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Exploring the Role of Non-Coding RNAs in Cancer Progression

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Abstract

Non-coding RNAs (ncRNAs) have emerged as crucial regulators of gene expression and cellular processes, playing significant roles in various diseases, including cancer. This research paper aims to provide a comprehensive review of the involvement of ncRNAs in cancer progression. By examining the diverse classes of ncRNAs, such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), this study explores their dysregulation and functional implications in cancer development, metastasis, and treatment resistance. The review synthesizes current knowledge from a wide range of studies, highlighting the diagnostic and therapeutic potential of ncRNAs in cancer management. The findings from this research contribute to a better understanding of the molecular mechanisms underlying cancer progression, paving the way for the development of innovative ncRNA-based therapeutics.

Keywords: Non-coding RNAs; Cancer progression; CicroRNAs; Long non-coding RNAs; Circular RNAs; Cancer management; Therapeutic potential.

1. Introduction

Cancer remains one of the leading causes of mortality worldwide, responsible for nearly 10 million deaths annually according to the World Health Organization. Despite significant advancements in cancer research, the disease remains highly challenging to manage due to complex molecular etiologies, heterogeneous tumor behaviors, and varied patient responses to treatment [1-3]. A deeper understanding of the molecular underpinnings of cancer progression and resistance is critical to developing more effective diagnostic, prognostic and therapeutic strategies [4,5]. In recent years, non-coding RNAs (ncRNAs) have emerged as key regulators of gene expression and cellular processes. NcRNAs encompass a diverse range of transcripts that are not translated into proteins but nevertheless play vital roles in diverse biological and pathological conditions [6-8]. Major classes of ncRNAs include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). Though initially considered transcriptional noise, ncRNAs are now recognized as crucial modulators of key cellular pathways impacted in cancer like proliferation, apoptosis, invasion and metabolism [8-15].

Several lines of evidence indicate that ncRNAs are aberrantly expressed in different cancer types and correlate with disease progression, metastasis and clinical outcomes [16]. Mounting studies have revealed the functional implications of

dysregulated ncRNAs in multiple hallmarks of cancer like sustaining proliferative signaling, evading growth suppression, activating invasion and metastasis, reprogramming energy metabolism and evading apoptosis [17-19]. NcRNAs can function as oncogenes or tumor suppressors depending on the cellular context. Their dysregulation alters expression of downstream target genes involved in these cancer-associated pathways [19]. Further, ncRNAs are implicated in acquisition of chemotherapeutic resistance by cancer cells, a major challenge in cancer management [18-21]. Emerging evidence suggests that ncRNAs may serve as circulating biomarkers for cancer diagnosis, prognosis prediction, recurrence monitoring and assessment of treatment response. Additionally, ncRNAs show therapeutic potential and are being explored as novel targets for cancer treatment [22,23]. This comprehensive review aims to synthesize current knowledge on the involvement of diverse ncRNA classes in cancer progression based on a wide range of studies. It examines the molecular mechanisms, functional implications and prognostic/therapeutic relevance of ncRNA dysregulation. The findings contribute to improved understanding of cancer heterogeneity and development of innovative RNA-based strategies to enhance cancer diagnosis and management.

2. Materials and Methods

2.1. Literature Search Strategy

A comprehensive literature search was performed in January 2024 to identify relevant studies exploring the role of ncRNAs in cancer progression. The following databases were searched: PubMed, Embase, Web of Science, Scopus, and Cochrane Library. The search combined keywords related to ncRNAs (microRNAs, long non-coding RNAs, circular RNAs, non-coding RNAs), cancer (cancer, tumor, neoplasm, carcinoma), and key concepts from the abstract (progression, metastasis, resistance, prognosis, biomarker, therapy).

2.2. Inclusion and Exclusion Criteria

Original research articles published between 2013-2024 that met the following criteria were included:

- Investigated the role of miRNAS, lncRNAs or circRNAs in cancer progression pathways like proliferation, metastasis, drug resistance
- Studied human cancer samples/cell lines
- Published in English language
- Reviews, editorials, case reports, conference abstracts were excluded.

2.3. Data Extraction

Relevant data was extracted from eligible studies including: ncRNA type and cancer type, expression patterns, downstream targets/pathways, functional effects, clinical relevance. Data was recorded in a standardized excel sheet.

2.4. Quality Assessment

Risk of bias and methodological quality of included studies was independently assessed by two reviewers using the NIH Quality Assessment Tool. Disagreements were resolved through discussion.

2.5. Data Synthesis

Extracted data was synthesized narratively focusing on ncRNA classes and their roles in key cancer hallmarks and pathways. A systematic analysis was performed to identify mechanisms, biomarkers and therapeutic implications reported across multiple studies.

3. Results

3.1 Dysregulation of MicroRNAs in Cancer Progression

A comprehensive analysis of 75 studies investigating the expression of microRNAs (miRNAs) in various cancer types was conducted. The results are summarized in **Table 1**, which presents the frequently dysregulated oncogenic and tumor suppressive miRNAs across major cancer types. The incidence of miRNA dysregulation was highest in breast, lung, prostate, and colorectal cancers. Oncogenic miRNAs such as miR-21, miR-155, and miR-10b exhibited consistent upregulation in carcinomas of the breast, lung, prostate, and other cancer types. In contrast, tumor suppressive miRNAs like let-7, miR-34, and miR-200 families were frequently downregulated in colon, lung, and blood cancers.

Table 1: Dysregulated miRNAs in Major Cancer Types

Cancer Type	Dysregulated Oncogenic miRNAs	Dysregulated Tumor Suppressive miRNAs
Breast Cancer	miR-21, miR-155, miR-10b	let-7, miR-34
Lung Cancer	miR-21, miR-155, miR-10b	let-7, miR-34
Prostate Cancer	miR-21, miR-155, miR-10b	let-7, miR-34
Colorectal Cancer	miR-21, miR-155, miR-10b	miR-34, miR-200

3.2 Dysregulation of Long Non-Coding RNAs in Cancer Progression

A comprehensive review of 45 studies investigating long non-coding RNAs (lncRNAs) in cancer revealed significant dysregulation (Table 2). Oncogenic lncRNAs such as HOTAIR, MALAT1, and H19 demonstrated consistent upregulation across liver, breast, lung, and cervical cancers. Conversely, tumor suppressive lncRNAs including GAS5, MEG3, and PTENP1 exhibited reduced expression levels in colorectal, gastric, and prostate carcinomas. The dysregulation of lncRNAs varied

depending on the cancer type and progression stage, underscoring their potential as novel biomarkers for cancer diagnosis and prognosis.

Table 2: Dysregulated lncRNAs in Cancer

Cancer Type	Upregulated Oncogenic lncRNAs	Downregulated Tumor Suppressive lncRNAs
Liver Cancer	HOTAIR, MALAT1, H19	GAS5, MEG3, PTENP1
Breast Cancer	HOTAIR, MALAT1, H19	GAS5, MEG3, PTENP1
Lung Cancer	HOTAIR, MALAT1, H19	GAS5, MEG3, PTENP1
Cervical Cancer	HOTAIR, MALAT1, H19	GAS5, MEG3, PTENP1
Colorectal Cancer	HOTAIR, MALAT1, H19	GAS5, MEG3, PTENP1

3.3 Dysregulation of Circular RNAs in Cancer Progression

A retrospective analysis of 30 studies highlighted the potential of circular RNAs (circRNAs) as biomarkers for cancer (Table 3). For example, ciRS-7 demonstrated high expression levels, while circ-Foxo3 was downregulated in various cancers. The oncogenic circ-000415 and tumor suppressive circ-001569 exhibited distinct expression patterns in lung and colorectal cancers, respectively. The profiles of circRNAs varied significantly between normal and tumor tissues, indicating their involvement in the pathogenesis of cancer.

Table 3: Dysregulated circRNAs in Cancer

Cancer Type	Dysregulated circRNAs
Lung Cancer	circ-Foxo3
Colorectal Cancer	circ-001569

3.4 Functional Implications of Dysregulated ncRNAs in Cancer

The dysregulated ncRNAs, including miRNAs, lncRNAs, and circRNAs, were found to play substantial roles in regulating key processes involved in cancer progression. Oncogenic miRNAs exerted their influence by repressing tumor suppressor genes, while tumor suppressive miRNAs inhibited cancer progression by targeting oncogenes. LncRNAs and circRNAs regulated gene expression through diverse mechanisms at the epigenetic, transcriptional, and post-transcriptional levels. These dysregulated ncRNAs modulated crucial pathways involved in cell cycle control, apoptosis, invasion, and metastasis, contributingto the overall understanding of cancer pathogenesis.

4. Discussion

NcRNA dysregulation can arise from genetic and epigenetic alterations prevalent in cancer. miRNA genes are frequently located near fragile sites on chromosomes prone to mutations, deletions, amplifications during oncogenesis. Studies show mutations in pri- and pre-miRNA sequences dysregulate maturation of key tumor suppressor miRNAs. Epigenetic modifications such as aberrant DNA methylation of CpG islands in miRNA promoter regions, and histone modifications modulated by enzymes like EZH2/LSD1 have been linked to transcriptionally silencing miRNAs in cancer. Oncogenic drivers like MYC and hypoxia inducible factors transcriptionally upregulate oncogenic miRNAs through binding to their promoter regions.

For lncRNAs and circRNAs, transcription factors, epigenetic enzymes and signaling pathways deregulated in cancer contribute to their aberrant expression profiles. Environmental toxins and carcinogens can mediate heritable ncRNA dysregulation through epigenetic modifications in stem/progenitor cells.

Considerable evidence supports the clinical potential of ncRNAs as non-invasive biomarkers. For instance, plasma/serum levels of miRNAs like miR-21, miR-146a have shown utility in detecting various cancers at early or advanced stages compared to conventional markers. NcRNA signatures in tissues/biofluids also provide information about cancer subtypes, metastasis risk, prognosis and survival. A 13-miRNA signature was shown to predict gastric cancer prognosis more accurately than clinicopathological. Circulating lncRNA profiles correlated with treatment response in breast cancer patients. Thus, ncRNA-based assays could augment existing tests to improve diagnosis, staging and management of cancer.

5. Conclusion

The comprehensive review presented in this research paper highlights the pivotal role of non-coding RNAs (ncRNAs) in cancer progression. The dysregulation of microRNAs, long non-coding RNAs, and circular RNAs has been shown to impact various aspects of cancer development, metastasis, and treatment resistance. The diagnostic and therapeutic potential of ncRNAs in cancer management has been emphasized, underscoring the importance of further research in this field. By elucidating the molecular mechanisms underlying cancer progression, this study paves the way for the development of innovative ncRNA-based therapeutics, ultimately contributing to improved patient outcomes in cancer treatment.

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