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REVIEW

The role of long non-coding RNA GAS5 in cancers

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Jiali Ji[1]
Xiaolan Dai[2]
Sai-Ching Jim Yeung[3]
Xuexin He[1]

[1]Department of Medical Oncology, The 2nd Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang, People's Republic of China; [2]Department of Pharmacy, School of Medicine, Shantou University, Shantou, Guangdong, People's Republic of China; [3]Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract: Long non-coding RNAs (lncRNAs) have shown potential as a biomarker in the diagnosis and prognosis in multiple cancers. LncRNAs are dysregulated in various cancers, playing either oncogenic or tumor suppressive roles. Emerging evidences have proved that the growth arrest-specific 5 (*GAS5*) lncRNA can function as a tumor suppressor in several cancers. LncRNA *GAS5* is downregulated in many types of cancer, regulating cellular processes such as cell proliferation, apoptosis and invasion. The low level of *GAS5* expression often elevates capacity of proliferation and predicts poorer prognosis in some cancers. This review aims to summarize the recent published literature on the biogenesis, regulation mechanism and function of *GAS5* in different types of cancers and explore its potential for cancer diagnosis, prognosis and treatment.

Keywords: lncRNA, GAS5, tumor suppressor, tumor

Introduction

The incidence of cancers has been increasing over the years.[1] It is universally acknowledged that cancer is a major health issue. Early detection of cancer can greatly increase the probability for curative therapy. Therefore, the search for new diagnostic and prognostic biomarkers and effective therapies goes on.

Advances in high-throughput sequencing have led to the discovery of novel non-coding RNAs (ncRNAs) in recent years. Long non-coding RNAs (lncRNAs) are a group of RNA molecules longer than 200 nucleotides in length that are distinct from known categories of structural RNAs.[2] LncRNAs, initially thought to be non-functional,[3] were found to play important roles in many human diseases, especially in malignancies.[4–10] Increasing evidence suggests that some lncRNAs have important roles in carcinogenesis and cancer progression, and may serve as diagnostic and/or prognostic biomarkers for some cancers.[11]

The growth arrest-specific 5 (*GAS5*) gene can encode ncRNAs of various sizes including a lncRNA.[12] *GAS5* is a tumor suppressor gene located at chromosome 1q25 and was first discovered in 1988 by screening highly expressed genes in growth-arrest cells.[13,14] Downregulation of *GAS5* expression is observed in many cancers. Clinical outcomes such as lymph node metastasis, tumor recurrence and overall survival are correlated with the expression of *GAS5* in various cancers.[15–17]

The level of *GAS5* expression regulates apoptosis, proliferation, invasion, epithelial–mesenchymal transition and metastasis of cancer cells,[18–21] and may have prognostic value in various clinical scenarios.[22–25] Although the precise molecular mechanism remains unclear, lncRNA *GAS5* certainly plays an important

Correspondence: Xuexin He
Department of Medical Oncology, The 2nd Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang, People's Republic of China
Tel +861 832 913 9569
Email xuexinhe@zju.edu.cn

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role in carcinogenesis and tumor progression. In our review, we will discuss the potential molecular mechanisms, recent research and clinical assessment of lncRNA *GAS5* in cancer. An improved understanding of lncRNA *GAS5* in cancer may provide new insights and inspiration for future clinical application.

Gene structure of GAS5

GAS5 belongs to the 5′-terminal oligopyrimidine (5′-TOP) gene family, which includes all ribosomal proteins, protein synthesis elongation factors as well as many genes without ribosome-related functions.[26] GAS5 is a non-protein-coding gene located at chromosome 1q25.1 [molecular location: Chromosome 1, NC_000001.11 (173,863,899 to 173,868,882, complement)] and composed of 12 exons which constitute a short open reading frame that does not encode a protein. Some parts of the introns with highly conserved regions are loci of some small nucleolar RNAs (snoRNAs). The essential biological activities of *GAS5* may depend, at least in part, on introns that encode multiple snoRNAs[27] and on lncRNA *GAS5*/snoRNA-derived PIWI-interacting RNA (piRNA).[12]

Molecular mechanisms of lncRNA GAS5

About 7 years ago, 4 main types of mechanisms of action for lncRNA were summarized: 1) signals for transcription, 2) decoys for transcription factors, 3) guides of transcription factors and 4) scaffolds for protein complexes that epigenetically modify chromatin.[28] More recently, the mechanisms of action were expanded to include: 1) lncRNA transcription-dependent activation or repression of neighboring genes, 2) inter-chromosomal interactions, 3) formation of nuclear structures (ie, paraspeckles) or R-loops, 4) lncRNAs acting as sponges of miRNAs, 5) regulating post-transcriptional mRNA decay and 6) regulating the cellular localization of RNA-binding proteins or DNA-binding proteins.[29]

The biological processes regulated by *GAS5* are summarized in Figure 1. Specifically for *GAS5*, review of the literature supports the following mechanisms:

Transcriptional regulation through acting as a decoy

Glucocorticoid hormones can accelerate catabolism, modulate the immune response and cell survival when the body is under internal or external stress.[30,31] Kino et al discovered that lncRNA *GAS5* can act as a decoy for glucocorticoid receptor (GR).[32] LncRNA *GAS5* can bind to the DNA-binding domain of GR and titrate down the amount of GR that is available to bind glucocorticoid response elements (GREs) in the genomic DNA. Although this RNA and protein interaction between lncRNA *GAS5* and GR blocks the binding between GRE and GR in the context of growth arrest and starvation, its relevance in cancer cells is unclear.

Transcriptional regulation through histone methylation/demethylation

In bladder cancer cells, lncRNA *GAS5* can directly interact with transcription factor E2F4 and increase its binding to the promoter region of enhancer of zeste homolog 2 (*EZH2*), a histone-lysine N-methyltransferase gene.[33] Consequently, transcription of miR-101 was upregulated and bladder cancer cell growth was suppressed. LncRNA

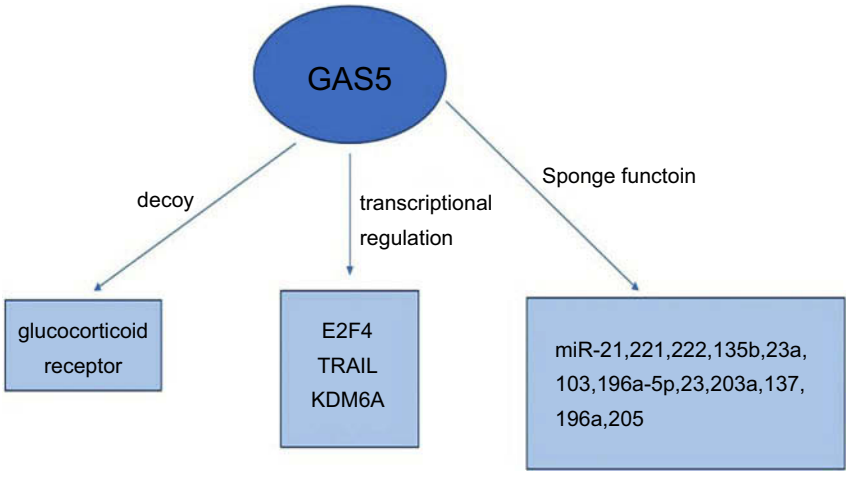

Figure 1 The biological processes regulated by LncRNA GAS5.

GAS5 can also indirectly regulate gene expression through its small RNA derivatives. For instance, *GAS5*-derived piRNA induces histone H3 lysine 4 methylation and histone H3 lysine 27 demethylation and resulted in increased transcription of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a proapoptotic protein.[12] The *GAS5*-derived piRNA binds to PIWIL1/4 proteins, which interact with WDR5 to recruit hCOMPASS-like complexes containing MLL3 and UTX (KDM6A), constituting a molecular mechanism relevant to tumor suppression. Nevertheless, it is very challenging to determine which biological effect of *GAS5* is attributable to the intact lncRNA, its small RNA derivatives or both.

Mirna sponge function

GAS5 can function as a competing endogenous RNA (ceRNA) to regulate signaling pathways and biological functions. Bioinformatics analysis of complementary regions of GAS5 to microRNAs identified 690 candidates, among which 234 microRNAs showed statistically significant binding.[34] In the context of cancer, LncRNA *GAS5* has been shown to bind to miR-21,[35,36] miR-221,[37] miR-222,[38,39] miR-135b, miR-23a and miR-103 et al.[40]

miR-21: LncRNA *GAS5* can suppress the expression of *miR-21*, an oncogene in various solid tumors and lymphoma expression.[35,36] Fibroblast factor1 (FGF1) is a mediator of the *GAS5*/miR-21 axis that regulates proliferation and apoptosis.[41] In NSCLC, suppression of *GAS5* expression can lead to chemoresistance to cisplatin because LncRNA *GAS5* competes with phosphatase and tension homolog (PTEN) for miR-21 binding.[42]

miR-221: *GAS5* can inhibit the expression of miR-221 and suppress cell proliferation, invasion and migration as well.[43]

miR-222: It can also suppress tumor by downregulating miR-222 resulted in reduced proliferation and invasion in glioma.[38]

miR-135b: The overexpression of *GAS5* can inhibit tumor growth and enhance radiosensitivity by downregulating *miR-135b* expression in non-small cell lung cancer.[44]

miR-23a: In non-small cell lung cancer, *GAS5* can directly interact with miR-23a and then reduce the expression of *miR-23a* which can promote cell proliferation and invasion.[45]

miR-103: The aberrant expression of miR-103 was found to promote colorectal cancer by downregulating the expression of PTEN and regulate growth and invasion of endometrial cancer cells through downregulating the suppressor of TIMP-3. *GAS5* can act as an inhibitor of miR-103 and then enhance the expression of PTEN to promote cancer apoptosis.[40]

miR-196a-5p: *GAS5* was proved to suppress the proliferation, migration and invasion of glioma stem cells by binding to miR-196a-5p, an onco-miRNA contribute to glioma pathogenesis.[46]

miR-23: *GAS5* can inhibit gastric cancer by regulating miR-23 as well.[47]

miR-203a: *GAS5* can negatively regulate the expression of miR-203a and keep miR-203a away from its target gene TIMP2 which can inhibit cancer cell metastasis in osteosarcoma.[48]

miR-137: In melanoma, *GAS5* can positively regulate miR-137 and then promote cell proliferation, migration and invasion.[49]

miR-196a and miR-205: Overexpression of *GAS5* can inhibit cell proliferation and invasion by binding to miR-196a and miR-205 in cervical cancer to suppress cell growth through aplasia Ras homolog member I (ARHI).[50]

Signaling pathway associated with lncRNA GAS5

It was reported that the inhibition of mammalian target of rapamycin (mTOR) pathway depends on *GAS5*.[51,52] In prostate cancer, *GAS5* was proved to inhibit cancer proliferation and progression by targeting miR-103 through the protein kinase B (AKT)/mTOR signaling pathway.[53] Overexpression of *GAS5* was proved to inhibit the miR-222 expression and then suppressed cell proliferation in gastric cancer through phosphatase and tensin homolog (PTEN)/phosphorylated protein kinase B (Akt)/phosphorylated mammalian target of rapamycin (mTOR) pathway as well.[54]

GAS5 is a downstream target of Notch pathway in breast cancer. Notch1 can promote breast cancer cells proliferation by modulating *GAS5*.[55] In NSCLC cells, *GAS5* overexpression was negatively correlated with the expression of EGFR pathway.[56] *GAS5* was associated with embryonic stem cells (CSCs) self-renewal by regulating NODAL signaling.[57] In pancreatic cancer cells, *GAS5* can inhibit the expression of miR-181c-5p and then prohibit cell chemoresistance through suppressing Hippo signaling.[58] We summarized the function of *GAS5* in various cancers in Figure 2.

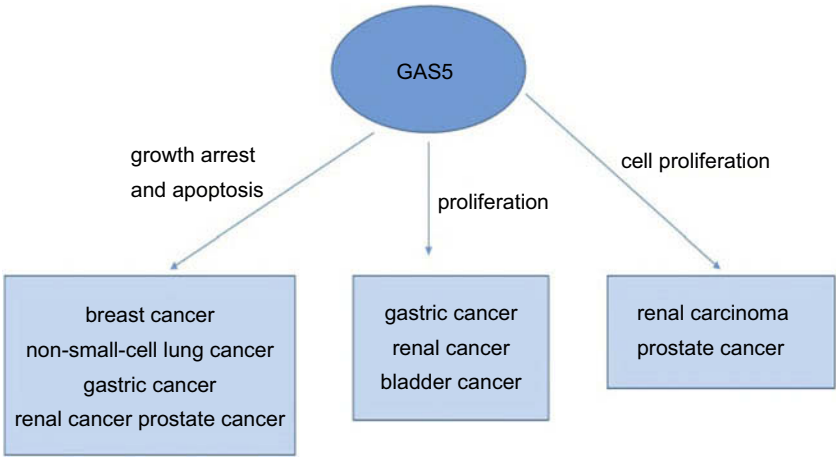

Figure 2 The function of LncRNA GAS5 in various cancers.

Function in various cancers

Gastrointestinal cancer

Colorectal cancer (CRC) was the third common cancer in the world. It was reported that the expression of *GAS5* in CRC was lower than those in normal tissue. Meanwhile, the low expression of *GAS5* was significantly associated with large tumor size, low grade, advanced TNM stage, higher local recurrence rate and distant metastasis rate.[43,59] The lower expression of *GAS5* was associated with poor overall survival. Univariate and multivariate analysis further revealed that *GAS5* was an independent prognostic factor for CRC. The overexpression of *GAS5* can inhibit proliferation, migration and invasion in CRC.[60] Yang et al have concluded that the overexpression of *GAS5* can induce G0/G1 cell cycle arrest and apoptosis.[61] Thus *GAS5* may become a novel prognostic marker and a potential target for CRC in the future.

Previous studies have found that lncRNA *GAS5* was downregulated in gastric cancer. Meanwhile, the downregulated level was significantly associated with larger tumor size and advanced pathologic stage. Patients with lower expression of *GAS5* have poorer disease-free survival and overall survival than those with higher *GAS5* expression. Vivo and vitro experiments further demonstrated that the *GAS5* can upregulate proliferation and induce apoptosis in gastric cancer.[17]

It was reported that *GAS5* expression was lower in pancreatic cancer than normal tissue. And overexpression of *GAS5* can inhibit cell proliferation in pancreatic cancer by decreasing G0/G1 phase and increasing S phase.[21] Downregulation of *GAS5* was associated with chemoresistance in pancreatic cancer as well.[58] Moreover, the overexpression of *GAS5* can inhibit pancreatic cancer cell tumorigenesis in vivo and suppress tumor metastasis.[62]

In hepatocellular carcinoma, overexpression of *GAS5* could promote prognosis, suppress proliferation and invasion of hepatoma cells. Low expression of *GAS5* was closely related with differentiation and poor overall survival.[35,63]

Wang et al have found that *GAS5* was downregulated in esophageal cancer (EC) and could inhibit the growth of EC.[64] However, Li et al reported that contrast to other cancers, the *GAS5* was overexpressed in EC. *GAS5* is proved to promote proliferation, metastasis and inhibited apoptosis in EC by regulating miR-301a.[65] The concrete role and regulation function of *GAS5* in EC still need further study.

Malignant pleural mesothelioma (MPM)

MPM is a malignant cancer with poor prognosis. Some lncRNAs have clinical significance like predicting metastasis and overall survival. Previous studies have shown that *GAS5* expression is lower in MPM cells and its expression could be regulated by drugs inducing growth arrest in MPM. The high level of *GAS5* could increase promoter activity. Moreover, *GAS5* could control cell cycles in a glucocorticoid receptor-decoy way. As a result, *GAS5* plays an important role in MPM and could be a targeted agent in the future.[66]

Urological malignancies

Renal cell carcinoma (RCC) is a common carcinoma with poor prognosis. Hui ping et al provide the first evidence that *GAS5* expression was lower in RCC cells and the

overexpression of *GAS5* can inhibit cell proliferation, induce cell apoptosis, arrest cell cycle, progress cell death and inhibit invasion. Therefore, the decreased expression of *GAS5* was associated with tumorigenesis and progression.[67,68]

In bladder cancer, accumulating studies have found that overexpression of *GAS5* can promote apoptosis in drug-induced resistance. The upregulated expression of *GAS5* can promote apoptosis by affecting GA induced apoptosis and inhibiting EZH2 transcription.[33] The level of *GAS5* was lower in bladder cancer tissues and the low expression of *GAS5* was positively related to higher pathological grades and could be a prognosis for disease-free survival of bladder cancer patients. Enhancement of *GAS5* can also reduce the chemotherapy resistance to doxorubicin via Bcl2.[69]

Prostate cancer is the most prevalent malignancy in male patients. Mouse xenograft models were used to explore the *GAS5* effects on prostate cancer. Overexpression of *GAS5* can significantly inhibit prostate cancer cell proliferation and tumor growth in vitro and vivo.[53]

Breast cancer

GAS5 expression is significantly downregulated in breast cancer cells. The overexpression of *GAS5* can induce or facilitated apoptosis in breast cancer cells and produce an increase in sensitivity to treatments by several different pathways.[18] Moreover, *GAS5* can promote the apoptosis of triple negative and estrogen receptor-positive breast cancer cells. Pickard et al have reported that the use of mTOR inhibitors may enhance *GAS5* levels to suppress cancer growth as well.[70] The plasma level of *GAS5* changes after surgery. The preoperative level of *GAS5* can reflect the active degree of proliferation in breast cancer. Thus, the plasma *GAS5* can be a biomarker to assess the prognosis evaluation after surgery.[16] The expression of *GAS5* was decreased in breast cancer cell from patients treated with trastuzumab and proved to contribute to trastuzumab resistance.[71] As a result, *GAS5* plays an important role in regulating breast cancer cells.

Lung cancer

Lung cancer is a common malignant cancer with the highest mortality in China. Compared with common tissues, the expression of *GAS5* was decreased in non-small cell lung cancer (NSCLC). Moreover, *GAS5* was declined in early stage before surgery compared with healthy control patients.[23] The overexpression of *GAS5* can inhibit NSCLC cell proliferation, promote apoptosis and improve radiosensitivity of NSCLC cells.[45] Decreased expression of *GAS5* is correlated with advanced TNM stages and larger tumor size. It can regulate NSCLC chemoresistance to cisplatin-based therapy as well.[42] Moreover, *GAS5* was found to be overexpressed in epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) sensitive cell lines compared with the resistant cell lines.[56] It is associated with the resistance of EGFR-TKIs. In the future, it can be a potential agent to deal with resistance of EGFR-TKIs.

Other cancers

Acute myeloid leukemia is a common hematologic cancer with genetically heterogeneous. It was found that overexpression of *GAS5* was associated with shorter overall survival.[72] In mantle cell lymphoma, targeting the control of *GAS5* may significantly improve survival.[73]

The expression of *GAS5* was downregulated in melanoma tissue compared with normal tissues. It was reported that expression of *GAS5* was related to distant metastases and TNM stage in melanoma by regulating miR-17 transcription. In the future, *GAS5* may be a potential target for the treatment of melanoma.[49]

GAS5 was proved to be downregulated in glioma. It was reported that *GAS5* can suppress glioma stem cells (GSCs) and further promote apoptosis.[46] The lower expression of *GAS5* was significantly related to increased rate of death, recurrence and progression.[74]

Osteosarcoma is a common malignancy with a high incidence of death in children and young adults. The expression of *GAS5* was found significantly decreased in osteosarcoma tissues and cells. *GAS5* can suppress cell growth, proliferation and epithelial–mesenchymal transition in osteosarcoma.[75]

In thyroid cancer, the expression of *GAS5* was lower than benign tumor tissues. The expression of *GAS5* was significantly related to tumor stage, lymph node metastasis, the multiple cancer foci of thyroid cancer, disease-free survival and overall survival.[76]

In head and neck cancer patients treated with radical chemoradiotherapy (CRT), the expression of *GAS5* was lower in patients achieved complete response than those with partial response and progressive disease. Thus, *GAS5* can be a prognostic biomarker for head and neck cancer in CRT therapy.[25]

Patients with low expression of *GAS5* was reported to have poorer disease-free survival and overall survival than those with higher level in ovarian cancer. And the overexpression

of *GAS5* can suppress ovarian cancer cell proliferation and promote apoptosis.[77] *GAS5* can act as a tumor suppressor lncRNA in endometrial cancer as well.[40]

In patients with cervical cancer, *GAS5* expression level was associated with FIGO stage, metastatic parameter, clinical staging and overall survival. The downregulation of *GAS5* was proved to enhance cell proliferation and invasion.[24,78] Moreover, the expression of *GAS5* can influence cisplatin resistance in cervical cancer by regulating the phosphorylation of Akt.[79]

Challenges and future perspectives

Cancer is a major health issue often associated with gene mutation. It is increasingly acknowledged that not only the change of the protein-coding genes but also non-protein-coding genes can contribute to different cancers. With lncRNA *GAS5* becomes a hot topic, much evidence indicates that lncRNA *GAS5* represents a potent tumor suppressor and is aberrantly expressed in various cancers. The suppressive function is involved in multiple pathways including proliferation, metastasis, invasion and CSCs. LncRNA *GAS5* can interact with miRNAs and then regulate different genes to regulate the related pathways (Table 1). It has been found that LncRNA *GAS5* is lower expressed in a variety of cancers including CRC, breast cancer, gastric cancer, hepatocellular carcinoma, osteosarcoma, esophageal carcinoma and pancreatic cancer. In tumors, lower expression of lncRNA *GAS5* is significantly associated with clinicopathological features such as TNM stage, histological grade, tumor size and distant metastasis (Table 1). Moreover, the expression of lncRNA *GAS5* can affect the survival and prognosis of some cancers. The exact mechanism of lncRNA *GAS5* action is not completely known. The molecular mechanism of lncRNA *GAS5* in cancer progression involves in GR, TRIB3, c-Myc, eIF4E, EZH2, TRAIL, CDK6, FGF1, PTEN, ARHI, CXCR4, (AKT)/mTOR, EGFR and NODAL pathway.

However, several challenges exist in the *GAS5* field, including the relatively low level in the plasma compared to the normal tissues. Nowadays, the studies of lncRNA *GAS5* are still in preclinical stage, the number of cancer patients involved is limited. The precious concentration of lncRNA *GAS5* in the serum of cancer patients and healthy patients has not been established. And the challenge here is the standardization of detection methods worldwide. It is unclear whether *GAS5* interact with additional chromatin-modifying enzymes through other molecular mechanisms.

GAS5 can also play an important role in non-cancer disease, such as cardiovascular disease, osteoarthritis, type 2 diabetes, inflammatory bowel disease and autoimmune disease.[80–84] It still needs more studies to discover the real function in various cancers. Future studies to the precise expression of *GAS5* in different diseases and disease progression, regression and response to therapies can be conducted to confirm its potential use as the biomarker in diagnosis and response to therapies.

Table 1 Related miRNAs in various cancers and lower expression of lncGAS5 is associated with clinical features

Cancer type	Related miRNA	Clinicopathological features
Colorectal cancer	miR-103, miR-221	Larger tumor size, low histological grade, advanced TNM stage, poor Prognosis, lymph node metastasis, local recurrence rate, distant metastasis rate
Cervical cancer	miR-196a, miR-205	Advanced FIGO stage and metastatic parameter, poorer overall survival
Gastric cancer	miR-222, miR-23a	Larger tumor size, advanced pathologic stage, poorer DFS, poorer OS
Pancreatic cancer	miR-181c-5p	Chemotherapeutic drug resistance, promote tumorigenesis and metastasis
Hepatocellular carcinoma	miR-21	Poor prognosis, differentiation, portal vein
Prostate cancer	miR-103	Poor outcome
Breast cancer	miR-21	Trastuzumab resistance
NSCLC	miR-23a, miR-135b	Advanced TNM stages and larger tumor size, poor tumor differentiation
Glioma cancer	miR-196a-5p, miR-222	-
Osteosarcoma	miR-203a	-
Melanoma	miR-137	-
Bladder cancer	-	Higher pathological grades, poor disease free survival, Enhance the chemotherapy resistance to doxorubicin
Thyroid cancer	-	Advanced TNM stages, lymph node metastasis, poor DFS, poor OS
Head and neck cancer	-	Higher complete response rate

Abbreviations: NSCLC, non-small cell lung cancer; DFS, disease free survival; OS, overal survival.

The potential of *GAS5* for cancer diagnosis has been supported by many studies. It can impact the chemotherapy sensitivity in certain cancer and provides a new strategy for overcoming drug resistance. Nowadays, precise medical treatments such as targeted therapies have the advantage of precise specificity and low toxicity. In future studies, lncRNA *GAS5* may serve as a new molecular target for the treatment of cancer.

Conclusion

In conclusion, the discovery of *GAS5* has provided new hope to cancer patients. Decreased expression of *GAS5* is associated with less proliferation, invasion and metastasis in cancer cells and always predicts advanced TNM stage, high recurrence and poor prognosis in various tumors. We hope to identify novel and sensitive biomarkers and therapeutic targets in cancer patients by understanding the molecular related pathways and clinicopathologic features in different cancers. Future investigation of *GAS5* may lead to novel therapeutic strategies.

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Disclosure

The authors report no conflicts of interest in this work.

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