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REVIEW

Long Non-Coding Small Nucleolar RNA Host Genes (SNHGs) in Endocrine-Related Cancers

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Abstract: Long non-coding RNAs (lncRNAs) are emerging regulators of a diverse range of biological processes through various mechanisms. Genome-wide association studies of tumor samples have identified several lncRNAs, which act as either oncogenes or tumor suppressors in various types of cancers. Small nucleolar RNAs (snoRNAs) are predominantly found in the nucleolus and function as guide RNAs for the processing of transcription. As the host genes of snoRNAs, lncRNA small nucleolar RNA host genes (SNHGs) have been shown to be abnormally expressed in multiple cancers and can participate in cell proliferation, tumor progression, metastasis, and chemoresistance. Here, we review the biological functions and emerging mechanisms of SNHGs involved in the development and progression of endocrine-related cancers including thyroid cancer, breast cancer, pancreatic cancer, ovarian cancer and prostate cancer.

Keywords: endocrine, cancers, lncRNA, SNHG

Introduction

Long non-coding RNAs (lncRNAs, >200 nucleotides in length) are emerging regulators of gene transcription.[1] The human genome estimated to encode >28,000 lncRNAs,[2] but only 15,778 lncRNAs are annotated in the current GENECODE version 27.[3] Therefore, more lncRNAs are yet to be discovered. Moreover, the known lncRNAs have not been studied in depth.

Accumulating evidence suggests lncRNAs play key roles in the development and progression of several cancers, acting as either oncogenes or tumor suppressors.[4] LncRNAs can regulate transcription, translation, protein modification, and the formation of RNA-protein or protein-protein complexes, depending on the cellular location.[5] For example, lncRNAs primarily located in the nucleus are involved in transcriptional regulation and mRNA processing, while cytoplasmic lncRNAs play roles in modulating mRNA translation by competing with proteins or in miRNA-mediated mRNA decoy.[5,6]

Small nucleolar RNAs (snoRNAs, 60–300 nucleotides in length) are more well-characterized than lncRNAs and are predominantly found in the nucleolus.[7] Most snoRNAs function as guide RNAs for the post-transcriptional modification of ribosomal RNAs and some spliceosomal RNAs, with some involved in the nucleolytic processing of the original rRNA transcript.[8] As shown in Figure 1, the majority of snoRNAs are encoded (hosted) in the introns of protein-coding and non-protein-coding genes, termed small nucleolar RNA host genes (SNHGs).[9–11] Primary RNA transcripts of host genes (including all exons and introns with their snoRNAs) are cut into different exons and introns. Exons are then re-spliced and function in the cytoplasm, while the introns are further processed into snoRNAs and play roles in the nucleolus.

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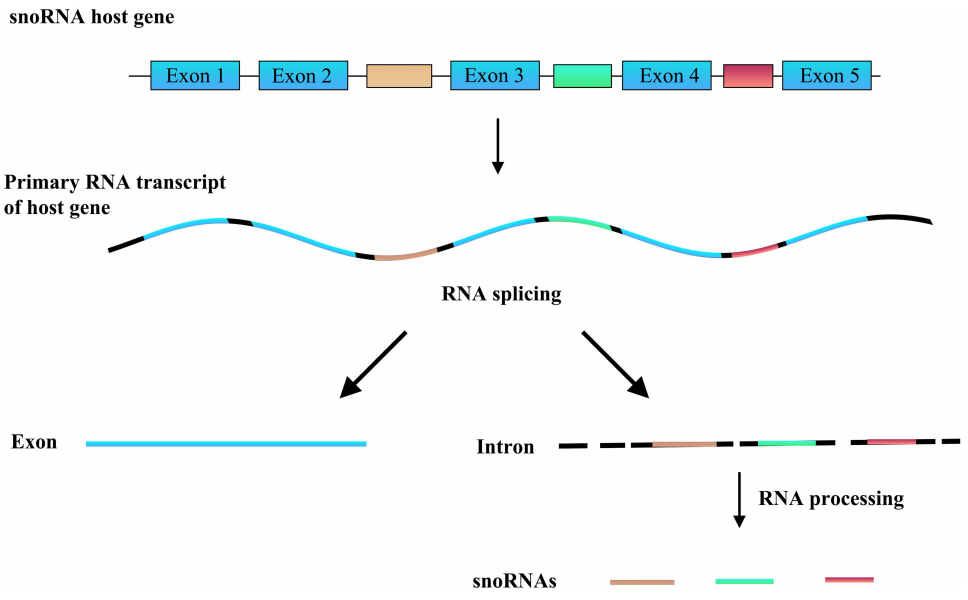

Figure 1 The synthetic pathway of snoRNAs.

Currently, there are 22 members of SNHG family (*SNHG1* to *SNHG22*) that have been shown to regulate proliferation, apoptosis, invasion, and migration in multiple cancers, including endocrine-related cancers (as summarized in Tables 1 and 2). These 22 SNHGs have diverse activities and mechanisms of action. For example, *SNHG1* has been shown to promote colorectal cancer cell growth by modulating histone methylation of gene promoters of the Kruppel Like Factor 2 (*KLF2*, a member of the KLF family, also exerts tumor-suppressive roles) and the cyclin-dependent kinase 4 inhibitor B (*CDKN2B*, a tumor suppressor).[12] *SNHG1* can also act as a sponge for *miR-154-5p* to upregulate expression of G1/S-specific cyclin-D2 (*CCND2*, which is involved in cell cycle progression).[12] Meanwhile, *SNHG13* serves as a competing endogenous RNA (ceRNA) of *miR-34a-5p*, leading to the derepression of Jagged 1 (*JAG1*) expression, which eventually triggers resistance to docetaxel in prostate cancer.[13]

This review aims to provide an overview on the current understanding of the regulation and function of SNHGs in endocrine-related cancers that arise from the endocrine glands or neuroendocrine tissues, including thyroid cancer, breast cancer, pancreatic cancer, ovarian cancer, and prostate cancer.[14]

Thyroid Cancer

Thyroid cancer is the most common malignancy of the endocrine system with enormous heterogeneity in terms of morphological features and prognosis.[15] Although the majority of cases of thyroid cancer tend to be biologically indolent and have an excellent prognosis, some are associated with more aggressive clinical behavior.[16]

SNHG1 may act as an oncogene in thyroid cancer by competing with *miR-199a-5p* and upregulating the expression of its target gene, the transcription factor (TF) *SP1*. In turn, *SP1* targets the promoter region of *SNHG1* and promote its transcription, forming a positive feedback loop to promote cancer cell proliferation and invasion.[17] Conversely, low expression of *SNHG2*, also known as growth arrest specific transcript 5 (*GAS5*), is associated with poor prognosis of patients with thyroid cancer.[18] Mechanistically, *GAS5* acts as a sponge for *miR-222-3p*, thereby modulating the expression of the phosphatase and tensin homolog (*PTEN*), leading to *PTEN*/protein kinase B (*AKT*) pathway activation and the suppression of thyroid cancer cell proliferation.[19]

SNHG7 is also markedly upregulated in thyroid cancer samples, with high *SNHG7* expression associated with shorter survival times.[20] Indeed, *SNHG7* knockdown leads to a suppression of thyroid cancer cell proliferation and migration, and induction of apoptosis via downregulating the acyl-CoA synthetase long chain family member 1 (*ACSL1*) and the brain-derived neurotrophic factor (*BDNF*).[21,22] In addition, bioinformatics analysis showed SNHG7 was associated with the processes of "protein translation", "viral life cycle", "RNA processing", "mRNA splicing", "histone ubiquitination", "endoplasmic reticulum-to-Golgi vesicle-mediated transport", "sister chromatid cohesion", "DNA damage checkpoint

Table 1 Characteristics of SNHG Members

SNHG Member	Aliases	Chromosomal Location	GENE ID	Associated Endocrine-Related Cancers
SNHG1	*LINC00057, NCRNA00057, U22HG, UHG, lncRNA16*	11q12.3	23642	Thyroid Cancer, Breast Cancer, Pancreatic Cancer, Ovarian Cancer, Prostate Cancer
GAS5	*NCRNA00030, SNHG2*	1q25.1	60674	Thyroid Cancer, Breast Cancer, Pancreatic Cancer, Ovarian Cancer, Prostate Cancer
SNHG3	*NCRNA00014, RNU17C, RNU17D, U17HG, U17HG-A, U17HG-AB*	1p35.3	8420	Breast Cancer, Ovarian Cancer
SNHG4	*NCRNA00059, U19H*	5q31.2	724102	Prostate Cancer
SNHG5	*C6orf160, LINC00044, NCRNA00044, U50HG*	6q14.3	387066	Breast Cancer, Ovarian Cancer
SNHG6	*HBII-276HG, NCRNA00058, U87HG*	8q13.1	641638	Breast Cancer, Prostate Cancer
SNHG7	*NCRNA00061*	9q34.3	84973	Thyroid Cancer, Breast Cancer, Pancreatic Cancer, Prostate Cancer
SNHG9	*NCRNA00062*	16p13.3	735301	Pancreatic Cancer
SNHG12	*ASLNC04080, C1orf79, LINC00100, NCRNA00100, PNAS-123*	1p35.3	85028	Thyroid Cancer, Breast Cancer, Ovarian Cancer, Prostate Cancer
DANCR	*AGU2, ANCR, KIAA0114, SNHG13, lncRNA-ANCR*	4q12	57291	Thyroid Cancer, Breast Cancer, Pancreatic Cancer, Ovarian Cancer, Prostate Cancer
SNHG14	*115HG, IC-SNURF-SNRPN, LNCAT, NCRNA00214, U-UBE3A-ATS, UBE3A-AS, UBE3A-AS1, UBE3A-ATS, UBE3AATS*	15q11.2	104472715	Breast Cancer, Pancreatic Cancer, Ovarian Cancer, Prostate Cancer
SNHG15	*C7orf40, Linc-Myo1g, MYO1GUT*	7p13	285958	Thyroid Cancer, Breast Cancer, Pancreatic Cancer, Ovarian Cancer, Prostate Cancer
SNHG16	*Nbla10727, Nbla12061, ncRAN*	17q25.1	100507246	Thyroid Cancer, Breast Cancer, Pancreatic Cancer, Ovarian Cancer
SNHG17	-	20q11.23	388796	Breast Cancer
SNHG20	*C17orf86, LINC00338, NCRNA00338, SCARNA16HG*	17q25.2	654434	Breast Cancer, Ovarian Cancer, Prostate Cancer
SNHG22	-	18q21.1	103091864	Ovarian Cancer

regulation", "translation", and "the spliceosome", suggesting further research directions for this lncRNA.[20]

SNHG12 is also upregulated (by 3.8-fold) in papillary thyroid carcinoma (PTC) tissues compared to normal adjacent tissue samples.[23] High *SNHG12* was associated with poorer progression in PTC in terms of tumor node metastasis (TNM) staging and lymph node metastasis (LNM).[24] *SNHG12* likely acts as a sponge for *miR-16-5p*, thereby inducing PTC cell proliferation, migration, and invasion, as well as inhibiting apoptosis.[25] *SNHG12* also promotes the proliferation and migration of PTC cells via the *Wnt/β-catenin* signaling pathway.[23] Meanwhile, *SNHG13*, also known as differentiation antagonizing non-protein coding RNA (*DANCR*), acts as a tumor suppressor in PTC: down-regulation of *DANCR* is associated with more aggressive clinical features of PTC.[26] *DANCR* is also a potential biomarker for PTC diagnosis, showing a sensitivity of 85.29% and a specificity of 66.18%.[26]

Table 2 SNHG Members in Endocrine-Related Cancers

SNHG Member	Mechanism	Related Signaling Pathway	Related Clinicopathological Characteristics	Prognostic Significance	Related Cell Biofunctions	Role	In vivo
Thyroid Cancer							
SNHG1	Positive feedback loop and ceRNA: *SP1/SNHG1/miR-199a-5p/SP1*		Tumor size		Proliferation, invasion	Oncogene	NO
GAS5	ceRNA: *GAS5/miR-222-3p/PTEN* Regulation: *GAS5/p-AKT*	*PI3K/AKT* signaling pathway	TNM stage, LNM, multiple cancer foci	DFS, OS	Proliferation	Antioncogene	YES
SNHG7	ceRNA: *SNHG7/miR-449a/ACSL1* Regulation: *SNHG7/BDNF*	*BDNF/TrkB* signaling pathway	Tumor size, TNM stage	DFS	Proliferation, migration, cell cycle, apoptosis	Oncogene	NO
SNHG12	ceRNA: *SNHG12/miR-16-5p*; Regulation: *SNHG12/β-catenin, MMP2, Cyclin D1*	*Wnt/β-catenin* signaling pathway	TNM stage, LNM		Proliferation, migration, invasion, apoptosis, cell cycle	Oncogene	YES
DANCR	–	–	T grade, TNM stage		–	Antioncogene	NO
SNHG15	ceRNA: *SNHG15/miR-200a-3p/YAP1*, *SNHG15/miR-510-5p*; Regulation: *SNHG15/β-catenin, E-cadherin, N-cadherin, Vimentin, MST1, LATS1*	*YAP1-Hippo* signaling pathway	Gender, tumor size, TNM stage, LNM, distant metastasis	DFS, OS	Proliferation, migration, invasion, apoptosis, EMT	Oncogene/ Antioncogene	YES
SNHG16	ceRNA: *SNHG16/miR-497*; Regulation: *SNHG16/BDNF*		TNM stage, LNM		Proliferation, migration, invasion, apoptosis	Oncogene	NO
Breast Cancer							
SNHG1	ceRNA: *SNHG1/miR-382-5p, SNHG1/miR-448/IDO*; Regulation: *SNHG1/ E-cadherin, N-cadherin, Vimentin, ZEB1*		TNM stage	OS	Treg cell differentiation, immune escape, proliferation, migration, invasion, EMT	Oncogene	YES
GAS5	ceRNA: *GAS5/miR-196a-5p, GAS5/miR-23a/ATG3, GAS5/miR-21/PTEN, GAS5/miR-378a-5p/SUFU, GAS5/miR-221-3p/DKK2*; Regulation: *GAS5/β-catenin, c-Myc, Cyclin D1, FOXO1, p-PI3K, p-AKT, miR-221/GAS5, miR-222/GAS5*	*PI3K/AKT* signaling pathway, Notch signaling pathway, *Wnt/β-Catenin* signaling pathway	Tumor size, TNM stage, histological grade, LNM, ER-	OS	Proliferation, invasion, apoptosis, autophagy, cell cycle, Chemosensitivity: DNC, Trastuzumab, Imatinib, PTX, CIS, Adriamycin	Antioncogene	YES
SNHG3	ceRNA: *SNHG3/miR-330-5p/PKM*, *SNHG3/miR-384/HDGF*		Histological grade, LNM, TNM stage, ER, Her-2		Glycolysis metabolism, proliferation, invasion, migration	Oncogene	NO
SNHG5	ceRNA: *SNHG5/miR-154-5p/PCNA*; Regulation: *SNHG5/ Cyclin D1*, p16			OS	Proliferation, apoptosis, cell cycle	Oncogene	YES

(*Continued*)

Table 2 (Continued).

SNHG Member	Mechanism	Related Signaling Pathway	Related Clinicopathological Characteristics	Prognostic Significance	Related Cell Biofunctions	Role	In vivo
SNHG6	ceRNA: *SNHG6/miR-26a/VASP, SNHG6/miR-26a/MAPK6*		Tumor size, TNM stage, distant metastasis		Proliferation, migration, invasion, cell cycle, apoptosis, EMT	Oncogene	YES
SNHG7	Activated by TF and ceRNA: *c-Myc/SNHG7/miR-34a-5p/LDHA; ceRNA: SNHG7/miR-186, SNHG7/miR-381*; Regulation: *SNHG7/Ki67, MMP-2, MMP-7, E-cadherin, Vimentin, Snail, Notch-1, Survivin, Cyclin D1*	*Notch-1* signaling pathway	T grade, LNM, distant metastasis	OS	Proliferation, glycolysis metabolism, migration, invasion, EMT	Oncogene	YES
SNHG12	Activated by TF: *c-MYC/SNHG12*		Tumor size, LNM		Proliferation, migration, apoptosis	Oncogene	NO
DANCR	ceRNA: *DANCR/miR-216a-5p*; Methylation: *DANCR/EZH2/SOCS3&CD44&ABCG2*; Phosphorylation: *DANCR/RXRA/PIK3CA*; Regulation: *DANCR/Snail, Slug, MMP-2, MMP-9, E-cadherin, Vimentin, CD133, OCT3/4, NANOG, p-p65, p65, p-STAT3, STAT3, SOX2, ABCG2, ALDH1*	*PI3K/AKT* signaling pathway	TNM stage, histologic grade, LNM	OS	Proliferation, invasion, migration, EMT	Oncogene	YES
SNHG14	ceRNA: *SNHG14/miR-193a-3p*; Acetylation: *SNHG14/PABPC1/Nrf2/HO-1*; Regulation: *SNHG14/c-PARP, c-Caspase-3*	*Nfr2* signaling pathway	LNM, distant metastasis, cardiac toxicity		Proliferation, invasion, cell cycle, Chemosensitivity: Trastuzumab	Oncogene	YES
SNHG15	ceRNA: *SNHG15/miR-411-5p/VASP, SNHG15/miR-381, SNHG15/miR-211-3p*; Regulation: *SNHG15/Bcl-2, Bax, VEGF, MMP-2, MMP-9, MMP-14, PCNA, Cyclin D1, c-Caspase-3, Snail, Vimentin, E-Cadherin*		Tumor size, TNM stage, LNM	OS	Proliferation, migration, invasion, apoptosis, cell cycle, Chemosensitivity: DDP	Oncogene	YES
SNHG16	ceRNA: *SNHG16/miR-30a/RRM2, SNHG16/miR-98/E2F5, RRM2-let-7a-5p-SNHG16/MAL2*			DFS, OS	Proliferation, invasion, migration	Oncogene	NO
SNHG17	ceRNA: *SNHG17/miR-124-3p*		TNM stage, LNM	OS	Proliferation, migration, invasion	Oncogene	YES
SNHG20	ceRNA: *SNHG20/miR-495/HER2*				Proliferation, migration, invasion	Oncogene	YES
Pancreatic Cancer							

(*Continued*)

Table 2 (Continued).

SNHG Member	Mechanism	Related Signaling Pathway	Related Clinicopathological Characteristics	Prognostic Significance	Related Cell Biofunctions	Role	In vivo
SNHG1	ceRNA: *SNHG1/miR-195/Cyclin D1*; Regulation: *SNHG1/p21, Vimentin, E-Cadherin, N-Cadherin, Notch-1, Hes-1, PI3K, p-AKT, t-AKT, Bcl-2, Bax*	*PI3K/AKT* signaling pathway, *Notch-1* signaling pathway	Tumor size, TNM stage	OS	Proliferation, apoptosis, cell cycle, migration, invasion	Oncogene	YES
GAS5	ceRNA: *GAS5/miR-221/SOCS3, GAS5/miR-32-5p/PTEN, GAS5/181c-5p*; Regulation: *GAS5/Vimentin, E-Cadherin, N-Cadherin, Snail, OCT4, CD133, Nanog, SOX2, CDK6*	*PI3K/AKT* signaling pathway			Proliferation, migration, invasion, cell cycle, EMT, Chemosensitivity: Gemcitabine	Antioncogene	YES
SNHG7	ceRNA: *SNHG7/miR-342-3p/ID4*		Tumor size, LNM, TNM stage, tumor differentiation	OS	Proliferation, migration, invasion	Oncogene	YES
SNHG9	-		N grade, distant metastasis	OS		Antioncogene	NO
DANCR	ceRNA: *DANCR/miR-33b/MMP16, DANCR/miR-135a/NLRP37, DANCR/miR-214-5p/E2F2, DANCR/miR-33a-5p/AXL*; Regulation: *DANCR/E-Cadherin, N-Cadherin, NLRP3*		Tumor size, T grade, N grade, TNM stage, LNM, vascular invasion, recurrence rates	PFS, OS	Proliferation, invasion	Oncogene	YES
SNHG14	ceRNA: *SNHG14/miR-101, SNHG14/miR-613/ANXA2*; Bind and regulation: *SNHG14/EZH2*; Regulation: *SNHG14/Vimentin, E-Cadherin, RAB5A, ATG4D*		LNM	DFS, OS	Proliferation, invasion, apoptotic, EMT, autophagy, Chemosensitivity: Gemcitabine	Oncogene	YES
SNHG15	Methylation: *SNHG15/EZH2/P15*	*&KLF2*; Regulation: *SNHG15/CDK2, CDK4, c-Caspase-3, c-Caspase-9*		Tumor size, TNM stage, LNM		Proliferation, apoptosis, cell cycle	
SNHG16	Oncogene ceRNA: *SNHG16/miR-200a-3p, SNHG16/miR-195/SREBP2, SNHG16/miR-218-5p*	YES	TNM stage, LNM, distant metastasis, tumor differentiation	OS	Proliferation, migration, invasion	Oncogene	YES
Ovarian Cancer							
SNHG1	Regulation: *SNHG1/β-catenin, Bax, Bcl-2, Caspase-9, c-Caspase-9, PARP, Vimentin, E-Cadherin, N-Cadherin, MMP-2, MMP-9, Lamin A, Cyclin D1, c-myc*	*Wnt/β-catenin* signaling pathway	Pathological grade, TNM stage	OS	Proliferation, migration, invasion, apoptosis, EMT	Oncogene	YES

(*Continued*)

Table 2 (Continued).

SNHG Member	Mechanism	Related Signaling Pathway	Related Clinicopathological Characteristics	Prognostic Significance	Related Cell Biofunctions	Role	In vivo
GAS5	ceRNA: *GAS5/miR-196a-5p/HOXA5, GAS5/miR-21/SPRY2*; Bind and regulation: *GAS5/E2F4/PARP1/MAPK*; Regulation: *GAS5/c-Caspase-3, Caspase-3, c-Caspase-7, Caspase-7, CDK4, CDK6, Cyclin D, ERK1/2, p-ERK, p-JNK, P38MAPK, GDF15, ASC, Cas-1, p-Cas-1, IL-1β, p-IL-1β, IL-18, p-IL-18, APAF1, p21*	*MAPK* signaling pathway	Tumor size, invasive depth, FIGO stage, histological type	DFS, OS	Proliferarion, cell cycle, apoptosis, migration, invasion, Chemosensitivity: DDP	Antioncogene	YES
SNHG3	Regulation: *SNHG3/GSK3β, Cyclin D1, CDK1, MMP-9, MMP-3, β-catenin*	*GSK3β/β-catenin* signaling pathway	FIGO stage, LNM	OS	Proliferation, invasion	Oncogene	NO
SNHG5	ceRNA: *SNHG5/miR-23a*		Tumor grade, FIGO stage, LNM	OS	Proliferation, apoptosis, Chemosensitivity: PTX	Antioncogene	YES
SNHG12	ceRNA: *SNHG12/miRNA-129/SOX4*			OS	Proliferate, migration	Oncogene	
DANCR	ceRNA: *DANCRmiR-145/VEGF*; Regulation: *DANCR/UPF1, IGF2*		Tumor stage, accompanied by metastatic loci		Proliferation, invasion, migration, angiogenesis	Oncogene	YES
SNHG14	ceRNA: *SNHG14/miR-219a-5p, SNHG14/miR-125a-5p/DHX33*; Regulation: *SNHG14/DGCR8*			OS	Proliferation, migration, invasion, cell cycle	Oncogene	NO
SNHG15	-		Cancer type, ascites, FIGO stage	PFS, OS	Proliferation, migration, invasion, Chemosensitivity: DDP	Oncogene	NO
SNHG16	Regulation: *SNHG16/p-AKT, AKT, MMP9*	*PI3K/AKT* signaling pathway	Clinical stage, tumor size, LNM, distant metastasis	OS	Proliferation, invasion, migration	Oncogene	NO
SNHG20	Regulation: *SNHG20/β-catenin, GSK-3β, p-GSK-3β, cyclin D1, c-myc, E-cadherin, P21, Vimentin*	*Wnt/β-catenin* signaling pathway	Histological grade, LNM	OS	Proliferation, migration, invasion, EMT	Oncogene	NO
SNHG22	ceRNA: *SNHG22/miR-2467/Gal-1*		Tumor size, CA125 expression	OS	Chemosensitivity: DDP, PTX	Oncogene	NO
Prostate Cancer							
SNHG1	ceRNA: *SNHG1/miR-377-3p/AKT2, SNHG1/miR-199a-3p/CDK7*		Gleason score, T grade	Biochemical RFS, OS	Proliferation, apoptosis, cell cycle	Oncogene	NO

(*Continued*)

Table 2 (Continued).

SNHG Member	Mechanism	Related Signaling Pathway	Related Clinicopathological Characteristics	Prognostic Significance	Related Cell Biofunctions	Role	In vivo
GAS5	ceRNA: *GAS5/miR-21/PDCD4/PTEN, GAS5/miR-1284/AKT, GAS5/miR-1284/HMGB1, GAS5/miR-103*; Regulation: *GAS5/γ-H2AX, H2AX, p-mTOR, mTOR, S6K1, p-S6K1*; SNP: rs55829688, rs14520427	*AKT/mTOR* signaling pathway	Clinical T stage, pathologic N stage, seminal vesicle invasion, lymphovascular invasion	DFS, OS	Proliferation, migration, invasion, apoptosis, cell cycle, radiosensitivity	Oncogene/ Antioncogene	YES
SNHG4	ceRNA: *SP1/SNHG4/miR-377/ZIC5*		Tumor stage, LNM	OS	Proliferation, invasion, migration	Oncogene	NO
SNHG6	-		Gleason score, T grade	DFS		Oncogene	NO
SNHG7	ceRNA: *SNHG7/miR-324-3p/WNT2B, SNHG7miR-503/Cyclin D1*; Regulation: *E-cadherin, N-cadherin, CDK4, CDK6*		T grade, TNM stage, Gleason score, bone metastasis, pelvic LNM	OS	Proliferation, migration, invasion, cell cycle, EMT	Oncogene	YES
SNHG12	ceRNA: *SNHG12/miR-195/CCNE1, SNHG12/miR-195, SNHG12/miR-133b*; Regulation: *Bcl-2, Bax, Caspase-3, c-Caspase-3, Caspase-9, c-Caspase-9, LC3, Beclin-1, p62, PTEN, PI3K, p-PI3K, AKT, p-AKT, mTOR, p-mTOR, β-catenin, c-Myc*	*Wnt/β-catenin* signaling pathway	Gleason score, clinical stage, bone metastasis, disease recurrence, serum PSA, LNM, new tumor event after treatment, lymph nodes examined, PSA value, residual tumor	OS	Proliferation, invasion, apoptosis, autophagy, cell cycle	Oncogene	YES
DANCR	ceRNA: *DANCR/miR-135a, DANCR/miR-34a-5p/JAG1*; Methylation: *DANCR/EZH2/TIMP2/3*; Regulation: *DANCR/PCNA, Ki-67, c-Caspase-3, Bax, LRP, p-gp, MRP1*	Notch signaling pathway			Proliferation, apoptosis, migration, invasion, Chemosensitivity: PTX, Docetaxel	Oncogene	YES
SNHG14	ceRNA: *SNHG14/miR-613*				Proliferation	Oncogene	YES
SNHG15	ceRNA: *SNHG15/miR-338-3p/FKBP1A*; Regulation: *E-cadherin, N-cadherin*				Proliferation, invasion, migration, EMT	Oncogene	NO
SNHG20	ceRNA: *SNHG20/miR-6516-5p/SCGB2A1*				Proliferation, invasion, apoptosis	Oncogene	NO

Abbreviations: LNM, lymph node metastasis; ER-, estrogen receptor-negative; Her-2, human epidermal growth factor receptor 2; FIGO, International Federation of Gynaecology and Obstetrics; DFS, disease-free survival; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; DNC, dendrosomal curcumin; PTX, paclitaxel; DDP, cisplatin.

The role of *SNHG15* in thyroid cancer remains controversial. *SNHG15* is upregulated in human PTC tissues and cell lines compared to controls, and was associated with gender, larger tumor size, LNM, advanced TNM stage, and poorer overall survival (OS).[27] Meanwhile, *SNHG15* downregulation attenuated cell proliferation, migration, and epithelial–mesenchymal transition (EMT) in PTC cells, as well as inducing apoptosis.[27] Mechanistically, *SNHG15* acts as a sponge for *miR-200a-3p*, thereby upregulating the Yes-associated protein 1 (*YAP1*) signaling pathway.[27] Alternatively, another study showed SNHG15 was downregulated in thyroid cancer tissues and cell lines and suppressed tumor progression,

indicating *SNHG15* may act as a tumor suppressor.[28] Moreover, inhibition of *SNHG15* by *miR-510-5p* promoted cell proliferation, migration, and invasion in thyroid cancer.[29] These diverse functions of *SNHG15* found in different studies may reflect the different subtypes of thyroid cancer; however, further research is required.

Finally, *SNHG16*, which functions as an endogenous sponge for *miR-497*, was upregulated in both PTC tissues and cell lines and shown to induce proliferation, migration, and invasion of thyroid cancer cells, while inhibiting apoptosis.[30] High expression of *SNHG16* was also positively associated with advanced TNM stage and LNM.[30]

In summary, *SNHG1, GAS5, SNHG7, SNHG12, DANCR, SNHG15*, and *SNHG16* all appear to play essential roles in thyroid cancer; although the function of *SNHG15* requires further confirmation.

Breast Cancer

Breast cancer is the most commonly diagnosed cancer worldwide and the leading cause of cancer-related death for women.[31] Although advances in early detection and cancer therapeutics have led to a decrease in mortality rates, breast cancer remains a significant public health concern. Some classes of breast cancer, such as triple-negative breast cancer (characterized by a lack of expression of the progesterone receptor, estrogen receptor, and Her-2), have a poor prognosis.[32] Many lncRNAs have been implicated in breast cancer development in recent years, which may eventually lead to better outcomes for these patients.[33]

The downregulation of *SNHG1* can suppress the proliferation and invasion of breast cancer cells by regulating *miR-382*.[34] In addition, *SNHG1* may inhibit the differentiation of regulatory T cells, promote *miR-448* expression, and reduce indoleamine 2,3 dioxygenase (*IDO*) levels in breast cancer.[35] Therefore, *SNHG1* may be a useful target in breast cancer treatment.

GAS5 was first reported to be a tumor suppressor in breast cancer in 2009.[36] Since then, studies have shown low *GAS5* expression is closely related to a more aggressive tumor phenotype, enhanced proliferation, and attenuated apoptosis in breast cancer cells.[37–39] *GAS5* can bind to *miR-196a-5p*, thereby partially alleviating its tumor-promoting effects, including invasion and downstream forkhead box O1 (*FOXO1*)/phosphatidylinositol 3-kinase (*PI3K*)/*AKT* signal pathway activation.[37] *Notch-1* also promotes breast cancer cell proliferation by downregulating *GAS5*.[40] *GAS5* can also act as a sponge for *miR-23a* to promote autophagy via the *GAS5-miR-23a-ATG3* axis in breast cancer.[38] Moreover, in drug-resistant breast cancer cells, *GAS5* overexpression increases chemosensitivity (eg to trastuzumab, imatinib, paclitaxel, cisplatin, among others), especially in triple-negative breast cancer cells.[39,41-46] Another study showed *miR-221/222* suppresses *GAS5* expression and enhances tumor growth in a mouse model of breast cancer xenografts.[47] Moreover, lower plasma *GAS5* levels were found in patients with a high *Ki67* proliferation index before surgery and in those with LNM after surgery.[48] Finally, bioinformatics analysis showed *GAS5* plays a role in "proliferation" and the "cell cycle", although the molecular mechanisms related to these regulatory pathways are unclear.[49]

There is evidence that lncRNA secreted in exosomes from cancer cells can regulate gene expression and signaling pathways in other niche cells. For example, breast cancer-derived cancer-associated fibroblasts can secrete increased amounts of *SNHG3* than healthy breast tissue cells, which in turn promotes the growth of breast cancer cells by regulating *miR-330-5p*/Pyruvate Kinase M1/M2 (*PKM*).[50] *SNHG3* can also act as a sponge for *miR-384*/hepatoma-derived growth factor (*HDGF*) to drive breast cancer cell proliferation, migration, and invasion.[51]

SNHG5 is an oncogene and acts as a sponge for *miR-154-5p*, reducing its ability to repress proliferating cell nuclear antigen (*PCNA*), thus promoting breast cancer proliferation, cell cycle progression, and inhibiting apoptosis.[52] *SNHG6* was also found to be highly expressed in breast cancer tissues and cell lines, and is associated with poorer clinicopathologic features.[53] Indeed, *SNHG6* knockdown inhibits breast cancer cell proliferation, migration, invasion, and G1 cell cycle arrest by acting as a sponge for *miR-26a-5p*, which regulates expression of the vasodilator-stimulated phosphoprotein (*VASP*)[54] and mitogen-activated protein kinase 6 (*MAPK6*).[55]

The expression of *SNHG7* is also upregulated in breast cancer tissues and cells compared to healthy tissues, with high *SNHG7* expression strongly related to tumor stage, distant metastasis, LNM, and OS.[56–58] Knocking down *SNHG7* inhibited breast cancer cell proliferation, invasion, and EMT.[56–58] Further mechanistic studies revealed *SNHG7* could act as a sponge to repress *miR-34a*,[57] *miR-186*,[58] and *miR-381*,[56] thereby activating the *Notch-1* pathway and glycolysis in breast cancer. Additionally, *c-Myc* (a TF) can bind to the *SNHG7* promoter and positively regulate its expression in breast cancer.[59]

Increased expression of *SNHG12* has been observed in triple-negative breast cancer.[60] *SNHG12* upregulation positively correlated with advanced tumor stage and size, and negatively correlated with OS.[60] *SNHG12* is a direct transcriptional target of *c-Myc*, and the *c-Myc*-induced upregulation of *SNHG12* enhances the proliferation of breast cancer cells and inhibits apoptosis.[60] *SNHG12* may also promote the migration of breast cancer cells by regulating the expression of matrix metalloproteinase 13 (*MMP13*).[60]

High *DANCR* levels can lead to shorter OS in triple-negative breast cancer, by acting as a sponge for *miR-216a-5p* and thereby promoting the proliferation and invasion of tumor cells.[61] *DANCR* can mediate protein assembly and modification in triple-negative breast cancer. For example, *DANCR* can bind to the phosphorylation site of retinoid X receptor alpha (*RXRA*) and suppresses its interaction with the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) promoter.[62] This leads to the activation of the *P13K/AKT* pathway, which in turn, promotes the proliferation and growth of triple-negative breast cancer cells.[62] *DANCR* may also participate in the enhancer of zeste homolog 2 (*EHZ2*)-mediated epigenetic repression of the suppressor of cytokine signaling 3 (*SOCS3*) in breast cancer cells.[63] Sha et al[64] proposed *DANCR* knockdown was associated with increased binding of *EZH2* to the promoters of *CD44* and *ABCG2* (two triple-negative breast cancer stem cell markers), and the concomitant reduction of expression of these genes decreased cancer cell proliferation and invasion. Furthermore, nanoparticle-mediated RNAi of *DANCR* was shown to be an effective therapy for triple-negative breast cancer.[65]

Upregulation of *SNHG14* in breast cancer tissues may also promote cancer cell proliferation and invasion.[66] In particular, *SNHG14* upregulates polyadenylate-binding protein 1 (*PABPC1*) expression by modulating H3K27 acetylation (H3K27ac) in the promoter of *PABPC1* gene, resulting in the activation of the nuclear factor E2-related factor 2 (*NRF2*) signaling pathway, which is involved in cell defense and survival against chemotherapy drugs.[66] Besides histone methylation, acetylation is another important form of histone modification.

Indeed, exosomal *SNHG14* was upregulated in trastuzumab-resistant human epidermal growth factor receptor 2 (*HER2*) breast cancer cells compared with parental breast cancer cells, and *SNHG14* knockdown re-sensitized breast cancer cells to trastuzumab treatment.[67] These results indicate *SNHG14* may be a promising therapeutic target for patients with HER2+ breast cancer. In addition, *SNHG14* may enhance breast cancer cell proliferation and invasion by acting as a sponge for *miR-193a-3p*.[68]

SNHG15 has also been shown to be highly expressed in breast cancer tissues and cell lines and is positively associated with larger tumor size, LNM, advanced TMN stage, and worse survival.[69,70] *SNHG15* primarily acts as a sponge for *miR-411-5p*[69] and *miR-211-3p*,[70] leading to the proliferation, migration, and invasion of breast cancer cells. Additionally, *SNHG15* knockdown enhances the cisplatin sensitivity of breast cancer cells by acting as a sponge for *miR-381*.[71] Moreover, bioinformatics analysis showed *SNHG16* might be associated with the prognosis of breast cancer.[72,73] In particular, *SNHG16* may interact with *miR-30a* to regulate the expression of ribonucleoside-diphosphate reductase subunit M2 (*RRM2*)[74] and competitively bind *miR-98* and the E2F Transcription Factor 5 (*E2F5*)[75] to promote the proliferation and invasion of breast cancer cells. Finally, *SNHG17*[76] and *SNHG20*[77] may also drive breast cancer progression by sponging *miR-124-3p* and *miR-495*, respectively.

In general, multiple SNHGs, including *SNHG1, GAS5, SNHG3, SNHG5, SNHG6, SNHG7, SNHG12, DANCR, SNHG14, SNHG15, SNHG16* and *SNHG20*, play a role in breast cancer. Targeting SNHGs, especially the treatment of drug-resistant breast cancer, is the future research direction.

Pancreatic Cancer

Pancreatic cancer is one of the most devastating human tumors, with high invasiveness, early metastasis, lack of specific symptoms, and high mortality. According to the most recent statistical data, the 5-year survival of pancreatic cancer is 9%, which is the lowest among all types of cancers and continues to increase (by 0.3% per year) in men.[78] The high fatality rate in pancreatic cancer is attributed to late diagnosis and resistance to current therapies. Recent studies demonstrate lncRNAs are critical in the pathogenesis of pancreatic cancer and are therefore potential biomarkers or drug targets.[79]

SNHG1 acts as an oncogene in pancreatic cancer and accelerates cancer cell growth.[80] In addition, *SNHG1* overexpression can promote *cyclin D1*-mediated pancreatic cancer proliferation by regulating the cell cycle.[81] Meanwhile, *SNHG1* downregulation inhibits the proliferation, migration, and invasion of pancreatic cancer cells by

suppressing the *Notch-1* signaling pathway.[80] Similarly, *SNHG1* downregulation inhibits the *PI3K/AKT* signaling pathway in pancreatic ductal adenocarcinoma (PDAC).[82]

By acting as a sponge for *miR-32-5p*, *GAS5* can promote the expression of *PTEN* and stop the activation of the *PI3K/AKT* signaling pathway, thereby inhibiting pancreatic cancer cell proliferation and survival.[83] *GAS5* also inhibits the expression of the oncogene cyclin-dependent kinase 6 (*CDK6*), although the underlying mechanisms have not been determined.[84] Studies also show *GAS5* reduces the chemoresistance of pancreatic cancer cells by downregulating *miR-181c-5p* and *miR-221*.[85,86]

SNHG7 is highly expressed in pancreatic cancer tissues and positively correlates with reduced OS. Meanwhile, *SNHG7* knockdown suppresses cell proliferation, migration, and invasion of pancreatic cancer cells by modulating the *miR-342-3p*/inhibitor of DNA binding 4 (*ID4*) axis.[87] Zhang et al[88] showed low expression of *SNHG9* in pancreatic cancer tissues and serums, while those with high *SNHG9* expression had significantly higher survival rates. This data indicates *SNHG9* may be a novel prognostic marker for pancreatic cancer.

High *DANCR* expression correlates with vascular invasion, advanced T grade, LNM, and advanced TNM stage, and is an independent risk factor for poor OS and progression-free survival (PFS) in PDAC.[89,90] Mechanistically, *DANCR* acts as an miRNA sponge, affecting the *miRNA-33a-5p*/Anexelekto (*AXL*) axis,[89] the *miRNA-33b/MMP16* axis,[91] the *miR-135a/NLRP3* axis,[92] and the *miR-214-5p/E2F2* axis[90] to promote cell proliferation, migration, invasion, and metastasis in pancreatic cancer.

The *SNHG14* oncogene also potentiates pancreatic cancer cell proliferation through modulation of annexin A2 (*ANXA2*) expression by acting as a ceRNA for *miR-613*.[93] It also acts as a sponge for *miR-10*, thereby enhancing autophagy, which underlies the chemoresistance of PDAC cells to gemcitabine.[94,95] Finally, *SNHG15* and *SNHG16* are upregulated in pancreatic cancer samples and are associated with progression in pancreatic cancer patients.[96,97] *SNHG15* may help repress *P15* and *KLF2* expression,[96] while *SNHG16* promotes cell proliferation, migration, and invasion of pancreatic cancer by sponging *miR-200a-3p*[98] and *miR-218-5p*.[97] *SNHG16* may also promote pancreatic cancer lipogenesis by directly regulating the *miR-195/SREBP2* axis.[99]

In short, many SNHGs have a significant predictive effect on the survival of pancreatic cancer patients, and can be used as a clinical prognostic marker in pancreatic cancer.

Ovarian Carcinoma

Ovarian cancer is the most lethal gynecological cancer in women globally.[100] Despite recent improvements in cytoreductive surgery and chemotherapy, the 5-year survival rate of ovarian cancer is still approximately 40–50% owing to its late diagnosis and the development of chemoresistance.[78] Therefore, understanding the molecular mechanisms of ovarian carcinogenesis may help improve diagnosis, therapy, and prevention.

Expression of *SNHG1* is increased in human epithelial ovarian cancer tissues and cell lines compared to normal healthy tissues, and promotes the proliferation and invasion of ovarian carcinoma cells through the regulation of EMT and the *Wnt/β-catenin* pathway.[101,102] Meanwhile, *GAS5* acts as a tumor suppressor and is expressed in low levels epithelial ovarian cancer samples.[103,104] Indeed, *GAS5* expression correlates with prognosis in epithelial ovarian cancer, including International Federation of Gynecology and Obstetrics (FIGO) stage, histological type, OS, and disease-free survival (DFS).[103,104] In terms of its mechanism of action, *GAS5* may block *CCAAT*/enhancer-binding protein beta (*CEBPB*)-mediated transcription of the growth/differentiation factor 15 (*GD15*), leading to decreased viability and increased apoptosis of ovarian cancer cells.[105] *GAS5* may also suppress the proliferation of ovarian cancer cells by sponging *miR-21*[106] and *miR-196a-5p*,[107] which regulate sprouty homolog 2 (*SPRY2*) and homeobox A5 (*HOXA5*) expression, respectively. *GAS5* is also implicated in inflammasome formation and pyroptosis, but the underlying mechanism is unclear.[108] Finally, *GAS5* has been linked to chemoresistance; in particular, *GAS5* overexpression control the expression of poly(ADP-ribose) polymerase 1 (*PARP1*) by recruiting the transcription factor *E2F4* to its promoter, which subsequently affects the mitogen-activated protein kinase (*MAPK*) pathway activity, further enhance the cisplatin sensitivity of ovarian cancer cells.[109]

Upregulation of *SNHG3* expression is associated with poor prognosis in ovarian cancer (including FIGO stage and LNM) and promotes proliferation and invasion by activating the *GSK3β/-catenin* signaling pathway.[110] Bioinformatics analysis has shown *SNHG3* is related to energy metabolism in the "glycolysis", "Kreb's cycle", and "oxidative phosphorylation" pathways, and to "drug resistance".[111] Similarly, *SNHG5* has been implicated in

chemoresistance: paclitaxel-resistant ovarian cancer tissues and cell lines have lower levels of *SNHG5*, while *SNHG5* overexpression can enhance paclitaxel sensitivity (likely by sponging *miR-23a*).[112]

SNHG12 is also upregulated in ovarian cancer tissues and enhances the proliferative and migratory capacity of cells via sponging *miR-129* and upregulating expression of *SOX4* (a TF).[113] In addition, *DANCR* levels are higher in ovarian cancer patients with worse tumor stage and accompanied by metastatic loci.[114] *DANCR* binds directly to *miR-145* and regulates vascular endothelial growth factor (*VEGF*) expression.[115] Indeed, knockdown of *DANCR* impairs ovarian tumor growth by inhibiting tumor angiogenesis.[115] In addition, *DANCR* may enhance the proliferation, migration, and invasion capacities of ovarian cancer cells by upregulating expression of the insulin-like growth factor 2 (*IGF2*)[116] and downregulating *UPF1* RNA Helicase And ATPase (*UPF1*) expression.[114]

Like *SNHG12*, *SNHG14* is highly expressed in ovarian cancer tissues and associated with poorer OS.[117,118] *SNHG14* may promote ovarian cancer cell progression by sponging *miR-125a-5p*[117] and *miR-219a-5p*,[118] or directly regulating the expression of DiGeorge syndrome chromosomal region 8 (*DGCR8*).[119] *SNHG15* and *SNHG16* may also serve as oncogenes in epithelial ovarian cancer. *SNHG16* has been shown to promote the proliferation, invasion, and migration of cancer cells via activation of the *PI3K/AKT* signaling pathway,[120] while the role of *SNHG15* is unclear.[121] *SNHG20* is also upregulated in ovarian cancer and is associated with shorter OS.[122] *SNHG20* knockdown suppresses *Wnt/β-catenin* signaling activity and EMT-associated gene expression, thereby inhibiting ovarian cancer cell proliferation, migration, and invasion.[123] Finally, the *SNHG22* oncogene may regulate the *miR-2467/Gal-1* axis to promote cisplatin- and paclitaxel-resistance of ovarian cancer cells.[124]

In a word, compared with other SNHGs, *GAS5* regulates the progression of ovarian cancer through various mechanisms, indicating its key role in the development of ovarian cancer.

Prostate Cancer

Prostate cancer is the most common malignancy in males and accounts for 10% of cancer-related deaths.[78] Androgen deprivation therapy (ADT) is the standard treatment for patients with biochemical recurrence after primary treatment, or with locally-advanced or metastatic disease. However, the majority of cancers will eventually acquire ADT resistance and progress to castration-resistant prostate cancer (CRPC).[125] Aberrantly expressed lncRNAs can be indicative of certain stages of prostate cancer progression, and may predict early progression or efficiently sustain tumor-related signaling pathways. Thus, lncRNAs may be applicable for the diagnosis of prostate cancer, as well as being potential criteria in the choice of therapy and new therapeutic targets of CRPC.[126]

SNHG1 upregulation in prostate cancer correlates with the Gleason score, T stage, and a short biochemical recurrence-free survival time.[127] *SNHG1* may promote prostate cancer cell proliferation by regulating the *miR-199a-3p/CDK7* axis[128] and the *miR-377-3p/AKT2* axis.[129] Conversely, *GAS5* levels are reduced in prostate cancer tissues and cell lines.[130–132] Low *GAS5* levels are associated with prostate-specific antigen level, Gleason score, and pathological stage.[130–132]

Most studies indicate that *GAS5* inhibits the proliferation, migration, and invasion of prostate cancer cells, and promotes apoptosis.[130–132] In terms of its mechanism of action, *GAS5* may act as a sponge for *miR-103*, which in turn, inactivates the *AKT/mTOR* signaling pathway, thus inhibiting prostate cancer cell proliferation.[131] In addition, two single nucleotide polymorphisms (SNPs) located in the chromosomal segment of *GAS5* (rs55829688 and rs145204276) can increase *GAS5* expression,[133–135] and are associated with improved survival in prostate cancer.[133] Patients with prostate cancer and the *GAS5* rs145204276 polymorphism are associated with a low risk of pathologic N stage and seminal vesicle invasion.[135] Furthermore, patients with prostate cancer aged >65 years who carry the *GAS5* rs145204276 polymorphism show decreased risk of clinical T stage, pathologic N stage, and lymphovascular invasion.[135] Differential expression of *GAS5* due to these SNPs likely affects the *miR-21*/programmed cell death 4 (*PDCD4*)/*PTEN* axis,[133] as well as the *miR-1284/AKT*[133] and *miR-1284*/high mobility group box 1 (*HMGB1*)[134] pathways. In addition, overexpression of *miR-145* can upregulate *GAS5* expression, although *GAS5* overexpression (or silencing) has no effect on *miR-145* levels.[132]

Enhancing *GAS5* expression may be particularly useful in androgen-sensitive prostate cancers.[136] Indeed, mTOR inhibitors enhance *GAS5* transcript levels in androgen-sensitive prostate cancer cell lines but have no effect on androgen-independent cell lines (which exhibit low endogenous levels of *GAS5*).[136] As further evidence of its tumor-suppressing role, *GAS5* is implicated in improving the radiosensitivity of prostate cancer cells. In particular,

GAS5 can enhance the α-Solanine-induced radiosensitivity of prostate cancer cells by negatively regulating *miR-18a*.[137]

Despite available evidence showing that *GAS5* acts as a tumor suppressor, some studies report *GAS5* may exist as an oncogene in prostate cancer. For example, Zhang and Chen et al.[138,139] found *GAS5* expression was higher in prostate cancer tissues than normal healthy tissues in both public databases and human tissue samples. In addition, functional analysis showed *GAS5* knockdown inhibited the proliferation and cell cycle progression of prostate cancer cells, while promoting apoptosis.[138] A bioinformatics analysis also showed high expression of *GAS5* correlated with poorer DFS in prostate cancer, and other studies show *GAS5* may be involved in regulating translational elongation, protein biosynthesis, transcription, protein translation, and proliferation.[138–140]

SP1-mediated upregulation of *SNHG4* can facilitate prostate cancer progression via the *miR-377*/zic family member 5 (*ZIC5*) axis.[141] Similarly, *SNHG6* overexpression was associated with shorter DFS in the Cancer Genome Atlas (TCGA) and Taylor datasets, with bioinformatics analysis revealing *SNHG6* is associated with "translation", "nuclear-transcribed mRNA catabolic processes", "ribosomal RNA processing", and "mRNA splicing".[142] *SNHG7* is also significantly upregulated in prostate cancer tissue and cell lines,[143,144] and correlates with the Gleason score, bone metastasis, pelvic LNM, TNM stage, and OS.[145] In terms of its mechanism of action, *SNHG7* knockdown was found to inhibit proliferation and promote *CCND1*-induced cell cycle arrest at the G0/G1 phase.[144] *SNHG7* can also promote EMT via regulating *miR-324-3p* and *WNT2B*, an important protein in the Wnt signaling pathway.[143] Therefore, targeting the *SNHG7/miR-324-p/WNT2B* axis may represent a novel therapeutic strategy for prostate cancer treatment.

As *SNHG12* acts as an oncogene, it may be a useful predictor of poor prognosis in prostate cancer. Indeed,

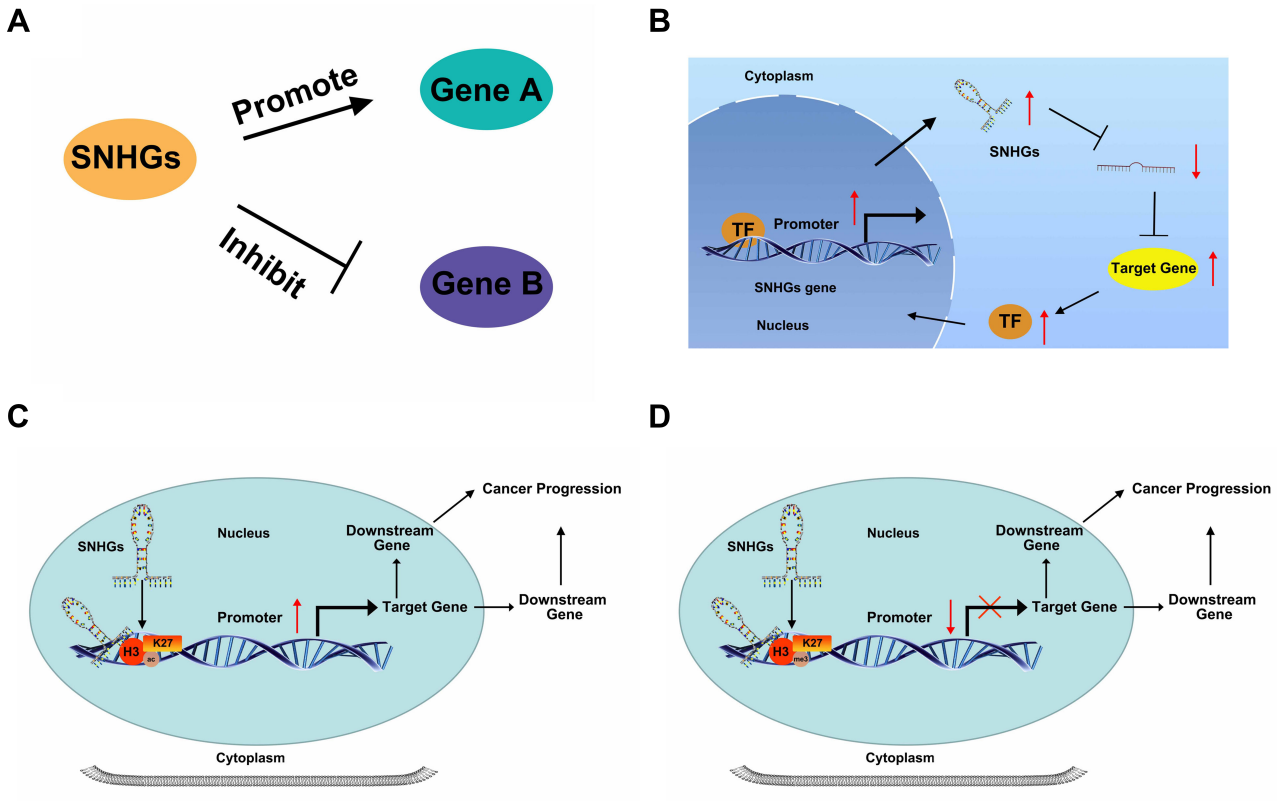

Figure 2 Schematic diagram of the functional mechanism of SNHGs. (**A**) SNHGs can promote or inhibit expression of downstream target genes. (**B**) Transcription factors (TF) bind to the promoter and activate transcription of SNHGs. SNHGs can then act as competing endogenous RNA sponges to regulate transcription of downstream target genes (ie TF), forming a positive feedback loop. SNHGs regulate promoter methylation (C) or acetylation (D) of downstream target genes and regulate tumor progression.

a study showed *SNHG12* acts as a sponge for *miR-195* and can activate the Wnt/β-catenin signaling pathway.[146] *SNHG12* can also promote cell viability and inhibit apoptosis and autophagy of prostate cancer cells via regulating the expression of the G1/S-specific cyclin-E1 (*CCNE1*) by sponging *miR-195*.[147] Bioinformatic analysis revealed higher expression of *SNHG12* was enriched in the "P53 signaling pathway", "cell cycle", "regulation of cell migration", "cellular metabolic process", "gene expression", and "Notch signaling pathway", and that *SNHG12* may target *miR-133b*.[148]

The oncogene *DANCR* has also been shown to promote the invasion and migration of prostate cancer cells in vitro and the metastasis of tumor xenografts in nude mice.[149] Mechanistically, *DANCR* works synergistically with *EZH2* to downregulate the expression of the tissue inhibitor of metalloproteinases (*TIMP*) 2/3.[149] Furthermore, downregulation of *DANCR* can increase the paclitaxel sensitivity of prostate cancer cells by negatively regulating the expression of *miR-135a*.[150] In addition, stimulation of the *DANCR/miR-34a-5p* axis enhanced docetaxel-resistance in prostate cancer via targeting *JAG1*, which in turn activates the *Notch* signaling pathway.[13] Finally, *SNHG14*,[151] *SNHG15*,[152] and *SNHG20*[153] may all act as oncogenes in prostate cancer via targeting *miR-613*, *miR-338-3p*, and *miR-6516-5p* to promote cell proliferation, migration, and invasion.

In conclusion, SNHGs plays an important role in the process and embody diversified treatment strategies in prostate cancer, especially in CRPC.

Conclusion

This review highlights that the abnormal expression of SNHGs is significantly related to poor prognosis (eg TNM stage, LNM, OS, DFS) and function (eg proliferation, invasion, migration, apoptosis, autophagy, and chemoresistance) in multiple endocrine-related cancers. Some SNHGs played similar roles in different tumors. For example, S*NHG1, SNHG3, SNHG4, SNHG6, SNHG7, SNHG12, SNHG14, SNHG16, SNHG17, SNHG20* and *SNHG22* promotes tumor growth as oncogenes, while *GAS5* and *SNHG9* played the role of tumor suppressor genes. In addition, *SNHG5, DANCR, SNHG15* played a dual role, which have attracted more scholars' attention. SNHGs could regulate the tumor process via various mechanisms, including direct regulation (promotion or inhibition) (Figure 2A), binding and being activated by TFs, acting as a ceRNA, activating different signaling pathways (Figure 2B), and regulating promoter methylation (Figure 2C) or acetylation of downstream target genes (Figure 2D). Both methylation and acetylation were histone modifications and their mechanisms were similar. The difference between them was that they bound and modified different histones, and then promoted or inhibited the expression of downstream genes. However, the SNHGs described in this review are only just the tip of the iceberg, and further mechanistic will be required as more SNHG family members are uncovered.

Abbreviations

ACSL1, acyl-CoA synthetase long chain family member 1; ADT, androgen deprivation therapy; *AKT*, protein kinase B; *ANXA2*, annexin A2; *AXL*, Anexelekto; *BDNF*, brain-derived neurotrophic factor; *CCND1/2*, cyclin-D1, cyclin-D2; *CCNE1*, cyclin-E1; C*DK6/7*, cyclin-dependent kinase 6, cyclin-dependent kinase 7; *CDKN2B*, cyclin-dependent kinase 4 inhibitor B; *CEBPB*, CCAAT/enhancer-binding protein beta; CeRNA, competing endogenous RNA; CRPC, castration-resistant prostate cancer; *DANCR*, Differentiation antagonizing non-protein coding RNA; DFS, disease-free survival; *DGCR8*, DiGeorge syndrome chromosomal region 8; *E2F5*, E2F Transcription Factor 5; *EHZ2*, enhancer of zeste homolog 2; EMT, epithelial–mesenchymal transition; FIGO, International Federation of Gynecology and Obstetrics; *FOXO1*, forkhead box O1; *GAS5*, growth arrest specific transcript 5; *GD15*, growth/differentiation factor 15; *HDGF*, hepatoma-derived growth factor; *HER2*, human epidermal growth factor receptor 2; *HMGB1*, high mobility group box 1; *HOXA5*, homeobox A5; *IDO*, indoleamine 2,3 dioxygenase; *IGF2*, insulin-like growth factor 2; *JAG1*, Jagged 1; *KLF2*, Kruppel Like Factor 2; LncRNA, long non-coding RNA; LNM, lymph node metastasis; *MAPK6*, mitogen-activated protein kinase 6; *MMP13*, matrix metalloproteinase 13; *NRF2*, nuclear factor E2-related factor 2; OS, overall survival; *PABPC1*, polyadenylate-binding protein 1; *PARP1*, poly (ADP-ribose) polymerase 1; *PCNA*, proliferating cell nuclear antigen; PDAC, pancreatic ductal adenocarcinoma; *PDCD4*, programmed cell death 4; PFS, progression-free survival; *PI3K*, phosphatidylinositol 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PKM*, pyruvate Kinase M1/M2; PTC, papillary thyroid carcinoma; *PTEN*, phosphatase and tensin homolog; *RRM2*, ribonucleoside-diphosphate reductase subunit M2; *RXRA*, retinoid X receptor alpha; SNHG, small nucleolar RNA host genes; SnoRNA, small nucleolar RNA; SNP, single nucleotide polymorphisms; *SOCS3*, suppressor of cytokine signaling 3; *SPRY2*, sprouty homolog 2; TCGA, the Cancer Genome Atlas; TF, transcription Factor; *TIMP*, tissue inhibitor of

metalloproteinases; TNM, tumor node metastasis; *UPF1*, *UPF1* RNA Helicase And ATPase; *VASP*, vasodilator-stimulated phosphoprotein; *VEGF*, Vascular endothelial growth factor; *YAP1*, Yes-associated protein 1; *ZIC5*, zic family member 5.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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