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Review

A review on the role of GAS6 and GAS6-AS1 in the carcinogenesis

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ABSTRACT

Growth arrest specific 6 (*GAS6*) encodes a protein that serves as a ligand for AXL receptor tyrosine kinase and stimulates cell proliferation. Notably, an antisense RNA, namely *GAS6-AS1* is transcribed from chromosome 13q34, near *GAS6* gene. In vitro functional experiments have demonstrated that *GAS6-AS1* can promote proliferation, migration and invasive properties of transformed cells through enhancing entry into S-phase. Notably, mechanistic investigations have shown that *GAS6-AS1* can regulate expression of *GAS6* at the transcriptional or translational stages through constructing a RNA-RNA duplex, thus enhancing expression of AXL and inducing AXL signaling. Both *GAS6* and its antisense transcript contribute in the pathogenesis of human malignancies. In the current review, we provide a summary of studies that appraised the role of these genes in the carcinogenesis.

1. Introduction

In a search to identify genes contributing in the G0 pre-replicative phase of the cell cycle, Schneider et al. used a subtraction library method and cloned cDNAs from serum-deprived fibroblasts. Their efforts led to identification of six members of the "growth-arrest-specific" family of genes or *GAS* genes [45]. All *GAS* genes except *GAS5* are mRNA-like genes i.e. they encode transcripts that are used as templates for protein synthesis. Yet, GAS5 is classified as a long non-coding RNA [11]. GAS6 or alternatively named as AXL Receptor Tyrosine Kinase Ligand has been shown to contribute in the stimulation of cell proliferation. *GAS6* gene is located on chromosome 13q34 and has 15 exons. The encoded protein has an NH2-terminal Gla domain, four epidermal growth factor (EGF)-like repeats and a number of tandemly repeated globular domains. The Gla domain and EGF-like repeats are not necessary for receptor binding. A deletion variant of Gas6 comprising only the globular domain region has been shown to be able to activate phosphorylation of Tyrosine-protein kinase receptor Tyro3 (Rse), demonstrating the ability of globular domains as signaling molecules. Rse is one of the three TAM receptor tyrosine kinases. Moreover, this study has shown association between activation of cell adhesion associated receptors and regulation of cell growth and differentiation [37]. Axl and Mer are other members of TAM receptors. These receptors instead of being involved in the development of embryo regulate tissue homeostasis during adulthood. They have essential roles in the regulation of homeostasis in a variety of mature tissues including immune and nervous systems. Notably, Gas6 and Protein S are two identified ligands for TAMs [31].

Notably, an antisense RNA, namely *GAS6-AS1* is transcribed from this location. This long non-coding RNA (lncRNA) has 5 exons. In vitro functional experiments have demonstrated that *GAS6-AS1* can promote proliferation, migration and invasive properties of transformed cells through enhancing entry into S-phase. Notably, mechanistic investigations have shown that *GAS6-AS1* can regulate expression of *GAS6* at the transcriptional or translational stages through constructing a RNA-RNA duplex, thus enhancing expression of AXL and inducing AXL signaling [55]. Both *GAS6* and its antisense transcript contribute in the pathogenesis of human malignancies. In the current review, we provide a summary of studies that appraised the role of these genes in the carcinogenesis.

2. GAS6

2.1. In vitro studies

A differential gene expression analysis between MCF-7 breast cancer cells and doxorubicin-resistant cells has led to identification of AXL as an important factor in induction of chemoresistance and metastasis in this

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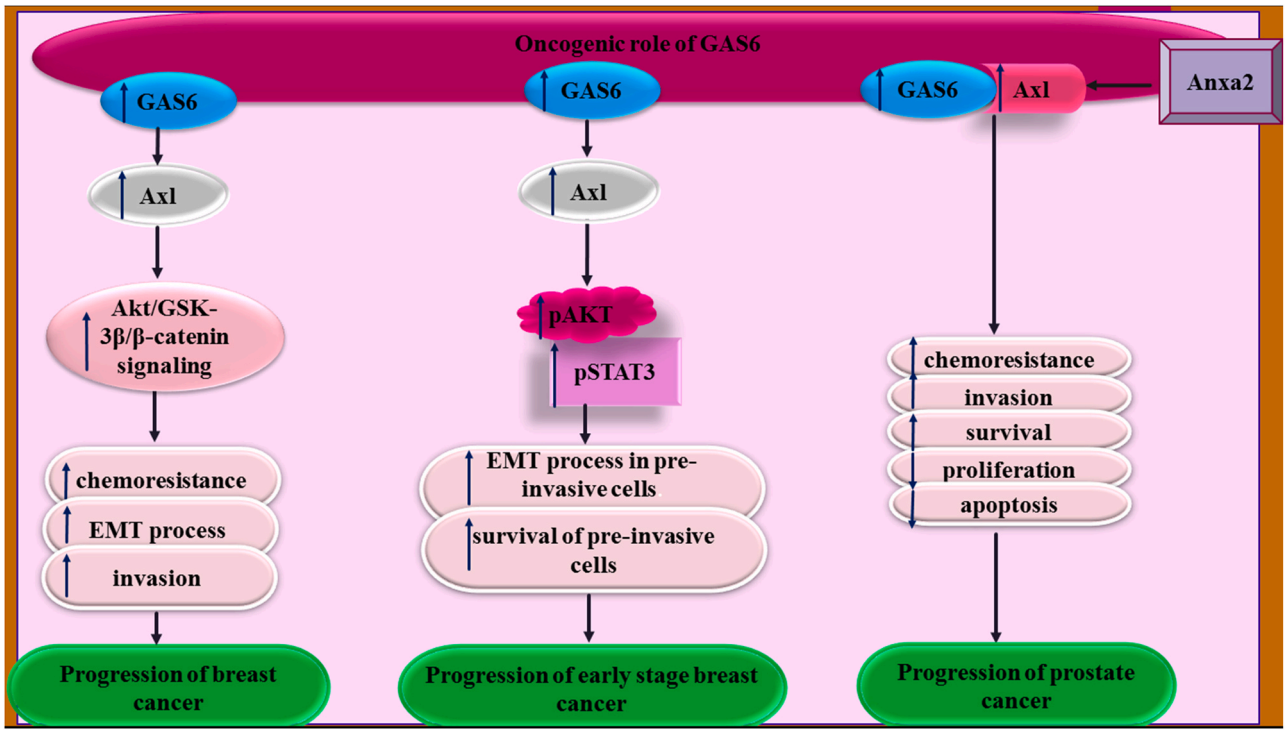

Fig. 1. Oncogenic role of GAS6 in breast and prostate cancers.

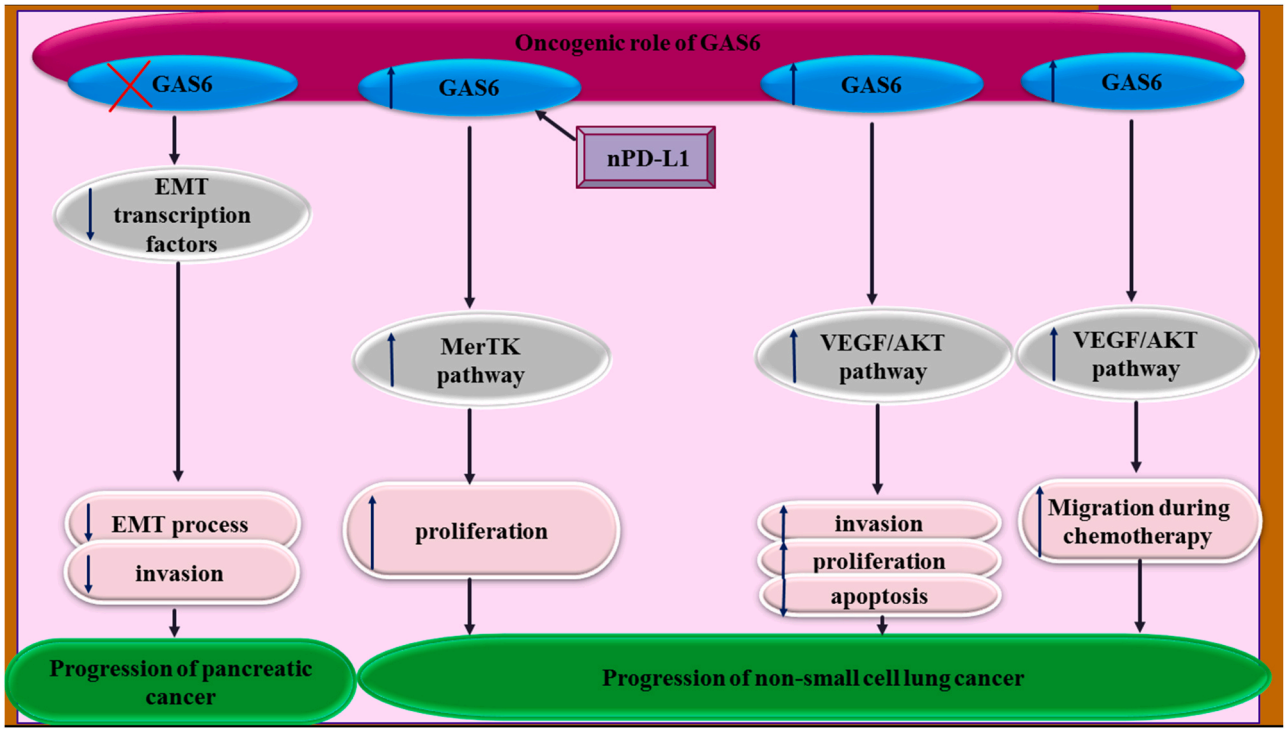

Fig. 2. Oncogenic role of GAS6 in pancreatic and lung cancers.

cancer. Knock-down of AXL has significantly reduced invasive and metastatic abilities of chemoresistant breast cancer cells and enhanced anti-cancer effects of doxorubicin. Akt/GSK-3β/β-catenin cascade has been identified as the mediator of AXL-induced pro-metastatic abilities. Importantly, *GAS6* has been found to regulate this molecular cascade through modulation of expression of AXL [49]. Experiments in a 3-D co-culture system have shown the ability of macrophage-produced Gas6 in activation of its receptor Axl and induction of downstream survival pathways such as Akt and STAT3. The resultant alteration in expression of E-cadherin has induced a malignant morphology [10].

The GAS6 receptor Axl has been shown to be over-expressed in metastatic prostate cancer cells, while being down-regulated in non-metastatic LNCaP cancer cells. Axl silencing in metastatic prostate cancer cells has reduced expressions of Snail, Slug, and N-cadherin

Table 1
In vitro studies related to the role of GAS6 in the carcinogenesis.

Tumor type	Targets/regulators and signaling pathways	Cell line	Function	References
Breast cancer	Axl signaling, Akt/GSK3β/β-catenin signaling	MCF-7, MCF-7/ADR	↑ GAS6: ↑ migration, ↑ invasion, ↑ EMT process, ↑ chemoresistance	[49]
	Axl, pAKT, pSTAT3	PN1a, MECs, PN1b	Δ GAS6: ↓ survival of pre-invasive cells in a paracrine fashion, ↓ EMT process in pre-invasive cells	[10]
Prostate Cancer	SDF-1, αvβ3, CD164, Anxa2, AXL, MAPK signaling pathway,	PC3 (CRL-1435), DU145 (HTB-81), LNCaP (CRL-1740), PCa, SaOS2 (HTB-85), MG63 (CRL-1427, LNCaP C4-2B)	↑ GAS6: ↓ proliferation, ↓ apoptosis, ↓ fraction of cells in G1/S/M/G2 states, ↑ survival, ↑ invasion, ↑ chemoresistance, ↑ fraction of cells in G0 state	[47]
	Axl, Hifl-α	PC3 (CRL-1435), DU145 (HTB-81), LNCaP (CRL-1740)	under normoxic conditions: ↑ GAS6: ↓ Axl protein under hypoxic conditions: ↑ GAS6: no changes in Axl protein	[39]
	Mer receptor signaling	PC3, DU145, LNCaP, PC3GFP and DU145GFP	↑ GAS6: ↑ CSCs	[23]
Pancreatic ductal adenocarcinoma	Snail 1, Snail 2, and Zeb 2, Vimentin,	KPC FC1242	Δ GAS6: ↓ EMT process	[19]
	–	PANC-1, MIA PaCa-2	↑ GAS6: ↑ proliferation, ↑ survival Δ GAS6-AS1: ↓ proliferation, ↓ survival	[41]
	–	NCI-H292 and Panc-1, SN12C, 293 T	Δ GAS6: ↓ proliferation, ↓ migration	[40]
Ovarian cancer	Akt	–	Δ GAS6: ↑ sensitize to cisplatin, ↓ Akt upregulation	[43]
Non-small cell lung cancer	MerTK	H1299 and HCC827	Δ GAS6: ↓ proliferation	[8]
	VEGF/AKT pathway	A549, HBE	↑ GAS6: ↑ proliferation, ↑ invasion, ↑inflammation probably, ↓ caspase 3 activity, ↓ apoptosis	[56]
	Axl	LCAFhTERT	Δ GAS6: ↓ growth, ↓ migration	[24]
Gastric cancer	Akt pathway, Axl	AGS, MKN1, MKN7, MKN28, MKN45, MKN74, GCIY, TMK1, and KATO3	Δ GAS6-AS1: ↓ invasion, ↑ apoptosis	[44]
Hepatocellular carcinoma	Axl, Slug, MAPK pathway	293 T, HA22T, Mahlavu	Δ Gas6/Axl signaling: ↓ invasion, ↓ migration, did not affect survival, did not affect proliferation Δ Slug: ↓ invasion-promoting activity of the Gas6/Axl pathway	[29]
Intestinal cancer	TNF- α, interleukin-8	SW480, HT29	↑ GAS6: ↑ proliferation, ↓ activation of immune responses in macrophages	[2]
Bladder cancer	Cyclin D1, cyclin E1, p27, p21, PI3K/AKT signaling	T24, UMUC3, 5637, J82, SV-HUC-1	Δ Gas6: ↓ proliferation, ↓ migration, ↓invasion, ↑ G1 phase arrest	[36]
Oral squamous cell carcinoma	E-cadherin, P-cadherin, N-cadherin	YD38	Δ Gas6: ↓ EMT process ↑ GAS6: ↑ migration, ↑ invasion, ↑ EMT process	[22]
Oral squamous cell carcinoma	Axl, NF-kB, PI3/Akt signaling, IKK	YD38, OEC-M1	Δ Gas6: ↓ M2 polarization	[6]
	Axl, ERK signaling, AKT signaling, GCSF, IL-2, IL-6, IL8	Ca9-22	↑ GAS6: ↑ invasion, ↑ AKT activation, ↓ ERK activation, ↓ pro-inflammatory cytokines	[16]
Esophageal cancer	Axl, PI3K/AKT signaling pathway, NF-κB signaling pathway, MMP2, MMP9	Eca109, TE1 cells	QGS-mediated inhibition of Gas6: ↓ migration, ↓invasion	[26]
	E-cadherin, N-cadherin, Snail	ECA109, TE13	QGS-mediated inhibition of Gas6: ↓ migration, ↓invasion, ↓ EMT process	[25]
Osteosarcoma	Axl, AKT signaling pathway	MG63 and U2OS	↑ GAS6: ↑ migration, ↑ invasion, ↓ apoptosis	[13]
Glioblastoma	LRIG2, AXL/SRC signaling	GBM, U87GR, U373GR	LRIG2-mediated enhancement of gefitinib-induced GAS6 upregulation: ↑ AXL activation, ↑ gefitinib resistance, ↓ G0/G1 cell cycle arrest, ↓ apoptosis	[7]
Schwannoma	Axl, survivin, cyclin D1 and FAK, NFκB, Src, FAK	Schwann and schwannoma cells	Δ Axl: ↓ Gas6-mediated proliferation, ↓ Gas6-mediated cell-matrix adhesion ↑ Axl: ↑ Gas6-mediated proliferation	[3]
Renal cell carcinoma	GAS6/AXL signaling, SRC, MET	SN12L1 and 7860	Δ GAS6/AXL signaling: ↓ invasion	[42]
–	Axl, PI3 kinase/Akt pathway	oligodendrocytes	Δ GAS6: ↓ survival ↑ GAS6: ↑ survival, ↓ TNFa cytotoxicity, ↓ TNFa-induced caspase activation, ↓ cell death	[46]

mesenchymal markers, while increasing levels of epithelial marker E-cadherin. This observation has shown involvement of Axl in the epithelial-mesenchymal transition (EMT) in prostate cancer. Notably, treatment of PC3 and DU145 cells with GAS6 has resulted in down-regulation of Axl protein levels. In addition, treatment with a hypoxia mimicking agent has blocked GAS6-associated down-regulation of Axl in these metastatic prostate cancer cell lines. In brief, GAS6 can regulate expression of Axl, an important mediator of metastasis. Expression of this gene is preserved in the hypoxic tumor niche to enhance metastasis-related signals [47]. Fig. 1 shows the mechanism of contribution of *GAS6* in the pathogenesis of breast and prostate cancers.

In pancreatic tumors, GAS6 is principally secreted by tumor associated macrophages (TAMs) and cancer associated fibroblasts (CAFs). Notably, suppression of GAS6 signaling can moderately reverse EMT process in tumor cells and increase activity if natural killer (NK) cells, thus hindering metastasis of pancreatic cancer. Notably, GAS6 has a simultaneous function on tumor cells and NK cells to facilitate metastatic processes in pancreatic cancer [19]. In pancreatic cancer tissues, expression of GAS6 has been verified in both M2-like macrophages and αSMA+ stromal cells. Moreover, ex-vivo experiments have shown expression of GAS6 in both bone-marrow originated macrophage and pancreatic fibroblast. Most notably, tumor sections with activated Axl receptor have been found to contain higher amounts of tumor associated macrophages and CAFs. Meanwhile, GAS6 can regulate activation of NK cells, since its blockade has resulted in restoration of NK cell activity and enhancement of infiltration of NK cells in the metastatic lesions [19].

Programmed cell death ligand 1 (PD-L1) has been reported to regulate proliferation of non-small cell lung cancer (NSCLC) cells through affecting Gas6/MerTK signaling. Nuclear translocation of PD-L1 has been shown to be increased via binding of Karyopherin β1 (KPNB1). Nuclear PD-L1 (nPD-L1) in conjunction with the transcription factor Sp1 regulates GAS6 expression at transcript level and enhances GAS6

Table 2
Animal studies related to the role of GAS6 in the carcinogenesis.

Tumor type	Animal models	Results	References
Breast cancer	BALB/cAnHsd (Balb/c) mice	Δ GAS6: ↓ transition to invasive cancer in early stage mammary lesions (↓tumor formation or ↓ transition from pre-invasive to invasive cancer)	[10]
Pancreatic ductal adenocarcinoma (PDA)	Female C57Bl/6 mice, syngeneic orthotopic KPC mice	Δ GAS6: ↓ metastasis, ↓ vimentin expression, did not affect angiogenesis, ↑ number of NKp46+ NK cells in lung metastatic lesions	[19]
	Female Athymic nude mice	Δ GAS6: ↓ tumor growth	[40]
Intestinal cancer	C57/BL6 mice, ApcMin mice	Δ GAS6: DSS-treated Gas6–/– mice indicated more severe colitis than the DSS-treated Gas6+/+ mice Δ GAS6: ↑ number of polyps, ↑ activities of NF-κB, and TNF-α mRNA levels	[2]
Bladder cancer (BC)	Male nude BALB/c mice	Δ GAS6: ↓ tumor volume, ↓ tumor weight, ↓ tumor size	[36]
Glioblastoma	Male athymic nude mice	LRIG2-mediated GAS6/AXL/SRC signaling: ↑ gefitinib resistance	[7]
Different cancer types	Gas6-deficient mice	Δ GAS6: ↓ tumor weight, ↓ tumor size, ↓ tumor growth, ↓ metastasis, ↓ proliferation, did not affect tumor angiogenesis, did not affect inflammation	[34]
Renal cell carcinoma (RCC)	–	Δ GAS6/AXL signaling: ↓ ccRCC metastatic ability	[42]

secretion to increase activity of the MerTK signaling [8]. Treatment of NSCLC cells with GAS6 has enhanced their proliferation and invasive properties, reduced activity of caspase 3, and increased levels of VEGF, pAKT, IL-2 and IL-6. Taken together, GAS6 can facilitate NSCLC progression through affecting VEGF/AKT signaling. Fig. 2 shows the oncogenic role of GAS6 in pancreatic and lung cancers.

Treatment of gingival cancer cells with GAS6 has enhanced invasive properties of these cells, enhanced expressions of GAS6 and AXL, reduced activity of ERK but enhanced activity of AKT, and reduced production of G-CSF, IL-2, IL-6, and IL-8. Thus, GAS6 enhances invasion of these cells through enhancement of AKT activity and reduction of levels of pro-inflammatory cytokines [16].

Gas6/Axl signaling has also been shown to activate the PI3K/Akt1 survival pathway to shield oligodendrocyte cells from apoptotic effects of TNFα [46]. Table 1 shows the results of in vitro studies related to the role of GAS6 in the carcinogenesis.

2.2. Animal studies

Experiments in a p53-null model of preliminary phases of mammary cancer have shown high expression of Gas6 in pre-invasive lesions with high macrophage infiltration, as compared with lesions with low macrophage infiltration. In vivo studies have shown the ability of F4/80 +CD11b+ macrophages to produce Gas6 in premalignant lesions. Most notably, macrophage-produced Gas6 could induce tumor-like features ex vivo [10]. Moreover, deletion of stromal Gas6 postpones primary phases of breast cancer progression and reduces tumor formation. However, it could not affect tumor growth in established tumors. Taken together, Gas6 produced by macrophages can regulate transition of premalignant lesions to invasive cancer [10]. In vivo studies have also shown that obstruction of Gas6 signaling in stromal cells can affect cancer cell plasticity, modulate NK cell activity and suppress metastasis of pancreatic cancer [19]. Almost all accomplished studies in different xenograft models of cancers have confirmed that GAS6 silencing decreases tumor burden and metastatic ability of malignant cells (Table 2).

2.3. Human studies

Immunochemical experiments have shown co-expression of Axl, GAS6, and Hif-1α in human prostate cancer and in bone metastases compared with normal tissues, indicating the role of these genes in the metastatic process in prostate cancer [47]. Activation of AXL and up-regulation of GAS6 has been correlated with poor prognosis and higher risk of metastasis in patients with pancreatic cancer. Thus, GAS6 has been suggested as a target for treatment of pancreatic cancer. Moreover, NK cells are potential markers for assessment of response to anti-GAS6 treatments [19]. Expression of GAS6 has also been shown to be higher in plasma samples of patients with hepatocellular carcinoma compared with normal controls [48]. In breast cancer, a single study has reported improvement in survival of patients parallel with over-expression of GAS6 [18], while another study reported no association between GAS6 transcript levels and patients' survival [38]. In ovarian cancer, NSCLC, acute myeloid leukemia, gastric cancer, bladder cancer, oral squamous cell carcinoma and glioblastoma, over-expression of GAS6 has been associated with poor clinical outcome. In lung cancer, patients with tumors expressing both tumor Axl and stromal Gas6 showed worse five-year disease-free survival than in both-negative group [24]. However, another study has indicated that the 5y-overal survival (OS) and disease-free survival (DFS) rates in the Gas6 mRNA high group were better than the Gas6 mRNA low group [20]. Table 3 shows the results of clinical studies related to the role of GAS6 in the carcinogenesis.

3. GAS6-AS1

3.1. In vitro studies

In vitro studies have indicated that GAS6-AS1 up-regulation suppresses progression of lung cancer. This lncRNA could inhibit glucose metabolism reprogramming. Functionally, GAS6-AS1 could suppress expression of glucose transporter GLUT1, an important modulator of metabolic pathways of glucose. GAS6-AS1 has a direct interaction with E2F1 transcription factor inhibiting E2F1 effect on GLUT1 transcription. This study has suggested a tumor suppressor role for GAS6-AS1 [35]. Another experiment in lung cancer cells has shown that GAS6-AS1 up-regulation suppresses migration and invasive properties of A549 and H1650 cells. Mechanistically, GAS6-AS1 acts as a sponge for miR-24-3p and releases its target, GTPase IMAP Family Member 6 from its inhibitory effects [12]. On the other hand, expression GAS6-AS1 has been shown to be increased in breast cancer cell lines. GAS6-AS1 silencing has inhibited proliferation, migration and invasion of these cells, while facilitating their apoptosis. GAS6-AS1 silencing has led to blockage of the PI3K/AKT pathway via suppressing expression of related proteins. This lncRNA acts as a sponge for miR-324-3p to increase expression of SETD1A. In fact, GAS6-AS1 activates PI3K/AKT pathway through influencing activity of the miR-324-3p/SETD1A axis [32]. Similarly, GAS6-AS1 acts as an oncogene in gastric cancer cells promoting proliferation, migration and invasion aptitude of these cells through enhancing their entry into S-phase. GAS6-AS1 can form a RNA-RNA duplex with GAS6 to regulate its expression at the transcriptional or translational phases, thus increasing AXL expression and activating AXL signaling [55]. Fig. 3 shows different roles of GAS6-AS in lung, gastric and breast cancers.

In hepatocellular carcinoma and acute myeloid leukemia, GAS6-AS1

Table 3
Clinical studies related to the role of GAS6 in the carcinogenesis (ANCTs: adjacent non-cancerous tissues, OS: overall survival, RFS: relapse-free survival, DFI: disease-free interval, DFS: disease-free survival, CSS: cancer-related symptom).

Tumor type	Numbers of clinical samples	Expression (Tumor vs. Normal)	Kaplan-Meier analysis	Univariate cox regression	Multivariate cox regression	References
Breast cancer	100 patient tissues of various breast cancer subtypes and nine ANCTs	Down	Patients with higher levels of GAS6 had improvement in OS and they significantly showed improved RFS over Gas6 low patients.	–	–	[18]
	23 formalin-fixed pre-invasive DCIS patient samples	Up	–	–	–	[10]
	69 pairs of human breast tumor samples and ANCTs	Up	–	–	–	[28]
	49 primary breast carcinomas patient specimens	Gas6 was positively correlated with a number of favorable prognostic variables such as lymph node negativity, younger age at diagnosis, smaller size of tumors, low Nottingham prognostic index scores, and low nuclear morphology.	–	The levels of Gas6 mRNA were not independently associated with DFI or OS.	The levels of Gas6 mRNA were not independently associated with DFI or OS.	[38]
Prostate cancer	Human prostate tissue microarrays	Down	–	–	–	[23]
Ovarian cancer	Meta-Analysis of DNA Microarray: 172 epithelial ovarian cancers, 40 ovarian borderline tumors, and 6 ovarian surface epithelium, 2 normal fallopian tubes	Up	GAS6 expression was an independent negative prognostic factor.	High levels of GAS6 were significantly correlated with shorter DFS.	–	[5]
Non-small cell lung cancer (NSCLC)	98 advanced metastatic NSCLC patients	Up	–	High expression of GAS6, AXL, and, and N stage were predictors for worse BM-OS outcomes.	Co-expression of AXL/GAS6 was an independent unfavorable risk factor for the overall study population.	[51]
	26 NSCLC patients and ANCTs	Up	–	–	–	[56]
	69 patients	Up	Patients with tumors expressing both tumor Axl and stromal Gas6 significantly showed worse five-year DFS than in the both-negative group.	–	–	[24]
	88 tissue samples	66 patients: down 22 patients: up	The 5y-OS and DFS rates in the Gas6 mRNA high group were better than the Gas6 mRNA low group.	–	–	[20]
Gastric cancer (GC)	ACRG analysis: 300 GC patients	Undetectable in GC cell lines but up-regulated in CAFs	Worse survival rates were found in the co-expression group of GAS6 and AXL gene.	–	–	[4]
	28 GC tissues and ANCTs	Up	–	–	–	[44]
Hepatocellular carcinoma (HCC)	30 HCCs and ANCTs	Not increased	–	–	–	[29]
	Plasma samples of 45 patients with HCC and 20 NCs	From stages I to III: up	–	–	–	[48]
Acute myeloid leukemia (AML)	270 bone marrow or blood samples from 270 patients	26% of patients were GAS6+, and 74% were GAS6−	–	–	Patients with GAS6+ expression showed shorter DFS and OS.	[50]
	Cancer Genome Atlas analysis: 71 AML patients	36 patients: up, 35 patients down	–	High levels of GAS6-mRNA were unfavorable for OS.	High expression of GAS6-mRNA was an independent factor for poor EFS and OS.	[54]
Bladder cancer (BC)	65 pairs of BC tissues and ANCTs	Up		–	–	[36]

(*continued on next page*)

Table 3 (*continued*)

Tumor type	Numbers of clinical samples	Expression (Tumor vs. Normal)	Kaplan-Meier analysis	Univariate cox regression	Multivariate cox regression	References
			High levels of GAS6 were significantly correlated with poor OS.			
Upper Tract Urothelial Carcinoma (UTUC)	161 UTUC patients	89 patients: up	–	Factors including tumor grade, LVI, advanced pathological T stage, high Axl IHC score, and high Gas6 IHC score were significant predictors for CSS in UTUC patients.	Factors including an advanced pathological T stage, high Axl IHC score, and high Gas6 IHC score were independently correlated with lower CSS.	[15]
Oral squamous cell carcinoma (OSCC)	128 OSCC patients and 145 healthy controls	Up	OSCC patients with high levels of serum Gas6 showed significantly poorer survival than patients with low levels of serum Gas6.	High levels of serum Gas6, late TNM stage and poor differentiation were significantly correlated with poor prognosis.	High levels of serum Gas6 was found to be an independent factor for poor OS in OSCC patients.	[22]
Pediatric thyroid carcinomas	17 thyroid papillary carcinomas patients	70.6% of cases: up	–	–	–	[21]
Glioblastoma	42 fresh-frozen and 79 paraffin-embedded glioma samples and 55 GBM samples	81% Gas6 mRNA, and 74% Gas6 protein: Moderate to high	High Axl expression and Axl/Gas6 co-expression were significantly correlated with shorter TTP, PFS <12 months, and poorer OS, OS <12 months.	–	High Axl expression and high Axl/Gas6 co-expression were significantly correlated with a shorter PFS.	[17]

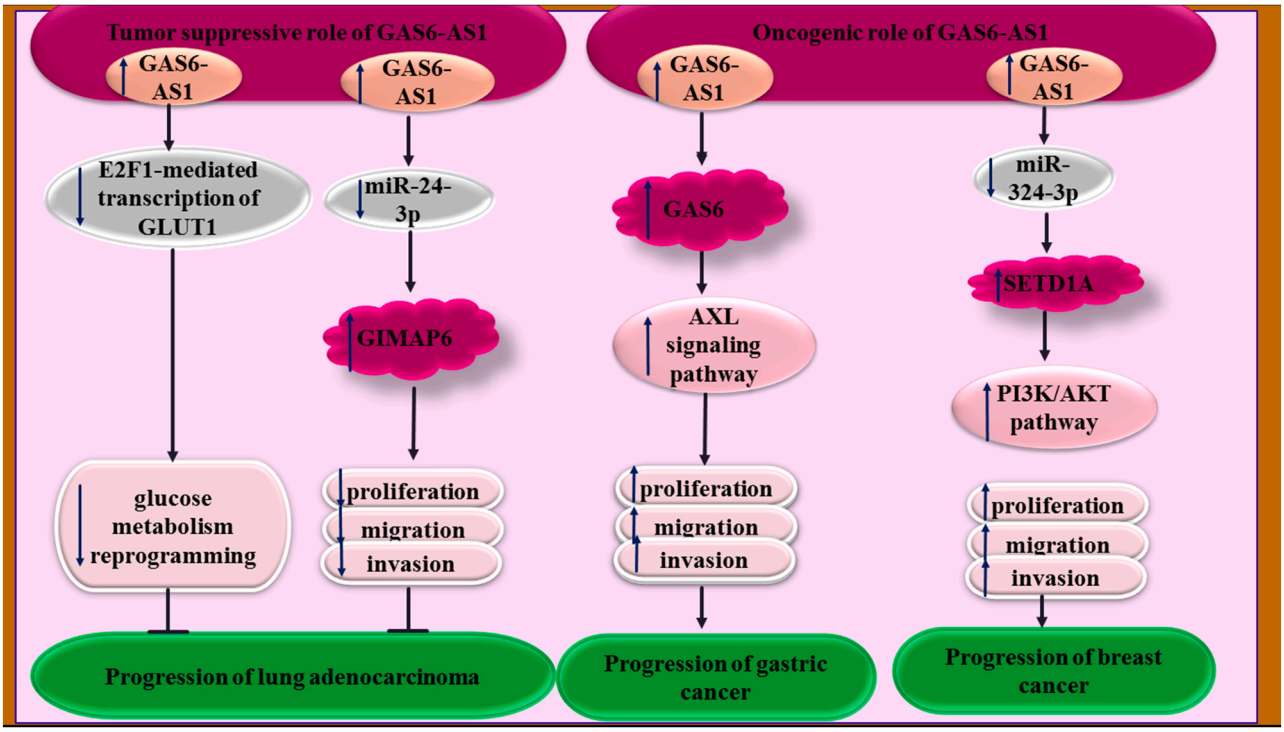

Fig. 3. Different roles of GAS6-AS in lung, gastric and breast cancers.

has oncogenic effects through sponging miR-585 [1] and miR-370-3p [30], respectively. Table 4 shows the results of in vitro studies related to the role of GAS6-AS1 in the carcinogenesis.

3.2. Animal studies

In vivo studies have validated the tumor suppressor role of GAS6-AS1 in NSCLC [35], while its oncogenic roles in gastric [55] and liver [1] cancers. Table 5 shows the results of animal studies related to the role of GAS6-AS1 in the carcinogenesis.

3.3. Human studies

Assessment of TCGA data of patients with papillary renal cell carcinoma has led to construction of a 17-lncRNA signature. GAS6-AS1 has been among lncRNAs with protective effect against this cancer. This lncRNA could also serve as a biomarker for the prognosis of these patients [53]. Similar with this study, over-expression of GAS6-AS1 has been correlated with better survival of patients with NSCLC [14]. On the other hand, another study in papillary renal cell carcinoma has shown that patients with high GAS6-AS1 expression levels significantly had

Table 4
In vitro studies related to the role of GAS6-AS1 in the carcinogenesis.

Cancer type	Targets/ regulators and signaling pathways	Cell line	Function	References
Non-small cell lung cancer	GLUT1, E2F1	A549, H1299, PC9, and H1975, HBE	Δ GAS6-AS1: ↑ proliferation, ↑ migration, ↑ invasion ↑ GAS6-AS1: ↓ proliferation, ↓ migration, ↓ invasion	[35]
	miR-24-3p, GIMAP6	A549 and H1650 cells	↑ GAS6-AS1: ↓ proliferation, ↓ migration, ↓ invasion	[12]
Gastric cancer	GAS6, AXL signaling pathway	SGC7901, BGC823	Δ GAS6-AS1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ S-phase Population, ↑ G0/G1-phase population ↑ GAS6-AS1: ↑ proliferation, ↑ migration, ↑ invasion, ↑ colony formation ability, ↑ S-phase Population, ↓ G0/G1-phase population	[55]
Breast cancer	miR-324-3p, SETD1A, PI3K/AKT pathway	MCF-7, MDA-MB-231, SKBR-3, and MDA-MB-468, MCF-10A	Δ GAS6-AS1: ↓ proliferation, ↓ migration, ↓ invasion, ↑ apoptosis	[32]
Hepatocellular carcinoma	miR-585, EIF5A2	L-O2, Hep3B, Huh7, Bel-7402	Δ GAS6-AS1: ↓ growth, ↓ metastasis	[1]
Acute myeloid leukemia	miR-370-3p, TSPAN3	–	Δ GAS6-AS1: ↓ viability, ↓ migration, ↓ invasion	[30]

Table 5
Animal studies related to the role of GAS6-AS1 in the carcinogenesis.

Cancer type	Animal models	Results	References
Non-small cell lung cancer	Female nude mice	↑ GAS6-AS1: ↓ tumor volume, ↓ tumor weight	[35]
Gastric cancer	Female BALB/c nude mouse	Δ GAS6-AS1: ↓ tumor volume, ↓ tumor growth ↑ GAS6-AS1: ↑ tumor volume, ↑ tumor growth	[55]
Hepatocellular carcinoma	Male BALB/c nude mice	Δ GAS6-AS1: ↓ tumor volume, ↓ ↓ tumor weight, ↓ tumor growth	[1]

shorter OS compared to patients with low GAS6-AS1 expression levels [27]. In breast cancer, two different studies have reported oncogenic [32] versus tumor suppressor role for this lncRNA [33], with the former reporting association between its over-expression and poor clinical outcome [32]. Table 6 summarizes the results of clinical studies related to the role of GAS6-AS1 in the carcinogenesis.

4. Discussion

GAS genes have essential roles in the regulation of cell cycle, thus they contribute in the pathogenesis of human cancers [9]. *GAS6* is a member of this family whose role in this process has been validated by different studies. This multifaceted protein has been shown to be produced by numerous kinds of cells and regulate versatile processes such as plasticity of malignant cells, angiogenic processes, and function of immune cells. However, the results of studies regarding the pattern of its expression in different cancers and even in a certain type of cancer such as breast or liver cancers are conflicting.

In breast, pancreatic, oral squamous cell and esophageal cancers, GAS6 has important roles in facilitation of EMT and enhancement of metastasis. In many types of cancers, GAS6 could enhance cell proliferation and malignant phenotypes of cells. GAS6 also can affect pathogenesis of non-malignant conditions. For instance, through acting as an autocrine growth factor, GAS6 can induce proliferation of mesangial cells via latent transcription factor STAT3 [52]. The regulatory role of GAS6 on STAT3 is also implicated in the pathogenesis of breast cancer [10].

Prognostic impact of GAS6 has been verified in ovarian cancer, NSCLC, acute myeloid leukemia, gastric cancer, bladder cancer, oral squamous cell carcinoma and glioblastoma. Although plasma levels of GAS6 has been shown to be increased in some cancer patients [48], application of this gene as a non-invasive marker in cancer diagnostics has not been assessed.

Notably, the antisense transcript for GAS6 has also been involved in the pathogenesis of human cancer through both GAS6-dependent and GAS6-independent mechanisms. A recent study has reported opposite trends in expressions of these two genes in breast cancer samples [28], while in gastric cancer these two genes have been similarly over-expressed [55]. This lncRNA can serve as sponge for miR-324-3p, miR-585 and miR-370-3p, to regulate expressions of SETD1A, EIF5A2 and TSPAN3. Thus, the interactions between GAS6-AS1 and miRNAs are the most probable route of participation of GAS6-AS1 in the tumorigenesis. The results of studies regarding the role of GAS6-AS1 in the carcinogenesis are even more conflicting than its sense transcript. The impact of its over-expression on patients' prognosis is extensively incompatible in different types of cancers. These inconsistencies cannot be explained by a possible tissue-specific role for this lncRNA, as even in a certain type of tissue (for instance, breast and renal tissues) both oncogenic and tumor suppressor roles have been reported. Future studies should assess expression and function of this lncRNA in different stages of cancer progression to find whether this factor can affect its role.

Taken together, both GAS6 and GAS6-AS1 can affect carcinogenesis through different mechanisms. Simultaneous assessment of their expression in different types of cancers can facilitate identification of their roles and interactions in each tissue type. Identification of the functional interactions between GAS6 and GAS6-AS1 in different

Table 6
Clinical studies related to the role of GAS6-AS1 in the carcinogenesis (ANCT: adjacent non-cancerous tissue).

Tumor type	Numbers of clinical samples	Expression (Tumor vs. Normal)	Function	Kaplan-Meier analysis	Univariate cox regression	Multivariate cox regression	References
Non-small cell lung cancer (NSCLC)	50 primary NSCLC patients and ANCTs	Down	Tumor suppressor	Low GAS6-AS1expression was correlated with shorter OS.	Histological grade, histological classification, TNM stage, and GAS6-AS1 expression were identified as four prognostic factors.	GAS6-AS1 expression was identified as a significant independent predictor of survival.	[14]
	80 pairs of LUAD tissues and ANCTs	Down	Tumor suppressor	–	–	–	[35]
Gastric cancer (GC)	55 pairs of GC tissues and ANCTs	Up	Oncogene	–	–	–	[55]
	40 pairs of GC tissues and ANCTs	Up	Oncogene				
Breast cancer (BC)	60 pairs of breast cancer tissues and ANCTs	Up	Oncogene	Higher GAS6-AS1 expression levels were associated with an unfavorable prognosis in breast cancer patients.	Higher GAS6-AS1 expression levels were correlated with poor OS.	–	[32]
	90 pairs of human breast tumor samples and ANCTs	Down	Tumor suppressor	–	–	–	[33]
	69 pairs of human breast tumor samples and ANCTs	Down	–	–	–	–	[28]
Hepatocellular carcinoma (HCC)	47 pairs of fresh HCC tissue samples and ANCTs	Up	Oncogene	HCC patients with high GAS6-AS1 expression significantly had shorter OS compared to patients with low GAS6-AS1 expression.	–	–	[1]
Papillary renal cell carcinoma	TCGA analysis: 321 KIRP tissues and 32 tumor-free adjacent normal tissues	Up	Oncogene	Patients with high GAS6-AS1 expression levels significantly had shorter OS compared to patients with low GAS6-AS1 expression levels.	–	GAS6-AS1 showed prognostic significance in this type of cancer.	[27]
Papillary renal cell carcinoma	TCGA analysis: 32 cancer-adjacent normal tissues and 289 cancer tissues	Down	Tumor suppressor	High expression of GAS6-AS1 was correlated with better survival.	–	GAS6-AS1 was identified as a potential prognostic biomarker.	[53]

healthy and diseased conditions can help in proper targeting of this axis in each context.

Conflict of interest

The authors declare they have no conflict of interest.

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