


Novel Tumor Suppressor lncRNA Growth Arrest-Specific 5 (GAS5) In Human Cancer

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Abstract: Long noncoding RNAs (lncRNAs) play crucial regulatory roles in fundamental biological processes, and deregulations of lncRNAs have been linked to numerous human diseases, especially cancers. Of particular interest in this regard is lncRNA GAS5, which is mainly identified as a tumor suppressor in several cancers. GAS5 was significantly low expressed in multiple cancers and was associated with clinic-pathological characteristics and patient survival, indicating a novel potential diagnostic and prognostic biomarker, and a therapeutic target for cancer. Functionally, GAS5 is involved in cell proliferation, metastasis, invasion, apoptosis, epithelial–mesenchymal transition (EMT), and drug resistance, among others, via multiple molecular mechanisms, such as binding to DNA sequences, forming RNA–DNA triplex complex, triggering or suppressing the expression of genes, binding proteins to form chromatin-modifying complex, which activates or represses gene expression, and acting as miRNA sponge to suppress miRNA expression, leading to regulation of miRNA target genes. This review provides an overview of the current state of knowledge and role of GAS5 in clinical relevance, biological functions and molecular mechanisms underlying the dysregulation of expression and function of GAS5 in cancer. Finally, the potential prospective role as diagnostic and prognostic biomarker and therapeutic target in cancer is discussed.

Keywords: GAS5, cancer, tumor suppressor, biomarker, therapeutic target

Introduction

There had been a preconception on the primacy of noncoding RNAs (ncRNAs) under the protein-coding RNAs for a long time. The development of techniques, such as genome-wide association studies, RIP-RNA sequencing, computational prediction of lncRNAs from ultra-deep RNA sequencing, and lncRNA chip-based screening, has made it possible for scientists to uncover the widespread expression profile and biological functions of ncRNAs.¹ ncRNAs are generally divided into two groups, namely small ncRNAs and long noncoding RNAs (lncRNAs) depending upon their transcript sizes.² A number of evidence show that lncRNAs function as chromatin modifier, transcriptional, post-transcriptional and translational regulators of gene expression in human physiological and pathological processes.³ Importantly, lncRNAs play key roles in human cancers.^{4,5} They are dysregulated in multiple cancers and act as tumor suppressors or oncogenes during tumorigenesis and have widespread biological functions, such as regulating cell proliferation, apoptosis, invasion, migration, differentiation, and drug resistance.^{6–8} Therefore, in-depth understanding of lncRNA biology may provide novel and better strategies for the diagnosis and even therapeutic potential in human cancer.

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One lncRNA human growth arrest-specific transcript 5 (GAS5), a multi-snoRNA host gene located at chromosome 1q25.1, comprises 12 exons and 11 introns, and encode the same 10 snoRNAs in corresponding introns with a short open reading frame (ORF), and is considered to have no function to encode proteins, rather spliced to yield two mature lncRNAs, termed GAS5a and GAS5b due to the presence of alternative 5'-splice donor sites in exon 7.^{9,10} As a lncRNA transcript of about 630 nt in length, which was primitively isolated from a subtraction cDNA library of growth-arrested cells, mature GAS5 was mainly identified as a tumor suppressor in human cancer.⁹

Saturating cell density or nutrient deprivation can increase GAS5 levels and accompany with growth arrest at post-transcriptional level, while GAS5 expression may be regulated in differentiating cells at transcriptional level.^{11,12} The former mechanism is perhaps best understood and involved an interplay between the nonsense-mediated decay (NMD) and the mammalian target of rapamycin (mTOR) pathways.^{13,14} GAS5 is a 5'-terminal oligopyrimidine RNA, whose translation is specifically controlled by the mTOR pathway.^{10,13,15} NMD is historically identified as a RNA quality control system to eliminate abnormal transcripts and control GAS5 function in mammalian cells.¹⁴ When mTOR activity is high, such as in actively growing cells, GAS5 translation is increased due to the presence of the 5'-TOP sequence. However, due to the short ORF and the presence of multiple termination codons in its sequence, the degradation of GAS5 transcripts via NMD happens, which further resulted in decrease in GAS5 levels. On the contrary, when mTOR pathway is inactivated, such as in growth-arrested cells, the translation of GAS5 short ORF is blocked and this in turn prevents NMD pathways, leading to the increased expression of GAS5.^{12,16}

In this review, we will describe the current knowledge about GAS5, from the clinical relevance, biological functions to molecular mechanisms, and the potential role of GAS5 in diagnostic and prognostic biomarker, and therapeutic target in human cancer.

GAS5 In Cancer

In recent years, GAS5 has raised increased attention due to its downregulation in a wide variety of malignancies, including non-small cell lung cancer (NSCLC),^{16,17} breast cancer (BC),^{18,19} hepatocellular carcinoma (HCC),^{20,21} esophageal carcinoma (EC),^{22,23} gastric cancer (GC),^{24,25}

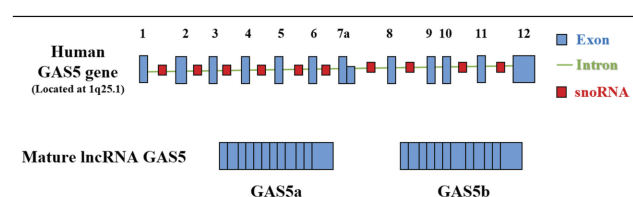


Figure 1 Human GAS5 gene and mature lncRNA GAS5 structure. Blue boxes represent the 12 exons and green lines represent the 11 introns of human GAS5 gene, and red boxes represent the snoRNA sequences present within 10 of its introns. Human GAS5 gene is located at 1q25.1 and comprises 12 exons and 11 introns. GAS5 transcribes to two types of mature lncRNA, namely GAS5a and GAS5b, due to the presence of alternative 5'-splice donor sites in exon 7.

colorectal cancer (CRC),^{26,27} pancreatic cancer (PC),^{28,29} cervical cancer (CC),^{30,31} ovarian cancer (OC),^{32,33} renal cell carcinoma (RCC)^{34,35} (Figure 1). Clinicopathological characteristics, such as overall survival (OS), disease-free survival (DFS), distant metastasis (DM), lymph node metastasis (LNM), tumor node stage (TNM) and tumor size, are highly correlated with the level of GAS5 expression in cancers,^{16,19,27,36,37} indicating that GAS5 can be a novel diagnostic and prognostic biomarker, as well as therapeutic target in many human cancers.^{38,39} Recent studies have demonstrated that GAS5 participates in multiple biological functions, such as cell proliferation, apoptosis, migration, invasion and epithelial-mesenchymal transition (EMT) and DNA repair in cancer.^{16,40–42} Additionally, GAS5 is also involved in modulating drug- and radio-sensitivities in human cancers.^{24,43–45} Moreover, GAS5 can exert its biological functions through multiple mechanisms, such as riborepression of steroid hormone, microRNAs (miRNAs) sponging and binding to mRNAs, thereby regulating protein-coding and noncoding gene expressions at transcriptional or post-transcriptional levels (Figure 2).^{25,38,39} Moreover, recent discovery of the more in-depth mechanisms and roles of GAS5 acting as potential biomarkers and therapeutic targets will open a promising area and hallmark feature for cancer diagnosis and treatment.

Clinical Relevance

GAS5 is expressed less in a number of malignancies, which was associated with clinio-pathological characteristics and patient prognosis, such as histological differentiation, tumor sizes, tumor node metastasis stage, lymph node metastasis (LNM), infiltration depth, vascular invasion, overall survival (OS), recurrence-free survival (RFS), disease-free survival (DFS), and/or prognostic biomarkers (Table 1). Based on this, GAS5 could be utilized as a diagnostic and

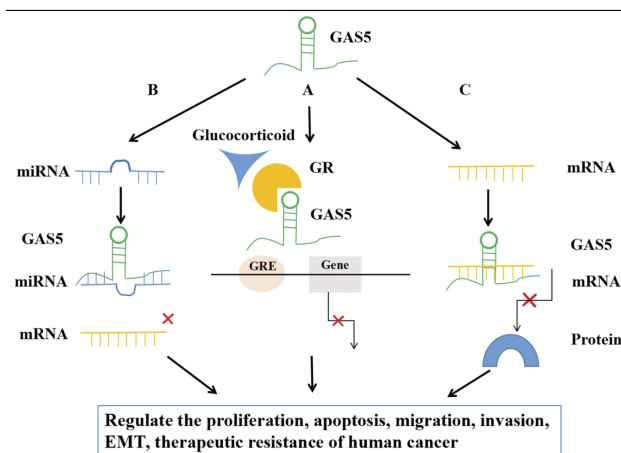


Figure 2 Mechanism of actions of GAS5 in cancer. There are three different molecular mechanisms of action described for GAS5 to regulate the proliferation, apoptosis, migration, invasion, epithelial–mesenchymal transition (EMT), metastasis and therapeutic resistance of human cancer. GAS5 could affect biological functions through riborepression of steroid hormone, miRNA sponge or binding to mRNAs at transcriptional and translation levels. **(A)** Transcriptional regulation by GAS5 through riborepression of steroid hormone. The glucocorticoid receptor (GR) regulates cell survival. GAS5 suppressed GR-induced transcriptional activity by acting as a decoy of the glucocorticoid response element (GRE) for binding to the GR. **(B)** Transcriptional regulation by GAS5 through miRNA sponge. GAS5 may regulate gene expression by binding to miRNAs and consequently preventing specific miRNAs from binding to their target mRNAs, thus regulating the expression of target gene thereby leading to anti-cancer or pro-cancer activities. **(C)** Translation regulation by GAS5 via binding to mRNAs. GAS5 can regulate gene translation by directly binding to its target mRNAs.

prognostic biomarker and therapeutic target in several cancer types. Lung cancer (LC) is one of the most common malignant tumors with the highest morbidity and

mortality.⁴⁶ NSCLC is the most common histological type of LC, which accounts for more than 80% of human LC types.⁴⁷ In NSCLC, GAS5 levels were reported to be significantly decreased in the cancerous tissues compared to the adjacent normal tissues and healthy controls, and were associated with clinicopathological features.^{43,44,48–52} One study showed that GAS5 was down-regulated in lung cancerous tissues compared to the adjacent normal tissues and related to tumor sizes and TNM stages.¹⁶ NSCLC tissues from patients with progressive disease (PD) had even lower GAS5 expression level.⁴⁴ Low expression of GAS5 was correlated with advanced clinical stage and larger tumor size in NSCLC⁵¹ and was also associated with poorer differentiation and advanced pathological stages.⁵² In plasma, the levels of GAS5 were significantly lower in patients with NSCLC than those of healthy controls, and GAS5 levels increased after surgery compared to preoperative GAS5 levels.¹⁷ The combination of carcinoembryonic antigen (CEA) and GAS5 could produce an area of 0.909 under the receiver-operating characteristic (ROC) curve in distinguishing NSCLC patients from healthy subjects.¹⁷ Another group also found that GAS5 expression levels were significantly increased in postoperative groups compared with preoperative ones, and the combination of GAS5, CEA and CA199 showed that the area under the ROC curve was 0.734.⁴⁹ In addition, single-nucleotide

Table 1 The Expression And Clinical Relevance Of GAS5 In Human Cancer

Cancer Type	Expression	Clinical Relevance	Reference
LC	Down	Small tumor size, early TNM stage and good differentiation, biomarker	16,17,43,44,48–52
BC	Down	Little LNM, small tumor size, early TNM stage and long OS time, biomarker	18,19,45,55–58
EC	Down	Early TNM stage	22,23,60
GC	Down	Small tumor size, early pathologic stage and good prognosis, biomarker	24,25,63–65
CRC	Down	Early clinical stage, little LNM, low DM rate, small tumor size and long OS time, biomarker	26,27,70–75
HCC	Down	Small tumor size, little LNM and good differentiation, biomarker	20,21,36,76,90
CC	Down	Early FIGO stage, biomarker	30,31,84,85
OC	Down	Small tumor size, early clinical stage, little LNM, long DFS and OS time, biomarker	32,33,81–83
PCa	Down	Long OS time, biomarker	86–88
RCC	Down	Long DFS time, biomarker	34,35,90
BCa	Down	Shallow invasive depth, low EORTC risk, high pathological grades, long DFS and RFS time, biomarker	92–95,148
GBM	Down	Long OS and DFS time, biomarker	90,102
TC	Down	Early TNM stage, little LNM, long DFS and OS time, biomarker	104,105
Melanoma	Down	Small tumor size, early TNM stage and low DM rate	107,108
Osteosarcoma	Down	Long OS time	110,111

Notes: Clinical relevance includes but not limited to histological differentiation, tumor sizes, tumor node metastasis (TNM) stage, lymph node metastasis (LNM), infiltration depth, vascular invasion, overall survival (OS), recurrence-free survival (RFS), disease-free survival (DFS), and/or prognostic biomarkers.

Abbreviations: LC, lung cancer; BC, breast cancer; EC, esophageal carcinoma; GC, gastric cancer; CRC, colorectal cancer; HCC, hepatocellular carcinoma; CC, cervical cancer; OC, ovarian cancer; PCa, prostate cancer; RCC, renal cell carcinoma; BCa, bladder cancer; GBM, glioblastoma; OSCC, oral squamous cell carcinoma; TC, thyroid cancer; LNM, lymph node metastasis; DM, distance metastasis.

polymorphism (SNP) rs145204276 of GAS5 acted as a protecting factor for LC risk, and patients with del/del genotype showed increased GAS5 expression level and decreased susceptibility of LC.⁵⁰ Together, these findings indicate that GAS5 is a highly specific and detectable diagnostic biomarker for LC. Breast cancer (BC) is one of the most common types of neoplasms and the second leading cause of death in women worldwide.⁵³ There are nearly 1.3 million newly diagnosed BC cases and approximately 500,000 deaths yearly in the world.⁵⁴ GAS5 levels were significantly decreased in BC tissues than those in adjacent normal breast epithelial tissues.^{18,55,56} One study showed low GAS5 expression in triple-negative breast cancer (TNBC) tissues than that of adjacent non-tumor tissues, and was associated with clinical stage, lymph node metastasis (LNM) and OS.¹⁹ Decreased expression of GAS5 was found in BC tissues and was negatively associated with later TNM stage and shorter OS time as well.⁴⁵ Intriguingly, BC patients aged less than 45 years old who had much lower GAS5 levels than those of old cases showed the poorer prognosis.⁵⁶ Others found that GAS5 levels were decreased frequently in estrogen receptor-negative (ER-) BC tissues and cells, and were related with large tumor size, advanced TNM stage.⁵⁷ BC patients with low GAS5 levels in plasma and a high Ki67 proliferation index before surgery were positively associated with LNM after surgery, indicating that plasma GAS5 may have the potential to assess the surgical effects and prognosis for patients with BC.⁵⁸ Together, GAS5 may provide a new perspective for understanding the molecular mechanisms of breast carcinogenesis, and a novel approach for the diagnosis and treatment of BC. Esophageal cancer (EC) is a common malignant tumor with a high mortality rate,⁵³ of which 90% of cases account for esophageal squamous cell carcinoma (ESCC).⁵⁹ GAS5 was frequently down-regulated in ESCC tissues, and patients with low GAS5 expression were associated with advanced stage of ESCC.²² GAS5 expression levels in serum were significantly lower in tumor tissues of patients with EC than those in adjacent healthy ones.²³ Another study also found that GAS5 was down-regulated in ESCC tissues and EC cells.⁶⁰ More studies exploring the contribution of GAS5 in the pathogenesis of ESCC and its complications should be encouraged. Gastric cancer (GC) is one of the most common malignant diseases in the world.⁶¹ Although great improvements have been made in the diagnosis and treatment of GC, the outcome of GC patients remains unsatisfactory with the 5-year OS rate less than 30%.⁶² GAS5 expression was significantly

reduced in GC tissues and cells relative to normal counterpart.^{24,25,37,63–65} Low GAS5 expression was associated with large tumor size and advanced pathologic stage.³⁷ Patients with lower GAS5 expression levels had poor DFS and OS than those with higher GAS5 expression, suggesting that GAS5 could be considered as an independent prognostic indicator for GC.³⁷ Lower expression of GAS5 was also correlated with larger tumor size and advanced clinical stage of GC.⁶⁴ In addition, the SNP rs145204276 of GAS5 was associated with the development and prognosis of GC, and the allele del of rs145204276 is associated with low GC susceptibility and low incidence rate of cancer progression and metastasis, and patients with del/del genotype had a high survival rate and early tumor stage in GC.⁶⁶ A similar finding was also reported by others, which showed a significant association with a decreased risk of GC, and patients with allele del were less likely to develop LNM.^{67,68} Together, the results above could enhance our understanding of the important role of GAS5 played in the molecular etiology and new biomarker for prognosis and a therapeutic target for GC intervention. Colorectal cancer (CRC) was predicted to be the second and third leading cause of cancer-related death in men and women, respectively, in Europe.⁶⁹ Low expression of GAS5 was observed in CRC tissues and cells compared to the normal ones.^{26,27,70–73} For example, GAS5 was expressed less in the tissues, plasma and exosomes of 158 cases with CRC patients than that of 173 cases of healthy controls and was associated with the TNM stage, LNM, rates of local recurrence and DM, indicating an independent prognostic factor for CRC.²⁷ Similar findings were reported in others.^{70–72} Lower expression of GAS5 was also associated with large tumor size, high histological grade and late TNM stage in CRC further confirming that GAS5 was an independent predictor for OS in CRC patients.⁷³ Similarly, reduced GAS5 levels were correlated with advanced clinical stage and LNM in CRC.⁷⁴ Also, rs145204276 mutation of GAS5 was significantly associated with the susceptibility and progression of CRC.⁷⁵ The allele del of rs145204276 was associated with 21% decreased susceptibility of CRC, and patients with allele del genotype were less likely to have LNM.⁷⁵ Together, GAS5 plays a crucial role in the clinicopathological characteristics and prognosis of CRC, which may provide significant clues for potential clinical utilities of CRC in the future. Hepatocellular carcinoma (HCC) ranks as the fifth-leading causes of cancer-related deaths for men in the United State.⁵³ Downregulation of GAS5 was found in HCC tissues and cells than those of

adjacent normal tissues and normal liver L02 cells, and predicted poor survival of HCC patients. Moreover, expression of GAS5 was correlated with the clinicopathological characteristics of HCC, and patients with high GAS5 expression had longer OS.^{20,21} Similarly, the expression level of GAS5 was reduced in HCC cases in comparison to normal ones and was associated with tumor size, LNM and clinical stage of HCC, suggesting a novel independent prognostic biomarker of OS of HCC patients.³⁶ Low expression of GAS5 was positively correlated with differentiation and portal vein tumor thrombosis, tumor size, lymph node metastasis and clinical stage of HCC patients.⁷⁶ Pancreatic cancer (PC) is one of the most common lethal malignancies, with a 5-year OS rate less than 5% due to the advanced stage of disease at initial diagnosis and the lack of effective therapies.⁷⁷ GAS5 was found to be decreased in human PC tissues and cells compared with those of normal ones.^{28,29,78} Lower expression of GAS5 in plasma was found in intraductal papillary mucinous neoplasms (IPMNs) compared to non-diseased controls, suggesting that a GAS5-based blood test may be used as an adjunct diagnostic tool for identifying IPMNs.⁷⁹ Thus, GAS5 may be used as a potential biomarker for diagnosis in patients with PC. Ovarian cancer (OC) is one of the most common gynecological malignancies in the world with low 5-year OS.^{53,80} Low expression GAS5 was found in OC tissues and cells,^{32,33,81} which was negatively associated with advanced clinical stage.³² Studies found that low GAS5 expression levels were correlated with large tumor size, advanced tumor stage, tumor invasive depth, poor DFS, and OS in patients with OC.^{81–83} These studies suggested that GAS5 represented a novel and a potential target for diagnosis and treatment of OC. Cervical cancer (CC) is the second most common cancer in women worldwide, and it is the leading cause of cancer death among women in developing countries.⁶¹ GAS5 expression was decreased in CC tissues and cells as well^{30,31,84,85} and was associated with FIGO stage, tumor invasion and metastasis of CC patients.³⁰ Patients with lower expression of GAS5 had shorter OS than those with higher GAS5 expression in CC.⁸⁵ Thus, the current knowledge about the role of GAS5 played in CC contributed to our better understanding of the pathogenesis of this malignancy and development of lncRNA-mediated diagnostic biomarker and therapeutic target in CC. Prostate cancer (PCa) is the most frequently diagnosed malignancy and the second leading contributor to cancer-related death among males in the United States.⁵³ GAS5 expression levels were reduced in the PCa tissues

and cells.^{86,87} Also, the rs145204276 and rs55829688 SNPs of GAS5 may be used as key indicators for the diagnosis and prognosis prediction of PCa.⁸⁸ Thus, GAS5 provides novel insights to identify potential diagnostic biomarker and therapeutic target for PCa in the clinic. Renal cell carcinoma (RCC) is the third most common urological tumor and represents about 3% of all cancers in adults.⁸⁹ Among all RCC cases, clear cell renal cell carcinoma (ccRCC) is the major histological subtype, which accounts for more than 70% of all RCC types. According to previous studies, GAS5 expression was decreased in RCC tissues compared to adjacent non-tumor kidney tissues and RCC cells.^{34,35} Reduction of GAS5 indicated tumor progression and recurrence and was independently associated with DFS of ccRCC patients.³⁴ RCC patients could be clustered by GAS5 and miR-34a co-expression profile, suggesting potential utilities of GAS5 and miR-34a for diagnostic and therapeutic roles in RCC.⁹⁰ These studies provide evidence that a decrease in GAS5 expression is associated with RCC genesis and progression, and this provided a potential attractive diagnostic biomarker and therapeutic approach for RCC. Bladder cancer (BCa) is the most common malignancy of the urinary system with a low OS.⁹¹ GAS5 expression was commonly downregulated in BCa specimens and cells.^{92–95} For example, lower levels of GAS5 were found in 82 bladder transitional cell carcinomas (BTCC) tissues and cells and were correlated with high pathological grades and short DFS time for BTCC patients.⁹⁴ Low GAS5 levels was also associated with invasive high-grade tumors, and high European Organization for Research and Treatment of Cancer (EORTC) risk in non-muscle-invasive bladder cancer (NMIBC) patients, and GAS5 loss was correlated with a higher risk for NMIBC short-term relapse and progression, making GAS5 a prognosis biomarker for NMIBC patients.⁹⁵ Together, acting as a tumor suppressor, GAS5 provided a novel therapeutic strategy and a potential diagnostic and prognostic biomarker for BCa. Glioma is a type of neurologically destructive human brain tumors with a poor prognosis, which accounts for nearly 80% of malignant brain tumors and 30% of all central nervous system tumors.⁹⁶ Low expression of GAS5 was observed in glioma tissues and cells compared with normal ones.^{97–99} Also, carriers of the GAS5 del allele were significantly associated with an elevated risk of glioma.¹⁰⁰ Glioblastoma (GBM) is a frequently diagnosed aggressive tumor with poor clinical outcome, which accounts for over 60% of primary brain tumors in the human central nervous system.¹⁰¹ GAS5 was significantly reduced in GBM.⁹⁰ Patients with high GAS5 levels

were associated with increased probability of OS and DFS rates in patients with GBM.¹⁰² These results suggested that GAS5 might have great potential to be used as a therapeutic target and biomarkers for GBM. Head and neck cancer (HNC) is a heterogeneous group of cancers originating from the upper aero-digestive tract and one of the ten most frequent cancers worldwide. Among those, nasopharyngeal carcinoma (NPC) is a common malignancy of HNC. GAS5 rs2067079 carriers presented a more remarkable increased risk of severe myelosuppression and severe neutropenia in NPC patients after the treatment with chemoradiotherapy.¹⁰³ Besides, compared with rs6790 AA genotype carriers, rs6790 GG and GA genotype carriers had increased incidence rate of severe myelosuppression and severe neutropenia in NPC patients.¹⁰³ These results indicated a potential role of GAS5 polymorphisms rs2067079 and rs6790 as predictive biomarkers for chemoradiotherapy-induced toxicities in NPC. The prevalence of thyroid cancer (TC) has increased worldwide in recent decades. GAS5 was expressed less in TC tissues and cells¹⁰⁴ and was significantly correlated with TNM staging, LNM and multiple cancer foci of TC.¹⁰⁵ The survival rate with high GAS5 expression was higher than that of low GAS5 expression during the DFS and OS periods, and thus GAS5 could be considered as an independent risk factor for prognosis in TC patients.¹⁰⁵ These findings suggested that GAS5 could also be potential for therapeutic target and diagnostic biomarker for TC. Skin cancer (SC) represents a major and growing public health problem. Low expression of GAS5 was observed in SC tissues compared to normal ones, and GAS5 could suppress cell proliferation and promote cell apoptosis in SC.¹⁰⁶ Melanoma is the most common form of skin cancer as well as the leading cause of death in patients with SC. The GAS5 expression was significantly lower in melanoma tumors relative to that in adjacent noncancerous tissues and correlated with larger tumor size, advanced TNM stage and higher incidences of ulceration and metastasis,¹⁰⁷ and significantly associated with DM and TNM stage.¹⁰⁸ Osteosarcoma is the most common primary malignant bone tumor developing in childhood and adolescence with poor outcome and the 5-year OS rate of patients with metastatic osteosarcoma is less than 20%.¹⁰⁹ GAS5 was down-regulated in MG-63 and OS732 osteosarcoma cells compared to normal hFOB1.19 cells.¹¹⁰ In addition, the genetic variant rs145204276 of GAS5 functioned as a protective factor in the incidence of OS possibly by upregulating the rate of methylation in the 7th CpG site of GAS5 promoter, which

could further increase GAS5 levels in osteosarcoma.¹¹¹ Thus, findings about GAS5 may offer a new potential therapeutic strategy for the patient with osteosarcoma.

Biological Behaviors

GAS5 was closely involved in proliferation, cell cycle arrest, apoptosis, migration, invasion, chemo-resistance and EMT contribution to the tumorigenesis processes in various tumor cells (Table 2). GAS5 could significantly inhibit the proliferation, invasion, and induce the apoptosis in vitro and in vivo in NSCLC.¹⁶ Overexpression of GAS5 inhibited cell proliferation and invasion and promoted apoptosis in vitro and inhibited tumor growth in vivo.⁴⁸ While silencing of GAS5 diminished the cell growth inhibition induced by cisplatin (DDP) in A549 cells, overexpression of GAS5 enhanced the DDP-inhibited cell viability in A549/DDP NSCLC cells.⁴⁴ GAS5 was also

Table 2 The Effects Of GAS5 On Phenotype In Human Cancer

Phenotype	Inhibition Or Promotion	Cancer Type
Proliferation	Inhibited	LC, BC, EC, GC, CRC, HCC, PC, CC, OC, PCa, RCC, BCa, glioma, OSCC, SC, melanoma, osteosarcoma
Apoptosis	Promoted	LC, BC, EC, GC, CRC, HCC, PC, ECa, CC, OC, RCC, BCa, glioma, SC, melanoma
Cell cycle arrest	Promoted	BC, EC, GC, CRC, PC, CC, PCa, RCC, BCa, melanoma
Migration	Inhibited	LC, BC, CRC, HCC, PC, CC, OC, RCC, glioma, OSCC, melanoma, osteosarcoma
Invasion	Inhibited	LC, EC, CRC, HCC, PC, CC, OC, RCC, glioma, OSCC, melanoma, osteosarcoma
EMT	Inhibited	PC, OSCC
Radio and drug therapy sensitivity	Promoted	LC, BC, GC, PC, CC, PCa, RCC, BCa, glioma
Angiogenesis	Inhibited	CRC

Abbreviations: LC, lung cancer; BC, breast cancer; EC, esophageal carcinoma; GC, gastric cancer; CRC, colorectal cancer; HCC, hepatocellular carcinoma; PC, pancreatic cancer; ECa, endometrial cancer; CC, cervical cancer; OC, ovarian cancer; PCa, prostate cancer; RCC, renal cell carcinoma; BCa, bladder cancer; GBM, glioblastoma; OSCC, oral squamous cell carcinoma; TC, thyroid cancer; SC, skin cancer.

found to induce cell apoptosis by enhancing DDP sensitivity in NSCLC.⁴⁴ Overexpression of GAS5 could attenuate proliferation and enhance apoptosis in TNBC cells as well.¹⁹ Moreover, expression of GAS5 was found to be decreased in BC tissues of trastuzumab-treated patients and SKBR-3/Tr (trastuzumab-resistant) BC cells.¹¹² Also, inhibition of GAS5 promoted proliferation SKBR-3 cells and reversed lapatinib-induced proliferation inhibition of SKBR-3/Tr BC cells.¹¹² Moreover, the expression of GAS5 increased following the treatment of dendrosomal curcumin (DNC) and facilitated the antitumor effect of DNC in BC cells.⁴¹ Thus, the combination of DNC and GAS5 might provide a potential for treatment of drug resistance in BC cells.⁴¹ Bharangin, a natural agent obtained from the roots of *pigmacopremna herbacea*, suppressed the proliferation and induced apoptosis via inducing GAS5 expression in BC cells.¹¹³ Paclitaxel (PCT) and bleomycin (BLM) increased expression of GAS5 in BC cells, and the accumulation of GAS5 in exosomes was noticed and showed a prevalent event in apoptotic processes in the MCF-7 and MDA-MB-231 BC cells.¹¹⁴ Interestingly, part of the GAS5 function as anti-tumor activity was observed within the hormone response element mimic (HREM) area of the GAS5 molecule in BC cells.^{115–117} Similar to GAS5, the expression of GAS5 HREM increased ultraviolet-C-induced apoptosis, cell death upon DNA damage and decreased cell viability in both hormone-sensitive and hormone-insensitive BC cells.¹¹⁵ Moreover, as summarized in one recent review article, overexpression of GAS5 inhibited tumor proliferation, migration and progression via regulating miRNAs expression, blockade of EMT, inhibiting cell cycle progression, and regulating relevant signaling pathways in several digestive malignancies.³⁹ GAS5 was found to be reduced in adriamycin (ADM)-resistant GC cells, and overexpression of GAS5 enhanced the anti-proliferation and pro-apoptosis activity of ADM in SGC-7901/ADM cells, suggesting that GAS5 could induce ADM sensitivity in GC cells.²⁴ Functional studies demonstrated that GAS5 inhibited proliferation and induced G0/G1 cell cycle arrest and apoptosis in CRC cells.⁷¹ Overexpression of GAS5 and the small nucleolar RNU44 (SNORD44) by oncolytic adenovirus inhibited growth and induced apoptosis in SW620 and LS174T CRC cells, and suppressed tumor growth in vivo.¹¹⁸ GAS5 could also inhibit migration and invasion of HCC cells in vitro and could suppress tumor metastasis in vivo.²⁰ Corylin, a flavonoid extracted from the nuts of *Psoralea corylifolia* L. (Fabaceae), which was

a widely used anti-inflammatory and anti-cancer agent in China, inhibited the proliferation, EMT, migration and invasion of Huh7 and HepG2 HCC cells through upregulation of GAS5.⁴⁰ Thus, the above findings suggested an important role of GAS5 in the occurrence, growth, and progression of HCC. Inhibition of GAS5 expression could also confer OC cells with faster proliferation and smaller percentage of apoptosis in vitro, and more aggressive tumor growth in vivo.⁸² GAS5 prohibited cell proliferation, colony formation, migration and invasion, and increased cell cycle arrest in Hela and Siha CC cells.¹¹⁹ Overexpression of GAS5 inhibited cell proliferation, migration and invasion, induced cell apoptosis, and arrested cell cycle in A498 RCC cells as well.³⁵ Oral squamous cell carcinoma (OSCC) is the most common cancer of HNC. Expression of GAS5 was comparatively low in OSCC, and overexpression of GAS5 inhibited proliferation, migration and invasion in OSCC cells.¹²⁰

Molecular Mechanisms

Studies have shown the high expression pattern and tumor suppressor role of GAS5 in many types of cancer, and dysregulation of expression of GAS5 is involved in biological functions, such as cell proliferation, apoptosis, migration and invasion, through modulating downstream target genes via multiple molecular mechanisms (Tables 2 and 3 and Figure 2). GAS5 could affect biological functions through riborepression of steroid hormone, miRNA sponge or binding to mRNAs at transcriptional and translational levels (Figure 2). GAS5 may also regulate gene expression by binding protein to epigenetically modulate the promoter histone methylation of target gene expression, serving as competing endogenous RNA (ceRNA) to sponge microRNA (miRNA) and through kinase signaling regulatory pathways, among others. GAS5 could significantly inhibit the proliferation, invasion, and induce the apoptosis in vitro and in vivo via regulating p53 and E2F transcription factor 1 (E2F1) expression¹⁶ and by inhibiting miR-23a in NSCLC cells.⁴⁸ GAS5 inhibited the high glucose (HG)-induced proliferation, anti-apoptosis, and migration of PC-9 and H1299 NSCLC cells through degradation of tribbles pseudokinase 3 (TRIB3) protein by ubiquitination, indicating that GAS5/TRIB3 might be novel targets for the prevention and treatment of diabetic NSCLC.¹²¹ In addition, exogenously expressed GAS5 repressed cell proliferation and invasion and enhanced the radiosensitivity of NSCLC cells in vitro and in vivo by suppressing miR-135b expression, which deepens our

Table 3 The Potential Target Genes Of GAS5 In Human Cancer

Cancer Type	Target Gene	Reference
LC	E2F1, TRIB3, EGFR, IGF1R, p53, miR-23a, miR-135b, miR-21	16,17,43,44,48–52,121,122
BC	miR-196a-5p, miR-23a, miR-222, miR-21	18,19,41,45,55–57,112,115,116,123,124
EC	miR-196a, miR-301a, PI3K, CHK2, JAK	22,23,60,127
GC	miR-23a, miR-222, p21, E2F1, YBX1, CDK6	24,25,63–65
CRC	miR-221, miR-182-5p, Wnt, AKT, NF- κ B, ERK	26,27,70–74,118
HCC	miR-544, miR-182, miR-21, vimentin	21,36,40,76,90,128,129
PC	miR-221, miR-181c-5p, miR-32-5p, CDK6	28,29,42,78,79
ECa	miR-103	132
CC	miR-21, miR-106b, miR-196a, miR-205, AKT	30,31,84,85,119,130
OC	miR-196a-5p, miR-21, cyclin D1, p21, APAF1	32,33,81–83,149
PCa	miR-21, miR-1284, miR-103, E2F1	86–88,133,134
RCC	miR-21, miR-223	34,35,90,135
BCa	E2F4, Bcl2, CCL1, CDK6	92–95,136,148,150
Glioma	mTOR, miR-18a-5p, miR-196a-5p, miR222	97–99,137–139
GBM	NA	90,102,140
OSCC	miR-21	120,141
TC	miR-222-3p	104,105
SC	NA	106
Melanoma	miR-137, G6PD, MMP2, MMP9	107,108,142,143
Osteosarcoma	miR-203a, miR-221	110,111,144

understanding of the mechanism of miRNA–lncRNA interaction and providing a potential therapeutic for patients with NSCLC.⁴³ Moreover, GAS5 inhibited the proliferation and colony formation capability of NSCLC cells and induced the sensitivity of DDP in NSCLC via

GAS5/miR-21/PTEN regulatory pathway.⁵¹ Also, GAS5 expression was significantly higher in gefitinib-sensitive cells than that in gefitinib-resistant cells.⁵² Overexpression of GAS5 was inversely correlated with the expression of the EGFR and insulin-like growth factor 1 receptor (IGF-1R) proteins and relevant signaling pathways, and reversed the gefitinib-resistance lung cancer cells in vitro and in vivo, indicating that GAS5 may overcome the resistance to EGFR-tyrosine kinase inhibitors (TKIs) in lung cancer.⁵² Conversely, knockdown of GAS5 resulted in decreased expression of carbamoyl phosphate synthetase-1 (CPS1) and aldo-keto reductase 1C2 (AKR1C2) target genes in lung cancer cells but not in normal cells, suggesting that GAS5 acted as a regulator in tumorigenesis without disturbing normal cell functions.¹²² The links of GAS5 and miRNAs in mediating the BC survival were also reported. Overexpression of GAS5 could attenuate proliferation and enhance apoptosis through directly binding to miR-196a-5p, thereby affecting forkhead box protein O1 (FOXO1)/phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) regulatory axis in TNBC cells.¹⁹ MiR-221/222 acted as oncomiRs via inhibition of GAS5, resulting in enhancing tumor growth in BC.⁵⁵ Conversely, restoration of GAS5 expression attenuated the anti-apoptotic effects of miR-221/222 in BC cells.⁵⁵ GAS5 also promoted autophagy in vivo and in vitro via GAS5/miR-23a/autophagy-related 3 (ATG3) regulatory axes in BC cells.⁵⁷ Likewise, GAS5 functioned as a tumor suppressor in vitro and in vivo in BC through the feedback GAS5/miR-21 regulatory mechanism.¹²³ Additionally, GAS5 levels decreased in MCF-7R tamoxifen (TAM)-resistant cells and overexpression of GAS5 enhanced cell sensitivity to TAM in MCF-7R cells by serving as a molecular sponge for miR-222, thus suppressing PTEN expression.⁴⁵ GAS5 suppressed the growth of HER2-positive BC cells by acting as a molecular sponge for miR-21, and this led to the de-repression of PTEN as well.¹¹² Conversely, silencing of the putative tumor suppressor and apoptosis-promoting gene GAS5 attenuated cell responses to chemotherapeutic agents; interestingly, GAS5 promoted the apoptosis of triple-negative and oestrogen receptor-positive cells in the presence of dual PI3K/mTOR inhibitor, such as imatinib, which may increase GAS5 expression levels. Thus, dual PI3K/mTOR inhibitor could improve apoptotic responses to conventional chemotherapies via enhancing GAS5 expression in BC.¹²⁴ GAS5 was increased during DNA damage-induced cell death using bleomycin (BLM) and c-radiation assays in caspase-3-deficient MCF-7

cells.¹²⁵ Tumor promoter Notch-1 could promote cell proliferation by negatively regulating GAS5 expression in T47D BC cells.¹²⁶ GAS5 functioned as a tumor suppressor in vitro and in vivo, and was regulated by miR-196a involved in RNA-induced silencing complex (RISC) in ESCC.²² Overexpression of GAS5 inhibited the proliferation and migration of EC9706 and KYSE510 ESCC cells by inactivating the PI3-K/Akt/mTOR signaling pathway.²³ Likewise, GAS5 significantly inhibited cell proliferation and invasion, and induced cell cycle arrest by activating the ATM-p-checkpoint kinase 2 (CHK2) pathways and regulating EMT-associated proteins.⁶⁰ The feedback loop between GAS5 and interferon (INF) signaling via the janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway played an important anti-tumor role of GAS5 in ESCC cells.¹²⁷ These findings contribute to our understanding of the mechanisms of miRNA-lncRNA interaction and may provide insight for new avenues in diagnosis and treatment of ESCC. GAS5 could function as a competing endogenous RNA (ceRNA) for regulation of miR-23a by binding to its 3' untranslated region (3' UTR) thereby suppressing metallothionein-2A (MT2A), and thus potentially serve as a therapeutic target in GC cells.²⁵ GAS5 induced growth arrest of GC cells by induction of cyclin-dependent kinase (CDK) inhibitor p21 and reduction of CDK6,⁶⁴ and through interacting with Y box binding protein 1 (YBX1) and regulating expression in GC cells.⁶³ GAS5 also suppressed proliferation via directly targeted and suppressed miR-222 expression, and thereby regulating PTEN/Akt/mTOR signaling pathway in GC cells.⁶⁵ GAS5 decreased cell proliferation and induced apoptosis via regulating cell cycle activator E2F1 and p21 expressions in GC cells.³⁷ Together, the results above could enhance our understanding of the important role of GAS5 played in the molecular etiology and new biomarker for prognosis and therapeutic target for GC intervention. Upregulated GAS5 also repressed invasion and migration in vitro and inhibited tumor growth, angiogenesis and metastases in vivo via inhibiting the Wnt/ β -catenin pathway in CRC indicating a tumor-suppressor role.²⁶ In addition, GAS5 inhibited proliferation, migration and invasion via suppressing miR-221 expression²⁷ and targeting Akt/extracellular regulated protein kinases (ERK) signaling pathways.⁷⁰ Also, GAS5/miR-182-5p/FOXO3a regulatory axis might play an important role in the regulation of cell growth and apoptosis, and serve as a target for therapeutic utilities in CRC.⁷⁴ GAS5 inhibited vascular endothelial growth factor (VEGF-A) and cytokine interleukin-10 (IL-

10) via NF- κ B, and ERK1/2 pathways may provide a potential mechanism underlying the GAS5-based therapies for CRC.⁷² GAS5 functioned as a tumor suppressor through GAS5/miR-182/angiopoietin-related protein 1 (ANGPTL1) axis in HCC cells.²⁰ Overexpression of GAS5 suppressed migration and invasion through negative regulation of miR-21²¹ and negatively regulating vimentin expression in HCC cells.⁷⁶ GAS5 were down-regulated in natural killer (NK) cells of patients with HCC, and more specifically, GAS5 enhanced the killing effect of NK cell through regulating IFN- γ secretion, NK cell cytotoxicity, the percentage of CD107a+NK cells on HCC via miR-544/runt-related transcription factor 3 (RUNX3) regulatory axis.¹²⁸ Moreover, GAS5 was elevated after HCV infection Huh7 cells and upregulated GAS5 inhibited HCV viral replication by decoying HCV NS3 protein, and this led to inhibit HCC cell migration and invasion.¹²⁹ GAS5 significantly inhibited cell growth of PC in vitro and in vivo.²⁸ Additionally, GAS5 antagonized chemo-resistance through miR-181c-5p/Hippo signaling pathway in PC cells.²⁸ Moreover, GAS5 inhibited cell proliferation and induced a cell cycle arrest by negatively regulating CDK6 expression in PC.²⁹ GAS5 suppressed the proliferation, migration, gemcitabine resistance, stem cell self-renewal and EMT in vitro, and promoted gemcitabine-induced inhibition of tumor growth and metastasis in vivo via the miR-221/suppressor of cytokine signaling 3 (SOCS3)⁴² and miR-32-5p/PTEN pathways in PC.⁷⁸ Thus, GAS5 functions as a tumor suppressor and control proliferation, migration and invasion via multiple mechanisms in PC. Moreover, GAS5 inhibited proliferation and colony formation and promoted apoptosis by triggering shaping of inflammasomes in OC cells.³³ Mechanistically, overexpression of GAS5 inhibited proliferation and induced apoptosis of OC via directly targeting miR-196a-5p and thereby reducing homeobox protein Hox-A5 (HOXA5) expression⁸² and through suppressing miR-21 expression and increasing subsequent sprouty homolog 2 (SPRY2) expression in OC cells.³² GAS5 could also suppress proliferation of OC cells via regulating p21, cyclin D1 and apoptosis protease activating factor 1 (APAF1) expressions.⁸¹ Moreover, exogenously expressed GAS5 inhibited proliferation and promoted apoptosis of OC cells by disrupting mitochondrial membrane potential and promoting BCL2 associated X (BAX), Bcl-2 homologous antagonist/killer (BAK), cleaved-caspase 3 and cleaved-caspase 9 expression.⁸³ Together, these studies suggested that GAS5 depressed proliferation and induced apoptosis

of OC via multiple mechanisms. Overexpression of GAS5 suppressed CC cell proliferation, invasion, and promoted apoptosis in vitro and hindered tumor growth in vivo through regulating miR-196a/FOXO1 and miR-205/PTEN pathways.³¹ Additionally, GAS5 could inhibit proliferation, migration, and enhance DPP sensitivity via regulating the phosphorylation of Akt in CC cells.⁸⁴ Moreover, GAS5 enhanced the activity of DPP-induced cell growth inhibition and apoptosis in DPP-resistance cell via GAS5/miR-21/E2F transcription factor 3 (E2F3)/STAT pathway in CC, suggesting that GAS5 could be a novel target for CC patients with DPP-resistance in clinical.¹¹⁹ Overexpression of GAS5 enhanced radio-sensitivity in SiHa CC cells, while GAS5 knockdown decreased radio-sensitivity in ME180 CC cells.¹³⁰ In-depth mechanism studies showed that GAS5 enhanced the radio-sensitivity of CC cells via inducing immediate early response 3 (IER3) through regulation of miR-106b expression.¹³⁰ GAS5 was increased during DNA damage-induced cell death using BLM and c-radiation in HeLa cells.¹²⁵ Interestingly, the induction of GAS5 was mainly restricted to irradiated cells, revealing a differential regulation of GAS5 during genotoxic stress.¹²⁵ Endometrial carcinoma (ECa) is one of the most frequent gynecologic malignancy and is also the fourth most common cancer among females in the United States.¹³¹ GAS5 was down-regulated in ECa cells and promoted cell apoptosis through miR-103/PTEN axis in ECa. Thus, acted as a tumor suppressor, GAS5 could be an important mediator in the pathogenesis of ECa.¹³² Moreover, the GAS5/miR-21 programmed cell death protein 4 (PDCD4)/PTEN and GAS5/miR-1284/Akt signaling pathways might be closely related to OS rate and prognosis in patient with PCa.⁸⁸ GAS5 inhibited cell proliferation and induced cell cycle arrest via interacting with E2F1 and thus enhancing the binding of E2F1 to the P27Kip1 promoter.⁸⁶ GAS5 played a vital role in decelerating PCa development via mediating the Akt/mTOR signaling pathway through targeting miR-103.⁸⁷ Overexpression of GAS5 could increase apoptosis and decrease cell survival in 22Rv1 and PC-3 cells and could also augment cell death of 22Rv1 induced by UV-C irradiation and chemotherapeutic drugs.¹³³ Cellular GAS5 expression can be enhanced by the use of mTOR inhibitors in androgen-dependent/sensitive PCa cells (LNCaP/22Rv1) but not in androgen-independent cells (PC-3 and DU145).¹³⁴ Silencing of GAS5 decreased the sensitivity to mTOR inhibitors in LNCaP and 22Rv1 cells, while GAS5 overexpression sensitized PC-3 and DU145 cells to these

agents.¹³⁴ The refractoriness of androgen-independent cells might be due to their low expression levels of GAS5 since GAS5 positively regulated mTOR inhibitor action.¹³⁴ Thus, potential therapeutic utilities such as increase in GAS5 expression in advanced PCa may be beneficial in promoting the effectiveness of chemotherapeutic and irradiation agents to enhance therapeutic outcomes of patients with PCa. Silencing of GAS5 also enhanced the tumorigenicity of A498 and 786-O RCC cells, and GAS5 might act as a ceRNA to regulate human ZRT, IRT-like protein 1 (hZIP1) by sponging miR-223 in ccRCC cells.³⁴ Moreover, GAS5 overexpression conferred sorafenib sensitive to RCC through miR-21/sex-determining region Y-box protein 5 (SOX5) regulatory pathway, suggesting that GAS5 could be a potential therapeutic target for sorafenib treatment in RCC.¹³⁵ Functionally, overexpression of GAS5 reduced viability and induced apoptosis via interacting with E2F transcription factor 4 (E2F4) and recruiting to enhancer of zeste homolog 2 (EZH2) promoter, which further repressed EZH2 transcription in T24 and EJ BCa cells.⁹³ GAS5 suppressed proliferation and induced cell cycle arrest via suppressing chemokine ligand 1 (CCL1) expression¹³⁶ and regulating CDK6 in BCa cells.⁹² Overexpression of GAS5 significantly inhibited proliferation, reduced the chemotherapy resistance to doxorubicin (DOX) and promoted apoptosis in T24/DOX cells via depressing the expression of anti-apoptosis protein B-cell lymphoma 2 (Bcl2).⁹⁴ Together, acting as a tumor suppressor, GAS5 provided a novel therapeutic strategy and a potential diagnostic and prognostic biomarker for BCa. GAS5 could inhibit malignant phenotypes of proliferation, migration and invasion by repressing miR-18a-5p expression⁹⁸ and directly targeting miR-222 and further increasing a pro-apoptotic factor Bcl-2-modifying factor (BMF) and Plexin C1 (PLXN C1) expression.⁹⁹ GAS5 suppressed glioma stem cells (GSCs) malignancy through a miR196a-5p/FOXO1 feedback regulatory loop.¹³⁷ The expression of GAS5 was lower in cisplatin-resistance cells than cisplatin-sensitive cells.⁹⁷ Silencing of GAS5 enhanced cell resistance to DDP in U87 cells, while elevation of GAS5 enhanced cell sensitivity to DDP in U138 cells by suppressing excessive autophagy through the activation of mTOR signaling.⁹⁷ The induction of GAS5 was observed during DNA damage-induced apoptosis in U251 and U87 cells using DOX, suggesting that the distinct regulation of GAS5 may be possibly involved in the process of cellular defense against genotoxic agents.¹³⁸ It was

also reported that GAS5 was up-regulated after EGFR-TKI erlotinib treatment in glioma cells.¹³⁹ Intriguingly, silencing of GAS5 sensitized T98 glioma cells to erlotinib, suggesting that GAS5 played a role in the mechanism of erlotinib resistance of glioma cells under certain genetic contexts.¹³⁹ One study found that DNA comet tail length of T98G was negatively correlated with the GAS5 levels, and miR-222/GAS5 might be involved in DNA damage and cytotoxic effects induced by an oral alkylating agent temozolomide (TMZ) in glioma cells.¹⁴⁰ On the contrary, inhibition of GAS5 promoted proliferation, migration, invasion and EMT of OSCC cells through the miR-21/PTEN pathway.¹⁴¹ In addition, GAS5 acted as a ceRNA, effectively becoming a sink for miR-222-3p, activating PTEN/Akt pathway, to play its tumor-suppressive role in vitro and in vivo in papillary thyroid carcinoma (PTC).¹⁰⁴ Knockdown of GAS5 increased proliferation through increase in cyclin D1, CDK4, and p27 expressions and inhibited apoptosis through an increase in Bcl-2 expression via oxidative status and redox balance signaling regulatory axis and interaction between GAS5 and the G6PD protein in melanoma cells.¹⁰⁷ GAS5 suppressed proliferation, migration and invasion in vitro and inhibited growth in vivo via GAS5/miR-137 pathway in melanoma cells.¹⁰⁸ Overexpressing GAS5 inhibited the migration and invasion by decreasing the matrix metalloproteinase-2 (MMP2) expression in SK-Mel-110 cells¹⁴² and MMP9 expressions in melanoma cells.¹⁴³ Together, these studies open up new opportunities for designing innovative agents for improving prognosis by site-directed overexpressing of GAS5 in melanoma. In osteosarcoma cells, GAS5 suppressed the proliferation, migration and EMT via regulating miR-221/aplasia Ras homologue member I (ARHI) regulatory pathway.¹⁴⁴ Silencing GAS5 significantly promoted viability, migration and invasion by acting as a sponge for miR-203a, sequestering miR-203a away from tissue inhibitor of metalloproteinases 2 (TIMP2) via deactivating PI3K/Akt/glycogen synthase kinase 3 beta (GSK3 β) and activating NF- κ B signaling pathways in MG-63 osteosarcoma cells.¹¹⁰ In addition, zinc finger and BTB domain-containing protein 7A (ZBTB7A) bound to the promoter of GAS5 and suppressed GAS5 expression, leading to a decline in endoplasmic reticulum (ER) stress-induced cell apoptosis by tunicamycin (TM) or thapsigargin (TG) in osteosarcoma cells, suggesting that miR-663a/ZBTB7A/GAS5 regulatory pathway might be essential for the growth osteosarcoma cells under ER stress.¹⁴⁵ Nevertheless, the tumor-suppressor potential

and clinical uses of GAS5 in various cancer types are still required to be further elucidated in the future.

Discussion

LncRNAs have raised widespread attention in recent years as a potentially new and crucial player of fundamental biological functions. With the help of next-generation sequencing technology, computational prediction of lncRNAs from ultra-deep RNA sequencing, and lncRNA chip-based screening, hundreds of lncRNAs are found to be associated with the initiation and development of human cancers. LncRNAs affect cancer cellular processes, such as proliferation, apoptosis, migration and invasion. Clinical data demonstrated that aberrant expression of lncRNAs was related to the outcomes of cancer patients. Moreover, researchers have begun to develop lncRNA-targeting therapy based on the evidence for the role of specific lncRNAs and their specific action in tumor development.

GAS5 lncRNA is down-regulated in multiple cancers and related to both clinicopathological characteristics and patient prognosis. Low expression levels of GAS5 predicted poor OS and RFS, and patients with low GAS5 expression were more prone to LNM and advanced TNM stage in various cancers. Given the correlations between GAS5 levels and clinicopathological characteristics, GAS5 could be used as a diagnostic and prognostic biomarker in cancer patients. Moreover, it also has the potential for monitoring therapeutic responses. However, the clinic value of GAS5 in distinguishing benign lesions and malignancies, monitoring early recurrence and guiding therapeutic still need further exploration and validation.³⁸ A large body of evidence has shown that modulation of GAS5 is capable of regulating cell proliferation, apoptosis, invasion, metastasis, EMT, therapeutic resistance in cancer and that these cellular mechanisms are likely to form the basis of its tumor-suppressor action. In preclinical observations, reductions in endogenous GAS5 expression may adversely impact the therapeutic responses in cancer. Advanced hormone-independent breast and prostate cancers often exhibit low levels of GAS5 expression.^{123,124,133} However, they can maintain the ability to respond to ectopic GAS5.^{124,133} Therefore, forced expression of GAS5 would be an attractive potential promising therapeutic strategy for these types of cancer. One simple way to achieve this goal may be to exploit the molecular mechanisms that control cellular GAS5 levels through the use of mTOR inhibitor as targeting mTOR are already

in clinical use.^{146,147} Also, DNA methylation modification is another mechanism in modulating GAS5 expression level. Thus, we can achieve GAS5 enhancement by using DNA methyltransferase inhibitor, which is independent of inherent GAS5 expression level. Given the fact that the translation from basic researches to clinical utilities still needs more in-depth experiments and exploration, more efforts are needed in understanding of the mechanisms underlying the contribution of GAS5 inhibition, which may unveil novel therapeutic strategies.

The molecular mechanism of cancer is a complicated biological process, which may involve in stepwise accumulation of gene mutations, genomic instability, epigenetic changes and aberrant protein-coding and noncoding gene expressions. Instead of the traditional concepts that only protein coding genes can play vital roles in biological processes, lncRNAs such as GAS5 provide a novel insight into the understanding of cancer occurrence and development, and even therapeutic potential. Regardless, targeting of GAS5 as a novel diagnosis biomarker and therapeutic approach still require an in-depth understanding of the biological functions and molecular mechanisms.³⁸ From a clinical perspective, more effort in understanding the role of GAS5 in cancer biology will provide opportunities of biological functions and molecular mechanisms for cancer occurrence, progression and treatment, and unveil a novel diagnostic biomarker and therapeutic target in improving patient outcome.

Conclusion And Prospective

Recent studies lead to significant progress in understanding the biology of lncRNA, including GAS5, and even in the development of biomarkers and therapeutic application. The present study is to assess the expression, function and mechanism of GAS5 and their clinical utilities in diagnosis and therapeutic potential in human cancer. Our current knowledge provides the basis that GAS5 may be a promising biomarker for cancer development and diagnosis and has potential utilities in cancer treatment. Moreover, GAS5 is associated with the clinical-pathological characteristics, prognosis of cancer, indicating that GAS5 may potentially be used as a predictive biomarker for cancer patients. It is necessary to systematically study with a larger patient cohort to accelerate its clinical application. In addition, the important role of SNP of GAS5 in cancer especially rs145204276 played in occurrence of several malignancies, such as hepatocarcinoma, colorectal cancer, and gastric cancer, and regulated the

original tumor-suppressor effect of GAS5 may open a hallmark feature of cancer prevention and treatment in the future.³⁹

Although GAS5 holds potential promise towards the discovery of novel diagnostic and therapeutic for cancer, there are still many challenges. Currently, the GAS5 research is still in its infancy, the biological functions and mechanism of GAS5 involved are more complicated than we can think and some still remain uncharacterized. The precise mechanism of down-regulation of GAS5 and its central downstream signaling pathway are still not clear and need further analysis and confirmation. Thus, more efforts are still needed to focus on understanding the mechanisms and regulation of GAS5 in cancer, such as the biochemical and structural nature of GAS5-miRNA and GAS5-protein interactions, all of which may provide an in-depth understanding of the role of GAS5 in cancer biology and offer evidence for the development of therapeutic strategies for cancer. Moreover, there are some unresolved issues to transfer the basic and translational areas into the clinical arena to benefit cancer patients. Thus, future well-designed, large-size and high-quality patient cohorts studies are required to explore not only functional characterization, but also optimize isolation procedures and tissue-specific delivery methods to confirm the clinical value for the use of GAS5 as a diagnostic and prognostic marker, and a therapeutic target in clinic in cancer.

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Author Contributions

All authors (YY and SSH) contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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