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Review Article

Expression and crucial role of long non-coding RNA FGD5-AS1 in human cancers

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Abstract: Long non-coding RNAs (lncRNAs) are transcribed by RNA polymerase II and are longer than 200 nucleotides. Several studies have revealed that lncRNAs are important regulators of cancer progression. The lncRNA FGD5-AS1, first identified in 2018, has emerged as a crucial regulator of processes related to carcinogenesis. The expression levels of FGD5-AS1 are known to be significantly up-regulated in a variety of human cancers. Moreover, FGD5-AS1 expression closely correlates with clinical features and poor prognosis and its expression has been shown to attenuate cell proliferation, cell migration, cell invasiveness, drug resistance, and the epithelial-mesenchymal transition through several pathways. Here, we provide an overview of the role of FGD5-AS1 in various cancers and discuss its potential clinical utility in tumor progression. In addition, we used a gene expression profiling interactive analysis dataset to explore associations between FGD5-AS1 pan-cancer expressions and prognoses.

Keywords: LncRNA, FGD5-AS1, mechanism, prognosis, clinical utility

Introduction

Cancers are complex diseases that are driven by many factors [1, 2], including changes in the transcriptome [3, 4], proteome [5, 6], and the metabolome [7, 8]. In addition, cancers still have high rates of morbidity and mortality [9-11], making them important public-health problems. Although cancer treatments have improved greatly in past years [12, 13], effective treatments for many cancers are still elusive. Therefore, further studies exploring cancer pathogenesis remain highly relevant.

Long non-coding RNAs (lncRNAs) have more than 200 nucleotides [14, 15], and are transcribed by RNA polymerase II [16]. When first identified, lncRNAs were considered to be transcriptional noise without biological functions [17-19]. However, a large literature has emerged recently supporting the idea that lncRNAs are important regulators of cancer progression for many solid tumors [20-24]. LncRNAs have been shown to affect cell proliferation, migration, and apoptosis by regulating gene expression at all levels: transcriptional, posttranscriptional, epigenetic, and by protein translation [25-27]. Several studies have also revealed that lncRNAs represent potential diagnostic biomarkers and targets for tumor treatments [28-30].

FGD5 antisense RNA 1 (FGD5-AS1), a novel lncRNA, was first identified in 2018 [31, 32]. Accumulating evidence has suggested that FGD5-AS1 is a functional factor in cancer, with up-regulated expression levels in several types of solid tumors. FGD5-AS1 expression has also been shown to be closely associated with several clinicopathologic features, indicating its possible use as a prognostic biomarker. Moreover, FGD5-AS1 has been shown to affect biological functions both by acting as a competing endogenous RNA (ceRNA) and by regulating other pathways. Here, we have summa-

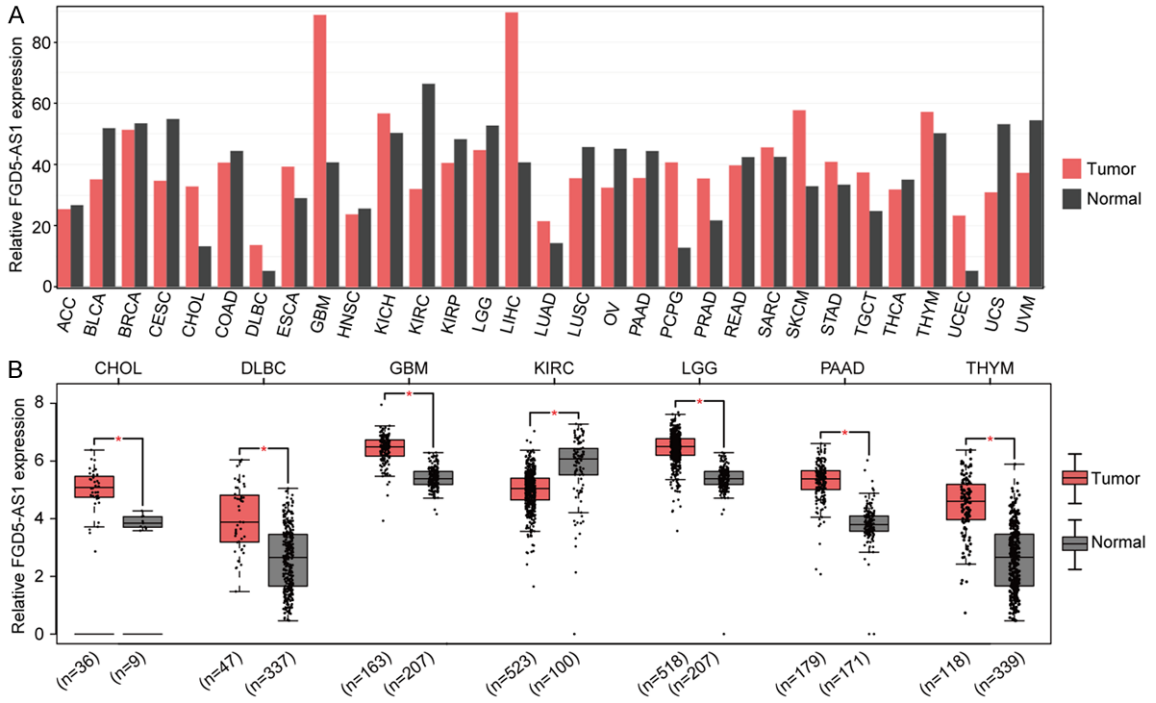

Figure 1. Pan-cancer expression patterns for lncRNA FGD5-AS1. A. FGD5-AS1 expression levels among 33 types of cancer and their paired normal tissues based on the gene expression profiling interactive analysis (GEPIA) dataset. B. High FGD5-AS1 expression levels were observed in CHOL, DLBC, GBM, LGG, PAAD, and THYM samples. However, decreased FGD5-AS1 expression was observed in KIRC samples.

Table 1. Clinical characters associated with FGD5-AS1 in different cancers

Type	Expression	Clinical characters	Refs
non-small cell lung cancer	upregulated	TNM stage, metastasis, and tumor sizes	[40, 41]
hepatocellular carcinoma	upregulated	overall survival	[65]
osteosarcoma	upregulated	tumor size, clinical stage, and 5-year survival rate	[64]
melanoma	upregulated	tumor thickness and tumor stage, overall survival, and disease-free survival	[66]
esophageal squamous cell carcinoma	upregulated	tumor size, TNM stage, lymph node metastasis, and overall survival	[61]

rized the literature related to the oncogenic roles and regulatory mechanisms of FGD5-AS1 in solid tumors and discuss its use for novel diagnostic and therapeutic strategies related to cancer.

Expression levels of FGD5-AS1 in different cancers

To systematically identify the expression of FGD5-AS1 in different cancers, we used the Gene Expression Profiling Interactive Analysis (GEPIA, http://gepia.cancer-pku.cn/) tool [32]. The results showed that FGD5-AS1 expression levels were dysregulated in many solid tumors (**Figure 1A**) and that it was significantly up-regulated in cholangiocarcinoma (CHOL) (**Figure 1B**). Similarly, significant increases in its expression were observed in lymphoma (DLBC), glioblastoma multiforme (GBM), brain low-grade glioma (LGG), pancreatic adenocarcinoma (PAAD), and thymoma (THYM). Interestingly, FGD5-AS1 expression was significantly down-regulated in kidney renal clear cell carcinoma (KIRC) (**Figure 1B**).

Clinical significance and functions of FGD5-AS1

Increasing evidence indicates that FGD5-AS1 plays crucial roles in cancer progression through demonstrated relationships between FGD5-AS1 expression and clinical significance (**Table 1**). Several studies have reported that FGD5-AS1 may be a prognostic biomarker for a variety of cancers. Below, we discuss the clinical significance and functions of FGD5-AS1 in different tumors (**Table 2**).

Table 2. Roles and functions of FGD5-AS1 in different cancers

Type	Role	Function	Refs
non-small cell lung cancer	oncogene	proliferation, viability, migration, invasion, autophagy, and EMT	[39-42]
hepatocellular carcinoma	oncogene	/	[65]
osteosarcoma	oncogene	viability, invasion, and apoptosis	[64]
melanoma	oncogene	/	[66]
glioma	oncogene	proliferation, migration, and invasion	[47]
glioblastoma	oncogene	proliferation, viability, migration, invasion, and tumor growth	[48, 49]
colorectal cancer	oncogene	proliferation, migration, invasion, and apoptosis	[67]
oral cancer	oncogene	proliferation, cell growth, migration, invasion, and apoptosis	[56, 57]
renal cell carcinoma	oncogene	proliferation, migration, EMT, and invasion	[68, 69]
esophageal squamous cell carcinoma	oncogene	proliferation, migration, invasion, apoptosis, and tumor growth	[61]
gastric cancer	oncogene	cancer proliferation, 5-FU chemoresistance, and tumorigenicity	[70]

Lung cancer

Lung cancer is a leading cause of cancer-related deaths in the world [33-35]. Many risk factors have been shown to contribute to it, including age, gender, race, environmental pollution, cigarette smoking, and pre-existing lung diseases [35, 36]. Non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer, accounting for approximately 85% of all lung cancer cases [37, 38].

FGD5-AS1 expression levels were found to be up-regulated in both NSCLC tissues and cells [39-41]. The levels of FGD5-AS1 have also been reported to be significantly correlated with many clinicopathologicfeatures (e.g., TNM staging, tumor size, and metastasis) [40, 41]. Elevated expression of FGD5-AS1 was correlated with a higher TNM stage, larger tumor size, and NSCLC metastasis. Furthermore, the up-regulation of FGD5-AS1 has been shown not only to accelerate cell proliferation, migration, invasiveness, and epithelial-mesenchymal transitions (EMTs) in NSCLC but also to increase cell viability in patients with NSCLC. Intriguingly, Fu et al. [42] reported that the expression of FGD5-AS1 was also increased in patients with cisplatin-resistant NSCLC. In addition, cell proliferation and motility were also found to be promoted by FGD5-AS1 expression, and FGD5-AS1 was reported to enhance cell autophagy in NSCLC by increasing the levels of both LC3-II/LC3-I and Beclin-1 protein, and by decreasing p62 expression. In contrast, the knockdown of FGD5-AS1 expression has been shown to inhibit tumor growth in patients with cisplatin-resistant NSCLC [42].

Glioma

Glioma is the most common type of primary intracranial tumor in the central nervous system [43, 44], and glioblastoma (GBM) represents the most common type of aggressive malignant glioma [45, 46]. FGD5-AS1 levels have been shown to be significantly up-regulated in both glioma tissue and cells [47], with similar findings in GBM tissue and cells [48, 49]. The down-regulation of FGD5-AS1 levels has been shown to attenuate proliferation capacity, invasiveness, and cell migration in both glioma and GBM, and both cell viability and colony-forming capacity were impaired as a result of FGD5-AS1 silencing [49]. In addition, FGD5-AS1 expression was positively correlated with tumor weights using *in vivo* studies for both glioma and GBM. Overall, these findings indicate that FGD5-AS1 functions as an oncogene and facilitates tumor progression in both glioma and GBM [47-49].

Oral cancer

Oral cancer (OC) continues to have a high mortality rate in head-and-neck cancer patients [50, 51], with oral squamous cell carcinoma (OSCC) being the most common type of oral cancer [52, 53]. Despite advances in clinical treatment, the prognosis of patients with OSCC remains poor [54, 55]. Several research groups have reported that FGD5-AS1 expression levels were markedly up-regulated in both OC tissues and cells [56, 57], and, FGD5-AS1 levels have been shown to be positively correlated with smoking, clinical staging, tumor staging, and tumor sizes in patients with OC [56]. Increased FGD5-AS1 expression has been re-

ported to significantly promote cell growth, migration, and invasiveness, while negatively inhibiting apoptosis in OC cells. In addition, xenograft studies using a nude-mouse model showed that FGD5-AS1 expression contributed OC tumor growth [56, 57].

Esophageal cancer

Esophageal cancer is the sixth most common cause of cancer-related death worldwide [58, 59], with esophageal squamous cell carcinoma (ESCC) being its most common type [60]. The search for effective treatments for esophageal cancer needs to continue. Gao et al. [61] observed that the expression of FGD5-AS1 was significantly increased in both ESCC tissues and cell lines. Moreover, FGD5-AS1 expression has been shown to be positively associated with tumor size, TNM staging, and lymph node metastasis, while being negatively associated with ESCC patient overall survival. Importantly, the silencing of FGD5-AS1 expression was shown to suppress cell proliferation, migration, and invasiveness in ESCC but promote cell apoptosis. Furthermore, *in vivo* experiments have demonstrated that FGD5-AS1 expression functioned to promote ESCC tumor growth [61].

Osteosarcoma

Osteosarcoma is the most frequent type of primary bone tumor, often occurring in children, adolescents, and young adults [62, 63]. Studies have reported that FGD5-AS1 levels in both serum and tissue were significantly elevated in patients with osteosarcoma [64], and that FGD5-AS1 might be used as a diagnostic biomarker for this type of cancer. In addition, FGD5-AS1 expression has been positively associated with both osteosarcoma tumor size and clinical staging, with increased serum and tissue expression levels being a poor predictor of prognosis. Biological functions, represented by measures of cell viability, invasiveness, and EMT capacity, have been reported to be enhanced by the up-regulation of FGD5-AS1 expression [64]. Therefore, FGD5-AS1 is also considered an oncogene for osteosarcoma tumorigenesis and progression.

Other cancer types

In addition to the above tumor types, studies have also found FGD5-AS1 expression levels to be significantly up-regulated in hepatocellular carcinoma [65], melanoma [66], colorectal cancer [67], renal cell carcinoma [68, 69], and gastric cancer [70]. Levels of FGD5-AS1 have been reported to be negatively associated with prognoses for both hepatocellular carcinoma [65] and melanoma [66], and FGD5-AS1 expression was found to be significantly correlated with both tumor thickness and advanced-tumor staging in melanoma [66]. Patients with lower FGD5-AS1 expression had higher overall survival and disease-free survival than patients with higher FGD5-AS1 expression in melanoma. Functionally, FGD5-AS1 has been shown to contribute to cell proliferation in colorectal cancer, renal cell carcinoma, and gastric cancer. Expression of FGD5-AS1 promoted cell proliferation and motility, and accelerated cell apoptosis in colorectal cancer [67], whereas knockdown of FGD5-AS1 inhibited cell proliferation, motility, and the EMT process in renal cell carcinoma [68]. Moreover, decreased FGD5-AS1 expression was shown to restrain chemoresistance to 5-FU in gastric cancer cells, and the up-regulation of FGD5-AS1 has been reported to promote the EMT process [70].

FGD5-AS1 regulatory mechanisms

FGD5-AS1 has been revealed to have important roles in both tumorigenesis and tumor development. It has been shown to affect tumor progression by regulating several pathways (**Figure 2**). In this section, we will summarize FGD5-AS1 regulatory mechanisms according to cell-biology functions in different cancers.

Cell proliferation

Cell proliferation is a fundamental characteristic of all organisms [71, 72], and this process becomes abnormal in many cancers [73, 74]. Growing evidence suggests that lncRNAs have fundamental roles in cellular proliferation related to cancer [22, 75, 76], and FGD5-AS1 has been shown to function as a ceRNA-type controller of this process. FGD5-AS1 has been reported to act as a ceRNA for hsa-miR-107 in NSCLC, resulting in accelerated cell proliferation through the increased expression of FGFRL1 [39] (**Figure 3**). Similarly, FGD5-AS1 has also been shown to promote NSCLC cell proliferation by regulating the miR-493-5p/DDX5 pathway [41], and its regulation of the miR-140-5p/WEE1 axis promoted cisplatin-resistant NSCLC cell proliferation but inhibited

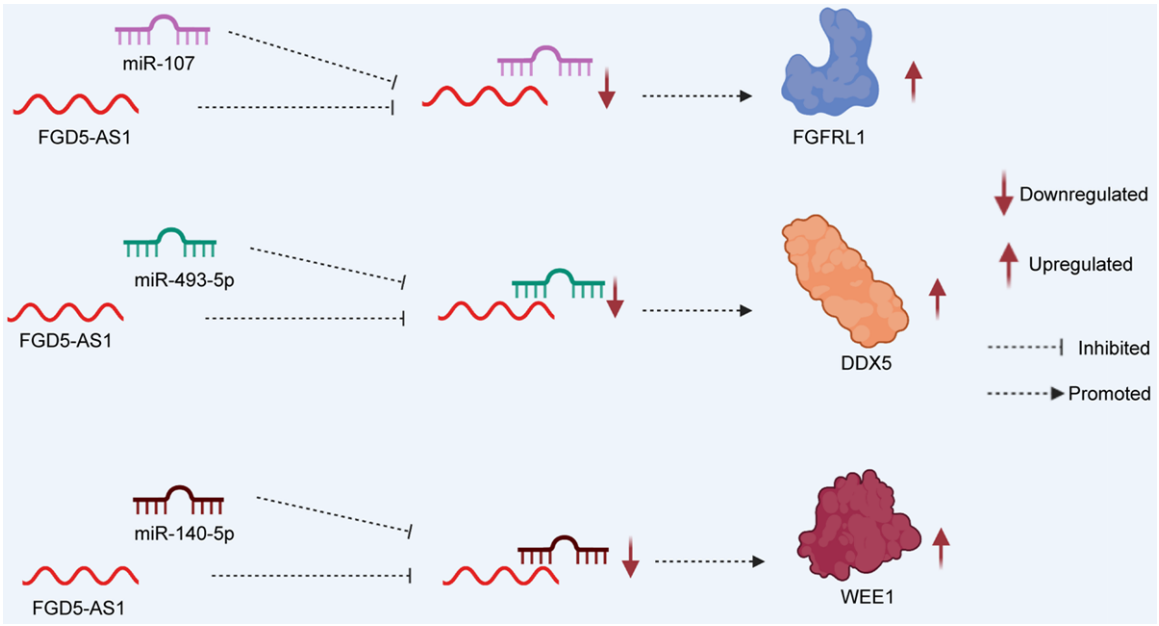

Figure 2. The regulatory mechanisms of FGD5-AS1 in lung cancer. FGD5-AS1 promoted NSCLC cell proliferation through a series of pathways, including the FGD5-AS1/miR-107/FGFRL1 pathway, the FGD5-AS1/miR-493-5p/DDX5 pathway, and the FGD5-AS1/miR-140-5p/WEE1 pathway. FGD5-AS1 increased the level of FGFRL1 by sponging miR-107. FGD5-AS1 also significantly downregulated miR-493-5p levels to promote the expression of DDX5 and enhanced the expression of WEE1 by sponging miR-140-5p.

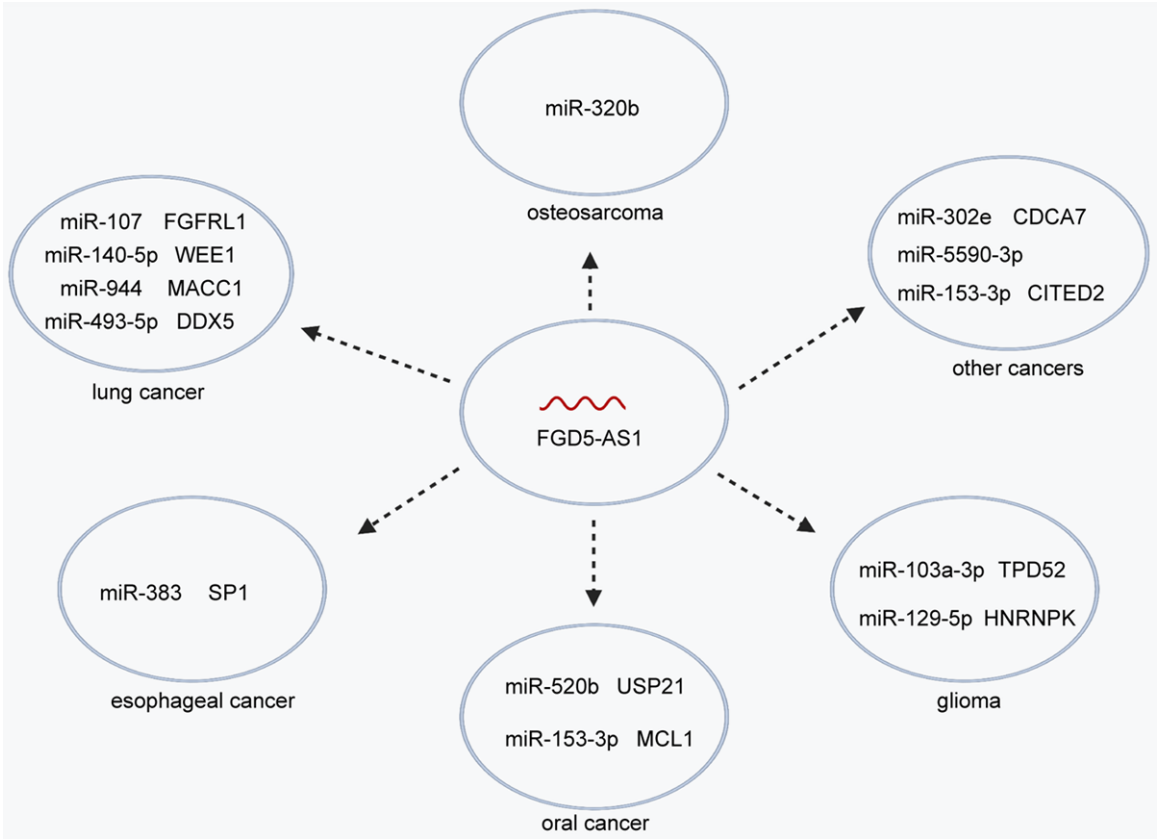

Figure 3. FGD5-AS1 interactions with target molecules in different cancers. FGD5-AS1 often acts as a competing endogenous RNA (ceRNA), contributing to cancer progression.

apoptosis [42] (**Figure 3**). In addition, FGD5-AS1 expression was reported to contribute to GBM cancer-cell proliferation through the down-regulation of HNRNPK by miR-129-5p sponging [49], and to promote GBM cell proliferation by regulating the Wnt/β-catenin pathway [47]. In colorectal cancer, FGD5-AS1 expression was shown to facilitate cancer-cell proliferation through the sponging of miR-302e to up-regulate CDCA7 expression [67], and in oral cancer [57], FGD5-AS1 was reported to attenuate the expression of miR-153-3p and up-regulate MCL1 to enhance cellular proliferation. Furthermore, cell proliferation in renal cancer was reportedly reduced by FGD5-AS1-inhibition of miR-5590-3p levels [68], although it was shown to promote cellular proliferation in ESCC by targeting miR-383 [61]. Similarly, cell proliferation in gastric cancer has been shown to be facilitated through the FGD5-AS1/miR-153-3p/CITED2 pathway [70].

Cell migration and invasiveness

A leading cause for the failure of cancer treatments is cancer metastasis [77]. The ability of cells to migrate and to invade other tissues has a direct effect on cancer metastasis [78, 79], and lncRNAs have been found to be significantly associated with cancer-cell capacities for both migration and invasiveness [80-82]. FGD5-AS1 has been shown to promote cell migration and cell invasion using several molecular pathways. In NSCLC, the down-regulation of FGD5-AS1 reduced migration and invasiveness by its action as a ceRNA for miR-944 [40], thereby increasing MACC1 expression. FGD5-AS1 was also shown to promote NSCLC cell migration and invasiveness by lowering the expression of miR-493-5p and up-regulating the level of DDX5 [41]. In cisplatin-resistant NSCLC cells, FGD5-AS1 was also reported to promote migration and invasiveness through the modulation of the miR-140-5p/WEE1 axis [42]. In osteosarcoma cells, FGD5-AS1 expression was shown to down-regulate the expression levels of miR-320b, which facilitated both cell migration and invasiveness [64]. In addition, FGD5-AS1 expression was reported to accelerate cell migration and invasiveness by activating the Wnt/β-catenin pathway in both glioma and GBM [47, 49]. In the case of GBM, FGD5-AS1 expression reduced miR-130-3p levels, resulting in increased TPD52 levels and the promotion of cell migration and invasiveness [48]. In colorectal cancer, FGD5-AS1 was shown to act as a ceRNA for miR-302e, thereby enhancing cell migration and invasiveness by up-regulating CDCA7 [67]. Cell invasiveness was also reported to be enhanced through the FGD5-AS1/miR-520b/USP21 and FGD5-AS1/miR-153-3p/MCL1 pathways in oral cancer [56, 57]. In renal cell carcinoma, FGD5-AS1 expression accelerated cell migration and invasiveness by activating ERK/AKT signaling via the sponging of miR-5590-3p [68], and in ESCC, FGD5-AS1 expression promoted tumor metastasis by inhibiting miR-383 levels and thereby up-regulating the expression of SP1 [61].

Chemoresistance and the epithelial-mesenchymal transition (EMT)

Although chemotherapy treatments are well-established for tumors [83, 84], drug resistance has reduced chemotherapy efficacy [85-87]. Therefore, determining the mechanisms responsible for tumor resistance will be very important for the future of clinical tumor treatment. In gastric cancer, Gao et al. found that elevated levels of FGD5-AS1 increased cell chemoresistance to 5-FU [70], and in NSCLC, the expression of FGD5-AS1 increased cisplatin resistance through by modulating the miR-140-5p/WEE1 pathway [42]. This not only provides guidance for potential clinical therapies, but also provides new insight into potential therapeutic targets for both gastric cancer and NSCLC.

EMT, the transdifferentiation process whereby epithelial cells become motile mesenchymal cells [88, 89], is known to be crucial for many biological processes, including embryonic development, fibrosis, and tumor progression [90-92]. In NSCLC, FGD5-AS1 expression was found to promote the EMT process by increasing the expression level of DDX5 through miR-493-5p sponging [41], and in renal cancer, FGD5-AS1 was reported to inhibit the expression of miR-5590-3p, thereby activating the ERK/AKT pathway to facilitate the EMT process [68].

The potential clinical utility of FGD5-AS1

Above, we have summarized the regulatory mechanisms, clinical significance, and func-

tions of FGD5-AS1 for different tumors, highlighting its potential for clinical use. Below, we discuss the potential clinical utility of FGD5-AS1 for cancer diagnosis, prognosis, and therapy.

FGD5-AS1 as a diagnostic biomarker

Diagnostic biomarkers have become important and gained attention because they offer the promise of early diagnosis for tumors and may improve patient prognoses [93-95]. FGD5-AS1 is such a promising biomarker for cancer diagnosis. FGD5-AS1 has been shown to be significantly up-regulated in NSCLC [39-42], hepatocellular carcinoma (HCC) [65], osteosarcoma [64], melanoma [66], glioma [47], GBM [48, 49], colorectal cancer [67], oral cancer [56, 57], renal cell carcinoma [68, 69], ESCC [61], and gastric cancer [70]. This was especially true for the significantly elevated serum levels of FGD5-AS1 from patients with osteosarcoma compared to serum levels from normal controls [64]. In addition, FGD5-AS1 expression has been shown to be significantly correlated with both TNM and clinical staging [40, 61, 64, 66], which may help to assess clinical severity in patients with tumors. However, the clinical application of FGD5-AS1 levels for diagnostic use still requires more basic and clinical research support.

FGD5-AS1 as a prognosis predictor

Current evidence suggests that lncRNAs significantly correlated with tumor-patient prognoses could be used as biomarkers for prognosis [76, 96]. Up-regulated FGD5-AS1 expression has been positively associated with poor prognoses (e.g., in HCC [65], osteosarcoma [64], melanoma [66], and ESCC [61]) and predicted shorter patient overall survival for HCC [65], melanoma [66], and ESCC [61]. FGD5-AS1 expression levels were also negatively correlated with 5-year survival rates in patients with osteosarcoma [64]. Using a multivariate analysis of melanoma data, the FGD5-AS1 expression level was determined to be an independent risk factor for both overall survival prognosis and disease-free survival [66].

Using the GEPIA online tool, we explored other associations between FGD5-AS1 expression levels and patient prognoses in several cancers [97]. The expression of FGD5-AS1 was significantly associated with prognoses for KIRC, liver hepatocellular carcinoma (LIHC), GBM, and for mesothelioma (MESO). For KIRC, decreased levels of FGD5-AS1 predicted shorter overall patient survival (**Figure 4A**), while high FGD5-AS1 expression was positively correlated with overall survival in LIHC patients (**Figure 4B**). In addition, its expression level was negatively correlated with disease-free survival in both GBM and KIRC (**Figure 4C** and **4D**). In contrast, up-regulated FGD5-AS1 expression was associated with shorter disease-free survival in both ACC and MESO [97] (**Figure 4E** and **4F**).

FGD5-AS1 as a therapeutic target

As FGD5-AS1 expression has been shown to affect carcinogenesis by regulating a variety of molecular pathways, this suggests that it may also be a therapeutic target for cancer treatments. FGD5-AS1-mediated regulation of biological functions is known to occur via many pathways in different cancers, including the hsa-miR-107/FGFRL1 [39], miR-493-5p/DDX5 [41], miR-140-5p/WEE1 [42], miR-129-5p/HNRNPK [49], Wnt/β-catenin [47], miR-302e/CDCA7 [67], and the miR-153-3p/MCL1 pathways [57]. In addition, the observation that up-regulated FGD5-AS1 expression also promoted cellular chemoresistance to 5-FU in gastric cancer may guide its future treatment [70]. Furthermore, as FGD5-AS1 has been shown to function as an oncogene in NSCLC [39, 42], HCC [65], osteosarcoma [64], melanoma [66], glioma [47], GBM [48, 49], colorectal cancer [67], oral cancer [56], renal cell carcinoma [68, 69], ESCC [61], and gastric cancer [70], its down-regulation could be used to block tumor progression for these cancers. For NSCLC, in vivo studies found that FGD5-AS1 knockdown attenuated tumor growth in cisplatin-resistant NSCLC [42], and in osteosarcoma [64], decreased both FGD5-AS1 expression and cell viability and invasiveness. For GBM, FGD5-AS1 silencing resulted in reduced cell viability, colony-forming capacity, cell proliferation, invasiveness, and promoted apoptosis [49].

Conclusions and future perspectives

FGD5-AS1, first identified in 2018, has emerged as a crucial factor in both tumorigenesis and tumor development. The expression levels of FGD5-AS1 have been shown to be significantly up-regulated in NSCLC, HCC, osteosar-

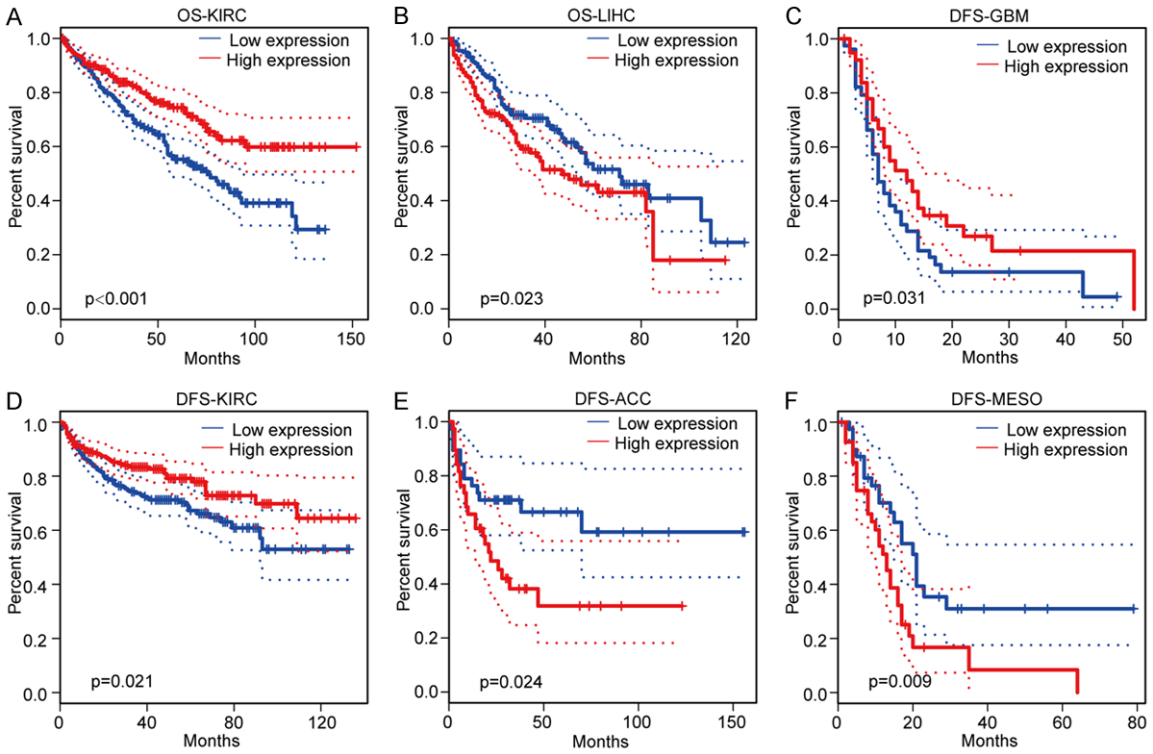

Figure 4. Pan-cancer prognostic predictions using FGD5-AS1 levels. A. KIRC patients with high FGD5-AS1 expressions had better overall survival (OS) times (P<0.001). B. LIHC patients with low FGD5-AS1 expressions had better OS times (P=0.023). C and D. Both GBM and KIRC patients with high FGD5-AS1 expressions had better disease-free survival (DFS) times (GBM, P=0.031; KIRC, P=0.021). E and F. Both ACC and MESO patients with low FGD5-AS1 expressions had better DFS times (ACC, P=0.024; MESO, P=0.009).

coma, melanoma, glioma, GBM, colorectal cancer, oral cancer, renal cell carcinoma, ESCC, and gastric cancer. In addition, FGD5-AS1 expression has been closely correlated with clinical features, including tumor size, tumor thickness, clinical staging, TNM staging, and metastasis. Moreover, FGD5-AS1 levels have been positively correlated with poor prognosis in HCC, osteosarcoma, melanoma, and ESCC. FGD5-AS1 expression is known to regulate cell proliferation, migration, invasiveness, drug resistance, and EMT by modifying different pathways, including the hsa-miR-107/FGFRL1 pathway, the Wnt/β-catenin pathway, the miR-302e/CDCA7 pathway, and miR-520b/USP21 pathway in different cancers. However, the specific regulatory mechanisms underlying the functions of FGD5-AS1 remain to be elucidated. FGD5-AS1 has also been shown to have an oncogenic role in tumor progression, and its down-regulation could be used to block the processes that promote carcinogenesis in these tumors. As a promising biomarker, FGD5-AS1 levels may also be used for cancer diagnosis and for predicting their prognoses, especially for the early diagnosis of tumors. However, these FGD5-AS1 clinical applications will require further systematic studies.

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Disclosure of conflict of interest

None.

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