snoRNAs and their derived sdRNAs: Emerging regulators, biomarkers, and therapeutic targets in human cancers (Review)

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Abstract. Small nucleolar RNAs (snoRNAs) are a conserved class of non-coding RNAs that guide 2'-O-methylation and pseudouridylation of ribosomal RNA. First identified over five decades ago, snoRNAs have emerged as critical regulators of cellular function, with high-throughput sequencing revealing their dysregulation in numerous human diseases, particularly cancer. In the present review, the biogenesis, classification, and modification mechanisms of snoRNAs and snoRNA-derived fragments (sdRNAs) are comprehensively summarized. Recent advances in understanding their non-canonical functions are highlighted, which extend beyond ribosomal RNA modification to include regulation of mRNA splicing, stability, and protein interactions. These diverse mechanisms enable snoRNAs to influence key cancer-related processes such as proliferation, metastasis, metabolic reprogramming, and therapy resistance. A comprehensive overview of snoRNA dysregulation across major cancer types is provided, including colorectal, hepatocellular, gastric, lung, breast, and ovarian cancers, with a detailed discussion of underlying molecular pathways. Furthermore, their emerging potential as diagnostic and prognostic biomarkers detectable in liquid biopsies is examined, as well as their promise as therapeutic targets amenable to antisense oligonucleotide and small molecule intervention. The present review integrates current knowledge of snoRNA/sdRNA biology and highlights critical gaps and future directions, providing a foundation for translating these regulatory RNAs into clinical oncology applications.

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Contents

1. Introduction

First identified in mammalian cells in 1960, snoRNAs are recognized as pivotal, naturally occurring guide RNAs. Typically ranging from 60 to 300 nucleotides in length, they function within ribonucleoprotein (RNP) complexes to precisely target specific cellular RNAs. While the human genome harbors over 1,000 annotated snoRNA genes, a striking 80% of these remain functionally enigmatic (1,2).

Accumulating evidence indicates that specific snoRNAs exert direct control over gene expression by governing mRNA stability, editing, and splicing-mechanisms that may operate autonomously from canonical RNA modification pathways (3,4). Notably, >50 snoRNAs have been implicated in dysregulation across over 12 cancer types, although the precise mechanisms underlying disease pathogenesis due to snoRNAs deletions or mutations are still largely elusive, primarily owing to limitations in current methodologies for comprehensive identification of snoRNA targets and their transcriptome-wide modification profiles (5).

In addition to their canonical forms, snoRNAs can undergo specific processing to generate smaller fragments ranging from 16 to 36 nucleotides, known as snoRNA-derived fragments (sdRNAs). First identified in 2008, sdRNAs represent a relatively unexplored class of small non-coding RNAs (ncRNAs), with their functional roles and regulatory mechanisms still largely undefined (6). These small fragments have emerged as functional molecules with regulatory roles distinct from their parental snoRNAs (7).

While several notable reviews have previously explored the biology of snoRNAs, many have predominantly focused on their canonical roles in ribosome biogenesis or provided generalized observational overviews of their dysregulation in specific cancer types. Furthermore, within existing literature, sdRNAs are frequently relegated to brief mentions rather than being critically evaluated as distinct, functionally significant regulatory entities. The present review extended beyond these previous works by applying a rigorous 'three-tier evidence framework' to systematically evaluate the clinical readiness of both snoRNAs and sdRNAs. Current knowledge was strictly stratified into fundamental mechanistic drivers (tier 1), retrospective tissue-based prognostic associations (tier 2), and highly actionable translational applications, such as liquid biopsies and nucleic acid therapeutics (NATs) (tier 3). By critically synthesizing these distinct levels of evidence and placing an unprecedented structural emphasis on the rapidly evolving sdRNA landscape, the present review provided a uniquely structured, translational roadmap for integrating these ncRNAs into precision oncology.

The article is a narrative review intended to provide an updated overview of the biogenesis, functions and clinical relevance of snoRNAs and sdRNAs in cancer. Rather than performing a formal systematic review or meta-analysis, representative original studies and recent review articles were qualitatively synthesized, with an emphasis on mechanistic insights, biomarker potential, liquid biopsy applications and therapeutic targeting. Furthermore, their emerging potential as diagnostic biomarkers and therapeutic targets in cancer was emphasized, providing novel perspectives for innovative strategies in cancer diagnosis and treatment. By integrating current knowledge and highlighting critical gaps in the field, the present review sought to provide a foundation for future research directions in snoRNA and sdRNA biology and their applications in oncology.

2. Biogenesis

snoRNAs, primarily originating from intronic sequences, commonly reside within genes that encode proteins vital for ribosome biogenesis and function. This genomic arrangement facilitates the synchronized expression of ribosomal components alongside their associated snoRNAs, thereby preserving cellular homeostasis (8,9). Notably, a subset of snoRNAs originates from introns of non-coding genomic regions, such as growth arrest-specific 5 (GAS5) and snoRNA host gene (SNHG)1, which produce distinct sets of eleven and nine snoRNAs, respectively (10,11).

The stability of intronically encoded snoRNAs is maintained through their cotranscriptional association with RNPs, which protect them from exonucleolytic degradation (12). These RNP complexes, along with auxiliary factors including nuclear assembly factor 1, sno/sca RNA-associated H/ACA assembly factor 1 homolog, and nuclear factor-like protein, ensure proper processing, stability, and nucleolar localization of snoRNAs (13). Following synthesis, snoRNPs are transported to Cajal bodies for further maturation before localizing to nucleoli, where they modify ncRNAs (14). Notably, the transcriptional regulation of snoRNAs varies across species. In plants and yeast, certain snoRNAs are transcribed in a polycistronic manner, whereas in the case of GAS5, snoRNAs are interspersed with exons. Furthermore, yeast exhibit a unique mechanism in which some snoRNAs are transcribed by RNA polymerase II, highlighting the evolutionary diversity in snoRNA transcription and processing mechanisms among different organisms (15).

3. snoRNA classes and functions

snoRNA classes and canonical function. snoRNAs play a central role in post-transcriptional modifications, primarily guiding 2'-O-ribose methylation and pseudouridylation of ribosomal RNAs (rRNAs) and small nuclear RNAs (snRNAs). These modifications enhance molecular interactions, promote rRNA folding, and ultimately optimize ribosome and spliceosome function (16,17). snoRNAs function as guide RNAs within snoRNP complexes, which include core proteins that provide catalytic activity and ensure target specificity via complementary base pairing (18-20).

snoRNAs are classified into 2 main groups: C/D box snoRNAs (SNORDs) and H/ACA box snoRNAs (SNORAs), which direct methylation and pseudouridylation, respectively. In addition to these, a third category, small Cajal body-specific RNAs (scaRNAs), exhibits hybrid features of both SNORDs and SNORAs, combining their functional properties to perform specialized roles in RNA modification. This diversity in snoRNA classes underscores their versatility and importance in RNA processing and cellular function (21). Characterization, biogenesis and canonical function of snoRNAs are shown in Fig. 1.

SNORDs. SNORDs are characterized by conserved C (RUGAUGA) and D (CUGA) motifs near their termini, forming a kink-turn structure. They also contain internal C' and D' boxes. These structural elements scaffold proteins such as nucleolar protein (NOP)56, NOP58, 15.5 kilodalton protein, and fibrillarin, which are essential for the stability, localization, and functional integrity of snoRNPs.

The target specificity of SNORDs is mediated by a short guide region, typically 10-21 nucleotides in length, located upstream of the D or D' boxes. This region, referred to as the antisense element, plays a critical role in recognizing and binding to complementary sequences on target RNAs. Fibrillarin, a core component of the snoRNP complex, serves as the catalytic force for methylating the fifth nucleotide upstream of the D or D' box motif, thus fulfilling the essential modification role of snoRNP. This precise targeting mechanism ensures the accurate and site-specific 2'-O-methylation of rRNAs and snRNAs, highlighting the sophisticated regulatory role of SNORDs in RNA processing and modification (22-24).

SNORAs. SNORAs are characterized by a 3' ACA tail and 2 hairpin structures connected by a hinge region containing a conserved (ANANNA) motif, known as the H motif or BOX H. Each hairpin contains an internal loop, termed the pseudouridylation pocket, which base-pairs with target RNAs. Typically, the uridine residue in the target RNA, positioned 14-15 nucleotides upstream of the H or ACA box, undergoes pseudouridylation. This reaction is catalyzed by dyskerin, a pseudouridine synthase within the H/ACA-associated snRNP

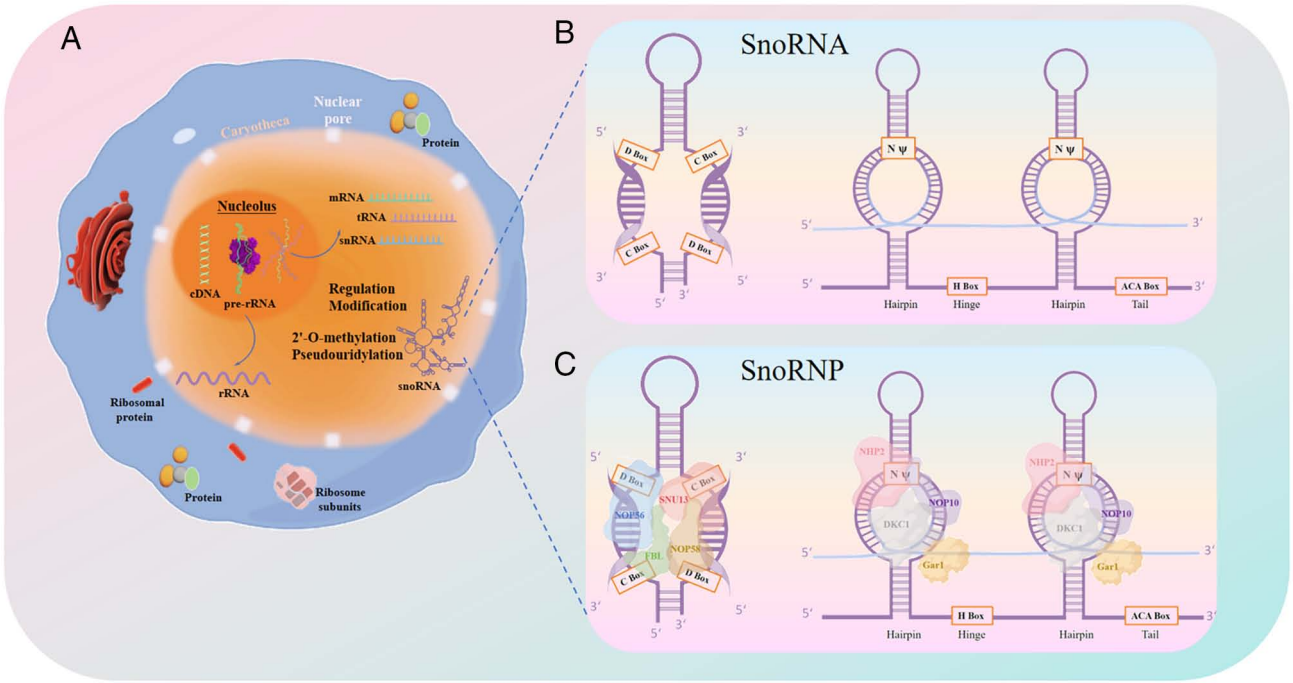

Figure 1. Characterization, biogenesis and canonical function of snoRNAs. (A) Genomic organization of snoRNAs: Intronic snoRNAs are processed from host gene transcripts, while some snoRNAs are transcribed from independent promoters. (B) Structural features of C/D box and H/ACA box snoRNAs and canonical functions: Showing conserved motifs (C/D boxes, H/ACA domains) and core binding proteins (fibrillarin and dyskerin). C/D box snoRNAs guide 2'-O-methylation of rRNA and snRNA; H/ACA box snoRNAs guide pseudouridylation. (C) Biogenesis pathway: snoRNAs associate with core proteins to form snoRNPs, are transported to Cajal bodies for maturation, and localize to nucleoli. snoRNA, small nucleolar RNA; rRNA, ribosomal RNA; snRNA, small nuclear RNA; snoRNP, small nucleolar ribonucleoprotein; mRNA, messenger RNA; tRNA transfer RNA.

complex, which also includes nuclear H/ACA ribonucleoprotein 2 (NHP2), NOP10, and glycine-argine rich protein 1 (25-27).

scaRNAs. scaRNAs are distinguished by their localization within Cajal bodies, specialized sub-nuclear compartments, mediated by a unique UGAG motif. These RNAs play critical roles in spliceosome and ribosome biogenesis, facilitating the precise methylation and pseudouridylation of snRNAs and rRNAs. By guiding these modifications, scaRNAs ensure the structural and functional integrity of these essential molecular complexes, underscoring their importance in cellular processes (28,29).

Noncanonical snoRNA functions. snoRNAs constitute a diverse and functionally versatile class of RNA molecules with multifaceted roles in cellular processes. Notably, approximately half of human snoRNAs are 'orphans' with uncharacterized functions (30). Recent studies have revealed diverse noncanonical roles beyond rRNA/snRNA modification, expanding our understanding of their roles beyond traditional paradigms and revealing previously unexplored biological activities (31,32).

Additional modifications of rRNAs and snRNAs. Emerging research indicates that snoRNAs may possess an expanded functional repertoire beyond prior recognition, encompassing diverse modification types and a broader spectrum of RNA targets. For instance, the orphan snoRNAs snR4 and snR45 facilitate the acetylation of two N4 cytidine residues in 18S rRNA by guiding the cytidine acetyltransferase Kre33 to its target sites, a process critical for maintaining the accuracy of protein synthesis (33). Advanced techniques such as chimeric enhanced crosslinking and immunoprecipitation have uncovered novel snoRNA-rRNA/snRNA interactions in an RNA-binding protein-dependent manner, revealing novel interactions and regulatory roles in RNA biogenesis (34).

Interaction with transfer RNAs (tRNAs). Post-transcriptional modifications of tRNAs, especially at the anticodon wobble position and the 3' end, play a vital role in stabilizing mRNA-tRNA interactions. For example, the methylation of cytidine at the wobble position, guided by SNORD97, targets the anticodon loop of elongator tRNAMet through sequence complementarity, enhancing tRNA functionality and protecting it from cleavage by stress-induced endonucleases such as angiogenin (35). Although recent studies have illuminated specific snoRNA-tRNA interactions (36,37), earlier co-immunoprecipitation experiments had already revealed physical associations between snoRNAs and tRNAs (38,39). This suggests that numerous additional interactions remain to be discovered, highlighting the profound complexity of snoRNA-mediated regulatory networks.

Interaction with mRNAs. Beyond their well-documented roles in ncRNA modification, high-throughput sequencing of ligated RNAs has uncovered surprising interactions between snoRNAs and mRNAs. A prominent example is SNORD83B, an orphan snoRNA that bolsters the stability of mRNAs-including NOP14, ribosomal protein S5, and serine/arginine-rich splicing factor 3 via direct base-pairing interactions (40). Research

reveals that SNORA73 forms stable secondary structures with target mRNAs via non-canonical RNA binding sequences. Additionally, SNORA73 engages with 7SL RNA, a crucial element of the signal recognition particle (SRP), assembling a 'mRNA-snoRNA-7SL RNA' ternary complex. This complex significantly boosts the binding affinity of target mRNAs to the SRP, facilitating the efficient translocation of the translational complex to the endoplasmic reticulum. Thereby, this interaction promotes the effective translocation and release of secretory proteins, revealing a novel role for snoRNAs in orchestrating protein trafficking and secretion (41). These findings highlight the wide-ranging and multifaceted roles of snoRNAs in cellular processes, extending well beyond their canonical functions in RNA modification.

Interaction with long ncRNAs (lncRNAs). Research has revealed that SNORD80, an intron-encoded SNORD originating from the GAS5 gene, orchestrates the 2'-O-methylation of GAS5 lncRNA. This critical modification bolsters the stability of the lncRNA, triggering its subsequent upregulation and ultimately fine-tuning cellular stress response mechanisms (42).

Interaction with proteins. Some snoRNAs function by binding proteins. SNORA13 departs from canonical snoRNA function by regulating cellular senescence independently of ribosomal interactions. Rather than modulating ribosomal translation, it directly binds MDM2, thereby activating the p53 pathway and inducing senescence (30). By contrast, SNORD46 governs metabolism and immune function through its specific interaction with interleukin (IL)-15. While wild-type SNORD46 binds IL-15 via G11, the G11A mutation significantly enhances this binding affinity and promotes obesity in knockin mice. Mechanistically, SNORD46 inhibits IL-15-dependent phosphorylation of CD36 and monoglyceride lipase in adipocytes-mediated by feline sarcoma-related kinase, effectively suppressing lipolysis and thermogenic browning. Concurrently, in natural killer (NK) cells, SNORD46 disrupts IL-15-driven autophagy, reducing NK cell viability during obesity. Notably, SNORD46 inhibitors effectively counteract these effects, alleviating obesity and restoring critical NK cell functions, including the antitumor efficacy of chimeric antigen receptor-NK therapy (43). Similarly, the snoRNA snR107 plays a distinct regulatory role in meiosis by interacting with the RNA-binding proteins meiosis mitotic inhibitor 1 and meiosis 2. This interaction establishes a reciprocal inhibition mechanism that tightly controls meiotic gene expression throughout sexual differentiation (44). SNORA73 exhibits a unique mechanism involving 5' end non-canonical structural binding to poly(ADP-ribose) polymerase 1 (PARP1), inhibition of PARP1 auto-PARylation, and formation of a specialized snoRNP complex with dyskerin pseudouridine synthase 1/NHP2 to modulate cancer genome stability (45).

Regulation of alternative splicing. snoRNAs have surfaced as pivotal regulators of alternative splicing, critically influencing the processing of key mRNAs such as 5-hydroxytryptamine serotonin receptor 2c (HTR2C). This intricate regulation is orchestrated by the orphan snoRNA SNORD115, which harbors an 18-nucleotide sequence perfectly complementary to the alternative exon 5b within HTR2C mRNA. SNORD115 actively promotes the inclusion of exon 5b, yielding a long, functional receptor isoform; conversely, its exclusion produces a non-functional variant. Beyond its splicing role, SNORD115 directly competes with adenosine deaminases acting on RNA (ADAR) enzymes, which catalyze crucial adenosine-to-inosine editing within this same region. Such editing can markedly alter three amino acids in exon 5, profoundly impacting G-protein coupling and downstream signaling cascades of the receptor. The influence of SNORD115 extends to at least five additional alternative splicing targets, powerfully underscoring its notable regulatory versatility (46). Similarly, SNORD116, residing at the same chromosomal locus as SNORD115, is implicated in splicing regulation, with numerous predicted binding sites precisely mapping to exon junctions (47). Other snoRNAs, such as SNORD27, demonstrably direct the splicing of the E2F7 transcription factor (4), while SNORD88C regulates the alternative splicing of fibroblast growth factor receptor 3 (FGFR3) by effectively masking cryptic splice sites, thereby preventing aberrant exon inclusion (48). These compelling findings illuminate the rapidly expanding role of snoRNAs in meticulously fine-tuning mRNA splicing and their profound potential impact on gene expression and cellular function.

Involvement in 3'-end processing. Beyond their well-established roles in post-transcriptional modifications and alternative splicing regulation, snoRNAs are gaining growing recognition for their involvement in mRNA 3'-end processing. Previous research reveals that a specific subset of snoRNAs interacts directly with the mammalian 3'-end processing complex, illuminating their function in poly(A) site selection. These snoRNAs specifically associate with factor interacting with poly(A) polymerase 1 (Fip1), a key cleavage and polyadenylation specificity factor component. Among them, SNORD50A has emerged as a pivotal regulator, inhibiting 3' mRNA processing for specific transcripts by occupying the interaction site between Fip1 and the poly(A) signal (3).

Extranuclear functions. While snoRNAs are traditionally linked to nucleolar functions, accumulating evidence indicates they also exert biological roles beyond the nuclear compartment. Under cellular stress conditions, specific snoRNAs, including SNORD32A, SNORD33, and SNORD35A, have been observed to accumulate in the cytosol, suggesting potential extranuclear functional activities (49).

4. sdRNAs: Biogenesis and function

Biogenesis of sdRNAs. The precise mechanisms generating smaller fragments from longer snoRNAs remain elusive. Current research confirms that certain snoRNA-derived miRNAs, including those from H/ACA scaRNA15 (ACA45), require the ribonuclease III Dicer (DICER) enzyme for their biogenesis. Comparative deep sequencing analysis of wildtype vs. DICER/DiGeorge syndrome critical region 8 (DGCR8) knockout embryonic stem cells revealed profound alterations in the length distribution patterns of SNORA-sdRNAs. These findings compellingly suggest the microprocessor complex (DICER/DGCR8) plays a substantial role in a process analogous to miRNA biogenesis. Conversely, the production of smaller fragments from SNORD appears to operate

through a distinct mechanism, evidenced by their continued generation despite the absence of functional DICER/DGCR8 components. However, comprehensive cross-linking studies of cellular RNAs with DGCR8 demonstrate extensive interactions between snoRNAs and DGCR8. Crucially, DGCR8-mediated cleavage of snoRNAs occurs independently of DICER, indicating the potential existence of an alternative sdRNA biogenesis pathway. This alternative route may involve other enzymatic components associated with DGCR8 (50,51). Based on their biogenesis and structural features, sdRNAs can be broadly classified into three categories: i) H/ACA-derived sdRNAs, typically 20-24 nt fragments originating from the 3' terminus; ii) C/D-derived sdRNAs, which include both longer (>26 nt) and shorter (17-19 nt) fragments primarily derived from the 5' end; and iii) sno-derived P-element-induced wimpy testis (PIWI)-interacting RNAs (piRNAs), which are associated with PIWI proteins and range from 26-31 nt (52,53). These distinct classes exhibit diverse functional properties, as discussed below.

Function of sdRNAs. High-throughput sequencing studies have revealed that snoRNAs undergo specific cleavage to produce smaller functional fragments, rather than simply suffering random degradation. This conclusion is bolstered by several key observations: First, the expression patterns of sdRNAs exhibit striking conservation across diverse species; second, an inverse relationship often exists between snoRNA abundance and sdRNA production, suggesting that highly abundant sdRNAs may originate from relatively low-expressed snoRNAs; and third, the selective presence of stable fragments from specific snoRNAs regions, as opposed to random degradation products from other parts of the same molecule, strongly implies the existence of a regulated stabilization mechanism (48).

From a structural and functional perspective, sdRNAs can be classified into distinct categories based on their biogenesis and physical characteristics. SNORAs primarily generate 20-24 nucleotide fragments preferentially derived from their 3' termini. By contrast, SNORDs produce two distinct size classes: Longer fragments over 26 nucleotides and shorter fragments ranging from 17-19 nucleotides, with the latter primarily originating from the 5' end. This phenomenon of sdRNA production appears pervasive, with experimental evidence demonstrating that >50% of all snoRNAs are capable of generating these smaller fragments (54,55). While the biological functions of numerous sdRNAs remain incompletely characterized, their widespread occurrence and evolutionary conservation strongly suggest diverse regulatory roles, some of which are increasingly being revealed through ongoing research. The biogenesis and function of sdRNAs are shown in Fig. 2.

miRNA-like functions. A particularly intriguing potential function of sdRNAs lies in their capacity to serve as a novel source of miRNA-like molecules. This hypothesis was initially investigated through comprehensive analysis of small RNAs co-immunoprecipitated with Agonaute RNA-induced silencing complex (RISC) catalytic component (AGO)1 and AGO2 proteins in 293 cells. Notably, among the AGO2-associated fragments, researchers identified a functionally significant sdRNA derived from ACA45. Extensive functional characterization, combining luciferase reporter assays with sophisticated bioinformatic prediction tools, revealed that ACA45 exhibits canonical miRNA-like activity by specifically targeting CDC2L6 mRNA. While ACA45 shares the requirement for DICER in its maturation pathway with classical miRNAs, it displays a distinctive processing mechanism that bypasses Drosha involvement (7). Evidence suggests that small RNAs processed from snoRNAs can adopt microRNA (miRNA)-like functions, though most associate with Argonaute proteins at levels insufficient to elicit detectable silencing activity (56). Supporting this notion, Brameier *et al* identified 11 distinct snoRNA-derived sequences capable of integrating into the RISC and mediating effective gene silencing. These 'sno-miRNAs' originate from SNORDs, including snR39b, U3 (two loci), U78, HBII-336, HBII-429, HBII-142, U27, U83a, U74, and U15a, and exhibit miRNA-like repression of reporter-gene mRNAs (57).

piRNA-like functions. Emerging evidence has established snoRNAs as a significant source of piRNAs, a distinct class of 26-31 nucleotide ncRNAs that form functional complexes with PIWI proteins, a specialized subgroup within the Argonaute protein family. These snoRNA-derived piRNAs participate in crucial biological processes, including transposon silencing and epigenetic regulation of gene expression. In a pivotal study conducted in primary T lymphocytes, researchers identified multiple piRNA candidates originating from snoRNAs. Particularly noteworthy was the discovery of a piRNA derived from SNORD63, which specifically interacts with an intronic sequence of the IL-4 pre-mRNA. This interaction facilitates the recruitment of the Trf4-Air2-Mtr4 complex, subsequently leading to the targeted degradation of IL-4 mRNA by nuclear exosomes (58).

Further expanding our understanding of snoRNA-derived piRNA functions, another investigation revealed that a piRNA originating from SNORD75 exhibits dual binding capability to PIWI-like protein 1 (PIWIL1) and PIWI-like protein 4 (PIWIL4) proteins. This interaction triggers a significant epigenetic transition, characterized by the replacement of repressive histone marks (H3K27me3) with active marks (H3K4me3) at specific genomic loci. This epigenetic reprogramming leads to transcriptional activation of the TNF-related apoptosis-inducing ligand (TRAIL) tumor suppressor gene, demonstrating the potential of snoRNA-derived piRNAs in regulating critical cellular processes and maintaining genomic stability (59).

siRNA-like function. Notably, a subset of sdRNAs exhibit near-perfect complementarity to target mRNAs, enabling them to direct transcript cleavage in a manner analogous to siRNAs.

Building on this concept, snoRNA modulator of gene expression vectors have been developed as a versatile tool for protein replacement in cultured cells. These vectors enable the efficient substitution of endogenous cellular proteins with tagged or mutated recombinant variants, offering a powerful approach for functional studies (60).

Regulation of pre-mRNA splicing. SNORD115 has emerged as a key regulator in the alternative splicing of HTR2C pre-mRNA, specifically facilitating the inclusion of exon

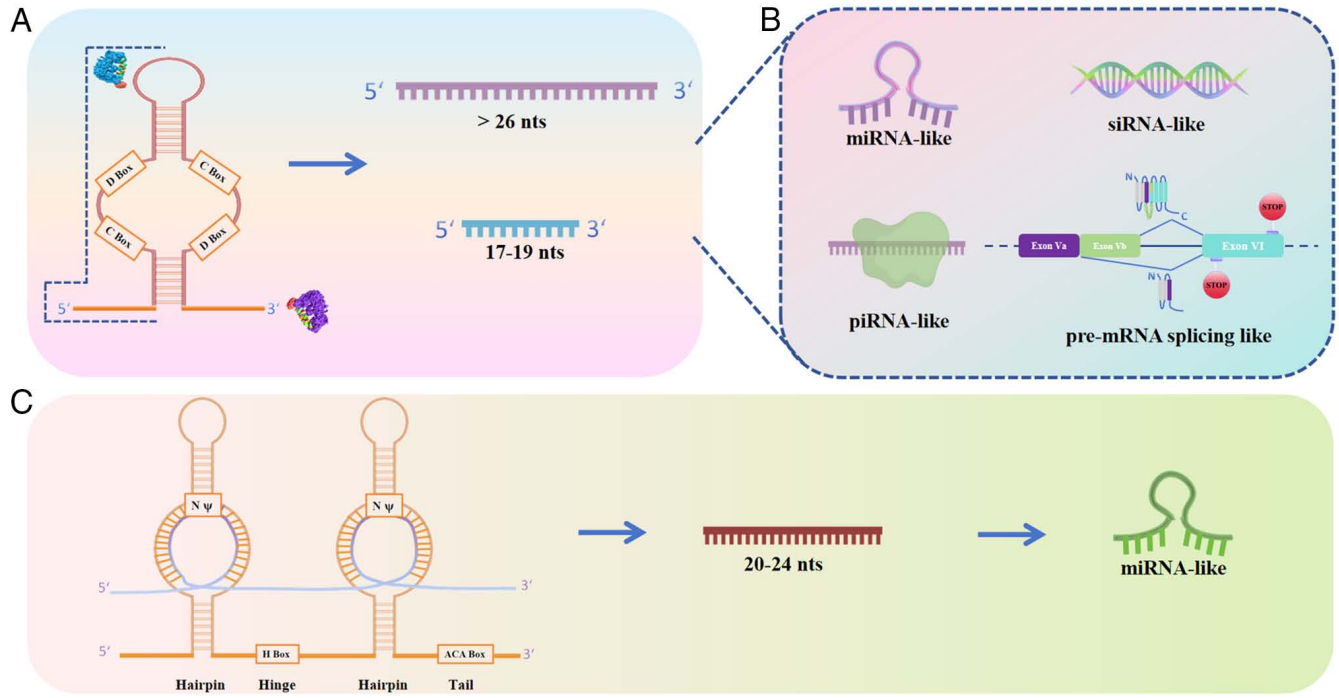

Figure 2. Biogenesis and function of sdRNAs. (A) Processing pathways of C/D box snoRNA-derived fragments. C/D box snoRNAs are processed via DGCR8-dependent or independent pathways to yield longer (>26 nt) and shorter (17-19 nt) fragments from the 5' end, which may adopt piRNA-like or miRNA-like functions. (B) Functional outcomes of sdRNAs. miRNA-like sdRNAs associate with AGO proteins and silence target mRNAs; piRNA-like sdRNAs bind PIWI proteins and regulate gene expression epigenetically; siRNA-like sdRNAs guide transcript cleavage through near-perfect complementarity. In addition, both full-length snoRNAs and specific sdRNAs have been implicated in the regulation of pre-mRNA alternative splicing (such as SNORD115 and SNORD88C), expanding their regulatory repertoire beyond RNA modification and gene silencing. (C) Processing pathways of H/ACA box snoRNA-derived fragments. H/ACA box snoRNAs are processed by DICER to generate 20-24 nt fragments predominantly from the 3' terminus, which can function as miRNA-like molecules. Representative examples from each category are indicated. snoRNA, small nucleolar RNA; sdRNA, snoRNA-derived fragments; DGCR8, DiGeorge syndrome critical region 8; AGO, Argonaute; PIWI, P-element-induced wimpy testis; piRNA, PIWI-interacting RNA; miRNA, microRNA; siRNA, small interfering RNA; DICER, ribonuclease III Dicer; SNORD, C/D box snoRNA.

5b to generate an extended variant. This regulatory function is particularly noteworthy as it occurs independently of the extensive RNA modifications typically required for the synthesis of long mRNA isoforms (61). The splicing regulatory capacity of SNORD115 extends beyond HTR2C, as it has been demonstrated to influence alternative splicing events in other pre-mRNA targets (62) Similarly, SNORD88C has been identified as a modulator of FGFR3 splicing events. Both SNORD115 and SNORD88C undergo specific processing to yield smaller fragments, with several of these sdRNAs overlapping with regions implicated in splicing regulation. However, the precise contribution of these sdRNA fragments, as opposed to the full-length snoRNAs, in splicing modulation remains to be fully elucidated (48). The mechanistic basis of sdRNA-mediated splicing regulation is not yet completely understood, but emerging evidence suggests a potentially significant role for interactions with a distinct group of heterogeneous (hn) RNPs. These hnRNP interaction partners differ from those associated with full-length snoRNAs and are themselves known to participate in splicing regulation.

5. Biological roles of snoRNAs in cancer

Emerging research has revealed that abnormal expression patterns and functional alterations of specific snoRNAs are associated with various malignancies. Mechanistic investigations have established that snoRNAs participate in multiple oncogenic processes, influencing crucial aspects of cancer biology such as tumor cell proliferation, metastatic potential, apoptotic regulation, and therapeutic resistance (31). Furthermore, substantial clinical evidence demonstrates a strong correlation between snoRNA dysregulation and critical clinicopathological parameters, including tumor staging, progression, and patient survival outcomes (31,63).

However, while extensive research links abnormal snoRNA expression to these malignancies (31,63), the evidential strength of these associations varies significantly across the literature. To systematically evaluate this landscape, as outlined in the Introduction, current studies were stratified into three tiers: i) Fundamental mechanistic investigations utilizing *in vitro* and animal models; ii) clinical association studies relying on retrospective analysis of tumor tissues; and iii) translational research evaluating non-invasive biomarkers (liquid biopsies) and therapeutic interventions. In the following sections, rather than merely cataloging reported findings, the roles of snoRNAs across specific cancer types are critically synthesized, explicitly distinguishing between preliminary molecular observations, established clinical correlations, and markers approaching translational readiness. Summary of snoRNA functions and mechanisms in various cancers is shown in Table SI, and clinical implications of snoRNAs in cancers are shown in Fig. 3.

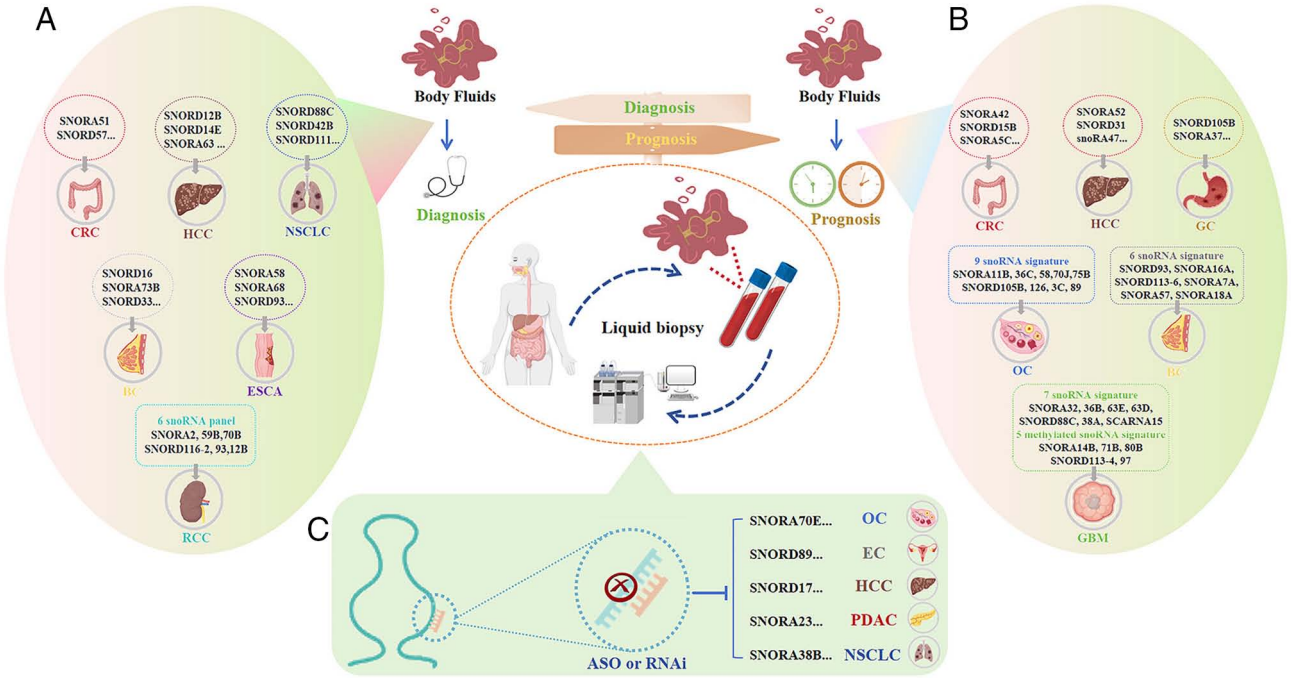

Figure 3. Representative examples highlighting the cross-cancer clinical implications of snoRNAs. (A) snoRNAs as diagnostic biomarkers: Emphasizing their cross-cancer applicability in liquid biopsies for non-invasive detection (such as SNORA51 in fecal samples for CRC, and SNORD33 in plasma for TNBC). (B) snoRNAs as prognostic biomarkers: Highlighting their conserved roles in driving shared oncogenic phenotypes, such as tumor proliferation, cell-cycle dysregulation, and invasion/metastasis, where the elevated expression of oncogenic snoRNAs (such as SNORA28 in CRC, and SNORD17 in HCC) consistently correlates with advanced TNM staging and poor overall survival across diverse malignancies. (C) snoRNAs as therapeutic targets: Demonstrating the pan-cancer potential of targeted interventions, where ASOs directed against key oncogenic snoRNAs (such as SNORD17, and SNORA74A) effectively suppress tumor growth and metastatic progression in preclinical models. This figure presents selected representative examples rather than an exhaustive overview to illustrate broader pan-cancer themes. snoRNA, small nucleolar RNA; CRC, colorectal cancer; SNORD, C/D box snoRNA; TNBC, triple-negative breast cancer; HCC, hepatocellular carcinoma; ASO, antisense oligonucleotide; SNORA, H/ACA box snoRNA; NSCLC, non-small cell lung cancer; BC, breast cancer; ESCA, esophageal carcinoma; OC, ovarian cancer; EC, endometrial cancer; PDAC, pancreatic ductal adenocarcinoma.

Colorectal cancer (CRC)

Mechanistic drivers of pathogenesis. Fundamental *in vitro* and *in vivo* investigations have revealed extensive snoRNA involvement in CRC progression. For instance, SNORA28 functioned as a molecular decoy recruiting bromodomain-containing protein 4, leading to increased H3K9 acetylation at the leukemia promoter, activating the JAK1/STAT3 pathway, which promoted CRC cell proliferation and conferred radioresistance (64). SNORA56 played a critical role in the pseudouridylation of 28S rRNA at the U1664 site, facilitating glutamate cysteine ligase catalytic subunit translation to inhibit ferroptosis and sustain tumor survival (65). SNORD11B exemplifies a dual regulatory mechanism in CRC through 2'-O-methylation, which simultaneously promoted 18S rRNA maturation at the G509 site to enhance ribosome biogenesis, and mediated the degradation of MIRLET7A1HG (pri-let-7a) at the G225 site to suppress let-7a-5p and upregulate oncogenic targets (66). Small Cajal body-specific RNA (SCARNA)12 accelerated CRC progression by activating the PI3K/AKT pathway (67). Another recent study showed that SNORA21 enhanced CRC cell proliferation, invasion, and migration through Hippo and Wnt signaling pathways, two critical cascades involved in cancer development and metastasis (68). SNORA24 was shown to promote tumor growth by promoting G_1/S phase transition and modulated p53 protein stability via the ubiquitin-proteasome pathway, suggesting its potential as a therapeutic target (69). SNORA42 has been implicated as a putative oncogene in CRC, promoting multiple malignant phenotypes including enhanced proliferation, migration, invasion, anoikis resistance, and overall tumorigenic potential (70). SNORA71A exerted its oncogenic effects through modulation of NF-κB and Toll-like receptor pathways, thereby promoting CRC cell proliferation, migration, and invasion (71).

SNORD12C and SNORD78 were demonstrated to catalyze 2'-O-methylation of 28S rRNA, stabilizing transcripts such as eukaryotic factor 4A-III and laminim subunit γ2 to promote CRC migration and survival (72). SNORD1C enhanced stemness and metastasis via Wnt/β-catenin pathway. Its suppression reduced β-catenin/transcription factor 7 expression, inhibiting tumorigenic properties (73). Conversely, SNORD44 and GAS5 exhibited tumor-suppressive properties by inhibiting growth and inducing apoptosis (74), while SNORD50A/B depletion amplified K-Ras activity and increased tumorigenic risk (75).

Tissue-based clinical and prognostic associations. These mechanistic findings are frequently supported by retrospective analyses of patient tissues, highlighting strong prognostic value. Clinically, high SNORA28 expression was shown to be associated with poor prognosis (64). Elevated SNORD11B indicated advanced TNM staging, lymph node metastasis, and a poor prognosis (66). High expression of SCARNA12 was linked to poor patient outcomes (67), and SNORA71A was correlated with advanced TNM staging and metastasis (71). SNORA42 served as an independent predictor of poor clinical outcomes (70).

Translational readiness and non-invasive diagnostics. The most translationally mature evidence involves liquid and fecal biopsies. SNORA51 in fecal samples exhibited strong promise for CRC screening, particularly in fecal immunochemical test-positive patients (76). SNORD15B and SNORA5C served as independent prognostic markers, linked to lymphatic invasion and colon polyp history (77). Serum SNORD1C discriminated patients with CRC from healthy controls [area under the curve (AUC)=0.748] and improved diagnostic accuracy with carcinoembryonic antigen (CEA) (AUC=0.838) (78). Circulating SNORD57 has emerged as a sensitive biomarker for early detection (79). Moreover, serum SNORA33 expression was closely associated with vascular invasion and declined following radical resection, demonstrating its diagnostic and monitoring potential. Notably, serum SNORA33 represents a promising non-invasive diagnostic biomarker for CRC, with its diagnostic performance minimally affected by patient age (80).

In summary, while the mechanistic landscape of snoRNAs in CRC, ranging from rRNA modification to epigenetic regulation, is increasingly well-defined, their clinical application remains in the exploratory phase. The dual role of snoRNAs as both functional drivers and stable liquid biopsy candidates highlights their diagnostic potential; however, bridging the gap between these preclinical findings and translational readiness will require rigorous independent validation in large-scale longitudinal cohorts and a deeper understanding of their roles in the complex tumor microenvironment (TME).

Hepatocellular carcinoma (HCC)

Mechanistic drivers of pathogenesis. In HCC, snoRNAs function as versatile regulators that drive malignancy by orchestrating distinct molecular axes beyond their canonical roles. In terms of metabolic reprogramming, transient receptor potential cation channel subfamily M member 8-mediated modulation of SNORA55 disrupted oxidative phosphorylation by targeting adenosine triphosphate (ATP) synthase subunits ATP5A1 and ATP5B, highlighting a direct link between snoRNAs and mitochondrial bioenergetics (81). Simultaneously, a broad spectrum of snoRNAs hijacks classical oncogenic signaling to promote invasion and epithelial-mesenchymal transition (EMT). For instance, SNORD126 and SNORA11 (also known as ACA11) activated the PI3K/AKT/mTOR cascade to drive robust cellular proliferation and migration (82-84), whereas snoU2_19 and SNORD76 perturbed the Wnt/β-catenin pathway to accelerate cell cycle progression and induce EMT (85,86).

Notably, snoRNAs target tumor suppressor surveillance to evade apoptosis through multi-faceted inactivation of the p53 pathway. SNORD17 was shown to exert a dual regulatory influence, whereby its sequestration of nucleophosmin 1 (NPM1) and MYB binding protein 1a (MYBBP1A) in the nucleolus suppressed p53-mediated apoptosis. Conversely, its depletion triggered the nucleoplasmic translocation of NPM1/MYBBP1A, which stabilized p53 via NPM1/mouse double minute 2 homolog (MDM2) interaction and activated p53 through MYBBP1A/p300-mediated acetylation. Notably, activated p53 reciprocally inhibited SNORD17 expression via promoter acetylation, establishing a sophisticated self-regulatory feedback loop (87). This regulatory network was further diversified by SNORA18L5, which promoted the MDM2-mediated degradation of p53 to inhibit apoptotic signaling (88), and SNORA42, which downregulated p53 to release cell cycle checkpoints and suppress apoptosis (89).

Beyond the p53 axis, SNORD52, which is frequently upregulated in HCC tissues, further drrove tumorigenesis by elevating and stabilizing cyclin-dependent kinase 1 (CDK1) levels, a process that was inversely correlated with up-frameshift suppressor 1 homolog expression (90). Furthermore, specific snoRNAs are pivotal for maintaining liver cancer stemness and translational fidelity. For instance, SNORD88B anchored WRN to inactivate the Hippo pathway and drive self-renewal, a capacity that was severely impaired upon its deficiency (91). In terms of post-transcriptional control, SNORD72 drove invasion and colony formation by counteracting lncRNA-LALR1-mediated suppression to stabilize inhibitor of DNA binding 2 mRNA (92). At the ribosomal level, snoRNAs exert bidirectional control: SNORA24 guided the pseudouridylation of 18S rRNA at positions 609 and 863, where loss of these modifications altered translational efficiency to promote survival in RAS-driven HCC (93); whereas SNORA23 acted as a tumor suppressor by orchestrating 2'-O-ribose methylation of 28S rRNA (cytidine4506) and inhibiting eukaryotic translation initiation factor 4E-binding protein 1 phosphorylation to restrict tumor growth (94).

Tissue-based clinical and prognostic associations. A landmark analysis from The Cancer Genome Atlas revealed 54 upregulated and 14 downregulated snoRNAs, establishing distinct prognostic signatures (95). Elevated SNORA47 expression was shown to be strongly correlated with intrahepatic metastasis, lymphatic invasion, and advanced TNM stage, and exhibited significantly shorter overall survival (OS) and higher recurrence rates, underscoring its prognostic value (96). Similarly, SNORD78 was revealed to be an adverse prognostic marker demonstrating a strong association with increased tumor burden (multifocal lesions), advanced stage, and distant metastasis, and was linked to poorer OS and recurrence-free survival (97). High SNORA51 was correlated with aggressive features including portal vein tumor thrombus, vascular invasion, advanced TNM stage, and shorter median survival (98). Conversely, downregulation of tumor-suppressors carries severe prognostic implications: Reduced SNORA52 predicted poor differentiation, capsular invasion, advanced TNM stage, and worse disease-free survival (DFS) and OS (99); decreased SNORD31 was correlated with larger tumor size, vascular invasion, and poor long-term survival (100); and reduced SNORD113-1 was strongly associated with worse survival outcomes (101). Furthermore, diminished SNORA71A was correlated with larger tumor size, multifocal lesions, capsular invasion, poor differentiation, and advanced TNM stage, predicting higher postoperative recurrence risk and reduced OS, serving as an independent prognostic indicator (102). SNORA11, SNORD124, and SNORD46 also demonstrated potential diagnostic and prognostic utility (103).

Translational readiness and non-invasive diagnostics. SNORA47 and SNORD126 were shown to be highly predictive in non-viral HCC, while SNORA80E and SNORA12 exhibited favorable outcomes in combined analyses (104). In HBV-related

HCC, signatures (downregulated SNORD12B/SNORD14E; upregulated SNORA63) offered diagnostic utility for early detection (105).

In summary, the role of snoRNAs in HCC spans a broad spectrum of evidential strength. At the mechanistic level, extensive *in vitro* and *in vivo* studies confirm that snoRNAs are fundamental drivers of HCC pathogenesis, orchestrating metabolic reprogramming, cell cycle dysregulation, and apoptosis evasion. Clinically, large-scale retrospective tissue analyses provide significant correlative evidence: Dysregulation of specific snoRNAs, whether through upregulation of oncogenic drivers or the suppression of tumor suppressors, acts as a powerful, independent prognostic indicator for intrahepatic metastasis, high recurrence risk, and poor OS. Most importantly, moving beyond retrospective tissue associations, specific snoRNA signatures are rapidly approaching translational readiness. Diagnostic panels, particularly those tailored for the early screening of HBV-related HCC, highlight the actionable, clinical utility of snoRNAs in precision oncology.

Gastric cancer (GC)

Mechanistic drivers of pathogenesis. In GC, *in vitro* evidence highlights complex snoRNA-protein interactions. SNORA37 facilitated the cap methyltransferase 1 (CMTR1)-ELAV-like RNA binding protein 1 (ELAVL1) complex to modulate CD44 alternative splicing, thereby promoting tumor cell proliferation, invasive potential, and metastatic dissemination (106). SNORD105B interacted with aldolase A to modulate the c-Myc signaling cascade, which ultimately enhanced the proliferative and metastatic capacities of GC cells (107). Furthermore, SNORA21 promoted gastric tumorigenesis by attenuating p53 activation through the SNORA21-CHK1-PERP-MDM2 regulatory axis (108). Additionally, the coordinated action of SNORA42, SNORA74A, and SNORD10 within serine/arginine-rich protein-specific kinase 1-mediated signaling networks directly facilitated tumor cell growth and GC development (109).

Tissue-based clinical and prognostic associations. These fundamental pathways manifest clinically as poor prognostic markers. In GC patient cohorts, elevated tissue expression of SNORA37 (alongside CMTR1, ELAVL1, and CD44) showed significant association with reduced OS, poor therapeutic response, and advanced disease progression (106). Similarly, elevated SNORD105B and SNORA21 was correlated with increased tumor burden, poor histological differentiation, and advanced TNM staging (107,108).

In GC, oncogenic snoRNAs drive progression via complex RNA-protein interactions. Clinically, their tissue upregulation strongly predicted advanced disease and poor survival. However, translationally actionable tools such as non-invasive liquid biopsies remain notably absent, representing a critical gap for future research.

Non-small cell lung cancer (NSCLC)

Mechanistic drivers of pathogenesis. Preclinical NSCLC models demonstrated that SNORD88C mediates 2'-O-methylation of 28S rRNA to enhance the translation of stearoyl-CoA desaturase-1, thereby promoting tumor cell proliferation and metastatic dissemination (110). SNORA42 was shown to modulate p53-dependent apoptotic mechanisms to drive tumorigenesis (111), while SNORA71A overcame G_0/G_1 checkpoints via MEK/ERK pathway activation, stimulating tumor cell growth, invasiveness, and metastasis (112). Additionally, NOP10 deletion suppressed cancer cell proliferation and reduced migratory and invasive capacities through the dysregulation of SNORA65, SNORA7A, and SNORA7B (113). Extensive research has elucidated the critical role of SNORA38B in driving NSCLC progression through dual mechanisms. Intracellularly, nuclear-localized SNORA38B exerted its oncogenic effects by direct physical interaction with the E2F transcription factor 1, which activates the GRB2-associated binding protein 2/AKT/mTOR signaling cascade to promote tumor cell proliferation and survival. Extracellularly, SNORA38B shaped an immunosuppressive TME by inducing IL-10 secretion. This cytokine shift recruited $CD4^+$ $FOXP3^+$ regulatory T cells while simultaneously reducing the infiltration of $CD3^+$ $CD8^+$ cytotoxic T lymphocytes, effectively enabling the tumor to evade immune surveillance. Translationally, targeting this axis using SNORA38B locked nucleic acids (LNAs) successfully restored $CD3^+$ $CD8^+$ T-cell infiltration in the TME, thereby increasing the sensitivity of NSCLC to immune checkpoint blockade (ICB) therapy (114).

Tissue-based clinical and prognostic associations. Clinically, these molecular events are strictly mirrored in retrospective tissue cohorts. Elevated tissue expression of SNORD88C, SNORD42B, SNORD111, and SNORD83A was consistently observed in patients with NSCLC relative to healthy individuals (110,115,116). Notably, the significant upregulation of SNORD60 in lung adenocarcinoma was directly correlated with adverse clinicopathological features, including lymph node metastasis and advanced TNM stage (117). Additionally, comprehensive sequencing analyses highlighted SNORA21 as a valuable tissue-based biomarker for predicting patient prognosis (118).

Translational readiness and non-invasive diagnostics. NSCLC research features encouraging translational readiness, particularly in non-invasive diagnostics and targeted therapies. Circulating SNORD88C, SNORD42B, and SNORD111 showed consistent elevation in plasma, enabling early-stage disease detection (110,115). Circulating SNORD83A combined with CEA demonstrated enhanced diagnostic capability (116), while circulating SNORD60 yielded 74.2% sensitivity and 75.3% specificity for early diagnosis (117).

Taken together, oncogenic snoRNAs in NSCLC drive proliferation, metastasis, and immune evasion. Clinically, their elevation in tumor tissues strictly correlates with advanced TNM stage, metastasis, and poor prognosis. Notably, circulating snoRNAs in NSCLC are emerging as promising candidate non-invasive biomarkers and potential therapeutic targets (such as LNA therapeutics), although their transition to clinical practice requires independent validation in large-scale cohorts.

Breast cancer (BC)

Mechanistic drivers of pathogenesis. Mechanistic evidence in BC models reveals that snoRNAs influence ribosomes,

stemness, and immune evasion. Knockdown studies confirmed that SNORA7B depletion enhanced proliferative, invasive, and migratory capacities (119), while targeting SNORD50A/B triggered cell cycle arrest and apoptosis via tripartite motif containing (TRIM)21-guanosine monophosphate synthetase (120), and targeting U3/U8 suppressed tumorigenic potential via impaired pre-rRNA processing (121). Conversely, SNORA71A acted as a powerful driver of metastasis through a precise molecular cascade by directly interacting with the G3BP stress granule assembly factor 1 protein, which subsequently stabilized Rho associated coiled-coil containing protein kinase 2 transcripts and modulated the TGF-β signaling pathway. This orchestrated signaling ultimately drove EMT, severely enhancing the proliferation, migration, and invasion of BC cells (122). SNORA68 was shown to bind U2 small nuclear RNA auxiliary factor 2 to upregulate nucleolar ribosomal protein L (RPL)23 and c-Myc, promoting cancer stemness and tumorigenesis (123). SNORA51 maintained stem cell-like properties via RPL3/NPM1/c-MYC (124). Furthermore, SNORA38 emerged as an oncogenic driver closely linked to the expression of the stemness marker octamer-binding transcription factor 4. SNORD67 directed U6 snRNA methylation to regulate lymph node metastasis (125), and SNORA47 promoted RPL11 transfer via early B-cell factor (EBF)3 to upregulate the expression of the oncogene c-Myc (126). SNORD46 inhibition enhanced NK cell-mediated antitumor immunity against triple-negative breast cancer (TNBC) (43), while U50A mediated everolimus resistance through mTOR downregulation (127).

Tissue-based clinical and prognostic associations. Multiple snoRNAs (SNORD15A, SNORD15B, SNORD22, SNORD17, and SNORD87) are frequently overexpressed (128). SNORA7B functions as a potential prognostic biomarker (119). Mirroring its mechanistic role in EMT, SNORA71A exhibited marked overexpression specifically in metastatic breast cancer tissues compared with non-metastatic cases (122). High SNORA51 was associated with poor prognosis (reduced OS and DFS) (124), while SNORA68 was strongly correlated with Ki-67 index and TNM stage (123). SNORA47 was associated with high TNM staging in Luminal A cohorts (126). SNORD90, SCARNA2, and SNORD78 effectively discriminated luminal subtypes; SNORD124 indicated aggressive $HER2^{+}$ variants; and a six-snoRNA signature was shown to hold prognostic value for predicting locoregional metastasis and clinical outcomes (129). SNORD16, SNORA73B, SCARNA4, and SNORD49B were demonstrated to possess early-stage diagnostic capability (130). Additionally, elevated SNORA38 was strongly associated with advanced disease characteristics, including increased tumor burden, nodal involvement, and advanced TNM stage, as well as poor OS outcomes (131).

Translational readiness and non-invasive diagnostics. Moving beyond tissue profiling, snoRNAs are demonstrating significant translational utility in liquid biopsies. A panel of four snoRNAs (SNORD16, SNORA73B, SCARNA4, and SNORD49B) has demonstrated significant capability as non-invasive biomarkers for the early-stage detection of BC (AUC=0.7305) (130). Furthermore, circulating SNORD33 levels demonstrated a significant correlation with platinum-based chemotherapy response in patients with metastatic TNBC, suggesting strong utility as a predictive liquid biopsy biomarker for chemotherapy efficacy (132).

Taken together, snoRNAs in BC regulate stemness, metastasis, and immune evasion through intricate RNA-protein networks. Clinically, specific snoRNA signatures possess potent prognostic and molecular subtyping capabilities in tumor tissues. Translationally, the identification of circulating snoRNAs as non-invasive diagnostic panels and predictive markers for chemotherapy response highlights their translational potential, warranting further investigation in prospective clinical trials.

Ovarian cancer (OC)

Mechanistic drivers of pathogenesis. *In vitro* assays have demonstrated that snoRNAs drive OC stemness and progression. SNORA70E was shown to promote OC development by mediating RAP1B pseudouridylation and PARP1 binding protein splicing (133). SNORA72 (134) and SNORD89 (135) upregulated stemness markers and activated Notch receptor 1 (Notch1)/c-Myc, thereby enhancing self-renewal, proliferation, and migratory potential. SNORD9 recruited methyltransferase like 3, to catalyze nuclear transcription factor Y subunit α methylation (136). Conversely, SNORA81 knockdown impaired 28S rRNA pseudouridylation, resulting in the suppression of cancer cell proliferation and migration (137).

Tissue-based clinical and prognostic associations. An H/ACA snoRNA signature (SNORA81, SNORA19, SNORA56) was shown to distinguish high-grade serous ovarian carcinoma from borderline tumors (137). Furthermore, a nine-snoRNA prognostic signature was established as an independent predictor of OC outcomes, serving as a highly promising prognostic biomarker (138).

In OC, oncogenic snoRNAs predominantly drive cancer stemness and migration by modulating key pathways such as Notch1/c-Myc. Clinically, multi-snoRNA signatures in tissues act as candidate diagnostic classifiers and independent prognostic predictors. However, OC currently lacks mature translational evidence for non-invasive liquid biopsies, indicating a critical gap for future development.

Endometrial cancer (EC)

Mechanistic drivers of pathogenesis. In EC, snoRNAs execute multifaceted oncogenic functions, primarily through RNA modifications. Notably, SNORA73B was shown to operate via a dual mechanism. First, it elevated the pseudouridine modification of mindbomb E3 uniquitin-protein ligase 3 mRNA, increasing its stability and protein expression, which subsequently reduced Jagged1 ubiquitination and led to the sustained activation of the Notch signaling pathway. Additionally, SNORA73B modulated the alternative splicing of regulator of chromosome condensation 1 (RCC1), favoring the production of oncogenic isoforms (RCC1-T2 and RCC1-T3). Together, these mechanisms potently enhance tumor cell proliferation, migration, and invasion while suppressing apoptosis (139). Furthermore, SNORD60 was shown to exhibit carcinogenic properties by binding fibrillarin, a 2'-O-methyltransferase, to catalyze the 2'-O-methylation modification of phosphatidylinositol-4,5-biphosphate 3-kinase catalytic subunit α mRNA,

thereby driving the PI3K/AKT/mTOR cascade and tumor progression (140). SNORD89 mediated 2'-O-methylation of Bim mRNA to disrupt the Bcl-2/Bax apoptotic balance (141), SNORD104 modified PARP1 mRNA to accelerate tumor growth (142), and SNORD99 modified gasdermin D to inhibit pyroptosis (143). Additionally, SNORD15B enhanced proliferation, invasion, and tumorigenicity through TRIM25 upregulation and cytoplasmic p53 accumulation (144).

Tissue-based clinical and prognostic associations. Clinically, the dysregulation of these mechanisms is mirrored in patient tissues. For instance, SNORD89 expression was shown to be significantly elevated in endometrial tumors with lymph node metastasis compared with non-metastatic cases, highlighting its potential as a tissue-based indicator of aggressive disease (141).

To synthesize these findings, evidence in EC relies heavily on mechanistic models where snoRNAs drive invasion and apoptosis evasion primarily via aberrant RNA modifications and alternative splicing. Clinically, their upregulation in tumor tissues is directly linked to adverse features such as metastasis. Yet, unlike HCC or NSCLC, translational tools such as non-invasive circulating biomarkers remain largely unexplored in EC, representing a significant translational gap for future studies.

Glioma

Mechanistic drivers of pathogenesis. U3 snoRNA was revealed to drive aerobic glycolysis and proliferation via the U3/ZBTB7A/HK2/LDHA axis (145) and recruited Ku-dependent DNA-dependent protein kinase sububit catalytic subunit to phosphorylate TRIM24, facilitating malignant transformation into epithelioid glioblastoma (GBM)-like tumors (146). SNORD113-3 was shown to govern GBM cell growth and glycolipid metabolism via the ADAR2/PHKA2/EBF1 axis (147), and SNORD88C enhances proliferation, migration, and invasion (148).

Tissue-based clinical and rognostic associations. Researchers have developed promising prognostic tools. A 7-snoRNA prognostic signature (SNORA32, SNORA36B, SCARNA15, SNORA63E, SNORA63D, SNORD88C and SNORD38A) and associated nomogram predicted lower-grade glioma survival with high sensitivity (148). Similarly, a 5-methylated-snoRNA (SNORA14B, SNORD113-4, SNORA71B, SNORA80B and SNORD97) risk signature has been validated as an independent prognostic indicator for glioma (149).

In glioma, snoRNAs uniquely drive malignant transformation by reprogramming aerobic glycolysis and lipid metabolism. Clinically, these metabolic drivers translate into highly sensitive prognostic nomograms and risk signatures in tumor cohorts. However, actionable liquid biopsies for non-invasive monitoring are still needed to bridge the gap toward clinical readiness.

Renal cell carcinoma (RCC)

Mechanistic drivers of pathogenesis. In clear cell RCC (ccRCC), *in vitro* and *in vivo* models have demonstrated that SNORA33 acts as a potent oncogenic driver. Mechanistically, it promoted tumor cell invasion and metastasis while simultaneously conferring resistance to the targeted therapy sunitinib through the activation of the JAK/STAT signaling pathway (150).

Tissue-based clinical and prognostic associations. Clinically, the dysregulation of this signaling pathway was strictly mirrored in patient tissue samples. Elevated tissue expression of SNORA33 served as a significant and direct indicator of unfavorable prognosis and reduced survival outcomes in ccRCC cohorts.

Translational readiness and non-invasive diagnostics. RCC research demonstrates notable translational progress, particularly in the realm of liquid biopsies. SNORD15A, SNORD35B, and SNORD60 exhibited significant diagnostic performance when isolated from urine sediments for early-stage RCC (151). Furthermore, circulating SNORD63 (urine) and SNORD96A (plasma) demonstrated high diagnostic accuracy (152). Most notably, a 6-snoRNA diagnostic panel (SNORA2, SNORD116-2, SNORA59B, SNORD93, SNORD12B, SNORA70B) isolated from urinary extracellular vesicles (EVs) outperformed standard clinical parameters; when combined with the Fuhrman grading system, its diagnostic AUC reached an impressive 0.800 (153).

Taken together, while mechanistic evidence in RCC highlights the role of snoRNAs in driving invasion and targeted therapy resistance, this field is uniquely characterized by its advanced translational readiness. Highly accurate, non-invasive snoRNA panels derived from urine and plasma are already demonstrating the potential to outperform standard clinical parameters for early cancer detection.

Other cancers

Mechanistic drivers of pathogenesis. The oncogenic mechanisms of snoRNAs span diverse tumor types, fundamentally driving progression and therapy resistance. In cervical cancer, SNORD6 scaffolded the E6-E6AP-p53 degradation complex to dysregulate apoptotic pathways (154). In bladder cancer, SCARNA12 interacted with H2A histone family member Z to enhance proliferative and metastatic capacities and to inhibit cell cycle arrest and apoptosis (155). SNORD35A modulated proliferation, invasion, and EMT in pancreatic cancer via the hepatocyte growth factor/c-Met pathway (156). In neuroblastoma, the SNHG25/SNORA50C axis stabilized histone deacetylase 1 to promote tumor growth and migration (157). Furthermore, in esophageal squamous cell carcinoma (ESCC), snoRNAs actively mediated treatment resistance. Specifically, SNORA58 conferred radioresistance by attenuating ionizing radiation (IR)-induced ferroptosis via the SNORA58/CTCF/JNK1 regulatory axis (158). Concurrently, SNORA80B established a feed-forward oncogenic loop by stabilizing cholesterol metabolism transcripts through an m^6A-YTH domain containing 1-dependent mechanism, promoting the accumulation of cholesterol/dihydrotestosterone (DHT) and lipid droplet formation. In turn, DHT-activated androgen receptor (AR) further upregulated SNORA80B expression, driving profound chemotherapy resistance (159).

Tissue-based clinical and prognostic associations. Clinically, the mechanistic dysregulation of these snoRNAs is frequently observed in patient tissue cohorts. Across these diverse

malignancies, the elevated tissue expression of these specific oncogenic snoRNAs consistently correlates with adverse clinicopathological features, including advanced disease staging, increased metastatic burden, and poor OS outcomes (154-159).

Translational readiness and non-invasive diagnostics. Beyond tissue-based associations, emerging evidence highlights the translational potential of snoRNAs in these cancers. Most notably in esophageal cancer, the identification of a specific snoRNA signature (SNORA58, SNORA68, and SNORD93) within tumor-educated platelets (TEPs) demonstrated high capability for early disease detection, representing a promising non-invasive liquid biopsy application (160). Therapeutically, targeted interventions are showing immense promise: Targeting the JNK signaling pathway represents a viable strategy to improve radiotherapy outcomes in patients with ESCC and elevated SNORA58 expression (158), while the pharmacological inhibition of SNORA80B using clinofibrate exhibited potent synergy with cisplatin to effectively overcome chemotherapy resistance in ESCC models (159).

To synthesize these findings, snoRNAs consistently act as fundamental drivers of tumor growth, metastasis, and therapy resistance across a wide spectrum of malignancies. While their prognostic value is firmly established in tumor tissues, innovative translational applications, ranging from TEP profiling for early diagnosis to targeted radiosensitization and chemosensitization strategies, underscore the rapidly expanding clinical utility of snoRNAs in pan-cancer settings.

6. sdRNAs in cancer

Given the growing recognition of sdRNAs in cancer pathogenesis, it is essential to critically evaluate their functional roles and clinical potential. Similar to full-length snoRNAs, the current understanding of sdRNAs is synthesized across three distinct tiers of evidential strength.

Mechanistic drivers of pathogenesis. Fundamental *in vitro* and *in vivo* models have elucidated the capacity of sdRNAs to actively drive or suppress tumor progression through complex molecular networks. In androgen-resistant prostate cancer (AR-PCa), specific fragments (sdRNA-D19b and sdRNA-A24) were shown to promote tumor aggressiveness by suppressing the expression of tumor suppressor genes CD44 and CDK12, thereby enhancing cellular proliferation, metastatic potential, and chemoresistance (161). Similarly, Patterson *et al* (162) revealed that SNORD93 undergoes processing into a functionally active, miRNA-like fragment (sdRNA93). This specific sdRNA was shown to regulate sarcosine metabolism by modulating pipecolic acid and sarcosine oxidase expression, directly driving cancer cell invasiveness (162). Conversely, certain sdRNAs exert potent tumor-suppressive effects. In breast cancer models, a specific sno-derived piRNA from the GAS5 locus (pi-sno75) actively upregulated the TRAIL pathway to induce apoptosis (59).

Tissue-based clinical and prognostic associations. Clinically, the profound dysregulation of these molecules is consistently reflected in patient tissue cohorts. In pancreatic ductal adenocarcinoma (PDAC), comprehensive RNA sequencing has identified severe sdRNA dysregulation, with specific fragments such as *hsa-sno-HBII-85-29* showing pronounced downregulation and *hsa-sno-HBII-296B* exhibiting high upregulation in tumor tissues (163). More broadly, by integrating small RNA sequencing data from 10,262 patient samples across 32 cancer types, Chow *et al* (164) constructed a comprehensive pan-cancer sdRNAome landscape. This landmark analysis revealed that sdRNA expression signatures are highly cancer-specific and possess the potential to independently stratify patient survival outcomes (164).

Translational readiness and biomarker potential. Beyond tissue associations, sdRNAs are emerging as highly translatable clinical tools, particularly in the realm of tumor immunology. A substantial cohort of sdRNAs demonstrates notable correlations with critical features of the tumor-immune microenvironment, including the expression of immunosuppressive markers, levels of $CD8^+$ T-cell infiltration, cytolytic T-cell activity, and tumor vascularization patterns (164). These specific immune-associated sdRNA signatures hold immense translational potential as predictive biomarkers for stratifying patient responses to immunotherapy (164). Furthermore, the identification of functionally active sdRNAs driving chemoresistance in advanced malignancies such as AR-PCa highlights the need for their further investigation as novel therapeutic targets (161).

To synthesize these findings, sdRNAs represent a previously underappreciated yet functionally prevalent class of ncRNAs. From orchestrating metabolic and epigenetic shifts to serving as candidate prognostic indicators and immune-microenvironment classifiers, sdRNAs demonstrate substantial clinical relevance. Transitioning these molecules from mechanistic discovery toward targeted clinical applications represents a critical and highly promising frontier in precision oncology.

7. Extracellular snoRNAs for cancer diagnosis and prognosis

Beyond their intracellular functions, snoRNAs are consistently detectable in diverse body fluids, where they exhibit remarkable stability due to two primary protective mechanisms, including encapsulation within EVs or association with high-density lipoprotein complexes (165,166). This stable circulation positions them as highly promising non-invasive biomarkers for early cancer detection and dynamic monitoring. A comprehensive summary of snoRNAs with diagnostic, prognostic, or therapeutic significance is provided in Table SII, while their broader clinical implications are illustrated in Fig. 3.

Diagnostic performance in liquid biopsies. Recent clinical investigations highlight the diagnostic potential of circulating snoRNAs, particularly when multiplexed with conventional markers. For instance, in NSCLC, integrating diminished serum exosomal SNORD116 and SNORA21 levels with conventional biomarkers (cytokeratin 19 fragment 21-1 and CEA) surged the diagnostic accuracy to an AUC of 0.917, effectively distinguishing metastatic from non-metastatic disease (167). Similarly, in ccRCC, a panel of four EV-associated snoRNAs (SNORD99, SNORD22, SNORD26, and SNORA50C)

isolated from non-invasive urine samples has emerged as a candidate diagnostic tool (153). Furthermore, a discovery-stage clinical study in pancreatic cancer identified a multi-marker panel (WASP family member 2, ADP-ribosylation factor 6, SNORA74A, and SNORA25) that exhibited promising diagnostic value (AUC >0.9), surpassing the standard carbohydrate antigen 19-9 biomarker in accurately detecting early-stage (0-IIA) pancreatic cancer (168).

Technical challenges and emerging solutions. Despite their clinical promise, significant technical hurdles hinder the accurate identification and quantification of circulating snoRNAs. Key challenges include RNA isolation biases stemming from their small size (60-300 nt), the lack of polyadenylation tails that complicates standard library preparation, and highly stable secondary structures that impair reverse transcription efficiency. Furthermore, the rigorous clinical translation of circulating snoRNAs is heavily dependent on overcoming critical methodological bottlenecks. These include standardizing specimen types (such as serum vs. plasma vs. EVs), optimizing pre-analytical handling (such as centrifugation protocols and minimizing freeze-thaw cycles), establishing consensus strategies for data normalization (given the lack of universal endogenous controls in biofluids), and selecting appropriate detection platforms (reverse transcription-quantitative PCR vs. small RNA-sequencing) to ensure cross-study reproducibility. However, recent advances in small RNA-sequencing technologies, including specialized adapter designs for non-polyadenylated RNAs, improved reverse transcriptases for structured RNAs, and snoRNA-specific bioinformatic pipelines, have markedly enhanced analytical sensitivity (169,170). These methodological refinements are actively accelerating the exploration of circulating snoRNAs as candidate liquid biopsy biomarkers, although standardizing these protocols for definitive clinical application requires further extensive investigation.

8. SnoRNA-targeting tools

Target discovery and therapeutic rationale. While the precise molecular mechanisms of snoRNAs in tumorigenesis remain incompletely characterized, growing evidence suggests these ncRNAs are potential candidates for cancer therapy. The recent development of snoRNA-enriched kethoxal-assisted RNA-RNA sequencing (snoKARR-seq) technology represents a paradigm shift, enabling the transcriptome-wide mapping of snoRNA-mRNA interactions and identifying over 1,000 novel snoRNA-mRNA pairs. These discoveries challenge traditional paradigms by revealing modification-independent regulatory roles, thereby exponentially expanding the potential therapeutic target space for rational drug design (41). Furthermore, proof-of-concept research, such as the engineered expression of SNORA73 fused to a secreted green fluorescent protein reporter to modulate protein secretion pathways, suggest that artificial snoRNAs could potentially compensate for deficient secretory proteins in malignancies (41).

NATs in preclinical models. The past decade has witnessed notable progress in translating ncRNA targets into precision medicine (171). NATs, primarily antisense oligonucleotides (ASOs), ASO gapmers, and LNA oligonucleotides, have emerged as the most promising modalities for snoRNA-directed interventions. Preclinical success using ASOs is well-documented across multiple malignancies. For instance, ASO-mediated silencing significantly suppressed tumor growth and tumorigenesis in HCC (SNORD17, SNORD88B, SNORA74A) (87,91,172), PDAC (SNORA23) (173), OC (SNORA70E, SNORD9) (133,136), and EC (SNORD89, SNORD104, SNORD99) (141-143). Beyond monotherapy, NATs show profound synergistic potential and ASO-mediated inhibition of SNORA13 was revealed to synergize with 5-fluorouracil in CRC (174), while LNAs targeting SNORA38B significantly enhanced $CD8^+$ T-cell infiltration, sensitizing NSCLC to ICB therapy (114).

Delivery hurdles and the frontier of small-molecule drugs (SMDs). Although intrathecal administration of ASOs has demonstrated clinical safety in human trials (175), broad oncological application faces significant barriers. To date, no ASO or LNA drugs have received FDA approval specifically for cancer treatment, primarily due to unresolved challenges regarding tumor-specific delivery and immune modulation. Emerging non-viral delivery strategies, such as engineered liposomes and hybrid carriers, show promise in addressing these limitations.

Consequently, SMDs represent a highly attractive parallel frontier. Compared with NATs, SMDs offer superior solubility, enhanced metabolic stability, lower production costs, and easier cellular penetration (176). Crucially, snoRNAs present multiple druggable structural features, including complex secondary/tertiary structures, conserved functional motifs, and distinct protein interaction interfaces within snoRNP complexes. While dedicated snoRNA-focused high-throughput screening campaigns are still in their infancy, the demonstrated success of miRNA-targeted screening platforms and *in silico* models provides a strong and viable precedent for the development of snoRNA-targeted SMDs (177).

Future challenges in clinical translation. Despite these promising preclinical results, the clinical translation of snoRNA-targeted therapeutics faces several hurdles that must be addressed: i) Efficient delivery to extrahepatic tumor tissues; ii) mitigating off-target effects and innate immune sensor activation; iii) overcoming the nuclear localization barrier of numerous snoRNAs; and iv) defining the stoichiometric requirements for functionally disrupting snoRNP complexes. Overcoming these barriers will require interdisciplinary innovations combining RNA chemistry, nanomedicine, and tumor biology.

9. Discussion

The rapid advancement of high-throughput transcriptomic and specialized RNA-interaction mapping technologies has fundamentally reshaped our understanding of snoRNA and sdRNA biology. Moving beyond their canonical roles in rRNA modification, these molecules are now recognized as integral components of a complex regulatory network, with their dysregulation being a hallmark of numerous malignancies. The present review synthesized evidence that snoRNAs

and sdRNAs contribute to tumorigenesis through a markedly diverse repertoire of mechanisms-from modulating mRNA splicing, stability, and translation to directly interfacing with signaling proteins and epigenetic regulators. Their presence in EVs and notable stability in circulation further underscore their potential as liquid biopsy biomarkers.

Beyond their cell-autonomous functions, emerging evidence suggests that snoRNAs may play critical roles in the TME. For instance, EV-associated snoRNAs have been detected in various biofluids and may mediate intercellular communication between cancer cells and stromal or immune cells. Additionally, SNORD46 has been shown to modulate NK cell function in obesity-associated cancer (43), hinting at broader immunomodulatory roles. Future studies should explore whether snoRNAs are actively transferred between cells in the TME and whether they contribute to immune evasion or therapy resistance.

However, despite this considerable progress, the field stands at a critical juncture, facing three intertwined gaps that must be bridged to translate mechanistic insights into clinical utility.

The first and most fundamental gap is the functional annotation deficit. While catalogs of dysregulated snoRNAs and sdRNAs in cancer are rapidly expanding, the precise molecular functions for the vast majority remain enigmatic, with many still classified as 'orphans' (1). The full oncogenic or tumor-suppressive potential of these RNAs cannot be harnessed without a systems-level understanding of their interaction networks, target spectra, and context-dependent roles. Closing this gap requires a concerted shift from descriptive profiling to mechanistic deconvolution. Emerging technologies such as snoKARR-seq, which maps transcriptome-wide snoRNA-mRNA interactions, alongside *in situ* RNA modification capture techniques, are pivotal. Future research must prioritize the systematic identification of *bona fide* targets (both RNA and protein), the functional consequences of their binding, and the integration of this data across different cancer types and states (such as treatment-naïve vs. resistant).

The second gap is the methodological and translational gap. The journey from identifying a promising cancer-associated snoRNA to a validated clinical biomarker or target is fraught with technical and biological challenges. Current detection methods struggle with the unique biochemistry of snoRNAs, including their small size, lack of poly-A tails, and stable secondary structures, leading to biases in isolation, sequencing, and quantification. Consequently, there is an urgent need for standardized, sensitive, and reproducible protocols for snoRNA/sdRNA detection from both tissues and liquid biopsies. Furthermore, the heavy reliance of the field on synthetic, unmodified RNAs for functional studies is a major limitation, as endogenous snoRNAs are extensively post-transcriptionally modified. Synthetic analogs may not recapitulate these native properties, potentially leading to misleading conclusions. Developing strategies to isolate and study endogenous snoRNPs in their native state, and to chemically synthesize or engineer RNAs that faithfully mimic their modified counterparts, is essential for accurate functional validation and therapeutic design. A major specific limitation in the field is the current lack of standardized criteria for defining and annotating sdRNAs. Unlike miRNAs, which benefit from well-established biogenesis hallmarks and centralized annotation databases (such as miRBase), sdRNAs exhibit significant heterogeneity in length, processing boundaries, and functional modalities. Consequently, different research groups often employ disparate bioinformatics pipelines, read-length thresholds, and alignment strategies to identify these fragments from small RNA sequencing data. This lack of methodological consensus leads to substantial variability and discordance across studies, severely complicating cross-study comparisons and meta-analyses. Establishing a unified nomenclature and rigorous, standardized annotation criteria, integrating precise cleavage signatures with structural and functional validation, is an urgent prerequisite to reliably distinguish *bona fide* regulatory sdRNAs from stochastic snoRNA degradation products and to ensure reproducibility in future clinical investigations (48,56).

The third gap is the therapeutic development gap. While proof-of-concept studies using ASOs or LNAs against specific oncogenic snoRNAs show impressive preclinical efficacy, significant hurdles remain for clinical adoption (171). The core challenges of *in vivo* delivery, achieving sufficient tumor-specific uptake while minimizing off-target effects and immunostimulation, are amplified for nuclear-localized targets. Moreover, the stoichiometric nature of snoRNP complexes raises critical questions about whether partial inhibition of a snoRNA is sufficient to disrupt an oncogenic program, or if near-complete knockdown is required. Overcoming this barrier will likely require exploring combination therapies (pairing snoRNA inhibition with chemotherapy, targeted therapy, or immunotherapy) and advancing the development of small-molecule inhibitors that disrupt snoRNA-protein interactions or functions (171,176,177).

Furthermore, the specificity of snoRNA-mRNA interactions identified by crosslinking-based methods remains a concern, as these techniques may capture transient or non-functional associations. Future advances in high-resolution structure determination and functional screening will be essential to resolve these uncertainties.

Addressing these outlined gaps demands a multidisciplinary approach, combining cutting-edge RNA biology, sophisticated bioengineering, and comprehensive clinical research. By elucidating function, refining analytical tools, and innovating delivery platforms, the potential of these RNAs as precise biomarkers and novel therapeutic levers can be fully realized, potentially adding a powerful new dimension to precision oncology.

10. Conclusion

SnoRNAs and their derived sdRNAs have firmly emerged as critical, multidimensional regulators of cancer biology, with diverse functions ranging from guiding RNA modifications to modulating signaling pathways and immune responses. Their dysregulation across multiple cancer types, coupled with their stability in biofluids, positions them as promising non-invasive biomarkers for early detection, prognosis, and treatment monitoring. Furthermore, the development of ASO- and LNA-based therapeutics targeting oncogenic snoRNAs has shown preclinical efficacy, paving the way for clinical translation. Future research should focus on: i) Elucidating the precise molecular

mechanisms of orphan snoRNAs using advanced technologies such as snoKARR-seq and cryogenic electron microscopy; ii) validating circulating snoRNA signatures in large, prospective cohorts; iii) exploring combination therapies that integrate snoRNA targeting with ICB or conventional chemotherapy; and iv) developing targeted delivery systems to enhance tumor-specific uptake while minimizing off-target effects. Addressing these challenges will be essential for realizing the full potential of snoRNA-based strategies in precision oncology.

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Authors' contributions

JM and ZP designed the scope and and structure of the review, performed structured literature searches, prepared the figures, and wrote major sections of the manuscript. FG critically synthesized and interpreted findings. HL and ZP revised major sections of the manuscript. ZP provided conceptual guidance and supervised the overall project. JM, HL and ZP secured the funding. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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