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Review

Function of noncoding RNA in regulating cancer cell plasticity

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Abstract

Recent advances have brought non-coding RNAs (ncRNAs) into the spotlight, revealing their critical regulatory roles in cancer cell plasticity. ncRNAs, such as microRNAs (miRNAs), transfer RNAs (tRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), are now recognized as key players in cellular processes such as chromatin remodeling, mRNA stability, and translation. This review delves into the diverse functions of ncRNAs in stem cells and cancer stem cells (CSCs) biology, emphasizing their impact on maintaining and modulating cellular states. We explore the mechanisms by which ncRNAs influence stem cell self-renewal and differentiation, including their roles in establishing pluripotency and directing differentiation. In the context of cancer, ncRNAs are pivotal in driving processes like epithelial-mesenchymal transition (EMT), which underlies metastasis and therapy resistance. By regulating gene expression and epigenetic landscapes, ncRNAs sustain the dynamic nature of CSCs, facilitating tumor growth and heterogeneity. The review also highlights the potential clinical applications of ncRNAs as biomarkers and therapeutic targets. Advances in ncRNA detection and manipulation have opened new avenues for developing diagnostic tools and innovative treatments. Liquid biopsies, which utilize ncRNAs from biological fluids, provide a minimally invasive approach to monitor tumor dynamics and progression. Uncovering the intricate networks regulated by ncRNAs makes it evident that these molecules play central roles in

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understanding cancer cell plasticity. Insights into their functions offer promising strategies for targeted cancer therapies, aiming to disrupt the adaptability of cancer cells and improve treatment outcomes.

Keywords: noncoding RNA; lineage plasticity; cancer stem cell; biomarker; therapeutic target

1. Introduction

It is estimated that up to 90% of the genome is actively transcribed into RNAs, yet only 1.5%–2.0% of the human genome consists of protein-coding genes [1–3]. In recent years, it has become clear that the non–protein-coding portion of the genome is not merely spurious transcriptional noise, as previously thought. Particularly, recent deep sequencing has revealed thousands of non-coding RNAs (ncRNAs) with diverse functions in gene expression and genomic architecture [4–7]. ncRNAs are a diverse class of RNA molecules that do not encode proteins but have regulatory roles in gene expression and cellular processes from chromatin remodeling to mRNA stability and translation [8]. ncRNAs can be classified into housekeeping and regulatory ncRNAs with two major size differences, short and long, based on the 200-nucleotide cutoff in mature transcript length [8,9]. Housekeeping ncRNAs, as their name suggests, are critical for general cellular function and demonstrate abundance in the cell. For example, circHIPK3, a circularized splicing product of HIPK3 precursor RNA, is essential for sponging of multiple miRNAs and modulating cell growth [10,11]. Some tRNA genes in the human genome, such as *n-Tr20*, have also been shown to regulate mTORC1 signaling and consequently reprogramming the synaptic transmission pathways of neuronal cells [12]. However, there is growing evidence of housekeeping ncRNAs contributing to cancer pathogenesis as well [13–15]. Short ncRNAs encompass well-characterized species such as microRNAs (miRNAs), small interfering RNAs (siRNAs), small nuclear RNAs, ribosomal RNAs, and transfer RNAs (tRNAs). Long noncoding RNAs (lncRNAs) can be categorized into various subgroups based on their genomic location and evolutionary origin, including long intergenic RNAs (lincRNAs), antisense RNAs, sense intronic RNAs, enhancer RNAs (eRNAs), circular RNAs (circRNAs) and pseudogenes. Extensive reviews have examined and summarized the oncogenic and tumor suppressive functions of noncoding transcripts, which are particularly evident for miRNAs [16–19], lncRNAs [20–23], and circRNAs [24,25].

Stem cells are unique in their ability to self-renew and differentiate into various cell types. Plasticity is a key feature of stem cells, regulated by reversible epigenetic modifications. While gene-restriction programs

are set during embryonic development as cell lineages form, stem cells maintain a level of flexibility for tissue regeneration [24–27]. In cancer, normal stem cell processes are often hijacked to confer malignant properties. Previous studies have identified the presence of cancer stem cells (CSCs) in various solid tumors such as breast, brain, melanoma, pancreatic, prostate, and ovarian cancers [28–34]. These CSCs exhibit properties akin to normal stem cells, including self-renewal, quiescence, and the ability to generate heterogeneous tumor cell populations. They also exhibit resistance to chemotherapy and radiotherapy [28]. This plasticity is largely governed by complex networks of genetic and epigenetic factors. More recently, ncRNAs have been implicated in maintaining cellular plasticity for both stem cells and CSCs. In normal stem cell fate, ncRNAs are crucial for establishing the pluripotent network and are vital for reprogramming somatic cells to achieve pluripotency [35]. Their involvement in cancer cell plasticity is becoming increasingly recognized, particularly in the context of epithelial-mesenchymal transition (EMT), a key process in cancer metastasis that contributes to therapy resistance [36]. In addition, ncRNAs are gaining increasing attention for their large number, specific expression profiles, functional roles, and potential clinical applications.

This review explores the role of ncRNAs in cellular plasticity in more recent advancements, with a focus on miRNAs, lncRNAs, circRNAs and tRNAs in stem cells, CSCs and subsequently the heterogeneity that exists in solid tumors, highlighting their functional relevance in maintaining and modulating cellular states. Potential therapeutic targets and strategies towards ncRNAs will also be explored.

2. Emerging Functional ncRNA Populations in Cancer

2.1 MicroRNAs

Small ncRNAs, characterized by their length of 20–30 nucleotides and their association with Argonaute family proteins, are categorized into three classes in animals: miRNAs, siRNAs, and PIWI-interacting RNAs [37]. Among these, miRNAs are the predominant class of small RNAs in most somatic tissues. Over 60% of human protein-coding genes have at least one conserved miRNA-binding site. When including the numerous non-conserved sites, it is likely that most protein-coding genes are regulated by miRNAs. miRNAs are small RNAs (approximately 22 nucleotides) that regulate gene expression post-transcriptionally by binding to the 3' untranslated regions (UTR) of target mRNAs, leading to their degradation or translational repression [37]. The biogenesis of miRNAs begins in the nucleus, where primary miRNAs are transcribed by RNA polymerase II, then processed by the Drosha-DGCR8 complex into precursor miRNAs, which are then exported to the cytoplasm. In the cytoplasm, Dicer further processes precursor miRNAs into mature

miRNAs, which are incorporated into the RNA-induced silencing complex (RISC) to regulate target mRNAs [38,39].

The most recent version of the miRBase database (v22) includes 38,589 entries representing hairpin precursor microRNAs from 271 organisms, though the functional relevance of many remains to be elucidated [40]. The dysregulation of miRNAs has been associated with cancer development and progression in various cancers [38]. For example, in pancreatic cancer with mutant KRAS, RAS-responsive element-binding protein 1 (RREB1) represses the promoters of miR-143 and miR-145. Simultaneously, both KRAS and RREB1 are targets of miR-143 and miR-145, creating a feedforward mechanism that amplifies the effect of RAS signaling [41]. The clinical utility of miRNAs is highlighted by aberrant miRNA levels indicating the physiological state of cancer cells, which can be detected through miRNA expression profiling and utilized for diagnosis and prognosis. In fact, miRNA profiling is often more accurate than mRNA profiling for classifying tumors because miRNA expression closely correlates with tumor origin and stage. It can also effectively classify poorly differentiated tumors, which are challenging to identify using standard histological methods [42–45]. Furthermore, circulating miRNAs in serum may serve as diagnostic tools. For instance, miR-141 expression levels in serum were reported to be elevated in patients with prostate cancer compared to healthy control individuals [46,47].

2.2 Long non-coding RNAs

Over the past decade, research has increasingly shown that the genomes of various species are extensively transcribed, leading to the production of numerous lncRNAs. lncRNAs are longer than 200 nucleotides and participate in a wide range of regulatory functions, including chromatin remodeling, transcriptional regulation, and post-transcriptional processing [48–50]. This broad definition includes a vast and highly diverse collection of intergenic transcripts, eRNAs, and sense or antisense transcripts overlapping other genes that vary in their biogenesis and genomic origin [51]. Most lncRNAs are transcribed by RNA polymerase II and undergo similar processing steps as mRNAs, including capping, splicing, and polyadenylation. However, lncRNAs typically do not encode proteins. Instead, they function through various mechanisms, including acting as molecular scaffolds, guides, decoys, and enhancers [49]. The resulting lncRNAs are typically capped with 7-methylguanosine at their 5' ends and polyadenylated at their 3' ends [52].

Data from the Human GENCODE project indicate that the human genome contains over 16,000 lncRNA genes; however, other estimates suggest there could be more than 100,000 human lncRNAs [53,54]. These lncRNAs are implicated in acquiring all the hallmarks of cancer, ranging from intrinsic abilities like enhanced proliferation and survival to changes in metabolism and interactions with the tumor

microenvironment (TME). They are transcriptionally regulated by key oncogenic or tumor-suppressive transcription factors, including p53 [55,56], MYC [57,58], the estrogen receptor [59], and signaling pathways such as Notch [60]. This regulation allows lncRNAs to contribute significantly to oncogenic or tumor-suppressive responses. Their tissue- and condition-specific expression patterns suggest strong potential as biomarkers as well, making them promising targets for clinical interventions. One such lncRNA, the tissue differentiation-inducing non-protein coding RNA (*TINCR*), is notably dysregulated in various cancers and influences tumor development and progression [61].

2.3 Circular RNAs

circRNAs are produced through an inefficient back-splicing process, in which a downstream splice donor is joined to an upstream splice acceptor, thus creating a covalently closed looped structure that lacks poly-adenylated tails. This process largely utilizes the canonical RNA splicing machinery. Most current research has focused on circRNAs derived from known genes, where in some cases, the circular isoform is much more predominant than its linear counterpart [10]. While escaping debranching can lead to the formation of intronic circRNAs, different mechanisms are involved in the generation of circRNAs comprising exonic sequences [62]. Various regulatory sequences [63,64] and protein factors [65–68] are implicated in this process, with circRNAs being produced both co-transcriptionally and post-transcriptionally [69,70]. circRNAs can act as miRNA sponges, regulate transcription, and interact with RNA-binding proteins.

The number of unique circRNAs produced in human cells (approximately 100,000) [71] is almost fivefold higher than that of protein-coding genes (approximately 20,000) [71–74]. Despite their widespread presence, most circRNAs have not been functionally characterized, and their biological roles remain largely unknown. However, their clinical utility is highlighted through their association with various physiological conditions and cellular features as well as with clinical characteristics such as histological grade, tumor size, metastasis stage, and cancer aggressiveness [75,76]. For example, CiRS-7/CDR1as is highly abundant in intratumoral stromal cells, which are widely used as a prognostic factor in colon and breast carcinomas [77,78]. Furthermore, the tissue and cell-type specificity enables better correlation with specific pathologies, allowing for improved differentiation between cancer subtypes [79–82].

2.4 Transfer RNAs

tRNAs are small ncRNA molecules ranging from 56 to 80 nucleotides long and represent a unique clover-leaf secondary structure. The human genome contains genes encoding separate fractions of tRNA

species that function either in the cytoplasm or mitochondria (mt-tRNAs) [83–85]. The complex secondary structure of tRNAs consists of 4 major regions: the amino-acid acceptor stem arm, D arm, T arm, and anticodon [86,87]. The anticodon is a triplicate of nucleotide bases which dictate one of the 20 amino acids to be deposited on the 3' end of the acceptor stem based on the degenerate coding system. Iso-acceptors, therefore, refer to tRNAs of different sequences, which "accept" the same amino acid during the process of mRNA translation.

The unique structural complexity of this small ncRNA population also translates to a wide array of chemical base modifications that each tRNA may harbor, ranging from as many as 14 to 30 modifications [88,89]. Canonically, tRNAs are critical for protein synthesis and draw the bridging gap from transcriptome to proteome translation, where the degenerate coding system is thought to have been fully explored. However, recent studies have also revealed the cleavage of tRNA species by angiogenin nucleases into smaller fragments – tRFs. tRFs expose sequence motifs that would otherwise be hidden in the uncleaved and folded native structure, and contribute to oncogenesis [90–92].

3. ncRNAs in Stem Cell Self-renewal and Differentiation

Stem cells are unspecialized cells capable of self-renewal and differentiation into any cell type of the organism, classified based on their developmental potency. Totipotent stem cells, like zygotes, can differentiate into all cell types, including extraembryonic structures [93]. Pluripotent stem cells, such as embryonic stem cells (ESCs) and induced pluripotent stem cells, can form cells of all germ layers but not extraembryonic structures. Multipotent stem cells, like hematopoietic stem cells (HSCs), can specialize in specific cell lineages, while oligopotent and unipotent stem cells have even more restricted differentiation abilities. ESCs, derived from the inner cell mass of the blastocyst, are pluripotent and capable of differentiating into any cell type, though their use in research is ethically debated. Somatic or adult stem cells, found throughout the body, aid in healing, growth, and cell replacement, with mesenchymal stem cells, neural stem cells (NSCs), HSCs, and skin stem cells being notable examples. Below, we summarize the contributions of ncRNAs to each of the three major categories of stem cells.

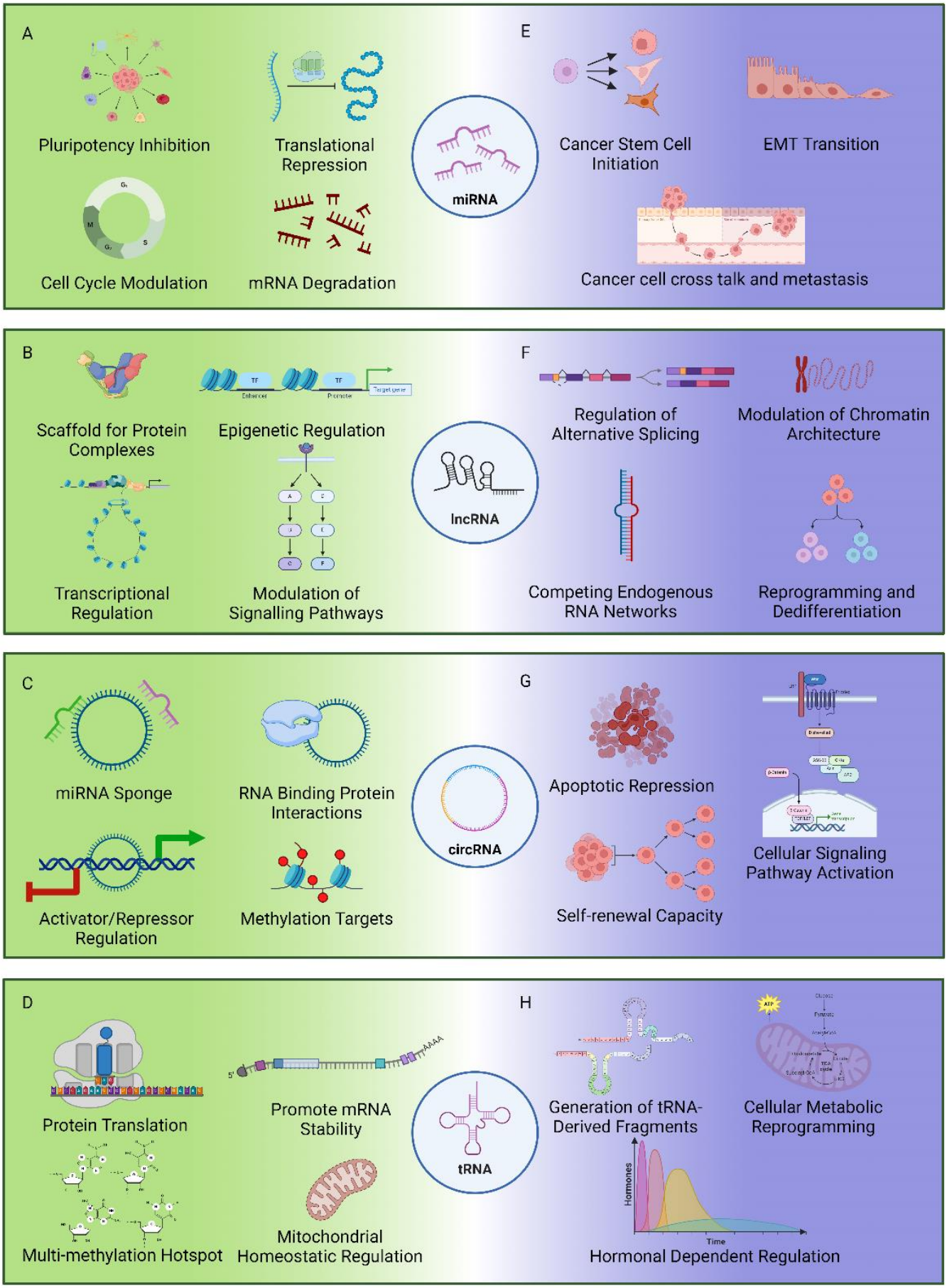
A
Pluripotency Inhibition
Translational Repression
Cell Cycle Modulation
mRNA Degradation
miRNA
E
Cancer Stem Cell Initiation
EMT Transition
Cancer cell cross talk and metastasis
B
Scaffold for Protein Complexes
Epigenetic Regulation
Transcriptional Regulation
Modulation of Signalling Pathways
lncRNA
F
Regulation of Alternative Splicing
Modulation of Chromatin Architecture
Competing Endogenous RNA Networks
Reprogramming and Dedifferentiation
C
miRNA Sponge
RNA Binding Protein Interactions
Activator/Repressor Regulation
Methylation Targets
circRNA
G
Apoptotic Repression
Self-renewal Capacity
Cellular Signaling Pathway Activation
D
Protein Translation
Promote mRNA Stability
Multi-methylation Hotspot
Mitochondrial Homeostatic Regulation
tRNA
H
Generation of tRNA-Derived Fragments
Cellular Metabolic Reprogramming
Hormones
Time
Hormonal Dependent Regulation

Figure 1. Roles of ncRNAs in Stem Cells (A to D) and CSCs (E to H). (A) miRNAs in stem cells. miRNAs play multiple roles in balancing self-renewal and differentiation. They achieve this balance through translational repression and mRNA degradation, controlling the levels of proteins vital for stem cell maintenance and lineage specification. Additionally, miRNAs modulate the cell cycle, ensuring proper progression through different phases essential for self-renewal and differentiation. (B) lncRNAs in stem cells. lncRNAs serve as scaffolds for protein complexes, facilitating the assembly of multi-protein complexes that are essential for various cellular functions. They also play a significant role in epigenetic regulation by interacting with chromatin modifiers to influence gene expression. Additionally, lncRNAs are involved in transcriptional regulation, where they modulate the activity of transcription factors and RNA polymerase. Furthermore, lncRNAs modulate signaling pathways, acting as key regulators of cellular signaling networks. (C) circRNAs in stem cells. circRNAs act as miRNA sponges, sequestering microRNAs and preventing them from binding to their target mRNAs, thereby regulating gene expression. They interact with RNA-binding proteins, influencing the stability, localization, and translation of mRNAs. Additionally, circRNAs are involved in activator/repressor regulation, modulating transcriptional activities. They also serve as targets for methylation, affecting gene expression and cellular functions. (D) tRNAs in stem cells. tRNAs play a fundamental role in protein translation, facilitating the translation of mRNA into proteins. They promote mRNA stability by protecting mRNAs from degradation, thereby ensuring efficient protein synthesis. tRNAs also serve as multi-methylation hotspots, influencing gene expression and cellular functions through epigenetic modifications. Additionally, tRNAs are involved in mitochondrial homeostatic regulation, maintaining mitochondrial function and energy production. (E) miRNAs in cancer cell plasticity. miRNAs facilitate CSC initiation and maintenance, which ultimately drive tumor initiation, growth, and recurrence. They also regulate EMT, enabling cancer cells to gain migratory and invasive properties necessary for metastasis. Moreover, miRNAs promote cancer cell crosstalk and metastasis by facilitating communication between cancer cells and their microenvironment, aiding in metastatic spread and colonization of new tissues. (F) lncRNAs in cancer cell plasticity. lncRNAs regulate alternative splicing, influencing the generation of diverse protein isoforms that contribute to cancer progression. They modulate chromatin architecture, affecting the accessibility of DNA to the transcriptional machinery and thus altering gene expression profiles. lncRNAs also participate in ceRNA networks, where they act as sponges for microRNAs, thereby regulating the availability of microRNAs to their target mRNAs. lncRNAs play a crucial role in reprogramming and dedifferentiation, processes that enable cancer cells to acquire stem cell-like properties and contribute to tumor heterogeneity and adaptability. (G) circRNAs in cancer cell plasticity. circRNAs contribute to apoptotic repression, enabling cancer cells to evade programmed cell death. They enhance the self-renewal capacity of CSCs, promoting tumor growth and recurrence. Additionally, circRNAs are involved in activating cellular signaling pathways that drive cancer progression and metastasis. (H) tRNAs in cancer cell plasticity. tRNAs contribute to the generation of tRFs, which can regulate gene expression and cellular processes. They play a role in cellular metabolic reprogramming, allowing cancer cells to adapt their metabolism to support rapid growth and survival. tRNAs also participate in hormone-dependent regulation, influencing hormone levels and signaling pathways that are crucial for cancer progression.

3.1 miRNA in stem cells

miRNA profiling during human development reveals specific miRNA signatures at various stages, suggesting roles in early lineage differentiation and developmental processes. These small regulatory

RNAs play various roles in cancer. miRNAs influence stem cell behavior through several mechanisms (Figure 1A). They regulate the expression of key transcription factors and signaling pathways that govern stem cell maintenance, differentiation, and self-renewal [94,95]. Additionally, miRNAs can modulate the cell cycle, promoting or inhibiting cell division as needed to maintain stem cell populations. They also participate in fine-tuning cellular responses to environmental cues, such as growth factors and cytokines, which further influences stem cell fate decisions. Furthermore, miRNAs are involved in epigenetic regulation by interacting with chromatin-modifying enzymes, thereby affecting the transcriptional landscape of stem cells [96]. Collectively, these mechanisms highlight the pivotal role of miRNAs, explained in further detail below.

3.1.1 Embryonic stem cells

Multiple layers of control regulate pluripotency and differentiation in human ESCs (hESCs). At the transcriptional level, the core factors OCT4, NANOG, and SOX2 establish a positive autoregulatory loop crucial for maintaining an undifferentiated state. On the post-transcriptional level, these transcription factors are directly repressed by *miR-145* through targeting of their 3’ UTR, thereby controlling the rate of differentiation of hESCs away from their pluripotent state [97,98]. Additionally, recent findings reveal that *OCT4* and *miR-302* collaborate to repress *NR2F2* at the transcriptional and post-transcriptional levels in undifferentiated hESCs. During differentiation, the decline of *OCT4* and *miR-302* permits the activation of *NR2F2*, which in turn inhibits *OCT4*, creating a feedback loop. This intricate interplay of transcriptional and post-transcriptional mechanisms not only sustains the pluripotency of hESCs but also facilitates the precise specification of neuroectoderm lineages during differentiation [99].

3.1.2 Hematopoietic stem cells

HSCs are affected by aging, leading to a decline in their self-renewal and regeneration capabilities, independent of their microenvironment. miRNAs play crucial roles in maintaining HSC function and can modulate tissue senescence in specific cell types [100,101]. *miR-146a* has been found to regulate the inflammatory response and maintain HSC homeostasis. Depletion of *miR-146a* leads to the fatigue of HSCs, the development of hematological tumors, and myeloproliferative neoplasms. It has been linked to chronic inflammation and age-related decline in HSC activity [102]. Another important miRNA, *let-7,* is highly active during embryogenesis and brain development and continues to be expressed in adult tissues [103,104]. In addition to its role in development, *let-7* plays a critical function in regulating HSC fate, working alongside *miR-99a/100, miR-125b-1/2*, and *LIN28B* to control

processes such as self-renewal, proliferation, quiescence, and differentiation [104,105]. Cluster 1-a (*let-7a-2, miR-100, miR-125b-1*) and Cluster 1-b (*let-7c, miR-99a, miR-125b-2*) are involved in maintaining HSPC homeostasis, primarily by inhibiting the TGFβ pathway and enhancing Wnt signaling [106]. Conversely, *LIN28B* represses *let-7*, inhibiting erythroid development and maintaining stemness.

3.1.3 Neural stem cells

MicroRNAs regulate neurogenesis through a feedback mechanism involving transcription factors and epigenetic factors. *miR-9* and the nuclear receptor TLX form a feedback loop that regulates neural stem cell proliferation and differentiation. *miR-9* targets TLX, reducing its expression to promote differentiation, while TLX represses *miR-9* to maintain stem cell self-renewal [107,108].

3.2 lncRNAs in stem cells

Recent literature suggests that close to a thousand lncRNAs have been identified as potential regulators of stem cell renewal [109]. lncRNAs influence stem cell behavior through several key mechanisms (Figure 1B). They act as molecular scaffolds, bringing together protein complexes and directing them to specific genomic locations, thereby modulating gene expression crucial for stem cell maintenance and differentiation. Additionally, lncRNAs can function as decoys, sequestering transcription factors, miRNAs, or other regulatory molecules away from their targets, thus impacting the transcriptional and post-transcriptional landscape of stem cells. They also play roles in chromatin remodeling by interacting with chromatin-modifying enzymes and altering the epigenetic state of stem cell-specific genes. Moreover, lncRNAs can serve as guides, directing chromatin-modifying complexes to specific genomic loci to activate or repress transcription. They also play a role in regulating post-translational modifications by acting as scaffolds. Several of those roles are highlighted below.

3.2.1 Embryonic stem cells

The lncRNA *Panct1* is involved in the pluripotency pathway in mouse ESCs. *Panct1* interacts with the protein TOBF1, recruiting it to the promoters of pluripotency genes during the early G1 phase of the cell cycle. This recruitment is crucial for the maintenance of the pluripotent state. Loss of *Panct1* and TOBF1 leads to the downregulation of pluripotency factors, indicating the essential role of lncRNAs in regulating ESC identity through protein interactions [110]. The lncRNA *Xist* plays a key role in regulating the fate of ESCs by initiating gene silencing through coating one of the two X chromosomes in female mammals. This process prevents gene dosage imbalance between

females and males [111]. *Xist* further influences ESC development through the use of TALE-based designer transcription factors, guiding cell differentiation and maintaining proper cellular function [112,113].

3.2.2 Hematopoietic stem cells

The lncRNA *H19* maintains the quiescent state of long-term hematopoietic stem cells (LT-HSCs), which are responsible for sustaining hematopoiesis over the lifetime of an organism. *H19* prevents LT-HSCs from excessive proliferation, which is essential for the long-term maintenance and self-renewal of HSCs [114,115]. It also acts as a molecular sponge for microRNAs that target *Igf2*, thus modulating the levels of IGF2 protein, which in turn interacts with the IGF1 receptor on HSCs.

3.2.3 Neural stem cells

Over the years, there has been increasing evidence of lncRNAs contributing to the neuronal structural development in murine models. For instance, *Evf2* regulates the transcription of *Dlx5* and *Dlx6* in the developing mouse forebrain by recruiting DLX and MECP2 transcription factors to regulatory elements in the *Dlx5/6* intergenic region [116]. Similarly, *Lacuna* acts as a negative regulator of neurogenesis by inhibiting the differentiation of NSCs into neurons, while also modulating a neighboring NSC differentiation-related gene Eomes [117]. While the aforementioned lncRNAs have a temporal-specific role during embryonic development, other lncRNAs such as *pnky* have been identified to function in a broader window across different stages of brain development. *Pnky* interacts with the splicing regulator PTBP1 to maintain NSCs and balance neurogenesis, with its knockdown leading to enhanced neuronal differentiation [118].

3.3 circRNAs in stem cells

Recent literature suggests that numerous circRNAs have been identified that regulate stem cell behavior [119]. circRNAs influence stem cell fate and function through several key mechanisms (Figure 1C). They can act as molecular sponges, sequestering miRNAs and preventing them from repressing their target mRNAs, which can be important for maintaining the balance of gene expression needed for stem cell maintenance and differentiation. Additionally, circRNAs are involved in regulating transcription by interacting with transcription factors and RNA-binding proteins, modulating the transcriptional landscape of stem cells. They also play roles in the splicing process, influencing the production of different isoforms of proteins essential for stem cell functions. Furthermore, circRNAs are implicated in the regulation of apoptosis and

cell cycle progression, which are critical for stem cell proliferation and survival. A few examples are provided below.

3.3.1 Embryonic stem cells

The circRNA *circBIRC6* functions by sponging microRNAs such as *miR-34a* and *miR-145*, which are involved in the down-regulation of genes that maintain pluripotency. By absorbing these microRNAs, *circBIRC6* prevents the premature differentiation of ESCs, thereby preserving their ability to self-renew [120]. In contrast to the involvement of specific circRNAs, the overall biogenesis of circular isoforms from the linear counterparts was demonstrated to be controlled by specific proteins such as FUS3 [121]. circRNAs regulated by *FUS* in mice are similarly regulated in human cells, indicating a conserved mechanism across species.

3.3.2 Hematopoietic stem cells

The circRNA *cia-cGAS* is significantly upregulated in LT-HSCs. This circRNA inhibits the activation of cGAS, an enzyme that triggers type I interferon production, a process that can lead to HSC failure if overactivated. By suppressing cGAS-induced type I interferon production, *cia-cGAS* ensures the proper function and longevity of HSCs [122]. Interestingly, as HSCs commit to their differentiated lineage, the abundance and expression patterns of circRNA change with a notable rise in key stages such as enucleation and platelet formation [123,124]. While hematopoietic cell-type-specific circRNA profiles have been identified, there is much left to be elucidated functionally.

3.3.3 Neural stem cells

Distinct circRNA profiles have also been identified in neural stem cells [125]. The circRNA *circHIPK2* is highly expressed at the early stages of NSC differentiation, with its levels decreasing over time. Silencing *circHIPK2* significantly promoted the differentiation of NSCs into neurons, as evidenced by increased expression of neuronal markers such as TUJ1, NeuN, and MAP2, without affecting their differentiation into astrocytes. Transplantation of NSCs transduced with *circHIPK2* siRNA into stroke-induced mice resulted in improved neuronal plasticity and functional recovery, indicating that *circHIPK2* acts as a regulatory molecule guiding NSCs towards a neuronal fate [126]. A recent study demonstrated that silencing of *circFAT3* affects the differentiation of neural progenitors and leads to changes in gene expression associated with neural development, including *FAT4* and *ERBB4* [127].

3.4 tRNAs in stem cells

The structural complexity, diverse sites of modifications, and post-transcriptional modifications of tRNAs present a multitude of factors that contribute to their uniqueness and facilitate biological interplay beyond their traditional role in protein synthesis [128,129]. tRNAs influence stem cell behavior through several key mechanisms (Figure 1D). They play a crucial role in maintaining the cellular protein synthesis machinery, ensuring the production of proteins necessary for stem cell renewal and differentiation. Additionally, tRNAs are involved in regulating gene expression through their interactions with ribosomes and other RNA molecules, impacting the translation efficiency and stability of specific mRNAs. Post-transcriptional modifications of tRNAs, such as methylation and pseudouridylation, can affect their stability and function, thereby influencing stem cell fate decisions. Furthermore, tRNAs can act as signaling molecules, participating in stress response pathways and modulating stem cell survival under adverse conditions. Several examples are detailed below.

3.4.1 Embryonic stem cells

The role of 5'-tRFs in stem cell differentiation was investigated in murine ESCs (mESCs), revealing their enrichment in differentiated cells. Krishna et al. identified a specific subset of tRNA loci contributing to 5'-tRFs and suggested an angiogenin-independent processing mechanism [129]. The study demonstrates that 5'-tRFs regulate translation at multiple steps, interact with target mRNAs and ribosomal proteins, and confer functional heterogeneity to ribosomes [130]. Notably, *tsGlnCTG* interacts with the RNA-binding protein Igf2bp1, destabilizing the Igf2bp1-c-Myc complex and reducing *c-Myc* mRNA stability, crucial for stem cell maintenance and differentiation [131,132]. Despite modest increases in tRF levels, their specific interactions with target transcripts and proteins are enhanced under differentiation conditions, indicating additional regulatory factors discussed below.

3.4.2 Hematopoietic stem cells

Pseudouridine (Ψ) is a universal modification found in all RNA species, predominantly catalyzed by the human pseudouridine synthase 7 (PUS7) enzyme [133]. PUS7 has been reported to be upregulated in HSCs compared to other pseudouridine synthase family members. Functional knockout of PUS7 in hESCs using CRISPR/Cas9 led to a noticeable increase in overall cell size and non-specific cell fate commitment during the differentiation phase. The absence of pseudouridylation impairs hematopoiesis and renders HSCs functionally defective, ultimately driving disease progression. This study also uncovered a previously unidentified subset of transfer RNA-derived fragments (tRFs) as novel binding targets

of PUS7, with Ψ playing a regulatory role in protein synthesis rates and stem cell fate establishment during embryogenesis [134].

3.4.3 Neural stem cells

Compared to the cytoplasmic tRNA with a consistent high ratio of tRNAs to cytoplasmic mRNAs for highly efficient protein translation, the mitochondrial genome only encodes for 22 mt-tRNAs [83] while harboring the same burden of recognizing all 20 amino acids. Consequently, mutations or modification differences applied to mt-tRNAs elicit more deleterious biological effects due to the insufficient availability of tRNA isoacceptor variants. METTL8, a methyltransferase that specifically deposits the m3C modification on mt-tRNA threonine/serine, was shown to be critical for controlling the differentiation capacity of cortical neural stem cells in a mouse model [135]. The deletion of METTL8 significantly suppresses synthesis of mitochondrial proteins, driving the earlier neuronal differentiation. Interestingly, the knockout effects are rescuable through pharmacological enhancement of the respiratory capability in mitochondria.

4. ncRNAs in Cancer Cell Plasticity and Heterogeneity

Cancers originating in different tissue sites are generally further categorized into molecular subtypes, acknowledging that the lineage plasticity of cells or tumors is intertwined with the transition from subtype one to subtype two. This plasticity contributes to the heterogeneity observed in solid tumors. For instance, the most prevalent and well-studied non-cutaneous cancer, breast cancer, is classified into two major histological subtypes: luminal and basal. These subtypes can be further distinguished into four molecular types: estrogen receptor positive/progesterone receptor positive ER+/PR+, estrogen receptor negative/progesterone receptor negative ER-/PR-, HER2+, and Triple Negative Breast Cancer (TNBC) [136]. High ER and PR expression in luminal breast cancer tumors historically have better prognosis than basal tumors. Consequently, previous studies have shown evidence of ER-low luminal tumors undergoing plasticity to gain characteristics of basal-like tumors through drivers such as *SOX10* expression, suggesting this plasticity is largely regulated by changes in transcriptomic dynamics [137,138].

On the other hand, the interactions between surrounding metabolites and the TME also influence cellular plasticity from the context of acquiring energy sources for survival and proliferation. Cancer cells are capable of switching between glycolysis, a glucose-dependent pathway, or the mitochondrial oxidative phosphorylation for metabolic functions. Specifically, the growth of cancer cells in a three-dimensional structure recapitulates metabolic plasticity of the TME, which favors

mitochondrial-dependent metabolism with greater glycolytic reserve potential and reduced dependency on glutamine supplementation [139]. In prostate cancer, increased levels of glutamine help drive resistance to radiotherapy. Therefore, metabolites also regulate the survival of CSCs in certain diseases [140].

4.1 miRNAs

Recent evidence suggests that miRNAs play a regulatory role in cancer cell plasticity [141], impacting processes such as self-renewal, differentiation, and resistance to therapy [142,143] (Figure 1E). They achieve this by modulating gene expression at the post-transcriptional level, which affects the behavior and characteristics of cancer cells. miRNAs can control EMT, a critical process for cancer metastasis, by targeting specific transcription factors and signaling pathways involved in this transition. Additionally, miRNAs influence the TME by altering the expression of genes involved in cell-cell communication and extracellular matrix remodeling. They can be packaged into exosomes and transported to other cells, thereby affecting gene expression and signaling pathways in recipient cells [144]. This crosstalk between cancer cells and their microenvironment facilitated by miRNAs contributes to the dynamic nature of tumor growth and metastasis. Through these mechanisms, miRNAs that are integral to the regulation of cancer cell plasticity are summarized in Table 1, with selected examples elaborated further below.

miRNAs function through complex mechanisms that are highly dependent on the specific cell type and molecular context. In glioma stem cells, *miR-34a* acts as a tumor suppressor by targeting and inhibiting the expression of oncogenes such as *c-Met, Notch-1*, and *Notch-2* [145]. These are key pathways for maintaining the self-renewal and survival of glioma cells. By downregulating these oncogenes, *miR-34a* induces cell cycle arrest, prevents cell migration, and promotes differentiation, thereby reducing the malignant potential of glioma stem cells. In prostate cancer, *miR-34a* functions through a different mechanism by directly targeting CD44, a surface adhesion molecule highly expressed in prostate CSCs, which are responsible for tumor initiation, metastasis, and resistance to therapies [146]. miR-34a binds to the 3'-UTR of CD44 mRNA, leading to its degradation and reduced protein expression. The knockdown of CD44 in prostate CSCs phenocopies the effects of *miR-34a* overexpression, inhibiting clonogenic expansion and metastasis. *In vivo* studies have shown that systemic delivery of *miR-34a* significantly reduces metastasis and extends the survival of mice with prostate cancer xenografts. This context-dependent activity of *miR-34a* underscores the complexity of its regulatory role across various cancers. Its ability to target distinct oncogenes or tumor suppressor genes in different cancer types reflects

its potential as a therapeutic tool. This adaptability suggests that its application could be tailored to address the specific molecular pathways that are dysregulated in each cancer type.

Table 1. Function of miRNAs in CSCs and their interaction partners

Mechanism	miRNA	Biological process	Cancer type	Reference
Suppressing CSC properties	*miR-34a*	NOTCH-1, NOTCH-2, c-Met CD44	Brain cancer Prostate cancer	[145] [146]
	MiR-200 family	BMI1 Suz12 Epigenetic modifications	Breast cancer Breast cancer Breast cancer	[147] [148] [149]
	miR-223-3p	NLRP3 inflammasome	Breast cancer	[150]
	miR-141	CD44, EZH2 and Rho GTPases	Prostate cancer	[151]
	miR-150	Nanog	Leukemia	[152]
	miR-508	CDH1, ZEB1, SALL4, BMI1, long noncoding RNA AK000053	Colorectal cancer	[153]
	let-7 b	Frizzled 4	Liver cancer	[154]
	let-7 a	Wnt1	Hepatocellular cancer	[155]
	let-7	H-RAS and HMGA2	Breast cancer	[156]
Promoting CSC Properties	*miR-31*	Wnt antagonists, including Dkk1	Breast cancer	[157]
	miR-21	PTEN, PDCD4, RECK	Gastric cancer	[158]
	miR-30 family	Ubc9, ITGB3, AVEN	Breast cancer	[159]
	miR-93	RGMB	Head and neck squamous cell carcinoma	[160]
	miR-106b	PTEN CASP7 TRAIL	Breast cancer Prostate cancer Hepatocellular carcinoma	[161] [162] [163]
	miR-92a	KLF4, GSK3β, DKK3	Colorectal cancer	[164]
	miR-217	DKK1	Hepatocellular carcinoma	[165]
	miR-452	SOX 7	Hepatocellular carcinoma	[166]
	miR-451	PI3K/Akt/mTOR	Multiple myeloma	[166]
	miR-126	PI3K/AKT/mTOR pathway	Acute myeloid leukemia	[167]
	miR-22	TET2	Myelodysplastic syndrome and leukemia	[168]

miR-31 plays a role in maintaining mammary stem cells and promoting breast cancer development and progression. *miR-31* is significantly enriched in breast cancer stem cells (BCSCs) (CD24+CD90+), showing a fivefold increase compared to CD24−CD90− cells [157]. This miRNA favors the expansion of BCSCs and their tumor-initiating capability. Loss of *miR-31* reduces metastasis, evidenced by lower levels of EMT-associated factors and metastasis inhibitors, a shift to a mesenchymal-like phenotype, reduced lung metastasis, and higher metastasis-free survival in PyVT/KO mice. Moreover, the expression of *miR-31* is regulated by the NF-κB pathway. miR-31 directly targets Wnt antagonists, including AXIN1, GSK3β, and DKK1, thereby activating the Wnt-β-catenin pathway, which ultimately contributes to tumor progression.

The *miR-200* family and *miR-205* play a crucial role in regulating EMT by targeting the transcriptional repressors ZEB1 and SIP1 [169,170]. These microRNAs are markedly downregulated in cells undergoing EMT, either due to TGF-β exposure or ectopic expression of the protein tyrosine phosphatase Pez. Enforced expression of *miR-200* alone can prevent TGF-β-induced EMT, indicating its critical role in maintaining the epithelial phenotype. Conversely, inhibition of these microRNAs induces EMT, characterized by loss of E-cadherin and gain of mesenchymal markers, along with enhanced cell motility. Moreover, the loss of miR-200 and *miR-205* is observed in invasive breast cancer cell lines and regions of metaplastic breast cancer specimens, suggesting that mechanisms involved in the downregulation of these microRNAs indeed contribute to tumor progression and metastasis [171].

4.2 lncRNAs

lncRNAs play pivotal roles in regulating cancer cell plasticity through several key mechanisms (Figure 1F) [172]. One of their most well-documented and well-established functions is their role in regulating alternative splicing, leading to diverse protein isoforms that enhance cancer cell adaptability [173–175]. lncRNAs also act as molecular scaffolds, organizing chromatin-modifying complexes and transcription factors at specific genomic loci, thereby altering chromatin architecture to activate or repress gene expression [176–178]. This impacts key cellular processes such as proliferation, differentiation, and the maintenance of CSC properties. Additionally, lncRNAs serve as competing endogenous RNAs (ceRNAs) by sequestering miRNAs, preventing them from binding to their target mRNAs. They further facilitate crosstalk, between cancer cells and the TME, influencing stromal and immune cell behavior to create a supportive niche for tumor growth and metastasis. lncRNAs also promote reprogramming and dedifferentiation, which enhance the stem-like state and resilience of cancer cells. These aspects are detailed in Table 2, with additional examples explored further below.

Table 2. Function of lncRNAs in CSCs and their interaction partners.

Mechanism	lncRNA	Biological process	Cancer type	Reference
Suppressing CSC properties	*lnc-DILC*	IL-6/Stat3	Liver cancer	[179]
	lncRNA-p21	β-catenin	Colorectal cancer	[180]
	lncRNA-BACE1-AS	Anisomycin	Ovarian cancer	[181]
	lncRNA-LBCS	SOX2	Bladder cancer	[182]
Promoting CSC Properties	*Xist*	IL-6/STAT3, let-7a-2-3p sponge	Breast Cancer	[183]
	H19	SOX2, OCT4 Let-7, LIN28	Prostate cancer Breast cancer	[184] [185]
	lncHOXA10	HOXA10	Liver cancer	[177]
	MALAT1	SOX2	Pancreatic cancer	[186]
	HOTAIR	PRC2 mir-7 c-Myc	Breast cancer Breast cancer Gallbladder cancer	[187] [188] [189]
	lncRNA SOX2-OT	SOX2, Yin Yang-1 SOX2	Pancreatic ductal adenocarcinoma Breast cancer	[190] [191]
	lncCUDR	HULC, β-catenin	Liver cancer	[192]
	lncHDAC2	PTCH1	Hepatocellular carcinoma	[193]
	lncTCF7	SWI/SNF	Hepatocellular carcinoma	[194]
	lncARSR	YAP/TEAD	Renal cell carcinoma	[195]
	lncSOX4	Stat3	Hepatocellular carcinoma	[196]
	lncDANCR	CTNNB1	Hepatocellular carcinoma	[197]
	lnc-β-catm	EZH2-dependent methylation, Wnt/β-catenin	Liver cancer	[198]

In prostate stem-like cells, *H19* has been shown to enhance stemness through its regulation of key pluripotency transcription factors, namely OCT4 and SOX2 [184]. Cells expressing high levels of *H19* display stem-like properties, including increased expression of stem cell surface markers, resistance to cell death, and enhanced sphere-forming capacity. Suppressing *H19* with siRNA leads to a decrease in OCT4 and SOX2 expression, which in turn reduces colony-forming potential and other stem cell-like characteristics. Conversely, overexpression of *H19* enhances these traits, promoting the maintenance of prostate CSCs. This suggests that in prostate cells, *H19* directly influences transcriptional regulators which govern stemness and survival. In

contrast, in BCSCs, *H19* plays a different regulatory role through an *H19/let-7/LIN28* pathway, highlighting the complexity of lncRNA functions. In this system, *H19* acts as a ceRNA to sponge the tumor-suppressive miRNA *let-7,* which leads to the upregulation of *LIN28*, a pluripotency factor that supports BCSC maintenance. *LIN28* further inhibits the maturation of *let-7*, creating a feedback loop that reinforces high levels of *H19* and *LIN28*, thereby sustaining BCSC properties such as self-renewal and tumorigenicity. This reciprocal negative feedback loop is essential for maintaining BCSCs and promoting their therapy resistance [185]. These examples underscore the context-dependent role of lncRNAs.

The lncRNA *MALAT1* plays a functional role in regulating cell cycle progression by modulating the expression of the oncogenic transcription factor B-MYB. *MALAT1* is differentially expressed throughout the cell cycle and is essential for both the G1/S and mitotic phases. Depletion of *MALAT1* activates p53 and its target genes, leading to cell cycle arrest and reduced cellular proliferation. This cell cycle arrest is particularly noteworthy as it implicates p53 as a major downstream mediator of *MALAT1* activity. Furthermore, *MALAT1* promotes the proliferation and invasiveness of CSCs in pancreatic and liver cancers by modulating the expression and pre-mRNA processing of key transcription factors involved in mitotic progression [186,199]. *MALAT1*-depleted cells also exhibit defects in chromosome segregation and spindle assembly, highlighting *MALAT1*'s role in maintaining genomic stability during mitosis [200].

lncRNA *HOTAIR* interacts with the Polycomb Repressive Complex 2 (PRC2) to modify histones and silence gene expression, affecting EMT and CSC maintenance [187]. In BCSCs, *HOTAIR* indirectly suppresses *miR-7,* which normally inhibits the oncogene *SETDB1*. This suppression facilitates EMT and the maintenance of the CSC pool by upregulating the STAT3 pathway, leading to increased expression of *c-myc*, *Twist*, and *miR-9* [188]. Moreover, *HOTAIR* modulates the expression of *HoxD10*, which contributes to *miR-7* downregulation and further promotes tumor invasiveness.

lncRNA SOX2 Overlapping Transcript (*SOX2-OT*) regulates the expression of the *SOX2* gene, a critical factor for maintaining pluripotency and self-renewal in stem cells. This lncRNA enhances the stem-like properties of cancer cells by upregulating *SOX2* expression. *SOX2-OT* is involved in various cancers, where it promotes tumor growth and CSC maintenance by regulating *SOX2* levels. This regulation contributes to the aggressiveness and recurrence of these malignancies [190,191,201].

4.3 circRNAs

circRNAs contribute to the plasticity of cancer cells under stress and therapeutic pressures through several mechanisms (Figure 1G) [202]. In cancer cells, circRNAs act as molecular sponges for miRNAs to prevent the repression of oncogenic targets, thus promoting cancer progression and metastasis. Additionally, circRNAs interact with RNA-binding proteins and transcription factors to modulate gene expression and stabilize mRNAs related to cancer, leading to changes in cell cycle progression, apoptosis resistance, and enhanced metastatic potential. This modulation of gene expression primarily supports cell survival and proliferation in cancer. Furthermore, circRNAs in cancer cells facilitate dynamic adaptability by regulating apoptosis and cell cycle pathways, enabling cancer cells to evade death and sustain growth. These circRNAs are detailed in Table 3 and further explained below.

Table 3. Function of circRNAs in CSCs and their interaction partners.

Mechanism	circRNA	Biological process	Cancer type	Reference
Suppressing CSC properties	*circZKSCAN1*	FMRP	Hepatocellular carcinoma	[203]
	circRGPD6	miR-26b/YAF2	Breast cancer	[204]
Promoting CSC Properties	*circAGFG1*	miR-4262 and miR-185-5p	Colorectal cancer	[205]
	hsa_circ_002178	miR-1258/KDM7A	Breast cancer	[206]
	circCTIC1	c-Myc	Colon cancer	[207]
	circE-cad	EGFR-STAT3	Glioblastoma	[208]
	circZNF800	miR-140-3p, miR-382-5, miR-579-3p	Colorectal cancer	[209]
	hsa_circ_0003222	miR-527	Non-small cell lung cancer	[210]
	hsa_circ_001680	miR-340	Colorectal cancer	[211]

The circRNA *circAGFG1* was found to be upregulated in colorectal cancer cell lines and its knockdown leads to a marked reduction in cell proliferation, migration, invasion, and stemness, while enhancing apoptosis [205]. This indicates the crucial role of *circAGFG1* in maintaining the CSC properties, including self-renewal and metastatic potential. The mechanism involves *circAGFG1* sponging *miR-4262* and *miR-185-5p*, which ordinarily suppress the expression of the transcription factor YY1. By sequestering these miRNAs, *circAGFG1* facilitates the upregulation of YY1, which in turn promotes the transcription of *CTNNB1*. The activation of the Wnt/β-catenin signaling pathway through this *circAGFG1/miR-4262/miR-185-5p/YY1/CTNNB1* axis enhances CSC properties and contributes to colorectal cancer progression and metastasis.

The circRNA *hsa_circ_002178* is significantly upregulated in breast cancer tissues and cell lines and its high expression correlates with poor clinical outcomes, including low survival rates, larger tumor size, lymph node metastasis, and advanced TNM stage. Mechanistically, *hsa_circ_002178* promotes the growth, invasion, and migration of breast cancer cells by modulating the *miR-1258/KDM7A* axis. Overexpression of *hsa_circ_002178* leads to the formation of microspheres, and increased levels of stemness markers (ALDH1, CD44, NANOG, and OCT4), and elevated ALDH1 activity, which are indicative of enhanced CSC properties. This circRNA acts as a sponge for *miR-1258*, thereby reducing the miRNA's inhibitory effect on *KDM7A*. *KDM7A*, in turn, facilitates the stem-like characteristics of breast cancer cells, contributing to tumor growth and metastasis [206].

The circRNA *circCTIC1* was found to be highly expressed in colon tumors and colon tumor-initiating cells (TICs), and its knockdown impaired the self-renewal capacity of these cells, whereas overexpression enhanced it. Mechanistically, *circCTIC1* interacts with the nuclear remodeling factor (NURF) complex, recruiting it to the *c-Myc* promoter, thereby facilitating the transcriptional activation of *c-Myc*, a core transcription factor for stemness. This interaction underscores the role of *circCTIC1* as a protein modulator, driving the self-renewal and tumorigenic potential of colon TICs through the NURF-mediated c-Myc pathway [207].

4.4 tRNAs

tRNAs in cancer cells can undergo extensive modifications, enhancing their stability and functionality to meet the increased demands for protein synthesis of rapidly proliferating cancer cells (Figure 1H). These modifications can affect the efficiency and accuracy of translation, promoting the production of proteins that support cancer progression and metastasis [212]. Additionally, tRFs have recently emerged as novel regulators in cancer, where they can act as signaling molecules, influencing gene expression, and modulating cellular stress responses. tRNAs and tRFs are often co-opted to support oncogenic processes, including the regulation of apoptosis, cell cycle progression, and metabolic reprogramming, enabling cancer cells to evade cell death, sustain growth, and adapt to hostile microenvironments. Thus, tRNAs in cancer cells play a multifaceted role in maintaining the plasticity and resilience of cancer cells, distinguishing their function from the more static roles they perform in normal cellular contexts. tRNAs affecting cancer cell plasticity are detailed in Table 4, with some examples highlighted below.

Table 4. Function of tRNAs in CSCs and their interaction partners.

Mechanism	tRNA	Biological process	Cancer type	Reference
Suppressing CSC properties	*tDR-000620*	Cytokine-cytokine receptor interaction, AMPK signaling pathway	Breast cancer	[213]
	tRF-17-79MP9PP	TGF-β1/Smad3 axis	Breast cancer	[214]
	tRF/miR-1280	JAG2, Gata1&3, miR-200b, ZEB1, SUZ12	Colorectal cancer	[215]
Promoting CSC properties	*Gly-tRF*	NDFIP2, AKT	Hepatocellular carcinoma	[216]

tDR-000620 has been identified as significantly downregulated in the CSCs of TNBC. *tDR-000620* was found to play a pivotal role in the suppression of CSC traits, including the inhibition of EMT, recurrence, and metastasis. In TNBC, where the CSC population is highly enriched, the downregulation of *tDR-000620* correlates with enhanced self-renewal and tumor-initiating capacities, driving aggressive tumor behavior. Moreover, low *tDR-000620* expression was shown to be an independent adverse prognostic factor for recurrence-free survival, further linking its role to poor clinical outcomes. Functional analyses suggest that *tDR-000620* is involved in immune-response pathways such as cytokine-cytokine receptor interactions and AMPK signaling, which are essential in the regulation of cell proliferation, metabolism, and stress responses [213].

tRF/miR-1280 has emerged as a key regulator of CSC-like properties and metastasis in colorectal cancer (CRC). This 17-base pair fragment was shown to suppress Notch signaling pathways that support the function and maintenance of CSCs, which are crucial for tumor progression and metastasis. tRF/miR-1280 is significantly downregulated in CRC tissues compared to adjacent normal tissues, and its ectopic expression reduces cell proliferation, colony formation, and metastasis, indicating a tumor-suppressive function. Mechanistically, *tRF/miR-1280* directly targets the JAG2 ligand, inhibiting the activation of Notch1 and Notch2 receptors, which are essential for sustaining CSC-like traits in CRC. Through the inactivation of Notch signaling, *tRF/miR-1280* leads to the downregulation of critical transcription factors like *Gata1* and *Gata3*, and it increases the expression of *miR-200b,* a key regulator of EMT. This cascade ultimately results in the repression of ZEB1 and SUZ12*,* key drivers of CSC maintenance and EMT, thus preventing tumor growth and metastasis [215].

Glycine tRNA-derived fragment (*Gly-tRF*) enhances liver CSC-like properties and promotes the migration of hepatocellular carcinoma (HCC) cells by targeting *NDFIP2*, a key regulator of ubiquitin ligase function. *Gly-tRF* is upregulated in HCC tissues and cell lines, where it drives EMT and increases the stemness and migratory capacity of cancer cells.

Mechanistically, Gly-tRF downregulates *NDFIP2* by binding to its mRNA 3'-UTR, thereby activating the AKT signaling pathway, a pathway known to contribute to tumor progression and metastasis [216].

5. Potential Clinical Implications of ncRNAs in CSCs

The role of ncRNAs in cancer cell plasticity and their contributions to cancer development and progression position them as highly valuable biomarkers with diagnostic, prognostic, and therapeutic potential. Notably, ncRNAs, including CSC-derived ncRNAs, can be detected in biological fluids such as blood and serum. They can be found either as circulating tumor nucleic acids or within secreted circulating tumor cells (CTCs) and extracellular vesicles like exosomes [217]. This capability enables liquid biopsies, offering the advantage of detecting and monitoring the molecular identity and evolution of tumors in a minimally invasive manner, thus facilitating precise prognostic and therapeutic interventions. The applicability of detecting ncRNA expression in liquid biopsies has been validated in the diagnosis, prognosis, and recurrence monitoring of several cancers [218–222]. Liquid biopsies also hold potential in overcoming the limitations of tissue biopsies by identifying molecular heterogeneity between primary and metastatic tumor sites and detecting early tumor formation, unresponsiveness to conventional therapies and disease relapse, often associated with CSC occurrence and their molecular dysregulation at the ncRNA level.

Over the past decade, there has been growing interest in targeting CSC-related or even CSC-specific ncRNAs for CSC elimination. Instead of using drugs to target ncRNAs expressed in CSCs, studies are widely exploring the transport of ncRNA analogs or inhibitors into cells using synthetic nucleic acids. However, many challenges remain in selecting the appropriate CSC-related ncRNA target that is essential for CSC survival and function, as well as accurately evaluating how the introduced oligonucleotide will impact a key biological pathway in CSCs.

5.1 Biomarkers and diagnostics

5.1.1 miRNAs

The ease of detection of miRNAs in blood and CTCs, coupled with resistance to degradation, underscores their clinical potential [47]. Circulating miRNAs have demonstrated diagnostic power in various cancers, especially gastrointestinal malignancies [223]. For instance, isolating miRNAs from CTCs in colorectal and breast cancers ensures specificity by excluding non-cancer-related miRNAs in the bloodstream [224,225]. However, limitations include low disease and tissue specificity and the potential for non-cancer-related miRNA elevation due to

conditions such as inflammation [226]. These challenges are less pronounced in exosome-derived miRNAs, which show higher tissue and cancer type specificity [227]. The diagnostic and prognostic value of miRNAs is supported by their ability to regulate multiple downstream gene targets and pathways involved in oncogenesis and CSC stemness. For instance, *miR-548c-3p* has been identified as a diagnostic and prognostic marker in prostate cancer, as elevated levels of this miRNA are associated with poor patient survival [228,229]. *MiR-548c-3p* overexpression is predominantly found in the CD133+α2β1Hi CD44+ prostate cancer subpopulation, where it displays stem cell-like characteristics [230,231]. This miRNA is linked to the activation of stem cell-related genes, enhancing self-renewal and conferring radioresistance.

5.1.2 lncRNAs

lncRNAs, known for their tissue-specific expression patterns, are valuable biomarkers for cancer diagnosis and prognosis. Their regulatory roles in CSC pathophysiology suggest significant translational impacts in oncogenesis, tumor prognosis, and therapy [232]. lncRNAs can be detected in body fluids and are resistant to RNase degradation, making them suitable for liquid biopsies [23,233]. Due to their easy detectability, lncRNAs can be employed to predict cancer behavior before, during, or after anti-cancer therapies. For example, *PCA3* is a non-coding RNA that is overexpressed in prostate cancer tissues compared to normal tissues. The detection of *PCA3* in urine has become a non-invasive diagnostic tool, complementing the traditional prostate-specific antigen test. The *PCA3* test helps improve diagnostic accuracy by reducing unnecessary biopsies in patients with elevated PSA levels but a lower risk of aggressive prostate cancer, making it a valuable biomarker in clinical settings [234].

5.1.3 circRNAs

The stability, specificity, and detectability of circRNAs in body fluids, including exosomes, make them promising biomarkers for early cancer detection, monitoring progression, and guiding therapy [235–237]. Studies have shown that circRNA levels can be associated with tumor grade, size, and metastasis, making them valuable tools in cancer diagnostics. For instance, *circFARSA* levels are elevated in the plasma of non-small cell lung cancer patients, correlating with tumor aggressiveness [238]. Additionally, circRNAs found in exosomes offer potential for early disease detection, as they circulate in body fluids and reflect the molecular state of the tissues from which they originated [239,240].

5.1.4 tRNAs

Chemical modifications of tRNAs, such as methylation, play critical roles in maintaining the fidelity and efficiency of translation, which can be altered in cancer cells to support tumor growth and progression [241]. tRFs are novel biomarkers that can be used for diagnosis, prognosis, and classification of tumor subtypes. Specific types include 5'-tRFs that are upregulated in prostate adenocarcinoma (PRAD) and have been shown to distinguish PRAD tumors from normal tissues with high sensitivity and specificity [242]. Furthermore, a tRF score, based on eight 5'-tRFs, is highly predictive of survival in PRAD patients and offers improved prognostic information when combined with the Gleason score. Based on 5'-tRF expression profiles, four distinct molecular subtypes of PRAD have been identified that are each associated with different survival outcomes and clinicopathological features. These subtypes also exhibit distinct genomic landscapes, offering further prognostic insights.

5.2 Targeting methods and delivery

5.2.1 miRNAs

Oncogenic miRNA expression can be effectively inhibited using antisense oligonucleotides (ASOs), which bind to miRNA targets via base-pair complementarity (Figure 2A). The function of ASOs is enhanced by incorporating various chemical configurations such as locked nucleic acids, anti-miRNA oligonucleotides, and antagomirs, which improve their stability and efficacy [243,244]. For instance, an antagomir specifically designed to target and knockdown the oncogene *miR-21* has been employed in breast cancer MCF-7 cells. This intervention resulted in a notable reduction of MCF-7 tumor growth in both *in vitro* and *in vivo* tumor xenograft models, achieved by inhibiting cell proliferation and inducing apoptosis [245].

Additionally, the suppression of oncogenic miRNAs can be achieved using "miRNA sponges" (Figure 2A). These sponges work by incorporating complementary binding sites for miRNA-targeted RNA into RNA transcripts expressed from strong promoters. This mechanism effectively sequesters miRNAs, preventing them from binding to their endogenous targets, thereby inhibiting miRNA activity in cultured cancer cells and mouse models [243]. Inhibiting *miR-22* with a specific "sponge" in LM2 cells, a highly metastatic breast cancer cell line, led to a significant decrease in breast cancer metastasis to the lungs [246]. In contrast, miRNA mimics or lentiviral vectors can be employed to elevate the expression levels of tumor suppressor miRNAs, which are typically found to be underexpressed in cancer cells [247]. RNA interference (RNAi) includes siRNAs and short hairpin RNAs (shRNAs). While siRNAs offer transient gene silencing due to their instability, shRNAs provide

durable and long-lasting effects *in vivo* [248,249]. Virus transfection, the primary method for delivering shRNA plasmids to target sites, can also be employed to introduce exogenously synthesized miRNA plasmids into cancer cells, thereby upregulating the corresponding miRNA.

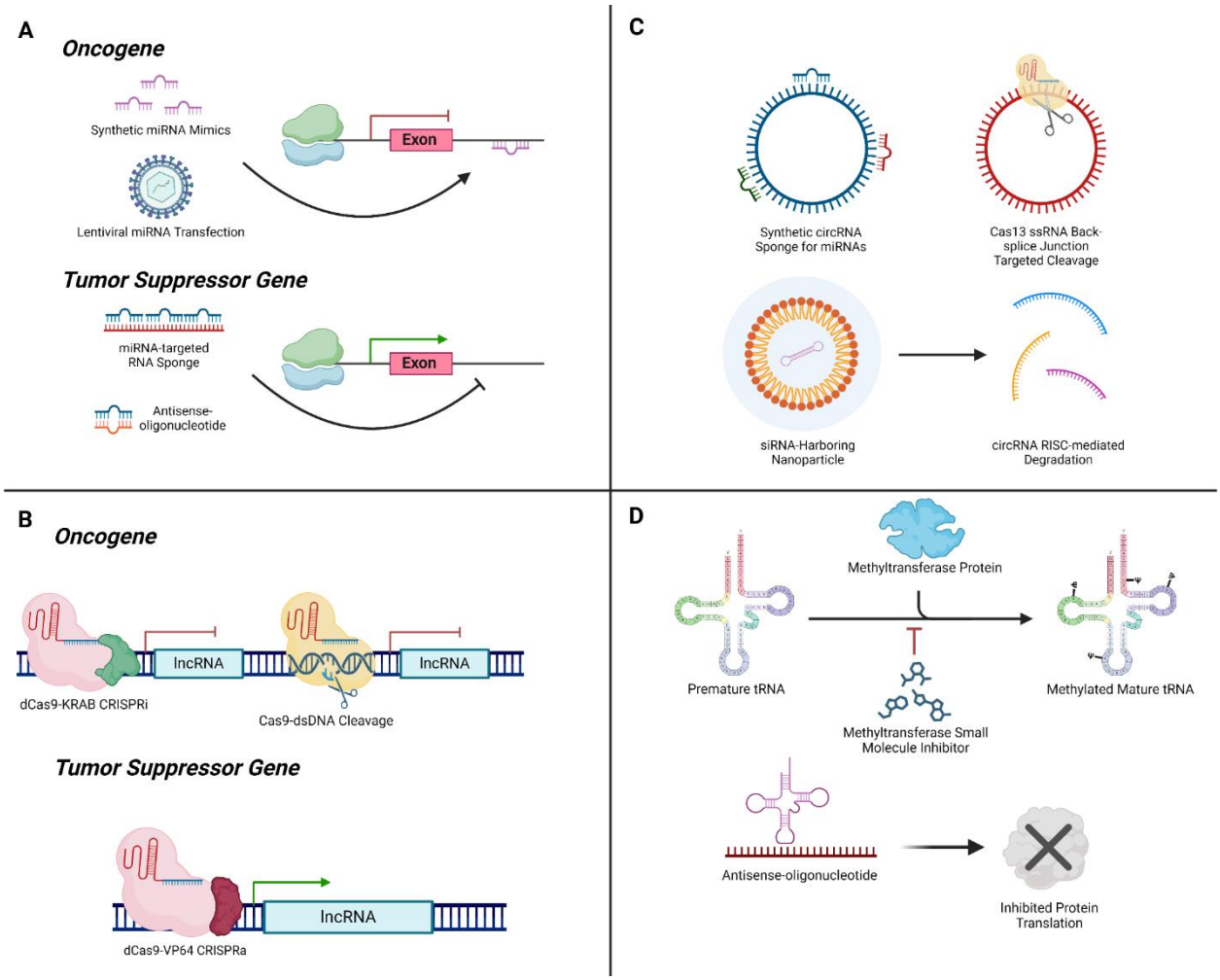

Figure 2. Therapeutic Potentials of ncRNAs. (A) Strategies for targeting oncogenes and tumor suppressor genes using miRNAs. For oncogenes, synthetic miRNA mimics and lentiviral miRNA transfection can inhibit oncogenic pathways. In contrast, for tumor suppressor genes, miRNA-targeted RNA sponges and ASOs can enhance the expression of these genes by sequestering miRNAs that would otherwise repress them. (B) CRISPR-based approaches for regulating oncogenes and tumor suppressor genes through lncRNAs. Oncogenes can be targeted using dCas9-KRAB CRISPR interference (CRISPRi) to inhibit gene expression or Cas9-dsDNA mediated cleavage for gene disruption. Tumor suppressor genes can be activated using dCas9-VP64 CRISPR activation (CRISPRa) to enhance their expression via lncRNAs. (C) Methods for targeting circRNAs in cancer therapy. Synthetic circRNA sponges can sequester miRNAs, while Cas13 ssRNA-mediated back-splice junction targeted cleavage and siRNA-harboring nanoparticles can lead to circRNA degradation through the RISC complex, reducing their oncogenic functions. (D) Approaches for modulating tRNA functions in cancer cells. Inhibition of methyltransferase proteins using small molecule inhibitors can prevent the methylation of tRNAs, thereby disrupting protein translation. Additionally, ASOs can bind to pre-mature tRNAs, preventing their maturation and function in protein synthesis.

5.2.2 lncRNAs

Additionally, lncRNAs can be targeted therapeutically due to their roles in inducing degradation, regulating transcription, and/or inhibiting interactions with other regulatory factors. Utilizing ASOs to target lncRNAs could be a promising strategy for cancer treatment. For example, the knockdown of *MALAT1* with ASOs has been shown to significantly inhibit tumor growth and metastasis in breast cancer [250] and lung cancer [251]. Recent research has demonstrated that CRISPR/Cas9 technology can effectively repress or activate the transcription of loci expressing lncRNAs [252,253] (Figure 2B). The CRISPR/Cas9 system has been utilized to target genomic DNA in cancer cells and animal cancer models. For instance, knocking out the lncRNA *NEAT1* and *MALAT1* inhibited the metastasis of cancer cells [254,255]. Many lncRNAs are uniquely expressed in various tissues and even among different individuals, making personalized treatment a viable clinical option based on each patient's specific situation. Although CRISPR/Cas9 theoretically offers broad adaptability and target specificity for genome editing, practical applications still face challenges due to potential off-target cleavage events [256,257]. RNAi has also been used to therapeutically target lncRNAs. Adenovirus vectors are widely used, with numerous clinical trials exploring their applications [249,258]. Adeno-associated viruses (AAVs), composed of non-enveloped, single-stranded DNA, are efficient gene delivery systems due to their non-pathogenicity, lack of immune response, and stability in live cells [259]. Optimized AAVs have been developed for targeting lncRNAs in human cancer cells, providing a strong foundation for tumor treatment in clinical settings [237]. Transfecting a gastric cancer cell line with *HOTAIR* shRNA through retroviral delivery significantly reduced cell spread in peritoneal dissemination [236].

5.2.3 circRNAs

Circular RNA transcripts are currently being developed and evaluated as potential therapeutics both *in vitro* and *in vivo*. This includes synthetic circRNAs that can bind to or sponge oncogenic miRNAs [260–262] (Figure 2C). Cancer-promoting circRNAs can be effectively targeted and silenced using RNAi, ASOs, or CRISPR-Cas13 technology by focusing on their unique backsplice junction sequences [263,264]. Nanoparticles have greatly enhanced the practical application of circRNA-based therapeutics *in vivo*. Nanoparticles are capable of carrying therapeutic agents and precisely delivering them to diseased tissues [265]. Lipid nanoparticles (LNPs) represent the most advanced system for nanoparticle-based drug delivery [266]. Nanoparticle delivery systems effectively address several challenges associated with RNAi molecules by protecting them from degradation, enhancing cellular uptake, and reducing immune activation [267,268]. Gold nanoparticles (AuNPs)

conjugated with siRNA targeting circDnmt1 effectively suppressed cellular autophagy, reduced tumor growth, and increased the lifespan of mice [269].

5.2.4 tRNAs

tRNA methyltransferases (TRMs) like hTRM9L and ALKBH8 have been linked to stress responses and cancer phenotypes, suggesting that modulating their activity could suppress cancer cell proliferation while sparing normal cells [269–271]. Furthermore, pseudouridine modifications and the production of tRFs can influence protein synthesis and cell differentiation, highlighting the complexity of tRNA modifications in cancer biology [134]. Understanding these mechanisms opens avenues for developing targeted therapies that disrupt specific tRNA modification pathways, potentially leading to novel cancer treatments that minimize harm to healthy tissues (Figure 2D).

5.3 Potential toxicity

5.3.1 miRNAs

While miRNA-based therapies, including the use of ASOs, miRNA sponges, and miRNA mimics, present promising strategies for modulating gene expression in cancer, potential toxicity remains an undeniable concern. ASOs, particularly those incorporating chemical modifications enhance stability and efficacy but may provoke off-target effects and unintended immune responses [272–274]. Additionally, miRNA sponges and viral vectors used for delivering shRNAs or miRNA mimics may inadvertently interfere with normal cellular functions by sequestering endogenous miRNAs that play critical roles in maintaining homeostasis. Furthermore, prolonged or high-dose administration of these therapeutic agents could disrupt essential pathways, leading to toxicity in non-cancerous tissues [275,276].

5.3.2 lncRNAs

While approaches like ASOs and CRISPR/Cas9 offer targeted knockdown or activation of lncRNAs, they may lead to unintended off-target effects, which could disrupt normal cellular processes and induce toxicity. For instance, lncRNAs often play crucial roles in the regulation of multiple biological pathways, and silencing them might interfere with vital functions in non-cancerous tissues. Despite their potential, challenges remain in understanding lncRNAs' cellular functions and their roles in cancer due to their incomplete conservation across species and limited structural and functional data [277,278]. Considering the vast number of deregulated lncRNAs in cancers, there remains a continued need to characterize those that play significant roles in specific processes within particular cancer types, subtypes, or subpopulations, such as CSCs.

Additionally, viral vectors used in RNAi-based therapies, such as AAVs, although generally safe, can elicit immune responses or trigger inflammatory pathways, especially when administered at high doses. Furthermore, CRISPR/Cas9 technology carries the risk of off-target cleavage events, which may result in genomic instability or unintended mutations.

5.3.3 circRNAs

While the use of circRNA-based therapeutics and nanoparticles holds great promise, potential toxicity remains a key concern in their clinical application. The long-term biocompatibility and potential adverse effects of these delivery systems must be carefully evaluated. For instance, LNPs, though highly effective in protecting RNA molecules from degradation and enhancing cellular uptake, can trigger immune responses or cause liver toxicity if improperly dosed or formulated. Similarly, while AuNPs have shown potential in targeting specific cancer-related circRNAs, their accumulation in tissues over time may lead to organ toxicity. Challenges in understanding circRNA functionality and molecular targets also persist. Moreover, the lack of discrimination between cancer and non-cancer patients in circulating circRNA levels limits their use as reliable cancer biomarkers. Although the exploration of circRNAs as potential biomarkers in cancer has shown promise, the field is still in its early stages, and much remains to be understood. Currently, there are no clinical trials underway, highlighting the need for further research to fully elucidate their clinical utility.

5.3.4 tRNAs

Toxicity concerns related to therapeutics targeting TRMs stem from the complex role these enzymes play in both cancer and normal cell functions. While modulating TRM activity, such as hTRM9L and ALKBH8, could effectively suppress cancer cell proliferation, there is a risk of off-target effects due to the essential role of tRNA modifications in normal cellular processes. These TRMs are involved in stress responses and protein synthesis regulation in both healthy and cancer cells. Therapies that disrupt specific tRNA modification pathways, such as pseudouridine modifications or tRFs, could inadvertently affect normal cell differentiation and protein production. As a result, there is a fine balance between achieving therapeutic efficacy and minimizing toxicity to healthy tissues. Ensuring selective targeting and reducing adverse side effects will be crucial in developing these therapies for clinical use. Similar to circRNAs, the global role of tRNAs is critical, as they are fundamental to the central dogma of molecular biology by facilitating the translation of RNA into proteins. However, whether targeting tRNAs as a therapeutic strategy is feasible remains open, warranting further investigation.

6. Challenges and Future Outlooks

Tumor cells differ in their tumorigenic potential, metastatic capability, and resistance to treatments. These characteristics are driven by both genetic diversity and cellular plasticity. Increasing evidence indicates that cellular plasticity is closely associated with tumor progression, metastasis, therapy resistance, and relapse and highlights the critical role of ncRNAs in regulating tumor cell plasticity.

Despite the promising advantages of non-invasive early ncRNA detection in liquid biopsies, analyzing various ncRNAs presents specific challenges. For instance, differing miRNA expression levels in blood/serum and solid tumors in the same patient can arise due to different secretion mechanisms or origins [279,280]. The spatio-temporal context of miRNA expression, as reported in previous studies, highlights the difficulty in determining disease site specificity using bulk detection methods.

lncRNAs potentially offer greater specificity due to their generally lower abundance in blood, but face challenges related to their size and stability ratio. These larger molecules are more prone to degradation, making sample integrity a time-sensitive issue, especially in clinical settings.

circRNAs, which are distinguishable from their linear isoforms by the unique sequence created by back-splicing, also present detection challenges. The exclusive junction site can be difficult to detect, and the assumption that the back-splice junction is the sole identifier of circularity can be limiting. Current fragmentation-based next-generation sequencing technologies are not optimal for circRNA detection, and third-generation long-read sequencing methods, while promising, are still in the early stages of establishing themselves as the future gold standard.

Lastly, tRNAs are well-characterized at the sequencing level, but their well-conserved genes can lead to a redundant amino acid coding system. This redundancy may lead to off-target labeling due to the inherent similarities between endogenous tRNA molecules or trigger widespread detrimental effects on protein-coding pathways. The highly conserved nature of tRNA may be its greatest strength or a major limitation in its application for therapeutic purposes, which remains to be investigated.

Given the previously mentioned limitations, the use of ncRNA expression patterns in liquid biopsies for diagnostic, prognostic, and therapeutic purposes is currently being extensively studied in large cancer patient cohorts and more detection methods are being discovered. This research aims to confirm their effectiveness as biomarkers in human cancers.

Analyzing the functions of cancer-related ncRNAs poses challenges, particularly in modulating their expression. Unlike protein-coding genes, where genetic knock-outs can be achieved by introducing a stop codon, lncRNA transcripts themselves are the functional units, complicating knock-out approaches [281–283]. Disrupting core promoters of ncRNA genes is also challenging due to their frequent association with protein-coding genes. Additionally, the efficiency of silencing lncRNAs with siRNAs is often lower than that of proteins because lncRNAs can form stable secondary structures that hinder siRNA binding. Overcoming these challenges requires the development of new strategies to modulate ncRNA expression and the creation of new models for functional studies [284]. These models, like organoids and patient-derived xenografts, can better recapitulate the TME and provide a more accurate assessment of ncRNA functions and their interactions with other cellular components. Future research should focus on identifying novel ncRNAs involved in cellular plasticity and elucidating their mechanisms of action. Emerging technologies, such as single-cell RNA sequencing and CRISPR-based ncRNA editing, will be instrumental in uncovering these regulatory networks. Furthermore, understanding the interplay between different types of ncRNAs and their collective impact on cellular states will provide deeper insights into stem cell biology and cancer. This includes studying the interactions between lncRNAs, miRNAs, and circRNAs, and how they coordinate to regulate gene expression and cellular behavior. Integrative approaches combining transcriptomics, proteomics, and metabolomics will be crucial in mapping the complex regulatory networks governed by ncRNAs.

Another challenge is ensuring the specificity of ncRNA targets involved in key pathways contributing to disease progression, particularly in cancer cell plasticity. The delivery of ncRNA molecules to specific subcellular locations and maintaining their stability are crucial to avoid both "on-target" and "off-target" side effects. The specificity of delivery and treatment towards tumor cells remains a hurdle to overcome. These limitations primarily include insufficient penetration into tumor tissues due to mechanical and biological barriers, ensuring the stability and integrity of ncRNAs in circulation, potential induction of ncRNA-related immunotoxicity, and the risk of off-target effects of ncRNAs.

One effective strategy to mitigate the harmful side effects caused by delivery vehicles is to conjugate the targeting RNA with a ligand that binds to receptors overexpressed in the target cells. This approach enhances cellular uptake without significantly altering biodistribution [285]. Such specificity is particularly advantageous in targeting cancer cells, where ligands like N-acetylgalactosamine can be conjugated to ASOs to bind asialoglycoprotein receptors highly expressed in the liver [286,287].

The development of nanoparticles as delivery vehicles has been a major focus to protect ncRNAs from degradation and enhance their delivery efficiency. However, the formation of a protein corona around nanoparticles *in vivo* can lead to their preferential uptake by mononuclear phagocytes, which poses a challenge to their effective delivery [288]. Modifying the surface characteristics of NPs, such as PEGylation, can reduce these unwanted interactions and improve targeting efficiency [289]. Rodlike supramolecular nanoassemblies made from degradable poly(aspartic acid) derivatives and hydroxyl-rich cellulose nanocrystals for efficient delivery of tumor-suppressive ncRNAs have also been explored. These nanoassemblies exhibit high gene transfection efficiency and low cytotoxicity, making them a promising platform for cancer therapy due to their biocompatibility and degradability [290]. Furthermore, physiological barriers such as the endothelial and blood-brain barriers, renal clearance, and the reticuloendothelial system need to be addressed to enhance ncRNA delivery. Strategies like the use of ionizable lipids that alter charge properties at different pH levels within endosomes have shown promise in facilitating endosomal escape and improving intracellular delivery [291].

Future research must focus on optimizing these delivery systems and understanding the intricate regulatory networks of ncRNAs in cancer cell plasticity. Advances in nanotechnology, chemical modifications, and bioengineering of delivery vehicles will be fundamental in overcoming these barriers. The integration of artificial intelligence and machine learning could also play a significant role in predicting the interactions of ncRNAs and selecting the most effective therapeutic targets [292].

Non-coding RNAs are pivotal regulators of stem cell and CSC self-renewal and differentiation. Their ability to modulate gene expression and cellular states makes them attractive targets for therapeutic intervention. Continued research into ncRNA functions and mechanisms will enhance our insights into of cellular plasticity and contribute to the development of novel cancer treatments.

Abbreviations

AAVs: Adeno-Associated Viruses
ASOs: Antisense Oligonucleotides
AuNPs: Gold Nanoparticles
BCSCs: Breast Cancer Stem Cells
ceRNAs: Competing Endogenous RNAs
circRNAs: Circular RNAs
CRC: Colorectal Cancer
CSCs: Cancer Stem Cells
CTCs: Circulating Tumor Cells
EMT: Epithelial-Mesenchymal Transition

eRNAs: Enhancer RNAs
ESCs: Embryonic Stem Cells
HCC: Hepatocellular Carcinoma
hESCs: Human Embryonic Stem Cells
HSCs: Hematopoietic Stem Cells
lncRNAs: Long Non-Coding RNAs
LNPs: Lipid Nanoparticles
mESCs: Murine Embryonic Stem Cells
miRNAs: MicroRNAs
mt-tRNAs: Mitochondrial-tRNAs
ncRNAs: Non-Coding RNAs
NSCs: Neural Stem Cells
NURF: Nuclear Remodeling Factor
PRAD: Prostate Adenocarcinoma
PUS7: Pseudouridine Synthase 7
RISC: RNA-Induced Silencing Complex
RNAi: RNA Interference
RREB1: RAS-Responsive Element-Binding Protein 1
shRNAs: Short Hairpin RNAs
siRNAs: Small Interfering RNAs
SOX2-OT: SOX2 Overlapping Transcript
TICs: Tumor-Initiating Cells
TINCR: Tissue Differentiation-Inducing Non-Protein Coding RNA
TME: Tumor Microenvironment
TNBC: Triple Negative Breast Cancer
tRFs: Transfer RNA-Derived Fragments
TRMs: Transfer RNA Methyltransferases
tRNAs: Transfer RNAs
UTR: Untranslated Region
Ψ: Pseudouridine

Ethics Statement

Not applicable.

Consent for Publication

Not applicable.

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Competing Interests

The authors have declared that no competing interests exist.

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