Angiogenic Factor with G Patch and FHA Domains 1 (AGGF1) Acts as Diagnostic Biomarker and Adverse Prognostic Factor of Hepatocellular Carcinoma (HCC): Evidence from Bioinformatic Analysis

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Material/Methods: The mRNA sequencing datasets and clinical features of HCC patients were extracted from The Cancer Genome Atlas database. The relationship between clinical features and AGGF1 expression was analyzed by Wilcoxon test. Further validation explorations were carried out using online database Oncomine. The diagnostic receiver operating characteristic curves of AGGF1 and alpha-fetoprotein were compared to examine the diagnostic efficacy of AGGF1. Survival analysis and Gene Set Enrichment Analysis were performed to explore the prediction value and potential mechanism of AGGF1 dysregulation in HCC.

Results: Comprehensive overexpression of AGGF1 was observed in HCC, correlating with poor overall survival. Upregulated level of AGGF1 was statistically associated with poor differentiated histological grade, advanced cancer stage and T classification. AGGF1 was a more effective diagnostic marker than alpha-fetoprotein in HCC. Several important pathways related to HCC including pathway in cancer and P53 signaling pathway were differentially enriched in the high AGGF1 expression phenotype.

Conclusions: AGGF1 was a potential diagnostic and prognostic marker for poor clinical outcomes in HCC patients. Moreover, vital pathways regulated by AGGF1 in HCC may include regulation of autophagy, Wnt signaling pathway, pathway in cancer, cell cycle, and P53 signaling pathway.

MeSH Keywords: Biological Markers • Carcinoma, Hepatocellular • Prognosis

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/919896
Background

Liver cancer accounts for a sixth of new neoplasm cases and a third of cancer-related mortality cases worldwide, with estimated 841,000 cases diagnosed and 781,000 deaths in 2018 [1]. Hepatocellular carcinoma (HCC), which usually occurs in patients with chronic liver disease, is the most predominant pathological type of liver cancer. HCC is usually diagnosed at the advanced stage; the 5-year overall survival (OS) rate of HCC is 10% for locally advanced and 3% for metastatic, respectively [2].

Angiogenesis plays a critical role in cancer growth and progression. As a hyper-vascularized tumor, the aggressive and metastatic features of HCC lead to poor clinical outcomes [2]. Angiogenic factor with G-patch and FHA domain 1 (AGGF1) is a novel pro-angiogenic factor that was initially characterized in Klippel-Trenaunay syndrome [3]. A previous study showed that AGGF1 was upregulated in HCC [4], while its potential roles as diagnostic and prognostic marker for HCC still need to be elucidated.

In this current study, we utilized the The Cancer Genome Atlas (TCGA) database to compare AGGF1 mRNA expression between HCC tumor tissues and adjacent tissues. We also attempted to explore the relationship between the expression of AGGF1 mRNA and clinical features and OS of HCC patients. Subsequently, we verified the credibility in Oncomine ([https://www.oncomine.org/](https://www.oncomine.org/)). Furthermore, Gene Set Enrichment Analysis (GSEA) was performed to identify the signaling pathways which would be involved in HCC.

Material and Methods

Collection of RNA-sequencing data and bioinformatics analysis

We firstly explored the expression and distribution of AGGF1 among different cancer tissues using GEPIA database ([http://gepia.cancer-pku.cn/](http://gepia.cancer-pku.cn/)) [5]. To create the data set, transcriptome profiling of The Cancer Genome Atlas Liver Hepatocellular Carcinoma (TCGA-LIHC) including 374 tumor and 50 adjacent normal samples were downloaded from the webserver ([https://portal.gdc.cancer.gov/](https://portal.gdc.cancer.gov/)), Workflow Type: HTSeq-FPKM, accessed on July 20, 2019). The corresponding survival and clinic profiles were also obtained from TCGA Data Portal with a total of 377 HCC patients. The clinical and AGGF1 mRNA expression matrix information were matched by sample ID. Oncomine is an online genome-wide expression cancer microarray database [6]. In order to further verify the TCGA analysis results, we conducted Oncomine exploration.

### Table 1. The Clinical Characteristics of HCC Patients from TCGA.

| Clinical characteristics | Total (%) | N=377 |
|-------------------------|-----------|-------|
| Age(y)                  |           |       |
| ≤60                     | 180       | (47.7) |
| >60                     | 196       | (52.0) |
| Unavailable             | 1         | (0.3)  |
| Gender                  |           |       |
| Female                  | 127       | (32.4) |
| Male                    | 255       | (67.6) |
| Follow-up state         |           |       |
| Living                  | 249       | (66.0) |
| Dead                    | 128       | (34.0) |
| Grade                   |           |       |
| G1                      | 55        | (14.6) |
| G2                      | 189       | (47.7) |
| G3                      | 124       | (32.9) |
| G4                      | 13        | (3.4)  |
| Unavailable             | 5         | (1.3)  |
| Stage                   |           |       |
| I                       | 175       | (46.4) |
| II                      | 87        | (23.1) |
| III                     | 86        | (22.8) |
| IV                      | 5         | (1.3)  |
| Unavailable             | 24        | (6.4)  |
| T                       |           |       |
| T1                      | 185       | (49.1) |
| T2                      | 95        | (25.2) |
| T3                      | 81        | (21.5) |
| T4                      | 13        | (3.4)  |
| TX                      | 1         | (0.3)  |
| Unavailable             | 2         | (0.5)  |
| N                       |           |       |
| N0                      | 257       | (68.2) |
| N1                      | 4         | (1.1)  |
| NX                      | 115       | (30.5) |
| Unavailable             | 1         | (0.3)  |
| M                       |           |       |
| M0                      | 272       | (72.1) |
| M1                      | 4         | (1.1)  |
| MX                      | 101       | (26.8) |

HCC – hepatocellular carcinoma; TCGA – The Cancer Genome Atlas.

Due to the datasets used in our study were public and available online, Ethical approval and informed consent are not required.

Gene Set Enrichment Analysis (GSEA)

In our study, the genomic expression profiles of 374 HCC samples were classified into high (n=187) and low (n=187) subgroups based on the median value of AGGF1 mRNA expression. GSEA, a computational approach determines statistically significant, concordant differences of a priori defined set of
genes, was carried out between the 2 subgroups [7]. The version of GSEA software was v3.0. Gene set permutations were performed 1000 times for each analysis. Enrichment results with a P-value <0.05 and false discovery rate (FDR) <0.25 were considered statistically significant.

Statistical analysis

The statistical analyses and plots were conducted using R (version 3.5.2) and SPSS (version 23.0) software. Differences in AGGF1 mRNA expression levels between adjacent and tumor tissues were assessed by using Wilcoxon signed-rank test, as well as the adjacent and paired tumor tissues. The receiver operating characteristic (ROC) curve was drawn to determine the diagnostic significance of AGGF1. The relationship between AGGF1 and clinical features were analyzed with Wilcoxon or Kruskal-Wallis test. Univariate and multivariate Cox regression analysis were performed to verify the association between AGGF1 expression and survival along with other clinical features. P value less than 0.05 was considered statistically significant.
Results

Characteristics of the study population from TCGA

As shown in Table 1, a total of 377 HCC patients were obtained from TCGA database, including 255 male patients and 122 female patients. The average age at diagnosis was 59.5 years (±13.5 years) with a 34% death rate in the last follow-up. The median time of the follow-up for patients was 19.2 months. In the TCGA cohort, the histopathologic distribution ranges from well, moderately, poorly differentiated to undifferentiated, also known as G1, G2, G3, and G4, respectively. The information of TNM stage and classification were also emerged below.
Associations between AGGF1 mRNA expression and clinical variables

Compared to normal tissues, AGGF1 mRNA expression was upregulated in multiple cancer tissues distributed in the body map (Figure 1A). In addition, we analyzed AGGF1 mRNA levels across different tumor samples paired with normal tissues (Figure 1B). A higher AGGF1 was observed in major tumors including breast invasive carcinoma (BRCA), cholangiocarcinoma (CHOL), glioblastoma multiforme (GBM), liver hepatocellular carcinoma (LIHC), and pancreatic adenocarcinoma (PAAD). Surprisingly, the expression of AGGF1 is lower in liver than other normal organs (Figure 1B). Also, as shown in Figure 2A, expression levels of AGGF1 were significantly higher in 374 TCGA HCC samples compared to 50 adjacent normal samples (P<0.001). The results coincided well with the data obtained from comparing 50 HCC cases to corresponding adjacent tissues (P<0.001, Figure 2B). Four different datasets (Chen liver [8], Roessler liver [9], Roessler liver 2 [9], and Wurmbach liver [10]) came to the same conclusion after comprehensive online analysis in Oncomine (P=0.002, Figure 2C). Oncomine analysis of HCC versus normal tissue also showed that AGGF1 was significantly overexpressed.

Alpha-fetoprotein (AFP) is the most widely used biomarker in screening and diagnosing HCC [11]. However, we need more efficient biomarkers for HCC diagnosis. To explore the diagnostic efficacy of AGGF1, we plotted the diagnostic ROC curve of AGGF1. Meanwhile, the diagnostic efficacy of AGGF1 was compared with that of AFP. The area under the curve (AUC) of AGGF1 was 0.873 (95% confidence interval [CI]: 0.836–0.909), which is significantly larger than AFP with an AUC value 0.705 (95% CI: 0.653–0.758). We further discussed the diagnostic efficiency of AGGF1 combined with AFP. The AUC value of the combined diagnosis was 0.929 (95% CI: 0.902–0.955) (P<0.05, Figure 2D). A more effective diagnosis was shown in the combined factors than either of AGGF1 and AFP (P<0.05). We finally compared the diagnostic efficacy of AGGF1 and AFP with other conditions such as age, gender, follow-up status, histological grade, cancer stage, TNM classification T, N, M, prognosis.
Figure 4. The association between AGGF1 expression and tumor grade (A), hepatitis virus infection status (B), satellites (C) and vascular invasion (D) in Oncomine Wurmbach Liver. AGGF1 – angiogenic factor with G patch and FHA domains 1.

Table 2. Univariate and multivariate analysis of AGGF1 expression and clinical parameters with OS among HCC patients.

| Parameters     | Univariate analysis |            |            |            | Multivariate analysis |            |            |
|----------------|---------------------|------------|------------|------------|-----------------------|------------|------------|
|                | HR                  | 95% CI     | p-Value    | HR          | 95% CI                | p-Value    |            |
| Age            | 1.01                | 1.00–1.03  | 0.177      |             |                       |            |            |
| Gender         | 0.82                | 0.56–1.21  | 0.317      |             |                       |            |            |
| Grade          | 1.12                | 0.87–1.45  | 0.382      |             |                       |            |            |
| Stage          | 1.67                | 1.36–2.06  | 1.12E-06   | 1.22        | 0.55–2.74             | 0.621      |            |
| T              | 1.65                | 1.36–2.01  | 5.82E-07   | 1.34        | 0.62–2.88             | 0.453      |            |
| AGGF1          | 1.14                | 1.04–1.26  | 0.008      | 1.11        | 1.01–1.22             | 0.038      |            |

HR – hazard ratio; CI – confidence interval; AGGF1 – angiogenic factor with G patch and FHA domains 1; OS – overall survival; HCC – hepatocellular carcinoma.
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Table 3. Gene sets enriched in the high AGGF1 expression phenotype.

| MSigDB collection          | Gene set name                              | ES   | NES   | NOM p-val | FDR q-val |
|----------------------------|--------------------------------------------|------|-------|-----------|-----------|
| c2.cp.kegg.v6.2.symbols    | KEGG_REGULATION_OF_AUTOPHAGY               | 0.654| 2.054 | <0.001    | 0.003     |
|                            | KEGG_TGF_BETA_SIGNALING_PATHWAY            | 0.643| 2.016 | <0.001    | 0.002     |
|                            | KEGG_WNT_SIGNALING_PATHWAY                 | 0.591| 2.007 | 0.002     | 0.002     |
|                            | KEGG_MTOR_SIGNALING_PATHWAY                | 0.644| 2.005 | <0.001    | 0.002     |
|                            | KEGG_PATHWAYS_IN_CANCER                    | 0.567| 1.983 | <0.001    | 0.003     |
|                            | KEGG_CELL_CYCLE                            | 0.684| 1.979 | <0.001    | 0.002     |
|                            | KEGG_P53_SIGNALING_PATHWAY                 | 0.584| 1.908 | <0.001    | 0.006     |
|                            | KEGG_MAPK_SIGNALING_PATHWAY                | 0.526| 1.890 | <0.001    | 0.006     |
|                            | KEGG_APOPTOSIS                              | 0.596| 1.882 | <0.001    | 0.007     |

ES – enrichment score; NES – normalized ES; NOM P-val – normalized P-value; AGGF1 – angiogenic factor with G patch and FHA domains 1. Gene sets with NOM P-value <0.05 and FDR q-value <0.05 were considered as significantly enriched.

The outcomes of the univariate and multivariate Cox regression analysis to explore potential prognostic risk factors were presented in Table 2. Univariate analysis revealed that later clinical cancer stage, worse TNM classification T and high level of AGGF1 are associated with a shorter OS of HCC patient (P<0.05). To further validate whether the 3 aforementioned factors can independently predict the prognosis of HCC, a multivariate Cox analysis was performed. The final results suggested that over-expression of AGGF1 was an independent risk factor for OS among HCC patients (HR=1.11, 95% CI: 1.01–1.22, P=0.038).

AGGF1-related signaling pathways identified using GSEA

As amount of dysregulated signaling pathways were responsible for tumorigenesis, a high AGGF1 mRNA level accompanied with lower survival probability may refer to a number of signaling pathways abnormally activated or inhibited by AGGF1 in HCC. We tried to elucidate the function of the AGGF1 via GSEA analysis between high and low AGGF1 expression data-sets. GSEA revealed significant differences (FDR q-val <0.05, normalized P<0.05) of many pathways observed in enrichment of MSigDB Collection (c2.cp.kegg.v6.2.symbols). The most significantly enriched signaling pathways were shown in Table 3 and Figure 5. Among these curated KEGG pathways, carcinogenesis and development associated, such as “regulation of autophagy”, “Wnt signaling pathway”, “pathway in cancer”, “cell cycle”, and “P53 signaling pathway” were differentially enriched in the high AGGF1 expression phenotype.

Discussion

The pathogenesis of HCC is complex. The main recognized causes are chronic hepatitis virus infection, alcohol abuse injury, aflatoxin poisoning, nonalcoholic fatty liver disease, gene dysregulation, and cell dysplasia [12]. Despite accumulating achievements in treatment, the OS of HCC is still dismal [13]. In recent years, biomarkers for diagnosing and predicting patient outcome came into blossom. AFP, a well-known biomarker different HCC stages (Figure 2E, 2F), and the results were stable and consistent with the previous results. The high diagnostic AUC value implies that AGGF1 can effectively distinguish HCC tissue from non-tumor and the combined diagnostic model of AGGF1 and AFP was the best.

Following these initial results, we then investigated the relationship between the AGGF1 mRNA expression and the clinical characteristics of HCC patients based on TCGA cohort (Figure 3). Statistic differences in AGGF1 expression were observed according to histological grade, cancer stage, and TNM classification T (P<0.05, Figure 3D–3F). Moreover, in the Oncomine Wurmbach liver cohort, higher mRNA levels of AGGF1 were associated with worse tumor grade, positive hepatitis virus infection, satellites and vascular invasion (Figure 4).

Prognostic valuation of AGGF1 for HCC

To evaluate the relationship between AGGF1 level and prognosis of HCC, a Kaplan-Meier survival analysis was performed in TCGA total cases (Figure 3I). The data revealed that higher mRNA expression levels of AGGF1 exhibited significantly poor OS than the lowers in HCC. We tried to elucidate the function of the AGGF1 via GSEA analysis between high and low AGGF1 expression data-sets. GSEA revealed significant differences (FDR q-val <0.05, normalized P<0.05) of many pathways observed in enrichment of MSigDB Collection (c2.cp.kegg.v6.2.symbols). The most significantly enriched signaling pathways were shown in Table 3 and Figure 5. Among these curated KEGG pathways, carcinogenesis and development associated, such as “regulation of autophagy”, “Wnt signaling pathway”, “pathway in cancer”, “cell cycle”, and “P53 signaling pathway” were differentially enriched in the high AGGF1 expression phenotype.
for HCC is widely applied in the clinic. However, its value in diagnosis and prognosis remains controversial [14]. Therefore, seeking new efficient biomarkers for HCC diagnosis and prognosis is urgently needed.

Previous studies reported that the pro-angiogenic factor AGGF1 was a tumor promoting factor of colorectal cancer through affecting Wnt/β-catenin signaling pathway [15,16]. Since then, a few tentative studies were carried out to investigate the role of AGGF1 in cancer [17–20]. Immunohistochemistry was performed in HCC and para-carcinomatous tissues in 2 separate studies [17,18]. The samples of both cohorts were small and protein levels of AGGF1 were expressed in semi-quantitative data, which could cause potential result bias. Our study firstly explored the expression and prognostic value of AGGF1 in HCC at the level of gene transcription with a large cohort.

Using online available datasets, we showed that the expression of AGGF1 in HCC was significantly different from that in normal cases. As for the phenomenon that lower expression

**Figure 5.** Enrichment plots from the GSEA in TCGA HCC. Several pathways and biological processes were differentially enriched in high (AGGF1) expression HCC. ES – enrichment score; NES – normalized ES; NOM

- **Enrichment plot: KEGG REGULATION OF AUTOPHY**
- **Enrichment plot: KEGG TGF-β SIGNALING PATHWAY**
- **Enrichment plot: KEGG WNT SIGNALING PATHWAY**
- **Enrichment plot: KEGG MITO SIGNALING PATHWAY**
- **Enrichment plot: KEGG PATHWAY IN CANCER**
- **Enrichment plot: KEGG MAPK SIGNALING PATHWAY**
- **Enrichment plot: KEGG APOPTOSIS**
- **Enrichment plot: KEGG TGF BETA SIGNALING PATHWAY**
- **Enrichment plot: KEGG CELL CYCLE**
- **Enrichment plot: KEGG P53 SIGNALING PATHWAY**
- **Enrichment plot: KEGG TGF-β SIGNALING PATHWAY**

- **Enrichment plot: KEGG REGULATION OF AUTOPHY**
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- **Enrichment plot: KEGG APOPTOSIS**
- **Enrichment plot: KEGG TGF BETA SIGNALING PATHWAY**
- **Enrichment plot: KEGG CELL CYCLE**
- **Enrichment plot: KEGG P53 SIGNALING PATHWAY**

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of AGGF1 in liver than other organs irrespective of the presence of cancer, we think it may be due to different sequencing platforms or tissue heterogeneity. AGGF1 RNA-seq profiles from TCGA and Oncomine were analyzed and revealed that high expression was positively correlated with malignant phenotype of HCC, including neoplasm histologic grade, cancer stage, satellites, vascular invasion, and survival. A negative result seen in stage N/M may be due to the single sample size of patients with lymph nodes and distant metastasis. Our result also showed a significant diagnostic value for HCC (AUC=0.873) which has not been reported previously. The diagnostic value of AGGF1 was higher than AFP (AUC=0.705, P<0.05). Furthermore, the striking value was achieved when we used the AGGF1 and AFP together to diagnose HCC. The results were still consistent and stable according to HCC staging. We first showed that AGGF1 was a useful biomarker for HCC diagnosis better than AFP, and we showed that combining AGGF1 with AFP should be utilized to diagnose HCC in clinic in the future.

Further Kaplan-Meier survival analysis showed that higher AGGF1 expression accompanied with a significantly decreased OS. The potential mechanism may be that AGGF1 influences the signaling pathway such as “regulation of autophagy”, “Wnt signaling pathway” and “pathway in cancer” etc, as GSEA identified. Our current study implied a correlation between HCC outcome and AGGF1. As a result, it may be a new potential biomarker for predicting prognosis of HCC.

A previous study showed that AGGF1 activated autophagy in a myocardial infarction model, which played an essential role in therapeutic angiogenesis [21]. The result of GSEA also showed the signaling pathway such as “regulation of autophagy”, “Wnt signaling pathway”, “pathway in cancer” etc, as GSEA identified. Our current study implied a correlation between HCC outcome and AGGF1. As a result, it may be a new potential biomarker for predicting prognosis of HCC.

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Conclusions
In conclusion, the present study was designed to identify whether AGGF1 was involved in the carcinogenesis or progression of HCC. AGGF1 has a high diagnostic and prognostic value for HCC together with AFP. Pathway in cancer, PS3 signaling pathway, etc., may act as vital pathways regulated by AGGF1 in HCC. Nevertheless, due to the limitations in our study design, the predictive value of AGGF1 in protein levels could not be clearly assessed. Further studies are needed to elucidate the biological function of AGGF1 in HCC.

Conflicts of interest
None.
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