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CRITICAL REVIEW

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Small nucleolar RNA host genes promoting epithelial–mesenchymal transition lead cancer progression and metastasis

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Abstract

The small nucleolar RNA host genes (SNHGs) belong to the long non-coding RNAs and are reported to be able to influence all three levels of cellular information-bearing molecules, that is, DNA, RNA, and proteins, resulting in the generation of complex phenomena. As the host genes of the small nucleolar RNAs (snoRNAs), they are commonly localized in the nucleolus, where they exert multiple regulatory functions orchestrating cellular homeostasis and differentiation as well as metastasis and chemoresistance. Indeed, worldwide literature has reported their involvement in the epithelial–mesenchymal transition (EMT) of different histotypes of cancer, being able to exploit peculiar features, for example, the possibility to act both in the nucleus and the cytoplasm. Moreover, SNHGs regulation is a fundamental topic to better understand their role in tumor progression albeit such mechanism is still debated. Here, we reviewed the biological functions of SNHGs in particular in the EMT process and discussed the perspectives for new cancer therapies.

Abbreviations: BCa, bladder cancer; BSG, basigin; CC, cervical cancer; ccRCC, clear cell renal cell carcinoma; CSCC, cervical squamous cell carcinoma; circRNAs, circular RNAs; CRC, colorectal cancer; EMT, epithelial–mesenchymal transition; EZH2, enhancer of zeste homolog 2; FKBP1A, FKBP prolyl isomerase 1A; GC, gastric cancer; HCC, hepatocellular carcinoma; HPV, human papillomavirus; lincRNAs, large intergenic ncRNAs; lncRNAs, long non-coding RNAs; miR, microRNA; MMP-2, matrix metalloproteinase-2; NPC, nasopharyngeal carcinoma; RCC, renal cell carcinoma; SKIL, ski-oncogene-like; SNHGs, small nucleolar RNA host genes; rRNA, ribosomal RNA; tRNA, transfer RNA; ZEB1, zinc finger E-box-binding homeobox 1; ZEB2, zinc finger E-box-binding homeobox 2.

KEYWORDS
cancer, EMT, long non-coding RNAs, small nucleolar RNA host genes

1 | INTRODUCTION

The class of non-coding transcripts comprises basically three wide categories: the transfer RNA (tRNA) and the ribosomal RNA (rRNA), which are elements of the translation machinery compartment, the small non-coding RNAs, which comprise, short interfering RNAs (siRNAs), Piwi-interacting RNAs (piRNAs), small nuclear and nucleolar RNAs (snRNAs and snoRNAs) and extracellular RNAs (exRNAs), and the long non-coding RNA (lncRNAs).[1–4] The latter is currently the main topic of several scientific investigations as they are still poorly known, even though they account for many cellular regulatory functions, and their dysregulation is often associated with pathologic conditions[5] such as degenerative diseases and cancers.[6–9]

Recently, it has been proposed an alternative classification of the large family of the lncRNA, although still not widely used: the imprinted lncRNAs, controlling the expression of imprinted genes[10]; the disease-associated lncRNAs, correlated with particular pathological conditions[11–13]; the pathogen-induced lncRNAs, secreted and modulated by exogenous microorganisms[14]; the bifunctional RNAs that might be also translated into proteins[15]; the molecular sponges that interfere with the activity of miRNAs reducing their cellular bioavailability[16]; the circular RNAs (circRNAs)[17]; the large intergenic non-coding RNAs (lincRNAs), which control gene expression through histone modifications.[18]

Long non-coding small nucleolar RNA host genes (lnc-SNHGs), the host genes for snoRNAs, are overexpressed in human cancers. SNHGs are able to induce proliferation, invasion, and metastasis.[19–21] Therefore, they are to date an interesting topic of investigation in order to propose as new anticancer therapies. Commonly, snoRNAs are derived by only introns transcript while if the transcript includes also exons, they will be defined as SNHGs.[19,22] Moreover, it was reported a positive correlation between a specific SNHG and its corresponding snoRNA and is often associated with the aggressiveness and the grade of progression of the disease.[23,24] Conversely, the inhibition of a target SNHG might downregulate also the expression of the corresponding snoRNA, as reported by Yu et al. who described that p53 activation reduced the expression level of SNHG1 suppressing as well the level of SNORD22, SNORD25, SNORD26, SNORD27, SNORD28, and SNORD75.[25] However, an element that easily distinguishes between snoRNAs and SNHGs is the cellular localization as the former are only nuclear while the latter are both in the nucleus and in the cytoplasm.[19]

To date were identified at least five different SNHGs molecular action mechanisms: two associated with a nuclear localization, where the SNHGs influence the DNA methylation and interact with transcription factors and repressor influencing gene transcription; three correlated with a cytoplasm localization, where they are reported to decrease the bioavailability of miRNAs through a molecular sponging activity, the repression of translation, and the prevention of ubiquitination (Figure 1).[26] All the SNHGs exert a crucial role in oncogenesis and cancer progression through their ability to influence all three levels of cellular information-bearing molecules, that is, DNA, RNA, and proteins. The most popular and known SNHGs are resumed in Table 1.[26] The present review aimed to explain the involvement of several important SNHGs in tumor progression and also discusses the relationship between SNHGs and miRNAs as modulatory arms in cancer management.

2 | SMALL NUCLEOLAR RNA HOST GENES IN EMT PROCESS

Epithelial to mesenchymal transition (EMT) comprises an intricate cascade of phenomena by which epithelial cells lose their apicobasal polarity and acquire mesenchymal features including a fibroblastoid morphology and a front-rear polarity.[27–29] EMT is a fundamental process in development, organogenesis, tissue repairing, cancer progression, and tumor metastasis.[29–31] Such transition is commonly induced by external microenvironmental factors and it is described as a reversible process, allowing cancer cells to evade regulated cell death, and contributing to immunosuppression in early phases while after dissemination they might revert to an epithelial status.[32–34] Indeed, EMT-induced cells demonstrate enhanced migration, invasion, and frequently express N-cadherin at the expense of E-cadherin reducing in this way the intercellular adhesion.[35–37] Moreover, to intricate an already debated and complex process, cancer cells are often reported to display different degrees of EMT phenotypes.[38–41]

As reported above, SNHGs exert multiple roles being able to act as molecular sponges for several miRNAs (Figure 2) or binding proteins modulating in that way multiple biological processes, including the EMT in cancer.[28] The known SNHGs in EMT are resumed in Table 2.

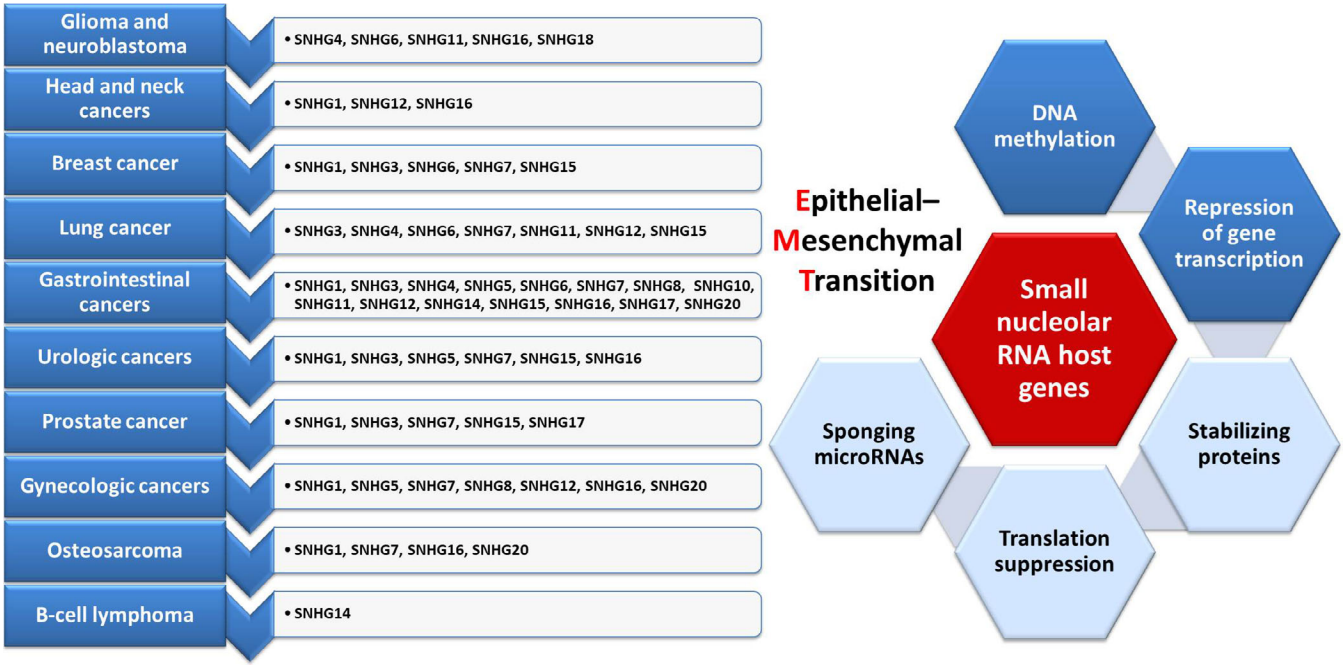

FIGURE 1 SNHGs can function through different mechanisms including DNA methylation, transcription repression, translation suppression, miRNAs sponging, and prevention of protein ubiquitination in cancers

TABLE 1 snoRNAs encoded by selected SNHGs

SNHGs	snoRNAs	Refs.
SNHG1	SNORD22, SNORD25, SNORD26, SNORD27, SNORD28, SNORD29, SNORD30, SNORD31	151
SNHG3	SNORA73A, SNORA73B	152
SNHG4	SNORA74A, SNORA74	152
SNHG5	SNORD50A, SNORD50B	153
SNHG7	SNORA17, SNORA43	154
SNHG8	SNORA24	155
SNHG11	SNORA71E, SNORA39	156
SNHG12	SNORA44, SNORA61, SNORA16A, SNORD99	157
SNHG14	SNORD116	158
SNHG15	SNORA9	159
SNHG16	snoRD1A, snoRD1B, snoRD1C	160
SNHG17	SNORA71A	161

2.1 | Glioma and neuroblastoma

Brain tumors are categorized as benign and malignant tumors of which the latter characterized by a great aggressive potency.[42,43] SNHG1 was reported to be overexpressed in invasive pituitary tumor tissues and cell lines promoting cell proliferation, migration, invasion, and EMT via its decoy capability toward miR-302/372/373/520 (miRNA-pool) leading to the upregulation of TGFBR2 and RAB11A.[44] It seems that the overexpression of SNHG16 coordinates with the EMT, invasion, and decline of survival rate in patients. In other words, SNHG16 knockdown is paired with the enhancement of apoptotic cell death and inhibition of tumor volumes in vivo. SNHG16-mediated decrease of miR-20a-5p correlated with malignancy of glioma.[45] Another study demonstrated that SNHG16 is able to upregulate the HNF4α via the inhibition of miR-542-3p in neuroblastoma, fueling in such a way cell proliferation, migration, invasion, and the EMT in vitro.[46] Moreover, it is established that SNHG6, 11 and 18 are upregulated in malignant glioma cells.[47–49] Besides, the level of SNHG6, 11, 16, and 18 are inversely correlated with the miR-101-3p, miR-154-5p and miR-20a-5p levels. It is noteworthy to mention that the level of SNHG6, 11, 16, and 18, and the level of miR-101-3p, miR-154-5p and miR-20a-5p respectively, are inversely correlated with the EMT, tumor volume, malignancy, and poor prognosis in nude mice and patients. It is demonstrated that SNHG6 regulates tumorigenesis through the modulation of miR-101-3p expression and SNHG16 enhances cell proliferation through the increasing of E2F1 factor.[48] Interestingly, SNHG18, a lncRNA involved in radioresistance, inhibits α-enolase nucleocytoplasmic transportation to promote invasion and EMT via upregulating β-catenin, SNAIL, SLUG, N-cadherin, and vimentin.[49] In last, it is important to note the role of SNHG4 in neuroblastoma as it was reported to be positively correlated with the patients' survival. Indeed, it represses neuroblastoma cell proliferation, stimulates cell apoptosis in vivo and in vitro, and inhibits

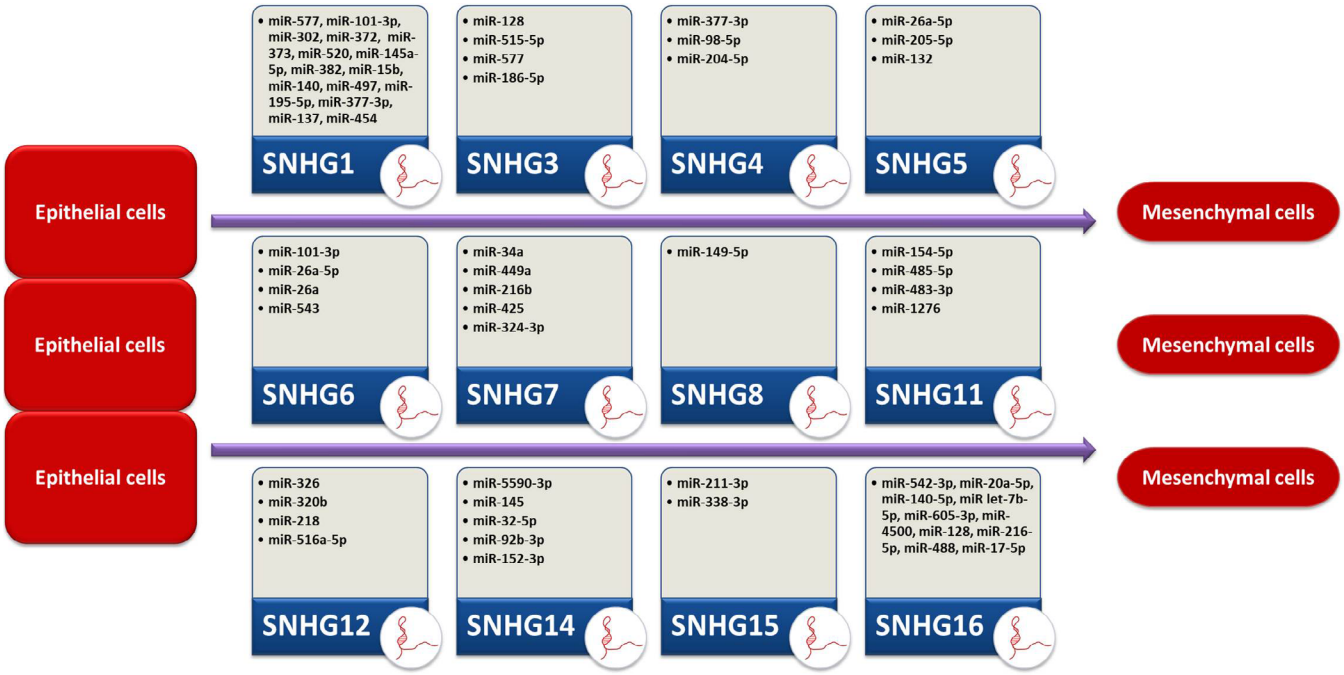

FIGURE 2 SNHGs can sponge miRNAs to induce EMT in cancer cells

migration and invasion abilities paired with a block of the EMT by the sponging of miR-377-3p.[50]

2.2 | Head and neck cancers

Nasopharyngeal carcinoma (NPC), a type of epithelial malignancy, is one of the most common head and neck epithelial neoplasms.[51–53] Various studies have examined lncRNA SNHGs effects and their mechanisms in the development and aggressiveness of NPC. For example, Lan et al.[51] demonstrated that SNHG1 through silencing of miR-145-5p increases the NUAK1 expression and thereby enhances the invasion of NPC cells by AKT signaling pathway and elicits EMT. In fact, they exhibited that the SNHG1/miR-145-5p/NUAK1 axis plays a critical role in NPC and thus can be targeted for treatment. It was also indicated that NPC metastasis is regulated by SNHG7, so that knockdown of SNHG7 suppresses cell invasion and cell migration of NPC and vice versa in NPC samples and nude mice. Recent findings showed that SNHG7 promotes NPC metastasis via eliciting the EMT process.[54]

Moreover, SNHG12 is another modulating factor of NPC cell proliferation, migration, and invasion. Overexpression of SNHG12 was detected in both NPC tissues and cell lines and is also significantly associated with patients' poor prognosis. The data identified that the silencing of SNHG12 resulted in inhibition of EMT activation and Notch-1 signal pathway.[52] On the other hand, the expression level of SNHG1 is upregulated in laryngeal carcinoma tissues and HEp-2 cells. Laryngeal carcinoma is comprised of ~25% of malignancy in head and neck cancers of which the most popular ones are laryngeal squamous cell carcinoma. It was demonstrated that SNHG1 upregulation significantly occurs in laryngeal carcinoma tissues rather than that in para-carcinoma tissues. The SNHG1 silencing suppresses cell proliferation, invasion, and metastasis, and activates apoptosis in HEp-2 cells. Reduced SNHG1 expression suppresses the invasion and migration of HEp-2 cells by suppressing the EMT and expressions of matrix metalloproteinase-2 (MMP-2) and MMP-9 in cells.[55] A relatively uncommon malignant tumor affecting the head and neck regions is the oral squamous cell carcinoma characterized by a poor overall 5-year survival rate.[56] Among several abnormally expressed lncRNAs, SNHG12 is often detected as an overexpressed lncRNA in this tumor and it was reported to regulate cell proliferation, migration, invasion, and EMT process via miR-326.[57] SNHG16 is another lncRNA closely associated with oral squamous carcinoma and its expression is correlated with c-Myc. It was reported to induce PCNA, MMP-2, MMP-9, E-cadherin along with reduction of N-cadherin and Snail starting the EMT induction.[58]

2.3 | Breast cancer

Breast cancer is to date considered the most frequent cancer in women.[59,60] Therefore, finding the involved molecular mechanisms in its pathology to design an effective

TABLE 2 The roles of SNHGs in EMT process

Cancer type	Cell line/animal model	SNHGs	Molecular mechanism of action and regulated signaling pathways	Targeted miRNAs	Refs.
Osteosarcoma	MG63 and U2OS cell lines, Nude mice	SNHG1	Sponging miRNAs and activation of WNT2B/Wnt/β-catenin signaling	miR-577	145
Osteosarcoma	MG63, U2OS, and SaOS2 cell lines	SNHG1	Sponging miRNAs and enhancing the expression of ROCK1	miR-101-3p	146
Osteosarcoma	MG63 and SaOS2 cell lines	SNHG7	Sponging miRNAs and regulation of TGF-β	miR-34a	147
Osteosarcoma	U2OS, HOS	SNHG16	Sponging miRNAs and upregulating ITGA6	miR-488	162
Osteosarcoma	MG63, U2OS, SaOS2, and HOS cell lines	SNHG20	Regulating Vimentin, ZEB1, ZEB2, and E-cadherin	—	148
Oral squamous cell carcinoma	CAL-27, SCC9, SCC-25	SNHG12	Sponging miRNAs and regulating E2F1	miR-326	57
Oral squamous cell carcinoma	NHOK, SCC-25, CAL-27	SNHG16	Promoting cancer progression and carcinogenesis	—	58
Oral squamous cell carcinoma	CAL27, TCA8113, OEC-M1, TW2.6	SNHG16	Sponging miRNAs and regulating CCND1	miR-17-5p	163
Pancreatic cancer	Human normal pancreatic cell line (HPDE6), pancreatic cell lines (BXPC3, CAPAN1, PANC1, SW1990	SNHG12	Sponging miRNAs and contributing cancer proliferation and invasion	miR-320b	120
Diffuse large B-cell lymphoma	A20, OCI-Ly7, DB, U2932, and FARAGE cell lines	SNHG14	Sponging miRNAs and upregulating ZEB1	miR-5590-3p	150
Diffuse large B-cell lymphoma	OCI-Ly7, OCI-Ly3	SNHG14	Sponging miRNAs and promoting oncogenesis and immune evasion	miR-152-3p	164
Neuroblastoma	SH-SY5Y and IMR-32 cell lines	SNHG4	Sponging miRNAs and promoting cancer proliferation, migration, and invasion	miR-377-3p	50
Neuroblastoma	(SKNBE-2, SK-N-SH, NHOK	SNHG16	Sponging miRNAs and regulating HNF4α axis via RAS/RAF/MEK/ERK pathway	miR-542-3p	46
Pituitary tumor	GH1 and RC-4B/C	SNHG1	Sponging miRNAs and activating the TGFBR2/SMAD3 pathway and RAB11A/Wnt/β-catenin signaling	miR-302, miR-372, miR-373, miR-520	44
Glioma	U87, U251, LN229, T98G, HEK293T	SNHG6	Sponging miRNAs and promoting tumorigenesis	miR-101-3p	48
Glioma	U87, U251, U343, HEB	SNHG11	Sponging miRNAs and promoting cell proliferation, invasion and migration	miR-154-5p	47
Glioma	M059J, M059K, U87	SNHG18	Disruption of α-enolase nucleocytoplasmic transport	—	49
Nasopharyngeal carcinoma	HEK293T, N69, CNE, HNE-1	SNHG1	Sponging miRNAs and downregulation of NUAK1	miR-145a-5p	51

(Continues)

TABLE 2 (Continued)

Cancer type	Cell line/animal model	SNHGs	Molecular mechanism of action and regulated signaling pathways	Targeted miRNAs	Refs.
Nasopharyngeal carcinoma	SUNE1, CNE1, CNE2 68, HNE-1	SNHG12	Modulating notch signaling pathway	—	52
Laryngeal squamous cell carcinoma	HEp-2	SNHG1	Promoting proliferation and metastasis	—	55
Breast cancer	MCF-7, MCF-10a, MDA-MB-231, ZR-75-30, MDA-MB-453	SNHG1	Sponging miRNAs and promoting proliferation and invasion	miR-382	64
Breast cancer	MCF-7, MDA-MB-231	SNHG3	Sponging miRNAs and regulating ZEB1	miR-186-5p	165
Breast cancer	MCF-7, SK-BR-3, MDA-MB-231, BT-549	SNHG6	Sponging miRNAs and regulating LAMC1	miR-543	166
Breast cancer	MCF7, SK-BR-3, MDA-MB-231	SNHG6	Promoting cell cycle progression	—	65
Breast cancer	MCF-7, MDA-MB-157, MDA-MB-231, MDA-MB-435	SNHG7	Sponging miRNAs and regulating Notch-1 pathway	miR-34a	66
Breast cancer	MCF-7, MDAMB-231, MCF-10a, BT-20, ZR-75-1	SNHG15	Sponging miRNAs and promoting proliferation, migration, and invasion	miR-211-3p	67
Non-small cell lung cancer	CMT-167, LLC, CMT-170, and CMT-181	SNHG3	Activating TGF-β pathway and IL-6/JAK2/STAT3 signaling	—	76
Lung cancer	SK-MES-1, NCI-H520, NCI-H1437, NCI-H1975, NCI-H2170	SNHG4	Sponging miRNAs and promoting the proliferation, migration, and invasiveness	miR-98-5p	77
Lung adenocarcinoma	H460, H1299, NCl-H358, NCl-H1650, A549, HCC827	SNHG6	Sponging miRNAs and regulating E2F7 expression	miR-26a-5p	78
Non-small cell lung cancer	A549, H1299	SNHG7	Sponging miRNAs and regulating TGIF2 axis	miR-449a	79
Non-small cell lung cancer	A549, HCC827, PC-9, NCI-H23, NCI-H1975	SNHG11	Sponging miRNAs and targeting BSG axis	miR-485-5p	80
Lung cancer	A549, H1299, H460, SPCA1	SNHG11	Activation of Wnt/β-catenin signaling pathway	—	81
Non-small cell lung cancer	A549, H1299	SNHG12	Sponging miRNAs and regulating Slug/ZEB2 signaling pathway	miR-218	82
Non-small cell lung cancer	A549	SNHG15	Promoting cell proliferation and invasion	—	83
Gastric cancer	GES-1, N87, SGC7901, MKN-28	SNHG1	Sponging miRNAs and regulation of the DCLK1/Notch1 axis	miR-15b	86
Gastric cancer	SGC-7901, HGC-27, MKN-1, MKN-28	SNHG1	Sponging miRNAs and regulation of the ADAM10 axis	miR-140	87
Gastric cancer	SNU719, AGS, HGC-27	SNHG4	Sponging miRNAs and promotes cell proliferation, migration, and invasion	miR-204-5p	167
Gastric cancer	BGC-823, SGC-7901, MGC-803, AGS	SNHG6	Sponging miRNAs and silencing p27	miR-101-3p	88

TABLE 2 (Continued)

Cancer type	Cell line/animal model	SNHGs	Molecular mechanism of action and regulated signaling pathways	Targeted miRNAs	Refs.
Gastric cancer	MKN-45, SGC7901, N87	SNHG7	Sponging miRNAs and regulating Snail-EMT axis	miR-34a	89
Gastric cancer	MKN-45, SGC7901	SNHG11	Sponging miRNAs and activating Wnt/β-catenin pathway and oncogenic autophagy	miR-483-3p/miR-1,276	168
Gastric cancer	GES-, BGC-823, SGC-7901, HGC-27	SNHG14	Sponging miRNAs and targeting SOX9 axis	miR-145	90
Gastric cancer	HGC-27, AGS	SNHG16	Downregulation of DKK3	—	91
Gastric cancer	BGC823, SGC-7901, MKN45	SNHG20	Regulating the GSK-3β/β-catenin signaling and inhibiting p21 expression	—	92
Esophageal squamous cell cancer	Eca109 and TE-1	SNHG1	Regulating notch signaling	—	93
Esophageal squamous cell carcinoma	KYSE150, KYSE410, KYSE450, EC109, EC9706	SNHG12	Regulation of BMI1 and CTNNB1	—	95
Esophagus cancer cell	eca109, EC9706, TE1, Kyse-30, Kyse-70	SNHG16	Sponging miRNAs and regulating ZEB1	miR-140-5p	169
Esophageal squamous cell carcinoma	(KYSE450, KYSE150, EC9706, and EC109	SNHG20	Modulating ATM-JAK-PD-L1 pathway	—	94
Colorectal cancer	Lovo, HCT116, SW480, CaCO-2, and HT29	SNHG1	Sponging miRNAs	miR-497, miR-195-5p	170
Colorectal cancer	SW480, SW620, HCT8, and HT-29	SNHG6	Sponging miRNAs and regulating EZH2 axis	miR-26a	171
Colorectal cancer	LoVo, RKO, HT29, HCT116, CaCO2, SW480, SW620	SNHG6	Targeting UPF1 and regulation of ZEB1	—	97
Colorectal cancer	SW480, SW620, LOVO, and HCT-116	SNHG7	Sponging miRNAs and upregulating GALNT1	miR-216b	98
Colorectal cancer	LoVo, RKO, SW480, HT-29	SNHG14	Sponging miRNAs and regulating SKIL axis	miR-32-5p	100
Colorectal cancer	HT-29, HCT-116, Caco-2, SW480, and SW62	SNHG14	Sponging miRNAs	miR-92b-3p	101
Colorectal cancer	LoVo, SW620, SW480, HCT116 and HT-29	SNHG14	Targeting EZH2-regulated EPHA7	—	102
Colon cancer	HEK-293 T, SW1116, HCT116, SW480, SW620	SNHG15	Interacting with Slug	—	96
Hepatocellular carcinoma	Huh-7 and HCCLM3	SNHG1	Sponging miRNAs and regulating E-cadherin, N-cadherin, and Vimentin	miR-377-3p	107
Hepatocellular carcinoma	MHCC97L, Hep3B, HepG2, Huh7, SMMC-7721, PLC/PRF/5, HCCLM3	SNHG3	Sponging miRNAs and modulating the CD151 pathway	miR-128	108
Hepatocellular carcinoma	MHCC-97 L, MHCC-97H, HepG2, Hep3B, SMCC-7721, Huh7	SNHG5	Sponging miRNAs and regulating GSK3β signal pathway	miR-26a-5p	109

(Continues)

TABLE 2 (Continued)

Cancer type	Cell line/animal model	SNHGs	Molecular mechanism of action and regulated signaling pathways	Targeted miRNAs	Refs.
Hepatocellular carcinoma	Huh7, Hep3B, HepG2, QGY-7701, MHCC97L, HCCLM9	SNHG6	Sponging miRNAs and regulating ZEB1 expression by interacting with UPF1	miR-101-3p	110
Hepatic carcinoma	HepG2, HCC-LM3	SNHG7	Sponging miRNAs and regulating Wnt/β-catenin signaling pathway	miR-425	112
Hepatocellular carcinoma	SK-hep1, HepG2, LO2, Huh6, Huh7, PLC5	SNHG8	Sponging miRNAs and promoting tumorigenesis and metastasis	miR-149-5p	113
Hepatocellular carcinoma	Hep3B, SNU-182, SNU-387, Huh-7, SK-Hep1	SNHG10	Modulating SCARNA13	—	114
Hepatocellular carcinoma	HepG2, Hep3B, Huh-7, SMMC7721	SNHG12	Sponging miRNAs and targeting HEG1	miR-516a-5p	172
Hepatocellular carcinoma	MHCC97H, HuH7, SMMC7721, Hep3B, HepG2	SNHG16	Sponging miRNAs and regulating CDC25B and HMGA2 expression	Let-7b-5p	115
Hepatocellular carcinoma	HCCLM3, MHCC97L, MHCC-97H	SNHG16	Sponging miRNAs and regulating TRAF6/NF-κB	miR-605-3p	116
Hepatocellular carcinoma	SMMC-7721, L02, MHCC-97H, HepG2	SNHG16	Sponging miRNAs and targeting STAT3	miR-4,500	117
Hepatocellular carcinoma	Huh-7, HepG2, SMCC7721, LO2, SK-hep1	SNHG17	Sponging miRNAs and upregulating RFX1	miR-3,180-3p	173
Hepatocellular carcinoma	MHCC97L, SMCC7721, MHCC97H and Huh-7	SNHG20	Promoting cell invasion	—	118
Renal cell carcinoma	A-498, ACHN, 786-O, Caki-1	SNHG1	Sponging miRNAs and promotes cancer progression and metastasis	miR-137	124
Renal cell carcinoma	ACHN, 786-O, A498, SN12-PM6	SNHG5	Sponging miRNAs and targeting ZEB1	miR-205-5p	121
Renal cell carcinoma	ACHN, OSRC-2, 786-O, 769-P, CAKI-1	SNHG15	Regulating the NF-κB signaling pathway	—	122
Bladder cancer	5,637, T24	SNHG3	Sponging miRNAs and regulating GINS2 axis	miR-515-5p	128
Bladder cancer	T24, J82 and SW780	SNHG7	Regulating proliferation and invasion	—	126
Bladder cancer	UM-UC-3,SW 780	SNHG16	Regulating invasion and migration	—	127
Prostate cancer	DU145, PC-3, 22RV1, LNCaP, and C4-2	SNHG1	Form a complex with hnRNPL and coregulating CDH1		174
Prostate cancer	RWPE-1, PC3, DU145, 22RV1 and LNCaP	SNHG3	Sponging miRNAs and upregulating SMURF1 expression	miR-577	132
Prostate cancer	RWPE, LNCaP, PC-3 and Du-145	SNHG7	Sponging miRNAs and regulating WNT2B axis	miR-324-3p	135
Prostate cancer	RWPE, LNCaP, DU145, PC3	SNHG15	Sponging miRNAs and regulating FKBP1A axis	miR-338-3p	134
Prostate cancer	RWPE-1, DU145, LNCaP, VCaP, PC-3	SNHG17	Regulating SNORA71B	—	133

TABLE 2 (Continued)

Cancer type	Cell line/animal model	SNHGs	Molecular mechanism of action and regulated signaling pathways	Targeted miRNAs	Refs.
Cervical cancer	Cancer cell lines	SNHG5	Sponging miRNAs and regulating SOX4 pathway	miR-132	175
Cervical cancer	HeLa, C-33A	SNHG7	Promoting cell proliferation, invasion, and prognosis	—	136
Cervical cancer	CaSki and SiHa	SNHG12	Regulating ERK/Slug pathway	—	137
Cervical cancer	Endl/E6E7	SNHG16	Sponging miRNAs and modulating WNT/β-catenin pathway	miR-128	176
Cervical cancer	HeLa, CaSki, SiHa, C33A	SNHG16	Sponging miRNAs and regulating ZEB1 signal pathway	miR-216-5p	139
Ovarian cancer	A2780, OCC1, H8710, SK-OV3	SNHG1	Sponging miRNAs and increasing ZEB1expression and activating Akt signaling	miR-454	177
Ovarian carcinoma	IOSE25, CAOV-3, SKOV-3, ES2 A2780	SNHG1	Regulating matrix metalloproteinases	—	141
Ovarian carcinoma	SKOV3, 62 ES2, CaOV3, HG-SOC	SNHG8	Activating Wnt/β-catenin pathway	—	142
Ovarian cancer	OVCAR3, SKOV3, A2780, and CAOV-3	SNHG20	Sponging miRNAs and regulating MCL1 expression	miR-338-3p	178

medication is of fundamental importance.[61–63] To reach this goal, some studies have focused on the role of SNHGs and miRNAs as the progressive and suppressor tumor biomolecules. For example, it was demonstrated that the level of SNHG1, 7 and 15 increased in breast cancer patients and cells in good agreement with the cancer invasion, poorer patient survival, cell proliferation, colony formation, and EMT. In other words, it is indicated that the knockdown of these SNHGs is correlated with the less EMT (upregulation of E-cadherin and downregulation of N-cadherin, vimentin, and ZEB1) and breast tumor growth.[64–67]

In fact, SNHG1, 6, 7, and 15 promote breast cancer sponging and thus inhibiting, miR-382-5p, miR-34a, and miR-211-3p, respectively. There is an important point in this regard related to the prominent role of miR-382-5p on SNHG1; in the presence of si-SNHG1 and miR-211-3p inhibitors, cells proliferate, migrate, and invade same as the presence of SNHG1 and miR-211-3p inhibitors abolish the function of si-SNHG1.[64] Meanwhile, the level of SNHGs is parallel to the tumor size, lymph nodes metastasis, and cancer pathological stage.[67] Interestingly, studies showed that knockdown of SNHGs led to apoptosis (cleaved caspase3 and BAX), however, apoptosis may trigger pro-oncogenes in cancers, as well. Therefore, apoptosis may acts as a double-edged knife, from one side it decreases cell proliferation and from the other side, it may provoke pro-oncogenes. Notwithstanding, despite the enhancement of apoptosis in vitro and the possibility of pro-oncogene activation, patient survival enhanced in the case with lower levels of SNHGs.[67] However, the pro-oncogenic role of Notch-1 and Survivin in the SNHG7-miR-34a axis should be under consideration.[66]

2.4 | Lung cancer

Lung cancer is considered the first lethal cancer in the world. The 5-year survival rate of lung cancer is merely around 10–15%.[68,69] As reported by the conventional pathological classification, lung cancer can be mainly divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is an intractable cancer and accounts for about 80% of lung cancers.[70–72]

lncRNAs are significant contributors to the regulatory mechanism of cancers[28,73] and they attended as both therapeutic and prognostic targets for the cancer treatment.[74,75] SNHG3 activated by E2F1 promotes cell proliferation and migration in NSCLC via TGF-β and IL-6/JAK2/STAT3 pathways.[76] SNHG4 acts as a sponge of miR-98-5p, promotes proliferation, migration, invasion, and EMT of lung cancer cells in in vivo studies.[77] SNHG6 may act as an oncogenic lncRNA in lung adenocarcinoma carcinogenesis by regulating the miR-26a-5p/E2F7

axis.[78] SNHG7 regulates cell progression in NSCLC by targeting the miR-449a/TGIF2 axis. On the other hand, the depletion of SNHG7 inhibits tumor growth in vitro and in vivo.[79] Overexpression of SNHG11 in NSCLC increases growth, migration, and EMT and acts as a miR-485-5p sponge to upregulate target to Basigin (BSG).[80] Also, SNHG11 operates via Wnt/β-catenin signaling pathway in which it is activated through SNHG11/miR-4436a/CTNNB1 ceRNA axis.[81] SNHG12 downregulates miR-218 and upregulates Slug/ZEB2 (zinc finger E-box-binding homeobox 2) EMT signaling pathway and thus activates cell migration and invasion.[82] Knocking down of SNHG15 in A549 cells can inhibit cell proliferation, invasion, and metastasis, and promote apoptosis.[83] All and all, in sum, SNHG may serve as a critical biomarker and a potential therapeutic target for the treatment of NSCLC.

2.5 | Gastrointestinal cancers

2.5.1 | Stomach cancers

Gastric cancer (GC), which is known as the fifth common malignant disease and also with the reputation of second leading cancer-related death worldwide, has only about 20% survival rate for 5 years.[84,85] lncRNAs play an important role in regulating gene expression and their dysregulation leads to tumorigenesis and metastasis.

During the progression of GC, miR-15b can be considered to act as a suppressor, however, DCLK1/Notch1 affects the EMT process and cell migration through the modulation of miR-15b, and SNHG1 regulates this micro RNA in GC.[86] In addition, proliferation and invasion of GC cells are promoted by SNHG1 via modulating the miR-140/ADAM10 axis.[87] Furthermore, at a post-transcriptional level, SNHG6 acts as an oncogene through regulating miR-101-3p/ZEB1 and silencing at a transcriptional level by recruiting enhancers of zeste homolog 2 (EZH2) for the promoter of p27.[88] Based on in vitro studies, downregulation of miR-34a is due to the attachment of SNHG7 that leads to enhancement of GC cell migration and invasion through the miR-34a-Snail-EMT axis.[89]

It was also indicated that the GC progression may be promoted through the upregulation of SNHG14 by the targeting of the miR-145/SOX9 axis and involvement of PI3 K/AKT/mTOR pathway.[90] Moreover, SNHG16 promotes EMT transition in GC through the DKK3 down-regulation.[91] SNHG20 activates the EMT process, which results in controlling GC cell invasion and also throughout its epigenetic silencing of the p21 and E-cadherin expression. SNHG20 mediates the oncogenic effects, which occur by binding with EZH2, and regulates the GSK-3β/βcatenin signaling pathway.[92] In an overall view, SNHGs can be a candidate for prognostic biomarkers and a target for new therapies in GC patients.

2.5.2 | Esophageal cancer

Noteworthy, SNHGs have an important role in esophageal cancer as well. For example, SNHG1, 12, 16, and 20 are responsible for cancer progression in part through the Notch, BMI1-CTNNB1, ZEB1, ATM-JAK-PD-L1 signaling pathways, respectively.[78,93–95]

2.5.3 | Colorectal cancer

Colorectal cancer (CRC), which arises from the epithelium mucous or gland of the colorectum, is the third most commonly diagnosed malignancy, and it is also known as the fourth most common cause of cancer-related death. Every year over 1.2 million patients are diagnosed with colon cancer worldwide, and it is known as the fourth most common cause of cancer-related death. SNHG15 promotes cancer cell survival, invasion, and metastasis through interaction with the Slug's C-terminal zinc finger domain.[96]

It is revealed that in CRC, SNHG6, and EZH2 transcripts are upregulated; meanwhile, miR-26a is downregulated in such tissues and cell lines. Furthermore, SNHG6 sponges miR-26a and regulates EZH2 expression, which results in the progress of the migration, invasion, and EMT in CRC cells. Moreover, it may target UPF1 and induces EMT via miR-101-3p, which regulates ZEB1, which results in activating TGF-β/Smad signaling pathway.[97] Also, cell proliferation and metastasis were promoted by overexpressed SNHG7 in vitro and in vivo, suggesting that SNHG7 exhibits oncogenic properties partially through the SNHG7/miR-216b/GALNT1 axis in CRC progression.[98] In patients, SNHG11 plays a protumorigenic role via enhancing cell growth, migration, and invasion.[99]

There are conflicting data about SNHG14: in one study, SNHG14 positively correlated ski-oncogene-like (SKIL) expression, which caused miR-32-5p/SKIL axis to sponge miR-32-5p, resulting in promotion in tumor metastasis in CRC.[100] In another research, forced expression of SNHG14 suppressed miR-92b-3p expression resulting in restriction of cell proliferation and EMT.[101] Furthermore, another study also suggests that SNHG14 recruits FUS and absorbing miR-186-5p, which inhibits EPHA7 by upregulating EZH2.[102] All in all, it can be concluded from the noted studies that SNHGs serve as a

decisive factor for human progressing CRC modulation, diagnosis, and treatment.

2.5.4 | Liver cancer

Hepatocellular carcinoma (HCC) is established as the fifth most pervasive malignancy worldwide.[103,104] The 5-year overall survival rate of patients with HCC is less than 30%.[105,106] SNHG1 was upregulated in HCC tissues and cells and progressed metastasis by sponging miR-377-3p.[107] It is revealed that SNHG3 promotes invasion via regulating the EMT by miR128/CD151/Akt/PI3K feedback loop signaling.[108] Moreover, it is indicated that SNHG5 directly binds to miR-26a-5p and regulates GSK3β expression.[109] SNHG6 activates the TGF-b1/Smad signaling pathway, which leads to EMT. SNHG6 also promotes ZEB1 expression by competitively binding miR-101-3p and increments Smad7 expression by directly binding UPF1. The upregulation of ZEB1 and downregulation of Smad7 induce EMT, ultimately leading to HCC invasion and metastasis.[110]

One of the classical signaling pathways in the regulation process of cell proliferation, differentiation, and tumorigenesis is Wnt/β-catenin, which is a classical signaling pathway.[111] Studies revealed that SNHG7 could promote proliferation and metastasis of HCC in vitro and in vivo through Wnt/β-catenin/EMT pathway as a miR-425 sponge.[112] SNHG8 increased proliferation and metastasis in vivo and in vitro through sponge miR-149 and caused an increment of PPM1F and HCC tumorigenesis.[113] SNHG10 regulates SCARNA13 expression via miR-150-5p/RPL4-c-Myb–positive feedback loop and SCARNA13 applies its oncogenic property by modulating SOX9 in HCC.[114] SNHG16, through its direct action on the let-7b-5p/CDC25B/ CDK1 axis, promotes the G2/M cell cycle transition and induces cell metastasis and EMT progression by regulating the let-7b-5p/HMGA2 axis in HCC.[115] SNHG16 represses HCC metastasis, EMT and NF-κB activation by interacting with miR-605-3p in vitro and in vivo.[116] SNHG16 promotes tumorigenesis and HCC development via sponging miR-4500 and targeting STAT3 expression.[117] In patients, SNHG20 mediates tumorigenesis effects on HCC cells throughout the regulation of E-cadherin expression via interacting with EZH2.[118]

2.5.5 | Pancreatic cancer

Pancreatic adenocarcinoma is to date the second leading cause of cancer-related death being often diagnosed in advanced stages when surgery and chemo/radiotherapies are useless.[119] SNHG12 was reported by Cao et al to be expressed in pancreatic cancer tissues and cell lines triggering the EMT process by enhancing cell growth and invasion via the absorption of miR-320b.[120]

2.6 | Urologic cancers

2.6.1 | Kidney cancer

Renal cell carcinoma (RCC) is one of the most popular malignant urogenital cancers with a high mortality rate per year and 5-year survival of ≤40%.[121–123] Several studies demonstrated that the lncRNA SNHGs function as the important regulators in the development of tumorigenesis.[124,125]

SNHG1 acts as a ceRNA to antagonize the effect of miR-137 and elicit RCC progression and metastasis. The overexpression of SNHG1 also predicts the poor prognosis of RCC. Moreover, reduced SNHG1 expression inhibited the proliferation, invasion, and EMT capacity in RCC through regulating miR-137.[124] SNHG5 also functions as an oncogene in clear cell renal cell carcinoma (ccRCC) by SNHG5/miR-205-5p/ZEB1 signaling axis. Actually, SNHG5 in a miR-205-5p-dependent manner targets ZEB1, a critical modulator of EMT, activates cell proliferation, migration, and invasion in ccRCC, in vitro and in vivo.[121] Meanwhile, SNHG15 silencing inhibited RCC invasion, migration, and EMT through modulating the nuclear factor-κB signaling pathway.[122]

2.6.2 | Bladder cancer

Bladder cancer (BCa) is the most common malignant tumor of the urinary system. Noteworthy, lncRNA SNHGs also function a critical role in the progress and metastasis of bladder cancer.[126–128] It was identified that the SNHG3 overexpression in bladder cancer tissues significantly correlated with poor clinical prognosis. SNHG3 positively enhanced the proliferation, migration, invasion, and EMT process of BCa cells by miR-515-5p/GINS2 axis, in vitro and in vivo. Evidently, SNHG3 sponge miR-515-5p under a ceRNA mechanism, which leads to GINS2 upregulation.[128] SNHG7 expression was also upregulated in bladder cancer tissues and cells. However, SNHG7 knockdown suppresses cell proliferation and invasion while promoting apoptosis; it also resulted in the upregulation of E-cadherin and downregulation of N-cadherin, Vimentin, and Snail.[126] Furthermore, findings indicated the overexpression of SNHG16 in TGF-β-induced BCa cells and BCa tissues. Mechanistically, SNHG16 induced EMT through miR-200a-3p/ ZEB1/ ZEB2 axis.[127]

2.7 | Prostate cancer

Prostate cancer is the second lethal cancer in men.[129] However, there are some strategies to cure or inhibit its progression such as surgery, cryotherapy, radiotherapy, chemotherapy, and high-intensity focused ultrasound therapy.[130,131] The same as other cancer, some SNHGs are overexpressed in prostate cancer and modulate the invasion of cancer such as SNHG3, 7, 15, and 17.[132,133] These SNHGs have some binding sites for miRNAs and both of them negatively influence their overexpression.

It is demonstrated that SNHG3, 7, and 15 sponge miR-577, miR-324-3p, and miR-338-3p, respectively.[132,134,135] Li et al. disclosed that SNHG3 through binding to miR-577 decline EMT and cell proliferation and enhance apoptosis in prostate cancer cells. In other words, SNHG3 negatively and positively affects the overexpression of miR-577 and SMURF-1 and vice versa the overexpression of SMURF-1 reverses the knock-downed SNHG3 function.[132] Moreover, others demonstrated that SNHG7 through the sponging of miR-324-3p positively regulates WNT2B and thereby modulates EMT, migration, and invasion of prostate cancer cells.[135] Zhang et al. revealed that SNHG15 can act as a competing endogenous RNA for the regulation of miR-338-3p and FKBP prolyl isomerase 1A (FKBP1A) to exert its invasive and oncogenic behaviors.[134] However, signal transducer and activator of transcription 5A (STAT5A) activates SNHG17 leading to SNORA71B transactivation via a positive feedback loop to exert its invasive potential.[133]

2.8 | Gynecologic cancers

2.8.1 | Cervical cancer

Cervical cancer (CC) is one of the most common gynecological malignancies worldwide.[136–140] LncRNA SNHGs function as tumor promoters in many cancers. For example, SNHG7 is significantly upregulated in cervical cancer tissues and promoted cell proliferation and invasion. However, SNHG7 knockdown led to the upregulation of E-cadherin, and downregulation of N-cadherin and Vimentin.[136] SNHG12 overexpression has been also reported in cervical squamous cell carcinoma (CSCC). SNHG12 upregulation may be caused by human papillomavirus (HPV) type 16 E6 and E7 oncogene via regulating the transcription factor of c-Myc. Moreover, SNHG12 induced EMT partly via ERK/Slug/E-cadherin pathway.[137]

The overexpression of SNHG16 was also identified in CC tissues and cell lines. Meanwhile, SNHG16 silencing suppressed proliferation and EMT through modulating apoptosis and cell cycle. SNHG16/miR-128 axis regulates the malignant phenotype of CC cells mediated by Wnt/β-catenin pathway.[138] SNHG16 was also overexpressed in cervical cancer tissues and cell lines. SNHG16 acts as an oncogene by sponging miR-216-5p. Data reported that SNHG16 promoted the tumorigenesis and progression in CC through the miR-216A-5p/ZEB1 axis and provides a potential therapeutic option against CC.[139]

2.8.2 | Ovarian cancer

Ovarian cancer is the third most common gynecologic malignant tumor.[141–143] lncRNA SNHGs have been confirmed as critical regulators in tumorigenesis. For instance, the upregulation of SNHG1 was detected in ovarian carcinoma tissues and cells. However, SNHG1 silencing suppresses the SKOV-3 cells proliferation, invasion, and metastasis underlying the mechanism of inhibiting the EMT and reducing the MMPs expressions.[141] SNHG8 also promotes cell proliferation, migration, EMT process, and stemness of ovarian carcinoma through activation of Wnt/β-catenin pathway. SNHG8 positively regulates CAPRIN1 through binding to it. In addition, CTNNB1 and Axin1 showed a binding affinity to CAPRIN1. Therefore, CTNNB1 (or Axin1) expression or Wnt/β-catenin pathway induction resulted in the upregulation of SNHG8.[142]

2.9 | Osteosarcoma

Osteosarcoma is a relatively rare malignant bone tumor, associated with young ages, which commonly occurs in the long bones of legs and arms.[144] SNHG1 was found upregulated in this kind of tumor and its expression is closely correlated with tumor size, TNM stage, and lymph node metastasis, promoting cell proliferation, migration, and the EMT process through miR-577, which acts as a ceRNA of SNHG1. Indeed, miR-577 targeted WNT2B, which in turn activates Wnt/β-catenin pathway.[145] EMT program might be also triggered through the SNHG1-mediated suppression of miR-101-3p, which physiologically regulates the expression of Rho-associated coiled-coil-containing protein kinase 1 (ROCK1).[146] SNHG7 acts as an oncogene in osteosarcomas promoting cancer cell proliferation and inhibiting apoptosis by decoying miR-34a in MG63 and SaOS2 cell lines.[147] Knockdown of SNHG7 leads to block TGF-β-induced EMT, inducing apoptosis and G1/S arrest as well. SNHG20 is another lncRNA reported to be overexpressed in osteosarcomas activating EMT via the modulation of Vimentin, ZEB1, ZEB2, and E-Cadherin.[148]

2.10 | Diffuse large B-cell lymphoma

Diffuse large B cell lymphoma is a lymphoid neoplasia and the most common form of non-Hodgkin lymphoma among adults.[149] SNHG14 was observed by Zhao L. et al to be upregulated in diffuse large B cell lymphoma cell lines and samples.[150] Its inhibition caused a slowdown in cell proliferation and blocked migration and EMT. Indeed, it acts by sponging and thus inactivating miR-5590-3p, which is responsible for the upregulation of ZEB1.

3 | CONCLUSION

Overexpressed SNHGs sponging miRNAs or binding proteins modulate EMT in cancer. Here, we aimed to highlight how SNHGs exert pleiotropic effects, acting on several cancer-related axes, and often stimulating the EMT phenomenon. Such induction is associated with an obvious increase in the malignancy properties leading to cancer progression and metastasis. However, several molecular mechanisms are still not completely clear and require focusing the attention of current scientific research. Being capable to induce such a cascade of events, SNHGs are the perfect targets for new anticancer therapies based on both antagonist peptides and interfering RNA. Knockdown of SNHGs increasing the level of sponged miRNAs effectively inhibit EMT process and mediate suppressing cancer cell proliferation, migration, and invasion. However, we still need to face many challenges applying such techniques in clinical practice, as the high risk of off-target effects makes such treatments very hazardous and as we currently lack a reliable delivery system, which might not induce a generalized immune response (i.e., viral vectors and exogenous conjugated proteins).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Diamantopoulos MA, Tsiakanikas P, Scorilas A. Non-coding RNAs: The riddle of the transcriptome and their perspectives in cancer. Ann Transl Med. 2018;6(12):1–17.
2. Fernandes JC et al. Long non-coding RNAs in the regulation of gene expression: Physiology and disease. Non-coding RNA. 2019;5(1):17.
3. Gao N et al. Long non-coding RNAs: The regulatory mechanisms, research strategies, and future directions in cancers. Front Oncol. 2020;10:1–13.
4. Statello L et al. Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol. 2021;22(2):96–118.
5. Di Gesualdo F, Capaccioli S, Lulli M. A pathophysiological view of the long non-coding RNA world. Oncotarget. 2014;5(22):10976.
6. Ma Y-S et al. Targeting long non-coding RNA to therapeutically regulate gene expression in cancer. Mol Therapy-Nucl Acids. 2020;21:712–724.
7. Zhou M et al. The patterns of antisense long non-coding RNAs regulating corresponding sense genes in human cancers. J Cancer. 2021;12(5):1499–1506.
8. Xu Y et al. The emerging regulatory roles of long non-coding RNAs implicated in cancer metabolism. Mol Ther. 2021. https://doi.org/10.1016/j.ymthe.2021.03.017. In Press.
9. Ming H et al. Long non-coding RNAs and cancer metastasis: Molecular basis and therapeutic implications. Biochim Biophys Acta (BBA)-Rev Cancer. 2021;1875(2):188519.
10. Sleutels F, Zwart R, Barlow DP. The non-coding air RNA is required for silencing autosomal imprinted genes. Nature. 2002;415(6873):810–813.
11. Matouk IJ et al. The H19 non-coding RNA is essential for human tumor growth. PLoS One. 2007;2(9):e845.
12. Ashrafizadeh M et al. Role of microRNA/epithelial-to-Mesenchymal transition Axis in the metastasis of bladder cancer. Biomolecules. 2020;10(8):1159.
13. Ashrafizadeh M et al. Wnt-regulating microRNAs role in gastric cancer malignancy. Life Sci. 2020;250:117547.
14. Zhou X et al. Helicobacter pylori infection related long non-coding RNA (lncRNA) AF147447 inhibits gastric cancer proliferation and invasion by targeting MUC2 and up-regulating miR-34c. Oncotarget. 2016;7(50):82770.
15. Hashimoto K et al. A liver X receptor (LXR)-β alternative splicing variant (LXRBSV) acts as an RNA co-activator of LXR-β. Biochem Biophys Res Commun. 2009;390(4):1260–1265.
16. Chen L et al. Long non-coding RNA CCAT1 promotes multiple myeloma progression by acting as a molecular sponge of miR-181a-5p to modulate HOXA1 expression. Cell Cycle. 2018;17(3):319–329.

17. Salzman J et al. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. PLoS One. 2012;7(2):e30733.
18. Mongelli A et al. The dark that matters: Long non-coding RNAs as master regulators of cellular metabolism in non-communicable diseases. Front Physiol. 2019;10:369.
19. Williams GT, Farzaneh F. Are snoRNAs and snoRNA host genes new players in cancer? Nat Rev Cancer. 2012;12(2): 84–88.
20. Huang L et al. Small nucleolar RNA host gene 1: A new biomarker and therapeutic target for cancers. Pathol-Res Pract. 2018;214(9):1247–1252.
21. Qin Y et al. Long non-coding small nucleolar RNA host genes (SNHGs) in endocrine-related cancers. Onco Targets Ther. 2020;13:7699.
22. Yang H et al. Long non-coding small nucleolar RNA host genes in digestive cancers. Cancer Med. 2019;8(18):7693–7704.
23. Xu T et al. Gene amplification-driven long noncoding RNA SNHG17 regulates cell proliferation and migration in human non-small-cell lung cancer. Mol Ther-Nucl Acids. 2019;17: 405–413.
24. Askarian-Amiri ME et al. SNORD-host RNA Zfas1 is a regulator of mammary development and a potential marker for breast cancer. RNA. 2011;17(5):878–891.
25. Yu F et al. p53 represses the oncogenic Sno-MiR-28 derived from a SnoRNA. PLoS One. 2015;10(6):e0129190.
26. Zimta A-A et al. An emerging class of long non-coding RNA with oncogenic role arises from the snoRNA host genes. Front Oncol. 2020;10:389.
27. Ashrafizadeh M et al. MicroRNAs and their influence on the ZEB family: Mechanistic aspects and therapeutic applications in cancer therapy. Biomolecules. 2020;10(7):1040.
28. Cheng J-T et al. Insights into biological role of LncRNAs in epithelial-mesenchymal transition. Cell. 2019;8(10):1178.
29. Ashrafizadeh M et al. Association of the Epithelial–Mesenchymal Transition (EMT) with Cisplatin resistance. Int J Mol Sci. 2020;21(11):4002.
30. Lu W, Kang Y. Epithelial-mesenchymal plasticity in cancer progression and metastasis. Dev Cell. 2019;49(3):361–374.
31. Yang MH et al. Brassinin represses invasive potential of lung carcinoma cells through deactivation of PI3K/Akt/mTOR signaling cascade. Molecules. 2019;24(8):1584.
32. Shibue T, Weinberg RA. EMT, CSCs, and drug resistance: The mechanistic link and clinical implications. Nat Rev Clin Oncol. 2017;14(10):611–629.
33. Loh C-Y et al. The E-cadherin and N-cadherin switch in epithelial-to-mesenchymal transition: Signaling, therapeutic implications, and challenges. Cell. 2019;8(10):1118.
34. Ko J-H et al. Bergamottin suppresses metastasis of lung cancer cells through abrogation of diverse oncogenic signaling cascades and epithelial-to-mesenchymal transition. Molecules. 2018;23(7):1601.
35. Pal M et al. Cadherin profiling for therapeutic interventions in epithelial Mesenchymal transition (EMT) and tumorigenesis. Exp Cell Res. 2018;368(2):137–146.
36. Mohammadinejad R et al. ZEB1 and ZEB2 gene editing mediated by CRISPR/Cas9 in A549 cell line. Bratislavske Lekarske Listy. 2020;121(1):31–36.
37. Lee JH et al. Farnesol abrogates epithelial to mesenchymal transition process through regulating Akt/mTOR pathway. Pharmacol Res. 2019;150:104504.
38. Aiello NM, Kang Y. Context-dependent EMT programs in cancer metastasis. J Exp Med. 2019;216(5):1016–1026.
39. Mohammadinejad R et al. EMT signaling: Potential contribution of CRISPR/Cas gene editing. Cell Mol Life Sci. 2020;77 (14):2701–2722.
40. Lee JH et al. Brusatol suppresses STAT3-driven metastasis by downregulating epithelial-mesenchymal transition in hepatocellular carcinoma. J Adv Res. 2020;26:83–94.
41. Hwang ST et al. Corilagin represses epithelial to mesenchymal transition process through modulating Wnt/β-catenin signaling cascade. Biomolecules. 2020;10(10):1406.
42. Shakeri S et al. Multifunctional polymeric nanoplatforms for brain diseases diagnosis, therapy and theranostics. Biomedicine. 2020;8(1):13.
43. Afshar EG et al. Graphene as a promising multifunctional nanoplatform for glioblastoma theranostic applications. FlatChem. 2020;22:100173.
44. Wang H et al. Lnc-SNHG1 activates the TGFBR2/SMAD3 and RAB11A/Wnt/β-catenin pathway by sponging MiR-302/372/373/520 in invasive pituitary tumors. Cell Physiol Biochem. 2018;48(3):1291–1303.
45. Yang B et al. Long non-coding RNA SNHG16 contributes to glioma malignancy by competitively binding miR-20a-5p with E2F1. J Biol Regul Homeost Agents. 2018;32(2):251–261.
46. Deng D, Yang S, Wang X. Long non-coding RNA SNHG16 regulates cell behaviors through miR-542-3p/HNF4α axis via RAS/RAF/MEK/ERK signaling pathway in pediatric neuroblastoma cells. Biosci Rep. 2020;40(5):1–13.
47. GENG Y et al. Long non-coding RNA SNHG11 promotes cell proliferation, invasion and migration in glioma by targeting miR-154-5p. Eur Rev Med Pharmacol Sci. 2020;24:4901–4908.
48. Meng Q et al. Long non-coding RNA SNHG6 promotes glioma tumorigenesis by sponging miR-101-3p. Int J Biol Markers. 2018;33(2):148–155.
49. Zheng R et al. Long noncoding RNA SNHG18 promotes glioma cell motility via disruption of α-Enolase nucleocytoplasmic transport. Front Genet. 2019;10:1140.
50. Yang H et al. LncRNA SNHG4 promotes neuroblastoma proliferation, migration, and invasion by sponging miR-377-3p. Neoplasma. 2020;67(5):1054–1062.
51. Lan X, Liu X. LncRNA SNHG1 functions as a ceRNA to antagonize the effect of miR-145a-5p on the down-regulation of NUAK1 in nasopharyngeal carcinoma cell. J Cell Mol Med. 2019;23(4):2351–2361.
52. Liu Z-B et al. Increased expression of lncRNA SNHG12 predicts a poor prognosis of nasopharyngeal carcinoma and regulates cell proliferation and metastasis by modulating notch signal pathway. Cancer Biomark. 2018;23(4):603–613.
53. Li F et al. Garcinol, a polyisoprenylated benzophenone modulates multiple proinflammatory signaling cascades leading to the suppression of growth and survival of head and neck carcinoma. Cancer Prev Res. 2013;6(8):843–854.
54. Xu W et al. lncRNA SNHG7 promotes tumorigenesis of nasopharyngeal carcinoma via epithelialtomesenchymal transition. Oncol Lett. 2020;19(4):2721–2726.

55. Lin S et al. Up-regulation of long non-coding RNA SNHG1 contributes to proliferation and metastasis in laryngeal squamous cell carcinoma. Eur Rev Med Pharmacol Sci. 2018;22(5): 1333–1341.
56. Leemans CR, Braakhuis BJ, Brakenhoff RH. The molecular biology of head and neck cancer. Nat Rev Cancer. 2011;11(1): 9–22.
57. Yin Y et al. SNHG12/miR-326/E2F1 feedback loop facilitates the progression of oral squamous cell carcinoma. Oral Dis. 2020;26(8):1631–1639.
58. Li S, Zhang S, Chen J. C-Myc induced upregulation of long non-coding RNA SNHG16 enhances progression and carcinogenesis in oral squamous cell carcinoma. Cancer Gene Ther. 2019;26(11):400–410.
59. Ashrafizadeh M et al. New insight into triple-negative breast cancer therapy: The potential roles of endoplasmic reticulum stress and autophagy mechanisms. Anti-cancer Agents Med Chem. 2021;21(6):679–691.
60. Ashrafizadeh M et al. Therapeutic and biological activities of berberine: The involvement of Nrf2 signaling pathway. J Cell Biochem. 2020;121(2):1575–1585.
61. Jia LY et al. Potential role of targeted therapies in the treatment of triple-negative breast cancer. Anticancer Drugs. 2016; 27(3):147–155.
62. Shanmugam MK et al. Thymoquinone inhibits bone metastasis of breast cancer cells through abrogation of the CXCR4 signaling axis. Front Pharmacol. 2018;9:1294.
63. Wang C et al. Triple negative breast cancer in Asia: An insider's view. Cancer Treat Rev. 2018;62:29–38.
64. Zheng S et al. SNHG1 contributes to proliferation and invasion by regulating miR-382 in breast cancer. Cancer Manag Res. 2019;11:5589.
65. Jafari-Oliayi A, Asadi MH. SNHG6 is upregulated in primary breast cancers and promotes cell cycle progression in breast cancer-derived cell lines. Cell Oncol. 2019;42(2):211–221.
66. Sun X et al. LncRNA SNHG7 contributes to tumorigenesis and progression in breast cancer by interacting with miR-34a through EMT initiation and the Notch-1 pathway. Eur J Pharmacol. 2019;856:172407.
67. Kong Q, Qiu M. Long noncoding RNA SNHG15 promotes human breast cancer proliferation, migration and invasion by sponging miR-211-3p. Biochem Biophys Res Commun. 2018; 495(2):1594–1600.
68. Wang L et al. Pan-HDAC inhibition by panobinostat mediates chemosensitization to carboplatin in non-small cell lung cancer via attenuation of EGFR signaling. Cancer Lett. 2018;417: 152–160.
69. Ong P-S et al. A novel combinatorial strategy using Seliciclib® and Belinostat® for eradication of non-small cell lung cancer via apoptosis induction and BID activation. Cancer Lett. 2016; 381(1):49–57.
70. Zappa C, Mousa SA. Non-small cell lung cancer: Current treatment and future advances. Transl Lung Cancer Res. 2016;5(3):288–300.
71. Jung YY et al. Oxymatrine attenuates tumor growth and deactivates STAT5 signaling in a lung cancer xenograft model. Cancer. 2019;11(1):49.
72. Lee JH et al. Ophiopogonin D, a steroidal glycoside abrogates STAT3 signaling cascade and exhibits anti-cancer activity by causing GSH/GSSG imbalance in lung carcinoma. Cancer. 2018;10(11):427.
73. Ma Z et al. The expanding roles of long non-coding RNAs in the regulation of cancer stem cells. Int J Biochem Cell Biol. 2019;108:17–20.
74. Pandya G et al. The implication of long non-coding RNAs in the diagnosis, pathogenesis and drug resistance of pancreatic ductal adenocarcinoma and their possible therapeutic potential. Biochim Biophys Acta (BBA)-Rev Cancer. 2020;1874(2): 188423.
75. Mishra S et al. Long non-coding RNAs are emerging targets of phytochemicals for cancer and other chronic diseases. Cell Mol Life Sci. 2019;76(10):1947–1966.
76. Shi J et al. LncRNA SNHG3 is activated by E2F1 and promotes proliferation and migration of non-small-cell lung cancer cells through activating TGF-β pathway and IL-6/JAK2/STAT3 pathway. J Cell Physiol. 2020;235(3):2891–2900.
77. Tang Y et al. LncRNA SNHG4 promotes the proliferation, migration, invasiveness, and epithelial–mesenchymal transition of lung cancer cells by regulating miR-98-5p. Biochem Cell Biol. 2019;97(6):767–776.
78. Liang R et al. SNHG6 functions as a competing endogenous RNA to regulate E2F7 expression by sponging miR-26a-5p in lung adenocarcinoma. Biomed Pharmacother. 2018;107:1434–1446.
79. Pang L et al. Long noncoding RNA SNHG7 contributes to cell proliferation, migration, invasion and epithelial to mesenchymal transition in non-small cell lung cancer by regulating miR-449a/TGIF2 axis. Thorac Cancer. 2020;11(2):264–276.
80. Cheng R et al. SNHG11 contributes to NSCLC cell growth and migration by targeting miR-485-5p/BSG axis. Biomed Pharmacother. 2020;128:110324.
81. Liu S et al. lncRNA SNHG11 promotes lung cancer cell proliferation and migration via activation of Wnt/β-catenin signaling pathway. J Cell Physiol. 2020;235(10):7541–7553.
82. Wang Y et al. Knockdown of SNHG12 suppresses tumor metastasis and epithelial mesenchymal transition via the Slug/ZEB2 signaling pathway by targeting miR218 in NSCLC. Oncol Lett. 2019;17(2):2356–2364.
83. Dong Y, Meng X, Li G. Long non-coding RNA SNHG15 indicates poor prognosis of non-small cell lung cancer and promotes cell proliferation and invasion. Eur Rev Med Pharmacol Sci. 2018;22(9):2671–2679.
84. Manu KA et al. Isorhamnetin augments the anti-tumor effect of capeciatbine through the negative regulation of NF-κB signaling cascade in gastric cancer. Cancer Lett. 2015;363(1): 28–36.
85. Manu KA et al. Simvastatin sensitizes human gastric cancer xenograft in nude mice to capecitabine by suppressing nuclear factor-kappa B-regulated gene products. J Mol Med. 2014;92 (3):267–276.
86. Phillips NS et al. Neuroanatomical abnormalities related to dexamethasone exposure in survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2020;67(3): e27968.
87. Guo W et al. LncRNA SNHG1 promoted HGC-27 cell growth and migration via the miR-140/ADAM10 axis. Int J Biol Macromol. 2019;122:817–823.

88. Yan K et al. LncRNA SNHG6 is associated with poor prognosis of gastric cancer and promotes cell proliferation and EMT through epigenetically silencing p27 and sponging miR-101-3p. Cell Physiol Biochem. 2017;42(3):999–1012.
89. Zhang Y et al. SNHG7 accelerates cell migration and invasion through regulating miR-34a-Snail-EMT axis in gastric cancer. Cell Cycle. 2020;19(1):142–152.
90. Liu Z et al. Long non-coding RNA SNHG14 contributes to gastric cancer development through targeting miR-145/SOX9 axis. J Cell Biochem. 2018;119(8):6905–6913.
91. Zhou C et al. LncRNA SNHG16 promotes epithelial-mesenchymal transition via down-regulation of DKK3 in gastric cancer. Cancer Biomark. 2019;26(4):393–401.
92. Liu J et al. Long noncoding RNA SNHG20 promotes gastric cancer progression by inhibiting p21 expression and regulating the GSK-3β/β-catenin signaling pathway. Oncotarget. 2017;8(46):80700.
93. Zhang Y et al. Downregulation of SNHG1 suppresses cell proliferation and invasion by regulating notch signaling pathway in esophageal squamous cell cancer. Cancer Biomark. 2018;21 (1):89–96.
94. Zhang C et al. Upregulation of long noncoding RNA SNHG20 promotes cell growth and metastasis in esophageal squamous cell carcinoma via modulating ATM-JAK-PD-L1 pathway. J Cell Biochem. 2019;120(7):11642–11650.
95. Wu D et al. Long noncoding RNA SNHG12 induces proliferation, migration, epithelial-mesenchymal transition and stemness of esophageal squamous cell carcinoma cells via post-transcriptional regulation of BMI1 and CTNNB1. Mol Oncol. 2020;14(9):2332–2351.
96. Jiang H et al. Long non-coding RNA SNHG15 interacts with and stabilizes transcription factor Slug and promotes colon cancer progression. Cancer Lett. 2018;425:78–87.
97. Wang X et al. LncRNA SNHG6 promotes proliferation, invasion and migration in colorectal cancer cells by activating TGF-β/Smad signaling pathway via targeting UPF1 and inducing EMT via regulation of ZEB1. Int J Med Sci. 2019;16 (1):51.
98. Shan Y et al. LncRNA SNHG7 sponges miR-216b to promote proliferation and liver metastasis of colorectal cancer through upregulating GALNT1. Cell Death Dis. 2018;9(7):1–13.
99. Xu W et al. Circulating lncRNA SNHG11 as a novel biomarker for early diagnosis and prognosis of colorectal cancer. Int J Cancer. 2020;146(10):2901–2912.
100. Ye T et al. SNHG14 promotes the tumorigenesis and metastasis of colorectal cancer through miR-32-5p/SKIL axis. In Vitro Cell Dev Biol Anim. 2019;55(10):812–820.
101. Zhang W et al. Upregulation of SNHG14 suppresses cell proliferation and metastasis of colorectal cancer by targeting miR-92b-3p. J Cell Biochem. 2020;121(2):1998–2008.
102. Di W et al. Long noncoding RNA SNHG14 facilitates colorectal cancer metastasis through targeting EZH2-regulated EPHA7. Cell Death Dis. 2019;10(7):1–13.
103. Mastron JK et al. Silymarin and hepatocellular carcinoma: A systematic, comprehensive, and critical review. Anticancer Drugs. 2015;26(5):475–486.
104. Dai X et al. Ascochlorin, an isoprenoid antibiotic inhibits growth and invasion of hepatocellular carcinoma by targeting STAT3 signaling cascade through the induction of PIAS3. Mol Oncol. 2015;9(4):818–833.
105. Swamy SG et al. Targeting multiple oncogenic pathways for the treatment of hepatocellular carcinoma. Target Oncol. 2017;12(1):1–10.
106. Mohan CD et al. Development of a novel azaspirane that targets the Janus kinase-signal transducer and activator of transcription (STAT) pathway in hepatocellular carcinoma in vitro and in vivo. J Biol Chem. 2014;289(49):34296–34307.
107. Qu A, Yang Q. LncRNA SNHG1 promotes cell progression and metastasis via sponging miR-377-3p in hepatocellular carcinoma. Neoplasma. 2020;67(3):557–566.
108. Zhang PF et al. LncRNA SNHG3 induces EMT and sorafenib resistance by modulating the miR-128/CD151 pathway in hepatocellular carcinoma. J Cell Physiol. 2019;234(3):2788–2794.
109. Li Y et al. Long non-coding RNA SNHG5 promotes human hepatocellular carcinoma progression by regulating miR-26a-5p/GSK3β signal pathway. Cell Death Dis. 2018;9(9):1–15.
110. Chang L et al. Upregulation of SNHG6 regulates ZEB1 expression by competitively binding miR-101-3p and interacting with UPF1 in hepatocellular carcinoma. Cancer Lett. 2016; 383(2):183–194.
111. He S, Tang S. WNT/β-catenin signaling in the development of liver cancers. Biomed Pharmacother. 2020;132:110851.
112. Yao X et al. lncRNA SNHG7 sponges miR-425 to promote proliferation, migration, and invasion of hepatic carcinoma cells via Wnt/β-catenin/EMT signalling pathway. Cell Biochem Funct. 2019;37(7):525–533.
113. Dong J et al. lncRNA SNHG8 promotes the tumorigenesis and metastasis by sponging miR-149-5p and predicts tumor recurrence in hepatocellular carcinoma. Cell Physiol Biochem. 2018;51(5):2262–2274.
114. Lan T et al. LncRNA SNHG10 facilitates hepatocarcinogenesis and metastasis by modulating its homolog SCARNA13 via a positive feedback loop. Cancer Res. 2019;79(13):3220–3234.
115. Li S et al. SNHG16 as the miRNA let-7b-5p sponge facilitates the G2/M and epithelial-mesenchymal transition by regulating CDC25B and HMGA2 expression in hepatocellular carcinoma. J Cell Biochem. 2020;121(3):2543–2558.
116. Hu YL et al. SNHG16/miR-605-3p/TRAF6/NF-κB feedback loop regulates hepatocellular carcinoma metastasis. J Cell Mol Med. 2020;24(13):7637–7651.
117. Lin Q et al. LncRNA SNHG16 aggravates tumorigenesis and development of hepatocellular carcinoma by sponging miR-4500 and targeting STAT3. J Cell Biochem. 2019;120(7): 11604–11615.
118. Liu J et al. Long non-coding RNA SNHG20 predicts a poor prognosis for HCC and promotes cell invasion by regulating the epithelial-to-mesenchymal transition. Biomed Pharmacother. 2017;89:857–863.
119. McGuigan A et al. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 2018;24(43):4846.
120. Cao W, Zhou G. LncRNA SNHG12 contributes proliferation, invasion and epithelial–mesenchymal transition of pancreatic cancer cells by absorbing miRNA-320b. Biosci Rep. 2020;40 (6):1–11.

121. Xiang W et al. The lncRNA SNHG5-mediated miR-205-5p downregulation contributes to the progression of clear cell renal cell carcinoma by targeting ZEB1. Cancer Med. 2020;9 (12):4251–4264.
122. Du Y et al. Knockdown of SNHG15 suppresses renal cell carcinoma proliferation and EMT by regulating the NF-κB signaling pathway. Int J Oncol. 2018;53(1):384–394.
123. Shanmugam MK et al. Abrogation of STAT3 signaling cascade by zerumbone inhibits proliferation and induces apoptosis in renal cell carcinoma xenograft mouse model. Mol Carcinog. 2015;54(10):971–985.
124. Zhao S et al. Long noncoding RNA small nucleolar RNA host gene 1 (SNHG1) promotes renal cell carcinoma progression and metastasis by negatively regulating miR-137. Med Sci Monit. 2018;24:3824.
125. Liu Y et al. Long noncoding RNA SNHG12 promotes tumour progression and sunitinib resistance by upregulating CDCA3 in renal cell carcinoma. Cell Death Dis. 2020;11(7): 1–17.
126. Zhong X et al. LncRNA-SNHG7 regulates proliferation, apoptosis and invasion of bladder cancer cells assurance guidelines. J BU ON. 2018;23(3):776–781.
127. Chen W et al. SNHG16 regulates invasion and migration of bladder cancer through induction of epithelial-to-mesenchymal transition. Hum Cell. 2020;33(3):737–749.
128. Dai G et al. LncRNA SNHG3 promotes bladder cancer proliferation and metastasis through miR-515-5p/GINS2 axis. J Cell Mol Med. 2020;24(16):9231–9243.
129. Shanmugam MK et al. Ursolic acid inhibits the initiation, progression of prostate cancer and prolongs the survival of TRAMP mice by modulating pro-inflammatory pathways. PLoS One. 2012;7(3):e32476.
130. Lee JH et al. Capsazepine inhibits JAK/STAT3 signaling, tumor growth, and cell survival in prostate cancer. Oncotarget. 2017;8(11):17700–17711.
131. Zhang J et al. Nimbolide-induced oxidative stress abrogates STAT3 signaling cascade and inhibits tumor growth in transgenic adenocarcinoma of mouse prostate model. Antioxid Redox Signal. 2016;24(11):575–589.
132. Li T et al. LncRNA SNHG3 sponges miR-577 to up-regulate SMURF1 expression in prostate cancer. Cancer Med. 2020;9 (11):3852–3862.
133. Wu G et al. LncRNA SNHG17 aggravated prostate cancer progression through regulating its homolog SNORA71B via a positive feedback loop. Cell Death Dis. 2020;11(5):1–14.
134. Zhang Y et al. LncRNA SNHG15 acts as an oncogene in prostate cancer by regulating miR-338-3p/FKBP1A axis. Gene. 2019;705:44–50.
135. Hu H. Knockdown of LncRNA SNHG7 inhibited epithelial-mesenchymal transition in prostate cancer though miR-324-3p/WNT2B axis in vitro. Pathol-Res Pract. 2019;215(10): 152537.
136. Zeng J et al. LncRNA SNHG7 contributes to cell proliferation, invasion and prognosis of cervical cancer. Eur Rev Med Pharmacol Sci. 2019;23(21):9277–9285.
137. Lai SY et al. Long noncoding RNA SNHG12 modulated by human papillomavirus 16 E6/E7 promotes cervical cancer progression via ERK/Slug pathway. J Cell Physiol. 2020;13: 7257–7269.
138. Wu C et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020; 180(7):934–943.
139. Zhu H et al. SNHG16/miR-216-5p/ZEB1 signal pathway contributes to the tumorigenesis of cervical cancer cells. Arch Biochem Biophys. 2018;637:1–8.
140. Ningegowda R et al. A novel 4, 6-disubstituted-1, 2, 4-triazolo-1, 3, 4-thiadiazole derivative inhibits tumor cell invasion and potentiates the apoptotic effect of TNFα by abrogating NF-κB activation cascade. Apoptosis. 2017;22(1): 145–157.
141. Ge J et al. Role of long non-coding RNA SNHG1 in occurrence and progression of ovarian carcinoma. Eur Rev Med Pharmacol Sci. 2018;22(2):329–335.
142. Miao W et al. LncRNA SNHG8 induces ovarian carcinoma cells cellular process and stemness through Wnt/β-catenin pathway. Cancer Biomarkers. (Preprint). 2020;28(4):459–471.
143. Ong MS et al. 'Lnc'-ing Wnt in female reproductive cancers: Therapeutic potential of long non-coding RNAs in Wnt signalling. Br J Pharmacol. 2017;174(24):4684–4700.
144. Misaghi A et al. Osteosarcoma: a comprehensive review. Sicot-J. 2018;4:1–8.
145. Jiang Z, Jiang C, Fang J. Up-regulated lnc-SNHG1 contributes to osteosarcoma progression through sequestration of miR-577 and activation of WNT2B/Wnt/β-catenin pathway. Biochem Biophys Res Commun. 2018;495(1):238–245.
146. Deng R, Zhang J, Chen J. lncRNA SNHG1 negatively regulates miRNA1013p to enhance the expression of ROCK1 and promote cell proliferation, migration and invasion in osteosarcoma. Int J Mol Med. 2019;43(3):1157–1166.
147. Deng Y et al. Long noncoding RNA SNHG7 promotes the tumor growth and epithelial-to-mesenchymal transition via regulation of miR-34a signals in osteosarcoma. Cancer Biother Radiopharm. 2018;33(9):365–372.
148. Zhang J et al. LncRNA SNHG20 is associated with clinical progression and enhances cell migration and invasion in osteosarcoma. IUBMB Life. 2018;70(11):1115–1121.
149. Li S, Young KH, Medeiros LJ. Diffuse large B-cell lymphoma. Pathology. 2018;50(1):74–87.
150. Zhao L et al. LncRNA SNHG14/miR-5590-3p/ZEB1 positive feedback loop promoted diffuse large B cell lymphoma progression and immune evasion through regulating PD-1/PD-L1 checkpoint. Cell Death Dis. 2019;10(10):1–15.
151. Marz M et al. Animal snoRNAs and scaRNAs with exceptional structures. RNA Biol. 2011;8(6):938–946.
152. Kim D-S et al. Activation of PARP-1 by snoRNAs controls ribosome biogenesis and cell growth via the RNA helicase DDX21. Molecular cell. 2019;75(6):1270–1285.e14.
153. Siprashvili Z et al. The noncoding RNAs SNORD50A and SNORD50B bind K-Ras and are recurrently deleted in human cancer. Nat Genet. 2016;48(1):53.
154. Boone DN et al. SNHG7 is a lncRNA oncogene controlled by insulin-like growth factor signaling through a negative feedback loop to tightly regulate proliferation. Sci Rep. 2020;10(1): 1–12.
155. McMahon M et al. A single H/ACA small nucleolar RNA mediates tumor suppression downstream of oncogenic RAS. Elife. 2019;8:e48847.

156. Dupuis-Sandoval F, Poirier M, Scott MS. The emerging landscape of small nucleolar RNAs in cell biology. Wiley Interdiscip Rev: RNA. 2015;6(4):381–397.
157. Bacolod MD, Barany F, Fisher PB. Can CpG methylation serve as surrogate markers for immune infiltration in cancer? Adv Cancer Res. 2019;143:351–384.
158. Lei M et al. Translocation breakpoint disrupting the host SNHG14 gene but not coding genes or snoRNAs in typical Prader-Willi syndrome. J Hum Genet. 2019;64(7):647–652.
159. Saeinasab M et al. SNHG15 is a bifunctional MYC-regulated noncoding locus encoding a lncRNA that promotes cell proliferation, invasion and drug resistance in colorectal cancer by interacting with AIF. J Exp Clin Cancer Res. 2019;38(1):1–16.
160. Christensen LL et al. SNHG16 is regulated by the Wnt pathway in colorectal cancer and affects genes involved in lipid metabolism. Mol Oncol. 2016;10(8):1266–1282.
161. Zhang Z et al. SNORA71A promotes colorectal cancer cell proliferation, migration, and invasion. Biomed Res Int. 2020; 2020:1–11.
162. Bu J et al. LncRNA SNHG16 promotes epithelial-mesenchymal transition by upregulating ITGA6 through miR-488 inhibition in osteosarcoma. J Bone Oncol. 2021;27:100348.
163. Wang Q et al. Silencing of LncRNA SNHG16 Downregulates Cyclin D1 (CCND1) to abrogate malignant phenotypes in Oral squamous cell carcinoma (OSCC) through Upregulating miR-17-5p. Cancer Manag Res. 2021;13:1831.
164. Tian Y et al. lncRNA SNHG14 promotes oncogenesis and immune evasion in diffuse large-B-cell lymphoma by sequestering miR-152-3p. Leuk Lymphoma. 2021;1–15.
165. Wan Q et al. SNHG3 promotes migration, invasion, and epithelial-mesenchymal transition of breast cancer cells through the miR-186-5p/ZEB1 axis. Am J Transl Res. 2021;13 (2):585.
166. Wang Y-Q et al. LncRNA SNHG6 promotes breast cancer progression and epithelial-mesenchymal transition via miR-543/LAMC1 axis. Breast Cancer Research and Treatment. 2021;1–14.
167. Wang S et al. lncRNA SNHG4 promotes cell proliferation, migration, invasion and the epithelial-mesenchymal transition process via sponging miR-204-5p in gastric cancer. Mol Med Rep. 2021;23(1):1–1.
168. Wu Q et al. lncRNA SNHG11 promotes gastric cancer progression by activating the Wnt/β-catenin pathway and oncogenic autophagy. Mol Ther. 2021;29(3):1258–1278.
169. Zhang K et al. SNHG16/miR-140-5p axis promotes esophagus cancer cell proliferation, migration and EMT formation through regulating ZEB1. Oncotarget. 2018;9(1):1028.
170. Bai J et al. lncRNA SNHG1 cooperated with miR-497/miR-195-5p to modify epithelial–mesenchymal transition underlying colorectal cancer exacerbation. J Cell Physiol. 2020;235(2):1453–1468.
171. Zhang M, Duan W, Sun W. LncRNA SNHG6 promotes the migration, invasion, and epithelial-mesenchymal transition of colorectal cancer cells by miR-26a/EZH2 axis. Onco Targets Ther. 2019;12:3349.
172. Chen P-P et al. LncRNA SNHG12 promotes proliferation and epithelial mesenchymal transition in hepatocellular carcinoma through targeting HEG1 via miR-516a-5p. Cell Signal. 2021;84:109992.
173. Ma T et al. Long non-coding RNA SNHG17 upregulates RFX1 by sponging miR-3180-3p and promotes cellular function in hepatocellular carcinoma. Front Genet. 2020;11:1–11.
174. Tan X et al. LncRNA SNHG1 and RNA binding protein hnRNPL form a complex and coregulate CDH1 to boost the growth and metastasis of prostate cancer. Cell Death Dis. 2021;12(2):1–14.
175. Zhang L et al. LncRNA SNHG5 promotes cervical cancer progression by regulating the miR-132/SOX4 pathway. Autoimmunity. 2021;54(2):88–96.
176. Wu W et al. Lnc-SNHG16/miR-128 axis modulates malignant phenotype through WNT/β-catenin pathway in cervical cancer cells. J Cancer. 2020;11(8):2201–2212.
177. Wu Y et al. Long non-coding RNA SNHG1 stimulates ovarian cancer progression by modulating expression of miR-454 and ZEB1. Mol Oncol. 2021;15(5):1584–1596.
178. Wang D et al. Long non-coding RNA SNHG20 promotes ovarian cancer development by targeting microRNA-338-3p to regulate MCL1 expression. Oncol Lett. 2021;21(2):1–1.

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