Long non-coding RNA GAS5 in human cancer (Review)

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Abstract. Long non-coding RNAs (lncRNAs) constitute a group of >200-nucleotide ncRNA molecules. lncRNAs regulate several cell functions, such as proliferation, apoptosis, invasion and metastasis. Meanwhile, lncRNAs are abnormally expressed in human malignancies, where they suppress or promote tumor growth. The present study focused on growth arrest-specific transcript 5 (GAS5), a well-known lncRNA that acts as a tumor suppressor but is suppressed in multiple types of cancer, including mammary carcinoma, prostate cancer, colorectal cancer, gastric cancer, melanoma, esophageal squamous cell carcinoma, lung cancer, ovarian cancer, cervical cancer, gliomas, osteosarcoma, pancreatic cancer, bladder cancer, kidney cancer, papillary thyroid carcinoma, neuroblastoma, endometrial cancer and liver cancer. Notably, GAS5 is overexpressed in liver cancer, potentially functioning as an oncogene. In the present study, the diagnostic and therapeutic roles of GAS5 in different tumors were reviewed, with a summary of the potential clinical application of the lncRNA, which may help identify novel study directions for GAS5.

Contents

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1. Introduction

As one of the deadliest diseases, cancer represents a growing clinical challenge worldwide (1), despite surgical, chemotherapeutic and radiotherapeutic advances (2,3). A reason for the poor prognosis in cancer is the lack of efficient pre-progression diagnostic methods and effective prognostic indicators to guide clinical treatment. Therefore, it is important and necessary to identify suitable biomolecules for the timely detection of cancer to inform clinical decisions.

Long non-coding RNAs (lncRNAs) constitute a group of >200-nucleotide ncRNAs (4,5). Due to the significant progress of sequencing technology witnessed in previous years, more and more lncRNAs are considered transcriptional noise and have been identified in the human genome (6-9). However, numerous studies have shown that lncRNAs contribute to human pathologies via regulation of downstream target effectors (10,11). lncRNAs can upregulate or downregulate tumorigenic genes (12,13). Pertinent to clinical practice, lncRNAs could serve as potential markers or therapeutic targets for developing diagnostic and therapeutic strategies in different types of human cancer (14,15).

The lncRNA growth arrest-specific transcript 5 (GAS5) is a novel tumor-suppressor lncRNA, which is downregulated in mammary carcinoma, stomach cancer, lung carcinoma, prostate cancer and other malignant tumors (16-18). A summary of research progression regarding the value of GAS5 in the diagnosis and treatment of different types of cancer is provided in the present study. In addition, the published mechanisms by which GAS5 regulates genes involved in tumor genesis are explored and the potential clinical application of GAS5 is reviewed.

2. Research background of GAS5

GAS5 was initially described by a report screening for potential tumor-suppressors whose expression levels were increased during growth stagnation (19). GAS5 is located on chromosome 1q25, with ~630 nucleotides (20). It is a 5'-terminal oligopyrimidine RNA comprised of 12 non-conserved exons (21). GAS5 introns are transcribed into 10 box C/D small nucleolar RNA (snoRNA) molecules and 2 mature lncRNAs (GAS5a and GAS5b) (21,22). Although GAS5 has a short open reading frame, it encodes no protein and functions as a snoRNA host gene (23).

GAS5 biologically functions through its introns, which encode a number of snoRNAs (22). Although the exact functions of GAS5 remain unknown, it encodes several snoRNAs regulating ribosomal RNA synthesis (22). The transcription products of GAS5 are widely found in tissues, but show instability in actively dividing cells (24). The spliced GAS5 RNA expression is decreased in growing cells, but increased in the growth stagnation period (25). Mourtada-Maarabouni *et al* (25) initially investigated the bioactivity of GAS5 in human T cells and demonstrated that GAS5 overexpression induces apoptosis and decreases the number of cells in the S-stage, while the silencing of GAS5 leads to the opposite results. These findings suggested that GAS5 is necessary to inhibit the growth of T cells (25). Several studies have been performed to elucidate the function of GAS5 in cancer. Notably, GAS5 expression levels are downregulated in several human solid tumors and such aberrant expression is negatively associated with tumor size, disease stage and prognosis (24,26,27). In addition, GAS5 has been shown to affect cell cycle progression and is essential for normal growth stagnation (28). High GAS5 expression levels inhibit cell cycle progression, whereas GAS5 suppression reduces apoptosis and promotes accelerated cell division (29,30), which will be described in detail later in this review.

3. GAS5 in various cancer types

Evidence has revealed that GAS5 is abnormally expressed in various human malignancies (16-18). GAS5 expression levels are downregulated in numerous malignant tumors, suggesting that GAS5 may have anticancer activity. In addition, GAS5 overexpression contributes to growth inhibition in various tumor cell lines *in vitro* (16-18). In this section, findings regarding GAS5 expression, clinical significance in various types of human cancer (Tables I and II) and the modulatory mechanisms of GAS5 in malignant tumors are discussed (Fig. 1).

Breast cancer. In comparison with non-cancerous tissue samples, cancer tissue specimens exhibit markedly reduced GAS5 transcription levels (16). The decrease in GAS5 expression levels suggests a plausible function of GAS5 in tumorigenesis. GAS5 is commonly downregulated in breast cancer tissue samples and cells, and this downregulation is associated with a large tumor volume, advanced tumor lymph node metastasis and estrogen receptor negativity (31). GAS5 could be used as a microRNA (miR)-23a sponge, which promotes autophagy and enhances the formation of autophagosomes after GAS5 overexpression (31). GAS5 downregulates phosphatase and tensin homolog (PTEN) induced by lapatinib in SKBR-3/Tr cells, suggesting that GAS5 may be a plausible target for overcoming drug resistance in mammary carcinoma (32). The decrease in GAS5 expression levels attenuates the responses of breast cancer cells to apoptosis stimulation (32). Additionally, the degree of mammary carcinoma cell death is associated with the expression levels of GAS5, suggesting that GAS5 is associated with patient prognosis (33). GAS5 may negatively regulate miR-21 via the RNA-induced silencing complex (RISC) in breast cancer (33). It is hypothesized that miR-21 and GAS5 modulate each other.

Prostate cancer (PCa). PCa is the second most prevalent cancer in men and the sixth leading cause of cancer-associated mortality in men in 2008 worldwide (34). Compared with normal prostate tissue or primary prostate cancer, metastatic prostate cancer cells show markedly reduced GAS5 expression levels (35). In addition, further studies have shown that high expression levels of GAS5 promote basal cell apoptosis of prostate cancer cells and enhance the effect of apoptosis stimulation (36,37). High GAS5 expression levels enhance cancer cell death induced by UV-C irradiation and chemotherapeutic drugs, while GAS5 downregulation attenuates these effects. GAS5 binds to the corresponding region of androgen receptor and suppresses transcription of this receptor (38). Therefore, improving the expression levels of cellular GAS5 alongside the administration of chemotherapeutics could provide an improved strategy for treating advanced PCa. Since androgen receptor is needed for the survival of prostate cancer cells, GAS5 downregulation may increase pro-survival signals via the androgen receptor pathway (39). The aforementioned findings indicate that GAS5 may have an antitumor function in human prostate cancer.

Colorectal cancer (CRC). CRC is one of the leading causes of cancer-associated mortality worldwide (40). GAS5 is specifically downregulated in CRC. The decrease in GAS5 expression levels is associated with advanced stage and lymph node metastasis in CRC (41). High expression levels of GAS5 suppress the proliferation of CRC cells and promote apoptosis (41). In addition, GAS5 downregulates miR-182-5p expression (41), while miR-182-5p upregulation abrogates the effects of GAS5 overexpression in CRC cells. Moreover, GAS5 upregulates FOXO3a in CRC cells (41). In another study, GAS5 was reported to inhibit cell division, inducing G_0/G_1 block and apoptosis, indicating that GAS5 could be considered as a potential therapeutic target in CRC (42). In summary, these data suggest that GAS5 contributes to the progression of CRC metastasis and may be used as a prognostic marker of CRC.

Gastric cancer (GC). GC represents one of the deadliest malignancies worldwide (43). The etiological mechanism of gastric cancer remains unclear, but various environmental and genetic factors are considered to induce GC progression (44-46). In previous years, it has been demonstrated that GAS5 downregulation contributes to GC growth and affects patient prognosis (47-50). GAS5 is downregulated, while miR-222 is upregulated in GC cells (51). In addition, GAS5 acts as a sponge via direct binding with and downregulation of miR-222 (51). Notably, mechanistic assays showed that the GAS5/miR-222 axis regulates GC cell proliferation via PTEN/Akt/mTOR signaling (51). Consequently, GAS5/miR-222/PTEN/Akt/mTOR signaling may be a potential target for gastric cancer treatment (51). GAS5 expression levels in gastric cancer tissues are markedly reduced compared with those of normal tissues, and decreased GAS5 expression levels are associated with increased tumor size and advanced clinical stage in gastric cancer (47). GAS5 induces GC cell growth arrest by suppressing the G_1-S transition (47). GAS5 effects may occur via p21 upregulation and CDK6 suppression (47). The aforementioned results indicate that GAS5 serves a role in GC etiology, suggesting that GAS5 may become a novel therapeutic target in gastric cancer.

Table I. Functional characterization of growth arrest-specific transcript 5 in various tumors.

Tumor type	Expression	Functional role	Associated gene	Role	Refs.
Breast cancer	Downregulation	Chemoresistance, autophagy	miR-23a, PTEN, miR-21	Tumor suppressor	31-33
Prostate cancer	Downregulation	Chemoresistance, apoptosis, metastasis	-	Tumor suppressor	35-39
Colorectal cancer	Downregulation	Proliferation, apoptosis, metastasis	miR-182-5p, FOXO3a	Tumor suppressor	41,42
Gastric cancer	Downregulation	Proliferation	miR-222, CDK6, PTEN/Akt/mTOR pathway, p21	Tumor suppressor	47,51
Melanoma	Downregulation	Migration, invasion, apoptosis	MMP2, G6PD	Tumor suppressor	54,55
Esophageal squamous cell carcinoma	Downregulation	Proliferation, migration, invasion	PI3K/Akt/mTOR pathway, miR-196a	Tumor suppressor	58,59
Non-small cell lung cancer	Downregulation	Metastasis, apoptosis	-	Tumor suppressor	60,61
Ovarian cancer	Downregulation	Proliferation, apoptosis	miR-196a-5p	Tumor suppressor	63,64
Cervical cancer	Downregulation	Proliferation, invasion, migration, chemoresistance	Akt, miR-106b, IER3	Tumor suppressor	66-69
Gliomas	Downregulation	Proliferation, invasion, migration	miR-222, miR-18a-5p	Tumor suppressor	73,74
Osteosarcoma	Downregulation	Proliferation, migration, EMT	miR-221, ARHI, miR-203a	Tumor suppressor	75,76
Pancreatic cancer	Downregulation	Proliferation, migration, EMT	SOCS3, CDK6, miR-221	Tumor suppressor	77,78
Bladder cancer	Downregulation	Proliferation, apoptosis	EZH2, CDK6, E2F4	Tumor suppressor	79,80
Renal cell carcinoma	Downregulation	Proliferation, migration, invasion	miR-223	Tumor suppressor	82
Papillary thyroid carcinoma	Downregulation	Proliferation	miR-222-3p	Tumor suppressor	83
Neuroblastoma	Downregulation	Proliferation, apoptosis	p53, BRCA1, GADD45A	Tumor suppressor	84
Endometrial cancer	Downregulation	Apoptosis	PTEN, miR-103	Tumor suppressor	85
Hepatocellular carcinoma	Downregulation	Proliferation, migration, invasion	miR-21, PDCD4, PTEN	Tumor suppressor	87

EMT, epithelial-mesenchymal transition; miR, microRNA.

Melanoma. Melanoma is an aggressive disease with an increasing incidence rate and is the leading cause of skin cancer-associated death in the United States (52). Although targeted therapy and immunotherapy have markedly

Table II. Clinical significance of growth arrest-specific transcript 5 in various types of tumor.

Cancer type	Clinicopathological features	Refs.
Breast cancer	Tumor size, lymph node metastasis	(31)
Colorectal cancer	Advanced clinical stage, lymph node metastasis	(41)
Gastric cancer	Poor prognosis, tumor size, advanced clinical stage	(47-50)
Non-small cell lung cancer	Tumor size, lymph node metastasis	(61)
Ovarian cancer	Tumor size, advanced FIGO stage (III-IV), poor prognosis	(62,63)
Bladder cancer	Advanced clinical stage	(79)
Hepatocellular carcinoma	Poor prognosis	(86)

TNM, Tumor-Node-Metastasis; FIGO, International Federation of Gynecology and Obstetrics.

improved melanoma treatment and patient quality of life, currently there are few suitable drugs for the treatment of this disease (53). Therefore, further assessment of the metastatic progression in melanoma is needed to develop novel targeted therapeutics. Overexpression of GAS5 inhibits the malignant potential of melanoma SK-Mel-110 cells, partly by reducing MMP2 expression levels and activity (54). One previous study showed that GAS5 has physical effects, with G6PD expression reducing GAS5-associated cell apoptosis, inducing G_1/S progression and altering reactive oxygen species levels in melanoma cells (55). These findings indicate that abnormal downregulation of GAS5 has a function in melanoma development.

Esophageal squamous cell carcinoma (ESCC). Esophageal cancer (EC) ranks 8th and 6th in incidence and mortality, respectively, among malignancies worldwide, and the majority of EC cases are ESCC (56,57). Functionally, GAS5 overexpression inhibits ESCC cell proliferation and reduces the migratory and invasive abilities of ESCC cells by inactivating the PI3K/Akt/mTOR signaling pathway (58). In addition, GAS5 represents a miR-196a target and functions as a tumor suppressor gene in ESCC (59). Furthermore, GAS5 is often downregulated in ESCC and associated with clinical stage. The decrease in GAS5 expression levels in ESCC is associated with miR-196a upregulation (59). GAS5 suppresses tumor growth in ESCC both in cell culture and animal models (59). Finally, miR-196a may downregulate GAS5 via the RISC (59). The aforementioned findings suggest that GAS5 downregulation contributes to ESCC development.

Non-small cell lung cancer (NSCLC). GAS5 expression levels are also associated with malignancy and metastasis in patients with NSCLC. Indeed, GAS5 upregulation leads to growth stagnation in NSCLC cells and promotes cell apoptosis both in cell and animal models (60). Meanwhile, GAS5 downregulation promotes tumor cell growth (60). In 72 NSCLC specimens, GAS5 expression levels were downregulated compared with those in adjacent noncancerous lung tissue samples. Downregulated GAS5 expression levels were associated with tumor size and lymph node metastasis (61). The aforementioned findings indicate that GAS5 may also serve as an NSCLC biomarker.

Ovarian cancer. Low GAS5 expression levels and high miR-196a-5p expression levels are associated with increased tumor volume and more advanced International Federation of Gynecology and Obstetrics stage (III-IV) in ovarian cancer (62,63). GAS5 downregulation is associated with increased survival, faster proliferation and reduced apoptosis rate of ovarian cancer cells, as well as increased tumor volume in rats (63). GAS5 can directly bind to and regulate miR-196a-5p. miR-196a-5p expression is elevated in ovarian cancer tissues and cell lines, suggesting that it could promote ovarian cancer (63). High GAS5 expression levels promote apoptosis in ovarian cancer cells (64). These results indicate that reduced GAS5 expression levels may be an indicator of poor prognosis in ovarian cancer and a plausible target for diagnosing and treating this malignancy.

Cervical cancer (CC). GAS5 is downregulated in multiple malignancies, including CC. A previous study showed that GAS5-knockdown can promote malignancy in CC cells (65), while GAS5 overexpression increases the resistance of CC cells to cisplatin by modulating Akt phosphorylation (66). In addition, according to bioinformatic prediction, GAS5 is a molecular sponge of miR-106b; reduced GAS5 and elevated miR-106b expression levels were found in clinical CC tissue samples from patients insensitive to radiotherapy (67,68). GAS5 regulates IER3 via miR-106b, and could enhance radiosensitivity in CC cells by suppressing miR-106b both in cell and animal models (69). Together, these findings suggest that GAS5 may be a novel plausible target for cervical cancer treatment.

Glioma. In comparison with non-cancerous cerebral tissues, gliomas show reduced GAS5 expression levels (70), which are associated with a longer survival time (71). It has been demonstrated that GAS5 expression levels are elevated under stress in glioma cells induced by DNA damage (72). Previously, Zhao *et al* (73) confirmed GAS5 exerts antitumor effects in glioma cells via direct targeting of miR-222.

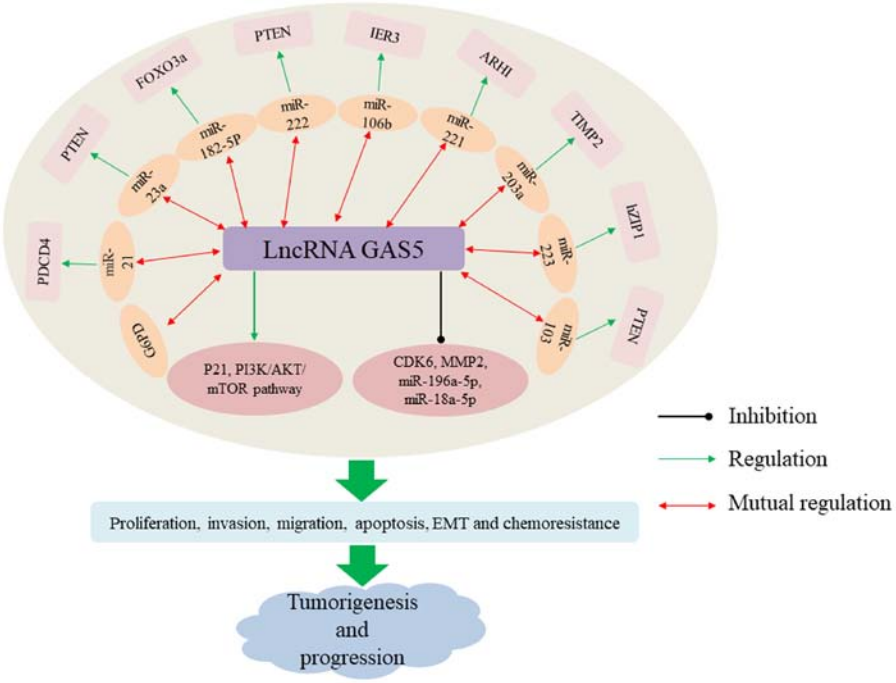

Figure 1. The regulatory mechanisms of GAS5 in human cancers. ARHI, A Ras homologue member I; CDK6, cyclin dependent kinase 6; EMT, epithelial-mesenchymal transition; FOXO3a, forkhead box O3; G6PD, glucose-6-phosphate dehydrogenase; GAS5, growth arrest-specific transcript 5; hZIP1, human ZRT, IRT-like protein 1; IER3, immediate early response gene3; MMP2, matrix metalloproteinase 2; mTOR: mammalian target of rapamycin; PDCD4, programed cell death 4; PI3K, phosphoinositide 3-kinase; PTEN, phosphate and tension homolog; TIMP2, tissue inhibitor of metalloproteinases-2.

GAS5 inhibits glioma cell proliferation both in cell and animal models, as well as cell migration and invasion. In addition, GAS5 downregulates miR-18a-5p, which in turn reduces GAS5 expression levels (74). It has also been found that GAS5 influences the biological properties of glioma cells by suppressing miR-18a-5p, thereby altering neogenin expression (74). These data indicate that GAS5 may present a novel therapeutic target for glioma treatment.

Osteosarcoma. Elevated GAS5 expression levels suppress proliferation, migration and epithelial mesenchymal transformation (EMT) in osteosarcoma cells (75). GAS5 shows direct binding to miR-221, decreasing the expression levels of miR-221 and upregulating ARHI. Additionally, a role for GAS5 in reducing tumor growth in osteosarcoma has been demonstrated *in vivo* (75). Competing with miR-221, GAS5 suppresses growth in osteosarcoma cells via miR-221/ARHI signaling (75). GAS5 may represent a tumor suppressor in osteosarcoma, isolating miR-203a from TIMP2 through sponge action (76). These findings suggest that abnormal GAS5 downregulation may promote tumor growth via miR-221/ARHI signaling.

Pancreatic cancer (PC). Previous studies have shown that GAS5 expression in PC is markedly decreased compared with that in non-cancerous pancreatic ductal cells. Overexpression of GAS5 enhances the expression of cytokine signal transduction factor 3 and inhibits proliferation, migration, gemcitabine resistance, stem-like characteristics and EMT in PC cells via direct binding to and downregulation of miR-221 (77). Furthermore, the expression levels of CDK6 are reduced by GAS5 in cell and animal models (77). CDK6 downregulation partly decreases GAS5-siRNA-associated tumor cell growth (78). The aforementioned results indicate that decreased GAS5 expression levels may promote growth and metastasis in PC by negatively regulating CDK6.

Bladder cancer. GAS5 expression levels in bladder cancer cells and clinical samples are low and inversely associated with disease stage, and elevated GAS5 expression levels inhibit bladder cancer cell proliferation (79). By interacting with the transcription factor E2F transcription factor 4, GAS5 downregulates EZH2 at the mRNA level and promotes apoptosis in bladder cancer cells, and GAS5 serves a role in GA-associated apoptosis in bladder cancer (79). Additionally, GAS5 exerts its effects in part via CDK6 regulation, as GAS5 downregulation increases CDK6 mRNA and protein expression levels, and since inhibition of GAS5 leads to significantly decreased G_0/G_1 phase and markedly increased S phase in bladder cancer cells (80). These data suggest that GAS5 may represent a novel target for treating bladder cancer.

Renal cell carcinoma (RCC). In comparison with non-cancerous cells, RCC cells show significantly downregulated GAS5 expression levels (81). GAS5 overexpression decreases the level of malignancy in RCC cells (82). A study showed that GAS5 serves as a competing endogenous RNA for miR-223; the inhibition of GAS5 attenuates the activity of miR-223 inhibitor on cell growth, apoptosis and invasion. Additionally, GAS5 downregulation facilitates tumor growth *in vivo*, which is abolished by hZIP1 overexpression (82). The aforementioned data indicates that GAS5 may present a novel target for RCC treatment.

Papillary thyroid carcinoma (PTC). GAS5 expression levels are markedly reduced in PTC tissue samples and cells. GAS5 overexpression suppresses PTC growth in cell and animal models. In addition, GAS5 is considered a target of miR-222-3p, which is abnormally elevated in PTC cells (83). These data indicate that GAS5 may present a novel target for treating PTC.

Neuroblastoma. GAS5 is highly expressed in both MYCN-amplified and non-amplified neuroblastoma cells, and GAS5 downregulation leads to elevated cell proliferation and reduced apoptosis and cell cycle arrest in neuroblastoma cells (84). In addition, deletion of GAS5 upregulates p53, BRCA1 protein and growth arrest and DNA-damage-inducible protein α, which seem to simultaneously regulate cell cycle arrest (84). These data indicate that abnormal GAS5 downregulation may promote neuroblastoma progression by inducing cell cycle arrest.

Endometrial cancer. GAS5 is downregulated and induces apoptosis in endometrial cancer cells (85). When endometrial cancer cells overexpress GAS5, PTEN is upregulated (85). Furthermore, bioinformatics prediction revealed that GAS5 could bind to miR-103 and significantly upregulate PTEN to induce apoptosis via miR-103 downregulation (85). Thus, GAS5 may be a regulator of endometrial cancer pathogenesis.

Hepatocellular carcinoma (HCC). The expression levels of GAS5 in HCC tissues is decreased compared with normal adjacent tissues, suggesting poor prognosis of HCC patients (86). Additionally, GAS5 suppresses hepatoma cell growth in association with vimentin regulation (86). Another study showed that GAS5 serves an anticancer role in HCC by negatively regulating miR-21 and its target protein PDCD4 and PTEN to alter the migratory and invasive features of HCC cells (87). In addition, Tao *et al* (88) reported that GAS5 may act as a proto-oncogene in HCC. Therefore, GAS5 may potentially be a novel target for HCC treatment.

4. Conclusions

GAS5 is downregulated in a number of human malignancies. GAS5 can induce apoptosis and inhibit the proliferative and metastatic properties of tumors. The exact molecular mechanisms by which GAS5 affects cancer development remain unclear. GAS5 may serve a role in tumorigenesis by regulating multiple tumor-associated molecules. Tumor inhibition by GAS5 has been described for numerous malignancies, such as breast cancer, prostate cancer, CRC, stomach cancer, melanoma, ESCC, NSCLC, ovarian cancer, cervical cancer, gliomas, osteosarcoma, pancreatic cancer, bladder cancer, RCC, PTC, neuroblastoma, endometrial cancer and HCC, indicating a role for this lncRNA as a tumor suppressor. In this review, the potential of GAS5 in diagnosing and treating different cancer types, and its potential clinical application, were summarized, pointing to a new direction for GAS5 research.

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Authors' contributions

XY wrote the original draft. The manuscript was revised by ZX, XL and RG. The authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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