REVIEW

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Small Nucleolar RNAs in Solid Tumors: A Brief Review of the Literature on These Potential Biomarkers

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Abstract

Objective: The objective of this study was to conduct an integrative review, addressing the key findings, biological functions, and clinical significance of these biomolecules in solid tumors. **Methods:** This document analyzes the main data on the involvement of snoRNAs in solid tumors. For this, Pubmed and Science direct were used, with keywords. Additionally, a search for the host gene was conducted using the snoDB tool, and its chromosomal location was identified using the Hugo Gene Nomenclature Committee (HGNC). **Results:** According to research conducted in the literature, the majority of snoRNAs were found to be overexpressed and described as regulators of processes such as invasion, cellular proliferation, apoptosis, and migration. They are associated with clinical prognostic factors such as metastasis and worse survival. **Conclusion:** Therefore, it is essential to expand the investigation of snoRNAs in oncology across different types of tumors. The utilization of these biomolecules may pave the way for innovative clinical applications, such as their use in the early detection of neoplasms in non-invasive samples and as therapeutic targets. Broadening research on snoRNAs across various tumor types is crucial.

Keywords: Biological function- biomarker- cancer- clinical significance- snoRNAs

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Introduction

Solid tumors are considered one of the leading causes of cancer-related deaths, due to their rapid tumor growth and local or distant metastasis. They pose critical challenges due to physiological characteristics and limitations in treatment options [1, 2]. Among the markers that have been extensively studied in these types of tumors are non coding RNAs (ncRNAs). There are several families of ncRNAs in mammals, some of which are: microRNAs (miRNAs), small interfering RNAs (siRNAs), piwi-interacting RNAs (piRNAs), transfer RNAs (tRNAs) and small nucleolar RNAs (snoRNAs) [3].

snoRNAs have an average size of 60-70 nucleotides (nt) and are widely distributed in the nucleolus of eukaryotic cells [4]. snoRNAs do not have a poly-A tail and are 5′-capped. While this modification is typical for their nuclear localization, it does not necessarily mean they are not exported from the nucleus. They can be divided into two subtypes, according to the motif present in the molecule: H/ACA (SNORA) and C/D box (SNORD). A third group is the SCARNA, discovered in 2002, which has presents both C/D and H/ACA domains and accumulates in Cajal bodies [5]. In vertebrates, most snoRNAs are encoded in intronic regions of coding genes or long non-coding RNAs (lncRNAs), and a small group of snoRNAs originate from intergenic regions [6].

Since their discovery, the functional role of snoRNAs under normal and pathological conditions has been investigated. SnoRNA expression can be modified by a variety of genetic alterations changes such as: a) overexpression; b) translocation; c) mutations; and d) copy number variations [7]. Epigenetic mechanisms can also alter gene expression such as: a) DNA methylation; and b) histone modification [7, 8]. Historically, the first snoRNA-associated human disease described is Prader-Willi syndrome (PWS), a rare genetic disorder characterized by hypotonia and hyperphagia [9, 10]. Currently, snoRNAs

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are known to be participate in a wide range of human diseases, including, congenital heart defects, and cancer [11, 10].

The demonstration that snoRNA expression varies in cancerous tissues challenges the old dogma, according to which snoRNAs only function maintaining of ribosome biogenesis [8, 12]. In recent years, several studies have presented promising data on the involvement of these biomolecules in different types of malignant neoplasms, through the regulation of several molecular pathways [13, 14]. In this context, the objective of this work was to carry out an integrative review addressing the main results, such as biological functions and clinical significance of these biomolecules in solid tumors.

Snornas in Lung Cancer

Works with snoRNAs in lung cancer began in 2010 when Liao et al. [15] observed that six snoRNAs (*SNORA80E, SNORA73B, SNORD33, SNORD66, SNORD76* and *SNORD78*) were overexpressed compared to tissue samples from individuals without cancer. Of these six snoRNAs, three (*SNORD33, SNORD66*, and *SNORD76)* had a sensitivity of 81.1% and a specificity of 95.8% in distinguishing lung cancer patients from normal individuals.

Subsequently, Mei et al. [16] demonstrated in 64 samples from patients with stage I lung cancer that *SNORA42* genomic amplification resulted in an overexpression of tumor stem cells. Silencing of this small nucleolar RNA reduces the transcript levels of genes associated with pluripotency, such as *OCT4, SOX2, NOTCH1, NANOG, SMO*, and *ABCG2*. These results suggest that *SNORA42* is essential for the expression of transcription factors in tumor stem cells.

Dysregulation of other snoRNAs such as *SNORA21, SNORD28, SNORA47, SNORD66, SNORA68, and SNORA78* was associated with worse overall survival, in addition to allowing differentiation between patients with stage I lung cancer and normal tissue [17]. *SNORD46* knockdown results in decreased cell viability, inhibition of invasion, and migration capacity [13].

Recently, two studies have addressed the identification of these biomolecules in non-invasive samples. In the first one, Dong et al. [18] observed that the expression of *SNORD55* was decreased in both plasma and tissue of patients in the early stages of the disease. Similar data were observed by Wang et al. [19] when investigating the expression of *SNORD83A*. These data support the potential of snoRNAs as biomarkers the early detection of lung cancer (Table 1). Another snoRNA, *SNORA38B*, was significantly expressed, and associated with poorer worse prognostic factors, including proliferation, migration, and cellular invasion, correlated with advanced disease stages, and decreased survival, thus representing a potential therapeutic target [20].

Two *snoRNAs, SNORD42B* and *SNORD111*, could serve as promising non-invasive biomarkers for early-stage lung cancer, as they were shown to have good sensitivity and specificity[39]. Finally, Wan et al. [21] observed six snoRNAs (*SNORD14A, SNORD59A, SNORD99, SNORD100, SNORD63*, and *SNORD19*) which are related to infiltration into the tumor immune microenvironment, thus predicting the prognosis and responsiveness to immunotherapy in lung cancer patients.

Table 1. List of snoRNAs Regarding Their Biological Role and Clinical Significance associated with Lung Cancer

snoRNAs	Chromosomal location*	Host Gene**	Biological Role and/or Clinical Significance	Expression Level	References
SNORD46	1p34.1	*RPS8*	Silencing of this snoRNA leads to a decrease in the invasive capacity of tumor cells	Upregulation	Gong et al. [13]
SNORD33, SNORD66 and SNORD78	19q13.33, 3q27.1, 1q25.1	*RPL13A, EIF4G GAS5*	Sensitivity and specificity in distinguishing tumor and non-tumor tissue	Upregulation	Liao et al. [15]
SNORA42	1q22	*KIAA0907*	Reduction of transcription levels of genes such as: *OCT4, SOX2, NOTCH1, NANOG, SMO* and *ABCG2*	Upregulation	Mei et al. [16]
SNORA21, SNORD28, SNORA47, SNORD66, SNORA68 and SNORA78	17q12, 11q12.3, 5q13.3, 3q27.1, 19p13.11, 16p13.3	*RPL23, SNHG1, ZBED3, EIF4G1, RPL18A, SNHG9*	Associated with worse prognostic factors	Upregulation	Gao et al. [17]
SNORD55	1p34.1	*RPS8*	Potential biomarker in non-invasive samples	Downregulated	Dong et al. [18]
SNORD83A	22q13.1	*RPL3*	Potential biomarker in non-invasive samples	Upregulation	Wang et al. [39]
SNORA38B	17q24.2	*NOL11*	Associated with worse prognostic factors, Potential therapeutic target	Upregulation	Zhuo et al. [20]
SNORD42B and SNORD111	17q11.2, 16q22.1	*RPL23A, SF3B3*	Potential biomarker in non-invasive samples	Upregulation	Wang et al., [19]
SNORD14A, SNORD59A, SNORD99, SNORD100, SNORD63 and SNORD19	11p15.1, 12q13.3, 1p35.3, 6q23.2, 5q31.2, 3p21.1	*-, ATP5F1B, C1orf79, RPS12, HSPA9, GNL3*	Potential biomarkers for immunotherapy	Upregulation	Wan et al. [21]
SNORD78	1q25.1	*GAS5*	Acts on EMT and on the proliferation of tumor cells through the arrest of the cell cycle	Upregulation	Zheng et al. [40]

*Host gene= https://bioinfo-scottgroup.med.usherbrooke.ca/snoDB/; **Chromosomal location = https://www.genenames.org/

Table 2. List of snoRNAs in Terms of Their Biological Role and Clinical Significance associated with Colorectal Cancer

snoRNAs	Chromosomal location*	Host Gene**	Biological Role and/or Clinical Significance	Expression Level	References
SNORA71A	20q11.23	*SNHG17*	Cell proliferation, migration, and invasion	Upregulation	Zhang et al. [22]
SNORA15, SNORA41 and SNORD33	7p11.2, 2q33.3, 19q13.33	*CCT6A, EEF1B2 and RPL13A*	Associated with worse prognostic factors	SNORA15 and SNORA41 Upregulation. SNORD33 Downregulated	Yang et al. [23]
SNORD1C	17q25.1	*SNHG16*	Potential biomarker in non-invasive samples	Upregulation	Liu et al. [24]
SNORD15B and SNORA5C	11q13.4, 7p13	*RPS3, TBRG4*	Associated with worse prognostic factors	Upregulation	Shen et al. [25]
SNORA21	17q12	*RPL23*	Potential biomarker for prognosis	Upregulation	Yoshida et al. [26]
SNORD126	14q11.2	*CCNB1IP1*	Activates the PI3K/AKT pathway	Upregulation	Fang et al. [27]
SNORA42	1q22	*KIAA0907*	Potential biomarker for recurrence and worse prognosis	Upregulation	Okugawa et al. [41]

*Host gene= https://bioinfo-scottgroup.med.usherbrooke.ca/snoDB/; **Chromosomal location = https://www.genenames.org/

Table 3. List of snoRNAs about Their Biological Role and Clinical Significance associated with Prostate Cancer

snoRNAs	Chromosomal location*	Host Gene**	Biological Role and/or Clinical Significance	Expression Level	References
SNORD50A	6q14.3	*SNHG5*	Potential tumor suppressor	Downregulated	Siprashvili et al. [61]
SNORA55	1p34.3	*PABPC4*	Cell proliferation and migration	Upregulation	Crea et al. [29]
SNORA42	1q22	*KIAA0907*	Potential biomarker for prognosis	Upregulation	Yi et al. [42]
SNORD78	1q25.1	*GAS5*	Associated with worse prognostic	Upregulation	Martens-Uzonova et al. [43]

*Host gene= https://bioinfo-scottgroup.med.usherbrooke.ca/snoDB/; **Chromosomal location = https://www.genenames.org/

Colorectal Cancer

Changes in snoRNAs have also been reported in colorectal cancer (CRC) (Table 2), and the data presented demonstrate promising results.show demonstrate promising results. Among these studies is one by Zhang et al. [22], who observed that the high expression of *SNORA71A* was statistically significant in patients with TNM stages and lymph node metastases, in addition to playing having a role in the proliferation, migration, and invasion of CRC cells. In the same paper, the functional analysis of genes that are co-expressed with *SNORA71A* revealed that this snoRNA is involved in the NF-kappa B, Toll-like, Jak-STAT signaling pathways. Therefore, small nucleolar RNAs, in particular *SNORA71A*, may be involved in one of the hallmarks of cancer, namely immune surveillance.

In another study, *SNORA15, SNORA41*, and SNORD33 were useful in the identification of cancerous tissue compared to normal tissue, so that the change in the expression of these biomolecules was also associated with

Table 4. List of snoRNAs in Terms of Their Biological Role and Clinical Significance associated with Hepatocellular Carcinoma

snoRNAs	Chromosomal location*	Host Gene**	Biological Role and/or Clinical Significance	Expression Level	References
SNORA18L5	-	*CHRNA7*	Tumor proliferation and growth p53 pathway	Upregulation	Cao et al. [30]
SNORA24	4q26	*SNHG8*	Associated with worse prognosis and mediates *RAS* oncogenic activity.	Upregulation	McMahon et al. [31]
snoU2_19	-	*KIAA1731*	Proliferation Wnt/B-catenin pathway	Upregulation	Wang et al. [36]
SNORD76	1q25.1	*GAS5*	Proliferation and EMT Wnt/B-catenin pathway	Upregulation	Jung et al. [32]
ACA11	4p16.3	*WHSC1*	Proliferation, migration, and invasion PI3K-Akt pathway	Upregulation	Wu et al. [33]
SNORD31	11q12.3	*SNHG1*	Associated with worse prognostic factors	Downregulated	Ding et al. [35]
SNORA52	11p15.5	*RPLP2*	Potential diagnostic and prognostic biomarker	Downregulated	Ding et al. [45]
SNORD52	6p21.33	*C6orf48*	Upregulates CDK1 and is associated with worse prognostic factors	Upregulation	Li et al. [46]
SNORD113-1	14q32.31	*MEG8*	Able to inactivate the phosphorylation of ERK1/2 and SMAD2/3 in the MAPK/ERK and TGF-β pathways	Downregulated	Xu et al. [47]
SNORD17	20p11.23	*SNX5*	Participate in cancer progression via p53 inhibition	Upregulation	Liang et al. [48]
SNORA47	5q13.3	*ZBED3*	Cell proliferation and regulation of EMT-associated markers	Upregulation	Li et al. [49]

*Host gene= https://bioinfo-scottgroup.med.usherbrooke.ca/snoDB/; **Chromosomal location = https://www.genenames.org/

Table 5. List of snoRNAs about Their Biological Role and Clinical Significance associated with Other Types of Cancers

snoRNAs	Chromosomal location*	Host Gene**	Biological Role and/or Clinical Significance	Expression Level	Type of cancer	References
SNORA71B	20q11.23	*SNHG17*	Associated with worse prognostic factors	Upregulation	Breast cancer	Duan et al. [50]
SNORA7B	3q21.3	*RPL32P3*	Proliferation, migration, and invasion	Upregulation	Breast cancer	Sun et al. [51]
SNORD50A/ and SNORD50B	6q14.3	*SNHG5*	Oncogenic role in wild-type breast cancer p53 pathway	Downregulated	Breast cancer	Su et al. [52]
SNORA71A	20q11.23	*SNHG17*	Associated with metastasis.	Upregulation	Breast cancer	Hu et al. [53]
SNORD89	2q11.2	*PPAN*	Proliferation, migration, and invasion	Upregulation	Ovarium cancer	Zhu et al. [54]
SNORA72	8q22.2	*RPL30*	Able to activate the Notch1/c-Myc pathway	Upregulation	Ovarium cancer	Zhang et al. [55]
SNORA70E	11q14.1	*RAB30*	Cell proliferation, decreased cell apoptosis, induced cell migration and invasion	Upregulation	Ovarium cancer	Chen et al. [56]
SNORA21	17q12	*RPL23*	Associated high expression and markers involved in EMT	Downregulated	Gallbladder cancer	Qin et al. [57]
SNORA74B	5q35.1	*ATP6V0E1*	Activation of the AKT/ mTOR pathway	Upregulation	Gallbladder cancer	Qin et al. [58]
ACA47, ACA10, SNORA58, HBII-316, U70, U8 and U66	17q25.2, 16p13.3,3q22.1, 2p23.2, Xq28, 17p13.1,1p22.1	*SEC14L1, RPS2, MRPL3, WDR43, RPL10, ULK4 and RPL5*	Associated with worse prognostic factors	Upregulation	Gastric cancer	Wang et al. [37]
SNORD105B	19q13.2	*HSPD1*	Migration, invasion, proliferation via c-Myc	Upregulation	Gastric cancer	Zhang et al. [38]
SNORD89	2q11.2	*RNF149*	Migration and proliferation	Upregulation	Endometrial cancer	Bao et al. [59]
SNORD6	11q21	*JOSD3*	E6-mediated degradation of p53	Upregulation	Cervical cancer	Li et al. [60]

*Host gene= https://bioinfo-scottgroup.med.usherbrooke.ca/snoDB/; **Chromosomal location = https://www.genenames.org/

the presence of metastatic lymph nodes and the degree of differentiation [23]. Regarding the identification of these biomolecules in non-invasive samples, *SNORD1C* showed demonstrated overexpression in the serum of patients with colorectal cancer, in addition to being associated with worse prognostic factors [24].

Furthermore, the snoRNAs *SNORD15B* and *SNORA5C* were also dysregulated in CRC, and with their expression was being associated with clinical-pathological parameters, including age, lymphatic invasion, and history of colon polyps, suggesting they have oncogenic functions in neoplasia progression and could predict poor patient prognosis [25].

In addition to the above snoRNAs, *SNORA21* has been previously implicated in cell proliferation and adhesion [26]. High levels of *SNORD126* in CRC cells upregulated the *PI3K/AKT* pathway and increased *FGFR2* expression. *FGFR2* has attracted considerable attention as a potential therapeutic target in gastric cancer. Therefore, these data suggest that *SNORD126*, in addition to acting on critical processes of carcinogenesis via *PI3/Akt* regulation, may be a potential therapeutic target [27].

Prostate Cancer

Prostate cancer is regarded as a multistep disease resulting from the accumulation of genetic alterations, including the activation of oncogenes and the inactivation of tumor suppressor genes. One of the deleted regions is 6q14-22, which encompasses the coding region of snoRNA U50, as observed by Dong et al. [28]. The deletion in this region is a candidate tumor suppressor gene.

SNORD50A-SNORD50B has been found deleted in several cancer types, with its loss linked to reduced survival. Furthermore, a microarray screen revealed direct binding of SNORD50A and SNORD50B to K-Ras [61].

Crea et al. [29], showed that trevealed that SNORA55 is upregulated in prostate cancer and was associated with poor a worse prognosis (Table 3), interacting with pro-oncogenic and inflammatory pathways. Inhibition of this snoRNA, in turn, interfered with the growth of malignant cells, thus preventing their invasion.

Hepatocellular Carcinoma

Another solid neoplasm in which the role of snoRNAs has been investigated is hepatocellular carcinoma (Table 4). *SNORA18L5* has already been associated with cell proliferation and tumor growth [30]. Meanwhile, *SNORA24* was associated with poor patient survival in addition to RAS-mediated oncogenic activity [31].

Aberrant expression of snoU2_19, in turn, facilitated the proliferation of hepatocellular carcionoma cells, inhibited apoptosis, and induced cell cycle progression,

such that the knockout of this biomolecule inhibited *Wnt*/B-catenin signaling by inducing the translocation of B-catenin [44]. Alterations in this pathway have also been related to the regulation of *SNORD76*. In human cancers, the Wnt/β-catenin pathway is positively activated, which has led to the development of several Wnt signaling inhibitors for cancer therapies [33].

Another snoRNA that regulates a key pathway in the carcinogenic process is *ACA11*. This small nucleolar RNA is capable of promoting cell growth, migration, and invasion through the activation of the *PI3K/AKT* pathway, and consequently the expression of *Cyclin D1* [33]. Altered expression of cyclin D1 has been reported to be associated with poor prognostic factors in several types of cancer, as in penile cancer [62].

Recently, the clinical significance of *SNORD31* has been observed in hepatocellular carcinomas. This snoRNA is downregulated and this expression pattern has been associated with poorer prognosis and shorter survival characteristics [35]. These findings serve as potential prognostic biomarkers and therapeutic targets for patients with hepatocellular carcinoma.

Other Types of Cancers

There are still few studies elucidating the role of snoRNAs in solid tumors. Some relevant data have been observed in gastric cancer, as an per the example of the work described by Wang et al. [37], where 8 snoRNAs (*ACA47, E2, ACA10, SNORA58, HBII-316, U70, U8,* and *U66*) were associated with lower survival, with a high predictive value [37]. Interesting data were also found for *SNORD105B*. Positive regulation of the expression of this snoRNA was associated with factors of worse prognosis, such as tumor size, differentiation, and pathological stage, in addition to implying proliferation, migration, invasion, and activation of the c-Myc pathway [38].

For other tumor types, the lack of information is much greater (Table 5). For some cancers, such as ovarian and gallbladder cancer, the literature only reports three studies for ovarian. Moreover, for penile cancer, there are no studies, furthering the need to explore the involvement of these biomolecules.

SnoRNAs may be involved in key processes of solid tumor carcinogenesis through the regulation of important pathways. The use of these biomolecules may pave the way for innovative clinical applications, such as their use in the early detection of neoplasms in non-invasive samples and as therapeutic targets. Therefore, it is essential to expand the investigation of snoRNAs in the field of oncology across different tumor types.

Author Contribution Statement

JDP, CRTDS, ASK: Paper design; methodology; data collection; manuscript writing. JDP, GEBS, WDCS, AGDMM, LRDS, EDSB, MGDOPDS, SSSDF, AALTJ, AMDS, CRTDS, ASK: Critical review and approval of the manuscript. JDP, ASK: Critical revision, editing, and approval of the manuscript; supervision of the work.

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