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

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ABBREVIATIONS

DBD, DNA-Binding Domain; GAS5, Growth Arrest-specific 5; GC, Glucocorticoid; GR, Glucocorticoid Receptor; GRE, Glucocorticoid Response Element; NC, Non-Coding; TGF, Transforming Growth Factor

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) inter-chromosomal 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:

tttcgaggtaggagtcgactcctgtgaggtatggtgctgggtgcggatgcagtgtggctctggatagcaccttatggacagttgtgtcccaaggaaggatgagaatagctactgaagtcctaaagagcaagcctaactcaagccattggcacacaggcattagacagaaagctggaagttgaaatggtggagtccaacttgcctggaccagcttaatggttctgctcctggtaacgtttttatccatggatgacttgcttgggtaaggacatgaagacagttcctgtcatacctttaaaggtatggagagtcggcttgactacactgtgtggagcaagttttaaagaagcaaaggactcagaattcatgattgaagaaatgcaggcagacctgttatcctaaactagggtttttaatgaccacaaca

agcaagcatgcagcttactgcttgaaagggtcttgcctcacccaagctagagtgcagtggcctttgaagctt
actacagcctcaaacttctgggctcaagtgatcctcagcctcccagtggtctttgtagactgcctgatggagt
ctcatggcacaagaagattaaaacagtgtctccaattttaataaatttttgcaatccaaaaaaaaaaaaaa
aaaaaaa

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].

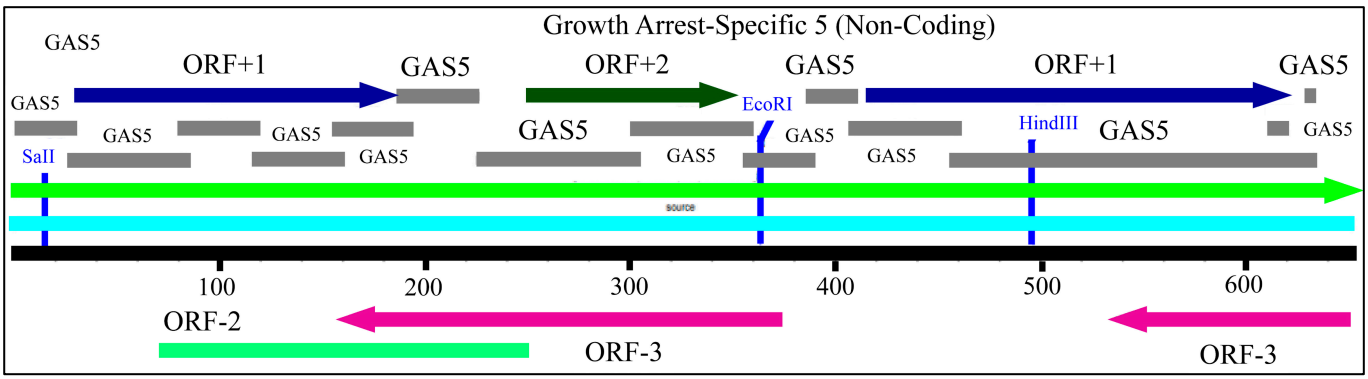

Figure 1. The human GAS5 gene with its exons, and its primary transcript sense and anti-sense open reading frames (grey shaded bars indicate the gene's exons. ORF+1 through ORF+2 are read in a 5'→3' direction, while ORF-2 through ORF-3 are read in a 3'→5' direction).

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**).

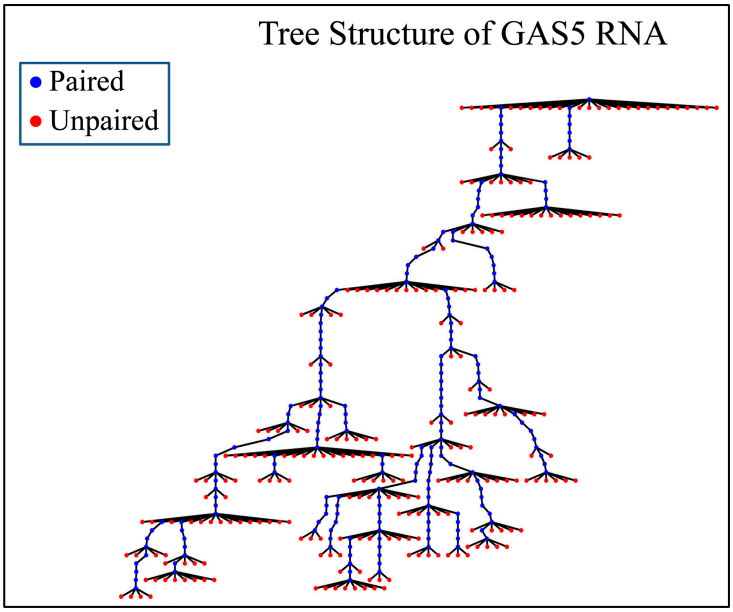

Figure 2. The tree structure of GAS5 RNA (In-house simulations, preliminary results and unpublished data).

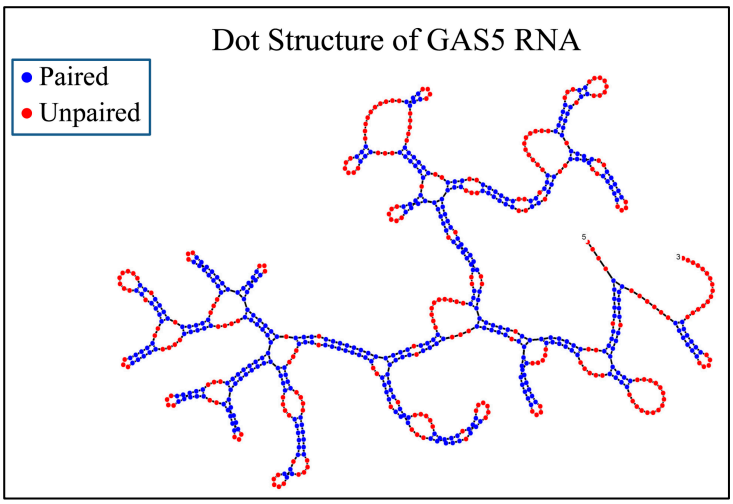

Figure 3. The secondary predicted structure of GAS5 RNA (In-house simulations, preliminary results and unpublished data).

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].

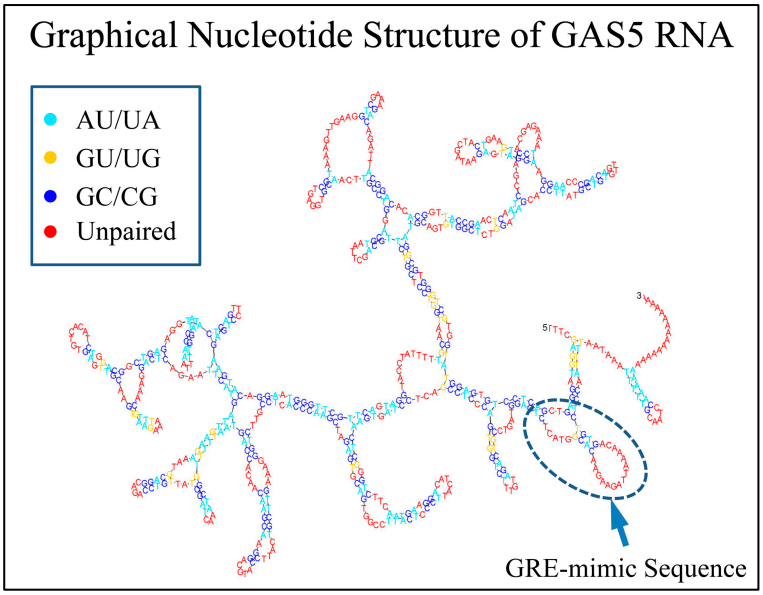

Figure 4. Two-dimensional structure of the human GAS5 RNA supported in part by the Wobble base-pairing (non-Watson-Crick base pairs). Besides the Watson-Crick base pairs (A–U, G–C), virtually every class of functional RNA presents G–U wobble base pairs. G–U pairs have an array of distinctive chemical, 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).

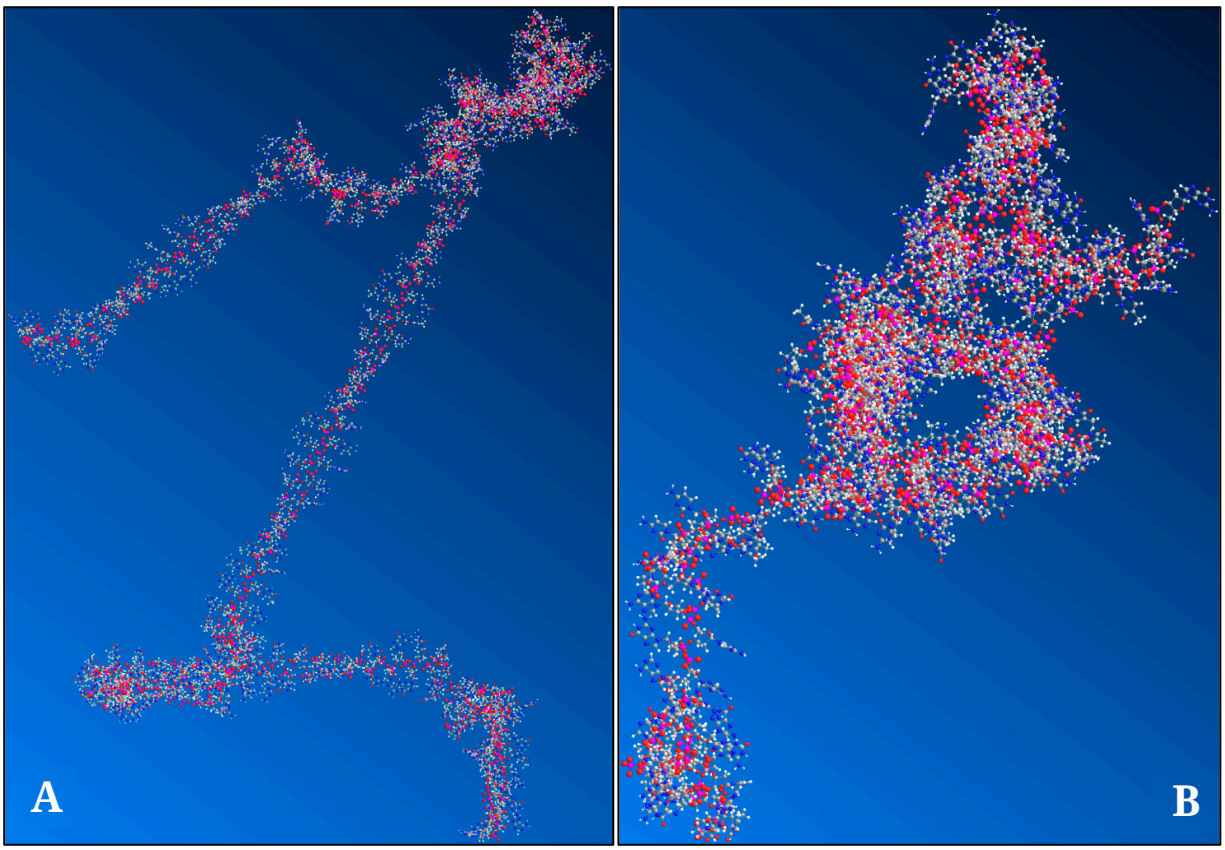

Figure 5. The 3D structure of GAS5 RNA is presented. The 3D structures of nucleotides 1–310 and 311–600 are presented in (**A**) and (**B**), respectively, after secondary structure and energy minimization computations (In-house simulations, preliminary results and unpublished data).

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, over-expression 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 hyper-methylation 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

[49,50]. 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-regulaterd 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 $p27^{Kip1}$ [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 $p27^{Kip1}$ 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.

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