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STATE-OF-THE-ART REVIEW

Functional role of lncRNAs in gastrointestinal malignancies: the peculiar case of small nucleolar RNA host gene family

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Long noncoding RNAs (lncRNAs) play crucial roles in normal physiology and are often de-regulated in disease states such as cancer. Recently, a class of lncRNAs referred to as the small nucleolar RNA host gene (SNHG) family have emerged as important players in tumourigenesis. Here, we discuss new findings describing the role of SNHGs in gastrointestinal tumours and summarize the three main functions by which these lncRNAs promote carcinogenesis, namely: competing with endogenous RNAs, modulating protein function, and regulating epigenetic marking. Furthermore, we discuss how SNHGs participate in different hallmarks of cancer, and how this class of lncRNAs may serve as potential biomarkers in cancer diagnosis and therapy.

Introduction

Only a small fraction of the human genome is protein coding [1]. In fact, thousands of transcribed RNAs are non-protein coding RNAs (ncRNAs). Non-coding RNAs can be classified into two main groups based on their transcript lengths: (a) small noncoding RNAs, with < 200 nucleotides, including well-known RNA species such as microRNAs (miRNAs), small nucleolar RNAs (snoRNAs), and Piwi-interacting RNAs (piRNAs) and (b) long non-coding RNAs (lncRNAs), which are longer than 200 nucleotides. Recent studies have shown that lncRNAs are widely involved in epigenetic modifications, and regulation of gene expression at

Abbreviations
5-FU, 5-fluorouracil; CCA, cholangiocarcinoma; ceRNA, competing endogenous RNA; CRC, colorectal cancer; EC, esophageal cancer; EMT, epithelial to mesenchymal transition; ESCC, esophageal squamous cell carcinoma; EZH2, enhancer of zeste homolog 2; GC, gastric cancer; GI, gastrointestinal; HCC, hepatocellular cancer; KLF4, Kruppel-like factor 4; lncRNA, long noncoding RNA; miRNA, microRNA; MRE, miRNA response element; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; piRNA, Piwi-interacting RNA; rRNAs, ribosomal RNA; SNHG, small nucleolar RNA host gene; snoRNA, small nucleolar RNA.

transcriptional and post-transcriptional levels, affecting various stages of cancer proliferation, invasion, and metastasis. These functions designate lncRNAs as suitable diagnostic or prognostic markers in cancer [2–4].

Small nucleolar RNAs are a class of conserved and abundant 60–300 nucleotide ncRNAs that accumulate in the nucleoli and are involved in post-transcriptional modification and maturation of ribosomal RNAs (rRNAs) and spliceosomal RNAs. The nucleolar RNAs exhibit diverse functions in post-transcriptional gene regulation and, based on specific motifs within the RNA structure, can be categorized into two main classes: H/ACA box snoRNAs (SNORAs) that provide target sites for nucleotide pseudouridylation and C/D box snoRNAs (SNORDs) that promote 2-*O*-ribose methylation [5–9]. In addition, recent studies indicate that snoRNAs are involved in carcinogenesis and can function either as oncogenes or tumour suppressors [4,9–11]. Of note, a small number of snoRNAs are transcribed by their own regulatory elements (i.e. promoter, terminator, and enhancers). In contrast, most snoRNAs are transcribed as intronic RNAs that are released by subsequent splicing of their host RNAs [12]. Among these host RNAs, the small nucleolar RNA host gene (SNHG) family represents a main class of lncRNAs that includes 32 identified members in the human genome (GENCODE V33). Although members of this lncRNA family do not encode proteins and were thought to mainly act as carriers of snoRNAs [5,13], new findings suggest that SNHG lncRNAs can contribute to various physiological functions. These lncRNAs have attracted great attention as key modulators of gene expression, protein function, cell signalling, and epigenetic modifications. Given these key functions, it is not surprising that SNHGs can participate in cancer initiation, promotion, and progression and serve as important prognostic markers. Accordingly, loss and gain of function experiments have suggested that SNHGs can serve as new therapeutic targets in cancer [10,14–16].

In this review, we discuss the molecular mechanisms by which SNHGs participate in cancer development, highlighting the current gaps and future directions in this research field. We particularly focus on gastrointestinal (GI) tumours that encompass esophageal (EC), gastric (GC), colorectal (CRC), hepatocellular (HCC), and pancreatic (PC) cancers [17]. These malignancies display high mortality risk, limited diagnostic biomarkers, and ineffective therapies. In recent years, the number of patients suffering from GI cancers has gradually increased (about 5 million patients in 2018), resulting in a higher mortality rate (approximately 3.5 million), which makes these malignancies a major cause of cancer-related deaths worldwide [18]. Although various treatment strategies can be applied [19], the overall survival rate remains low in advanced disease stages, presenting an urgent need for new diagnostic and therapeutic markers [20].

Molecular mechanisms of SNHG family in GI cancers

After the discovery of *SNHG1* in 1997 by Frey et al. [21] other studies identified 22 additional members of the family that play critical roles in GI cancers (Table 1). These studies revealed that the carcinogenic properties of SNHGs are related to their functional domains including DNA-binding, RNA-binding, and protein-binding domains [22], as shown in Fig. 1. In this section, we summarize the main functions of the SNHG family in GI cancer development.

Acting as competing endogenous RNAs

miRNAs have been recognized as key regulators in normal physiology across multiple organisms. The function of miRNAs can be inhibited by competitive inhibitors known as miRNA-sponges and antisense oligonucleotides [23,24]. Salmena et al. first presented the competing endogenous RNA (ceRNA) hypothesis in 2011 [25] suggesting that lncRNAs can compete with miRNAs using shared miRNA response elements (MREs). lncRNAs with ceRNA activity interact with miRNAs and prevent their binding to target mRNAs due to sequence similarities, ultimately controlling gene expression [26,27]. After this seminal discovery, many cancer-related genes (both coding and non-coding) were identified, that contain MREs [14]. In recent years, increasing studies have shown the involvement of lncRNA-miRNA-mRNA regulatory networks in tumour initiation, progression, and pathogenesis including many GI malignancies (Table 2) [14,28]. Here, we used published studies and gathered all SNHGs that have a role in GI malignancies and summarized all potential interactions with miRNAs and their target mRNAs (Table S1). Based on this analysis, we calculated the connection degree of each gene (SNHG, miRNA, or mRNA) to show its importance in the ceRNA network (Table S2). Furthermore, connections that have two parameters were selected: *SNHG* genes (more than 10) and miRNAs (more than 4) and summarized in Table S3, Additional file. Finally, the ceRNA network (as Sankey diagram) was built using the online software sankeyMATIC (https://sankeymatic.com/build/) as illustrated in Fig. 2. In this section, we review some examples of SNHGs that function as ceRNAs in GI cancers.

Table 1. Small nucleolar RNA host genes (SNHGs) contribute to digestive system malignancies (GENCODE V33).

Name	Synonym	Coding region	Length of longest variant (nt)	No. of exons	No. of isoforms	No. of snoRNAs hosted	Name of snoRNAs	Digestive tract malignancies	Accession no.
SNHG1	*linc00057/UHG*	11p12.3	1137	11	12	8	*SNORD22, SNORD25, SNORD26, SNORD27, SNORD28, SNORD29, SNORD30*, and *SNORD31*	ESCC, GC, CRC, HCC, PC, CCA	ENSG00000255717
SNHG2	*GAS5*	1q25.1	630	12	29	11	*SNORD44, SNORD47, SNORD74, SNORD75, SNORD76, SNORD77, SNORD78, SNORD79, SNORD80, SNORD81*, and *SNORD103*	ESCC, GC, CRC, HCC, PC	ENSG00000234741
SNHG3	*RNU17D/U17HG*	1p35.3	2238	4	2	2	*SNORA73A* and *SNORA73B*	GC, CRC, HCC	ENSG00000242125
SNHG4	*U19H*	5q31.2	1264	7	4	2	*SNORA74D* and *SNORA74A*	HCC	ENSG00000281398
SNHG5	*U50HG/C6orf160*	6q14.3	534	6	2	2	*SNORD50A (U50)* and *SNORD50B (U50′)*	GC, CRC, HCC	ENSG00000203875
SNHG6	*U87HG*	8q13.1	727	3	3	1	*SNORD87*	ESCC, GC, CRC, HCC	ENSG00000245910
SNHG7	*NCRNA00061*	9q34.3	2176	6	3	2	*SNORA17A* and *SNORA17B*	ESCC, GC, CRC, HCC, PC	ENSG00000233016
SNHG8	*LINC00060*	4q26	653	4	3	1	*SNORA24*	ESCC, GC, CRC, HCC, PC	ENSG00000269893
SNHG9	*NCRNA00062*	16p13.3	345	2		1	*SNORA78*	PC	ENSG00000255198
SNHG10	*C14orf62/LINC00063*	14q32.13	1980	3	2	1	*SCARNA13*	HCC	ENSG00000247092
SNHG11	*C20orf198/LINC00101*	20q11.23	1101	6	3	2	*SNORA60* and *SNORA71E*	HCC	ENSG00000174365
SNHG12	*C1orf79/LNC04080*	1p35.3	1383	5	8	4	*SNORA16A, SNORA44, SNORA61* and *SNORD99*	GC, CRC, HCC	ENSG00000197989
SNHG13	*DANCR/ANCR*	4q12	1189	4	3	1	*SNORA26*	GC, CRC, HCC, CCA	ENSG00000226950
SNHG14	*UBE3A-ATS*	15q11.2	19 263	148	23	33	*SNORD109A, SNORD109B, SNORD115*, and *SNORD116-1 to SNORD116-30*	GC, CRC, HCC, PC	ENSG00000224078
SNHG15	*C7orf40*	7p13	738	5	5	1	*SNORA9*	GC, CRC, HCC, PC	ENSG00000232956
SNHG16	*Nbla10727*	17q25.1	2538	6	4	3	*SNORD1A, SNORD1B*, and *SNORD1C*	ESCC, GC, CRC, HCC, PC	ENSG00000163597
SNHG17	*NONHSAG031748*	20q11.23	1301	8	14	4	*SNORA71A, SNORA71B, SNORA71C*, and *SNORA71D*	GC, CRC	ENSG00000196756

Table 1. (Continued).

Name	Synonym	Coding region	Length of longest variant (nt)	No. of exons	No. of isoforms	No. of snoRNAs hosted	Name of snoRNAs	Digestive tract malignancies	Accession no.
SNHG18	*CTD-2001E22.2*	5P15.31	1503	3	2	1	*SNORD123*	HCC	ENSG00000250786
SNHG19	*SNORD60HG*	16p13.3	357	2	2	1	*SNORD60*	ESCC, CRC, HCC	ENSG00000260260
SNHG20	*C17orf86/ SCARNA16HG*	17q25.2	2183	3	3	1	*SCARNA16*	ESCC, GC, CRC, HCC	ENSG00000234912
SNHG22	*NA*	18q21.1	37 037	4	2	1	*SCARNA17*	ESCC, GC, CRC, HCC	ENSG00000267322.2
SNHG23	*MEG8*	14q32.2-q32.31	4572	51	17	40	*SNORD113-1 to 9* and *SNORD114-1 to 31*	PC	ENSG00000225746

miR-195

miR-195 belongs to the miR-15/107 family and is known to act as a tumour suppressor [29]. *SNHG1* is shown to sponge *miR-195* [30,31] or compete with *miR-195-5p* to regulate PDCD4 expression, a protein that exists in the nucleus of proliferating cells, leading to HCC progression [32]. A recent study also shows that downregulation of *SNHG12* promotes cancer progression via altered interaction of *miR-195-5p* and BCL-9 (a member of the WNT signalling pathway) in esophageal squamous cell carcinoma (ESCC) [33]. It is also demonstrated that *SNHG16* contributes to HCC carcinogenesis via direct interaction with miR-195, in which *SNHG16* downregulation decreases the proliferation and invasion of HCC cells [34]. Moreover, *SNHG16* lncRNA promoted carcinogenesis in PC by regulating the *miR-195*/SREBP2 ceRNA axis [35].

miR-140

Given its tumour suppressor role, dysregulation of *miR-140* can lead to tumourigenesis in various tissues [36–38]. *SNHG1* can serve as a *miR-140* sponge and can influence the downstream target *ADAM10* to promote gastric cancer cell proliferation and invasion [39]. More mechanistic studies showed that *SNHG1* can interact with *miR-140*, enhances TLR4 expression, and leads to the activation of NF-κB signalling in cholangiocarcinoma (CCA) [40]. In ESCC, *SNHG16* interacts with *miR-140-5p* and upregulates the miRNA target gene *ZEB1* which consequently leads to ESCC cell proliferation, migration, and epithelial-to-mesenchymal transition (EMT) [41]. Furthermore, this lncRNA induces sorafenib resistance in HCC by interacting with *miR-140-5p* [42,43]. It was also demonstrated that *SNHG20* can upregulate the N-MYC regulated gene family member 3 (*NDRG3*), by ceRNA effects on *miR-140-5p*, leading to resistance of GC cells to 5-fluorouracil (5-FU) [44].

miR-222

Several SNHGs can interact with *miR-222*, which is a miRNA deregulated in several cancers with both oncomiR and tumour-suppressor functions [45]. For instance, *GAS5* can act as a ceRNA for *miR-222* to regulate PTEN, AKT, and mTOR proteins and affects GC cell proliferation through PTEN/AKT/mTOR pathway [46]. Additionally, *GAS5* can bind to *miR-222-3p* and regulates the expression of PTEN, LC3B, and cleaved Caspase-3 and phosphorylation of AKT in CRC [47].

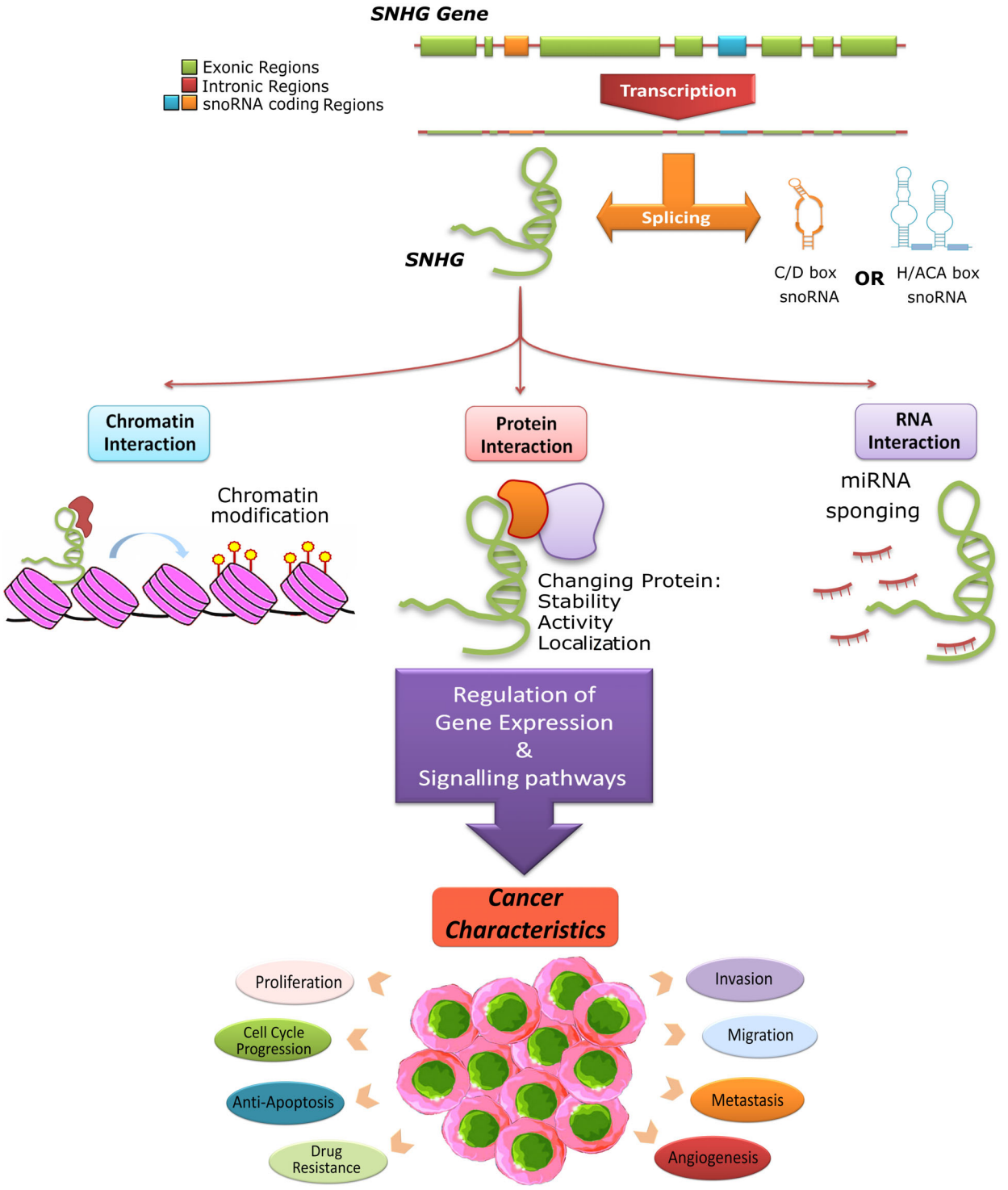

Fig. 1. An overview of small nucleolar RNA host gene (SNHG) family biogenesis and functions in GI tumours. These functions mainly rely on interactions with macromolecules (RNA, protein, and DNA) and include ceRNA activity, protein interactions, and chromatin remodelling, leading to deregulated gene expression and aberrant signalling pathways.

Table 2. Functional characterization of SNHG family lncRNAs in gastrointestinal cancers.

			Function in cancer cells							Molecular mechanism						
										ceRNA network				Protein network		
SNHG	Associated digestive cancer	Misregulation	Proliferation	Apoptosis	Invasion/ migration/ metastasis	Tumouri-genicity	Clinicopatho logical features	Poor survival	Ref.	Target miRNA (as ceRNA)	Target mRNA	Related signalling pathway	Ref.	Target protein	Related signalling pathway	Ref.
SNHG1	ESCC	Up	↑	↓	↑		↑	↑		miR-338	CST3		[169]	E-cadherin, Vimentin, N-cadherin, NOTCH	NOTCH	[83]
										miR-204	HOXC8		[170]			
	GC	Up	↑	↓	↑	↑	↑	↑	[172]	miR-140	ADAM10		[39]	DNMT1		[171]
										miR-15b	DCLK1	NOTCH1	[82]		NOTCH	[173]
	CRC	Up	↑	↓	↑	↑	↑	↑		miR-145	p70S6k, E2F3		[174]	E-cadherin, β-catenin, CCND1, LEF, TCF4, TCF7, MMP7, MMP9, c-MYC	WNT/β-catenin	[104–106]
										miR-154-5p	CCND2		[116]	P53		[175,176]
										miR-137	RICTOR, AKT, SGK1, p70S6K1, L3II/LC3I		[177]			
	HCC	Up	↑		↑	↑	↑	↑	[179,180]	miR-195			[30,31]	FAS, BAX, CDKNIA		[178]
										miR-195-5p	PDCD4		[32]	DNMT1, N-cadherin, NOTCH-1, HES1, Vimentin, E-cadherin		[84]
										miR-140-5p	CDK4	EMT	[117]			
										miR-376a	FOXK1, Snail		[181]	SLC3A2	AKT	[96]
										miR-195	AEG-1		[31]	DNMT1. P53		[84]
	PC	Up	↑		↑	↑	↑	↑	[183]	miR-195	CCND1		[182]		PI3K/AKT	[97]
														N-cadherin, HES1, Vimentin, NOTCH-1	NOTCH	[184]
	CCA	Up	↑	↓	↑	↑	↑			miR-140	TLR4	NF-κB	[185]	BCL-2, BAX	PI3K/AKT	[97]
SNHG2 (GAS5)	ESCC	Up/Down	↓	↑	↓	↓	↓	↓		miR-301a	CXCR4	NF-κB, WNT/β-catenin	[186]	PI3K		[98]
										miR-196a			[188]	PI3K, CHK2, Vimentin, N-cadherin	ATM-CHK2, EMT	[187]

Table 2. (Continued).

			Function in cancer cells							Molecular mechanism						
										ceRNA network				Protein network		
SNHG	Associated digestive cancer	Misregulation	Proliferation	Apoptosis	Invasion/ migration/ metastasis	Tumouri-genicity	Clinicopatho logical features	Poor survival	Ref.	Target miRNA (as ceRNA)	Target mRNA	Related signalling pathway	Ref.	Target protein	Related signalling pathway	Ref.
														IFN	JAK/STAT	[189]
	GC	Down	↓	↑	↓	↓	↓	↓	[192–194]	miR-106a-5p		AKT/mTOR	[191]	P21, CDK6		[190]
										miR-222		PTEN/AKT/mTOR	[46]	E2F1, CCND1		[194]
										miR-21	BCL-2, BAX, Caspase-3		[195]			
										miR-23a		MT2A	[197]	YBX1, P21		[196]
	CRC	Down	↓	↑	↓	↓	↓	↓	[198–201]	miR-222-3p	PTEN, LC3B, Beclin1	PTEN	[47]	AKT, ERK		[99]
										miR-221			[203]	VEGF-A, IL-10	ERK1/2, NF-κB	[202]
														YAP, YTHDF3		[204]
										miR-182-5p	FOXO3a		[205]	IL-12, iNOS, IL-1β, TNF-α IL-10, TGF-β, Arg-1, Fizz-1		[114]
															WNT/β-catenin	[107]
														NODAL	NODAL	[149]
	HCC	Down	↓	↑	↓	↓	↓	↓	[208,209]	miR-21	PDCD4-PTEN		[207]	Vimentin		[206]
											PTEN		[135]			
										miR-1323	TP53INP1		[210]			
										miR-135b	RECK		[211]			
										miR-126-3p			[212]			
										miR-544	RUNX3		[161]			
										miR-222		VEGF	[136]			
	PC	Down	↓	↑	↓	↓				miR-221	SOCS3	EMT	[138]	CDK6		[213]
										miR-32-5p	PTEN		[60]			
										miR-181c-5p		Hippo signalling	[137]			
SNHG3	ESCC	Up	↑		↑	↑		↑	[214]	miR-186-5p	METTL3		[215]	SNAIL, TWIST		[214]
	GC	Up	↑		↑	↑		↑		miR-326	TWIST		[216]			
										miR-3619-5p	ARL2		[150]			
	CRC	Up	↑			↑		↑		miR-182-5p	c-MYC, CCNB1, CCND2, CDK4, E3F1		[217]			
										miR-539	RUNX2		[218]			
										miR-370-5p	EZH1		[219]			
	HCC	Up	↑	↓	↑	↑	↑	↑	[221]	miR-128		CD151	[220]			
										miR-139-5p	BMI1		[222]			

Table 2. (Continued).

			Function in cancer cells							Molecular mechanism						
										ceRNA network				Protein network		
SNHG	Associated digestive cancer	Misregulation	Proliferation	Apoptosis	Invasion/ migration/ metastasis	Tumouri-genicity	Clinicopatho logical features	Poor survival	Ref.	Target miRNA (as ceRNA)	Target mRNA	Related signalling pathway	Ref.	Target protein	Related signalling pathway	Ref.
										miR-326	SMAD3, ZEB1		[223]			
										miR-148a-3p	DNMT1		[224]			
	CCA	Up							[225]							
SNHG4	GC	Up	↑	↓	↑	↑	↑	↑		miR-204-5p	E-caherin, N-cadherin, and Snail		[226]			
	CRC	Up	↑	↓	↑					miR-590-3p	CDK1		[227]			
	HCC	Up						↑	[229,230]	miR-154, miR-206	E2F	MAPK/ERK, mTOR	[228]			
SNHG5	ESCC	Down	↑		↑	↑	↑	↑						E-cadherin, N-cadherin, vimentin, CD24, MYLK, IGF2BP1	EMT	[85]
	GC	Up	↓	↑	↓	↓	↓	↓				[61,132,139,231]	miR-32	KLF4		[61]
													BAX, MRP1, MDR1, BCL-2		[139]	
													miR-20a	METase		[232]
	miR-101-3p	ZEB1	EMT	[129]												
	CRC	Up	↑	↓	↑	↑				miR-132-3p	CREB5		[234]	SPAT2		[233]
HCC	Up	↑	↓	↑	↑	↑	↑		[48,108,235]	miR-26a	GSK3β	WNT/β-catenin	[48]	UPF1	WNT/β-catenin	[108]
										miR-23c	HMGB2		[235]			
SNHG6	ESCC	Up	↑	↓	↑	↑	↑	↑	[237,238]	miR-186-5p	HIF1α		[236]			
										MiR-101-3p	EZH2		[64]			
	GC	Up	↑	↓	↑	↑	↑	↑		miR-101-3p	P27		[129]			
										miR-325-3p	GITR		[141]			
										miR-1297	BCL-2		[140]			
	CRC	Up	↑	↓	↑	↑	↑	↑	[242]	miR-26a-5p, miR-26b-5p, miR-214-3 p	EZH2		[240,241]	hnRNPA1		[239]
										miR-181a-5p	E2F5		[243]			
										miR-760	FOXC1		[244]			
										miR-194-5p	ULK1		[142]			
										miR-101-3p	UPF1, ZEB1	TGF-β/SMAD, EMT	[66]	EST1	PI3K/AKT/mTOR	[100]

Table 2. (Continued).

			Function in cancer cells							Molecular mechanism						
										ceRNA network				Protein network		
SNHG	Associated digestive cancer	Misregulation	Proliferation	Apoptosis	Invasion/ migration/ metastasis	Tumouri-genicity	Clinicopatho logical features	Poor survival	Ref.	Target miRNA (as ceRNA)	Target mRNA	Related signalling pathway	Ref.	Target protein	Related signalling pathway	Ref.
										miR-101-3p	TCF, β-catenin	WNT/β-catenin	[67]			
	HCC	Up	↑	↓	↑	↑	↑	↑	[245]	miR-26a, miR-26b	TAK1	NF-κB/JNK/P38	[49]	PARP, BAX, cleaved Caspase-3, PARP, CCND1, CDK4, CDK6, c-MYC		[65]
										Let-7c-5p	c-MYC		[246]			
										miR-101-3p	ZEB1, MMP-2/9		[65]			
										miR-139-5p	SERPINH1		[247]			
										miR-6509-5p	HIF1A		[248]			
	PC	Up	↑	↓	↑	↑				miR-26a-5p	FUBP1		[249]			
	CCA	Up	↑		↑			↑		miR-101-3p	E2F8		[154]			
SNHG7	ESCC	Up	↑	↓		↑	↑		[250,251]	miR-625			[251]	P15, P16		[250]
	GC	Up	↑	↓	↑		↑		[252,253]	miR-485-5p			[253]	P15, P16		[252]
										miR-34a	SNAIL	EMT	[254,255]			
	CRC	Up	↑	↓	↑	↑	↑	↑	[257–259]	miR-34a	GALNT7	PI3K/AKT/mTOR	[257]	FAIM2		[256]
										miR-216b	GALNT1		[258]			
										miR-485-5p, miR-193a-5p			[260]			
	HCC	Up	↑	↓	↑	↑	↑	↑		miR-122-5p	RPL4		[262]	RBM5		[261]
										miR-34a	SIRT1		[263]			
										miR-425	β-catenin, MMP9, N-cadherin, E-cadherin	WNT/β-catenin /EMT	[264]			
	PC	Up	↑		↑	↑		↑		miR-342-3p	ID4		[266]	NOTCH	Notch1/Jagged1/ Hes-1	[265]
										miR-146b-5p	Robo1		[267]			
SNHG8	GC	Up	↑	↓	↑	↑	↑	↑		miR-491	PDGFRA		[270]	EBV proteins (LF3, BHRF1, BHLF1, BNLF2)		[268,269]
	CRC	Up	↑		↑			↑		miR-663			[271]			
										miR-588	ATG7		[272]			

Table 2. (Continued).

			Function in cancer cells							Molecular mechanism						
										ceRNA network				Protein network		
SNHG	Associated digestive cancer	Misregulation	Proliferation	Apoptosis	Invasion/ migration/ metastasis	Tumouri-genicity	Clinicopatho logical features	Poor survival	Ref.	Target miRNA (as ceRNA)	Target mRNA	Related signalling pathway	Ref.	Target protein	Related signalling pathway	Ref.
	HCC	Up	↑		↑	↑	↑	↑		miR-149	PPM1F		[273]			
										miR-149-5p			[273]			
										miR-542-3p, miR-4701-5p	TET3, E2F2		[274]			
	PC	Up	↑	↓			↑	↑	[143]							
SNHG9	HCC	Up	↑		↑			↑						GSTP1		[275]
	PC	Down					↓		[276]							
SNHG10	GC	Up	↑		↑					miR-495-3p	CTNNB1		[278]	PBX3		[277]
	CRC	Up	↑		↑			↑		miR-3690			[279]			
	HCC	Up	↑		↑	↑	↑	↑		miR-150-5p	RPL4		[280]	SCARNA13	EMT	[280]
SNHG11	GC	Up	↑	↓	↑	↑	↑			miR-184	CDC25A					
										miR-483-3p, and miR-1276	CTNNB1, ATG12	WNT/β-catenin, EMT	[281]			
	CRC	Up	↑		↑	↑	↑	↑	[86]					p-YAP, p-LATS1	EMT, Hippo pathway	[86]
														IGF2BP1		[281]
														AK4, ENO1, HK2, Twist1	HIF-1 pathway	[282]
	HCC	Up	↑	↓	↑			↑	[230]	miR-184	AGO2		[283]			
	PC	Up	↑	↓	↑	↑				miR 324 3p	VEGFA		[155]			
SNHG12	ESCC	Down	↑	↓	↑	↑	↑	↑		miR-195-5p	BCL-9	WNT/β-catenin	[33]			
										miR-6835-3p	BMI1, CTNNB1	EMT	[87]			
	GC	Up	↑		↑		↑	↑		miR-320	CRKL, ERK, AKT	ERK, AKT	[284]	YWHAZ	AKT/GSK3β	[101]
										miR199a/b-5p			[285]			
										miR-16			[286]			
	CRC	Up	↑	↓	↑	↑	↑	↑		miR-16			[288]	CDK4, CDK6, CCDN1, Caspase-3		[287]
	HCC	Up	↑	↓	↑		↑	↑		miR-199a-5p	MLK3	NF-κB	[289]			
										miR-516a-5p	HEG1	EMT	[290]			
	PC	Up	↑	↓	↑					miR-320b	E-cadherin, N-cadherin, Vimentin	EMT	[291]			
SNHG13 (DANCR)	GC	Up	↑		↑	↑	↑	↑	[292]							
	CRC	Up	↑		↑	↑	↑	↑	[293,295,296]	miR-557	HSP27		[294]	E-cadherin, Vimentin	EMT	[293]

Table 2. (Continued).

			Function in cancer cells							Molecular mechanism						
										ceRNA network				Protein network		
SNHG	Associated digestive cancer	Misregulation	Proliferation	Apoptosis	Invasion/ migration/ metastasis	Tumouri-genicity	Clinicopatho logical features	Poor survival	Ref.	Target miRNA (as ceRNA)	Target mRNA	Related signalling pathway	Ref.	Target protein	Related signalling pathway	Ref.
	HCC	Up	↑		↑	↑		↑	[298]	miR-27a-3p	LIMK1, Vimentin E-cadherin, N-cadherin	EMT progression	[297]			
	CCA	Up	↑	↓	↑	↑			[122]					FBP1		[122]
SNHG14	CRC	Up/Down	↓/↑	↑/↓	↓/↑	↓/↑	↓/↑	↓/↑		miR-32-5p	SKIL, Smad2, Smad3, TGF-β1, β-catenin, c-MYC, CCND1	TGF-β WNT/β-catenin	[62]			
										miR-3940-5p	NAP12		[299]			
										miR-519b-3p	DDX5		[300]			
										miR-186	ATG14		[301]			
										miR-3940-5p	NAP1L2		[299]			
										miR-92b-3p	E-cadherin, N-cadherin, Vimentin		[302]			
	HCC	Up	↑	↓	↑	↑	↑	↑		miR-4673	SOCS1		[304]	PABPC1	PTEN	[303]
										miR-876-5p	SSR2		[305]			
	PC	Up	↑	↓	↑	↑	↑			miR-613	ANXA2		[306]			
										miR-101			[68]			
SNHG15	GC	Up	↑	↓	↑	↑	↑	↑		miR141	PD-L1		[162]	MMP2, MMP9		[88]
										miR-506-5p	Caspase-3, cleaved Caspase-9, BCL-2, BAX		[307]			
										miR-92a	Caspase 3, BCL-2, BAX		[308]			
	CRC	Up	↑	↓	↑	↑	↑	↑	[310]	miR-338-3p	FOS, RAB14		[309]	SLUG	EMT	[89]
														AIF		[144]
	HCC	Up	↑		↑		↑	↑	[312]	miR-141-3p	ZEB1, E2F3		[311]			
										miR-490-3p	HDAC2		[313]			
	PC	Up	↑	↓	↑	↑	↑		[314]	miR-345-5p	RAB27B		[313]			
SNHG16	ESCC	Up	↑	↓	↑	↑	↑	↑		miR-140-5p	ZEB1	EMT	[41]	β-catenin, CCND1, c-MYC	WNT/β-catenin	[109]
	GC	Up	↑	↓	↑	↑	↑	↑	[316]	miR-135a	JAK2, STAT3	JAK2/STAT3	[315]	DDK3	EMT	[90]
										miR-628-3p	NRP1		[317]			
										miR-506-3p	PTBP1		[318]			

Table 2. (Continued).

			Function in cancer cells							Molecular mechanism						
										ceRNA network				Protein network		
SNHG	Associated digestive cancer	Misregulation	Proliferation	Apoptosis	Invasion/ migration/ metastasis	Tumouri-genicity	Clinicopatho logical features	Poor survival	Ref.	Target miRNA (as ceRNA)	Target mRNA	Related signalling pathway	Ref.	Target protein	Related signalling pathway	Ref.
	CRC	Up	↑	↓	↑	↑	↑	↑		miR-302a-3p	AKT		[53]	ASCL2, ETS2, c-MYC	WNT/β-catenin	[319]
										miR-200a-3p			[320]			
										miR-124-3p	MCP-1	EMT	[321]			
										miR-132-3p	USP22		[322]			
	HCC	Up/Down	↓/↑	↑/↓	↓/↑	↓/↑	↓/↑	↓/↑		miR-302a-3p	FGF19		[54]			
										miR-4500	STAT3		[323]			
										miR-17-5p	P62	mTOR, NF-κB	[324]			
										miR-195			[34]			
										miR-186			[325]			
										miR-140-5p			[42,43]			
										miR-93			[146]			
	PC	Up	↑		↑	↑	↑	↑		miR-218-5p	HMGB1		[326]			
										miR-302b-3p	SLC2A4		[55]			
										miR-195	SREBP2		[35]			
SNHG17	ESCC	Up	↑	↓	↑	↑	↑	↑		miR-338-3p	SOX4		[327]	c-Myc	PI3K/AKT	[102]
	GC	Up	↑	↓	↑	↑	↑	↑	[329]					P15, P16, CDK4		[328]
	CRC	Up	↑	↓	↑	↑	↑	↑	[330]	miR-23a-3p	CXCL12		[156]			
	HCC	Up	↑	↓	↑	↑	↑	↑	[331–334]	miR-3180-3p	RFX1	EMT	[332]	ERH, TBCA, TDO2, PDK4		[331]
														LRPPRC, c-Myc		[333]
	PC	Up	↑	↓	↑	↑				miR-942			[335]			
SNHG18	HCC	Down					↓		[336]							
SNHG19	ESCC	Up							[337]							
	CRC	Up							[338]							
	HCC	Up							[339]							
SNHG20	ESCC	Up	↑	↓	↑		↑	↑							EMT ATM/JAK/ PD-L1	[91]
	GC	Up	↑		↑	↑	↑	↑		miR-495-3p	ZFX	ERK-MAPK	[340]	p-GSK3β, β-catenin	WNT/β-catenin	[110]
										miR-140-5p	NDRG3		[44]			
	CRC	Up	↑		↑	↑	↑	↑		miR-495	STAT3		[342]	P21, CCNA1		[341]
	HCC	Up	↑	↓	↑	↑	↑	↑	[343]					E-cadherin, ZEB1, ZEB2, Vimentin, N-cadherin		[92]
														HBx, PTEN		[344]

Table 2. (Continued).

SNHG	Associated digestive cancer	Misregulation	Function in cancer cells: Proliferation	Apoptosis	Invasion/ migration/ metastasis	Tumourigenicity	Clinicopathological features	Poor survival	Ref.	Molecular mechanism: ceRNA network: Target miRNA (as ceRNA)	Target mRNA	Related signalling pathway	Ref.	Protein network: Target protein	Related signalling pathway	Ref.
SNHG22	ESCC	Up	↑		↑	↑				miR-429	SESN3		[345]			
	GC	Up	↑	↓	↑	↑	↑	↑		miR-200c-3p	Notch1		[127]			
										miR-361-3p	HMGA1	Wnt/β-catenin	[157]			
	CRC	Up	↑	↓	↑	↑		↑		miR-128-3p	E2F3		[346]			
	HCC	Up	↑	↓	↑	↑	↑	↑		miR-16-5p	DNMT1		[158]			
SNHG23	PC	Up							[128]	miR-34a	EZH2		[128]			
										miR-302	EZH2					

miR-26

Both upregulation and downregulation of *miR-26* can occur in cancer, and *miR-26* can act either as an oncogene or tumour-suppressor. Studies have shown that *SNHG5* can bind to *miR-26a-5p* and regulate the expression of its downstream target *GSK3β*. As GSK3β is an important player in WNT/β-catenin signalling, *SNHG5* can, therefore, promote HCC carcinogenesis by activating WNT/β-catenin signalling [48]. *SNHG6* can also act as a sponge for *miR-26a* and *miR-26b* and regulates their target gene *TAK1* that mediates activation of NF-κB and JNK/P38 [49].

miR-302

miR-302 family includes *miR-302a/b/c/d* and *miR-367* that are expressed mainly in human embryonic stem cells and are downregulated rapidly after differentiation [50]. Based on their inhibitory function, this miRNA family can suppress more than 450 target mRNAs in humans [51]. The majority of miR-302s act as tumour suppressors but some also have opposite function [52]. It was demonstrated that *SNHG16* can regulate *AKT* expression by interacting with *miR-302a-3p* and promoting CRC through *SNHG16/miR302a-3p*/AKT axis [53]. Furthermore, in HCC, upregulation of *SNHG16* is associated with poor prognosis via sponging *miR-302a-3p* and regulating *FGF19* levels [54]. The *SNHG16* lncRNA also contributes to pancreas adenocarcinoma through *miR-302b-3p*/SLC2A4 axis that is involved in glucose homeostasis [55].

miR-32

Aberrant expression of *miR-32* is associated with a variety of GI tumours [56–59]. Several studies demonstrated that expression of some of the *miR-32* target genes can be modulated via SNHGs ceRNA activity. It was shown that *GAS5* can positively affect the *PTEN* expression by decreasing the level of miR-32-5p [60]. Furthermore, overexpression of *SNHG5* in GC cell lines decreases the mature *miR-32* via a ceRNA activity. As *Kruppel-like factor 4* (*KLF4*) is a known target of *miR-32*, *SNHG5/miR-32/KLF4* axis can act as a key pathway in GC carcinogenesis [61]. Moreover, *SNHG14* can sponge *miR-32-5p* and regulate its downstream target gene named *SKIL*. This axis (*SNHG14/miR-32-5p/SKIL*) can promote CRC development by regulating TGF-β and WNT/β-catenin pathways by affecting p-SMAD2, p-SMAD3, TGF-β1, β-catenin, c-MYC, and CCND1 expression levels [62].

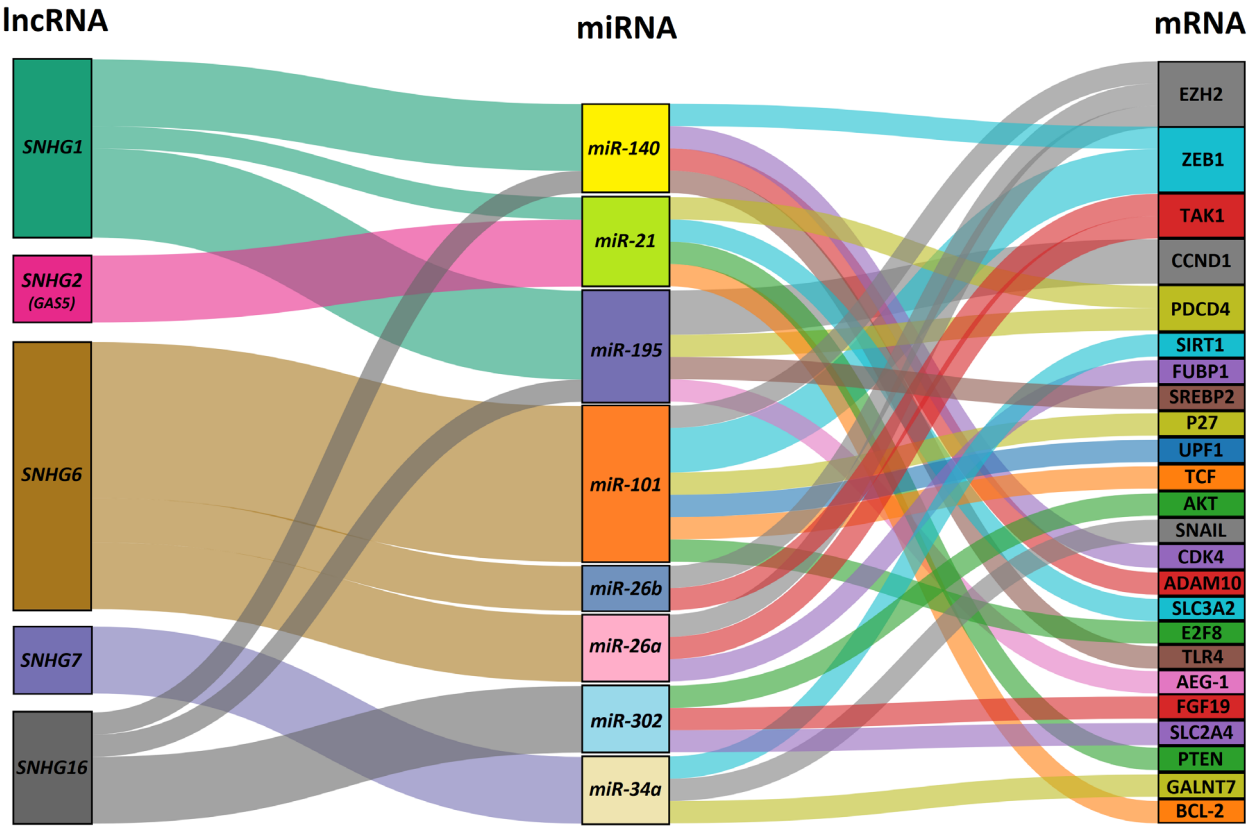

Fig. 2. Sankey diagram for the ceRNA network (lncRNA-miRNA-mRNA) in GI cancers. Each gene is represented by a rectangle, and the connection degree of each gene is shown based on the rectangle size. Genes were selected based on the most abundant SNHGs, miRNAs, and mRNAs with functional roles in GI carcinogenesis.

miR-101

miR-101 serves as a tumour-suppressor miRNA and its downregulation promotes tumour proliferation, invasion, and metastasis, as well as drug resistance [63]. *SNHG6* inhibits apoptosis through binding to *miR-101-3p* and regulating EZH2 expression in ESCC [64]. RNA pull-down, RNA immunoprecipitation, and luciferase reporter assays confirmed that *SNHG6* regulates *miR-101-3p* in a ceRNA-dependent manner. This *SNHG6- miR-101-3p* interaction affects *ZEB1* expression (a key regulator of EMT) and increases MMP-2/9 expression in HCC [65]. Moreover, it was demonstrated that *SNHG6* can activate the TGF-β/SMAD pathway in CRC by targeting UPF1 and upregulating ZEB1 to induce EMT [66]. The *SNHG6* lncRNA can also regulate the expression of *β-catenin* and *TCF4* by interacting with *miR-101-3p*, consequently promoting CRC carcinogenesis by affecting WNT/β-catenin signalling [67]. It was also demonstrated that *miR-101* can be sequestered by *SNHG14* to promote pancreatic ductal adenocarcinoma (PDAC) leading to gemcitabine resistance in PDAC cells [68].

Regulating protein activity and signalling cascades

A growing number of studies suggest that lncRNAs can exert their regulatory roles via several mechanisms that include affecting the cellular localization of target proteins, altering protein stability, modulating protein modifications, or regulating protein–protein interactions, ultimately leading to altered signalling pathways during cancer development [69–77]. In this section, we review some of the important signalling pathways that are influenced by SNHGs in cancer as summarized in Table 2 and Fig. 3.

Epithelial to mesenchymal transition

The EMT is a biological process during which the epithelial phenotype is converted to a mesenchymal-like one. This phenomenon can contribute to some pathological conditions including tumour progression and metastasis. In this process, cell adhesion molecules such as E-cadherin, and cytokeratin are downregulated whereas mesenchymal cadherins, matrix

metalloproteinases, and Vimentin are upregulated, leading to loss of cell–cell adhesion and gain of cell movement abilities (migration and invasion) [78–80].

Various SNHG lncRNAs exert specific functions in cancer progression via regulating EMT [81]. For instance, *SNHG1* promotes EMT by regulating the potential cancer stem cell marker DCLK1 in GC [82]. Depletion of *SNHG1* in ESCC [83] and HCC [84], reduces EMT via upregulation of E-cadherin, and downregulation of Vimentin and N-cadherin expression. Other examples of EMT-promoting SNHGs include amongst others: *SNHG5* which interacts with MTA2, leading to its ubiquitin-mediated degradation in ESCC [85]; *SNHG11* which enhances Hippo signalling by negatively regulating p-YAP and p-LATS1 in CRC [86]; *SNHG12* that activates BMI1 and increases the stability of CTNNB1 in ESCC [87]; and *SNHG15* that upregulates the expression of MMP2 and MMP9 (matrix metalloproteinase molecules, which are implicated in invasion and metastasis) in GC [88]. The *SNHG15* lncRNA also shows a nuclear localization and can bind to the zinc finger domain of SLUG to prevent its ubiquitination and degradation, leading to EMT in CRC cells [89]. Furthermore, following *SNHG16* knockdown in ESCC, the expression levels of E-cadherin and β-catenin increased while N-cadherin and Vimentin decreased, indicating that upregulation of *SNHG16* can promote cell migration via regulating EMT [41]. In addition, this lncRNA can lead to the upregulation of DDK3 protein and therefore induces EMT via *SNHG16*/*DDK3*/*β-catenin* axis in GC [90]. Lastly, *SNHG20* can facilitate metastasis via regulating the activation of ATM/JAK/PD-L1 pathway in ESCC [91] whereas *SNHG20* is associated with downregulation of E-cadherin and upregulation of ZEB1, ZEB2, Vimentin, and N-cadherin in HCCs [92].

AKT signalling

AKT signalling regulates different cellular processes related to tumourigenesis including cell proliferation, migration, and survival [93]. Phosphorylation of AKT by PDK1 or mTOR leads to the activation of its downstream targets and cancer progression [94,95]. Some studies indicated that lncRNAs "including SNHGs" can modulate the AKT pathway leading to GI malignancies. For example, overexpression of *SNHG1* activates AKT signalling via regulating SLC3A2, which leads to drug resistance [96]. Investigation of proteins related to the PI3K/AKT pathway confirmed that *SNHG1* also regulated the activity of this signalling pathway in PC [97]. On the other hand, ectopic expression of *GAS5* in ESCC cells led to reduced PI3K expression and reduction of phosphorylation of AKT and mTOR [98]. Furthermore, increasing *GAS5* inhibited AKT and ERK at both mRNA and protein levels, leading to CASP9 elevation and CASP3 inhibition in CRC [99]. Further investigation revealed that EST1 protein levels decreased significantly after *SNHG6* overexpression in CRC, hence this lncRNA can regulate cell proliferation via PI3K/AKT/mTOR signalling pathway [100]. *SNHG12* can bind to its target named HuR in the cytoplasm and increases YWHAZ mRNA stability which promoted AKT phosphorylation and, therefore, AKT/GSK3β pathway activation in GC [101]. Lastly, *SNHG17* mediates the PI3K/AKT pathway by enhancing the expression level of c-MYC in ESCC [102].

WNT/β-catenin signalling

WNT/β-catenin cascade is a key signalling pathway that can be activated in two different manners β-catenin-dependent and β-catenin-independent [103]. Increasing lines of evidence have confirmed the role of lncRNAs (including SNHGs) in WNT/β-catenin signalling. For example, the expression level of E-cadherin, β-catenin, CCND1, LEF, TCF4, TCF7, MMP7, MMP9, and c-MYC showed significant changes after *SNHG1* knockdown [104–106]. More investigations in CRC revealed that downregulation of *GAS5* can also influence angiogenesis and metastasis via activation of WNT/β-catenin signalling [107]. Upregulation of *SNHG5* in hepatocellular carcinoma decreased the level of UPF1 and increased WNT1, WNT3a, and WNT10a which promote WNT-signalling [108]. Han et al. showed that WNT-signalling is inhibited in response to *SNHG16* downregulation in ESCC, as evidenced by alterations in β-catenin, CCND1, and c-MYC expression levels [109]. Lastly, *SNHG20* regulates WNT/β-catenin signalling by increasing the expression levels of p-GSK3β and β-catenin in GC cells [110].

TGF-β signalling

TGF-β is a multifunctional cytokine that belongs to the evolutionary conserved transforming growth factor superfamily [111] and drives a signalling pathway that regulates cell proliferation, differentiation, and motility [111,112]. To date, many lncRNAs (including *SNHGs*) have been identified as regulators of TGF-β signalling [113]. Studies in CRC revealed that *GAS5* depletion leads to decreased IL-12, iNOS, IL-1β, and TNF-α in M1 macrophages, and increased IL-10, TGF-β, Arg-1, and Fizz-1 in M2 macrophages. This finding showed

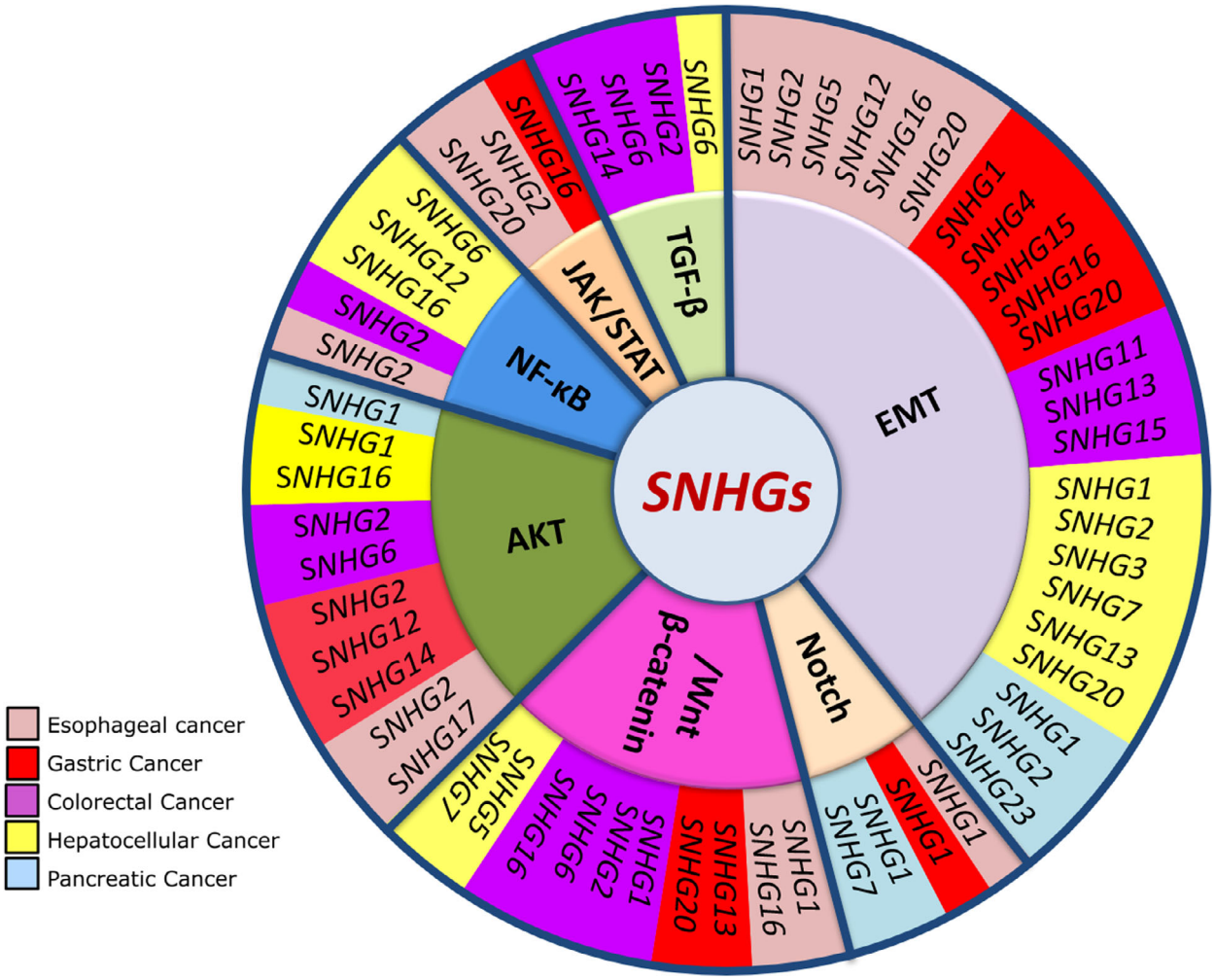

Fig. 3. The impact of aberrant expression of SNHG family members on various signalling pathways. Each GI malignancy is highlighted in a different colour in the outer circle.

that *GAS5* can prevent CRC cell immune-scape and tumour growth via polarizing M1 macrophages [114]. It is also demonstrated that *SNHG6* can activate the TGF-β/SMAD pathway by targeting UPF1 and increasing tumour growth and metastasis [66]. In this regard, direct interactions between *SNHG6* and UPF1 activates the TGF-β/SMAD pathway in HCC [65].

Epigenetic regulation

Over the past few years, new evidence emerged confirming the crucial role of lncRNAs in epigenetic regulation. Aberrant expression of lncRNAs including SNHGs can act as key regulators of histone methylation, histone acetylation, and DNA methylation to facilitate chromatin remodelling in various malignancies [115]. One of the best-studied interactions between SNHG and epigenetic modifiers has been reported for the PRC2 complex (Fig. 4). SNHG family members can interact with enhancer of zeste homolog 2 (EZH2) and control transcription of target genes. For example, *SNHG1* can interact with EZH2 to silence KLF2 and CDKN2B in CRC cells, leading to enhanced tumour growth [116]. Other interactions between EZH2 and SNHG members have been reported, including interaction with *SNHG1* to downregulate *CDKN1A* and *CDKN2B* expression in HCC [117] and *CDKN1A* in CCA [118]; with *SNHG3* to regulate MED18 expression in GC [119]; with *SNHG6* to control P21 expression in CRC [120]; with *SNHG13 (DANCR)* to regulate *lncRNA-LET* in GC [121]; with *SNHG13* to modulate FBP1 expression in CCA [122]; with *SNHG15* to control P15 and *KLF2* silencing in PC [123]; with *SNHG17* to downregulate RUNX3 [124] and repress P17 and P15 [125] in GC and also P57 in CRC [126]; with *SNHG20* to downregulate E-cadherin in GC [110] and HCC [92]; with *SNHG22* to alter five

suppressing genes including E-cadherin, EAF2, ADRB2, rap1GAP, and RUNX3 in GC [127] and finally with *SNHG23 (MEG8)* to control *miR-34a* and *miR-302* in PC [128].

Small nucleolar RNA host genes can also alter the EZH2 chromatin binding ability. For example, chromatin immunoprecipitation assays showed that depletion of *SNHG6* in GC, reduces EZH2 chromatin binding and H3K27me3-deposition at the *P27* promoter, leading to increased P27 expression [129]. Furthermore, *SNHG6* can control the expression of the senescence factor P21, a mechanism that is dependent on the EZH2 function [130]. Moreover, a negative correlation was observed between *SNHG14* and EPHA7 expression in CRC. Mechanistically, *SNHG14* was found to interrupt the interaction between EZH2 and *miR-186-5p* leading to the release of EZH2 from the chromatin and hypermethylation of the *EPHA7* promoter [131].

In addition to the effects on the PRC2 complex, SNHGs can also influence other epigenetic regulators. For example, *SNHG5* can interact with MTA2 and trap this protein in the cytoplasm leading to increased acetylation of histone 3 and P53 and increased tumourigenicity in GC [132]. Moreover, upregulation of *SNHG6* leads to a strong global hypomethylation in HCC and reduced expression of MAT1A protein by activation of *miR-1297*/FUS pathway that resulted in *MAT1A* mRNA transportation from the nucleus to the cytoplasm. In contrast, this lncRNA increased MAT2A by preventing the interaction between *miR-1297* and *MAT2A* 3′-UTR [133]. Altogether, these studies demonstrate that SNHGs can directly interact with epigenetic regulators and modulate their chromatin binding or enzymatic activities.

The role of SNHG family in hallmarks of cancer

Small nucleolar RNA host genes play crucial roles in promoting carcinogenesis by affecting the expression or activity of downstream targets, ultimately promoting different hallmarks of cancer. In the previous section, some examples of how the SNHG family contributes to cell proliferation, evading apoptosis, and metastasis were discussed. Here, we summarize SNHGs functions on other hallmarks of cancer with a particular focus on GI malignancies.

Chemotherapy resistance

Drug resistance can be acquired in cancer cells via genetic mutations or epigenetic alterations in multiple pathways that include amongst others: increased expression of ABC transporters, which direct the drugs out of cells; activation of pathways that prevent cell death; enhancement of DNA repair; increase in tolerance to stress conditions; or alterations in drug metabolism [134]. In this regard, members of the SNHGs can contribute to drug resistance in different ways. For example, in HCC, *SNHG1* contributes to sorafenib resistance via interacting with *miR-21* and subsequently inducing *SLC3A2* and AKT signalling [96]. In HCC, overexpression of *GAS5* promotes doxorubicin [135] and cisplatin [136] sensitivity by increasing PTEN expression and sponging mir-222, respectively. *GAS5* lncRNA also decreases MDR-1 protein level through binding to *miR-181c-5p*, ultimately promoting chemoresistance in PC cells [137]. *GAS5*/*miR-221* interaction also promotes PC gemcitabine resistance through EMT progression [138]. Furthermore, in GC, *SNHG5* promotes cisplatin resistance by altering the expression of apoptosis-specific genes (*BAX* and *BCL-2*) and chemo-resistance-specific genes (*MDR1* and *MRP1*) [139]. In gastric cancer, *SNHG6* interacts directly with *miR-1297* to regulate BCL-2 expression [140] and *miR-325-3p* to target GITR expression [141] leading to cisplatin resistance and tumour progression. This lncRNA also sponges *miR-26a-5p* and promotes 5-FU chemoresistance in CRC [142]. Other examples of drug resistance mediated by SNHGs include *SNHG8* which alters the expression of Caspase-3 and PARP to promote chemo-resistance in pancreatic adenocarcinoma [143]; *SNHG15* that interacts with AIF and increases resistance to 5-FU in CRC [144]; and *SNHG16* that contributes to 5-FU resistance by targeting *miR-506-3p* in GC [145] and *miR-93* in HCC [146].

Stemness

Recent studies have revealed that lncRNAs can induce stemness in cancer cells by modulating gene expression at transcriptional and post-transcriptional levels [147,148]. For example, *GAS5* is essential for maintaining stemness in CRC through regulating NODAL signalling [149] and in PC via promoting EMT [138]. In GC, *SNHG3* upregulates stemness genes including *OCT4*, *SOX2*, and *CD44* [150] and in HCC, the direct interaction between *SNHG5* and UPF1 regulates stemness factors [108]. Furthermore, depletion of *SNHG12* in ESCCs results in decreased expression of stemness genes including *SOX2*, *SOX4*, *OCT4*, and *NANOG* [87].

Neo-angiogenesis

Tumour angiogenesis is another hallmark of cancer that involves the sprouting of novel vessels from

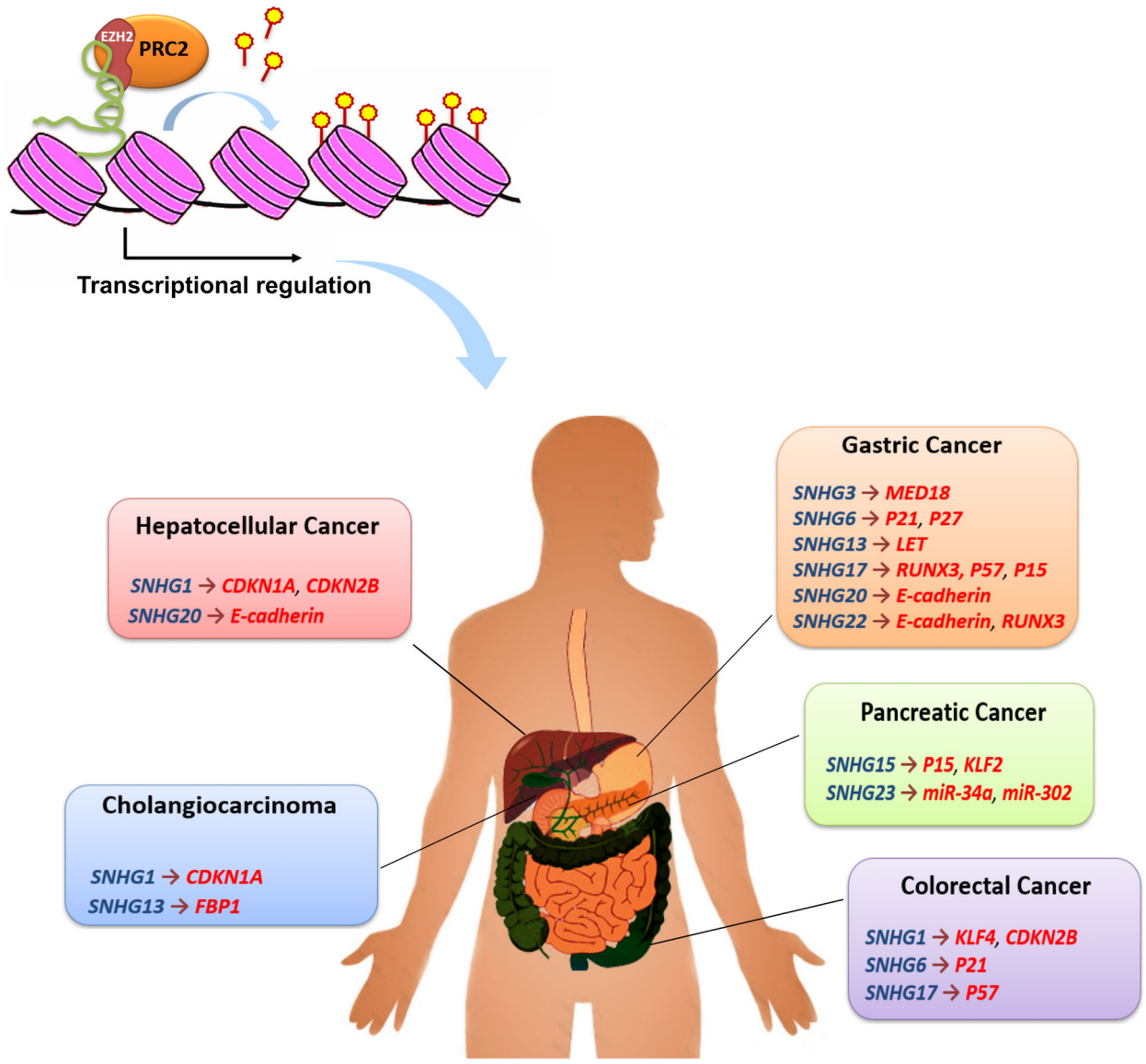

Fig. 4. Dysregulation of small nucleolar RNA host gene (SNHG) family members is associated with altered epigenetic modifications in various GI malignancies via, among others, the PRC2 complex.

existing ones. This phenomenon is a multistep process that is adapted under some pathological conditions, such as carcinogenesis and provides oxygen and essential nutrients to cancer cells that is essential for solid tumours growth beyond 2 mm. This process is regulated by a balanced act of anti-angiogenic (angiostatin, endostatin, tumstatin, and IL-12) and pro-angiogenic (VEGF, bFGF, EGF, PDGF, Ang-1, and Ang-2) factors in the tumour microenvironment [151]. Recent studies demonstrate that lncRNAs can participate in angiogenesis as pro- or anti-angiogenesis mediators [152,153]. For example, lncRNA *GAS5* inhibits angiogenesis and metastasis of colorectal cancer through the WNT/β-catenin signalling pathway [107]. *SNHG6* promotes angiogenesis via direct interaction with *miR-101-3p* and subsequent activation of E2F8 in CCA [154]. *SNHG11* facilitates angiogenesis by targeting *miR-324-3p* and regulating the level of VEGF-A in PC [155]. *SNHG17* can exert its role in angiogenesis by sponging *miR-23a-3p* and modulating CXCL12 expression [156]. Lastly, *SNHG22* can induce angiogenesis via *miR-361-3p*/HMGA1/WNT/β-catenin axis in GC cells [157] and *miR-16-5p*/VEGF in HCC cells [158].

Immune-escape

Various mechanisms can contribute to the escape of cancer cells from the immune system; these include, amongst others, defects in presenting tumour antigens, abnormal metabolism, resistance to cytotoxic immune response, and acquiring stem cell-like phenotypes. Recent studies revealed that lncRNAs can regulate immune system evasion by controlling immune response genes [159,160]. For example, *GAS5* depletion leads to the polarization of M1 macrophages and a decrease in IL-12, IL-1β, iNOS, and TNF-α levels, promoting immune escape in CRC cells [114]. In contrast, *GAS5* enhances the NK cell's cytotoxicity in HCC by regulating the *miR-544-RUNX3* axis [161]. In GC, *SNHG15* can regulate *PD-L1* expression via *SNHG15* ceRNA activity on *miR-141* and leads to resistance of cancer cells to the immune system [162].

Conclusion

As cancer represents a major health challenge, new diagnostic and prognostic biomarkers for early diagnosis or timely treatment are urgently required [18]. With new next-generation sequencing and ultra-deep RNA sequencing methods, lncRNAs have attracted widespread attention as oncogenes or tumour suppressor genes in various cancers [163,164]. Furthermore, recent clinical findings indicate that lncRNAs can be released into extracellular fluids, such as blood plasma/serum, which provide opportunities for using lncRNAs as potential diagnostic or prognostic markers [165]. SNHG family is a large family of lncRNAs with 32 members, that encode snoRNAs at their intronic regions. Originally, SNHGs were thought to solely regulate gene expression via releasing the snoRNAs embedded in their introns [166]. However, more recent studies indicate that these host genes also have additional biological functions that are independent of their co-transcribed snoRNAs [10,167]. Members of the SNHG family have been recognized as oncogenes, based on their significant dysregulation (mainly upregulation) in various cancers [168]. SNHGs play a key role in the initiation, progression, and pathogenesis of GI malignancies via multiple cellular processes and are linked to clinicopathological features such as TNM stage, lymphatic metastasis, tumour size, and shorter overall survival (Table 2). Moreover, some members of this family impact the chemotherapy response of tumour cells, and thus can provide novel targets to overcome drug resistance in cancer. In this regard, SNHGs oncogenic activity can be targeted by silencing techniques, such as RNA interference or CRISPR-Cas9 genome editing. Altogether, as SNHGs act as upstream regulators of a broad range of biological processes, they can provide new hopes for more targeted and/or more efficient cancer diagnosis or therapy.

Although the importance of SNHGs in GI carcinogenesis is well-documented, we are still at the early stages of understanding the involvement and applications of SNHGs in cancer. Firstly, additional members of the SNHG family (e.g. *SNHG24* to *SNHG32*) are not studied yet in GI cancers and will require further investigation through bioinformatics and experimental approaches. Secondly, little is known about the SNHGs expression levels in circulating body fluids such as plasma or serum samples. In this regard, a combinatorial panel of several SNHGs may increase the diagnostic or prognostic power of lncRNAs to provide a non-invasive method in the early stages of cancer. Finally, additional studies are required to investigate the downstream responses to SNHGs targeting therapeutic purposes. In this regard, a lower dose of antisense oligonucleotides is generally required for targeting and inhibiting the oncogenic functions of SNHGs/lncRNAs compared to other anti-cancer drugs. Addressing these open questions will provide a better understanding of the SNHGs biology and may lead to new and more effective cancer diagnostic or therapeutic approaches.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

All authors contributed to the study conception and design. All authors read and approved the final manuscript.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Interactions of the ceRNA network in GI malignancies.
Table S2. The connection degree of each gene in the ceRNA network.
Table S3. Most abundant genes and their interactions in the ceRNA network in GI malignancies.