Abstract: The growth arrest-specific transcript 5 (GAS5) is a >200-nt IncRNA molecule that regulates several cellular functions, including proliferation, apoptosis, invasion and metastasis, across different types of human cancers. Here, we reviewed the current literature on the expression of GAS5 in leukemia, cervical, breast, ovarian, prostate, urinary bladder, lung, gastric, colorectal, liver, osteosarcoma and brain cancers, as well as its interaction with various miRNAs and its effect on therapy-related resistance in these malignancies. The general consensus is that GAS5 acts as a tumor suppressor across different tumor types and that its up-regulation results in tumor sensitization to chemotherapy or radiotherapy. GAS5 seems to play a previously unappreciated, but significant role in tumor therapy-induced resistance.

Keywords: GAS5; malignancy; proliferation; invasion; metastasis; tumor growth

1. Introduction

The massive and rapid increase in the amount of human genome-scale DNA sequencing and the parallel development of methods to exploit these data drive the biomedical research today in a significant transition. The three billion base pairs of human DNA do not provide information about the function of the genes, or how cells grow, divide, form organisms, how mistakes in them are reflected in diseases, and how to develop a drug. Thus, it is important to construct a catalogue of expressed or suppressed genes for each cellular function, in order to understand how each component works within living cells. The transcriptome, i.e., the genes that are transcribed into mRNA, determines the phenotype and function of each cell [1]. Thus, alterations in gene expression are highly dynamic; they drive cellular phenotypic characteristics, DNA replication and cell division, as well as how a cell responds to an extracellular stimulus or perturbation. The understanding of when, where and to what extent a gene is expressed, can elucidate the regulatory mechanisms and biological pathways that lead to, maintain or reverse multiple drug-resistance in cancer treatment. Almost twenty years ago, the non-coding RNAs (ncRNAs) were discovered [2,3] and provided a breakthrough in our understanding of the functionality of the human genome. To take advantage of the large and rapidly increasing body of genome-scale sequence information, new technologies are required to exploit this information by characterizing biological processes and by studying the synchronous expression of a high number of genes. A variety of techniques has evolved to monitor, rapidly and efficiently, the transcript abundance of all genes in an organism [4].

Thousands of genes have been identified through high throughput methodologies, and a plethora of them have been studied for their role in tumor progression, as well as therapy-induced resistance.
2. The Long Non-Coding RNA Repressor GAS5

The ncRNAs are essential players in many cellular processes, from normal development to oncogenic transformation, offering an additional level of regulatory complexity in the transcription of mammalian genes [5–7]. They can be divided into microRNAs (miRNAs), piwi-interacting (piRNAs), small nucleolar (snoRNAs), long non-coding (lncRNAs) and other types of ncRNAs [7,8] and are implicated in various aspects of growth, such as neuronal, muscle and germline development [9–11]. One such lncRNA is the growth arrest-specific 5 (GAS5), which was originally found to accumulate in growth-arrested cells, acting as a decoy hormone response element for the glucocorticoid receptor (GR) and hence, blocking the upregulation of gene expression by activated GR [12–14] (Figure 1). GAS5 has a 5′ upstream oligopyrimidine tract sequence (5′TOP class genes) [15,16]. Serum starvation or treatment with inhibitors of protein translation can attenuate the translation of these 5′TOP RNAs and affect their degradation [17], leading to high numbers of spliced, mature GAS5 RNA molecules [16].

![Figure 1. Secondary structure of the growth arrest-specific 5 (GAS5) RNA, showing the glucocorticoid receptor element (GRE)-mimic sequence (a), along with the 3D structure of the GRE-mimic sequence (b) (the 3D structure of the GRE-mimic was obtained from the Protein Data Bank with reference no. 4MCE [18]).](attachment:image.png)

The regulation of the GR function is a complicated process, still unknown to a great extent. The role of GAS5 was previously reported in childhood obesity, where it was shown to act as a regulatory repressor element of the GR [13]. In addition, GAS5 was shown to play a role in metabolic processes such as obesity, anorexia or overweight situations. Interestingly, its expression in in vivo samples was influenced by methylation differences on its promoter region. If metabolic disorders are affected by gene expression and regulation, then, in the short-term, this should be evident in GR-related genes and regulatory elements such as GAS5. On the other hand, in the long-term perspective, metabolic disorders could be reflected in premature events, and be marked on the genome as methylated genes, as for example in infancy. These findings indicate that GAS5 manifests multifaceted roles in various physiological processes, including tumor ontogenesis [19]. GAS5 acts as a gene regulatory element through three basic modes of action. The first refers to its direct connection to its target gene, post-transcriptionally (Figure 2a). The second includes the indirect mechanism, which involves the binding of GAS5 with a regulatory protein (e.g., GR) and the subsequent regulation of gene transcription (Figure 2b). There is also a secondary, indirect mode of action, which involves the formation of a GAS5/protein complex further acting as a regulatory element for the transcribed gene (Figure 2c).
GAS5 was elevated due to treatment and the second, which double back and complement each other with a hairpin structure [23,24] (Figure 1a). These same GRE elements are preserved in mouse Gas5, which is the only other Gas5 sequence (GRE-2), which double back and complement each other with a hairpin structure [23,24] (Figure 1a). These same GRE elements are preserved in mouse Gas5, which is the only other Gas5 sequence (GRE-2), which double back and complement each other with a hairpin structure [23,24] (Figure 1a). These same GRE elements are preserved in mouse Gas5, which is the only other Gas5 sequence (GRE-2), which double back and complement each other with a hairpin structure [23,24] (Figure 1a).

Yet, the role of GAS5 in Tumor Therapy-Related Resistance is important and needs to be further understood [13,16,27–29].

3. GAS5 in Tumor Therapy-Related Resistance

The role of GAS5 in cancer ontogenesis and progression is a relatively new subject of investigation. Yet, the role of GAS5 in therapy-induced resistance observed across different types of tumors is important and needs to be further understood [13,16,27–29].

3.1. GAS5 in Leukemia

GAS5 expression was recently found to be tightly linked to therapy progression in acute lymphoblastic leukemia (ALL) [30]. In the study of Gasic et al. [30], GAS5 expression was reduced at day 33 of the induction therapy as compared to day 15, yet with still higher levels, compared to the time of diagnosis. This report suggested two interesting findings. The first was that GAS5 expression was elevated due to treatment and the second, GAS5 expression was low at diagnosis. At the same time, a recently discovered polymorphism in GAS5 was found to be linked with poor prognosis in...
acute myeloid leukemia (AML) patients [31]. The interesting finding was that GAS5 molecules without the polymorphism, rs55829688 CC, were found to manifest higher expression levels in peripheral blood cells, compared to those that bared the polymorphism, rs55829688T [31]. However, in another report, it was shown that the down-regulation of GAS5 led to the rescue of primary and malignant T-lymphocytes from the inhibition of the mammalian target of rapamycin (mTOR) [32]. In particular, this study showed that GAS5 has tumor suppressor activity since it could suppress tumor growth, while, when silenced, tumor cells recovered and increased their proliferation rate [32] (Figure 3).

**Figure 3.** The action of GAS5 on different tumor types. GAS5 down-regulation or mutations are related to poor prognosis, as well as chemo- and radioresistance. On the other hand, the upregulated GAS5 functions as a tumor suppressor and is related to chemo- and radiosensitivity.

### 3.2. GAS5 in Cervical Cancer

Cervical cancer ranks second in women and is the fourth leading cause of deaths related to cancers. It can be very aggressive and, as such, it is still the subject of intense research. There are few reports regarding GAS5 in cervical cancer. A recent study found that GAS5 interacts with miR-106b and this complex inhibits the expression of the immediate early response 3 gene (IER3), leading to sensitivity to radiation therapy [33]. In another report, GAS5 over-expression was shown to be connected to the down-regulation of miR-21 and the subsequent phosphorylation of STAT3 and E2F3 [33]. GAS5 over-expression can also reduce the expression of two miR-21 targets: TIMP3 and PDCD4 [33]. All these events have been observed to lead to a G0/G1 arrest and enhancement of cisplatin-induced apoptosis [33]. Similarly, another study was in agreement with the findings by Gao et al. (2019), suggesting that GAS5 negatively regulates miR-21 and upheaves cisplatin resistance [34] (Figure 3).

### 3.3. GAS5 in Breast Cancer

Breast cancer is the most common type of malignancy in women and a leading cause of death. It is a complex, heterogeneous disease classified into hormone-receptor-positive, human epidermal growth factor receptor-2 overexpressing (HER2+) and triple-negative breast cancer (TNBC) based on histological features [35]. Although early diagnosis is of paramount importance for the treatment and prognosis of this tumor, there is still a lot to understand on the mechanisms of action of GAS5 in it [36]. Overall, GAS5 is also considered to function as a tumor suppressor in breast cancer [27,37–39]. This was also reported in a recent work, which indicated that GAS5 is down-regulated in breast cancer and that it negatively impacts disease prognosis [33]. A way to alleviate GAS5 down-regulation was proposed via the inhibition of the mTOR signaling pathway [40]. Interestingly, the magnitude of cell death, in vitro, was directly proportional to GAS5 expression levels [40]. Finally, GAS5 was able to promote apoptosis in estrogen receptor (ER)-positive cells and in the case of GAS5 silenced cells, the inhibition of the PI3K/mTOR signaling pathway was able to recover GAS5 expression [40]. This finding was quite interesting, because it postulated that in the case of low levels of GAS5 expression, the inhibition of the mTOR pathway could be a complementary therapeutic target in the treatment of breast cancer. Furthermore, GAS5 has been linked to trastuzumab resistance, which is a main obstacle...
in HER2-positive breast cancer cells [41]. Li et al. (2016), showed that the down-regulation of GAS5 is partly responsible for trastuzumab and lapatinib resistance. Both drugs interrupt the HER2/neu and EGFR pathways. In agreement with previous studies, it becomes evident that GAS5 acts as tumor suppressor by interacting with miR-21 [41]. Tamoxifen is one of the basic chemotherapeutic agents in the treatment of breast cancer. In a recent report, it was shown that the down-regulation of GAS5 is related to tamoxifen resistance. In particular, it was found that GAS5 functions as a sponge for miR-222 suppressing PTEN expression and thus, inhibiting tamoxifen resistance. On the contrary, GAS5 down-regulation functions reversely and tamoxifen resistance is promoted [42]. These findings are in agreement with a recent report where it was shown that GAS5 is down-regulated in breast cancer tissues and linked to chemotherapy resistance [43]. Consequently, it seems that GAS5 can be considered as new player in cancer ontogenesis, progression and prognosis, as well as it may have prognostic and therapeutic applications in this disease. Several new drugs have been designed and synthesized for the treatment of breast cancer (Figure 3).

3.4. GAS5 in Ovarian Cancer

Ovarian cancer is a grave gynecological tumor and there are not many studies concerning the role of GAS5 in it or its association with chemoresistance in this tumor. However, similar to other gynecological tumors, it seems that all studies converge to the conclusion that GAS5 acts as a tumor suppressor in ovarian cancer, as well [44–47]. In a recent study, GAS5 was found to be down-regulated in this disease [41]. In particular, in a meta-analysis of 561 microarrays and 136 RNA-seq specimens, GAS5 was down-regulated and manifested high sensitivity and specificity in predicting platinum-based chemoresistance [48]. GAS5 was also found to be down-regulated in epithelial ovarian cancer in another study, where it was related to disease prognosis, in particular [49]. At the same time, GAS5 was found to be down-regulated in cisplatin resistant tumors. On the contrary, its up-regulation had the opposite effect, which significantly enhanced the sensitivity of ovarian cancer cells to cisplatin, both in vivo and in vitro. Further on, the up-regulation of GAS5 was found to increase both the ratio of G0/G1 arrest and apoptosis in ovarian cancer [42]. The same study reported that a probable mechanism for GAS5 action was mediated through the regulation of PARP1 by recruiting the transcription factor E2F4 to its promoter and subsequent MAPK pathway activity [50] (Figure 3).

3.5. GAS5 in Prostate and Bladder Cancers

Both prostate [51] and bladder cancers [52] are considered to be two major tumor types and causes of cancer-related deaths. In prostate cancer, GAS5 was found to be down-regulated, while it was down-regulated in radio-resistant prostate tumor cells [53]. This effect, was found to be alleviated by the addition of a-Solanine, which up-regulates GAS5 and at the same time, confers sensitivity to radiotherapy [53]. Similarly, GAS5 was found to be down-regulated in transitional cell carcinomas of the urinary bladder, and its down-regulation was found to be positively correlated with higher pathological grades of the tumor [54]. However, in an in vitro system, GAS5 overexpression could reduce chemo-resistance to doxorubicin and promoted apoptosis [54] (Figure 3).

3.6. GAS5 in Lung Cancer

Lung cancer is the most common cause of death from tumor-related diseases [55]. A recent study reported that GAS5 is down-regulated in lung cancer cells and at the same time, its knockdown increased cis-platin IC50 in an in vitro system, while its overexpression decreased it [56]. In the same study, it was found that GAS5 knockdown resulted in decreased autophagy in vitro, and therefore, resistance to cis-platin [56]. Similarly, GAS5 up-regulation was found to be a significant factor of inhibition of tumorigenesis and an enhancer of radiosensitivity [57]. In addition, the mechanism of enhancement of radiosensitivity was found to function via the suppression of miR-135b in non-small cell lung cancer cells [57]. Another recent study confirmed that GAS5 plays a significant role in non-small cell lung cancer, participating in cis-platin resistance. Cao et al. reported that chemo-sensitivity is
modulated by the tumor suppressor PTEN [58]. In the same study, it was found that a significant low GAS5 expression in non-small cell lung cancer patients was correlated with poorer prognosis. In an in vitro system, GAS5 knockdown promoted cell viability and regulated chemo-sensitivity to cis-platin. The authors showed that GAS5 competed with PTEN for miR-21 binding, indicating a strong evidence that GAS5/miR-21/PTEN interactions are significant in cis-platin sensitivity in non-small cell lung cancer cells [58]. Similarly, GAS5 was found to bind miR-21 and miR-23a, at the same time up-regulating PTEN and inhibiting PI3K/Akt phosphorylation [59]. This mechanism was found to function as an angiogenesis inhibitor, signifying that GAS5 could be targeted therapeutically in order to inhibit angiogenesis in non-small cell lung cancer [59] (Figure 3).

3.7. GAS5 in Gastric and Colorectal Cancers

Gastric cancer is the fourth most common malignancy, and the second most common cause of cancer-related deaths in the world [60]. GAS5 also plays a significant role as a tumor suppressor in gastric cancer [61–64]. A recent study highlighted the fact that GAS5 expression was significantly down-regulated in gastric cancer tissues, and that it was down-regulated in adriamycin-resistant cells [65]. GAS5 was also found to have higher levels of promoter methylation in SGC-7901 cells, conferring resistance to chemotherapy [65]. There are no reports on the role of GAS5 in chemoresistance in colorectal cancer; yet, reports suggest that GAS5 is responsible for tumor suppression, inhibition of proliferation, metastasis and invasion [66]. In addition, a recent study indicated that GAS5 inhibits angiogenesis and metastasis in colorectal cancer by suppressing the Wnt/beta-catenin signaling pathway, which is dedicated to promoting cell invasion and migration in this type of tumor (Figure 3) [67]. Recently, a 5-bp indel polymorphism (rs145204276) was found in the GAS5 promoter region and proposed to have a carcinogenic effect [68].

3.8. GAS5 in Liver Cancer

Liver cancer, in particular, hepatocellular carcinoma, is predominately present in eastern Asia and its rates are increasing in the northern hemisphere [69]. Liver cancer has a very fast progressing time span posing a significant threat to life. There are no reports on the role of GAS5 in chemosensitivity or chemoresistance in liver cancer. Yet, there are some interesting reports suggesting that GAS5 plays a synergistic role in the anti-tumor action of flavonoids and phytochemicals. In particular, phytochemicals, such as curcumin, resveratrol, sulforaphane, berberine and gambogic acid, have all been examined for their connection with non-coding RNAs. GAS5 was reported as one of the ncRNAs that is regulated by phytochemicals, which can synergistically affect tumor development and progression. When phytochemicals were administered in combination with chemotherapeutics, they were found to have an additive effect on the overexpression of GAS5 and the sensitization of cancer cells to chemotherapy. Finally, a recent study showed that corylin, a flavonoid extracted from the plant Psoralea corylifolia L. (Fabaceae), suppresses tumor growth and progression [70]. The interesting finding was that corylin was found to exert such effects on tumor growth through activation of GAS5 [70] (Figure 3).

3.9. GAS5 in Brain Tumors

Brain tumors, or tumors of the central nervous system, along with their extreme diversity, present a special case of malignancy due to the anatomical position in which they are diagnosed. This point is further strengthened by the fact that in several tumors, either benign or extremely aggressive, surgical excision is a drastic solution towards therapy, while in the case of brain tumors, this is not always the case, or it is less feasible. There are no studies connecting GAS5 to chemoresistance. In fact, there are very few studies on the role of GAS5 in brain tumors, in general. Yet, all the present studies agree that GAS5 functions as a tumor suppressor and inhibits tumor proliferation, invasion, metastasis and migration [71–75] (Figure 3).
3.10. GAS5 in Osteosarcoma

Another tumor type that we investigated is osteosarcoma. Osteosarcoma is a rare malignancy of the childhood with an incidence of 4–5 new cases per million per year [76]. It is an aggressive malignant neoplasm that arises from primitive transformed cells of mesenchymal origin, exhibits osteoblastic differentiation and produces malignant osteoid [77]. There are no reports concerning the role of GAS5 in osteosarcoma with respect to chemotherapy-related resistance. However, there are some reports referring to GAS5 as a significant gene in the tumor’s progression. In particular, miR-663a and ZBTB7A were found to protect osteosarcoma from endoplasmic reticulum stress-induced apoptosis, through the down-regulation of GAS5 [78], while in a similar study the CtBP1-HDAC1/2-IRF1 transcriptional complex was also found to be down-regulated in osteosarcoma cells [79]. In addition, it was found that GAS5 sponges miR-203a [80] and miR-221 [81], thus suppressing tumor growth and inhibiting tumor invasion (Figure 3).

4. The Special Case of GAS5 and miRNAs

4.1. GAS5 and miRNAs in Leukemia

The topic of GAS5 and miRNAs could not escape the attention of the present work. There are very few reports on the connection between GAS5 and miRNAs. In the case of leukemia, there is one report suggesting the interaction of GAS5 with miR-222, since their expression is negatively correlated [82]. In this study, it was also found that GAS5 over-expression was related to the inhibition of leukemic cells proliferation, the enhancement of leukemic cell apoptosis and the inhibition of tumor cell invasion [82] (Table 1).

4.2. GAS5 and miRNAs in Cervical Cancer

Similarly, few reports are available on the connection of GAS5 and miRNAs in cervical cancer. Yet, all studies agree that GAS5 acts as a suppressor or “sponge” for oncogenic miRNAs, whereas its overexpression is closely related to tumor suppression and induction of therapy-related sensitivity. In particular, previous studies indicated that GAS5 interacts with miR-222 [82], miR-106b [33], miR-135a [83], miR-21 [84] and miR-205 [34,85], conferring tumor suppressor properties and induction of sensitivity to chemo- and radiotherapy (Table 1).

4.3. GAS5 and miRNAs in Breast Cancer

The association between GAS5 and miRNAs has been widely studied in breast cancer. A recent study highlighted the role of GAS5 in breast cancer and Adriamycin resistance, through the gene’s interaction with miR-221-3p [86]. Another report showed that GAS5 manifested tumor suppressor effects and induced chemosensitivity to breast cancer cells by indirectly targeting the miR-378-5p/SUFU signaling pathway [87], as well as by competitively binding miR-196a-5p [87]. Additionally, GAS5 appeared to be a direct target of miR-221/222, suppressing tumor proliferation and enhancing tumor cell apoptosis [88]. In another report, it was shown that GAS5 stimulates autophagy through the miR-23a/ATG3 axis, where it acts as a miRNA sponge [89]. Interestingly, miR-21 also has an oncogenic role in breast cancer, where it induces chemo- and radiosensitivity [41] (Table 1).
Table 1. Summary of the relation of GAS5 and miRNAs in several tumors.

| Tumor                | miRNA         | Relation between GAS5 and miRNA | GAS5 Effect on Tumor | Effect on Therapy-Related Resistance | Citation                          |
|----------------------|---------------|---------------------------------|----------------------|-------------------------------------|----------------------------------|
| Leukemia             | miR-222       | Direct Suppression               | Tumor suppressor     | Unknown                             | Jing et al. (2019) [82]          |
|                      | miR-106b      | Direct Suppression/Sponge        | Tumor suppressor     | Induces chemo- and radiosensitivity | Gao et al. (2019) [33]           |
| Cervical Cancer      | miR-135a      | Direct Suppression               | Tumor suppressor     | Induces chemo- and radiosensitivity | Yan et al. (2020) [83]           |
|                      | miR-21        | Direct Suppression               | Tumor suppressor     | Induces chemo- and radiosensitivity | Yao et al. (2019), Li (2016) [41,84] |
|                      | miR-205       | Direct Suppression               | Tumor suppressor     | Induces chemo- and radiosensitivity | Yang et al. (2017), Wen et al. (2017) [34,85] |
|                      | miR-221-3p    | Direct Suppression/Sponge        | Tumor suppressor     | Induces chemo- and radiosensitivity | Chen et al. (2020) [86]          |
|                      | miR-378-5p    | Indirect Suppression/Sponge      | Tumor suppressor     | Induces chemo- and radiosensitivity | Zheng et al. (2020) [87]         |
|                      | miR-221/222   | Direct Suppression               | Tumor suppressor     | Induces chemo- and radiosensitivity | Zong et al. (2019), Gu et al. (2018) [42,88] |
|                      | miR-23a       | Direct Suppression/Sponge        | Tumor suppressor/induces autophagy | Unknown | Gu et al. (2018) [89] |
|                      | miR-196a-5p   | Direct Suppression/Sponge        | Induces autophagy    | Unknown                             | Li et al. (2018) [90]            |
|                      | miR-196a-5p   | Direct Suppression               | Tumor suppressor     | Induces chemo- and radiosensitivity | Zheng et al. (2020) [87]         |
|                      | miR-21        | Direct Suppression/Sponge        | Tumor suppressor     | Induces chemo- and radiosensitivity | Li (2016) [41]                   |
| Breast Cancer         | miR-196a-5p   | Direct Suppression               | Tumor suppressor     | Induces chemo- and radiosensitivity | Zhao et al. (2018) [46]          |
| Ovarian Cancer        | miR-196a-5p   | Direct Suppression               | Tumor suppressor     | Induces chemo- and radiosensitivity | Chen et al. (2017) [91]          |
| Prostate Cancer       | miR-940       | Indirect Suppression             | Tumor suppressor     | Unknown                             | Unknown                          |
|                      | miR-18a       | Indirect Suppression             | Tumor suppressor     | Induces chemo- and radiosensitivity | Yang et al. (2019) [53]          |
| Tumor          | miRNA | Relation between GAS5 and miRNA | GAS5 Effect on Tumor | Effect on Therapy-Related Resistance | Citation                        |
|---------------|-------|---------------------------------|----------------------|-------------------------------------|---------------------------------|
| Lung Cancer   | miR-21| Indirect Suppression            | Tumor suppressor     | Induces chemo- and radiosensitivity | Chen et al. (2020) [92]         |
|               | miR-29-3p | Indirect Suppression            | Tumor suppressor     | Induces chemo- and radiosensitivity | Cheng et al. (2019) [59]        |
|               | miR-21 | Indirect Suppression            | Tumor suppressor     | Induces chemo- and radiosensitivity | Cao et al. (2017) [58]          |
|               | miR-205| Direct Suppression              | Tumor suppressor     | Unknown                             | Dong et al. (2019) [93]         |
|               | miR-135b | Direct Suppression              | Tumor suppressor     | Unknown                             | Xue et al. (2017) [57]          |
|               | miR-23a | Indirect Suppression            | Tumor suppressor     | Unknown                             | Mei et al. (2017) [94]          |
| Gastric Cancer| miR-18a| Direct Suppression              | Tumor suppressor     | Unknown                             | Wei et al. (2020) [95]          |
|               | miR-106a-5p | Indirect Suppression          | Tumor suppressor     | Unknown                             | Dong et al. (2019) [63]         |
|               | miR-222 | Direct Suppression/sponge       | Tumor suppressor     | Unknown                             | Li et al. (2017) [96]           |
| Colorectal Cancer| miR-182-5p | Direct Suppression/sponge      | Tumor suppressor     | Induces chemo- and radiosensitivity | Cheng et al. (2018) [97]        |
|               | miR-221 | Indirect Suppression            | Tumor suppressor     | Unknown                             | Liu et al. (2018) [98]          |
| Liver Cancer  | miR-222 | Direct Suppression/sponge       | Tumor suppressor     | Induces chemo- and radiosensitivity | Zhao et al. (2020) [99]         |
|               | miR-21 | Direct Suppression/sponge       | Tumor suppressor     | Unknown                             | Wang et al. (2018), Hu et al. (2016) [100,101] |
|               | miR-544 | Indirect Suppression            | Tumor suppressor     | Unknown                             | Fang et al. (2019) [102]        |
|               | miR-135b | Indirect Suppression            | Tumor suppressor     | Unknown                             | Yang et al. (2019) [103]        |
|               | miR-34a | Indirect Suppression            | Tumor suppressor/sponge | Unknown                           | Toraih et al. (2018) [104]      |
| Glioma        | miR-106b | Indirect Suppression            | Tumor suppressor/sponge | Unknown                           | Huang et al. (2020) [105]       |
|               | miR-18a-3p | Indirect Suppression          | Tumor suppressor/sponge | Unknown                           | Liu et al. (2018) [73]          |
| Osteo-sarcoma | miR-663a | Indirect Suppression            | Tumor suppressor/sponge | Unknown                           | Zhang et al. (2019) [79]        |
|               | miR-203a | Indirect Suppression            | Tumor suppressor/sponge | Unknown                           | Wang et al. (2018) [80]         |
|               | miR-221 | Direct Suppression              | Tumor suppressor/sponge | Unknown                           | Ye et al. (2017) [81]           |
4.4. GAS5 and miRNAs in Ovarian Cancer

Although ovarian cancer is very common in women, there is only one report investigating the association between miRNAs and GAS5 in it. In this, the role of miR-196-5p in relation to GAS5 was reported. GAS5 down-regulation was found to be related to high miR-196-5p expression, which induced tumor cell proliferation and progression. Thus, GAS5 up-regulation confers tumor cell proliferation inhibition [46] (Table 1).

4.5. GAS5 and miRNAs in Prostate and Bladder Cancers

In the case of prostate and bladder cancers, two reports highlighted the connection of GAS5 with miRNAs. In particular, it was reported that GAS5 is down-regulated due to its targeting from miR-940 [91]. The relation between GAS5 and miR-940 was reported to be a possible prognostic factor. Finally, a recent study indicated that GAS5 negatively regulates miR-18a and, thus, confers radiosensitivity in human prostate cells [53] (Table 1).

4.6. GAS5 and miRNAs in Lung Cancer

Several reports have also identified the connection between GAS5 and miRNAs. A recent report showed that GAS5 probably indirectly regulates miR-21, whereas its over-expression suppresses miR-21 expression and, hence, increases radiosensitivity of lung tumor cells [92]. Recently, it was also shown that miR-29-3p antagonizes GAS5 for binding PTEN [59]. It was also reported that GAS5 exosomes are the basic vehicle of transmission conferring tumor inhibition [59]. The connection of GAS5/PTEN and miRNAs is also stated to be of significance through the competitive binding with miR-21 [58]. Similarly, the role of GAS5/PTEN is also shown to be of significance in lung cell proliferation and metastasis in connection to miR-205 [93]. Another recent study suggested that GAS5 directly binds and suppresses miR-135b, enhancing radiosensitivity [57]. Finally, a connection between GAS5 and miR-23a has been reported, where miR-23a was found to suppress GAS5 expression and enhance tumor cell proliferation and tumorigenesis [94] (Table 1).

4.7. GAS5 and miRNAs in Gastric and Colorectal Cancers

In gastric cancer, three miRNAs have been reported to relate to GAS5, miR-18a [95], miR-106a-5p [63] and miR-222 [96]. In the case of miR-18a, it was reported that GAS5 directly binds to it, inhibiting tumor growth via the stimulation of the activity of natural killer (NK) cells [95]. On the other hand, GAS5 functions as sponge for miR-106a-5p, inactivating the Akt/mTOR pathway [63]. Finally, miR-222 was reported to directly bind to GAS5 similarly, as in all previous cases, suppressing tumor cell proliferation [96]. In colorectal cancer, two different miRNAs were reported, miR-182-5p [97] and miR-221 [98]. GAS5 could directly bind to miR-182-5p and inhibit tumor cell proliferation through the miR-182-5p/FOXO3a axis [97]. Similarly, miR-221 is negatively regulated to GAS5 expression. If overexpressed, GAS5 can suppress miR-221 expression and subsequently inhibit tumor cell proliferation in colorectal cancer [98] (Table 1).

4.8. GAS5 and miRNAs in Liver Cancer

In the case of gastric cancer, five miRNAs have been reported to be related to GAS5, miR-222 [99], miR-21 [100,101], miR-544 [102], miR-135b [103] and miR-34a [104]. GAS5 was shown to sensitize hepatocellular cancer cells to chemotherapy by sponging miR-222 [99]. Similarly, GAS5 directly acts as a sponge for miR-21, suppressing its expression and subsequently inhibiting hepatocellular carcinoma proliferation [100,101]. In the case of miR-544, GAS5 negatively regulates its expression, inhibiting tumor cell proliferation [102]. GAS5 inhibits cell proliferation also through the miR-544/RUNX3 pathway [102], where it stimulates NK cell activity and inhibits tumor growth [95]. In addition, GAS5 and miR-135b reversely correlated and as reported in other tumors, GAS5 over-expression reduces miR-135b expression and, thus, inhibits tumor cell proliferation [103]. Finally, miR-34a
manifested a different mode of action with respect to GAS5. It appeared that GAS5 and miR-34a were positively correlated in three types of tumors; in hepatocellular carcinoma, glioblastoma and renal cell carcinoma [104]. GAS5 under-expression was also related to tumor progression and proliferation (Table 1).

4.9. GAS5 and miRNAs in Brain Tumors

Since brain tumors are not easily manageable, there are not many reports on the connection of GAS5 and miRNAs. The existent studies are concerned with reports on glioma. In particular, two miRNAs are found to be related to GAS5. The miR-106b-5p [105] and miR-18a-5p [73]. Both of them were found to be significantly up-regulated in glioma cells, while GAS5 was down-regulated. Additionally, it was found that GAS5 over-expression results in miRNA down-regulation (Table 1).

4.10. GAS5 and miRNAs in Osteosarcoma

Three miRNAs are related to GAS5 in osteosarcoma: miR-663a [79], miR-203a [80] and miR-221 [81]. The miR-663a indirectly suppresses GAS5 through the inhibition of its target, ZBTB7A [79]. Moreover, miR-203a suppresses GAS5, deactivates TIMP2, but activates the PI3K/AKT/GSK2β pathway with simultaneous inhibition of the NF-κB signaling cascade [80]. Therefore, GAS5 indirectly regulates miR-203a, as also supported by their reverse-correlated expression. Finally, GAS5 can directly suppress miR-221 through the miR-221/ARH1 pathway [81] (Table 1).

5. Discussion

Functional ncRNAs affect every aspect of the biology in many organisms, from bacteria to higher eukaryotes. Specifically, they affect all stages of the coding sequence, including mRNA transcription, degradation and translation, and/or the nuclear translocation of proteins [5,106,107]. Among them, GAS5 is mechanistically related to the bacterial 6S RNA, which binds the RNA polymerase and inhibits transcription [107,108]. Regarding nuclear receptor related ncRNAs, the ncRNA coactivator steroid receptor RNA activator (SRA) enhances nuclear receptor-induced transcriptional activity by associating with cofactor proteins, its stem-loop interacting protein, called SLIRP, and a pseudo-uridine synthase PuS1p [109,110]. GAS5 is distinct from SRA in its activity and mode of action, while, similarly to SRA and other ncRNAs, its interaction with regulatory proteins might be critical for Gas5-mediated suppression of GR-induced transcriptional activity. Indeed, in relation to complex transcriptional regulation of endogenous, chromatin-associated genes [49], it would be interesting to investigate if GAS5 can mimic the conformation of chromatin-integrated DNA interaction with histone-bound proteins and/or other chromatin components, with which the GR normally interacts to stimulate the transcription of endogenous, glucocorticoid-responsive genes.

In the present study, we explored the expression of GAS5 along with that of various miRNAs across different tumor types and focused on its role in therapy-related sensitivity to these cells. The main conclusion is that GAS5 seems to exert a tumor-suppressive role in the process of carcinogenesis across all tumor types. It does so, by interacting with or modulating the expression of various gene targets. As such, GAS5 participates in tumor growth, proliferation, invasion, metastasis inhibition, as well as the induction of apoptosis. However, it seems that GAS5 is also involved in the therapeutic response of cancer patients. Here, we review both in vitro and in vivo studies showing that GAS5 contributes to the sensitization of cancer cells to chemotherapy and radiotherapy [33]. The tumor suppressive role of GAS5 was recently supported by others as well [111–113], and all clues suggest that GAS5 could be used a promising biomarker for disease diagnosis, tumor progression, or even as a therapeutic marker. However, there are a few studies investigating in-depth the role of GAS5 in human tumors. Apart from differential expression, diverse genetic variants within GAS5 have also been proposed to affect drug response, and could, thus, facilitate the categorization and dose adjustment [111].
6. Conclusions

Several studies highlight that GAS5 plays an important role in various pathological and physiological conditions. Overall, GAS5 acts as a tumor suppressor, whose down-regulation is directly connected to tumor progression, tumor cell proliferation and therapy-related resistance across different types of tumors. The agreement of different studies on the role of GAS5 makes it a new attractive target for the prognosis and therapy of different cancer types.

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Abbreviations

- ALL: Acute Lymphoblastic Leukemia
- AML: Acute Myeloid Leukemia
- AR: Androgen Receptor
- GAS5: Growth Arrest Specific 5
- GR: Glucocorticoid Receptor
- GRE: Glucocorticoid Response Element
- lncRNAs: long non-coding RNAs
- miRNA: microRNA
- MR: Mineralocorticoid Receptor
- MRE: Mineralocorticoid Response Element
- ncRNA: non-coding RNA
- NK: Natural Killer cells
- piRNAs: piwi-interacting RNAs
- PR: Progesterone Receptor
- snoRNAs: small non-coding nucleolar RNAs
- SRA: Steroid Receptor RNA Activator
- TAD: Transactivation Domain

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