Review

The Non-Coding RNA Repressor GAS5 of the Glucocorticoid Receptor: Insights to Its Role in Human Malignancies

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ABSTRACT

Background: GAS5 is expressed in growth arrested cells as a result of nutrient deprivation or growth factor withdrawal. Besides its roles in metabolism, GAS5 has been studied in a variety of human cancers. The aim of the present work was to review the literature and report all recent findings of the roles of GAS5 in a variety of tumors.

Methods: An electronic literature search was conducted by the authors using the keywords “GAS5” and “cancer”, and then individually searched for each type of cancer that was brought up by the first search. Original articles and systematic reviews were selected, and the titles and abstracts of the papers were screened to determine whether they met the eligibility criteria. In addition, we performed computer-based structural analysis on the human GAS5 RNA for extending our understanding on its biological and/or pathological actions.

Results: We have found that the majority of studies, irrespectively of tumor types, confirm the role of GAS5 as a tumor suppressor gene. Especially, more recent findings have also highlighted GAS5 interaction with miRNAs contributing even more to its tumor inhibiting role. In particular, we could outline two miRNAs, which came up throughout our review; miR-222 and miR-21. GAS5, miR-222 and miR-21 could pose potential prognostic and diagnostic biomarkers for a variety of tumors, making them quite useful in cancer clinic.

Conclusions: For certain, more studies are required in order to better understand the role of GAS5 in tumor biology, and in particular the signaling pathways in which the gene participates.

KEYWORDS: GAS5; glucocorticoid receptor; tumors; tumor mechanisms
INTRODUCTION

The environment together with the intrinsic state of the organism direct their cellular components to rest, grow, proliferate, differentiate or go into apoptosis [1]. One of the key regulators dictating cell phase maintenance or transition is the availability of nutrients and subsequent changes in cell growth, which globally alter the transcriptional profiles of certain sets of genes, including those for energy metabolism, stress and the immune response, through modulating the expression levels and/or activity of numerous upstream transcription factors and transcriptional regulatory molecules [2,3].

In consistent with this, expanding numbers of non-coding (nc) RNAs with transcriptional regulatory functions have been reported recently, along with the suggestion that they offer an additional level of regulatory complexity in the transcription of mammalian genes [4,5]. Sense and antisense sequences are transcribed from up to 80% of the coding and non-coding (nc) RNA-producing genes expressed in mammalian cells [6,7]. Since the discovery of ncRNAs, four types of the biological mechanisms have been attributed to them in association with their partner protein molecules: (a) signals for transcription, (b) decoys for transcription factors, (c) guides of transcription factors/cofactors and (d) scaffolds for protein complexes that epigenetically modify chromatin [8]. Their unique actions on the regulation of other ncRNAs and genome DNA conformation have also highlighted that they participate in (a) ncRNA transcription-dependent activation or repression of complementary genes, (b) interchromosomal interactions, (c) formation of nuclear structures or R-loops, (d) ncRNAs acting as attractors of miRNAs, (e) regulating post-transcriptional mRNA decay and (f) regulating the cellular localization of RNA-binding proteins or DNA-binding proteins. Further, recent reports indicate that they may act also as factors enhancing phase separation and participate in the assembly of nuclear bodies and the transcriptional complex formed on the regulatory elements [9,10].

Among such ncRNA, the growth arrest-specific 5 (GAS5) was originally found to be accumulated in growth-arrested cells [11]. Its encoding gene, GAS5 (Homo sapiens), is one of the 5′-terminal oligopyrimidine (5′TOP) class genes, characterized by an upstream oligopyrimidine tract sequence [12,13]. Growth arrest by serum starvation or treatment with inhibitors of protein translation is associated with attenuated translation of 5′TOP RNAs and the restraint of their degradation [14], resulting in marked accumulation of spliced, mature GAS5 RNA [13]. The function(s) of GAS5 RNA is largely unknown and intense research is taking place in order to
unravel its role in eukaryotic cell physiology and homeostasis. Previous reports have highlighted that in yeast two-hybrid screening experiments, GAS5 was a strong interactant of the DNA-binding domain (DBD) of the glucocorticoid receptor (GR), another ubiquitous molecule with major functions in behavioral [15,16], cardiovascular [17], metabolic [18] and immune homeostasis [19–21]. Relative starvation produces a favorable metabolic profile and prolongs life in several organisms, while increased glucocorticoid secretion or activity is associated with an unfavorable metabolic profile and decreased life expectancy [19,22,23]. Thus, the GAS5-GR interaction observed might be of physiologic and/or pathologic importance.

Besides its roles in metabolism, GAS5 has been studied in a variety of human cancers as a potential factor influencing their cell proliferation, metabolism and apoptosis, and further, as a potential diagnostic biomarker for evaluating prognosis/disease courses of cancer patients. In the present study, we attempted to review the literature for the role of GAS5 in human malignancies.

THE STRUCTURE OF THE GAS5 RNA

One important aspect towards the understanding of RNA function is the determination of RNA structure as it can be derived from its sequence. RNA structure has a two-level complexity. The first level concerns the prediction of its secondary structure, which is discrete in nature, since it concerns the pairing of nucleotides or not. The second level concerns the prediction of its tertiary structure, which gives more information about its function. The algorithm in use, was based on a previously developed dynamic programming algorithm proposed by Zuker (1989) [24,25]. The algorithm estimates the RNA molecule thermodynamically determined, free energy minimization. In general, thermodynamic parameters for the prediction of free energy of RNA folding are the backbone of many proposed algorithms [25–29]. Methods of implementation can be generally divided in two main categories; the first is based on the extrapolation of loop parameters through experimentally determined structure formation for RNA molecules and the second on knowledge-based approaches. Knowledge-based approaches mainly rely on motif frequencies occurrence.

The RNA sequence was obtained from http://www.ncbi.nlm.nih.gov/nuccore/NR_002578.2 and was downloaded as *.gb file. The sequence was as follows:

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tttcgaggttagaagctgcactcctgtgaggtatggtgctgggtgcggatgcagtgtggctctggatagcacctt
atggacagttgtgtcccaaggaaggatgagaatagctactgaagtcctaaagagcaagcctaactcaag
ccattggccacacaggcattagacagacagacagacagacagacagacagtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtg
Gene information is presented in Figure 1. The determination of the RNA secondary structure takes place through the interaction between its bases, including hydrogen bonding and base stacking. There are several methods for determining RNA secondary structure. One approach utilizes the nearest-neighbor model and minimizes the total free energy associated with an RNA structure [24]. The minimum free energy is estimated by summing individual energy contributions from base pair stacking, hairpins, bulges, internal loops and multi-branch loops. The energy contributions of these elements are sequence- and length-dependent and have been experimentally determined [24].

Thus, secondary structure was predicted using the nearest-neighbor model with free-energy minimization as reported previously and implemented in Matlab® computing environment [24]; the result is presented in Figures 2–4. We have also predicted the three-dimensional and tertiary structures of GAS5, which is presented in Figure 5. The GAS5 RNA has been reported that does not have conserved sequences, yet the introns of the GAS5 gene were found to have highly conserved sequences [30]. Several studies have highlighted the fact that the GR-DBD manifests a high affinity for GAS5 RNA [31]. In particular, the DNA GC response element (GRE) contains two half-sites such as AGAACA, whereas GAS5 hairpin competes with DNA for binding to GR-DBD [31]. An interesting finding suggested that although DNA and RNA manifest nearly identical affinities for the GR-DBD, GR does not dimerize when it binds to RNA [31,32]. Further on, GR-DBD specifically recognizes the GAS5 RNA through the GRE-mimic sequence, which is a hairpin located in nucleotides 538–576 [31,32] (Figure 4).
GAS5 IN TUMORS

Cancer is considered to consist of the 21st century epidemic. It is estimated that within the next 30 years almost the incidence of new cancer cases will double, thus one out of three individuals will suffer from some kind of malignancy [33]. Therefore, it is imperative for modern research to investigate the causes and therapeutic approaches to them. Towards that end technology has allowed the identification of new target molecules, as well as new gene regulatory mechanisms.

The omics era and the post-genomic era are considered to be the milestones of modern biological research. For example, microarray and high throughput sequencing methods have allowed us to identify new tumor markers, as well as novel molecules, such as long ncRNAs [34–38].
**Figure 4.** Two-dimensional structure of the human GAS5 RNA supported in part by the Wobble base-pairing (non-Watson-Crick base pairs). Besides the Watson-Crick base pairs (A–U, G–C), virtually every class of functional RNA presents G–U wobble base pairs. G–U pairs have an array of distinctive chemical, structural and conformational properties: they have high affinity for metal ions, they are almost thermodynamically as stable as Watson-Crick base pairs, and they present conformational flexibility to different environments (In-house simulations, preliminary results and unpublished data).

**Figure 5.** The 3D structure of GAS5 RNA is presented. The 3D structures of nucleotides 1–310 and 311–600 are presented in (A) and (B), respectively, after secondary structure and energy minimization computations (In-house simulations, preliminary results and unpublished data).
GAS5 is a tumor suppressor gene that has been thoroughly examined in malignancies [18]. However, there are several cancer research areas where GAS5 has not been studied as for example the case of diseases in the central nervous system [39]. GAS5 expression has been found to participate in the majority of human tumors, as it has been found to regulate apoptosis, proliferation, mesenchymal transition and metastasis [40]. Therefore, in the next sections we will discuss the role of GAS5 in various tumor types individually.

**GAS5 in Uterine Cervical Cancer**

Uterine cervical cancer is considered to be the second most common cancer and the fourth leading cause of deaths related to cancers in women [41]. It is a type of tumor that can be very aggressive with devastating effects on the suffering patient. Fortunately, early diagnosis of this cancer results in many cases to complete remission or cure. A recent report has found that GAS5 is down-regulated in cervical cancer tissues, which was in agreement with the initial postulation of GAS5 as a tumor suppressor gene [42]. In addition, in the same study in an in vitro model, overexpression of GAS5 led to suppression of proliferation, invasion and migration [42]. Moreover, experiments in mice have confirmed the mechanism of action of GAS5 by inhibiting tumor growth and metastasis [42]. In addition, in another report, it has been found that hypermethylation of the GAS5 gene is related to tumor progression and metastasis, while GAS5 overexpression is related to tumor inhibition and cell cycle arrest [43]. Another interesting report showed that GAS5 was down-regulated in cervical tumors while it was up-regulated in the adjacent tissues, and it was also found that GAS5 down-regulation was connected to poor prognosis [44,45]. Finally, an interesting finding showed that GAS5 regulates miRNA expression, particularly miR-196a, miR-205 and miR-21 [46,47]. Suppression of those miRNAs led to tumor suppression and was linked with better prognosis. In particular, it was found that GAS5 functions as a molecular sponge for miRNAs and more specifically it was found that miR-205 and miR-196a are GAS5-targeting miRNAs [47]. Further on, in the case of miR-21, it was shown that GAS5 directly functions as a molecular sponge, suppressing its function and probably does not allow miR-21 to interact with other tumor suppressor genes, such as PDCD4, TPM1, RECK and TIMP3, which are all potential targets for miR-21 [46].

**GAS5 in Breast Cancer**

The case of breast cancer is one of the well-studied tumors, both with respect to its biology as well as with respect to GAS5. One of the most recent reports has shown that GAS5 is regulated by c-Myc, and in particular, Myc inhibition led to down-regulation of GAS5, indicating a tumor promoting mechanism [48]. In line with previous studies for the role of miRNAs, it is also reported that several miRNAs are regulated by GAS5 in breast cancer. In particular, miR221/222 promote tumor growth and inhibit apoptosis.
On the other hand GAS5, interacts with miR-23a inducing autophagy [51], binds to miR-196a-5p suppressing proliferation and invasion [52] and finally interacts with miR-21, which in turn leads to tumor suppression [53]. At the same time, numerous recent studies agree on the fact that down-regulation of GAS5 is tightly connected to tumor progression, invasion, metastasis and cell cycle progression [54–58]. As in the case of cervical cancer, it was also shown for breast cancer that GAS5 is direct mediator of miR-221/222, and in particular, miR-221/222 suppresses GAS5 expression subsequently promoting tumor growth [49]. Interestingly, miR-222 regulates GAS5 over the PTEN/Akt/mTOR pathway conferring tumor growth and proliferation [59,60]. In addition, miR-21 was also found in breast cancer to interact with GAS5 [53]. GAS5 binds to miR-21 and inhibits the miRNA to further silence tumor suppressor genes such as PTEN, and PI3K as a consequence activate Akt-mediated cell growth and proliferation [53]. Further on, in the same study it was shown that TPM1, PDCD4 and TIMP3 are also direct targets of miR-21 [53].

In addition to the suppression of miRNA expression/functional inhibition by GAS5 as explained above, several reports have shed some biological insight into another explanation of GAS5 as a tumor suppressor. In particular, it has been found that Notch-1 expression promotes tumor cell proliferation through down-regulation of GAS5 [61]. Also, several other ncRNAs, such as SNORD44 [62] and RT2 [63], were found to be regulated by Notch-1, along with GAS5, indicating their mutual cooperation in suppressing tumor growth.

**GAS5 in Ovarian Cancer**

As in the case of cervical and breast cancer, ovarian cancer is a significant malignancy of the female reproductive system, as it is the seventh most frequent cancer in women [64]. Several studies have investigated the biological role of GAS5 in ovarian cancer. It has been found that GAS5 stimulates apoptosis in ovarian tumor cells, through the mitochondrial apoptosis pathway [65]. In particular, GAS5 stimulates BAX and BAK expression, and down-stream caspase expression [65]. Similarly to aforementioned gynecological cancers, GAS5 down-regulation is associated with tumor cell proliferation, invasion, metastasis and poor prognosis in ovarian cancer [66,67]. In particular, in a recent report it has been found that GAS5 acts as a decoy of CEBPB, leading to GDF15 down-regulation, which in ovarian cancer functions in the exact opposite way, meaning that GAS5 down-regulation fails to decoy CEBPB followed by GDF15 over-expression and ultimately allows tumor growth and proliferation [68]. On the other hand, GAS5 overexpression leads to down-regulation of IL18 inducing apoptosis of tumor cells [69]. Finally, in the case of GAS5-regulator miRNAs, there is one report suggesting that miR-21 has been found to be overexpressed in ovarian cancer, with a simultaneous down-regulation of GAS5. miR-21 expression is reversed.
when GAS5 is overexpressed, Thus GAS5 causes tumor suppression by inhibiting their proliferation through suppression of miR-21 [70].

**GAS5 in Prostate Cancer**

In prostate cancer, miR-145 inhibits proliferation and induces apoptosis by up-regulating GAS5, while GAS5 down-regulates miR-18a [71,72], as well as miR-103 [73], and is related to better prognosis [74]. At the same time, a gene expression meta-analysis study has shown that GAS5 is targeted by miR-940, leading to its down-regulation and tumor progression [74]. A very interesting recent report has shown that mutations in the GAS5 gene is linked to the transition of benign prostate to aggressive prostate cancer, thus indicating its role in tumor differentiation and progression [75]. All studies referring to prostate cancer, all agree that GAS5 up-regulation is tightly linked to tumor suppression, inhibition of proliferation and good prognosis [76–80]. More in-depth studies have reported that a possible mechanism of GAS5 action in prostate cancer is through targeting of p27Kip1 [81] and AKT/mTOR pathway [73,82].

**GAS5 in Lung Cancer**

Lung cancer remains the leading cause of cancer-related death worldwide and is expected to account for 28% of all male cancer deaths and 26% of all female cancer deaths in 2013 [83]. GAS5 has been found to play a significant role in lung cancer biology, as many studies have reported their results on this phenomenon. In particular, all studies agree that GAS5 plays a significant tumor suppressing and pro-apoptotic role in lung cancer both in small cell [84–92], non-small cell lung cancer [83–92], lung adenocarcinoma [93,94] and malignant pleural mesothelioma [95]. In addition, it has been reported that circulating levels of GAS5 could be possible biomarkers for diagnosis and prognosis for lung cancer [86].

**GAS5 in Gastric Cancer**

Gastric cancer is the fifth leading type of cancer and the third leading cause of death from cancer, making up 7% of cases and 9% of deaths [96]. As in the previous cases GAS5 down-regulation leads to gastric tumor progression and invasion [97,98], while GAS5 overexpression plays a role as a tumor suppressor and pro-apoptotic agent [58,59,99–101]. Several miRNAs have been shown to interact with GAS5 and regulate tumor growth in gastric cancer. Interestingly, as in the case of breast cancer, miR-222 regulates GAS5 over the PTEN/Akt/mTOR pathway conferring tumor growth and proliferation [59]. Finally, in a very recent report it has been found that a GAS5 variant regulates p27Kip1 conferring high risk for gastric cancer [102]. This variant consists of a functional five-base pair (AGGCA/-) insertion/deletion polymorphism (rs145204276). The variant is located in the promoter region of the GAS5 gene and the deletion brings about an
elevation in gene transcription as compared to the promoter variant with the insertion [102].

**GAS5 in Colorectal Cancer**

Colorectal cancer is one of the most common tumors and the third deadliest from all cancers [103]. Although it can be very aggressive, early diagnosis can lead to complete remission/cure. It is a well-studied tumor with respect to GAS5. One interesting finding is that, as in the cases of gastric and breast cancer, GAS5 down-regulates miR-222 through the PTEN pathway conferring tumor suppression and pro-apoptosis [104]. Another novel finding is that GAS5 functions as a tumor suppressor through the miR-182-5p/FOXO3a axis in colorectal cancer [105]. Also, some studies have shown that GAS5 expression can be a predictive biomarker for metastasis [106,107] and tumor progression of this cancer [104,108–110]. The properties of GAS5 as a biomarker have been studied more extensively in colorectal cancers as compared to other tumor types.

**GAS5 in Liver Cancer**

Liver cancer is the sixth most frequently diagnosed cancer and the fourth leading cause of cancer-related death globally in 2018, with approximately 841,000 new cases and an estimated 782,000 deaths annually [111]. There are not many studies on the role of GAS5 in liver cancer whereas most studies are occupied with the biology of GAS5 in Hepatocellular Carcinoma (HCC). One of the main findings in the role of GAS5 in HCC is that its over-expression is tightly linked to tumor invasion inhibition, through interaction with miR-135b [112], as well as through interaction with miR-21 [113]. On the other hand, down-regulation of GAS5 has been reported to lead to poor prognosis, tumor invasion enhancement and promotion of tumor cell proliferation [57,114,115]. One of the recent biological mechanisms detected was that GAS5 mediates the interaction of corylin and inhibits epithelial mesenchymal transition thus suppressing HCC progression and metastasis [116]. Finally, in a recent study it has been reported that treatment of HCC cells with sorafenib, a protein kinase inhibitor, resulted in GAS5 up-regulation along with miR-126-3p [117]. The interesting finding was that silencing of GAS5 in HCC cells resulted in up-regulation of miR-126-3p, indicating a regulatory relation between those two genes. In this study, the simultaneous sensitivity of HCC cells to sorafenib and GAS5 up-regulation confirmed the role of GAS5 as a tumor suppressor genes, as well as it indicated a negative regulation between GAS5 and miR-126-3p [117]. A similar mechanism was also recently reported between GAS5 and miR-1323 [118]. In that study, it has been found that silencing of GAS5 lead to increased HCC cell proliferation, while miR-1323 inhibition restricted proliferation. The simultaneous inhibition of GAS5 and miR-1323 balanced those effects and manifested similar results as in the reference samples [118]. Both studies, agree that GAS5
plays a significant role as a tumor suppressor gene in hepatic cancer, which is in agreement with previous studies.

**GAS5 in Brain Cancer/Tumors**

Brain tumors are considered to be the most notorious type of tumors, mainly due to the anatomical characteristics of brain and its unique biology without replication. Brain tumors, no matter if they are benign or malignant can pose a serious threat to life because they affect brain tissue, which is vital for survival. Similarly, as in previous cases, GAS5 down-regulation is linked to poor prognosis in glioblastomas and gliomas [119,120]. Thus, up-regulation of GAS5 functions potentially as a tumor suppressor and anti-proliferative agent in gliomas [121–123]. Interestingly, as in discussed for breast and gastric cancer, GAS5 interacts with miR-222 also in glioma causing tumor growth arrest and apoptosis [124]. Another interesting report showed that GAS5 suppresses tumor growth in glioma through the miR-196a-5p/FOXO1 pathway [125]. Finally, GAS5 suppresses proliferation, migration and invasion of glioma cells by negative regulation of miR-18a-5p [126]. There are fewer studies for other brain tumors, yet all agree that GAS5 functions as a tumor suppressor and in particular, this has been reported for glioblastoma [119,121,127]. There are no studies up to date for the role of GAS5 in medulloblastoma, astrocytoma, ependymoma, meningioma and other rarer brain tumor types. In summary, brain tumors are the least studied types of cancer with respect to GAS5. In that sense, it is apparent that many more studies are required in order to gain more knowledge in the biology of brain tumors.

**GAS5 in Bladder Cancer**

There are not many studies concerning the role of GAS5 in bladder cancer. Yet, as in the previous cases it is unanimously accepted that GAS5 down-regulation is linked to bladder tumor cells progression and growth [128–130], while GAS5 expression functions as a tumor suppressor and activator of apoptosis [131–133]. Finally, in a very recent report it has been shown that a single nucleotide polymorphism (SNP) in GAS5 is suspected for increased risk of bladder cancer [134].

**CONCLUSIONS**

GAS5 is a long ncRNA discovered in the early 90s’ [11–13]. From that time and on, several studies have shed light on its role in different functions of human and animal physiology and at the same time in human malignancies. From our review, we have found that almost all studies, irrespectively of tumor types, confirm the role of GAS5 as a tumor suppressor. Especially, more recent findings have also highlighted GAS5 interaction with various miRNAs, contributing even more to its tumor inhibiting role. In particular, we could outline two miRNAs, which came up throughout our review; miR-222 and miR-21. More specifically
bioinformatics and experimental analyses have shown that miR-222 has a possible binding site within the GAS5-3' UTR (3’-untranslated regions) [135], while similarly GAS5 has a binding site for miR-21 sharing a common binding site with PTEN for miR-21 [84]. It is possible that these molecules could play an important role in tumor biology as well as tumor growth, invasion and metastasis. Thus, it is not an exaggeration to say that GAS5, miR-222 and miR-21 could pose potential prognostic and diagnostic biomarkers for a variety of tumors. For certain, more studies are required in order to better understand the role of GAS5 in tumors and in particular in brain tumors, which have been the least studied types of tumors with respect to GAS5.

AUTHOR CONTRIBUTIONS

KH: Drafted the manuscript, reviewed literature. TK: Drafted the manuscript, proof-edited the manuscript, reviewed literature. GIL: Drafted the manuscript, proof-edited the manuscript and gave final permission for publication.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

REFERENCES

1. Lloyd Alison C. The Regulation of Cell Size. Cell. 2013;154(6):1194-205.
2. Sellick CA, Reece RJ. Eukaryotic transcription factors as direct nutrient sensors. Trends Biochem Sci. 2005;30(7):405-12.
3. Han ES, Hickey M. Microarray evaluation of dietary restriction. J Nutr. 2005;135(6):1343-6.
4. Mattick JS. The functional genomics of noncoding RNA. Science. 2005;309(5740):1527-8.
5. Pang KC, Frith MC, Mattick JS. Rapid evolution of noncoding RNAs: lack of conservation does not mean lack of function. Trends Genet. 2006;22(1):1-5.
6. Chen J, Sun M, Kent WJ, Huang X, Xie H, Wang W, et al. Over 20% of human transcripts might form sense-antisense pairs. Nucleic Acids Res. 2004;32(16):4812-20.
7. Katayama S, Tomaru Y, Kasukawa T, Waki K, Nakanishi M, Nakamura M, et al. Antisense transcription in the mammalian transcriptome. Science. 2005;309(5740):1564-6.
8. Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs. Mol Cell. 2011;43(6):904-14.
9. Hnisz D, Shrinivas K, Young RA, Chakraborty AK, Sharp PA. A Phase Separation Model for Transcriptional Control. Cell. 2017;169(1):13-23.
10. Alberti S. Phase separation in biology. Curr Biol. 2017;27(20):R1097-102.
11. Schneider C, King RM, Philipson L. Genes specifically expressed at growth arrest of mammalian cells. Cell. 1988;54(6):787-93.
12. Coccia EM, Cicala C, Charlesworth A, Ciccarelli C, Rossi GB, Philipson L, et al. Regulation and expression of a growth arrest-specific gene (gas5) during growth, differentiation, and development. Mol Cell Biol. 1992;12(8):3514-21.

13. Smith CM, Steitz JA. Classification of gas5 as a multi-small-nucleolar-RNA (snoRNA) host gene and a member of the 5'-terminal oligopyrimidine gene family reveals common features of snoRNA host genes. Mol Cell Biol. 1998;18(12):6897-909.

14. Amaldi F, Pierandrei-Amaldi P. TOP genes: a translationally controlled class of genes including those coding for ribosomal proteins. In: Jeanteur P, editor. Progress in molecular and subcellular biology. Vol. 18. Berlin (Germany): Springer-Verlag; 1997. p. 1-17.

15. Pang W, Lian FZ, Leng X, Wang SM, Li YB, Wang ZY, et al. Microarray expression profiling and co-expression network analysis of circulating LncRNAs and mRNAs associated with neurotoxicity induced by BPA. Environ Sci Pollut Res Int. 2018;25(15):15006-18.

16. Meier I, Fellini L, Jakovcevski M, Schachner M, Morellini F. Expression of the snoRNA host gene gas5 in the hippocampus is upregulated by age and psychogenic stress and correlates with reduced novelty-induced behavior in C57BL/6 mice. Hippocampus. 2010;20(9):1027-36.

17. Simion V, Haemmig S, Feinberg MW. LncRNAs in vascular biology and disease. Vascul Pharmacol. 2019;114:145-56.

18. Shi X, Sun M, Liu H, Yao Y, Song Y. Long non-coding RNAs: a new frontier in the study of human diseases. Cancer Lett. 2013;339(2):159-66.

19. Mayama T, Marr AK, Kino T. Differential Expression of Glucocorticoid Receptor Noncoding RNA Repressor Gas5 in Autoimmune and Inflammatory Diseases. Horm Metab Res. 2016;48(8):550-7.

20. Sudhalkar N, Rosen C, Melbourne JK, Park MR, Chase KA, Sharma RP. Long Non-Coding RNAs Associated with Heterochromatin Function in Immune Cells in Psychosis. Non-coding RNA. 2018;4(4):43.

21. Tu J, Tian G, Cheung HH, Wei W, Lee TL. Gas5 is an essential IncRNA regulator for self-renewal and pluripotency of mouse embryonic stem cells and induced pluripotent stem cells. Stem Cell Res Ther. 2018;9(1):71.

22. Kino T, Chrousos GP. Glucocorticoid Effect on Gene Expression. In: Steckler T, Kalin NH, Reul JMHM, editors. Handbook on Stress and the Brain Part 1. Amsterdam (The Netherlands): Elsevier BV; 2004. p. 295-312.

23. Kino T, Hurt DE, Ichijo T, Nader N, Chrousos GP. Noncoding RNA gas5 is a growth arrest- and starvation-associated repressor of the glucocorticoid receptor. Science Signal. 2010;3(107):ra8.

24. Mathews DH, Sabina J, Zuker M, Turner DH. Expanded sequence dependence of thermodynamic parameters improves prediction of RNA secondary structure. J Mol Biol. 1999;288(5):911-40.

25. Zuker M. On finding all suboptimal foldings of an RNA molecule. Science. 1989;244(4900):48-52.

26. McCaskill JS. The equilibrium partition function and base pair binding probabilities for RNA secondary structure. Biopolymers. 1990;29(6-7):1105-19.
27. van Batenburg FH, Gultyaev AP, Pleij CW. An APL-programmed genetic algorithm for the prediction of RNA secondary structure. J Theor Biol. 1995;174(3):269-80.

28. Gultyaev AP, van Batenburg FH, Pleij CW. The influence of a metastable structure in plasmid primer RNA on antisense RNA binding kinetics. Nucleic Acids Res. 1995;23(18):3718-25.

29. Gultyaev AP, van Batenburg FH, Pleij CW. The computer simulation of RNA folding pathways using a genetic algorithm. J Mol Biol. 1995;250(1):37-51.

30. Johnsson P, Lipovich L, Grander D, Morris KV. Evolutionary conservation of long non-coding RNAs; sequence, structure, function. Biochim Biophys Acta. 2014;1840(3):1063-71.

31. Parsonnet NV, Lammer NC, Holmes ZE, Batey RT, Wuttke DS. The glucocorticoid receptor DNA-binding domain recognizes RNA hairpin structures with high affinity. Nucleic Acids Res. 2019;47(15):8180-92.

32. Hudson WH, Pickard MR, de Vera IM, Kuiper EG, Mourtada-Maarabouni M, Conn GL, et al. Conserved sequence-specific lincRNA-steroid receptor interactions drive transcriptional repression and direct cell fate. Nat Commun. 2014;5:5395.

33. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913-21.

34. Braoudaki M, Lambrou GI. MicroRNAs in pediatric central nervous system embryonal neoplasms: the known unknown. J Hematol Oncol. 2015;8:6.

35. Braoudaki M, Lambrou GI, Giannikou K, Milionis V, Stefanaki K, Birks DK, et al. Microrna expression signatures predict patient progression and disease outcome in pediatric embryonal central nervous system neoplasms. J Hematol Oncol. 2014;7:96.

36. Braoudaki M, Lambrou GI, Giannikou K, Papadodima SA, Lykoudi A, Stefanaki K, et al. miR-15a and miR-24-1 as putative prognostic microRNA signatures for pediatric pilocytic astrocytomas and ependymomas. Tumour Biol. 2016;37(7):9887-97.

37. Braoudaki M, Lambrou GI, Papadodima SA, Stefanaki K, Prodromou N, Kanavakis E. MicroRNA expression profiles in pediatric dysembryoplastic neuroepithelial tumors. Med Oncol. 2016;33(1):5.

38. Braoudaki M, Lambrou GI, Vougas K, Karamolegou K, Tsangaris GT, Tzortzatou-Stathopoulou F. Protein biomarkers distinguish between high- and low-risk pediatric acute lymphoblastic leukemia in a tissue specific manner. J Hematol Oncol. 2013;6:52.

39. Zhao HY, Zhang ST, Cheng X, Li HM, Zhang L, He H, et al. Long non-coding RNA GAS5 promotes PC12 cells differentiation into Tuj1-positive neuron-like cells and induces cell cycle arrest. Neural Regen Res. 2019;14(12):2118-25.

40. Ji J, Dai X, Yeung SJ, He X. The role of long non-coding RNA GAS5 in cancers. Cancer Manag Res. 2019;11:2729-37.

41. Franco EL, Schlecht NF, Saslow D. The Epidemiology of Cervical Cancer. The Cancer J. 2003;9(5):348-59.
42. Wang X, Zhang J, Wang Y. Long noncoding RNA GAS5-AS1 suppresses growth and metastasis of cervical cancer by increasing GAS5 stability. Am J Transl Res. 2019;11(8):4909-21.

43. Yang W, Xu X, Hong L, Wang Q, Huang J, Jiang L. Upregulation of IncRNA GAS5 inhibits the growth and metastasis of cervical cancer cells. J Cell Physiol. 2019;234(12):23571-80.

44. Li Y, Wan YP, Bai Y. Correlation between long strand non-coding RNA GAS5 expression and prognosis of cervical cancer patients. Eur Rev Med Pharmacol Sci. 2018;22(4):943-9.

45. Cao S, Liu W, Li F, Zhao W, Qin C. Decreased expression of IncRNA GAS5 predicts a poor prognosis in cervical cancer. Int J Clin Exp Pathol. 2014;7(10):6776-83.

46. Wen Q, Liu Y, Lyu H, Xu X, Wu Q, Liu N, et al. Long Noncoding RNA GAS5, Which Acts as a Tumor Suppressor via microRNA 21, Regulates Cisplatin Resistance Expression in Cervical Cancer. Int J Gynecol Cancer. 2017;27(6):1096-108.

47. Yang W, Hong L, Xu X, Wang Q, Huang J, Jiang L. LncRNA GAS5 suppresses the tumorigenesis of cervical cancer by downregulating miR-196a and miR-205. Tumour Biol. 2017;39(7):1010428317711315.

48. Tokgun PE, Tokgun O, Kurt S, Tomatir AG, Akca H. MYC-driven regulation of long non-coding RNA profiles in breast cancer cells. Gene. 2019;714:143955.

49. Zong Y, Zhang Y, Sun X, Xu T, Cheng X, Qin Y. miR-221/222 promote tumor growth and suppress apoptosis by targeting IncRNA GAS5 in breast cancer. Biosci Rep. 2019;39(1):BSR20181859.

50. Gu J, Wang Y, Wang X, Zhou D, Shao C, Zhou M, et al. Downregulation of lncRNA GAS5 confers tamoxifen resistance by activating miR-222 in breast cancer. Cancer Lett. 2018;434:1-10.

51. Gu J, Wang Y, Wang X, Zhou D, Wang X, Zhou M, et al. Effect of the LncRNA GAS5-MiR-23a-ATG3 Axis in Regulating Autophagy in Patients with Breast Cancer. Cell Physiol Biochem. 2018;48(1):194-207.

52. Li S, Zhou J, Wang Z, Wang P, Gao X, Wang Y. Long noncoding RNA GASS suppresses triple negative breast cancer progression through inhibition of proliferation and invasion by competitively binding miR-196a-5p. Biomed Pharmacother. 2018;104:451-7.

53. Zhang Z, Zhu Z, Watabe K, Zhang X, Bai C, Xu M, et al. Negative regulation of lncRNA GAS5 by miR-21. Cell Death Differ. 2013;20(11):1558-68.

54. Esmaatabadi MJ, Motamedrad M, Sadeghizadeh M. Down-regulation of IncRNA, GAS5 decreases chemotherapeutic effect of dendrosomal curcumin (DNC) in breast cancer cells. Phytomedicine. 2018;42:56-65.

55. Lu X, Fang Y, Wang Z, Xie J, Zhan Q, Deng X, et al. Downregulation of gas5 increases pancreatic cancer cell proliferation by regulating CDK6. Cell Tissue Res. 2013;354(3):891-6.

56. Mourtada-Maarabouni M, Pickard MR, Hedge VL, Farzaneh F, Williams GT. GAS5, a non-protein-coding RNA, controls apoptosis and is downregulated in breast cancer. Oncogene. 2009;28(2):195-208.
57. Tu ZQ, Li RJ, Mei JZ, Li XH. Down-regulation of long non-coding RNA GAS5 is associated with the prognosis of hepatocellular carcinoma. Int J Clin Exp Pathol. 2014;7(7):4303-9.
58. Yu X, Li Z. Long non-coding RNA growth arrest-specific transcript 5 in tumor biology. Oncol Lett. 2015;10(4):1953-8.
59. Li Y, Gu J, Lu H. The GAS5/miR-222 Axis Regulates Proliferation of Gastric Cancer Cells Through the PTEN/Akt/mTOR Pathway. Dig Dis Sci. 2017;62(12):3426-37.
60. Li W, Zhai L, Wang H, Liu C, Zhang J, Chen W, et al. Downregulation of LncRNA GAS5 causes trastuzumab resistance in breast cancer. Oncotarget. 2016;7(19):27778-86.
61. Pei J, Wang B. Notch-1 promotes breast cancer cells proliferation by regulating LncRNA GAS5. Int J Clin Exp Med. 2015;8(8):14464-71.
62. Yuan S, Wu Y, Wang Y, Chen J, Chu L. An Oncolytic Adenovirus Expressing SNORD44 and GAS5 Exhibits Antitumor Effect in Colorectal Cancer Cells. Hum Gene Ther. 2017;28(8):690-700.
63. Sterbova M, Pazourkova E, Santorova-Pospisilova S, Zednikova I, Tesarova P, Korabecna M. The use of Human Inflammatory Response and Autoimmunity RT2 lncRNA PCR Array for plasma examination in breast cancer patients prior to therapy. Neoplasma. 2019;2019:641-6.
64. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Cancer Biol Med. 2017;14(1):9-32.
65. Gao J, Liu M, Zou Y, Mao M, Shen T, Zhang C, et al. Long non-coding RNA growth arrest-specific transcript 5 is involved in ovarian cancer cell apoptosis through the mitochondria-mediated apoptosis pathway. Oncol Rep. 2015;34(6):3212-21.
66. Li J, Huang H, Li Y, Li L, Hou W, You Z. Decreased expression of long non-coding RNA GAS5 promotes cell proliferation, migration and invasion, and indicates a poor prognosis in ovarian cancer. Oncol Rep. 2016;36(6):3241-50.
67. Zhao H, Yu H, Zheng J, Ning N, Tang F, Yang Y, et al. Lowly-expressed lncRNA GAS5 facilitates progression of ovarian cancer through targeting miR-196-5p and thereby regulating HOXA5. Gynecol Oncol. 2018;151(2):345-55.
68. Guo LL, Wang SF. Downregulated Long Noncoding RNA GAS5 Fails to Function as Decoy of CEBPB, Resulting in Increased GDF15 Expression and Rapid Ovarian Cancer Cell Proliferation. Cancer Biother Radiopharm. 2019;34(8):537-46.
69. Ma C, Wang W, Li P. LncRNA GAS5 overexpression downregulates IL-18 and induces the apoptosis of fibroblast-like synoviocytes. Clin Rheumatol. 2019;38(11):3275-80.
70. Ma N, Li S, Zhang Q, Wang H, Qin H, Wang S. Long non-coding RNA GAS5 inhibits ovarian cancer cell proliferation via the control of microRNA-21 and SPRY2 expression. Exp Ther Med. 2018;16(1):73-82.
71. Xie X, Dai J, Huang X, Fang C, He W. MicroRNA-145 inhibits proliferation and induces apoptosis in human prostate carcinoma by upregulating long non-coding RNA GAS5. Oncol Lett. 2019;18(2):1043-8.
72. Yang J, Hao T, Sun J, Wei P, Zhang H. Long noncoding RNA GAS5 modulates alpha-Solanine-induced radiosensitivity by negatively regulating miR-18a in human prostate cancer cells. Biomed Pharmacother. 2019;112:108656.

73. Xue D, Zhou C, Lu H, Xu R, Xu X, He X. LncRNA GAS5 inhibits proliferation and progression of prostate cancer by targeting miR-103 through AKT/mTOR signaling pathway. Tumour Biol. 2016;37:16187-97.

74. Chen X, Yang C, Xie S, Cheung E. Long non-coding RNA GAS5 and ZFAS1 are prognostic markers involved in translation targeted by miR-940 in prostate cancer. Oncotarget. 2018;9(1):1048-62.

75. Zhu L, Zhu Q, Wen H, Huang X, Zheng G. Mutations in GAS5 affect the transformation from benign prostate proliferation to aggressive prostate cancer by affecting the transcription efficiency of GAS5. J Cell Physiol. 2019;234(6):8928-40.

76. Ma C, Shi X, Zhu Q, Li Q, Liu Y, Yao Y, et al. The growth arrest-specific transcript 5 (GASS): a pivotal tumor suppressor long noncoding RNA in human cancers. Tumour Biol. 2016;37(2):1437-44.

77. Pickard MR, Mourtada- Maarabouni M, Williams GT. Long non-coding RNA GAS5 regulates apoptosis in prostate cancer cell lines. Biochim Biophys Acta. 2013;1832(10):1613-23.

78. Shain SA. Exogenous fibroblast growth factors maintain viability, promote proliferation, and suppress GADD45alpha and GAS6 transcript content of prostate cancer cells genetically modified to lack endogenous FGF-2. Mol Cancer Res. 2004;2(11):653-61.

79. Xu X, Hou J, Lv J, Huang Y, Pu J, Wang L. Overexpression of LncRNA GAS5 suppresses prostatic epithelial cell proliferation by regulating COX-2 in chronic non-bacterial prostatitis. Cell Cycle. 2019;18(9):923-31.

80. Zhang Y, Su X, Kong Z, Fu F, Zhang P, Wang D, et al. An androgen reduced transcript of LncRNA GAS5 promoted prostate cancer proliferation. PLoS One. 2017;12(8):e0182305.

81. Luo G, Liu D, Huang C, Wang M, Xiao X, Zeng F, et al. LncRNA GAS5 Inhibits Cellular Proliferation by Targeting P27(Kip1). Mol Cancer Res. 2017;15(7):789-99.

82. Yacqub-Usman K, Pickard MR, Williams GT. Reciprocal regulation of GAS5 lncRNA levels and mTOR inhibitor action in prostate cancer cells. Prostate. 2015;75(7):693-705.

83. Shi X, Sun M, Liu H, Yao Y, Kong R, Chen F, et al. A critical role for the long non-coding RNA GAS5 in proliferation and apoptosis in non-small-cell lung cancer. Mol Carcinog. 2015;54(Suppl 1):E1-12.

84. Cao L, Chen J, Ou B, Liu C, Zou Y, Chen Q. GAS5 knockdown reduces the chemosensitivity of non-small cell lung cancer (NSCLC) cell to cisplatin (DDP) through regulating miR-21/PTEN axis. Biomed Pharmacother. 2017;93:570-9.

85. Esfandi F, Taheri M, Omrani MD, Shadmehr MB, Arsang-Jang S, Shams R, et al. Expression of long non-coding RNAs (lncRNAs) has been dysregulated in non-small cell lung cancer tissues. BMC cancer. 2019;19(1):222.

86. Kamel LM, Atef DM, Mackawy AMH, Shalaby SM, Abdelraheim N. Circulating long non-coding RNA GAS5 and SOX2OT as potential biomarkers for diagnosis.
and prognosis of non-small cell lung cancer. Biotechnol Appl Biochem. 2019;66(4):634-42.
87. Li C, Lv Y, Shao C, Chen C, Zhang T, Wei Y, et al. Tumor-derived exosomal IncRNA GAS5 as a biomarker for early-stage non-small-cell lung cancer diagnosis. J Cell Physiol. 2019;234(11):2072-7.
88. Liang W, Lv T, Shi X, Liu H, Zhu Q, Zeng J, et al. Circulating long noncoding RNA GASS is a novel biomarker for the diagnosis of nonsmall cell lung cancer. Medicine. 2016;95(37):e4608.
89. Mei Y, Si J, Wang Y, Huang Z, Zhu H, Feng S, et al. Long Noncoding RNA GASS Suppresses Tumorigenesis by Inhibiting miR-23a Expression in Non-Small Cell Lung Cancer. Oncol Res. 2017;25(6):1027-37.
90. Wu Y, Lyu H, Liu H, Shi X, Song Y, Liu B. Downregulation of the long noncoding RNA GAS5-AS1 contributes to tumor metastasis in non-small cell lung cancer. Sci Rep. 2016;6:31093.
91. Xue Y, Ni T, Jiang Y, Li Y. Long Noncoding RNA GASS Inhibits Tumorigenesis and Enhances Radiosensitivity by Suppressing miR-135b Expression in Non-Small Cell Lung Cancer. Oncol Res. 2017;25(8):1305-16.
92. Zhang N, Yang GQ, Shao XM, Wei L. GAS5 modulated autophagy is a mechanism modulating cisplatin sensitivity in NSCLC cells. Eur Rev Med Pharmacol Sci. 2016;20(11):2271-7.
93. Dong S, Qu X, Li W, Zhong X, Li P, Yang S, et al. The long non-coding RNA, GAS5, enhances gefitinib-induced cell death in innate EGFR tyrosine kinase inhibitor-resistant lung adenocarcinoma cells with wide-type EGFR via downregulation of the IGF-1R expression. J Hematol Oncol. 2015;8:43.
94. Zhou Y, Wu K, Jiang J, Huang J, Zhang P, Zhu Y, et al. Integrative analysis reveals enhanced regulatory effects of human long intergenic non-coding RNAs in lung adenocarcinoma. J Genet Genomics. 2015;42(8):423-36.
95. Renganathan A, Kresoja-Rakic J, Echeverry N, Ziltener G, Vrugt B, Opitz I, et al. GAS5 long non-coding RNA in malignant pleural mesothelioma. Mol Cancer. 2014;13:89.
96. Theodoratou E, Timofeeva M, Li X, Meng X, Ioannidis JPA. Nature, Nurture, and Cancer Risks: Genetic and Nutritional Contributions to Cancer. Annu Rev Nutr. 2017;37:293-320.
97. Sun M, Jin FY, Xia R, Kong R, Li JH, Xu TP, et al. Decreased expression of long noncoding RNA GAS5 indicates a poor prognosis and promotes cell proliferation in gastric cancer. BMC Cancer. 2014;14:319.
98. Zhang N, Wang AY, Wang XK, Sun XM, Xue HZ. GAS5 is downregulated in gastric cancer cells by promoter hypermethylation and regulates adriamycin sensitivity. Eur Rev Med Pharmacol Sci. 2016;20(15):3199-205.
99. Dong S, Zhang X, Liu D. Overexpression of long noncoding RNA GAS5 suppresses tumorigenesis and development of gastric cancer by sponging miR-106a-5p through the Akt/mTOR pathway. Biol Open. 2019;8(6):bio041343.
100. Liu Y, Zhao J, Zhang W, Gan J, Hu C, Huang G, et al. IncRNA GAS5 enhances G1 cell cycle arrest via binding to YBX1 to regulate p21 expression in stomach cancer. Sci Rep. 2015;5:10159.
101. Sun W, Yang Y, Xu C, Xie Y, Guo J. Roles of long noncoding RNAs in gastric cancer and their clinical applications. J Cancer Res Clin Oncol. 2016;142(11):2231-7.

102. Aminian K, Mashayekhi F, Mirzanejad L, Salehi Z. A functional genetic variant in GAS5 IncRNA (rs145204276) modulates p27(Kip1) expression and confers risk for gastric cancer. Br J Biomed Sci. 2019;76(2):83-5.

103. Marley AR, Nan H. Epidemiology of colorectal cancer. Int J Mol Epidemiol Genet. 2016;7(3):105-14.

104. Liu L, Wang HJ, Meng T, Lei C, Yang XH, Wang QS, et al. lncRNA GAS5 Inhibits Cell Migration and Invasion and Promotes Autophagy by Targeting miR-222-3p via the GAS5/PTEN-Signaling Pathway in CRC. Mol Ther Nucleic Acids. 2019;17:644-56.

105. Cheng K, Zhao Z, Wang G, Wang J, Zhu W. lncRNA GAS5 inhibits colorectal cancer cell proliferation via the miR1825p/FOXO3a axis. Oncol Rep. 2018;40(4):2371-80.

106. Kong H, Wu Y, Zhu M, Zhai C, Qian J, Gao X, et al. Long non-coding RNAs: novel prognostic biomarkers for liver metastases in patients with early stage colorectal cancer. Oncotarget. 2016;7(31):50428-36.

107. Zheng Y, Song D, Xiao K, Yang C, Ding Y, Deng W, et al. lncRNA GAS5 contributes to lymphatic metastasis in colorectal cancer. Oncotarget. 2016;7(50):83727-34.

108. Liu L, Meng T, Yang XH, Sayim P, Lei C, Jin B, et al. Prognostic and predictive value of long non-coding RNA GAS5 and miRNA-221 in colorectal cancer and their effects on colorectal cancer cell proliferation, migration and invasion. Cancer Biomark. 2018;22(2):283-99.

109. Yang Y, Shen Z, Yan Y, Wang B, Zhang J, Shen C, et al. Long non-coding RNA GAS5 inhibits cell proliferation, induces G0/G1 arrest and apoptosis, and functions as a prognostic marker in colorectal cancer. Oncol Lett. 2017;13(5):3151-8.

110. Zhu X, Wang D, Lin Q, Wu G, Yuan S, Ye F, et al. Screening key lncRNAs for human rectal adenocarcinoma based on lncRNA-mRNA functional synergistic network. Cancer Med. 2019;8(8):3875-91.

111. Baumeister SE, Leitzmann MF, Linseisen J, Schlesinger S. Physical activity and the risk of liver cancer: a systematic review and meta-analysis of prospective studies and a bias analysis. J Natl Cancer Inst. 2019;111(11):1142-51.

112. Yang L, Jiang J. GAS5 Regulates RECK Expression and Inhibits Invasion Potential of HCC Cells by Sponging miR-135b. Bio med Res Int. 2019;2019:2973289.

113. Hu L, Ye H, Huang G, Luo F, Liu Y, Liu Y, et al. Long noncoding RNA GAS5 suppresses the migration and invasion of hepatocellular carcinoma cells via miR-21. Tumour Biol. 2016;37(2):2691-702.

114. Chang L, Li C, Lan T, Wu L, Yuan Y, Liu Q, et al. Decreased expression of long non-coding RNA GAS5 indicates a poor prognosis and promotes cell proliferation and invasion in hepatocellular carcinoma by regulating vimentin. Mol Med Rep. 2016;13(2):1541-50.
115. Wang Y, Jing W, Ma W, Liang C, Chai H, Tu J. Down-regulation of long non-coding RNA GAS5-AS1 and its prognostic and diagnostic significance in hepatocellular carcinoma. Cancer Biomark. 2018;22(2):227-36.

116. Chen CY, Chen CC, Shieh TM, Hsueh C, Wang SH, Leu YL, et al. Corylin Suppresses Hepatocellular Carcinoma Progression via the Inhibition of Epithelial-Mesenchymal Transition, Mediated by Long Noncoding RNA GAS5. Int J Mol Sci. 2018;19(2):380.

117. Faranda T, Grossi I, Manganelli M, Marchina E, Baiocchi G, Portolani N, et al. Differential expression profiling of long non-coding RNA GAS5 and miR-126-3p in human cancer cells in response to sorafenib. Sci Rep. 2019;9(1):9118.

118. Zhang F, Yang C, Xing Z, Liu P, Zhang B, Ma X, et al. LncRNA GAS5-mediated miR-1323 promotes tumor progression by targeting TP53INP1 in hepatocellular carcinoma. OncoTargets Ther. 2019;12:4013-23.

119. Shen J, Hodges TR, Song R, Gong Y, Calin GA, Heimberger AB, et al. Serum HOTAIR and GAS5 levels as predictors of survival in patients with glioblastoma. Mol Carcinog. 2018;57(1):137-41.

120. Wang Y, Xin S, Zhang K, Shi R, Bao X. Low GASS Levels as a Predictor of Poor Survival in Patients with Lower-Grade Gliomas. J Oncol. 2019;2019:1785042.

121. Chen L, Han L, Wei J, Zhang K, Shi Z, Duan R, et al. SNORD76, a box C/D snoRNA, acts as a tumor suppressor in glioblastoma. Sci Rep. 2015;5:8588.

122. Garcia-Claver A, Lorente M, Mur P, Campos-Martin Y, Mollejo M, Velasco G, et al. Gene expression changes associated with erlotinib response in glioma cell lines. Eur J Cancer. 2013;49(7):1641-53.

123. Liu Q, Sun S, Yu W, Jiang J, Zhuo F, Qiu G, et al. Altered expression of long non-coding RNAs during genotoxic stress-induced cell death in human glioma cells. J Neurooncol. 2015;122(2):283-92.

124. Zhao X, Wang P, Liu J, Zheng J, Liu Y, Chen J, et al. Gas5 Exerts Tumor-suppressive Functions in Human Glioma Cells by Targeting miR-222. Mol Ther. 2015;23(12):1899-911.

125. Zhao X, Liu Y, Zheng J, Liu X, Chen J, Liu L, et al. GAS5 suppresses malignancy of human glioma stem cells via a miR-196a-5p/FOXO1 feedback loop. Biochim Biophys Acta Mol Cell Res. 2017;1864(10):1605-17.

126. Liu Q, Yu W, Zhu S, Cheng K, Xu H, Lv Y, et al. Long noncoding RNA GASS regulates the proliferation, migration, and invasion of glioma cells by negatively regulating miR-18a-5p. J Cell Physiol. 2018;234(1):757-68.

127. Toraih EA, Alghamdi SA, El-Wazir A, Hosny MM, Hussein MH, Khashana MS, et al. Dual biomarkers long non-coding RNA GAS5 and microRNA-34a co-expression signature in common solid tumors. PLoS One. 2018;13(10):e0198231.

128. Avgeris M, Tsilimantou A, Levis PK, Tokas T, Sideris DC, Stravodimos K, et al. Loss of GAS5 tumour suppressor lncRNA: an independent molecular cancer biomarker for short-term relapse and progression in bladder cancer patients. Br J Cancer. 2018;119(12):1477-86.

129. Liu Z, Wang W, Jiang J, Bao E, Xu D, Zeng Y, et al. Downregulation of GASS promotes bladder cancer cell proliferation, partly by regulating CDK6. PLoS One. 2013;8(9):e73991.
130. Quan J, Pan X, Zhao L, Li Z, Dai K, Yan F, et al. LncRNA as a diagnostic and prognostic biomarker in bladder cancer: a systematic review and meta-analysis. OncoTargets Ther. 2018;11:6415-24.

131. Cao Q, Wang N, Qi J, Gu Z, Shen H. Long noncoding RNAGASS acts as a tumor suppressor in bladder transitional cell carcinoma via regulation of chemokine (CC motif) ligand 1 expression. Mol Med Rep. 2016;13(1):27-34.

132. Droop J, Szarvas T, Schulz WA, Niedworok C, Niegisch G, Scheckenbach K, et al. Diagnostic and prognostic value of long noncoding RNAs as biomarkers in urothelial carcinoma. PLoS One. 2017;12(4):e0176287.

133. Wang M, Guo C, Wang L, Luo G, Huang C, Li Y, et al. Long noncoding RNA GAS5 promotes bladder cancer cells apoptosis through inhibiting EZH2 transcription. Cell Death Dis. 2018;9(2):238.

134. Rakhshan A, Esmaeili MH, Kahaei MS, Taheri M, Omrani MD, Noroozi R, et al. A Single Nucleotide Polymorphism in GAS5 lncRNA is Associated with Risk of Bladder Cancer in Iranian Population. Pathol Oncol Res. 2019. https://doi.org/10.1007/s12253-019-00693-2

135. Li Z, Yu Z, Meng X, Zhou S, Xiao S, Li X, et al. Long noncoding RNA GASS impairs the proliferation and invasion of endometrial carcinoma induced by high glucose via targeting miR-222-3p/p27. Am J Transl Res. 2019;11(4):2413-21.

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