REVIEW

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Recent Advances in Cancer Immunotherapy Aided by Regulatory Non-Coding RNA: A Review

Debabrat Baishya[1]*, Arpita Barman[1], Bijuli Rabha[1], Kaushik Kumar Bharadwaj[1], Joyeeta Talukdar[2]

Abstract

Cancer immunotherapies have remodeled the way many different forms of cancer are treated by, leveraging the immune system to recognize and attack malignant cells. These therapies have demonstrated durable responses in cancers affecting the blood, bone marrow, and lymph nodes, solidifying their role as a cornerstone of modern oncology. However, despite their success, current immunotherapy tools and techniques require further refinement.Regulatory non-coding RNAs (ncRNAs), actively transcribed by the mammalian genome, play crucial roles in regulating a wide range of cellular processes. They are key players in epigenetic mechanisms that govern differentiation, development, and the progression of invasive carcinogenesis. Emerging evidence suggests that regulatory ncRNAs are also pivotal in cancer immunity, acting as drivers of immune responses in the development of metastatic tumors. These ncRNAs influence the tumor microenvironment (TME), modulate the immune system, and affect the efficacy of immune checkpoint inhibitors and T cell therapies by regulating various signaling pathways.This review article explores the diagnostic and therapeutic potential of ncRNAs in cancer immunotherapy, highlighting their role in modulating carcinogenesis and antitumor immunity. By understanding the influence of regulatory ncRNAs, we can pave the way for the development of prognostic biomarkers and more effective tumor immunotherapies.

Keywords: Regulatory non-coding RNAs- tumor microenvironment- epigenetic regulations

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Introduction

Emerging evidence has revealed non-coding RNAs (ncRNAs) as central architects of gene regulation, revolutionizing our understanding of genome functionality. RNA plays a crucial function in gene expression and regulation.The central dogma of molecular biology reported in late 1950 posited that the messenger RNA is the pillar in this RNA model. Many discoveries such as housekeeping RNAs (rRNA, tRNA)supported this model [1, 2, 3]. However, the discovery of ncRNAs have dramatically challenged the functional understanding of genome. ncRNAs are the junk RNA of the transcriptome that lack the ability of protein coding potential which are found in non-coding regions of eukaryotic genomes [4]. Only 2% of the human genome represents protein coding genes, while the vast portion of the genome is made up of non-coding RNA, which accounts for 98% of the transcriptome [5]. ncRNAs exhibit diverse functional capacities, categorized into housekeeping and regulatory types. Housekeeping ncRNAs include small nucleolar RNAs (snoRNAs), which are involved in the chemical modification of ribosomal and small nuclear RNAs, small nuclear RNAs (snRNAs) that participate in pre-mRNA splicing, guide RNAs (gRNAs) directing site-specific RNA modifications, RNase P RNAs essential for processing precursor tRNAs, telomere-related RNAs crucial for maintaining telomere integrity, and signal recognition particle RNAs (SRP RNAs) which assist in ribosome targeting to the endoplasmic reticulum. Each of these plays a vital role in maintaining fundamental cellular functions and stability. In contrast, regulatory ncRNAs, such as long non-coding RNAs (lncRNAs), microRNAs (miRNAs), piwi-interacting RNAs (piRNAs), and circular RNAs (circRNAs), are involved in modulating gene expression and various cellular events. [6, 7]. Regulatory ncRNAs act as pivotal riboregulators, playing a crucial role in the post-transcriptional regulation of both coding and non-coding gene regions. These ncRNAs impact a broad spectrum of cellular processes through diverse gene regulatory mechanisms, which can influence disease development. Recent studies indicate that ncRNAs also mediate gene silencing, a key form of epigenetic modification, and this mechanism is associated with several diseases, including cancer. The involvement of regulatory ncRNAs in these complex

*[1]Department of Bioengineering and Technology, Gauhati University, Gwahati-781014, Assam, India. [2]Department of Biochemistry, All India Institute of Medica Sciences, New Delhi, India. *For Correspondence: drdbaishya@gmail.com*

regulatory networks underscores their significance in both disease pathology and potential therapeutic applications [8 -11]. The integration of ncRNAs into therapeutic strategies represents a promising frontier in medicine. Advances in RNA-based therapies, including antisense oligonucleotides and RNA interference, pull the specific interactions of ncRNAs to target disease-associated genes. Additionally, the potential for ncRNAs to serve as biomarkers for early diagnosis and prognosis of diseases highlights their utility in clinical settings.Continued research into the functional diversity and regulatory mechanisms of ncRNAs is essential for understanding their roles in cellular homeostasis and disease. As our knowledge of ncRNA biology expands, it will lay the groundwork for innovative diagnostic and therapeutic approaches, offering fresh opportunities for personalized medicine and targeted treatments.

Cancer is a multifaceted genetic disorder characterized by a series of progressive mutations in cellular DNA, which ultimately lead to the malignant transformation of normal cells. The role of the immune system in cancer prevention has garnered substantial empirical support from contemporary research. Studies consistently show that individuals with compromised immune function exhibit a markedly increased susceptibility to cancer compared to those with robust immune systems [12 -14]. Understanding the genetic and molecular mechanisms underlying cancer has led to the exploration of novel therapeutic targets. Recent research has illuminated how ncRNAs are deeply embedded in regulating various aspects of cancer biology. Earlier studies confirmed the role of lncRNAs in the regulation of cancer development and progression, including growth, metastasis, and recurrence [15, 16]. A major challenge in treating metastasis is the biological heterogeneity of cancer cells, which often leads to diagnosis at more advanced stages. In response, researchers are investigating innovative approaches to address this issue. One promising strategy is immunotherapy, which aims to activate the immune system more effectively to combat cancer. As weak immune system functionality within the cancer microenvironment is now recognized as a key hallmark of cancer, enhancing immune responses through such therapies could significantly improve treatment outcomes. [17]. Immunotherapy has demonstrated remarkable and durable efficacy, establishing itself as a crucial fourth pillar in cancer treatment. Emerging evidence highlights that regulatory non-coding RNAs play significant roles in various stages of tumor immunity [18, 19]. Gaining a deeper understanding of how ncRNAs regulate cancer immunity could unveil novel therapeutic targets and strategies. Therefore, this review aims to elucidate the functions of regulatory non-coding RNAs, offering new insights into cancer diagnosis and the advancement of immunotherapeutic approaches.

Unravelling the biogenesis of regulatory non-coding RNA

Regulatory non-coding RNAs (ncRNAs) represent a diverse class of RNA molecules that, despite their lack of long open reading frames, play crucial roles in the regulation of gene expression. These ncRNAs can range from a mere handful of nucleotides to several thousand, reflecting a remarkable variability in their structure and function. The biogenesis of these regulatory ncRNAs, primarily controlled by RNA polymerase II, often involves complex processes of polyadenylation and splicing [5]. The biogenesis of small non-coding RNAs (sncRNAs) has complex linkage with RNA interference (RNAi). SncRNAs form complexes with Argonaute proteins, leading to mature sncRNAs that bind to complementary mRNA targets, silencing them effectively. Among sncRNAs, microRNAs (miRNAs) are processed in both the nucleus and cytoplasm. Primary miRNAs (pri-miRNAs), characterized by their hairpin structure, are cleaved by the endonuclease DROSHA in the nucleus to produce precursor miRNAs (pre-miRNAs). These are then exported to the cytoplasm, where they are further processed by DICER and incorporated into RNA-induced silencing complexes (RISCs) with Argonaute proteins, forming mature miRNAs that direct the silencing of target mRNAs. Long non-coding RNAs (lncRNAs), typically over 200 nucleotides in length, encompass various types such as long intergenic non-coding RNAs (lincRNAs), enhancer ncRNAs, and transcribed ultraconserved regions (T-UCRs). lncRNAs participate in numerous cellular functions, including chromatin remodeling, transcriptional regulation, and post-transcriptional processing, demonstrating their versatile roles in gene regulation [10, 20-24]. Long non-coding RNAs (lncRNAs) are primarily processed within the nucleus and exhibit features akin to protein-coding genes. These features encompass conserved promoter regions, distinct chromatin structures at their promoters, and regulation mediated by transcription factors and morphogens. Furthermore, lncRNAs demonstrate diverse tissue-specific expression patterns and undergo complex splicing events, including the generation of alternative splice variants [25, 26]. Circular RNAs (circRNAs), a distinct subset of long non-coding RNAs (lncRNAs), are characterized by their single-stranded, closed-loop structure. These circRNAs are derived from previously coding transcripts, and their biogenesis is precisely controlled by specific cis-acting elements and trans-acting factors. circRNAs are primarily generated through head-to-tail back-splicing, where the 3′ end donor site is joined to an upstream 5′ end acceptor site, or through intron hybridization. Additionally, some circRNAs originate from excised lariat introns [27 -31]. Figure 1 illustrates the biogenesis pathways of various regulatory ncRNAs, including lncRNAs, miRNAs, and circRNAs, and schematically depicts their regulatory mechanisms in tumor immunity. This visual representation underscores the complexity and significance of ncRNA biogenesis and their roles in cellular regulation and disease contexts.

Regulatory non-coding RNA in cancer immunity: Mechanism and functions

Regulatory ncRNAs govern a remarkable variety of biological functions including transcriptional interference, telomere maintenance, epigenetic changes, X chromosome inactivation, genome imprinting, post-transcriptional and translational control, structural organization, cell

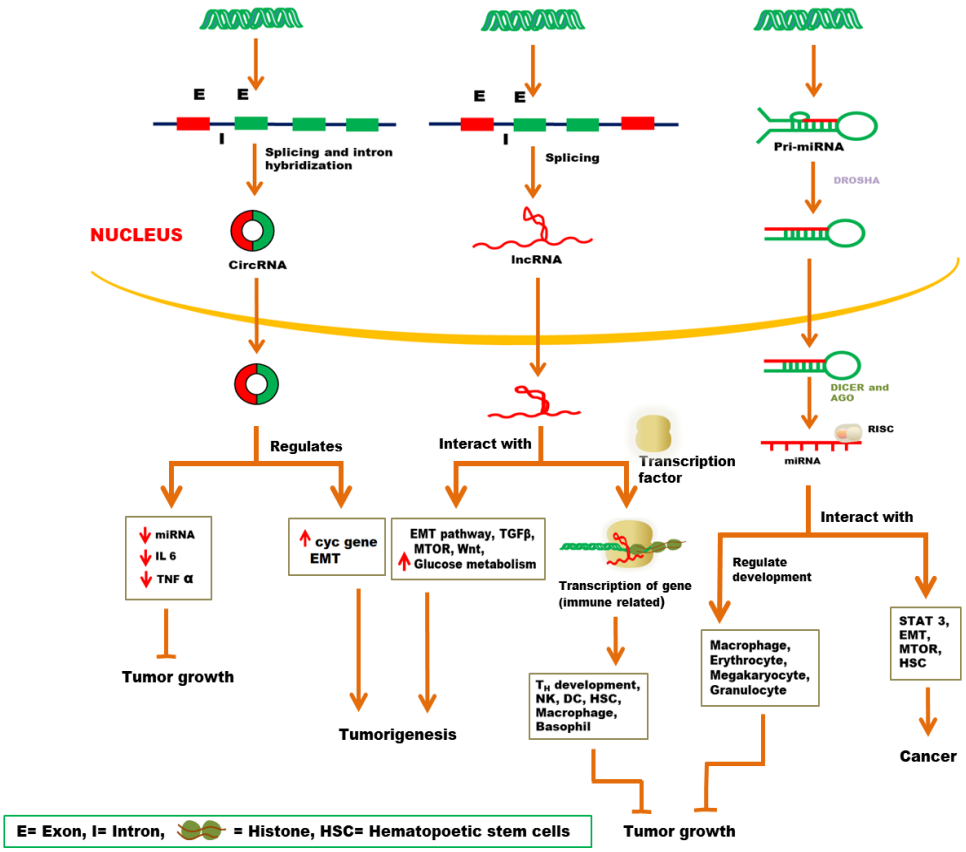

Figure 1. Biogenesis of Regulatory ncRNAs(lncRNA,miRNA,circRNA) and Schematic Depicts of Their Regulatory Mechanism in Tumor Immunity. a) circRNAs biogenesis occur in nucleus; it downregulatetumour inflammation inhibition (↓IL6 and ↓TNF-α)leading to inhibition of cancer growth also upregulate c-mycand EMT signaling to cause cancer. b)lncRNA biogenesis also processed in nucleus; it upregulate different sigalling pathways by interact with them resulting evolution of carcinogenesis and it may regulate the transcription of various immune related genes also involve in their development and differentiation leading to inhibition of tumor evolution. c)miRNAs biogenesis processed in both nucleus and cytoplasm; it also interact with signaling pathways and regulate the development of immune componenets resulting tumor evolution and tumor growth inhibition respectively.

differentiation and development [32]. ncRNAs are integral to a range of biological processes, including transcriptional regulation, telomere maintenance, and epigenetic modifications. Within the nucleus, lncRNAs and miRNAs modulate gene expression by influencing transcriptional machinery and chromatin remodeling. In the cytoplasm, these ncRNAs regulate mRNA processing, protein modifications, and cell signaling pathways [33]. In the context of cancer immunity, regulatory ncRNAs are of particular interest due to their significant roles in modulating immune responses. They can influence the expression of genes associated with immune cell function, tumor progression, and the response to immune checkpoint inhibitors. By affecting these pathways, ncRNAs can either promote or inhibit the development and progression of cancer, making them valuable targets for therapeutic strategies aimed at enhancing cancer immunity [34]. Their ability to modulate these processes underscores their potential as biomarkers and therapeutic targets for enhancing cancer treatment. The immune system is actively engaged in cancer progression and dissemination, which involves several critical stages: the release of tumor antigens, their presentation to immune cells, activation of immune responses, migration and infiltration of immune cells into tumor tissues, and the elimination of cancer cells. This continuum of events, referred to as the cancer-immunity cycle, was extensively described by Mellman and Chen in 2013 [35]. lncRNAs and miRNAs are critical in regulating the self-renewal and differentiation of hematopoietic stem cells (HSCs). They modulate the process by which HSCs continuously renew themselves and differentiate into various specialized immune cells. lncRNAs are notably present in diverse immune cell types including monocytes, macrophages, dendritic cells, neutrophils, T cells, and B cells. They are involved in guiding their development and differentiation [36 -38]. Some lncRNA like NeST induce synthesis of IFN-γ in CD8 + T cells [39], lincRNA-Cox2, which regulate the transcription of immune genes [40] , and *GATA3-AS1* that participate in differentiation of Th2 cells [16]. Recent studies have highlighted that various lncRNAs play a critical role in regulating dendritic cell (DC) functions, which are essential for balancing pathogen elimination and immune tolerance. Key lncRNAs involved in this regulation include lnc-DC, lincRNA-Cox2, lincRNA-EPS, and AS-IL-1a. Among these, lnc-DC (long non-coding RNA in dendritic cells) exhibits a dual function by enhancing both antigen presentation and the

differentiation of CD4+ T cells [41, 42]. lncRNAs are involved in regulating the maturation of antigen-presenting cells (APCs) and the expression of pro-inflammatory cytokines. lncRNA TCONS_00019715 has been reported to facilitate macrophage polarization towards the M(IFN-γ + LPS) phenotype, which is associated with increased inflammatory activity. In contrast, lncRNA Cox-2 can impede tumor growth by inhibiting the polarization of M2 macrophages, thus affecting the immune response within the tumor microenvironment [43, 44]. Long non-coding RNAs (lncRNAs) have been identified as potential tumor suppressors, with some shown to enhance MHC I expression and promote antigen processing in cancer cells. Elevated levels of miRNA (miR-135) have been observed in colon tumors, correlating with reduced antigen-presenting cell (APC) levels. Within the tumor microenvironment (TME), lncRNAs influence the expression of anti-apoptotic factors like tumor necrosis factor-alpha (*TNF-α*) and interact with the NFκB pathway, often through Toll-like receptor (TLR)-mediated mechanisms. TLRs, in turn, stimulate the expression of various lncRNAs, including lincRNA-Cox2 [45 - 47]. Tumor cells develop resistance to immune responses by skewing the balance between pro-apoptotic and anti-apoptotic signals, resulting in tumor immune escape (TIE). Regulatory non-coding RNAs (ncRNAs) are crucial in this process, as they modulate the expression of pro- and anti-apoptotic factors. For example, in breast cancer, miR-195, miR-24-2, and miR-365 have been found to reduce Bcl-2 levels, thus augmenting tumor cell death. In contrast, miR-125b and miR-106a contribute to high *Bcl-2* expression, inhibiting apoptosis in leukemia, prostate cancer, lymphomas, and breast cancer cells, which enhances their proliferation and invasion. Moreover, the hyperactivation of the Wnt/β-catenin signaling pathway is often linked to cancer development and progression. This pathway is regulated by various lncRNAs and miRNAs. miR-93 and miR-145 target β-catenin to modulate Wnt/β-catenin signaling, while Smad7 acts to downregulate this pathway. These regulatory mechanisms demonstrate complex interactions between ncRNAs and signaling pathways in cancer biology [48 - 54]. Several regulatory non-coding RNAs (ncRNAs) have been identified as activators of the *p53* pathway, with their roles examined in both *p53*-proficient and *p53*-deficient cells. Comparative analyses of gene expression profiles and *p53*-binding patterns under genotoxic or oncogenic stress have revealed multiple direct lncRNA targets of *p53*. These findings enhance our understanding of how ncRNAs interact with *p53*, shedding light on their potential impact on cellular responses to stress and their contributions to tumorigenesis [55, 56]. Again, the epithelial-mesenchymal transition (EMT) signaling pathway plays a significant role in the progression of epithelial tumors. Key transcription factors involved in this pathway drive molecular changes by reducing the expression of epithelial cadherin (*E-cadherin*) while increasing the levels of neural cadherin (*N-cadherin*) and vimentin, which facilitates carcinogenesis. These transcription factors not only contribute to tumor development but also promote immunosuppression and aid in achieving tumor immune escape (TIE). Recent studies have shown that miRNAs such as miR-21, miR-137, miR-34a, and miR-106a/b regulate EMT by targeting specific transcription factors like ZEB1, Snail, and Twist1. For instance, miR-21 has been reported to inhibit EMT in colorectal cancer by suppressing both Snail and *E-cadherin* expression. Similarly, miR-137 and miR-34a impede EMT in ovarian cancer by downregulating Snail expression. These insights signal the crucial role of miRNAs in modulating EMT and their potential impact on tumor progression and immune evasion [57 - 63]. However, the key pathways underlying EMT and tumorigenesis remain incompletely understood. Recent studies have identified lncRNAs like LINC01186 and lncRNA-HIT as key regulators in the TGF-β signaling pathway, significantly impacting cell migration and invasion in lung and breast cancer cells, respectively. However, the depth of their mechanistic roles remains underexplored [64, 65]. Although promising, these findings warrant deeperanalysis on how these lncRNAs interact with other pathways and their potential relevance across multiple cancer types. The current evidence supporting these lncRNAs is valuable. But however, further validation is required to address potential limitations and inconsistencies. Moreover, translating these insights into clinical therapies poses challenges such as specificity and delivery. Future research should focus on overcoming these obstacles and expanding the investigation to other lncRNAs and cancers to fully realize their therapeutic potential. Certain lncRNAs have been identified as interactors with the polycomb repressive complex 2 (PRC2), often through the recruitment of enhancer of zeste homolog 2 (EZH2) or other PRC2 components, suggesting a mechanism by which lncRNAs regulate EMT [66, 67]. Although these findings shed light on the potential regulatory roles of lncRNAs in EMT, a comprehensive evaluation is necessary to fully understand their functional implications. The mechanism through which lncRNAs influence EMT via PRC2 could involve several plausible pathways: lncRNAs may guide PRC2 to specific genomic loci to modulate histone modifications, thereby repressing genes that maintain epithelial characteristics or activating those that promote mesenchymal traits. Alternatively, lncRNAs might alter the recruitment or activity of PRC2, affecting its ability to regulate target genes. Despite these possibilities, the evidence remains preliminary, and further research is needed to elucidate the exact molecular mechanisms and determine the broader applicability of these interactions across different cancer types. Addressing these questions will be crucial for advancing targeted therapies that leverage lncRNA-PRC2 interactions to modulate EMT and cancer progression. Recent research has highlighted the role of circular RNAs (circRNAs) in modulating immune responses and tumor progression. For instance, circAmotl1 has been shown to enhance *STAT3* expression via the *STAT3* signaling pathway and promote nuclear c-myc expression in tumor cells, potentially driving carcinogenesis [36]. However, a deeper understanding of how circAmotl1 influences c-myc and its broader impact

on tumor dynamics is needed. Similarly, hsa_circRNA_002178 affects breast cancer development by downregulating miR-328-3p and upregulating COL1A1, and its silencing can reduce tumor inflammation and growth by lowering *IL-6* and *TNF-α* levels [68, 69]. To advance the field, future research should focus on elucidating the precise molecular mechanisms by which circRNAs like circAmotl1 and hsa_circRNA_002178 modulate cancer progression and immune responses. Additionally, studies should explore the consistency of these findings across various cancer types and investigate the potential of targeting circRNAs for therapeutic applications. Addressing these areas will be crucial for utilizing circRNAs in cancer treatment and improving our understanding of their role in tumor biology.

Application of regulatory non-coding RNA in cancer immunotherapeutics

RNA-based therapeutics have transitioned from conceptual frameworks to tangible treatments, with non-coding RNAs (ncRNAs) emerging as a notable class of therapeutic agents. Unlike protein-coding RNAs, ncRNAs exert their effects by modulating gene expression without encoding proteins. Their therapeutic potential lies in their ability to regulate gene expression at the post-transcriptional level. ncRNAs achieve this by binding to specific messenger RNAs (mRNAs), thereby inhibiting their translation or promoting their degradation, which can disrupt tumorigenic pathways and influence cancer progression [70]. Despite promising preclinical and early clinical data, translating ncRNA-based therapies into routine clinical practice presents several challenges. To overcome these hurdles, future research should focus on improving the delivery mechanisms and stability of ncRNA therapeutics, understanding their interactions with target mRNAs, and evaluating their effectiveness across various cancer types. Addressing these challenges is crucial for advancing ncRNA-based therapies from experimental stages to widespread clinical use. miRNAs are short, approximately 20–25 nucleotides in length, and play a crucial role in the post-transcriptional regulation of gene expression. Since their initial discovery in *Caenorhabditis elegans* in 1993, miRNAs have emerged as significant non-coding RNAs (ncRNAs) involved in gene silencing [71]. They function by binding to complementary sequences in target messenger RNAs (mRNAs), resulting in either mRNA degradation or translational repression. This regulatory mechanism constitutes a major form of epigenetic alteration, influencing various cellular processes. Owing to their ability to modulate gene expression, miRNAs are implicated in numerous diseases, including human carcinogenesis [10]. Their significance in cancer is particularly noteworthy since they influence tumor proliferation, metastasis, and resistance to therapies, rendering them key targets for research study and prospective treatment strategies.

The regulatory roles of key ncRNAs are analyzed, highlighting their potential as standalone or combinatorial therapies. Their value as predictive biomarkers for anticancer immunotherapy is also examined. A comprehensive summary of the roles and applications of miRNA is presented in Supplementary Table 1, that details the functions and applications of lncRNA. Additionally, Table 2 provides an overview of the functions of siRNA and circRNA.

Inflammation and ncRNA in Cancer Immunotherapy

Inflammation is recognized as a significant indicator of malignant growth, with over 20% of tumors attributed to chronic inflammation. Immune regulatory molecules such as cytokines and chemokines play pivotal roles in managing immune responses and are integral to immunotherapy. The discovery of ncRNAs has added a new layer of control over immunity and inflammatory processes, spurring interest in inflammation-related research. In a study by Cao and colleagues, 82 lncRNAs were screened using Spearman correlation analysis with the immune score, identifying five key lncRNAs-AC005014.2, AC010503.4, AL450384.2, LINC00930, and SH3BP5-AS1 that were downregulated in bladder cancer tissues compared to normal bladder epithelial cells. Additionally, an in silico approach introduced the ncRI dataset, which compiles experimentally validated ncRNAs in inflammatory diseases from over 2,000 publications, totaling 11,166 curated entries, including 1,377 lncRNAs, 1,976 miRNAs, and 107 other ncRNAs from humans, rodents, and mice[131, 132]. The analysis of studies, such as those conducted by Cao and colleagues, reveald that while promising, ncRNA-based therapies face significant hurdles that must be overcome before they can be integrated into routine clinical practice. Challenges such as enhancing the delivery mechanisms and stability of ncRNA therapeutics, deciphering their complex interactions with target mRNAs, and assessing their efficacy across diverse cancer types are pivotal areas that require further exploration. By addressing these issues, the potential of ncRNA-based therapies to transform cancer immunotherapy can be fully realized, offering a new frontier in the fight against cancer.

Regulatory non coding RNA as immune checkpoint blocker

Immune-checkpoint proteins on T cells regulate immune responses, acting to prevent the immune system from attacking tumor cells when engaged by specific tumor-expressed proteins. Key proteins such as *CTLA-4, TIM-3, LAG-3, BTLA, PD-1*, and its ligand *PD-L1* are central to this regulatory process, with elevated levels of PD-1 and *PD-L1* often indicating a poor prognosis due to their suppression of the anticancer immune response. Immune checkpoint blockade therapies have significantly advanced cancer treatment by reactivating T cell activity and enhancing their survival. However, traditional therapies that rely on monoclonal antibodies tend to target single molecules, which limits their ability to address entire physiological pathways or multiple targets simultaneously. Regulatory non-coding RNAs (ncRNAs) present a promising alternative, as they can target multiple genes concurrently, offering a more comprehensive approach to modulating the immune system. Incorporating ncRNAs into cancer immunotherapy could potentially overcome the limitations of traditional treatments, paving the way

Table 1. Various lncRNA and Their Role in Cancer Immunotherapy

lncRNA	Cancer type	*In vitro/ in vivo*	Model	Function	references
ANRIL	Burkitt lymphoma	*in vitro*	Burkitt lymphoma cells	ANRIL silencing inhibited proliferation; promoted the apoptosis ↓cyclin D1, ↓E2F transcription factor 1 ↓Bcl-2	[104]
MIR22HG	colorectal cancer	*in vitro*	LoVo and HCT116	acts as tumor suppressor, silencing ofMIR22HG enhances tumor cell proliferation and survival overexpression of MIR22HG triggers T cell infiltration, enhancing Immunotherapy	[105]
AK036396	Lung , Colon cancer	*in vitro*	LLC, CT-26 cell	AK036396 knockdown downregulate PMN-MDSC immunosuppression Administration of siAK036396 delays tumor progression, stability of Fcnb	[106]
F630028O10Rik	Lung cancer	*in vitro*	LLC, MS1	↓VEGFA, ↓VEGFR2 inhibitendothelialcells clone formation, migration, invasion Injection of cholesterol-modified siRNA-F63into mice tumour tissues	[107]
		in vivo	C57BL/6 mice	inhibit tumour growth and progression by modulating tumour angiogenesis	
LINC00449	Leukemia	*in vitro*	AML cells	overexpression of LINC00449 inhibit the cell proliferation and invasion	[108]
lncMX1-215	HNSCC Ovarian cancer	*in vitro*	HN4, HN6 and HN30 Cal27, SCC4, SCC25 Detroit 562 ,293 T, SCC7	inhibits tumor proliferation capacity suppress cancer metastasis	[109]
		in vivo	BALB/c nude mice		
HOTTIP		*in vitro*	Neutrophils	enhance IL-6 expression,↑PD-L1	[110]
LINC-PIN	lung ,colon cancer	*in vitro*	HCT116, A549, &DLD1	Inhibits migration as well as invasion of cancer cells both in vitro/ in vivo	[111]
		in vivo	Mice		

for a more effective and multifaceted therapeutic strategy [133 - 135]. miR-142-5p has been shown to directly suppress *PD-L1* expression in tumor cells by binding to its 3' untranslated region (3'UTR). This downregulation of *PD-L1* not only enhances antitumor immunity but also significantly inhibits pancreatic cancer growth in vivo [92]. The findings suggest that miR-142-5p could serve as a promising therapeutic agent in cancer immunotherapy by targeting the PD-1/*PD-L1* axis. This highlights the potential of microRNA-based interventions to modulate immune checkpoints, offering a novel strategy to enhance the effectiveness of existing treatments and overcome resistance in pancreatic and possibly other cancers. Another study revealed that miR-149-3p significantly impacts cancer immunotherapy in triple-negative breast cancer by downregulating mRNAs responsible for encoding immune checkpoint proteins such as PD-1, TIM-3, BTLA, and Foxp1. This downregulation effectively reverses CD8+ T cell exhaustion, a key challenge in cancer treatment, and restores their cytokine secretion capabilities [88]. These findings suggest that targeting miR-149-3p could be a promising approach to overcoming immune resistance in this aggressive form of breast cancer, offering a new direction for therapeutic. In addition, studies highlighted the crucial role of microRNAs in modulating immune checkpoint pathways with miRNA like miRNA-424-5p [73], miRNA-5119[76], miRNA-200a [77], miRNA-148a-3p [83], Let-7 family protein [86], microRNA-192-5p, microRNA-149-3p [88], miRNA-142-5p [92], miRNA-424(322) [93], miRNA-621[95] and miRNA-374b [98] demonstrating a significant association with the inhibition of immune checkpoint proteins such as *PD-L1*. This inhibition is particularly important because *PD-L1* is a key player in immune evasion by cancer cells, allowing tumors to suppress the immune response. By downregulating *PD-L1* and other immune checkpoint molecules, these miRNAs can effectively disrupt this suppression, reactivating the immune system's ability to recognize and attack tumor cells. Regulatory non-coding RNAs, such as siRNA, lncRNA, and circRNA, have emerged as significant players in the modulation of *PD-L1* activity. One such study revealed that the long

Table 2. Various siRNA and circRNAand Their Role in Cancer Immunotherapy

siRNA	Cancer type	*In vitro/ in vivo*	Model	Function	references
ODC-targeting siRNA	ESCC	*in vitro*	M2 macrophage	↓IL-10 and TGF-β, ↑IL-12p35	[112]
STAT3+PD-L1 siRNA	Skin melanoma Breast cancer	*in vitro*	B16-F10 & 4T1 cell lines	↓PD-L1 and STAT3 genes Suppresses proliferation, migration, and angiogenesis suppresses cancer progression	[113]
		in vivo	BALB/C and C57BL/6J mice		
siRNA-loaded nanocarrier	-	*in vitro*	CD8+ T-cells from human blood	enhanced T-cell survival ↓PD-L1	[114]
siRNA-loaded PCAnp	Colon cancer	*in vitro*	T cells of colon cancer bearing mice	enhanced T cell responses blockade of A2AR & CTLA-4	[115]
siRNA-PD-L1 imatinib in a liposomal NP	Melanoma	*in vitro*	B16F10 cells	↑cancer cell apoptosis delayed tumor growth	[116]
NP-siCD47 /CCL25	Breast Cancer	*in vitro*	4T1 cells	tumor infiltration of CCR9+CD8+ T cells ↓CD47,PD-1/PD-L1 blockade	[117]
IL-6- & STAT3 SiRNA+TMC Np	Breast Cancer Colorectal Cancer Melanoma	*in vitro*	4T1, CT26, B16-F10	↓IL-6/STAT3 expression	[118]
PD-1 siRNA/ PD-L1 siRNA loaded PLGA np	Colon cancer	*in vitro*	CTLs MC38 tumor-bearing mice	↓mTOR signaling cosilencing of PD-1 and PD-L1	[119]
		in vivo		showed more significant tumor growth suppression and long-term tumor inhibition in colon cancer	
siRNA-PD-L1	-	*in vitro*	-	co-delivery of siRNA-PD-L1 and doxorubicin can block the inhibitory signal responding to T cells and enhancecytotoxicity of Dox against tumor cells	[120]
siLuc	Hepatocellular carcinoma	*in vivo*	Mice model	knockdown of Luc (siLuc)significant reductionin Luc activity for mice receiving NP-delivered siLuc treatments were confirmed by Luminescence imaging of the tumors confirming successfulsiRNA delivery and gene silencing	[121]
siPDL1	Pancreatic cancer	*in vitro*	PAN 02 cell line	Combination therapy consisting of gemcitabine and MN-siPDL1	[122]
		in vivo	and mice model	in a syngeneic murine pancreatic cancermodel resulted in a significant reduction in tumor growth and an increase in survival	
PD-1 siRNA	skin cancer	*in vitro*	B16 cell line and	PD-1 siRNA delivered by attenuated	[123]
		in vivo	C57BL/6 mice	Salmonella to melanoma-bearing mice in combination with pimozide showed optimal therapeutic effect on melanoma	
Si-ChLa NPs +Dendritic cell	breast cancer	*in vivo*	Mice	decreased tumor growth and metastasis ↓CD73 ↓Regulatory T ↓myeloid derived suppressor cells (MDSCs) ↓ and tumor associated macrophages ↑T cells, ↑inflammatory cytokines ↑interferon (IFN)-γ, ↑(IL)-17 ,↓IL-10	[124]
siRNA Targeting Notch1	Melanoma	*in vitro*	B16F1	↓cell proliferation	[125]
		in vivo	mice	↓ Notch1, ↓hey1, ↓tumor growth ↑tumor-infiltrating CD8+ T lymphocytes and IFN-γ	
siIL-10RA+siTGF-βR	cervical cancer	*in vitro*	dendritic cell TC-1 P0 tumour model	initiated the strongest antigen-specific CD8(+) T cell immune responses	[126]
HPV Targetting	-	*in vivo*	C57BL/6 mice	reduced tumor growth	[127]
siRNA polyplex encapsulated in PLGA np	Melanoma	*in vitro*	DC	STAT3 silencing by nps restored DC maturation ↑CD86,↑TNF-α ↑T cell proliferation	[128]

Table 2. Continued

siRNA	Cancer type	*In vitro/ in vivo*	Model	Function	references
Hsacirc0009361	colorectal cancer	*in vitro* *in vivo*	CRC tissues and cells Mice	↑expression of APC2 and inhibited the activity of the Wnt/β-catenin pathway by competitively combining with miR-582 inhibited the growth & metastasis of CRC	[129]
circCACTIN	Gastric cancer	*In vitro*	BGC-823,MGC-803	↑CircCACTIN expression Knockdown of circCACTIN inhibited GC cells proliferation migration, invasion	[130]
		In vivo	BAL/BC Mice model	circCACTIN up-regulation promoted GC tumor growth and EMT, and circCACTIN down-regulation inhibited GC tumor growth and EMT SGC-7901 cell line	

non-coding RNA HOTTIP enhances immune evasion in ovarian cancer by upregulating *IL-6*, which in turn drives *PD-L1* expression in neutrophils. This insight suggests that HOTTIP could be a valuable therapeutic target in ovarian cancer, offering a novel approach to counteract the tumor's immune escape mechanisms and potentially improve treatment efficacy [110]. In yet another study, the circular RNA hsa_circ_0020397 was identified as a miR-138 sponge, leading to increased expression of TERT and *PD-L1*. This modulation impacts key cellular processes, including viability, apoptosis, and invasion of colorectal cancer cells [136]. The generalized mechanisms of non-coding regulatory RNAs, with a focus on miRNAs, are illustrated in Figure 2, while Figure 3 provides an overview of checkpoint-inhibiting receptors and their interactions. These figures collectively enhance our understanding of how regulatory RNAs function as immune checkpoint modulators, offering insights into their potential as therapeutic targets in cancer treatment.

Regulatory non coding RNA in T cell therapy

Immune cells called T cells have their own proteins

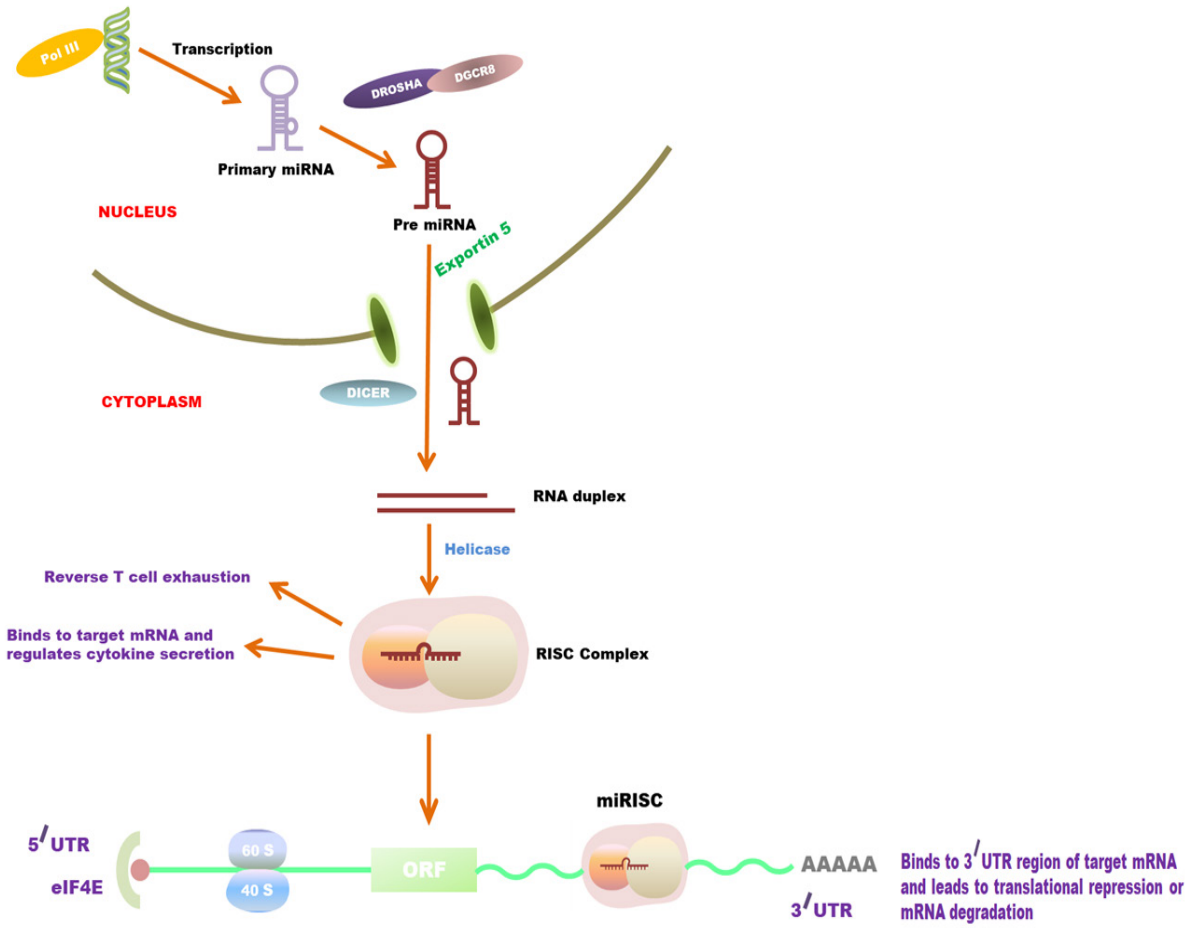

Figure 2. Generalized Mechanism of PD 1 and PDL1 Degradation by microRNA. Likewise, other types of regulatory ncRNA, such as circRNA, lncRNA, siRNA also follow this pathway for regulation of PD1-PDL1

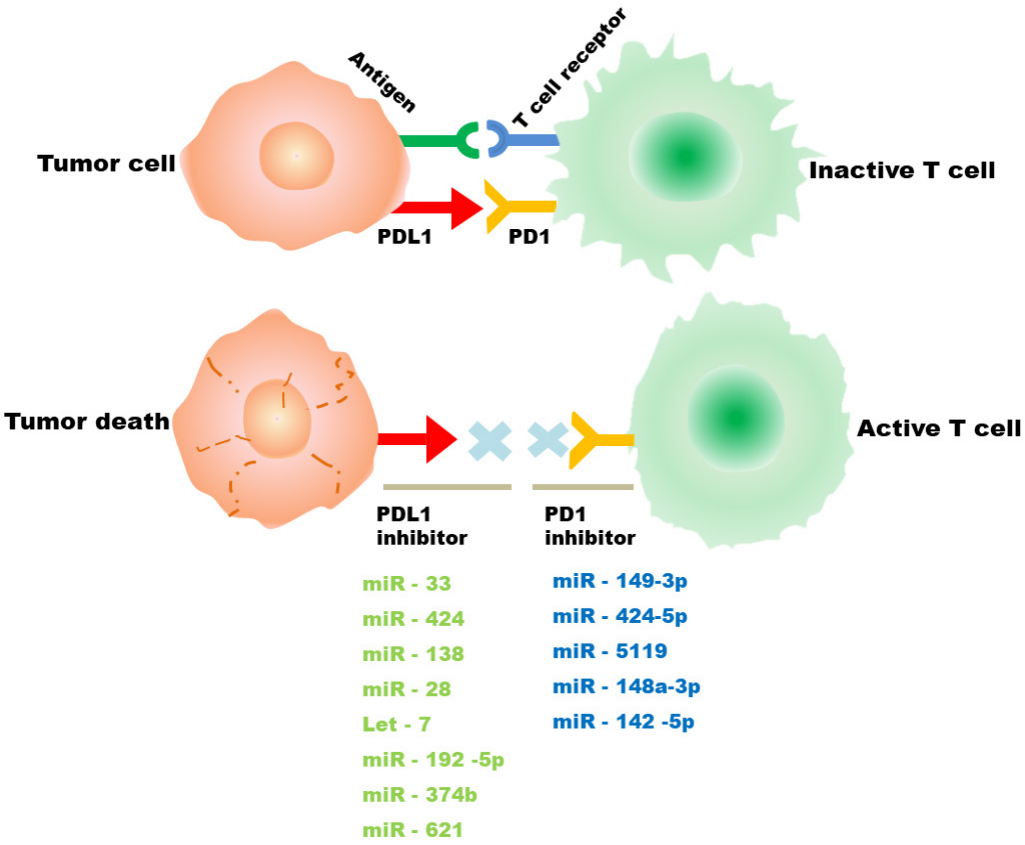

Figure 3. Schematic Diagram Showing PD1- PD L1 Interaction and Their Inhibitors

called receptors that attach to foreign antigens and help trigger other parts of the immune system to destroy the foreign substance. There are many evidences that reveals the association between T cell exhaustion and dysfunction with cancer. During the process of exhaustion, T cells chronically exposed to tumor antigen and viral antigen gradually loses the ability to kill cancer cell [137]. CAR T-cell therapy is a type of adaptive cell transfer therapy in which a patient's T cells (a type of immune cell) are genetically engineered in the laboratory and reinfused to the patient's body where they specifically recognized and eliminate cancer cells [138]. A recent study on T cell therapy has been reported that treatment of CD8+ T cells with an miR-149-3p mimic reduced apoptosis, attenuated changes in mRNA markers of T-cell exhaustion and downregulated mRNAs encoding PD-1, TIM-3, BTLA and Foxp1. Also the treatment with miR-149-3p promoted the capacity of CD8+ T cells to kill targeted 4T1 mouse breast tumor cells [88]. In addition, there are more studies conducted on T cell therapy, which used siRNA mediated therapy in T cell therapy. Thiramanas [114] showed the effect of siRNA-loaded Nano carrier used in T cell therapy. They transfected CD8+ T cell with siRNA loaded Nano carrier which resulted in enhancement of survival of T cell. In another study, siRNA loaded PCA nanoparticle used in T cell therapy were used which also resulted in T cell enhancement and ability to kill tumor cell [115].

Regulatory non coding RNA in Dendritic cell (DC) therapy

The advancement of dendritic cell (DC)-based immunotherapy represents a significant leap in cancer treatment, leveraging patient-derived DCs to mount potent anti-tumor immune responses. Recent innovations reveal the promise of combining DC vaccines with complementary therapies to enhance their therapeutic impact. For example, research has shown that siRNA polyplexes encapsulated in PLGA nanoparticles can effectively silence *STAT3*, leading to enhanced DC maturation and increased expression of activation markers such as CD86 and *TNF-α*, thereby boosting T cell proliferation. Additionally, studies using miR-5119 mimics in DCs have demonstrated improved T cell functionality and increased cytokine production in breast cancer models. Future progress in this field should focus on optimizing these therapies through strategic combinations with other immunotherapeutic agents, refining adjuvant selection, and perfecting administration routes and timing. Ensuring that DCs are thoroughly matured and fully capable of activating effector T cells will be essential for advancing DC-based immunotherapy and achieving more effective, personalized cancer treatments [139, 128, 76].

Non-coding RNAs (ncRNAs) have been shown to play a significant role in modulating tumor immunity by affecting various biological processes. These include influencing macrophage polarization, enhancing or inhibiting NK cell cytotoxicity, and regulating T cell responses [115, 98, 86, 78, 79, 101]. By targeting these key immune functions, ncRNAs can impact the overall efficacy of the immune response against tumors. Recent advancements in the study of non-coding

RNAs (ncRNAs) have illuminated their pivotal roles in modulating tumor immunity. Comprehensive lncRNA microarray analyses have identified 9,343 deregulated lncRNAs in proinflammatory macrophages, with lncRNA TCONS_00019715 emerging as a key regulator in driving macrophage polarization towards the M1 phenotype, thereby amplifying tumoricidal responses. Additionally, lncRNAs such as Flicr have been linked to prognosis in colorectal cancer, while lncRNA NKILA facilitates tumor immune evasion and lncRNA Tim3 impedes antitumor immunity. lncRNAs also significantly influence natural killer (NK) cell cytotoxicity and the PD-1/*PD-L1* signaling pathway. For instance, microRNA-130a has been shown to enhance NK cell-mediated killing of non-small cell lung cancer (NSCLC) cells by targeting *STAT3*. However, *STAT3* overexpression can negate the beneficial effects of miR-130a on NK cell activity [98, 140, 79]. These findings suggest that ncRNAs are not only integral to understanding tumor immune dynamics but also represent promising targets for novel therapeutic strategies aimed at improving cancer immunotherapy.

Regulatory non coding RNA in Nanomedicine

Nanotechnology, since its emergence in the 1990s, has rapidly advanced, distinguished by its nanometer-scale dimensions, biodegradability, and the ability to covalently interact with a diverse array of small molecule drugs. These properties enable precise targeting of sub-nuclear sites, thus revolutionizing the potential for treating cancer and other diseases. Among the various strategies developed for the effective delivery of nanomedicines into the nucleus, RNA interference (RNAi) has become a particularly influential technique. Recent studies have demonstrated the efficacy of combining siRNA-loaded liposomal nanoparticles with therapeutic agents such as imatinib to target *PD-L1* in skin melanoma. This approach has been shown to induce significant apoptosis in cancer cells in vitro and inhibit tumor growth in vivo. [116]. These innovations underscore the potential of RNAi-mediated nanotechnology to transform cancer therapy through enhanced specificity and targeted delivery. In a significant study, researchers demonstrated that targeting *STAT3* and *IL-6* with siRNA-loaded chitosan nanoparticles markedly curtails cancer cell progression, illustrating the advanced capabilities of nanotechnology in disrupting critical tumor growth pathways. Similarly, another study employed PLGA nanoparticles to deliver siRNAs targeting both PD-1 and its ligand, achieving notable suppression of colon tumor growth [119]. miRNAs have emerged as a powerful contender in the battle against cancer, owing to their ability to simultaneously target multiple oncogenic pathways. In another significant study, the therapeutic potential of lipid nanoparticles (LNPs) encapsulating miR-634 were explored. When administered intravenously, these LNPs demonstrated a remarkable capacity to reduce tumor growth in a xenograft mouse model implanted with BxPC-3 pancreatic cancer cells [141]. This research underscores the tumor-suppressive power of miR-634 and highlights the promise of LNPs as an advanced delivery system, capable of enhancing the effectiveness of miRNA-based cancer therapies. We have tried to highlight diverse array of application of regulatory ncRNA in nanomedicine through a schematic representation as shown in Figure 4.

Major Challenges faced by ncRNA based therapeutics

The therapeutic targeting of noncoding RNAs (ncRNAs), including microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), has emerged as an innovative approach for treating various cancers and other diseases. Despite the significant strides made towards the clinical application of RNA-based therapeutics—such as the development of antisense oligonucleotides and small interfering RNAs (siRNAs), with several gaining FDA approval trial outcomes have been inconsistent. Some studies report robust therapeutic effects, while others reveal limited efficacy or notable toxicity. As a

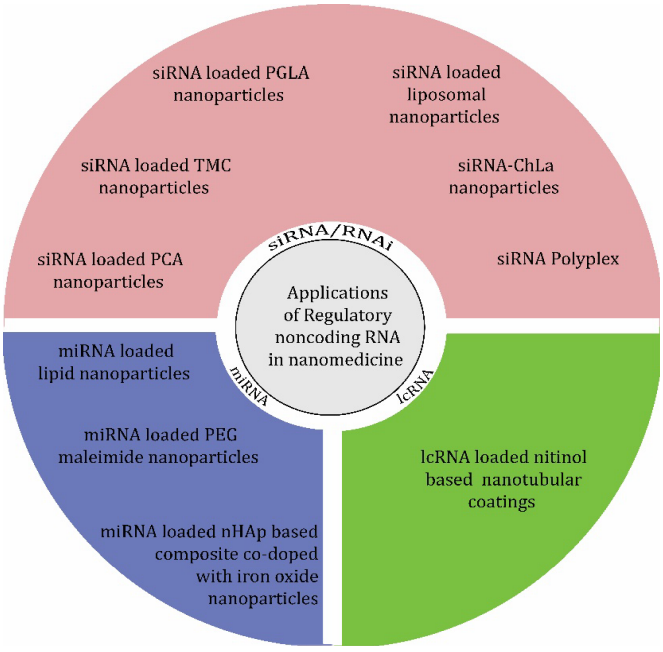

Figure 4. Applications of Regulatory ncRNA in Naomedicine

result, alternative therapeutic entities like antimiRNAs are undergoing clinical testing, and lncRNA-based therapeutics are garnering increasing interest.

However, despite their promise, ncRNA-based therapies face considerable challenges. Chief among these are issues of specificity, tolerability, targeted delivery, avoidance of off-target effects, reduction of toxicity, and the ability to overcome mutations and drug resistance. One of the most significant obstacles is the efficient and precise delivery of oligonucleotide-based therapies particularly anti-miRNA, miRNA mimics, siRNA, and shRNA—into specific tissues and cells. The dual role of certain ncRNAs across different tissues complicates this further; for example, miR-26a promotes gliomagenesis but exhibits both tumor-suppressive and oncogenic roles in hepatocellular carcinoma, underscoring the need for context-specific therapeutic strategies.

There is also a critical need for more extensive preclinical and clinical studies to advance our understanding and application of ncRNA therapeutics. Current research predominantly relies on chemically synthesized oligonucleotides with extensive chemical modifications. However, the development of bioengineered or recombinant RNA molecules produced and folded in living cells represents a novel and potentially superior class of agents for both basic research and drug development, warranting rigorous evaluation.

A landmark achievement in RNA-based therapeutics was the FDA approval of Patisiran, which utilizes a lipid nanoparticle (NP) delivery system to accumulate in the liver and inhibit transthyretin production. Despite its success, Patisiran is not universally recognized as a therapeutic drug for broader applications, particularly due to its limited target specificity.

Off-target effects represent another significant concern, demanding meticulous consideration during the design of oligonucleotide-based drugs. Factors such as RNA structure, protein interactions, and mismatches at cleavage sites can lead to unintended consequences, further complicating therapeutic development.

Moreover, the functional impact of ncRNAs can vary dramatically across different cancer types. For instance, lncRNA Xist functions as a tumor suppressor in osteosarcoma, cervical cancer, and breast cancer, yet acts as an oncogene in pancreatic, gastric, thyroid, colon, hepatocellular, non-small-cell lung, bladder cancers, glioblastoma, and nasopharyngeal carcinoma. Such functional variability poses significant challenges in predicting therapeutic outcomes and necessitates a deeper understanding of ncRNA biology in diverse pathological contexts.

Another complicating factor is the inconsistency between short-term chemical inhibition of ncRNAs and long-term genetic deletion. Chronic loss-of-function of ncRNAs may trigger adaptive responses that compensate for their absence, raising concerns about the durability of therapeutic efficacy over time. This highlights the challenge of whether the effectiveness of ncRNA-targeting drugs may diminish as the cellular network adapts to reduced ncRNA activity.

Finally, the fundamental differences between targeting lncRNAs and miRNAs must be carefully considered and addressed. miRNAs, by modulating a broad spectrum of targets, create a complex landscape where it is difficult to establish a direct correlation between target engagement and therapeutic efficacy. Additionally, the sequestration of oligonucleotides within various cellular compartments further complicates their therapeutic impact.

In conclusion, despite rapid advancements in cancer biology, the role of noncoding RNAs (ncRNAs) in cancer immunotherapy remains only partially understood. Abnormally expressed ncRNAs hold promise as diagnostic and prognostic biomarkers, as well as therapeutic targets for cancer management. However, there is an urgent need for more in-depth studies to unravel the novel mechanisms by which ncRNAs influence cancer initiation and progression, particularly through immunotherapeutic approaches. The challenges of translating ncRNA research into clinical practice must be addressed to embrace the paradigm shift from protein-coding to non-coding RNA therapeutics. As ncRNA research advances, the development of new methodologies based on Artificial Intelligence (AI) and Machine Learning (ML) will be crucial for identifying different types of ncRNAs, their interacting molecules, biological functions, and roles in diseases. In recent years, noncoding RNA-loaded nanoparticles have emerged as significant players in drug delivery, offering enhanced efficacy and optimized material size. The integration of nanotechnology and AI could provide innovative solutions to many formulation and development challenges. To efficiently prioritize and study ncRNAs, a multi-phased approach is required. This should include the implementation of long-read, high-depth sequencing, and the improvement of computational tools like AI and ML. AI-driven signaling amplification systems could be employed to visualize different regulatory ncRNAs. Looking ahead, AI is poised to play a pivotal role in transforming healthcare towards precision medicine. To achieve these goals, integrative efforts in immunotherapy must consider a multi-disciplinary approach, combining nanomaterials, computational systems biology, molecular biology, and clinical medicine. These approaches should be intelligently synergized to overcome the current challenges and fully realize the therapeutic potential of ncRNAs. In conclusion, while ncRNA-based therapeutics hold significant promise, their successful translation into clinical practice will require a concerted effort across multiple domains of science. Ongoing research and innovation will be vital in unlocking the full potential of ncRNAs, paving the way for their use in advanced therapeutic applications.

Author Contribution Statement

We would like to acknowledge the contributions of all authors in the preparation of this manuscript. The conceptualization, writing, and editing of the manuscript were primarily carried out by DB. AB contributed to writing the first draft and data acquisition, while BR was responsible for data acquisition, figure drawing, and writing the initial draft. KKB was involved in writing the first draft and editing. JT assisted with data acquisition

and editing

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None.

Conflict of Interest

The authors of this manuscript declares no conflict of interest.

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