Review paper

SnoRNAs: The promising targets for anti-tumor therapy

Xiaoyun Hu [a, b, c, 1], Wanlin Cui [a, b, 1], Min Liu [a, b, 1], Fangxiao Zhang [d, 1], Yingqi Zhao [a, b], Mingrong Zhang [a, b], Yuhang Yin [a, b], Yalun Li [e], Ying Che [a, b], Xianglong Zhu [a, b], Yuxuan Fan [a, b], Xiaolan Deng [f, ***], Minjie Wei [a, b, c, g, **], Huizhe Wu [a, b, c, g, *]

[a] Department of Pharmacology, School of Pharmacy, China Medical University, Shenyang, 110122, China
[b] Liaoning Key Laboratory of Molecular Targeted Anti-tumor Drug Development and Evaluation, Liaoning Cancer Immune Peptide Drug Engineering Technology Research Center, Key Laboratory of Precision Diagnosis and Treatment of Gastrointestinal Tumors, Ministry of Education, China Medical University, Shenyang, 110122, China
[c] Scientific Experimental Center, School of Pharmacy, China Medical University, Shenyang, 110122, China
[d] The Second Department of Infectious Diseases, The First Affiliated Hospital of China Medical University, Shenyang, 110001, China
[e] Department of Anorectal Surgery, The First Affiliated Hospital of China Medical University, Shenyang, 110001, China
[f] Department of Systems Biology, Beckman Research Institute of City of Hope, Monrovia, CA, 91016, USA
[g] Shenyang Kangwei Medical Laboratory Analysis Co., Ltd., Shenyang, 110000, China

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ABSTRACT

Recently, small nucleolar RNAs (snoRNAs) have transcended the genomic "noise" to emerge as pivotal molecular markers due to their essential roles in tumor progression. Substantial evidence indicates a strong association between snoRNAs and critical clinical features such as tumor pathology and drug resistance. Historically, snoRNA research has concentrated on two classical mechanisms: 2'-O-ribose methylation and pseudouridylation. This review specifically summarizes the novel regulatory mechanisms and functional patterns of snoRNAs in tumors, encompassing transcriptional, post-transcriptional, and post-translational regulation. We further discuss the synergistic effect between snoRNA host genes (SNHGs) and snoRNAs in tumor progression. More importantly, snoRNAs extensively contribute to the development of tumor cell resistance as oncogenes or tumor suppressor genes. Accordingly, we provide a comprehensive review of the clinical diagnosis and treatment associated with snoRNAs and explore their significant potential as novel drug targets.

1. Introduction

Small nucleolar RNAs (snoRNAs) were previously regarded as housekeeping genes and often neglected. Nonetheless, the human genome is increasingly being annotated with snoRNAs [1–3]. Eukaryotic cells mainly harbor snoRNAs in the nucleolus, typically ranging in length from 60 to 250 nucleotides [4]. These can be divided into box C/D snoRNAs, which govern 2'-O-ribose methylation; and box H/ACA snoRNAs, which govern pseudouridylation [4–6]. Moreover, another particular subclass of snoRNAs is known as small Cajal body-specific RNAs (scaRNAs). ScaRNAs govern the alteration of small nuclear RNA (snRNA) 2'-O-ribose methylation and pseudouridylation in the subnuclear Cajal body [7,8]. SnoRNAs are mainly derived from introns of protein-coding genes or non-protein coding genes, thus these genes are also known as snoRNA host genes (SNHGs) [9–11]. Afterwards, mature snoRNAs are cleaved and processed, giving rise to metabolically durable snoRNA fragments recognized as snoRNA-derived RNAs (sdRNAs), a subset of which share features with microRNAs (miRNAs) [12–16]. Furthermore, many snoRNAs without ribosomal RNA (rRNA) or snRNA recognition targets are labeled as "orphan snoRNAs".

The participation of snoRNAs in cancer development has been associated with multiple biological processes, including cell proliferation, invasion, apoptosis, and metastasis [17–20]. There is a growing interest regarding the involvement of snoRNAs in different

cancer types. Previous studies have primarily focused on the two traditional mechanisms of snoRNAs: 2'-O-ribose methylation and pseudouridylation of rRNAs. Recent research has suggested that snoRNAs have additional non-classical functions, such as the regulations of transcriptional, post-transcriptional, and post-translational processes. These findings expand the downstream of snoRNAs and indicate the additional implications of snoRNAs in the onset and progression of cancer. Consequently, this review aimed to summarize the classical and novel non-classical functional pathways of snoRNAs in tumor formation, as well as the significant implications of SNHGs on cancer progression. This review also summarized recent studies on snoRNAs involved in mediating resistance to anti-cancer drugs, highlighting the potential clinical applications of snoRNAs, as biomarkers, and therapeutic targets for anti-cancer therapy. Finally, we proposed diagnosis and treatment strategies to effectively combat tumors with snoRNAs involved. With these scientific advances, our review provided directions and insights for future investigations, facilitating a deeper comprehension of snoRNA function and advancements in the application in tumor treatment.

2. Classical mechanisms of snoRNAs in cancer

SnoRNAs can be categorized into two families, namely C/D box snoRNAs (SNORDs) and H/ACA box snoRNAs (SNORAs), based on their secondary structures and conserved sequence motifs. SNORDs perform site-specific 2'-O-methylation of ribose, whereas SNORAs facilitate uridine isomerization [21−23]. These classical modification mechanisms influence the folding and stability of rRNA, consequently affecting the onset and progression of cancer [24−26]. SnoRNAs dynamically interact with proteins to generate catalytically active small nucleolar ribonucleoprotein (snoRNP) complexes, which are essential for RNA synthesis, transport, and function [6,27−29]. Each snoRNA family contains a distinct set of binding proteins. The SNORDs family comprises four highly conserved core proteins: fibrillarin (FBL), nucleolar protein 56 (NOP56), NOP58, and 15.5KD [30−32]. The binding proteins of SNORAs, including dyskerin pseudouridine synthase 1 (DKC1), GAR1 ribonucleoprotein (GAR1), NHP2 ribonucleoprotein (NHP2),

and nucleolar protein 10 (NOP10), are conserved and crucial for pseudouridylation processes [16,33,34]. The classical mechanisms of snoRNAs are shown in Fig. 1.

More specifically, snoRNAs are primarily recognized as mediators of 2'-O-methylation and pseudouridylation in rRNA and snRNAs. However, recent discoveries of their roles in modifying messenger RNAs (mRNAs) are highly significant. This highlights the evolving landscape of snoRNAs in post-transcriptional regulation and offers a new perspective for understanding the molecular mechanisms driving cancer progression.

2.1. SNORDs mediate 2'-O-methylation modification of target RNA

Most SNORDs use antisense complementarity to direct 2'-O-methylation modifications at specific sites on rRNA [35]. Antisense complementarity refers to the ability of a 10−21 nt segment upstream of the C/D box to form base pairs with the target RNA, resulting in site-specific modifications [36,37]. Elevated expression of SNORD89 in endometrial cancer (EC) cells interacts with FBL to hinder the translation of B cell lymphoma-2 (BCL-2)-like protein 11 (BIM) through 2'-O-methylation. This leads to decreased BIM protein levels, which promotes the proliferation and migration of EC cells [38]. SNORD104 binds to FBL to increase the stability and nuclear localization of poly(adenosine diphosphate (ADP)-ribose) polymerase 1 (PARP1) mRNA via 2'-O-methylation, promoting EC proliferation [39]. SNORD60 interacts with FBL to enhance the stability and expression of PIK3CA mRNA through 2'-O-methylation, thereby regulating phosphatidylinositol 3-kinase/protein kinase B/ mammalian target of rapamycin (PI3K/AKT/mTOR) pathway and promoting the progression of EC [40]. Additionally, SNORD127 specifically recognizes the Gm1447 site on 18S rRNA, upregulating the 2'-O-methylation levels of Gm1447 and subsequently promoting the activity of leukemia stem cells [41]. In glioblastoma (GBM), SNORD17 methylates KAT6B via 2'-O-methylation, promoting angiogenesis and providing potential avenues for targeted therapy in clinical settings [42]. SNORD11B mediates 2'-O-methylation at the G509 site on 18S rRNA in colorectal cancer (CRC), promoting the processing and maturation of 18S rRNA. Furthermore, SNORD11B induces 2'-O-methylation modification at the G225 site on
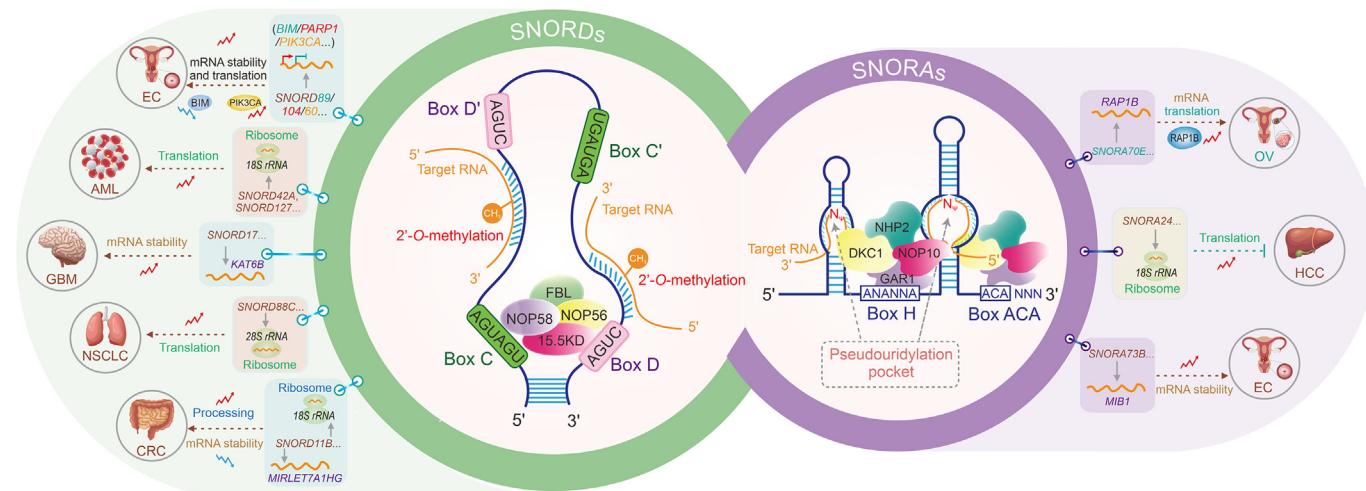

Fig. 1. The classical mechanisms of small nucleolar RNAs (snoRNAs) involved in tumor initiation and development. Based on conserved sequence elements, snoRNAs are classified as C/D box snoRNAs (SNORDs) and H/ACA box snoRNAs (SNORAs). SNORDs contain sequence elements termed C (UGAUGA) and D (CUGA) boxes, usually present in duplicates (C' and D' boxes). SNORAs contain sequence elements termed H (ANANNA) and ACA boxes. SNORDs are responsible for the 2'-O-methylation modification of target RNAs by binding with proteins fibrillarin (FBL), nucleolar protein 56 (NOP56), NOP58, and 15.5KD. SNORAs are responsible for the pseudouridine modification of target RNAs by binding with proteins dyskerin pseudouridine synthase 1 (DKC1), GAR1 ribonucleoprotein (GAR1), NHP2 ribonucleoprotein (NHP2), and nucleolar protein 10 (NOP10). BIM: B cell lymphoma-2 (BCL-2)-like protein 11; PARP1: poly (adenosine diphosphate (ADP)-ribose) polymerase 1; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; mRNA: messenger RNA; EC: endometrial cancer; 18S rRNA: 18S ribosomal RNA; AML: acute myeloid leukemia; KAT6B: lysine acetyltransferase 6B; GBM: glioblastoma; NSCLC: non-small cell lung cancer; CRC: colorectal cancer; RAP1B: RAS-related protein 1B; OV: ovarian cancer; HCC: hepatocellular carcinoma; MIB1: mindbomb E3 ubiquitin protein ligase 1.

MIRLET7A1HG (*pri-let-7a*). This modification leads to *pri-let-7a* degradation, reduced expression of mature tumor suppressor *let-7a-5p*, and the upregulation of downstream oncogene cellular MYC (c-MYC) and rat sarcoma (RAS) translation, thereby promoting colorectal tumorigenesis [43].

Collectively, SNORDs can influence tumor onset and development through 2'-O-methylation modifications, providing novel insights into cancer regulation and treatment.

2.2. SNORAs mediate pseudouridine modification of target RNA

SNORAs are crucial for pseudouridylation, a process that modifies specific sites in eukaryotic rRNA and snRNA. Pseudouridylation involves the conversion of uridine to pseudouridine in the targeted RNA molecules [22,44]. SNORA molecules possess a conserved secondary structure known as the "hairpin-hinge hairpin tail." The guiding sequence of SNORA is located in one or two hairpins within this structure, forming the "pseudouridylation pocket" [44]. This pocket facilitates non-canonical base pairing with the target uridine through interactions with pre-rRNA. In ovarian cancer (OV), *SNORA70E* interacts with dyskerin and induces pseudouridylation of *RAP1B* mRNA, subsequently leading to increased RAP1B protein levels and promoting the proliferation, invasion, and migration of OV cells [45]. *SNORA73B* binds to DKC1, enhancing the stability and expression of *MIB1* mRNA through pseudouridylation. This process leads to increased Jagged 1 (JAG1) ubiquitin levels and activation of the neurogenic locus notch homolog (NOTCH) pathway, ultimately promoting the development of EC [46]. Therefore, SNORAs that mediate pseudouridine modification of target RNA offer a novel perspective for cancer diagnosis and treatment.

2.3. Increasingly important role in ribosome translation of snoRNA-mediated classical modifications

The ribosome, often referred to as the "protein-producing machine", facilitates the dehydration condensation of amino acids to form peptide chains during the translation process [47,48]. Thus, modifications in rRNA, particularly 2'-O-methylation and pseudouridylation, contribute to the plasticity of ribosomal translational functions, a critical factor given the evidence that these modifications regulate cancer cell translational programs [21]. For example, rRNA with 2'-O-methylation has been shown to affect the

ribosome's ability to translate mRNA in HeLa cells [21]. Reduced pseudouridylation levels alter ribosomal activity, particularly impacting translation mediated by internal ribosome entry site (IRES) and overall translation fidelity in breast cancer (BRCA) cells [49]. Aberrant rRNA methylation, regulated by the P53/FBL axis, compromises ribosomal translation fidelity, activating the translation of oncogenes such as *IGF1R* dependent on the IRES, thereby promoting BRCA progression [49]. In recent years, mounting evidence suggests that snoRNA-mediated classical modifications play a significant role in ensuring the fidelity of ribosome translation, potentially influencing cancer onset and progression [24—26]. *SNORD42A* guides 2'-O-methylation at the U116 site on *18S rRNA*, promoting the translation of ribosomal proteins in acute myeloid leukemia (AML) and enhancing leukemia cell proliferation and survival [50]. *SNORD45C* induces 2'-O-methylation modification at the C174 site of *18S rRNA*, remodeling mRNA translation in cervical cancer (CC) cells [51]. *SNORD127* mediates 2'-O-methylation at the G1447 site on *18S rRNA* to promote preferential translation of mRNAs, driving AML stem cell phenotypes [41]. *SNORA24* guides the modification of pseudouridines in *18S rRNA* to decrease translational miscoding and stop codon readthrough frequencies, resulting in the suppression of hepatocellular carcinoma (HCC) development during RAS-induced aging [52]. Furthermore, *SNORD88C* promotes 2'-O-methylation at the C3680 site on *28S rRNA* in non-small cell lung cancer (NSCLC), which increases the translation of the downstream lipogenic enzyme stearoyl-CoA desaturase 1 (SCD1), thereby promoting NSCLC proliferation and metastasis [53]. In conclusion, the significance of snoRNA-mediated classical modifications for ribosome translation is steadily growing, providing valuable insights into tumor regulation patterns. The classical mechanisms of those crucial snoRNAs in tumor initiation and development are summarized as shown in Table 1 [38—43,45,46,50—53] and Fig. 1.

3. The regulation of snoRNA expression

SnoRNAs are metabolically stable products due to their conservative secondary structure and ability to form complexes with proteins and RNA [31]. SnoRNAs exhibit relatively longer half-lives (24—48 h) compared to mRNAs (less than 6 h), with their levels regulated by both synthesis and degradation mechanisms in the cell [2,54,55]. It is now widely recognized that abundant functional snoRNAs are dysregulated in cancer, showing differential

Table 1
The classical mechanisms of small nucleolar RNAs (snoRNAs) involved in tumorigenesis and progression.

SnoRNA	Mechanism	Target RNA	Biological function	Related tumor type	Refs.
SNORD89	Regulating 2'-O-methylation modification	*BIM* mRNA	Promoting tumor occurrence and development	EC	[38]
SNORD104	Regulating 2'-O-methylation modification	*PARP1* mRNA	Promoting tumor growth	EC	[39]
SNORD60	Regulating 2'-O-methylation modification	*PIK3CA* mRNA	Promoting tumorigenesis and progression	EC	[40]
SNORD127	Regulating 2'-O-methylation modification	*18S* rRNA	Promoting the activity of cancer stem cells	AML	[41]
SNORD17	Regulating 2'-O-methylation modification	*KAT6B* mRNA	Promoting vasculogenic mimicry	Glioblastoma	[42]
SNORD11B	Regulating 2'-O-methylation modification	*18S* rRNA and *MIRLET7A1HG* (*pri-let-7a*) mRNA	Promoting tumor cell proliferation and invasion and inhibiting apoptosis	CRC	[43]
SNORA70E	Guiding pseudouridine modification	*RAP1B* mRNA	Promoting tumor occurrence and development	OV	[45]
SNORA73B	Guiding pseudouridine modification	*MIB1* mRNA	Promoting tumor cell proliferation, migration, and invasion and inhibiting apoptosis	EC	[46]
SNORD42A	Regulating 2'-O-methylation modification	*18S* rRNA	Promoting tumor cell proliferation	AML	[50]
SNORD45C	Regulating 2'-O-methylation modification	*18S* rRNA	/	CC	[51]
SNORA24	Guiding pseudouridine modification	*18S* rRNA	Inhibiting tumor development	HCC	[52]
SNORD88C	Regulating 2'-O-methylation modification	*28S* rRNA	Promoting tumor growth and metastasis and inhibiting autophagy	NSCLC	[53]

/: no data. SNORDs: C/D box snoRNAs; *BIM*: B cell lymphoma-2 (BCL-2)-like protein 11; mRNA: messenger RNA; EC: endometrial cancer; *PARP1*: poly(adenosine diphosphate (ADP)-ribose) polymerase 1; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; rRNA: ribosomal RNA; AML: acute myeloid leukemia; *KAT6B*: lysine acetyltransferase 6B; CRC: colorectal cancer; *RAP1B*: RAS-related protein 1B; OV: ovarian cancer; *MIB1*: mindbomb E3 ubiquitin protein ligase 1; CC: cervical cancer; HCC: hepatocellular carcinoma; NSCLC: non-small cell lung cancer.

expression across cancer types, stages, and metastasis, and actively influencing tumor progression [56−58]. Recent studies have indicated that snoRNA expression can be transcriptionally regulated through interactions with transcription regulators and DNA methylation. Additionally, most snoRNAs are coded with introns of coding and non-coding genes, making their expression dependent on host gene transcription and splicing events [59,60]. Thus, elucidating the regulatory mechanisms of snoRNA expression in tumor development is both important and intriguing.

3.1. SnoRNA expression regulated by transcription regulators

There is increasing evidence that transcription factors play a pivotal role in modulating snoRNA expression, which is crucial for maintaining cellular homeostasis and ultimately influencing cancer progression [57,58,61,62] (Fig. 2). In mice with *P53* mutation and osteosarcoma (OS), snoRNAs were upregulated through E26 transformation-specific sequence 2 (ETS2)-dependent transcriptional regulation, facilitating tumor metastasis and suggesting ETS2 as a potential therapeutic target for P53-mutant osteosarcoma [57]. P53, acting as a tumor suppressor, can inhibit *SNORD17* transcription, thereby suppressing the progression of HCC [58]. Additionally, amino-terminal enhancer of split (AES) has been identified as a co-transcriptional factor that affects multiple RNA processing pathways at the transcriptional level in acute myeloid leukemia 1-eight-twenty-one (AML1-ETO)-induced leukemogenesis [61,62].

3.2. Inhibition of snoRNA transcription by DNA methylation

DNA methylation is a common epigenetic mechanism that regulates gene expression. DNA methylation primarily occurs on cytosine-phosphate-guanine (CpG) islands in the gene promoter regions. High levels of CpG island methylation play an important role in cancer induction [63] (Fig. 2). High-throughput sequencing has revealed that DNA methylation inhibits snoRNA transcription, affecting cancer progression [56,64,65]. Gong et al. [64] analyzed

snoRNA expression in 31 cancer types and observed a negative association between the methylation level of the cg06726167 site upstream of *SNORD118* host gene and its expression in diverse cancers. In HCC patients, CpG island methylation in the gene promoter region of *SNORD113-1* was significantly higher compared to adjacent non-tumor tissue, leading to a marked downregulation of its expression. *SNORD113-1* exhibits tumor suppressor properties by inhibiting the phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) and mothers against decapentaplegic homolog 2/3 (SMAD2/3) in the mitogen-activated protein kinase (MAPK/ERK) and transforming growth factor beta (TGF-β) pathways, thus suppressing the proliferation of HepG2 and Huh7 cancer cells [56]. Furthermore, extensive evidence shows the widespread occurrence of highly methylated 5'-CpG islands in host genes, including *SNORD123*, *U70C*, and *ACA59B* in colorectal and lung cancer cell lines, leading to epigenetic silencing of the associated snoRNAs [65].

3.3. Dependence of snoRNA expression on their host gene transcription and splicing events

Recent studies have revealed that most snoRNAs are derived from introns of coding or non-coding genes, with their expression relying on the transcription levels and splicing events of the host genes [59,60] (Fig. 2). For instance, Fafard-Couture et al. [2·2] recently demonstrated that the transcription and splicing activities of host genes determine the expression and conservation of encoded snoRNAs through comprehensive analysis. Similarly, Boivin et al. [66] found the snoRNAs embedded within introns of protein-coding genes are generated via the transcription and splicing activities of their host genes.

The production of full-length transcripts (also known as pre-RNA), including exons and introns, is encoded by host genes. Among these transcripts, introns with nuclear localization are further processed into smaller molecules ranging from 65 to 300 nucleotides, thus defined as snoRNA [60]. Consequently, the
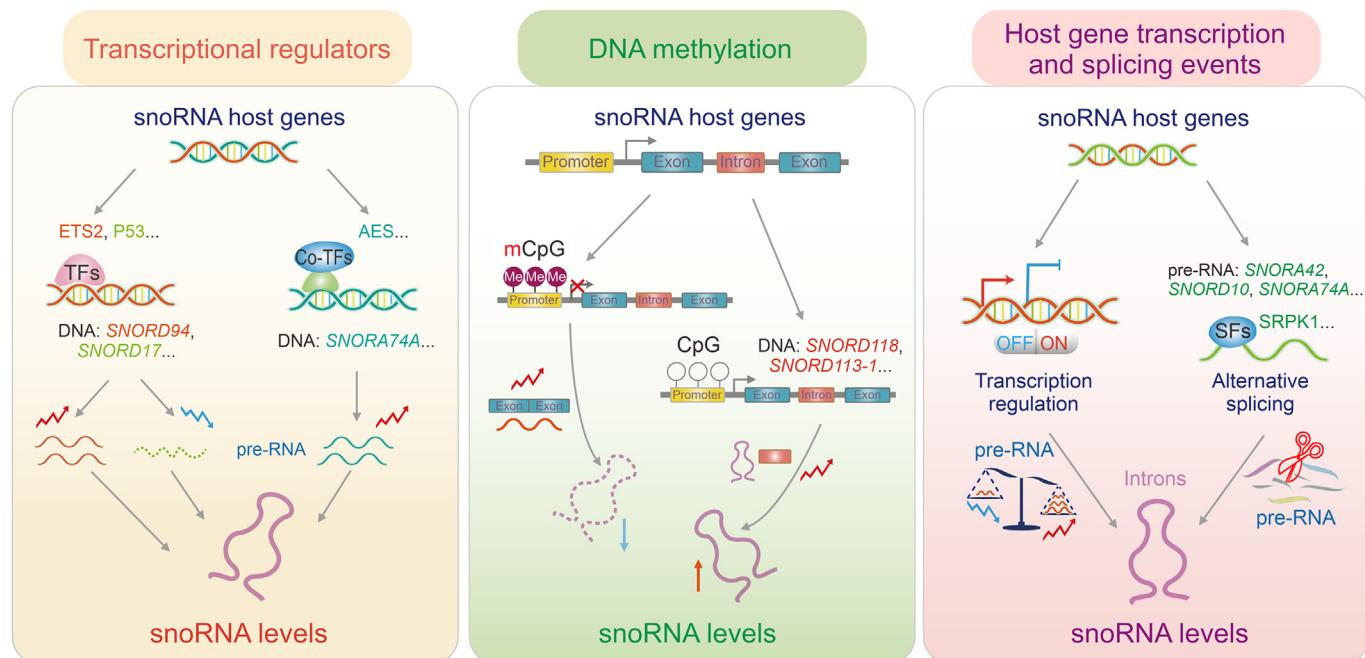

Fig. 2. Small nucleolar RNAs (SnoRNA) expression regulated by transcription regulators. SnoRNA expression is regulated mainly through three patterns: dynamic regulation by transcription regulators, transcriptional inhibition by DNA methylation, and dependence on host gene transcription and splicing events. ETS2: E26 transformation-specific sequence 2; TFs: transcription factors; SNORDs: C/D box snoRNAs; AES: amino-terminal enhancer of split; mCpG: methylated cytosine-phosphate-guanine (CpG); SRPK1: serine-arginine protein kinase 1; SFs: splicing factors.

abundance of the encoded snoRNAs directly depends on the transcriptional regulation of their host genes. For instance, *snoRNA U14−U24* and *E3* are derived from *SNHG1*, which is actively transcribed into pre-RNA and released through the processing of excised introns [9]. Additionally, existing evidence suggests co-expression between intronic snoRNAs and their host genes, further confirming their transcriptional regulatory pattern [11,67].

Furthermore, the splicing patterns of host genes significantly influence the expression of their encoded snoRNAs [59]. Specifically, transcripts from genes encoding multiple snoRNAs typically generate alternative transcript isoforms, allowing for the differential expression of individual co-encoded snoRNAs [2]. A representative study confirms that the splicing factor serine-arginine protein kinase 1 (SRPK1) upregulates the expression of *SNORA42*, *SNORD10*, and *SNORA74A*, which is associated with increased gastric cancer cell proliferation [68]. Additionally, splicing events in host genes produce considerable amounts of nonsense-mediated mRNA decay-sensitive splice variants with premature termination codons, impacting the levels of encoded snoRNAs [59,69]. Interestingly, multi-SNHGs can fine-tune the levels of their encoded individual snoRNAs through post-transcriptional alternative splicing events [69]. For instance, the gene *C17orf76-AS1* encodes and regulates multiple individual snoRNAs, such as *SNORD49B*, *SNORD49A*, and *SNORD65* by yielding alternative transcript isoforms, enabling their differential expression [69].

In summary, these studies have elucidated the complex regulatory relationship between host genes and their intron-encoded snoRNAs, offering intriguing insights into the mechanisms governing snoRNA expression (Table S1 [56−58,62,65,68] and Fig. 2).

4. Emerging mechanisms of snoRNAs in cancer

SnoRNAs significantly influence tumor development and progression. In recent years, novel regulatory mechanisms have been discovered that are crucial in the development and occurrence of tumors, in addition to the two traditional mechanisms. The primary regulatory mechanisms include the transcriptional and post-transcriptional as well as post-translational regulation of snoRNAs (Fig. 3). Multiple studies have indicated that snoRNAs could indirectly regulate tumor development and progression by selectively modifying target RNAs, whereas direct binding of snoRNAs to target RNAs regulates their post-transcriptional modifications and contributes to post-translational regulation.

4.1. Transcriptional and post-transcriptional regulation by snoRNAs

4.1.1. SnoRNAs regulate gene transcription by crosstalk with transcription factors

The interaction between snoRNAs and transcription regulators could modulate the expression levels of crucial cancer-related genes, thereby initiating malignant tumor development [70,71] (Fig. 3). For instance, in NSCLC, *SNORA38B* facilitates the transcription of the downstream *GAB2* gene by directly interacting with the transcription factor E2F transcription factor 1 (E2F1), leading to activation of the AKT/mTOR pathway and driving the progression of NSCLC [70]. In addition, *SNORD126* can directly bind to heterogeneous nuclear ribonucleoprotein K (hnRNPK), resulting in the upregulation of *FGFR2* transcription and activation of the PI3K-AKT pathway, thereby facilitating the progression of HCC [71]. Thus, understanding the interactions between snoRNAs and transcription regulators is crucial for understanding the molecular basis of cancer.

4.1.2. SnoRNAs trigger alternative pre-RNA splicing

SnoRNAs are a type of snRNA molecules that play a crucial role in regulating gene expression. Recent studies have demonstrated that snoRNAs can induce diverse biological alterations in tumors by affecting target splicing and RNA levels [12,45,72−74] (Fig. 3). *SNORA70E* is a splicing regulatory factor that influences the selective splicing of *PARPBP* in OV, resulting in the exclusion of exon 4 of the *PARPBP-88* transcript and generation of a novel transcript, *PARPBP-15*. This action subsequently facilitates the invasion, migration, and proliferation of OV cells [45]. Similarly, *SNORD27* competitively binds to splicing factors in HeLa cells, resulting in the exclusion of exon 12 of *E2F7* pre-mRNA, while inhibiting the inclusion of silencing exons in *FER*, *ZBTB37*, *MAP4K3*, and *ABCA8* pre-mRNA. This ultimately contributes to cell proliferation [72]. *SNORD88C* (also known as *HBII-180C*) regulates the splicing of fibroblast growth factor receptor 3 (*FGFR3*) mRNA, contributing to the development of various cancers [12,75,76]. Moreover, a recent study showed that *SNORD75* can regulate the splicing of *GAS* pre-long non-coding RNA (lncRNA) based on N^6-methyladenosine (m^6A) modification factors by recruiting and binding to the methyltransferase-like 3 (METTL3)/METTL14 complex [73]. These findings suggest potential avenues for cancer treatment and highlight the crucial role of snoRNAs in regulating gene expression and cancer progression.

4.1.3. SnoRNAs participate in alternative polyadenylation (APA) processing of the pre-mRNA 3'-untranslated region (UTR)

APA is a crucial post-transcriptional regulatory mechanism in the mRNA maturation process of eukaryotic cells. It is used to modify and process the 3'-end of precursor mRNA [77]. SnoRNAs regulate APA modification, which in turn regulates mRNA 3'-end processing and affects the expression of cancer-related genes [78,79] (Fig. 3). *SNORD12B* is upregulated in GBM cells. FIP1L1 (also known as FIP1) binding facilitates the use of the distal poly(A) site of the transcriptional repressor *ZBTB4* during APA, resulting in an increased proportion of the long 3'-UTR transcript of *ZBTB4*, which downregulates ZBTB4 expression, ultimately inhibiting glucose and lipid metabolism and the proliferation of GBM cells [78]. Additionally, *SNORD50A* functions as a direct APA regulator that inhibits *SVL* mRNA 3'-end processing in HeLa cells by disrupting the FIP1-PAS interaction [79,80].

4.1.4. SnoRNAs regulate mRNA stability

Several studies have shown that snoRNAs can function as post-transcriptional regulators that influence mRNA stability, thereby contributing to cancer development [58,81] (Fig. 3). For example, *SNORA71A* binds to G3BP1, a protein that regulates mRNA stability, increases its stability, and upregulates *ROCK2*, a negative regulatory factor of TGF-β. This promotes the growth and metastasis of BRCA [81]. Upregulated *SNORD17* binds to NPM1, reducing the stability of the tumor suppressor protein, P53, and promoting the onset and metastasis of HCC [58]. Therefore, snoRNAs play a significant role in cancer progression by regulating mRNA stability and influencing specific signaling pathways. Further in-depth studies will provide a clearer understanding of the specific mechanisms by which these molecules affect various diseases.

4.1.5. sdRNAs with miRNA-like functions

SnoRNAs can generate smaller molecules that bind to the argonaute (AGO) protein, exhibiting a function similar to that of miRNA. These small molecules are referred to as sdRNAs or sno-miRNAs. Preliminary research has shown that the snoRNA *ACA45* can produce stable sdRNA, specifically *ACA45* sRNA, in HEK293 cells [14]. Similar to miRNAs, this molecule can bind complementarily to the 3'-UTR of *CDC2L6* and inhibit its expression [14]. SdRNAs can mimic the functions of miRNAs by completely or partially binding to target mRNA, promoting gene silencing, and affecting the onset and development of tumors [82−84] (Fig. 3). For example,
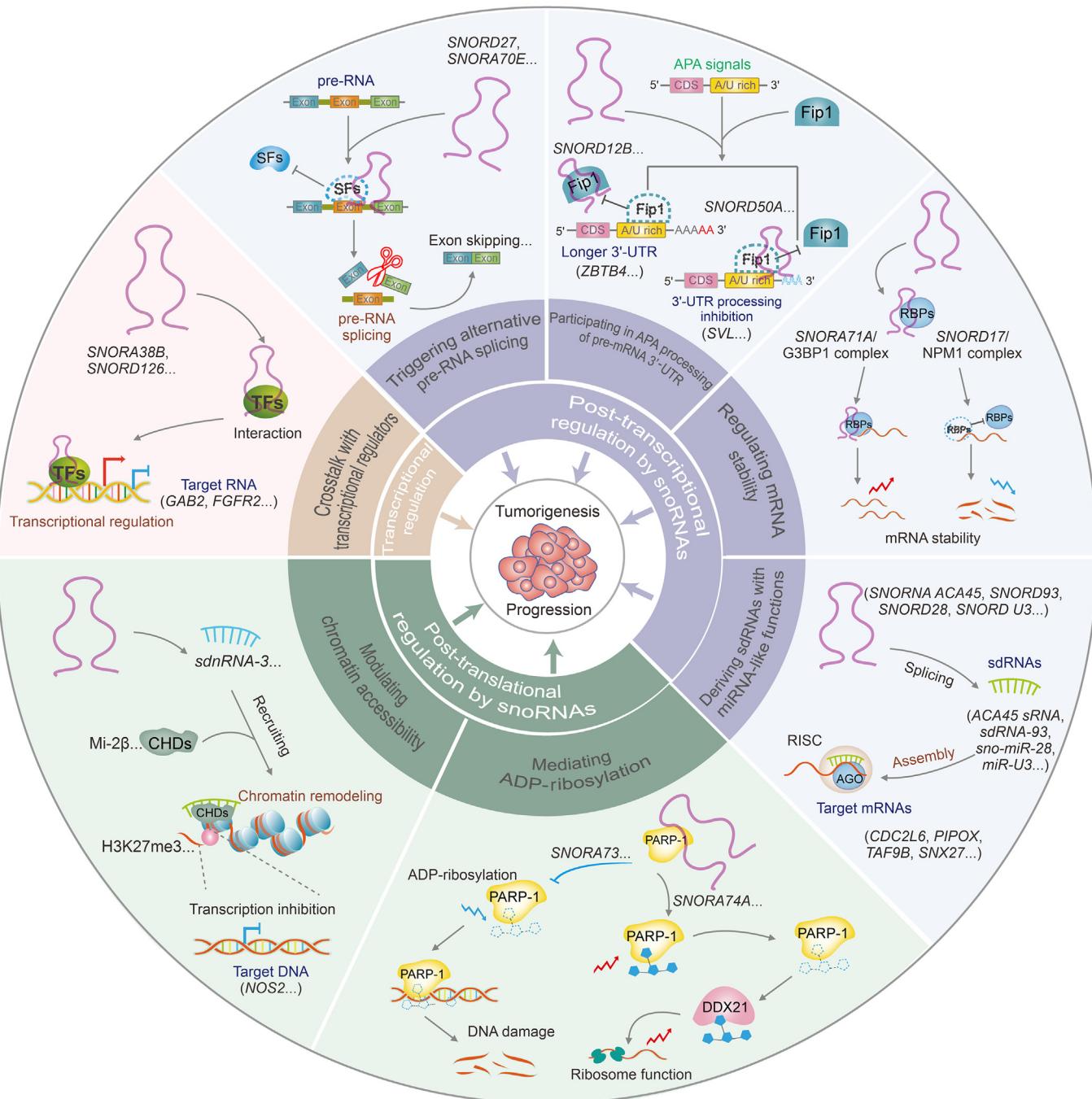
Fig. 3. The emerging mechanisms of small nucleolar RNAs (snoRNAs) involved in tumorigenesis and progression. SnoRNAs affect the biological functions of multiple target genes, and thus tumor progression, through three main regulatory mechanisms. The first is the transcriptional regulation of snoRNAs, including the crosstalk between snoRNAs and transcription regulators. The second is the post-transcriptional regulation of snoRNAs, including snoRNAs triggering alternative pre-RNA splicing, participating in alternative polyadenylatio (APA) processing of the pre-messenger RNA (mRNA) 3'-untranslated region (UTR), regulating mRNA stability, and deriving snoRNA-derived RNAs (sdRNAs) with microRNAs (miRNA)-like functions. The last is the post-translational regulation of snoRNAs, including snoRNAs mediating adenosine diphosphate (ADP)-ribosylation and modulating chromatin remodeling. *FGFR2*: fibroblast growth factor receptor 2; TFs: transcription factors; SFs: splicing factors; CDS: coding sequence; SNORDs: C/D box snoRNAs; RBPs: RNA binding proteins; G3BP1: G3BP stress granule assembly factor 1; NPM1: nucleophosmin 1; RISC: RNA-induced silencing complex; AGO: argonaute; PARP1: poly(ADP-ribose) polymerase 1; DDX21: DEAD-box helicase 21; *sdnRNA-3*: small nucleolar-derived RNA 3; CHDs: chromodomain helicase DNA binding proteins; H3K27me3: tri-methylation at lysine 27 of histone H3.

snoRNA93-derived *sdRNA-93* (also known as *HBII-336*) exhibits miRNA-like characteristics. In BRCA cells, this highly expressed *sdRNA-93* can bind to the *PIPOX* 3'-UTR and suppress its expression, thereby inducing invasive characteristics in specific BRCA cell types (e.g., MCF-7 and MDA-MB-231) [82]. In addition, *sno-miR-28* contributes to the proliferation of BRCA cells by directly targeting the upregulated *TAF9B* 3'-UTR and indirectly reducing P53 stability [83]. Box C/D snoRNA *U3* is overexpressed in multiple types of cancer [85]. Lemus-Diaz et al. [84] observed the transformation of *U3* snoRNA into *miR-U3* in HCT116 cells, sharing characteristics with miRNA. This enables *miR-U3* to bind to the 3'-UTR of *SNX27* mRNA, potentially influencing various cellular functions. Similarly,

miR-U3 also binds to the 3'-UTR of *ZBTB4*, reducing the stability of *ZBTB7A* mRNA. This results in downregulation of ZBTB7A protein expression, promoting glioblastoma cell glycolytic capacity and proliferation [86]. Targeting these functional snoRNAs and their smaller molecular derivatives, such as with antagonistic antisense oligonucleotides (ASOs) and small molecules, could be an effective strategy, similar to the inhibition of oncogenic miRNAs [87,88]. Thus, these findings provide insights into the development of novel cancer treatments.

4.2. Post-translational regulation by snoRNAs

4.2.1. SnoRNAs mediate ADP-ribosylation

SnoRNAs affect the post-translational modification of nuclear proteins by influencing the catalytic activity of PARP1, which has implications for cancer occurrence and development [89,90] (Fig. 3). Recent research has revealed that *SNORA73*, a chromatin-related orphan snoRNA, can bind to PARP1 to form snoRNP, which inhibits the automatic poly(ADP-ribosyl)ation of PARP1, thereby affecting the levels of DNA damage. Consequently, this process contributes to increased genomic instability and AML progression [89]. Kim et al. [90] found that *SNORA74A* could activate PARP-1 self-modification in BRCA1/2 wild-type BRCA cells. This activation leads to site-specific ADP-ribosylation of DEAD-box helicase 21 (DDX21) via its interaction with PARP-1 and the RNA helicase DDX21. Consequently, this process promotes the growth of BRCA cells by enhancing ribosome biosynthesis and protein translation. Further in-depth research is warranted to investigate the regulatory mechanisms of these snoRNAs on PARP1 and DNA damage repair (DDR) pathways to improve our understanding of the significant roles in cancer progression.

4.2.2. SnoRNAs and sdRNAs modulate chromatin remodeling

SnoRNAs facilitate the selective recruitment and binding of chromatin modifiers to regulate chromatin accessibility. Schubert et al. [91] found that snoRNAs can interact with drosophila decondensation factor 31 (DF31) to form ribonucleoprotein (RNP) complexes, resulting in the decondensation of higher-order chromatin structures and maintenance of high-level chromatin structures. Thus, snoRNAs and their derivatives may influence cancer development through chromatin structural modifications [65,92] (Fig. 3). Bisphenol A promotes the development of prostate cancer by inhibiting the activity of *SNORD59A*, *SNORD82*, *SNORD116*, and *SNORD117* through the recruitment of histone H3 lysine 9 trimethylation (H3K9me3), H3K4me3, and H3K27me3 [92]. Recent studies have identified Dicer-independent small non-coding RNA (sncRNA) derived from snoRNAs (sdnRNA)-*sdnRNA-3* and snRNAs/snoRNAs that inhibit *NOS2* transcription in macrophages. This is accomplished by recruiting the Mi-2β protein, thereby blocking the accessibility of the *NOS2* gene promoter and promoting tumor growth [93]. These findings provide novel insights into the regulation of macrophage function in cancer immunity.

In summary, the regulatory mechanisms of snoRNAs in tumor development are complex and comprehensive, providing novel insights into these conditions (Table S1 [12,14,45,70−73,78−84,86,89,90,92,93] and Fig. 3).

5. Mechanisms of SNHGs in cancer

As mentioned above, unlike independent transcription pattern, a significant portion of snoRNAs is transcribed from sequences within introns of protein-coding or non-coding host genes [2,59]. SnoRNAs show a strong correlation in abundance with SNHGs; however, the expression relationship between snoRNAs and their coding host genes is largely uncorrelated [2]. Fafard-Couture et al. [2] explain that this discrepancy is due to the presence of more dual-initiation promoters in protein-coding host gene/snoRNA pairs than in non-coding host gene/snoRNA pairs. Interestingly, the functional roles also differ significantly between coding genes, many of which are related to the translational apparatus, and non-coding SNHGs. The architecture of SNHGs varies to uncouple the expressions of the host genes and snoRNAs, thus meeting diverse snoRNA abundance levels and functional requirements. This suggests that the functions of SNHGs may actually reflect those of snoRNAs [2]. Therefore, clarifying the pivotal roles of SNHGs is essential to uncovering the intricate roles of snoRNAs in tumors.

SNHGs have been implicated in the regulation of cellular homeostasis and cancer biology, in addition to contributing to the etiology of cancer, as shown in Table 2 [94−97] and Fig. 4A. *SNHG5*, the host gene of snoRNA *U50*, serves as a tumor suppressor in gastric cancer by sequestering metastasis-associated protein 2 (MTA2) in the cytoplasm, thereby impeding cancer progression. This finding indicates that *SNHG5* may be a promising therapeutic target for gastric cancer [94]. The lncRNA *SNHG6* promotes CRC cell migration, invasion, and epithelial-mesenchymal transition by regulating the *miR-26a*/enhancer of zeste 2 polycomb repressive complex 2 subunit (*EZH2*) axis [95]. *SNHG15* has been implicated in prostate cancer development via the *miR-338-3p*/FK506-binding protein (FKBP) prolyl isomerase 1A (*FKBP1A*) axis [96]. *SNHG12* promotes the proliferation and invasiveness of papillary thyroid cancer cells by targeting *miR-16-5p* [97]. *SNHG1*, *SNHG6*, *SNHG16*, and *SNHG20* play important roles in HCC progression via various regulatory mechanisms [98]. Additionally, the majority of SNHGs (*SNHG1*, *SNHG12*, *SNHG20*, *SNHG15*, and *SNHG16*) function by sequestering tumor-suppressing microRNAs, thereby enabling the production of oncogene transcripts in malignancies [99].

Moreover, snoRNAs and their associated SNHGs are significantly involved in human cancer progression. SNHGs regulate the expression of homologous snoRNAs through positive feedback loops, thus influencing cancer onset and progression, as shown in Table 2 [100,101] and Fig. 4B. The lncRNA *SNHG17* positively regulates its homologous gene *SNORA71B* in prostate cancer cells [100]. *SNHG17* functions as a sponge for *miR-339-5p*, resulting in the

Table 2
Mechanisms of small nucleolar RNAs (snoRNA) host genes (SNHGs) in cancer.

SNHG	snoRNA	Mechanism	Biological function	Tumor type	Refs.
SNHG5	*U50*	Trapping MTA2 in the cytosol	Inhibiting tumor development	Gastric cancer	[94]
SNHG6	/	Sponging *miR-26a*	Promoting tumorigenesis and metastasis	CRC	[95]
SNHG15	/	Sponging *miR-338-3p*	Promoting proliferation	Prostate cancer	[96]
SNHG12	/	Sponging *miR-16-5p*	Promoting growth and invasion	Papillary thyroid cancer	[97]
SNHG17	*SNORA71B*	Sponging *miR-339-5p*	Promoting tumorigenesis and metastasis	Prostate cancer	[100]
SNHG10	*SCARNA13*	Sponging *miR-150-5p*	Promoting tumorigenesis and metastasis	Hepatocellular cancer	[101]
SNHG5	*SNORA50C*	Recruiting DKC1	Promoting tumorigenesis and metastasis	Hepatocellular cancer	[102]

/: no data. MTA2: metastasis-associated protein 2; CRC: colorectal cancer; DKC1: dyskerin pseudouridine synthase 1.
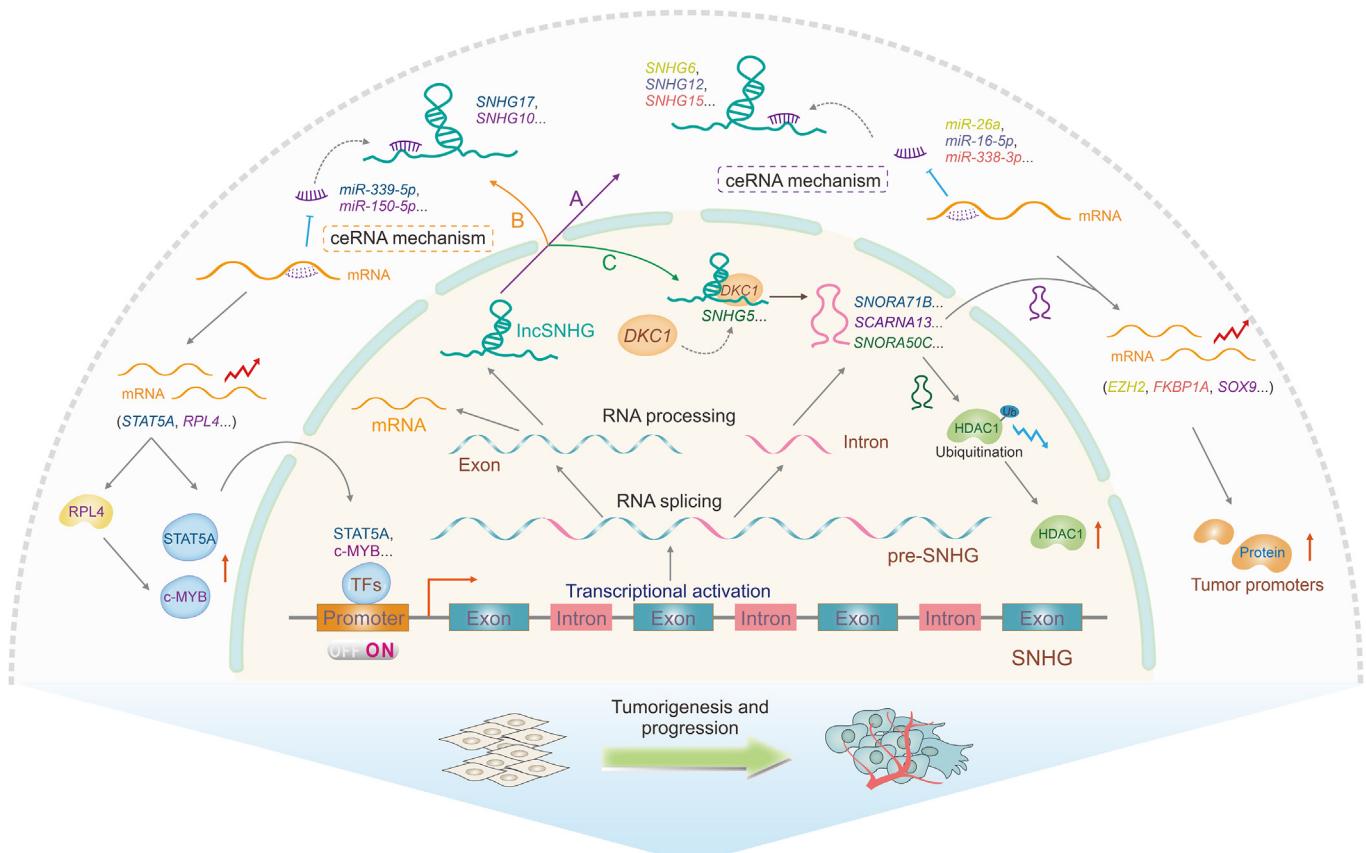
Fig. 4. Regulatory mechanisms of small nucleolar RNAs (snoRNAs) derived from long non-coding snoRNA host gene (lncSNHGs) induce consistent biological functions in cancer. Long non-coding RNA snoRNA host genes (lncRNA SNHGs) and their homologous snoRNAs are derived from the same primary transcript, pre-SNHGs. SnoRNAs are usually derived from introns and lncRNA SNHGs are usually derived from exons. LncRNA SNHGs and snoRNAs participate in tumorigenesis and development through three regulatory pathways. (A) LncRNA SNHGs sponge microRNAs (miRNAs) through the ceRNA mechanism and inhibit the degradation of downstream messenger RNAs (mRNAs), which in turn promotes tumor progression. (B) LncRNA SNHGs, through the competing endogenous RNA (ceRNA) mechanism, upregulate transcription factors, forming a positive feedback loop to upregulate their homologous snoRNAs. (C) LncRNA *SNHG5* recruits dyskerin pseudouridine synthase 1 (DKC1) to promote *SNORA50C* accumulation and inhibits histone deacetylase 1 (HDAC1) ubiquitination, promoting hepatocellular cancer progression. The yellow color denotes *SNHG6*/miR-26a/enhancer of zeste 2 polycomb repressive complex 2 subunit (*EZH2*) axis. The grey color denotes *SNHG12*/miR-16-5p axis. The peach color denotes *SNHG15*/miR-338-3p/FK506-binding protein (FKBP) prolyl isomerase 1A (*FKBP1A*) axis. The blue color denotes *SNHG17*/miR-339-5p/signal transducer and activator of transcription 5A (*STAT5A*)/*SNORA71B* axis. The purple denotes *SNHG10*/miR-150-5p/ribosomal protein L4 (*RPL4*)/MYB proto-oncogene, transcription factor (c-Myb)/*SCARNA13*/SRY-box transcription factor 9 (*SOX9*) axis. The green denotes *SNHG5*/DKC1/*SNORA50C*/HDAC1 axis. TFs: transcription factors.

upregulation of signal transducer and activator of transcription 5A (STAT5A) and subsequent activation of *SNORA71B*, thereby exacerbating the progression of prostate cancer [100]. In HCC, *SNHG10* expression is positively correlated with its corresponding snoRNA, *SCARNA13*. *SNHG10* regulates *SCARNA13* expression through a positive feedback loop involving *miR-150-5p*, ribosomal protein L4 (RPL4), and MYB proto-oncogene, transcription factor (c-MYB). Conversely, *SCARNA13* regulates the oncogenic activity of SRY-box transcription factor 9 (SOX9) in HCC by promoting cellular proliferation, invasion, and migration [101]. Besides, SNHGs can interact directly with snoRNAs and affect their expression, as shown in Table 2 [102] and Fig. 4C. In neuroblastoma (NB), *SNHG5* promotes the accumulation of its homologous gene *SNORA50C* and assembly of the associated snoRNP by recruiting DKC1. *SNORA50C* suppresses the ubiquitination of histone deacetylase 1 (HDAC1) and upregulates the expression of the oncogenic factor HDAC1 in NB cells. This process facilitated the proliferation and migration of NB cells [102]. Taken together, research on SNHGs and snoRNAs offers preliminary insights into cancer occurrence and progression, potentially advancing diagnosis and treatment strategies for cancer patients. However, further studies are needed to elucidate the distinct roles of snoRNAs and their host genes. Specifically, research distinguishing the contributions of snoRNAs from those of their host

genes would be particularly valuable for understanding their individual impacts on cancer.

6. SnoRNA-mediated tumor drug resistance

6.1. SnoRNAs mediate multidrug resistance by regulating tumor cell stemness

Multiple studies have demonstrated the regulatory role of snoRNAs in the maintenance of tumor cell stemness, which has significant implications for tumor onset and progression [41,103,104] (Fig. 5). Remarkably, *SNORD127* triggers preferential translation of amino acid transporter mRNAs in a codon-dependent manner to drive AML stem cell phenotypes, such as self-renewal [41]. Similarly, *SNORD89* activates the NOTCH1/cellular MYC (c-MYC) pathway and induces stemness in OV cells, as shown in Table 3 [103]. *SNORA38* positively correlates with OCT-4 stem cell marker and regulates the stemness of BRCA cells [104]. Moreover, snoRNAs can transform tumor stem cells by regulating the expression of stem cell markers, resulting in uncontrolled tumor proliferation and drug resistance, as shown in Table 3 [105,106]. *SNORD1C* overexpression in CRC activates the Wnt/β-catenin pathway, resulting in the upregulation of *CD44*, *SOX2*, and other stem cell genes. This activation enhances
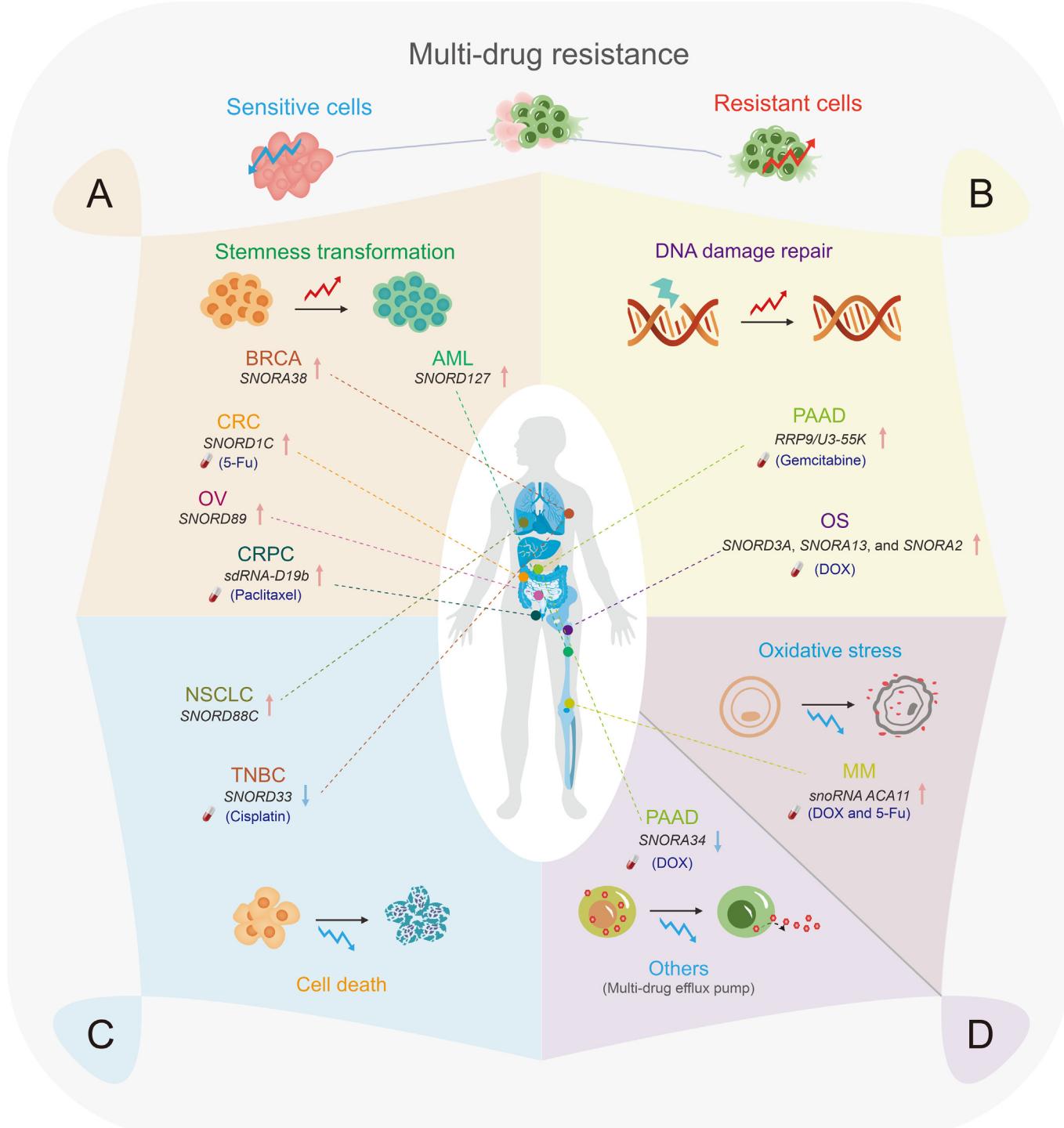
Fig. 5. Small nucleolar RNAs (snoRNAs) mediating tumor multi-drug resistance. (A) Some snoRNAs promote tumor drug resistance by promoting cell stemness transformation. (B) Some snoRNAs promote tumor drug resistance by promoting DNA damage repair (DDR). (C) Some snoRNAs mediate tumor drug resistance by regulating cell death. (D) Some snoRNAs promote tumor multi-drug resistance by inhibiting oxidative stress. Others, such as *SNORA34*, can downregulate the membrane transporter protein adenosine triphosphate (ATP) binding cassette subfamily C member 1 (ABCC1) to inhibit tumor drug resistance. Red arrows denote promoting drug resistance and blue arrows denote reversing drug resistance. BRCA: breast cancer; AML: acute myeloid leukemia; CRC: colorectal cancer; 5-Fu: 5-fluorouracil; OV: ovarian cancer; SNORDs: C/D box snoRNAs; CRPC: castration-resistant prostate cancer; sdRNA: snoRNA-derived RNAs; PAAD: pancreatic adenocarcinoma; RRP9: ribosomal RNA (rRNA) processing 9; OS: osteosarcoma; NSCLC: non-small cell lung cancer; TNBC: triple-negative BRCA; MM: multiple myeloma; 5-FU: 5-fluorouracil; DOX: doxorubicin.

colon cancer cell proliferation and cell cycle progression and con- tributes to 5-fluorouracil (5-FU) resistance in these cells [105]. In addition, *sdRNA-D19b* increased the proliferation and metastasis of castration-resistant prostate cancer (CRPC) cells by selectively targeting the 3'-UTR of the *CD44* mRNA. This mechanism confers resistance to paclitaxel drugs [106]. This study proposed sdRNAs as potential biomarkers and therapeutic targets for future clinical in- terventions in CRPC [106].

Table 3
Small nucleolar RNAs (snoRNAs) involved in tumor drug resistance.

SnoRNA	Mechanism	Biological function	Drug sensitivity	Related tumor type	Refs.
SNORD88C	Guiding 2'-O-methylation of *28S* rRNA and upregulating SCD1	Inhibiting autophagy and promoting growth and metastasis	/	NSCLC	[53]
SNORD89	Activating the NOTCH1/c-MYC pathway	Promoting tumor cell proliferation and self-renewal ability	/	OV	[103]
SNORD1C	Activating the Wnt/β-catenin pathway	Promoting tumor cell proliferation, migration, and invasion	/	CRC	[105]
sdRNA-D19b	Targeting the 3'-UTR of *CD44* genes	Promoting tumor cell proliferation and migration	Paclitaxel (−)	CRPC	[106]
SNORD3A, *SNORA13*, and *SNORA2*	Downregulating TOP2A and upregulating GADD45A	Promoting tumor development	DOX (−)	Human osteosarcoma	[111]
U3 snoRNA-related protein, RRP9/U3-55K	Activating the AKT signaling pathway	Promoting tumor growth	Gemcitabine (−)	Pancreatic cancer	[112]
SNORD33	Binding to MeCP2	Promoting tumor cell apoptosis	Cisplatin (+)	Triple-negative BRCA	[116]
SNORNA ACA11	Inhibiting *NRF2* transcriptional activity	Promoting tumor development	DOX (−) and 5-FU (−)	MM	[122]
SNORA34	Deriving *hsa-miR-1291* to target 3'-UTR of *ABCC1*	Promoting tumor cell sensitivity	DOX (+)	Pancreatic cancer	[125]

/: no data. (−) refers to downregulation and (+) refers to upregulation. SNORDs: C/D box snoRNAs; rRNA: ribosomal RNA; SCD1: stearoyl-CoA desaturase 1; NSCLC: non-small cell lung cancer; NOTCH1: neurogenic locus notch homolog protein 1; c-MYC: cellular MYC; OV: ovarian cancer; CRC: colorectal cancer; *CD44*: CD44 molecule; CRPC: castration-resistant prostate cancer; TOP2A: DNA topoisomerase II alpha; GADD45A: growth arrest and DNA damage inducible 45A; DOX: doxorubicin; RRP9: ribosomal RNA processing 9; AKT: protein kinase B; MeCP2: methyl cytosine-phosphate-guanine-binding protein 2; BRCA: breast cancer; *NRF2*: NF-E2-related factor 2; 5-FU: 5-Fluorouracil; MM: multiple myeloma; *ABCC1*: ATP binding cassette subfamily C member 1.

6.2. SnoRNAs or their associated regulatory proteins mediate tumor chemoresistance via the DDR pathway

Tumor cells possess a robust DNA repair mechanism that effectively repairs chemotherapy-induced DNA damage, thereby enhancing drug resistance [107–109]. Doxorubicin (Dox)-induced DNA damage in colon cancer cells results in the expression of growth arrest-specific transcript 5 (GAS5)-derived snoRNA in a P53-dependent pathway, suggesting that snoRNA may influence DNA damage [110]. SnoRNAs and their associated proteins are involved in DDR, which has implications for drug resistance, as shown in Table 3 [111,112] and Fig. 5. The upregulation of *SNORD3A*, *SNORA13*, and *SNORA2* expression in Dox-resistant osteosarcoma cells is crucial for the synthesis of Dox-resistant proteins by downregulating the Dox target DNA topoisomerase II alpha (TOP2A), upregulating the DNA damage sensor growth arrest and DNA damage inducible 45A (GADD45A), and regulating the mechanisms involved in DNA repair and ribosome formation. Consequently, these molecular mechanisms contribute to the development of Dox resistance in osteosarcoma [111]. Therefore, the identification and targeting of specific snoRNAs or their downstream genes present novel therapeutic prospects for chemoresistant osteosarcoma. In addition, gemcitabine resistance in pancreatic adenocarcinoma (PAAD) is induced by the U3 snoRNA-related protein, rRNA processing 9 (RRP9)/U3-55K. This protein activates the AKT signaling pathway, reducing DNA damage and impeding cell apoptosis [112]. Therefore, the combination of the AKT inhibitor MK-2206 and gemcitabine shows potential as a therapeutic strategy for patients with gemcitabine-resistant pancreatic cancer.

6.3. SnoRNAs mediate chemoresistance by regulating cell death

Cell death pathways such as apoptosis, autophagy, and necrosis have distinct morphological and biochemical characteristics. Apoptosis is typically associated with cell contraction, whereas autophagy is characterized by cytoplasmic vacuolization and autophagosome formation. These autophagosomes facilitate the elimination of substances via lysosomes [113–115]. SnoRNAs have the potential to influence tumor progression by regulating cell death, as shown in Table 3 [53,116] and Fig. 5. *SNORD88C* promotes the growth and metastasis of NSCLC by inducing 2'-O-methylation of *28S* rRNA. This process enhances the translation activity of the downstream target gene *SCD1*, reduces the number of autophagosomes, and inhibits autophagy [53]. And the resistance of tumor cells to anti-cancer drugs is influenced by disruption of the snoRNA-mediated apoptotic mechanism [116]. *SNORD33* binds to methyl CpG-binding protein 2 (MeCP2) and disrupts its interaction with target genes. Therefore, the expression of anti-apoptotic proteins (myeloid leukemia 1 (MCL-1) and BCL-2) decreases, whereas that of pro-apoptotic proteins (caspase-3 (Cas3) and Cas9) increases. Therefore, the promotion of tumor cell apoptosis leads to the reversal of cisplatin resistance in triple-negative BRCA cells [116].

6.4. SnoRNAs mediate chemoresistance by regulating reactive oxygen species (ROS)

ROS are generated during oxidative stress. Increased cellular ROS levels activate multiple antioxidant mechanisms in tumor cells [117,118]. This suppresses ROS generation, resulting in increased resistance to cancer therapies [119–121]. Previous studies have demonstrated the involvement of snoRNAs in regulating cellular oxidative stress and promoting tumor resistance [122–124] (Fig. 5). *ACA11*, an orphan snoRNA, inhibits oxidative stress, promotes MM cell proliferation, and enhances resistance to Dox and 5-FU, as shown in Table 3 [122]. *ACA11* inhibits nuclear factor erythroid 2 (NF-E2)-related factor 2 (NRF2) transcriptional activity in multiple myeloma (MM). This inhibition increases ROS-dependent biological processes, including *pre-47S rRNA* synthesis, protein synthesis, and ribosome biogenesis [123,124]. Moreover, *ACA11* overexpression enhances MM cell responsiveness to the proteasome inhibitor bortezomib [124].

6.5. Others

SnoRNAs regulate multidrug resistance-associated protein (MRP1)/adenosine triphosphate (ATP) binding cassette subfamily C member 1 (ABCC1) expression, affecting intracellular drug transport and promoting multidrug resistance in cancer cells. In

pancreatic cancer, *hsa-miR-1291* from *SNORA34* specifically targets the 3'-UTR of the membrane transport protein ABCC1, leading to the downregulation of its expression. Consequently, drug accumulation increases within cells, causing a reversal of mitoxantrone resistance in cancer cells, as shown in Table 3 [125].

7. Therapeutic strategies and clinical implications of cancer-associated snoRNAs

7.1. SnoRNAs as diagnostic and prognostic biomarkers in cancer

SnoRNAs play a significant role in cancer and can be readily detected in different body fluids, including plasma and serum [126−128] (Fig. 6). SnoRNAs have emerged as promising diagnostic and prognostic biomarkers owing to advancements in high-throughput sequencing and bioinformatics technology, which have radically changed in recent years [129]. Notably,

thermostable group II intron reverse transcriptases RNA sequencing (TGIRT-seq) exhibits high fidelity, processivity, and strand-displacement activity, along with proficient template-switching capabilities. Evidence indicates that TGIRT-seq allows comprehensive profiling of structured sncRNAs, including snoR-NAs, revolutionizing our understanding of snoRNA expression. This method offers a novel strategy for evaluating tumorigenesis and outcomes [2,130]. Further, Xie et al. [131] identified *SNORA11*, *SNORD124*, and *SNORD46* as key snoRNAs with potential implications in HCC diagnosis and treatment. This discovery was made by analyzing transcriptome data from The Cancer Genome Atlas (TCGA) and The International Cancer Genome Consortium (ICGC) datasets. Similarly, *SNORD15A*, *SNORD35B*, and *SNORD60* are significantly overexpressed in cancerous tissues and urine, making them useful biomarkers for the early diagnosis and potential therapeutic targets for renal cell carcinoma (RCC) [132]. In esophageal cancer (ESCA), the upregulation of *SNORA58*,
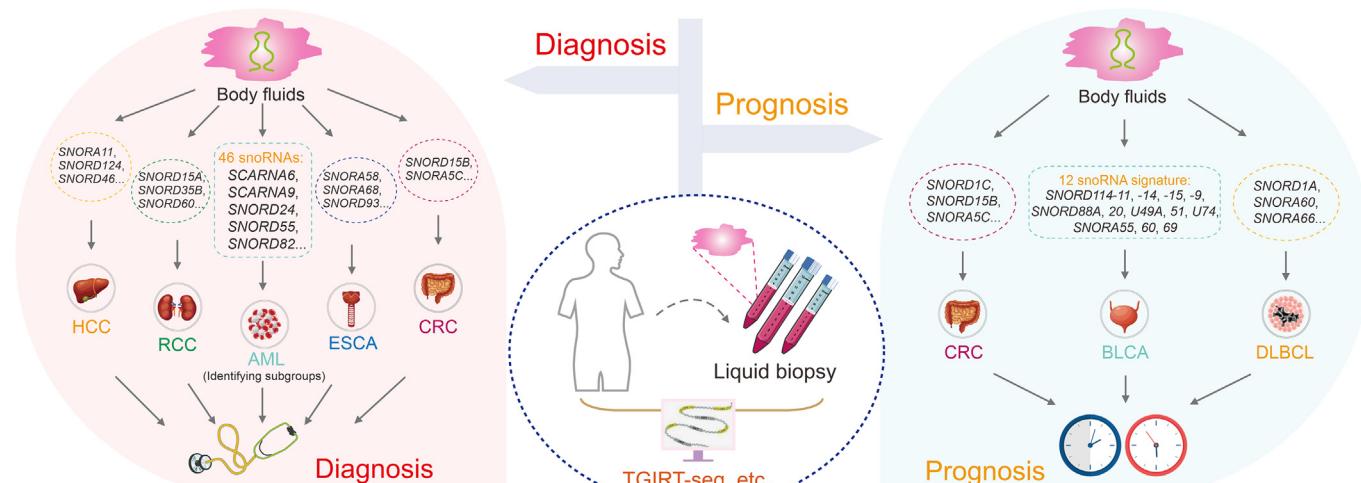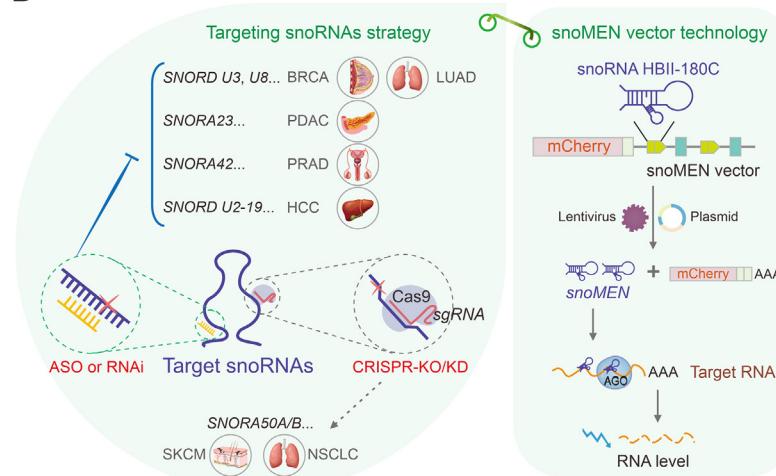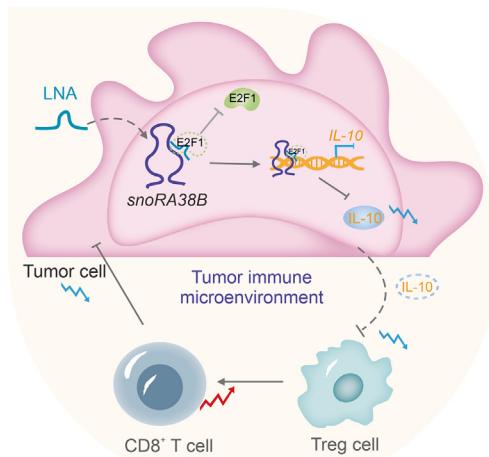

Fig. 6. Therapeutic strategies and clinical implications of cancer-associated small nucleolar RNAs (snoRNAs). (A) SnoRNAs act as liquid biopsy biomarkers for tumor early diagnosis and prognosis evaluation. (B) Current cancer therapeutic strategies for targeting oncogenic snoRNAs include antisense oligonucleotide (ASO) technology, small interfering RNA (siRNA), short hairpin RNA (shRNA), clustered regularly interspaced short palindromic repeats (CRISPR)/caspase-9 (Cas9) technology, and snoRNA modulator of gene expression (snoMEN) vector technology. (C) Targeting tumor immune microenvironment (TIME)-related *SNORA38B* by locked nucleic acid (LNA) increases the infiltration of CD8$^+$ T cells, and inhibits proliferation of non-small cell lung cancer (NSCLC) cells. SNORAs: H/ACA box snoRNAs; SNORDs: C/D box snoRNAs; HCC: hepatocellular carcinoma; RCC: renal cell carcinoma; AML: acute myeloid leukemia; ESCA: esophageal cancer; CRC: colorectal cancer; TGIRT-seq: thermostable group II intron reverse transcriptases RNA-seq; BLCA: bladder cancer; DLBCL: diffuse large B-cell lymphoma; BRCA: breast cancer; LUAD: lung adenocarcinoma; PDAC: pancreatic ductal adenocarcinoma; PRAD: prostate adenocarcinoma; RNAi: RNA interference; sgRNA: single guide RNA; KO/KD: knockout/knockdown; SKCM: skin cutaneous melanoma; NSCLC: non-small cell lung cancer; AGO: argonaute; LNA: locked nucleic acid; E2F1: E2F transcription factor 1; IL-10: interleukin-10; Treg cell: regulatory T cell.

SNORA68, and *SNORD93* is observed in both ESCA patients and early-stage patients. Additionally, combining snoRNAs with the existing tumor marker carcinoembryonic antigen is shown to enhance the diagnostic ability in ESCA patients [133]. In diffuse large B-cell lymphoma (DLBCL), a triple snoRNA prognostic risk model consisting of *SNORD1A*, *SNORA60*, and *SNORA66* was constructed. The study revealed that the upregulation of *SNORD1A* and *SNORA60* was associated with poor prognosis in DLBCL patients, while *SNORA66* was upregulated in the low-risk group, serving as a protective factor. This study provides novel insights into the prognostic significance of snoRNAs in DLBCL [134].

The oncogenic properties of *SNORD15B* and *SNORA5C* in CRC suggest that these two snoRNAs could serve as promising biomarkers for the diagnosis and prognostic prediction of CRC [135]. Moreover, distinct B-cell malignancies exhibit the abnormal expression of specific snoRNAs [136,137]. Teittinen et al. [137] identified 46 snoRNAs with differential expression between B-cell precursor acute lymphoblastic leukemia (BCP-ALL) and T-cell acute lymphoblastic leukemia (T-ALL) using large-scale parallel sequencing (sequencing by oligonucleotide ligation and detection (SOLiD)). These snoRNAs have potential applications as diagnostic biomarkers or therapeutic targets.

SnoRNAs exhibit diverse characteristics in cancer and can serve as reliable prognostic markers [138,139] (Fig. 6). A risk assessment classifier was developed in bladder cancer (BLCA), using the expression profiles of 12 survival-related snoRNAs. Clinical outcomes vary between high- and low-risk patient groups. This characteristic makes it a reliable prognostic predictor for patients with BLCA [138]. Cai et al. [139] identified TIIsno-snoRNA characteristics associated with immune infiltration by analyzing integrated expression profiles of snoRNAs in 21 purified immune cell lines, 43 colon cancer cell lines, and 3 data sets. Patients with lower TIIsno scores exhibited better responses to immune therapy. This feature may serve as an indicator for predicting prognosis and response to immune treatment in patients with colon cancer.

7.2. Application of snoRNAs in targeting cancer therapy

SnoRNAs are implicated in carcinogenesis through diverse regulatory mechanisms. These molecules can be targeted for cancer therapy owing to their oncogenic potential [140]. Several cancer therapeutic strategies have been developed to target snoRNAs, including clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9, small interfering RNA (siRNA), short hairpin RNA (shRNA), and ASO technologies [87]. ASOs can effectively silence non-coding RNA. ASOs may serve as effective and targeted therapeutic interventions that target specific cancer-related snoRNAs. Additionally, ASOs can inhibit cancer cell tumorigenicity, both *in vitro* and *in vivo*. *In vitro* experiments have demonstrated that targeting box C/D snoRNAs *U3* and *U8* can eliminate tumorigenicity in lung (H1944) and BRCA (MCF-7) cells [85,141]. *SNORA23* upregulates SYNE2 expression, promoting increased survival and invasiveness in pancreatic ductal adenocarcinoma (PDAC) cells. Targeting *SNORA23* with ASOs reduces the growth and metastasis of xenograft tumors [142]. Therefore, ASO technology shows promise as a novel cancer therapy that targets tumor-associated snoRNAs. Both siRNA and shRNA induce degradation of target genes and inhibit tumor progression by degrading oncogenes [88,143,144]. In fact, siRNA and shRNA have been shown to be quite inefficient on the highly structured mRNA but can precisely silence snoRNA due to its conserved secondary structure and crucial RNA-binding sequences. For example, *SNORA42* expression is significantly higher in prostate cancer tissues than in adjacent tissues. Transfection with anti-*SNORA42* siRNA significantly reduced the growth rate of DU145 and PC3 prostate cancer cells and induced

apoptosis [143]. Wang et al. [144] observed a correlation between increased *snoU2_19* expression and invasive phenotypes in HCC patients. Additionally, the use of *snoU2_19*-shRNAs to knock out *snoU2_19* effectively inhibited cell cycle proliferation and progression in SK-HEP-1 and HCCLM3 HCC cells. Furthermore, CRISPR/Cas9 gene editing technology has been used to remove snoRNAs, specifically *SNORA50* A/B, resulting in increased tumorigenicity in CHL-1 melanoma, A549 lung cancer, and NCI-H23 cells [145].

Additionally, the snoRNA gene expression regulator (snoRNA modulator of gene expression (snoMEN)), a vector technology derived from snoRNA, may also benefit targeted cancer therapy [146]. The snoMEN technology functions as an antisense gene suppression technique that targets intron sequences of nuclear pre-mRNAs, resulting in the downregulation of genes and the regulation of RNA targets [147]. The snoMEN vector selectively induced apoptotic death in *miR21*-overexpressed human lung adenocarcinoma cells by targeting specific sequences in *pri-miR21* [148]. Therefore, snoMEN vectors have potential for future anti-cancer therapies.

7.3. Tumor immune microenvironment (TIME)-related snoRNAs in immunotherapy

SnoRNAs have been linked to several components of the TIME, including CD8$^+$ T cell infiltration, cytotoxic T cell function, and tumor vasculature [149,150]. SnoRNA targeting can improve the efficacy of cancer immunotherapy [70]. *SNORA38B* promotes the recruitment of CD3$^+$FOXP3$^+$ regulatory T cells (Tregs) to the NSCLC tumor microenvironment by stimulating interleukin-10 (IL-10) secretion. This results in decreased infiltration of CD3$^+$CD8$^+$ T cells, promoting tumor development and immune suppression. The application of locked nucleic acids (LNAs) targeting *SNORA38B* can significantly improve the TIME and increase the responsiveness of NSCLC cells to immune checkpoint blockade therapy [70]. Therefore, targeting TIME-associated snoRNAs has the potential to modulate cancer sensitivity to immunotherapy, providing novel modalities and insights into combination therapies for cancer.

8. Conclusion

SnoRNAs were previously disregarded as a subtype of non-coding RNAs (ncRNAs) in cancer cells. In recent years, there has been an increasing interest in the study of snoRNAs and their function in tumor development, specifically in 2'-O-ribose methylation and pseudouridylation. However, a comprehensive understanding of the intricate link between snoRNAs and cancer remains limited. Several studies have revealed that snoRNAs display atypical characteristics and expression patterns. This review introduces the regulation of snoRNA expression from three perspectives: dynamic regulation by transcription regulators, transcriptional inhibition by DNA methylation, and dependence on host gene transcription and splicing events. Importantly, we provide a concise overview and explanation of the three novel molecular mechanisms regulated by cancer-associated snoRNAs: 1) the transcriptional regulation of targets by snoRNAs including the crosstalk between snoRNAs and transcription regulators (TRs); 2) the regulation by snoRNAs in post-transcriptional processes, including pre-RNA splicing, mRNA 3'-end APA, mRNA stability, and formation of sdRNAs with miRNA-like functions, indirectly regulating tumor occurrence and development; and 3) the effects of snoRNAs on ADP-ribosylation and chromatin remodeling following target RNA translation. The non-classical cancer regulatory mechanisms of snoRNAs undoubtedly enhance our understanding of cancer and open novel avenues for tumor treatment. SnoRNAs may

influence drug resistance in tumor cells by regulating cellular stemness, DDR, cell death pathways, and oxidative stress. Consequently, they could be considered as promising therapeutic targets for cancer treatment, particularly in relation to drug resistance. Furthermore, the cross-talk and feedback mechanisms between SNHGs and snoRNAs have significant implications for cancer progression, warranting further research.

SnoRNAs play a critical role in cancer biology and have significant clinical implications. Dysregulated snoRNAs are potential therapeutic targets for cancer treatment and serve as diagnostic and prognostic markers. Silencing of snoRNAs, which are recognized for their oncogenic characteristics, can potentially lead to the reversal of cancer clinical outcomes. Additionally, targeting tumor immunity-associated snoRNAs has the potential to improve the efficacy of cancer immunotherapy. Therefore, comprehending the mechanisms driving snoRNAs is imperative to enhance our understanding of cancer and holds immense potential for diverse applications in the field. The study of snoRNAs in cancer is an emerging research area. Advancements in high-throughput sequencing technology have facilitated the identification of numerous abnormally expressed snoRNAs in cancers. This technology has also facilitated the development of tools for experimental research. At the current stage, researchers are diligently working to compile a comprehensive overview of snoRNA genetics and pharmacogenomics, with the aim of serving as a clinical reference guide and establishing a foundation for future advancements in snoRNA-targeted therapy. However, the implementation of snoRNA-based treatments in clinical practice may require considerable time. Further research will contribute to a better understanding of the clinical significance of these snoRNAs.

CRediT authorship contribution statement

Xiaoyun Hu: Writing − original draft, Conceptualization. **Wanlin Cui:** Writing − original draft. **Min Liu:** Writing − original draft. **Fangxiao Zhang:** Data curation, Writing − original draft. **Yingqi Zhao:** Writing − review & editing. **Mingrong Zhang:** Writing − review & editing. **Yuhang Yin:** Writing − review & editing. **Yalun Li:** Writing − review & editing. **Ying Che:** Writing − review & editing. **Xianglong Zhu:** Writing − review & editing. **Yuxuan Fan:** Writing − review & editing. **Xiaolan Deng:** Writing − review & editing. **Minjie Wei:** Writing − review & editing. **Huizhe Wu:** Writing − review & editing.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Acknowledgments

Appendix A. Supplementary data

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