Noncoding RNA in Non-Small Cell Lung Cancer: A Survey

Abstract

Noncoding RNAs (ncRNAs), including long noncoding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs), have emerged as pivotal regulators in cancer biology, particularly in non-small cell lung cancer (NSCLC). This survey paper explores the multifaceted roles of ncRNAs in the epigenetic regulation and metabolic reprogramming of NSCLC within the tumor microenvironment, highlighting their potential as therapeutic targets. The paper delves into the mechanisms by which ncRNAs influence gene expression through DNA methylation, histone modifications, and chromatin remodeling, emphasizing their impact on oncogenes and tumor suppressor genes. Furthermore, it examines the metabolic adaptations in NSCLC, driven by ncRNAs, which support cancer cell survival and proliferation under nutrient-deprived conditions. The interaction of ncRNAs with immune and stromal components of the tumor microenvironment is scrutinized, revealing their role in modulating immune responses and therapy resistance. The survey also discusses the current advancements in RNA therapeutics targeting ncRNAs, including innovative delivery systems and the challenges faced in clinical applications. By integrating ncRNAs into network medicine, the paper enhances the understanding of disease interactions, setting the stage for innovative RNA-based therapeutic approaches in NSCLC. This comprehensive analysis underscores the significance of ncRNAs in cancer pathogenesis and their potential in advancing NSCLC treatment strategies, paving the way for future research opportunities in this dynamic field.

1 Introduction

1.1 Significance of ncRNAs in Cancer Biology

Noncoding RNAs (ncRNAs), previously considered 'junk' RNA, are now recognized as vital regulators in cancer biology, significantly influencing oncogenesis and various cellular processes [1, 2]. This category includes long noncoding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs), each contributing uniquely to gene regulation and cellular homeostasis [3]. Despite the absence of evolutionary constraints, ncRNAs exhibit a remarkable capacity for inter-RNA binding, akin to artificial neural networks.

LncRNAs play multifaceted roles in gene regulation, affecting chromatin remodeling, histone modification, and nuclear organization, which are crucial for cellular differentiation and oncogenic transformation. CircRNAs have emerged as significant players in human cancers, presenting opportunities as biomarkers and therapeutic targets due to their distinct molecular functions and biosynthesis pathways. The complex networks formed by ncRNAs, such as competing endogenous RNA (ceRNA) networks, are essential for maintaining gene expression homeostasis and are implicated in tumorigenesis and cancer progression [4].

The therapeutic potential of targeting ncRNAs is gaining attention, with ongoing research addressing the challenges and promises of such strategies in chronic diseases, particularly cancer [5]. As our understanding of ncRNAs evolves, their roles in disease progression and potential as biomarkers and

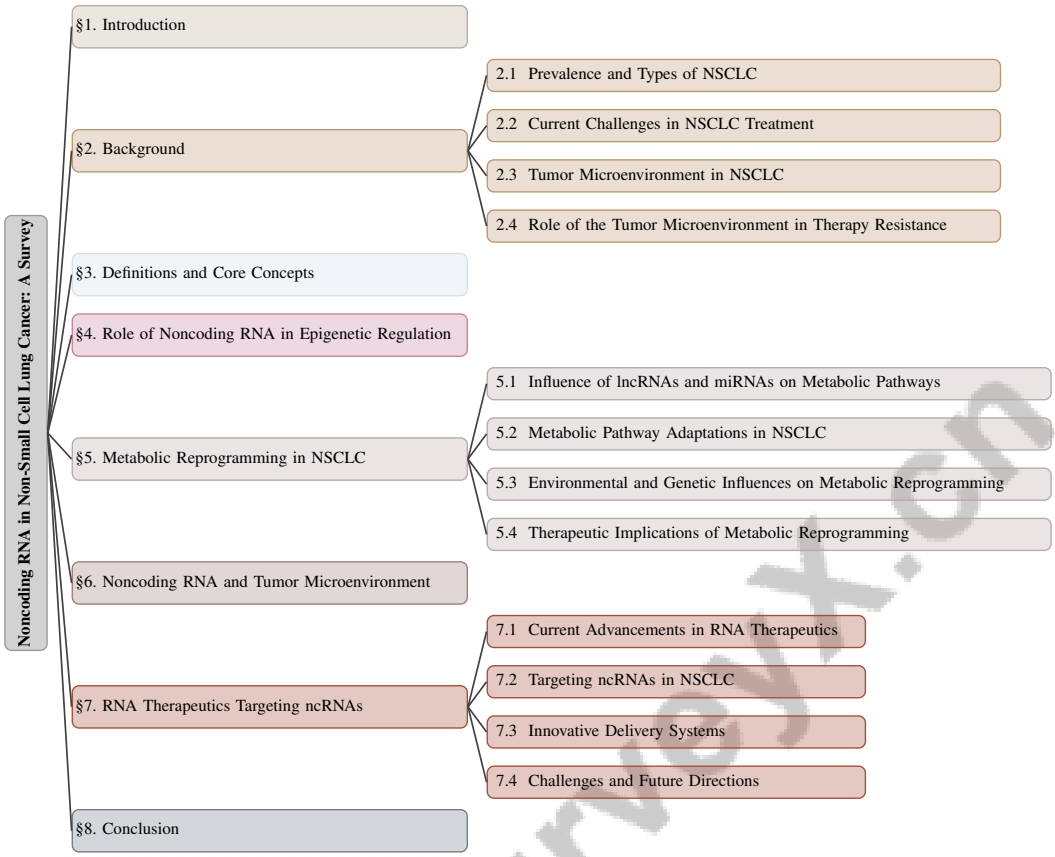

Figure 1: chapter structure

therapeutic targets become increasingly significant, particularly in the context of non-small cell lung cancer (NSCLC).

1.2 Focus on Non-Small Cell Lung Cancer (NSCLC)

Non-small cell lung cancer (NSCLC) constitutes approximately 85% of lung cancer cases, primarily categorized into lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC), each with distinct molecular and clinical characteristics [6]. The complexity and heterogeneity of NSCLC pose significant treatment challenges, necessitating a deeper understanding of its molecular mechanisms.

The investigation of ncRNAs in NSCLC is critical due to their regulatory roles in tumorigenesis. NcRNAs, particularly lncRNAs and miRNAs, are pivotal in modulating gene expression and are involved in various cancer-related pathways. Their interactions, especially between lncRNAs and miRNAs, can be systematically analyzed using genome-scale datasets to construct comprehensive regulatory networks, yielding insights into their functions in NSCLC [7]. CircRNAs have also been identified as key players in lung cancer, underscoring their potential as biomarkers and therapeutic targets [8].

Epigenetic modifications are another crucial area of study in NSCLC, significantly contributing to cancer development and progression [9]. These modifications are closely linked with ncRNA-mediated regulatory mechanisms, highlighting the importance of exploring ncRNA interactions within the epigenetic landscape of NSCLC. Understanding these interactions is vital, as the genotype-phenotype map imposes constraints on accessible phenotypes relevant to ncRNA studies [10].

Integrating ncRNA interactions into predictive models is essential for advancing our understanding of NSCLC mechanisms [11]. Such approaches can enhance targeted therapies' precision, crucial for improving patient outcomes in NSCLC [12]. As research continues to elucidate the multifaceted roles of ncRNAs in NSCLC, their centrality to both pathogenesis and potential treatment becomes increasingly evident.

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1.3 Scope of the Paper

This survey comprehensively examines the roles of noncoding RNAs (ncRNAs) in non-small cell lung cancer (NSCLC), emphasizing their involvement in epigenetic regulation and metabolic reprogramming within the tumor microenvironment. It encompasses various subclasses of ncRNAs, specifically microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs), all of which are integral to cancer pathogenesis. Recent findings indicate that ncRNAs participate in diverse regulatory mechanisms, including competing endogenous RNA (ceRNA) networks, which influence gene expression and contribute to tumor development and progression. Additionally, the differential expression profiles of circRNAs in multiple cancers, such as liver, gastric, lung, and colorectal cancers, highlight their potential as biomarkers and therapeutic targets, offering promising avenues for enhancing cancer diagnosis and treatment outcomes [8, 4, 13]. The survey explores the intricate mechanisms through which lncRNAs regulate gene expression, particularly in the nucleus, via interactions with chromatin and other molecular entities, influencing processes like DNA methylation and histone modifications.

Furthermore, the paper investigates the structural and functional characteristics of circRNAs, focusing on their biosynthesis and molecular functions while excluding non-circular RNA mechanisms [13]. It also addresses the potential of RNA-based therapeutics, discussing the challenges and opportunities in targeting ncRNAs for NSCLC treatment. By integrating ncRNAs into network medicine, the survey enhances the understanding of disease interactions, vital for advancing therapeutic strategies [3]. This focused analysis aims to elucidate the dynamic interplay between ncRNAs and the tumor microenvironment, which contributes to disease progression and therapeutic resistance, thereby paving the way for innovative RNA-based therapeutic approaches in NSCLC.

1.4 Structure of the Survey

This survey is systematically organized to thoroughly explore noncoding RNAs (ncRNAs) in the context of non-small cell lung cancer (NSCLC). The paper begins with an introduction that establishes the significance of ncRNAs in cancer biology, specifically focusing on NSCLC. The background section provides an overview of NSCLC, discussing its prevalence, types, and the challenges faced in current treatment paradigms while highlighting the tumor microenvironment's role in therapy resistance.

Subsequently, the survey clarifies key terms such as noncoding RNA, metabolic reprogramming, epigenetic regulation, and tumor microenvironment, which are essential for the foundational understanding necessary for later discussions. The next section examines the role of ncRNAs in epigenetic regulation, exploring mechanisms like DNA methylation, histone modification, and chromatin remodeling, categorizing lncRNAs based on their interactions with chromatin and RNA-binding proteins [14].

Further, the survey investigates metabolic reprogramming in NSCLC, detailing how ncRNAs influence metabolic pathways, including glycolysis and lipid metabolism, while analyzing the environmental and genetic factors contributing to these alterations. The interactions between ncRNAs and the tumor microenvironment are scrutinized, focusing on immune modulation, angiogenesis, and stromal interactions, alongside categorizing circRNAs based on their roles as miRNA sponges [8].

The subsequent section elaborates on the potential of RNA therapeutics targeting ncRNAs in NSCLC, highlighting recent advancements in therapeutic strategies, innovative delivery systems to enhance efficacy, and significant challenges in clinical applications, such as specificity, tolerability, and overcoming cellular barriers to effective RNA delivery. This discussion is framed within the evolving landscape of targeted therapies in NSCLC, emphasizing precision medicine's importance and integrating novel RNA-based approaches in cancer treatment [15, 16, 17, 18, 5]. The survey concludes with a synthesis of key findings, underscoring ncRNAs' potential as therapeutic targets and biomarkers while suggesting future research directions to further enhance understanding and treatment of NSCLC.The following sections are organized as shown in Figure 1.

2 Background

2.1 Prevalence and Types of NSCLC

Non-small cell lung cancer (NSCLC) constitutes around 85% of all lung cancer cases and is categorized into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, each with unique genetic and clinical features [6]. Adenocarcinoma, prevalent among non-smokers, is marked by glandular differentiation, whereas squamous cell carcinoma, linked to smoking, is characterized by keratinization. Large cell carcinoma, identified by exclusion, lacks specific features. The complexity of NSCLC is compounded by the involvement of noncoding RNAs (ncRNAs) like lncRNAs, miRNAs, and circRNAs in gene regulation and oncogenic pathways [1]. Despite advancements in targeted therapies, the unclear classification and experimental challenges of lncRNAs, due to their low abundance and specificity, present hurdles in treatment [19]. Understanding NSCLC's molecular diversity is crucial for improving therapeutic strategies and patient outcomes [12].

2.2 Current Challenges in NSCLC Treatment

NSCLC treatment is challenged by its complexity and heterogeneity, particularly due to the metabolic interactions between cancer-associated fibroblasts and cancer cells, which complicate therapeutic implications [20]. The vast genetic landscape of ncRNAs further complicates their role in NSCLC [10]. The dual role of ncRNAs, acting as oncogenes or tumor suppressors depending on context, necessitates a nuanced understanding of their functions [1]. Additionally, the complexity of ncRNA networks and challenges in RNA-based therapeutic delivery to target tissues are significant obstacles [5]. The heterogeneity of lncRNAs and limited understanding of circRNA mechanisms further complicate treatment [21, 2]. Drug resistance remains a critical issue, requiring insights into underlying mechanisms and effective combination therapies [17]. Innovative approaches leveraging ncRNAs are essential to advance NSCLC therapeutic strategies.

2.3 Tumor Microenvironment in NSCLC

The tumor microenvironment (TME) in NSCLC comprises diverse cellular and non-cellular components, including immune cells, stromal cells, and the extracellular matrix, all crucial for tumor progression and therapy resistance [22]. The TME influences molecular events that contribute to adaptive resistance, posing challenges for effective treatment [23]. Complex interactions between TME components and cancer cells promote metastasis and affect therapy efficacy. Lactate metabolism, a key aspect of the TME, acts as a signaling molecule in immune evasion and angiogenesis, affecting gene expression through lactylation [24]. Targeting pathways within the TME, such as EGFR and PI3K/AKT/mTOR, is vital for enhancing targeted therapy efficacy and overcoming resistance [17]. Understanding the TME's role is essential for developing innovative NSCLC therapies.

2.4 Role of the Tumor Microenvironment in Therapy Resistance

The TME significantly contributes to therapy resistance in NSCLC, complicating treatment [25]. Interactions between tumor and stromal cells within the TME modulate cancer behavior and treatment responses [26]. The TME supports immune evasion and tumor growth through intricate cellular interactions, exacerbating resistance [27]. Current methods often fail to adequately analyze immune and stromal contributions within the TME, leading to suboptimal strategies [22]. The TME's adaptive mechanisms enable cancer cells to evade therapies [23]. Challenges in targeting the TME include the high degradation rate of therapeutic agents like siRNA and ineffective delivery systems [28]. Understanding TME interactions is crucial for developing strategies to overcome resistance and improve NSCLC treatment outcomes [29].

In recent years, the understanding of cancer biology has evolved significantly, particularly with the identification of various molecular components that contribute to tumorigenesis. This review aims to synthesize these advancements, particularly focusing on the roles of noncoding RNAs, epigenetic regulation, metabolic reprogramming, and the tumor microenvironment. Figure 2 illustrates these core concepts, categorizing key elements and their functions while highlighting their critical roles in cancer progression and therapeutic potential. By integrating these components, we can better appreciate the complexity of cancer biology and the multifaceted approaches required for effective treatment strategies.

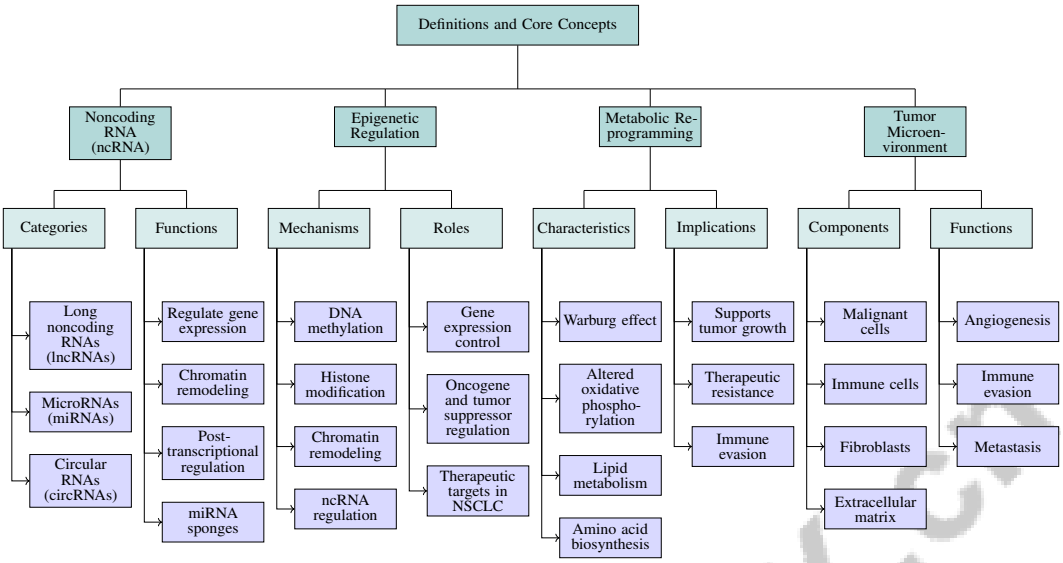

Figure 2: This figure illustrates the core concepts in cancer biology, focusing on noncoding RNAs, epigenetic regulation, metabolic reprogramming, and the tumor microenvironment. It categorizes key elements and functions, highlighting their roles in cancer progression and therapeutic potential.

3 Definitions and Core Concepts

3.1 Noncoding RNA (ncRNA)

Noncoding RNAs (ncRNAs) are RNA molecules that do not translate into proteins but are essential in regulating gene expression and cellular processes. They are mainly categorized into long noncoding RNAs (lncRNAs) and microRNAs (miRNAs), each playing distinct roles in chromatin remodeling and gene regulation [19]. LncRNAs, originating from various genomic regions, perform diverse functions such as signaling, decoying, scaffolding, and guiding, crucial for maintaining cellular homeostasis [19]. In contrast, miRNAs post-transcriptionally regulate gene expression by binding to target mRNAs, leading to their degradation or translational repression. Their interactions within regulatory networks highlight their significance as oncogenic drivers and tumor suppressors, presenting opportunities for targeted therapies [1, 30, 11, 4].

NcRNAs also function as an associative memory system, influencing cellular processes similar to artificial neural networks. Circular RNAs (circRNAs), a class of ncRNAs, act as miRNA sponges and modulate protein interactions, with their stable circular structure enhancing regulatory network participation. Dysregulated circRNA expression is linked to various diseases, emphasizing their importance in both normal physiology and pathology [13, 4, 2].

The regulatory functions of ncRNAs are central to understanding their roles in health and disease. Their dysregulation, particularly in cancer, underscores the need for comprehensive investigations into their mechanisms and therapeutic potential. Advances in RNA-based therapies, with numerous antisense oligonucleotide treatments in clinical trials, highlight the promising role of ncRNAs in targeted cancer interventions [6, 2, 31, 5].

3.2 Epigenetic Regulation

Epigenetic regulation involves heritable modifications in gene expression without altering the DNA sequence, crucial for understanding ncRNAs' roles in cancer via gene accessibility and expression modulation [32]. Key epigenetic mechanisms include DNA methylation, histone modification, chromatin remodeling, and ncRNA regulation, each playing a pivotal role in gene expression control [33].

DNA methylation involves adding methyl groups to cytosine residues in CpG dinucleotides, leading to transcriptional repression by obstructing transcription factor binding. Histone modifications, such

as acetylation and methylation, alter chromatin structure, regulating gene accessibility [32]. Chromatin remodeling, facilitated by ATP-dependent complexes, further modifies nucleosome dynamics, affecting DNA accessibility for transcription factors [34].

NcRNAs influence epigenetic regulation by directing chromatin-modifying complexes to specific genomic loci, affecting chromatin accessibility and gene expression [31]. They are involved in establishing and maintaining epigenetic marks essential for cellular state stability across divisions [35].

In NSCLC, epigenetic mechanisms regulate oncogenes and tumor suppressor genes, contributing to disease heterogeneity and progression. Targeting epigenetic pathways offers a promising therapeutic strategy, as interventions aimed at specific modifications can potentially reverse aberrant gene expression patterns driving tumorigenesis. The reversibility of epigenetic alterations and their responsiveness to external factors make epi-drugs a significant potential in enhancing anti-tumor effects and overcoming drug resistance in NSCLC management [9, 31, 6, 17]. Understanding the interplay between ncRNAs and epigenetic regulation provides valuable insights into NSCLC's molecular mechanisms and highlights potential therapeutic targets.

3.3 Metabolic Reprogramming

Metabolic reprogramming, a hallmark of cancer, involves dynamic alterations in cellular metabolism supporting rapid proliferation and survival under varying conditions. This process reorganizes metabolic pathways to meet the increased energy and biosynthetic demands of tumor cells, often driven by oncogenes and tumor suppressors regulating key metabolic nodes [36]. The Warburg effect, characterized by enhanced glycolysis and lactate production despite sufficient oxygen, exemplifies metabolic reprogramming in cancer cells, facilitating rapid ATP generation and production of intermediates for growth and division.

Cancer cells also exhibit alterations in oxidative phosphorylation, lipid metabolism, and amino acid biosynthesis, adapting to nutrient-poor and hypoxic environments. The interplay among these pathways is intricate, regulated by signaling cascades balancing energy production with macromolecule synthesis necessary for proliferation [36]. Oncogenes like MYC and tumor suppressors such as p53 modulate enzyme and transporter expression involved in these pathways.

Metabolic reprogramming supports tumor growth and contributes to therapeutic resistance and immune evasion. Understanding these metabolic alterations provides insights into potential therapeutic targets, as disrupting key pathways can impair tumor growth and sensitize cancer cells to treatments. Investigating metabolic reprogramming is increasingly recognized as critical for developing innovative cancer therapies, aiming to exploit metabolic vulnerabilities arising as tumor cells adapt to challenging microenvironments during progression and metastasis [36, 37, 38].

3.4 Tumor Microenvironment

The tumor microenvironment (TME) is a complex, dynamic milieu crucial for progression and therapy resistance in NSCLC. Comprising a heterogeneous mix of malignant cells, immune cells, fibroblasts, and extracellular matrix components, the TME actively influences tumor behavior [27]. It is an active participant in cancer development, contributing to processes such as angiogenesis, immune evasion, and metastasis.

Characterized by diverse immune cells, including T cells, macrophages (notably M2-type), and dendritic cells, the TME can be co-opted by cancer cells to create an immunosuppressive environment inhibiting effective immune responses while facilitating tumor growth and metastasis. Non-malignant cells, such as cancer-associated fibroblasts and adipocytes, further promote tumor progression by enhancing cell proliferation and aiding extracellular matrix reorganization, supporting cancer cell migration and invasion. Understanding these interactions is crucial for developing targeted therapeutic strategies disrupting these processes and enhancing treatment efficacy [26, 27]. Fibroblasts, particularly cancer-associated fibroblasts (CAFs), secrete growth factors and cytokines that modulate the tumor milieu, facilitating invasion and metastasis. The extracellular matrix (ECM) provides structural support and biochemical cues influencing cell adhesion, migration, and proliferation.

The TME's role in NSCLC underscores the need for therapeutic strategies targeting not only cancer cells but also supportive elements within the microenvironment. Understanding the TME's complexity

and its interactions with cancer cells is essential for advancing therapeutic interventions and improving patient outcomes in NSCLC [26, 27, 25, 29].

4 Role of Noncoding RNA in Epigenetic Regulation

The role of noncoding RNAs (ncRNAs) in epigenetic regulation has become a crucial focus in molecular biology, revealing their significant influence on gene expression through various epigenetic mechanisms. These include long noncoding RNAs (lncRNAs) and microRNAs (miRNAs), which modulate chromatin dynamics and gene expression, particularly in non-small cell lung cancer (NSCLC). This section explores the pathways and interactions through which ncRNAs impact epigenetic regulation, emphasizing their multifaceted roles in chromatin dynamics and gene expression modulation.

4.1 Mechanisms of Epigenetic Regulation by ncRNAs

NcRNAs significantly shape the epigenetic landscape, affecting gene expression via DNA methylation, histone modifications, and chromatin remodeling. In NSCLC, ncRNAs like lncRNAs and miRNAs regulate oncogenes and tumor suppressor genes. LncRNAs serve as scaffolds in ribonucleoprotein complexes, interacting with chromatin-modifying enzymes to influence epigenetic marks [21]. LncRNAs such as Xist highlight their regulatory potential in tumorigenesis by interacting with proteins and genes, crucial for chromatin architecture and gene regulation [19]. MiRNAs modulate gene expression post-transcriptionally through ceRNA networks, where ncRNAs act as decoys, influencing gene expression via competitive interactions.

The adaptability of ncRNA-mediated regulation is evident in their responsiveness to environmental changes, highlighting their dynamic nature in NSCLC and potential as therapeutic targets. This adaptability allows modulation of epigenetic states to counteract aberrant gene expression patterns in cancer. Moreover, circRNAs' expression levels and roles across various cancers underscore their potential as diagnostic and prognostic biomarkers [8].

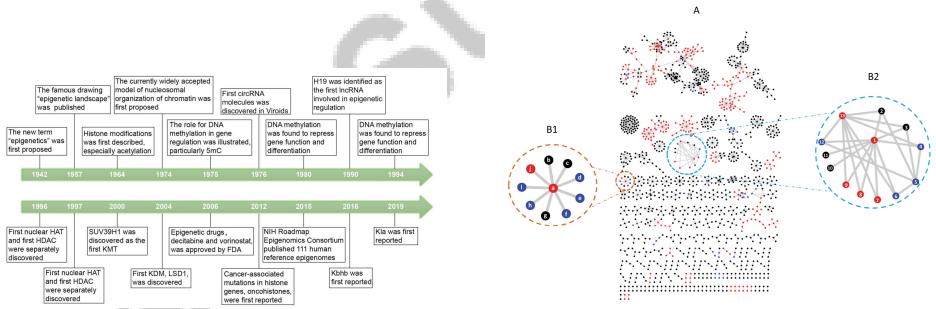

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Figure 3: Examples of Mechanisms of Epigenetic Regulation by ncRNAs

Figure 3 illustrates the diverse mechanisms by which ncRNAs regulate gene expression at the epigenetic level, influencing chromatin structure, DNA methylation, and histone modification. These mechanisms include guiding chromatin-modifying complexes to specific loci, modulating transcription, and forming repressive chromatin states. Understanding these processes is crucial for uncovering ncRNAs' broader implications in development, differentiation, and disease, highlighting their therapeutic potential [33, 7].

4.2 ncRNAs and Chromatin Accessibility

NcRNAs are vital in modulating chromatin structure and accessibility, influencing gene expression patterns in NSCLC. LncRNAs and miRNAs engage in complex regulatory networks affecting chromatin dynamics. Transcriptome-wide analyses reveal miRNAs target lncRNAs and protein-coding transcripts, indicating lncRNAs' broader regulatory roles [7]. This crosstalk between ncRNA classes is essential for fine-tuning gene expression and maintaining chromatin homeostasis.

NcRNAs influence chromatin accessibility by recruiting chromatin-modifying complexes to specific genomic loci, altering histone modifications and nucleosome positioning. Statistical mechanics frameworks, accounting for entropic contributions of hierarchical structures, provide accurate predictions of binding interactions, underscoring the complexity of ncRNA-mediated chromatin regulation [39]. Despite advances, challenges remain in experimentally validating lncRNAs' precise mechanisms, requiring sophisticated techniques to capture their transient, context-specific interactions [21].

4.3 Role of Lactate and Epigenetic Modifications

Lactate, once seen as a mere byproduct of anaerobic metabolism, is now recognized as a key signaling molecule in the tumor microenvironment, affecting epigenetic programming through histone lactylation. This modification impacts gene expression and cellular behavior, crucial for understanding cancer progression and immune responses [24]. In NSCLC, the tumor microenvironment's metabolic landscape modulates chromatin accessibility and gene expression.

The dynamic epigenome is shaped by intrinsic and extrinsic factors, with nucleosome positioning influencing gene accessibility through DNA properties, transcription factor binding, and chromatin remodeling [34]. Environmental fluctuations significantly affect gene expression and cellular fate, highlighting stochastic processes' role in cellular behavior [40].

NcRNAs, including lncRNAs and miRNAs, mediate lactate's effects on epigenetic modifications by guiding chromatin-modifying complexes to specific loci, modulating epigenetic marks, and influencing chromatin accessibility and gene expression [31]. LncRNAs' structural motifs and interactions with chromatin-modifying complexes underscore their regulatory capacity in epigenetic modulation [41]. RNA-based computational models, like RPC-snRC, highlight ncRNAs' intricate regulatory potential [42].

The interplay between lactate, ncRNAs, and epigenetic modifications highlights the multifaceted nature of cancer's epigenetic regulation, where DNA methylation leads to gene silencing and histone acetylation enhances expression [43]. Understanding these interactions is crucial for elucidating NSCLC's molecular underpinnings, offering insights into potential therapeutic targets and innovative treatments leveraging metabolic and epigenetic factors.

5 Metabolic Reprogramming in NSCLC

Metabolic reprogramming in non-small cell lung cancer (NSCLC) is a critical transformation in nutrient and energy utilization that supports cancer cell growth and survival. This process results from a complex interaction of molecular and environmental influences that reshape metabolic pathways beyond mere cell proliferation. Investigating noncoding RNAs (ncRNAs), particularly long noncoding RNAs (lncRNAs) and microRNAs (miRNAs), is essential as they are key regulators in this context. The following subsections explore the impact of these ncRNAs on metabolic pathways, emphasizing their significance in NSCLC's metabolic landscape.

5.1 Influence of lncRNAs and miRNAs on Metabolic Pathways

In NSCLC, ncRNAs, especially lncRNAs and miRNAs, are pivotal in regulating metabolic pathways, offering potential therapeutic avenues. Studies highlight cancer cells' adaptability across tumor types and microenvironments, partly mediated by ncRNAs that influence crucial metabolic pathways such as glycolysis, amino acid metabolism, and lipid metabolism [36, 20]. LncRNAs act as molecular scaffolds, facilitating interactions among metabolic enzymes and regulatory proteins, thereby modulating pathways vital for cancer cell survival and proliferation. They are linked to glycolytic enzyme regulation, impacting glycolytic flux in NSCLC cells [20]. Concurrently, miRNAs target mRNAs of metabolic enzymes, affecting their expression and activity, which is essential for maintaining cancer cells' metabolic flexibility in nutrient-deprived and hypoxic environments [36].

The interaction between cancer-associated fibroblasts (CAFs) and cancer cells further illustrates ncRNAs' roles in metabolic reprogramming. CAFs secrete metabolites and signaling molecules that alter the tumor microenvironment's metabolic landscape, influencing cancer cell metabolism [20]. NcRNAs mediate these interactions by regulating metabolic enzymes and transporters, impacting

glycolysis and lipid metabolism. Their ability to modulate these interactions underscores their therapeutic potential, paving the way for innovative NSCLC treatment strategies [38].

Advancements in computational methods, such as convolutional neural networks (CNNs) for RNA structure classification, have enhanced understanding of ncRNA functions, providing improved classification accuracy through visual RNA structure representations [44]. These insights are crucial for identifying ncRNAs involved in metabolic reprogramming and developing targeted therapies that exploit NSCLC cells' metabolic vulnerabilities.

5.2 Metabolic Pathway Adaptations in NSCLC

Metabolic reprogramming in NSCLC involves significant adaptations in pathways essential for rapid cancer cell proliferation and survival, driven by oncogenes and tumor suppressors that modulate key metabolic nodes [36]. A prominent alteration is the increased reliance on aerobic glycolysis, or the Warburg effect, where glucose is preferentially converted to lactate even in oxygen presence, facilitating rapid ATP production and generating biosynthetic intermediates [20]. NSCLC cells also exhibit changes in oxidative phosphorylation, lipid metabolism, and amino acid biosynthesis, intricately regulated by ncRNAs. LncRNAs and miRNAs influence these processes by modulating enzyme expression and activity [20, 36].

The tumor microenvironment, including CAFs and other stromal components, significantly influences NSCLC metabolic adaptations. NcRNAs mediate these interactions by regulating metabolic enzymes and transporters, affecting pathways like glycolysis and lipid metabolism [20]. This highlights ncRNAs' therapeutic potential, offering insights into innovative NSCLC treatment strategies.

Recent advancements in computational methods, including CNNs for RNA structure classification, have improved understanding of ncRNA functions by enhancing classification accuracy through visual representations [44]. These insights are vital for identifying ncRNAs impacting metabolic reprogramming and developing targeted therapies that exploit NSCLC cells' metabolic vulnerabilities.

5.3 Environmental and Genetic Influences on Metabolic Reprogramming

Metabolic reprogramming in NSCLC is shaped by environmental factors and genetic predispositions, forming the cancer cells' metabolic landscape. Environmental elements like nutrient availability, oxygen levels, and growth factors critically influence metabolic pathways in the tumor microenvironment (TME). The TME's composition, including tumor-associated macrophages, CAFs, and the extracellular matrix, promotes tumor survival, proliferation, and metastasis [26, 27]. Hypoxic TME conditions drive genetic and epigenetic adaptations, enhancing invasive capabilities. Nonmalignant cells like adipocytes and lymphocytes regulate tumor behavior and therapy response, emphasizing the importance of these factors for effective cancer treatment.

Genetic predispositions also significantly affect NSCLC metabolic reprogramming by modulating critical metabolic enzymes and regulatory proteins. This reprogramming allows cancer cells to adjust energy production and biosynthetic pathways, facilitating aerobic glycolysis, glutaminolysis, and altered amino acid metabolism, crucial for rapid growth and proliferation. Genetic factors impact tumor-microenvironment interactions, potentially leading to therapy resistance by promoting dysregulated metabolic pathways as novel therapeutic targets [36, 37]. Oncogenes and tumor suppressors, such as MYC and p53, regulate metabolic nodes critical for cancer cell metabolism, driving preferential pathway utilization to meet increased energy and biosynthetic demands.

Current research highlights nucleosome dynamics' role in gene regulation, emphasizing DNA sequence, nucleosome positioning, and transcription factor accessibility interplay [34]. This interplay is crucial for understanding how genetic factors influence metabolic reprogramming, as nucleosome positioning affects transcription factors' accessibility to metabolic genes, modulating expression and activity.

Integrating environmental and genetic influences on metabolic reprogramming underscores NSCLC's metabolic adaptations' complexity. These influences support tumor growth and contribute to therapeutic resistance, underscoring the need for novel strategies targeting cancer cells' metabolic vulnerabilities. By investigating environmental factors, genetic predispositions, and metabolic pathways, researchers can design targeted therapies leveraging NSCLC cells' unique metabolic vulnerabilities, enhancing treatment efficacy [6, 37, 20, 36].

5.4 Therapeutic Implications of Metabolic Reprogramming

Metabolic reprogramming in NSCLC presents significant therapeutic implications, offering strategies to target altered metabolic pathways characteristic of cancer cells. This reprogramming reveals unique vulnerabilities for therapeutic exploitation. Targeting key metabolic pathways like glycolysis, lipid metabolism, and amino acid biosynthesis is promising, as these pathways are often upregulated to meet cancer cells' increased energy and biosynthetic demands [20].

Advancements in RNA-based technologies have enhanced targeting precision and efficacy for these metabolic pathways. CNNs for RNA classification show faster, more accurate results than traditional methods, facilitating ncRNA identification critical for metabolic reprogramming [45]. This approach enables developing targeted therapies exploiting lncRNAs' structural conservation, essential for functionality.

Integrating siRNA delivery systems with targeted therapies, such as tri-block nanoparticles delivering siRNA with tyrosine kinase inhibitors like gefitinib, exemplifies combining metabolic targeting with existing strategies to enhance NSCLC treatment efficacy. This approach addresses metabolic reprogramming challenges crucial for cancer cell adaptation and survival in response to treatment. It tackles therapy resistance driven by metabolic adaptations, manifesting as glycolysis reliance or oxidative phosphorylation dependence. Understanding these dysregulated pathways reveals potential therapeutic targets in tumors resistant to conventional treatments [36, 38, 37, 20, 23]. NcRNAs' computational capabilities, akin to artificial neural networks, suggest potential therapeutic strategies targeting these regulatory mechanisms in NSCLC. Leveraging ncRNAs' computational properties, researchers can develop sophisticated models predicting and modulating cancer cells' metabolic states, offering insights into novel therapeutic approaches.

Exploring metabolic reprogramming in NSCLC underscores targeting the tumor microenvironment (TME) to reverse resistance mechanisms and improve therapeutic outcomes. As research advances understanding of ncRNAs and metabolic pathways' complex interactions, there is potential to develop innovative therapies targeting cancer cells' metabolic dependencies. This is significant given ncRNAs' role as crucial regulators in various cancer types, influencing gene expression and cellular signaling. Elucidating ncRNA interaction networks can identify novel biomarkers and therapeutic targets, paving the way for more effective cancer treatments and improved patient outcomes [1, 11, 4].

6 Noncoding RNA and Tumor Microenvironment

6.1 ncRNA Interaction with Immune Components

Noncoding RNAs (ncRNAs), including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs), are pivotal in modulating immune responses within the tumor microenvironment (TME) of non-small cell lung cancer (NSCLC). These molecules orchestrate complex regulatory networks, notably through competing endogenous RNA (ceRNA) interactions, influencing gene expression by sequestering miRNAs. Dysregulation of ncRNAs can significantly impact cancer progression and immune evasion, making them valuable biomarkers and therapeutic targets in NSCLC [1, 4, 2, 11]. LncRNAs and miRNAs regulate immune cell infiltration, activation, and function, affecting tumor progression and metastasis through modulation of cytokines, chemokines, and immune checkpoint molecules, thus influencing immune surveillance and evasion mechanisms.

LncRNAs notably affect the differentiation and function of immune cells, including T cells, macrophages, and dendritic cells, via epigenetic modifications and chromatin remodeling. They act as molecular scaffolds or decoys interacting with transcription factors and signaling molecules. For instance, lncRNAs like Xist and MALAT1 regulate immune responses by affecting PD-L1 expression, an immune checkpoint molecule crucial for T cell activation and immune evasion by cancer cells [14, 7, 46].

MiRNAs play a critical role in post-transcriptional regulation of immune-related genes, influencing the expression of cytokines and receptors essential for immune cell recruitment and activation. Their functions are mediated through interactions with mRNAs and lncRNAs, creating a complex network that modulates immune responses. The expression of miRNAs is tightly controlled by epigenetic mechanisms, ensuring precise regulation of immune functions [2, 7, 47, 43]. Depending on the

context, miRNAs can either suppress or enhance immune responses, highlighting their potential as therapeutic targets in NSCLC.

Recent therapeutic advancements targeting ncRNAs have shown promise in enhancing anti-tumor immunity and improving immunotherapy efficacy [26]. Understanding ncRNA interactions with immune components in the TME is crucial for developing novel strategies leveraging the immune system to combat NSCLC.

6.2 ncRNA and Stromal Cell Modulation

NcRNAs, including miRNAs and lncRNAs, are critical regulators of stromal cell behavior within the TME of NSCLC. Through ceRNA interactions, ncRNAs modulate gene expression, influencing tumor progression by altering interactions between cancer cells and stromal components, thus presenting opportunities as biomarkers and therapeutic targets [1, 4, 2, 26]. Stromal cells, such as cancer-associated fibroblasts (CAFs), endothelial cells, and immune cells, engage in dynamic interactions with cancer cells, crucial for tumor growth, metastasis, and therapy resistance.

LncRNAs significantly influence stromal cell functions by regulating biomolecule secretion, including growth factors, cytokines, and extracellular matrix components by CAFs, affecting the TME's structural and biochemical characteristics. They interact with chromatin-modifying complexes and regulatory proteins, facilitating gene expression and signaling pathway regulation within the TME [48, 19]. Some lncRNAs activate fibroblasts, promoting a pro-tumorigenic phenotype that supports cancer cell invasion and metastasis.

MiRNAs similarly regulate stromal cell behavior post-transcriptionally by targeting mRNAs encoding critical signaling molecules and transcription factors, modulating stromal cell differentiation, proliferation, and activation, influencing disease progression [47, 7, 5]. The intricate interactions between miRNAs and lncRNAs indicate a complex regulatory network crucial for mediating tumor-promoting and tumor-suppressing activities within the TME.

Targeting ncRNAs that affect stromal cell functions offers therapeutic opportunities to disrupt cancer-stromal cell interactions in NSCLC. By manipulating ncRNAs, the TME can be reshaped, inhibiting tumor progression and enhancing existing therapies' effectiveness. Understanding ncRNA-stromal cell interactions is vital for developing novel therapeutic strategies targeting the TME to improve NSCLC patient outcomes [26, 2].

6.3 Epigenetic and Metabolic Interactions

NcRNAs critically regulate the interplay between epigenetic and metabolic pathways within the TME, influencing gene expression and cellular metabolism in NSCLC. NcRNAs, including lncRNAs and circRNAs, integrate signals from intrinsic factors like oncogene activation and extrinsic factors such as nutrient availability and hypoxia, affecting metabolic adaptations crucial for cancer cell survival and proliferation [27].

Epigenetic modifications, including DNA methylation and histone modifications, interact with metabolic pathways, influencing tumor behavior and therapy resistance. These epigenetic marks can exhibit phase transitions similar to physical systems, revealing a complex relationship between epigenetic regulation and metabolic processes, further complicated by extrinsic noise affecting ncRNA-target interactions and gene expression patterns [3].

In NSCLC, ncRNAs facilitate crosstalk between epigenetic and metabolic pathways. LncRNAs interact with chromatin-modifying complexes, regulating metabolic gene accessibility, impacting their expression and activity. The structural features of lncRNAs enhance their capacity to form stable protein complexes, amplifying their regulatory potential [19]. CircRNAs also regulate gene expression, with implications in various diseases, suggesting potential as biomarkers and therapeutic targets [13].

Identifying microenvironmental cues that influence cancer therapy efficacy underscores the importance of understanding epigenetic and metabolic interactions. Innovative RNA classification techniques, such as CNNs transforming RNA sequences into image representations, enhance classification accuracy and reduce computational complexity, facilitating a nuanced understanding of ncRNAs' structural and functional roles in biological processes, aiding in identifying potential

drug targets [49, 44, 42]. Understanding these interactions is crucial for developing targeted therapies exploiting ncRNAs' regulatory potential to modulate the TME, improving NSCLC treatment outcomes.

7 RNA Therapeutics Targeting ncRNAs

7.1 Current Advancements in RNA Therapeutics

Recent progress in RNA therapeutics has expanded the scope of targeting noncoding RNAs (ncRNAs) in non-small cell lung cancer (NSCLC). Techniques such as antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), microRNAs (miRNAs), RNA aptamers, and messenger RNAs are being developed to target previously 'undruggable' genes in diseases like cancer and neurodegenerative disorders. Several agents have received FDA approval, with ongoing improvements in RNA chemistry and delivery methods enhancing their efficacy and safety. The 2018 approval of patisiran marked a significant milestone in RNA interference (RNAi) therapeutics, indicating a promising future for RNA-based cancer treatment strategies [15, 18, 5, 50, 51]. These modalities have shown promise in modulating gene expression, offering new avenues for intervention in chronic diseases.

Advancements in delivery technologies, particularly lipid nanoparticles, have improved RNA molecules' stability and cellular uptake, overcoming pharmacokinetic barriers. Targeted nanoconjugate platforms, such as tri-block nanoparticles (TBN), have shown potential in delivering siRNA and therapeutic agents like gefitinib to KRAS mutant NSCLC cells, achieving significant oncogene knockdown and enhanced cell death [17].

Innovative computational approaches, including deep learning methods, have enhanced therapeutic target identification by accurately classifying ncRNAs. Future research will focus on hybrid methodologies that integrate primary and secondary structural features of ncRNAs to improve classification performance and deepen the understanding of their roles in biological processes and disease mechanisms [6, 30, 11, 42].

The development of antisense oligonucleotide therapies highlights the growing interest in targeting ncRNAs. These therapies, alongside FDA-approved ASOs, emphasize RNA treatments' potential in personalized medicine. The stability and abundance of circular RNAs (circRNAs) further elucidate their roles in cancer biology and potential clinical applications [8]. As our understanding of ncRNA functions evolves, the transformative potential of RNA therapeutics in cancer treatment becomes increasingly apparent.

7.2 Targeting ncRNAs in NSCLC

Targeting noncoding RNAs (ncRNAs) in non-small cell lung cancer (NSCLC) offers a promising therapeutic strategy due to their critical roles in gene regulation and tumor progression. MALAT1, a long noncoding RNA, has emerged as a potential target for cancer treatment, warranting further investigation into its complex interactions within tumor biology [52]. The differential responses of lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) to therapeutic agents underscore the importance of tailored approaches in ncRNA targeting, with LUAD often responding better to targeted therapies and LUSC benefiting from immune checkpoint inhibitors [6].

However, RNA-based therapeutics face challenges such as rapid RNA degradation, metabolic instability, and effective intracellular delivery. RNA's susceptibility to nucleases and its limited ability to permeate cell membranes complicate delivery efforts, necessitating innovative systems [53]. Ionizable lipids have shown promise in enhancing RNA delivery, yet their clinical effectiveness remains under investigation [53].

Challenges in delivering RNA therapeutics are compounded by immune-related toxicities, off-target effects, and pharmacokinetic limitations, which must be addressed to ensure the safe and effective targeting of RNAi drugs [51]. Advancements in delivery technologies, such as lipid nanoparticles and targeted nanoconjugates, are crucial for improving RNA stability and cellular uptake.

The integration of immune and stromal signatures in classifying LUAD into distinct subgroups has enhanced prognostic accuracy and treatment response predictions, highlighting the need for precise ncRNA targeting within the tumor microenvironment [22]. Continued research into RNAi therapeutics and their clinical applications remains a primary focus, with efforts directed at refining delivery

strategies and overcoming inherent challenges [50]. Leveraging these insights, ncRNA-targeted therapies have the potential to revolutionize NSCLC treatment.

7.3 Innovative Delivery Systems

Advancing innovative delivery systems for RNA therapeutics is crucial for enhancing efficacy and specificity, particularly in non-small cell lung cancer (NSCLC). This survey categorizes RNA delivery systems into viral and non-viral vectors, focusing on non-viral methods such as nanoparticles and conjugates [16]. Non-viral vectors offer advantages, including reduced immunogenicity and improved safety profiles compared to viral approaches.

Nanoparticle-based systems have emerged as a promising methodology for RNA therapeutics, providing a versatile platform for RNA encapsulation and targeted delivery. Lipid nanoparticles (LNPs) have been transformative in mRNA vaccine delivery, significantly enhancing stability and cellular uptake. Comprising ionizable lipids, phospholipids, cholesterol, and PEGylated lipids, these nanoparticles protect RNA from degradation and facilitate transport into cells, addressing challenges such as susceptibility to nucleases and cellular membrane penetration. Recent LNP advancements have propelled COVID-19 vaccine development and broadened the application of RNA-based therapies targeting various diseases, including cancer and genetic disorders [15, 16, 53]. Ionizable lipids in LNPs promote endosomal escape, overcoming major delivery challenges.

Beyond lipid-based systems, polymeric nanoparticles and conjugate-based methods improve RNA therapeutics' pharmacokinetics and biodistribution. These advanced systems can be engineered for specific tissue or cell type targeting, enhancing therapeutic indices by ensuring precise action while minimizing off-target effects. Such targeted approaches are vital for the efficacy of RNA-based therapeutics, including small-interfering RNAs, microRNAs, and ASOs, supported by innovative delivery methods like nanoparticles and extracellular vesicles [16, 54, 5, 15]. Targeted nanoconjugates incorporating ligands for specific cell surface receptors further refine RNA delivery precision, allowing selective targeting of cancer cells.

The incorporation of computational tools and machine learning algorithms has significantly improved the design and optimization of RNA delivery systems, addressing critical challenges such as intracellular delivery, stability, and immune response activation [5, 15, 16]. These computational approaches facilitate the prediction of RNA structure-function relationships and delivery efficiency, paving the way for more effective delivery platforms. As research progresses, refining these innovative delivery systems holds significant promise for overcoming barriers associated with RNA therapeutics, ultimately enhancing clinical applications in NSCLC and other diseases.

7.4 Challenges and Future Directions

The development of RNA therapeutics for non-small cell lung cancer (NSCLC) encounters challenges, including the complexity of noncoding RNA (ncRNA) regulatory networks, delivery system inefficiencies, and potential adverse immune responses. Current RNA-based therapies are limited by rapid RNA degradation in biological environments and restricted tissue specificity [18]. Addressing these issues necessitates advancements in innovative delivery systems, such as lipid nanoparticles and targeted nanoconjugates, to enhance RNA stability and cellular uptake [16]. Future research should prioritize improving these delivery technologies, exploring novel chemical modifications, and addressing safety and efficacy challenges in clinical contexts [50].

The intricate nature of ncRNA interactions within the tumor microenvironment (TME) complicates therapeutic strategies, requiring a comprehensive understanding of TME components and the development of combinatory therapies to enhance treatment efficacy [29]. Context-specific roles of ncRNAs underscore the need for comprehensive mapping of ncRNA networks using advanced sequencing technologies [1]. This approach could facilitate the identification of ncRNAs as biomarkers and therapeutic targets, expanding the potential for RNA-based treatments [2].

Long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs) present additional exploration opportunities. Future research should aim to clarify lncRNA classifications, understand their functional mechanisms, and investigate their roles in health and disease using advanced sequencing and imaging techniques [19]. Similarly, elucidating the molecular mechanisms governing circRNA functions and identifying novel circRNAs in disease contexts are crucial for advancing RNA therapeutics [13].

Exploring genotype-phenotype (GP) map biases and their implications in RNA therapeutics targeting ncRNAs offers another research avenue, potentially informing the design of more effective RNA-based interventions [10]. Addressing safety concerns associated with RNAi therapeutics, including off-target effects and immune-related toxicities, remains a critical focus [51]. By advancing delivery systems, exploring novel RNAi triggers, and enhancing the stability of RNA molecules, researchers can broaden the therapeutic potential of RNA-based therapies in NSCLC and beyond [55].

8 Conclusion

8.1 ncRNA as Biomarkers and Therapeutic Targets

Noncoding RNAs (ncRNAs) have emerged as pivotal elements in the landscape of cancer biology, particularly in non-small cell lung cancer (NSCLC), offering substantial promise as biomarkers and therapeutic targets. The diverse roles of ncRNAs, including long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs), in gene regulation and cellular processes, are critical for advancing treatment strategies in NSCLC. The structural attributes of lncRNAs are instrumental in their epigenetic regulatory functions, providing valuable insights into disease mechanisms and therapeutic avenues. The potential of ncRNAs as biomarkers is underscored by their complex regulatory functions, warranting further exploration to fully understand their roles. Understanding ncRNA classifications, such as tRNA-derived small RNAs (tsRNAs), is crucial due to their regulatory significance, impacting disease diagnostics and therapeutics. CircRNAs, in particular, have shown promise as cancer biomarkers and therapeutic targets, yet their clinical application requires further validation. The associative memory system models of ncRNAs highlight their potential in genetic regulation and disease intervention. Enhancing therapeutic efficacy involves exploring improved delivery methods and specificity assessments for ncRNAs in NSCLC treatment. Integrating ncRNAs into combined therapeutic strategies, particularly those merging targeted treatments with immunotherapies, is essential for addressing current treatment challenges and improving NSCLC patient outcomes. Continued investigation into the multifaceted roles of ncRNAs is crucial for developing innovative therapeutic approaches and enhancing the precision of cancer diagnostics and treatment.

8.2 Emerging Perspectives in ncRNA Research

Emerging trends in ncRNA research are poised to significantly influence future therapeutic strategies for NSCLC. The focus on the functional roles of ncRNAs, particularly lncRNAs and circRNAs, emphasizes their potential as therapeutic targets and biomarkers. Recent advances call for standardized methodologies in studying extracellular vesicles, vital for understanding ncRNA transport and intercellular communication roles. Such standardization will enhance the exploration of ncRNA interactions within the tumor microenvironment, improving RNA-based therapeutic interventions. Developing strategies to enhance the targeting and delivery efficiency of RNA therapeutics is another critical research area. Innovations in delivery systems, such as lipid nanoparticles and targeted nanoconjugates, aim to overcome challenges related to ncRNA stability and specificity, thereby augmenting their therapeutic potential in NSCLC. These advancements promise more effective and personalized RNA-based therapies to tackle the heterogeneity and complexity of NSCLC. Moreover, integrating computational models and machine learning approaches in ncRNA research is expected to yield deeper insights into regulatory networks and functional dynamics. These tools will facilitate the identification of novel ncRNA targets and the development of predictive models for treatment response, ultimately advancing precision oncology. As research continues to unravel the complexities of ncRNA biology, the potential for ncRNA-based therapies to transform NSCLC treatment becomes increasingly evident. Ongoing exploration of ncRNA functions and interactions will be vital for developing innovative therapeutic approaches that leverage these molecules' unique properties to enhance patient outcomes.

8.3 Future Directions and Research Opportunities

Future research on ncRNAs and NSCLC should prioritize key areas to deepen understanding and enhance therapeutic strategies. Investigating the mechanistic details of ncRNA functions within the tumor microenvironment (TME) holds promise, particularly in identifying reliable biomarkers for TME-targeted therapies and developing combinatory approaches that integrate TME targeting with existing cancer treatments. Additionally, exploring lactate metabolism and lactylation, which

significantly influence tumor progression and immune responses, could yield novel therapeutic targets. Integrating computational models with experimental validation is essential for elucidating complex interactions within competitive endogenous RNA (ceRNA) networks, highlighting the therapeutic potential of targeting these interactions. Advancements in modeling techniques, such as stochastic partial differential equation models, offer opportunities to refine our understanding of epigenetic regulation and its implications in cancer. Future research should focus on refining model parameters and integrating experimental data to validate predictions, enhancing the applicability of these models to broader biological systems. Improving delivery methods for RNA therapeutics remains critical, with efforts directed towards exploring the therapeutic potential of newly identified ncRNAs and understanding the regulatory networks involving ncRNAs. Developing targeted therapies against specific lncRNAs, such as MALAT1, alongside investigating other lncRNAs' therapeutic potentials, are important avenues for future study. Moreover, developing molecular signatures that can distinguish between lung cancer subtypes is essential for advancing personalized medicine. Future research should focus on enhancing these signatures and exploring emerging therapies targeting specific oncogenic pathways. Expanding datasets and refining benchmark tasks to encompass a broader range of applications in RNA research will also contribute to advancing ncRNA-based therapies. Finally, integrating advanced structural determination techniques with genetic manipulation methods, such as CRISPR/Cas9, will be crucial for elucidating the functional domains of lncRNAs and their therapeutic potential. Addressing these research opportunities will propel the field towards more precise and effective ncRNA-based therapies for NSCLC.

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