatory networks continue to limit the widespread clinical implementation of ncRNA-based therapeutics. Future research priorities should focus on developing advanced delivery systems, including engineered exosomes and chemically modified ncRNAs, while improving our understanding of ncRNA regulatory networks through systems biology approaches.

The integration of emerging technologies, including single-cell RNA sequencing, CRISPR-based functional screens, and artificial intelligence-driven target prediction, will accelerate the discovery and validation of ncRNA therapeutic targets. The convergence of ncRNA biology with other emerging fields, such as ferroptosis and immunotherapy, opens new frontiers for cancer treatment.

Success in ncRNA-based cancer therapeutics will require continued collaboration between basic researchers, clinicians, pharmaceutical companies, and regulatory agencies. The establishment of standardized protocols for ncRNA analysis, therapeutic development, and clinical validation will be essential for advancing the field. As our understanding of ncRNA mechanisms continues to evolve, these molecules hold tremendous promise for revolutionizing cancer diagnosis, prognosis, and treatment, ultimately improving outcomes for cancer patients worldwide.

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