Comprehensive Analysis of Prognostic Significance and Immune Infiltration for FAM83 Family in Cervical Cancer

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Primary research

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Abstract

**Background:** This study aimed to explore the expression of Family with sequence similarity 83 (FAM83) members in cervical cancer, its prognostic value, related signaling pathways, regulatory mechanisms, and immune infiltration. It's of great value to explore the potential role of FAM83 family in cervical cancer and provide a new scientific basis for targeted therapy.

**Methods:** The expression, gene mutations and prognostic value of FAM83 family members in cervical cancer were analyzed by various bioinformatics tools and databases. We further explored the interaction regulation network and immune infiltration between FAM83 family members and their closely related genes through a series of databases. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes pathways (KEGG) enrichment were also conducted.

**Results:** This study showed that the expression levels of FAM83A/B/C/D/E/F/G/H gene were upregulated in cervical cancer, the expression of FAM83B/C/D/E/F/G/H were related to tumor stages of cervical cancer, and the promoter methylation of FAM83A/D/E/F/G genes in cervical cancer were lower than those in normal tissues. What's more, high expression of FAM83A, FAM83B, and FAM83H mRNA was associated with shortened overall survival. GO results showed that FAM83A, FAM83B, and FAM83H and their closely related genes can play an important role in cell-cell junction, calcium-dependent protein binding, regulation of peptidase activity, inflammatory response. KEGG analysis results showed that FAM83A, FAM83B, and FAM83H and their closely related genes were significantly enriched in cancer pathways, estrogen signaling pathway, MAPK signaling pathway. Furthermore, FAM83A, FAM83B, and FAM83H are all closely related to lymphocytes (Tcm_CD4, Tcm_CD8, and neutrophils) and immunomodulators (TGFB1, TGFB1, and TNFSF9).

**Conclusions:** With multiple databases, we found that the high expression of FAM83A, FAM83B, and FAM83H were associated with the shortened survival time and poor prognosis in patients with cervical cancer, and also closely correlated with lymphocytes and immune infiltration, suggesting that FAM83A, FAM83B, and FAM83H played an important role in the occurrence, development, malignant biological behavior, and immune infiltration of cervical cancer, which provides an important theoretical basis for early diagnosis and targeted therapy for cervical cancer.

Background

Cervical cancer is one of the common malignant tumors in women worldwide, its incidence ranks first among malignant tumors of the female reproductive system in China, and is the most common cause of death in patients with gynecological malignancies \[^1\]. The risk factors for cervical cancer include long-term persistent high-risk HPV infection, smoking, long-term oral contraceptives, and immunosuppression. With the development of cervical cancer screening and vaccines, the incidence and mortality rate of cervical cancer in developed countries has declined significantly \[^2-3\]. However, about 80% of new cases and 85% of deaths occur in developing countries, where 70% of patients were already in the advanced
stage at the time of diagnosis. Therefore, the prevention, diagnosis, and treatment of cervical cancer remain the focus of researchers’ attention.

The Family with sequence similarity 83 (FAM83) has eight protein family members, which all contain highly conserved N-terminal protein domains with unknown functions, named the DUF1669 domain, and no other significant similar sequences have been found outside the DUF1669 domain. They were classified and named FAM83A-H according to the conservation of this domain, and the C-terminus of each FAM83 family member is composed of non-spherical disordered sequences. Studies have shown that FAM83 family proteins bind to CK1 through the DUF1669 domain and regulate the activity of isoenzymes. In addition, the DUF1669 domain plays an important role in the interaction between FAM3A, FAM83B, and FAM83F and RAF1, indicating that the DUF1669 domain plays various cellular regulatory roles in FAM83 family members. Bissell et al. first discovered that FAM83A can promote resistance to EGFR tyrosine kinase inhibitors of breast cancer cells. Jackson et al. found that FAM83B promotes the malignant transformation of epithelial cells of breast through binding to downstream RAS proteins CRAF and is a potential oncogene. The above studies confirmed for the first time that a new protein family plays an important role in EGFR and RAS signal transduction. In recent years, many studies have shown that abnormal expression of FAM83 family members plays an important role in the occurrence, development, and malignant biological behavior of many malignant tumors, including gastric cancer, lung cancer, ovarian cancer, and breast cancers, which can serve as a potential molecular biomarker for evaluating clinical prognosis. Therefore, exploring the FAM83 family and related molecular regulation mechanisms is of great value in assessing the prognosis of cervical cancer and can provide new research directions for clinical diagnosis and treatment.

Current studies have shown that FAM83A and FAM83H have a potential value in assessing the prognosis of patients with cervical cancer and guiding individualized treatment. However, there are no relevant reports on the expression, prognostic value, biological function, and molecular mechanism of most FAM83 family members in cervical cancer. In this study, we comprehensively and objectively analyzed the relationship between FAM83 family members and the occurrence, development, and prognosis of cervical cancer and the related functional regulatory networks based on various bioinformatics databases, which will help to provide new strategies for the prevention and treatment of cervical cancer.

**Materials And Methods**

**Oncomine**

The Oncomine database is currently the world's largest oncogene chip database and integrated data mining platform. So far, the database has collected 715 gene expression data sets and 86,733 samples of cancer tissues and normal tissues. The Oncomine database in the present study was used to analyze the expression of FAM83 mRNA in cancer tissues and corresponding
normal tissues. The screening conditions were as follows: "Cancer Type: cervical cancer"; "Gene: FAM83A-H"; "Analysis Type: Cancer vs. Normal Analysis"; and Critical values: \( P \) value < 0.05, Fold change > 1.5, gene rank = top 10%.

**Gene Expression Profiling Interactive Analysis (GEPIA) dataset**

GEPIA \([18]\) is a visual analysis website based on the TCGA transcriptome database, which contains the RNA sequencing expression data of 9,736 tumor samples and 8,587 normal samples from TCGA and GTEx. GEPIA includes various analysis modules, such as differential expression analysis of tumor tissues and normal tissues, analysis of different cancer types or pathological stages, survival analysis, correlation analysis, and dimensionality reduction. It also provides customized functions, such as single gene analysis, tumor type analysis, and multi-gene analysis.

**UALCAn**

UALCAn (http://ualcan.path.uab.edu) \([19]\) is an online analysis and mining website for cancer data. It is based on the analysis of related cancer data in the TCGA database, which can identify related genes by biomarker and perform expression profile and survival analyses. It can also analyze the relative expression of query genes in tumor samples and normal samples and analyze the relative expression based on cancer stage, tumor grade, or other clinicopathological characteristics in different tumor subgroups. It is a simple, fast, and effective TCGA data mining and analysis website tool.

**Kaplan–Meier Plotter**

The Kaplan–Meier (KM) plotter (http://kmplot.com) \([20]\) contains 10,188 cancer samples, including 4,142 breast cancer, 1,648 ovarian cancer, 2,437 lung cancer, and 1,065 gastric cancer patients. In our study, the KM plotter was used to analyze the prognosis of FAM83 mRNA members in cervical cancer patients. The genes were divided into high- and low-expression groups according to the median gene expression. The plotter can display 95% confidence intervals and hazard ratios (HR) of log rank \( P \) values. The screening conditions were as follows: "Cancer Type: Cervical squamous cell carcinoma"; "Gene: FAM83A-H"; "Survival: OS"; and "Follow up threshold: All".

**cBioPortal**

cBioPortal for Cancer Genomics (http://www.cbioportal.org) \([21]\) is an open-access public resource for interactive exploration of multiple cancer genomics data sets, which derived from TCGA, ICGC, GEO, and other databases. The types of integrated genomic data include somatic mutations, DNA copy number alterations, mRNA expression levels, DNA methylation, and protein abundance. cBioPortal can display the genomic data for cancer research samples in a visual form. It can also help researchers explore genetic changes between samples, genes, and pathways and integrate them with clinical research. In the present study, cBioPortal was used to analyze FAM83 family member alterations in cervical squamous cell...
carcinoma (CESC) and endocervical adenocarcinoma (TCGA, Provisional) sample. The genomic profiles included mutations, structure variants, and copy number alterations.

**GeneMANIA analysis**

GeneMANIA (http://www.genemania.org) \(^{[22]}\) is a flexible, user-friendly Web interface that can predict gene function, analyze gene lists, and sort genes with clear functions. It is also used to construct protein–protein interaction networks, protein–DNA interactions, signaling pathways, physiological and biochemical reactions, gene and protein expression, and for protein domain and phenotype screening. We used GeneMANIA to visualize the functions and regulatory networks of molecules related to FAM83 family members.

**LinkedOmics analysis**

The LinkedOmics database (http://www.linkedomics.org/login.php) \(^{[23]}\) is a multi-omics and clinical database based on a web platform, containing samples from 32 cancer types and a total of 11,158 patients from the TCGA database data. The LinkFinder module of LinkedOmics was used to study the differentially expressed genes associated with FAM83 family members in the TCGA_CESC data set (n = 304) in the present study. The Pearson correlation coefficient was utilized for statistical analysis. LinkFinder performs statistical analysis for each differentially expressed gene related to FAM83 family members. All results are presented in the form of a volcano map, heat map, or scatter plot.

**Metascape**

The Metascape (http://metascape.org) \(^{[24]}\) is a free, user-friendly gene list analysis tool for gene annotation and analysis, which integrates multiple authoritative databases, such as Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), UniProt, and Drugbank Resources. It can not only complete pathway enrichment and biological process annotation, but also perform gene-related protein network analysis. In the present study, Metascape was used to perform GO and pathway enrichment analysis of FAM83 family members and their related differentially expressed genes. Gene Ontology (GO) included biological process, cellular component, and molecular function and KEGG pathway. Restriction conditions were as follows: \(P\) value < 0.01, minimum count of 3, and enrichment factor > 1.5 identified statistical significance.

**TISDIB**

The TISIDB (http://cis.hku.hk/TISIDB)\(^{[25]}\) database integrates 988 reported immune-related anti-tumor genes, high-throughput screening technology, molecular profiling and multi-omics data, and immunological data collected from seven public resources \(^{[21]}\). The database can be used to analyze the correlation for selected genes with lymphocytes, immunomodulators, and chemokines. In the present study, the TISIDB database was used to analyze the correlation between the expression levels of FAM83 family members and lymphocytes and immunomodulators.
Results

The mRNA levels of FAM83 family members in patients with cervical cancer

Oncomine database collected a total of eight FAM83 family members in different tumor types. The Oncomine database was used to compare the transcription levels of FAM83 family members in cervical cancer tissues and normal tissue. The results showed that compared to normal cervical tissues, the mRNA levels of FAM83A, FAM83D, FAM83E, and FAM83G were increased in cervical cancer tissues (Fig. 1 and Table 1) (all $P < 0.05$). In the Biewenga Cervix dataset, the expression level of FAM83A in CESC was significantly higher than that in normal tissues (fold change $= 1.795$, $P = 0.001$). In the two datasets, the expression level of FAM83D mRNA in cervical cancer patients was significantly higher than that in the normal group. In the Biewenga Cervix dataset, the expression level of FAM83D in CESC was higher than that in normal tissues (fold change $= 2.95$, $P = 1.09E-04$). In the Pyeon multi-cancer dataset, the expression level of FAM83D in the cervical cancer group was higher than that in normal tissues (fold change $= 1.742$, $P = 1.1E-02$). In the Scotto Cervix 2 dataset, the expression level of FAM83E in CSCC was higher than that in normal cervical tissue (fold change $= 2.298$, $P = 1.00E-03$). In addition, the expression level of FAM83G in CSCC in the Biewenga Cervix dataset was higher than that in normal tissues (fold change $= 1.889$, $P = 1.00E-03$).
| Types of cervical cancer vs. normal tissues | Fold change | t-test | p-value       | Ref               |
|-------------------------------------------|-------------|--------|---------------|-------------------|
| FAM83A Cervical Squamous Cell Carcinoma vs. Normal | 1.795       | 4.78   | 1.00E-03      | Biewenga Cervix[26] |
| Cervical Cancer vs. Normal                | 1.343       | 1.432  | 8.20E-02      | Pyeon Multi-cancer[27] |
| FAM83B Cervical Squamous Cell Carcinoma vs. Normal | 1.071       | 0.771  | 2.39E-01      | Biewenga Cervix   |
| Cervical Cancer vs. Normal                | 1.172       | 1.371  | 8.90E-02      | Pyeon Multi-cancer |
| FAM83C Cervical Cancer vs. Normal          | 1.045       | 0.239  | 4.06E-01      | Pyeon Multi-cancer |
| Cervical Squamous Cell Carcinoma vs. Normal | -1.116      | -1.996 | 9.56E-01      | Biewenga Cervix   |
| FAM83D Cervical Squamous Cell Carcinoma vs. Normal | 2.95        | 7.844  | 1.09E-04      | Biewenga Cervix   |
| Cervical Cancer vs. Normal                | 1.742       | 2.388  | 1.10E-02      | Pyeon Multi-cancer |
| FAM83E Cervical Squamous Cell Carcinoma vs. normal | 2.298       | 3.246  | 1.00E-03      | Scotto Cervix 2[28] |
| Cervical Squamous Cell Carcinoma Epithelia vs. normal | -1.041      | -0.422 | 6.60E-01      | Zhai Cervix[29] |
| High Grade Cervical Squamous Intraepithelial Neoplasia vs. normal | -1.093      | -0.931 | 8.15E-01      |                  |
| Cervical Cancer vs. Normal                | 1.042       | 0.603  | 2.76E-01      | Pyeon Multi-cancer |
| Cervical Squamous Cell Carcinoma vs. Normal | -1.786      | -4.86  | 9.97E-01      | Biewenga Cervix   |
| FAM83F Cervical Squamous Cell Carcinoma vs. Normal | 1.202       | 4.214  | 1.16E-04      | Biewenga Cervix   |
### Types of cervical cancer vs. normal tissues

| Types of cervical cancer vs. normal tissues | Fold change | t-test | p-value | Ref |
|-------------------------------------------|-------------|--------|---------|-----|
| Cervical Cancer vs. Normal                | 1.104       | 0.875  | 1.94E-01| Pyeon Multi-cancer |
| FAM83G                                    | NA          |        |         |     |
| FAM83H                                    | 1.889       | 5.77   | 1.00E-03| Biewenga Cervix |
| Cervical Cancer vs. Normal                | 1.289       | 1.98   | 2.80E-02| Pyeon Multi-cancer |

#### Correlation between FAM83 family members and tumor stages, promoter methylation in patients with CESC (GEPIA and UALCAN)

The GEPIA online website was used to analyze the expression of FAM83 family members in CESC and normal cervical tissues. The results showed that the expression levels of FAM83A, FAM83B, FAM83C, FAM83D, FAM83E, FAM83F, FAM83G, and FAM83H in CESC were significantly higher than those in normal tissues (all $P<0.05$) (Fig. 2A–H). We further confirmed that the expression level of FAM83A, FAM83B, FAM83C, FAM83D, FAM83F, FAM83G, and FAM83H in CESC were significantly higher than those in normal tissues in UALCAN (all $P<0.05$). The expression level of FAM83E in CESC was also higher than that in normal tissues, but the difference was not statistically significant (Fig. 2I–P and Additional file: Table S1) ($P>0.05$).

The relationship between the expression of FAM83 family members and tumor stage in 298 cases of CESC was further explored using the UALCAN online website (Fig. 3C). The results showed that in CESC, the expression levels of FAM83B and FAM3C in stage 3 were significantly higher than those in stage 1 (both $P<0.05$) (Fig. 3B). The expression levels of FAM83D and FAM83G in stages 2 and 3 were higher than those in stage 1 (all $P<0.05$) (Fig. 3D and Fig. 3G). The expression level of FAM83E in stages 2 and 3 were lower than those in stage 1 (all $P<0.05$) (Fig. 3E). The expression level of FAM83F in stage 3 was lower than that in stage 1 ($P<0.05$) (Fig. 3F). The expression level of FAM83H in stages 3 and 4 were higher than that in stage 1 (all $P<0.05$) (Fig. 3H). There was no significant difference in FAM83A expression among various tumor stages ($P>0.05$) (Fig. 3A and Additional file: Table S2). The relationship between the expression of FAM83 family members and promoter methylation were further analyzed in 307 cases of CESC (Fig. 3C). The results showed that in CESC, the promoter methylation levels of FAM83A, FAM83D, FAM83E, FAM83F, and FAM83G were lower than those in normal tissues ($P<0.05$) (Fig. 3A, and Fig. 3D–G), while the promoter methylation levels of FAM83B, FAM3C, and FAM83H were not significantly different between CESC and normal tissues ($P>0.05$) (Fig. 3A-B and Fig. 3H; Additional file: Table S3).

#### Genomic alteration and gene interaction network of FAM83 family members in patients with cervical cancer
The cBioPortal was used to analyze the mutation frequency of FAM83 family members in cervical cancer. Based on the Cervical Squamous Cell Carcinoma (TCGA, PanCancer Atlas) and Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma (TCGA, Firehose Legacy) datasets, 605 patients and 607 samples were analysed. There are 93 samples of genetic alteration in all FAM83 family members (15%), and the percentage of genetic alteration of FAM83 family members is between 1%-4% (FAM83A, 2.4%; FAM83B, 3%; FAM83C, 4%; FAM83D, 2.5%; FAM83E, 1.5%; FAM83F, 1%; FAM83G, 2%; and FAM83H, 4%) (Fig. 4A–B). Co-expression networks of eight FAM83 family members was constructed by GeneMANIA. The results showed that the above family members are closely associated with shared protein domains and co-expression. Furthermore, the changes and functions of genes, such as MYEOV (myeloma overexpressed), POF1B (POF1B actin binding protein), IPPK (c inositol-pentakisphosphate 2-kinase), KDF1 (keratinocyte differentiation factor 1) LAD1 (ladinin 1) were significantly correlated with FAM83 family members (Fig. 4C).

Prognostic values of FAM83 family members in patients with CESC

The prognostic values of FAM83 family members in CESC patients were explored by GEPIA. The survival significance map showed that FAM83A, FAM83B, FAM83G, and FAM83H in CESC have important prognostic values (Fig. 5A). The KM plotter was further used to explore the relationship between FAM83 family members and prognosis. The censored data were set as the overall survival (OS), and 304 cases of CESC in the database met the criteria in clinical stages. The KM plotter showed that the OS in CESC patients with high mRNA expression levels of FAM82A (HR = 2.07 (1.29–3.32), log rank P = 0.002), FAM83B (HR = 1.7 (1.02–2.84), log rank P = 0.039), and FAM83H (HR = 2.17 (1.24–3.78), log rank P = 0.0053) were significantly lower than those in patients with low expression (all P < 0.05) (Fig. 5C–D and Fig. 5J), while the OS in CESC patients with high mRNA expression levels of FAM82D (HR = 0.53 (0.29–0.99), log-rank P = 0.0043), FAM83E (HR = 0.54 (0.34–0.87), log-rank P = 0.0098), and FAM83F (HR = 0.6 (0.37–0.98), log-rank P = 0.039) were significantly higher than those in patients with low expression (all P < 0.05) (Fig. 5D–F). However, the expression levels of FAM83C and FAM83G mRNA were not significantly correlated with OS in CESC patients (P > 0.05) (Fig. 5E and Fig. 5I) (Fig. 5B).

Interaction analysis of co-expression genes correlated with FAM83A/B/H in cervical cancer

The Function module in LinkedOmics was used to analyze the mRNA sequencing data of 304 CESC patients from TCGA database. As shown in the volcano map, there were 2,643 genes that are significantly positively correlated with FAM83A (dark red dots), and 5,216 genes that are significantly negatively correlated with FAM83A (dark green dots; false discovery rate [FDR] < 0.01; Fig. 6A). The heat map showed the top 50 gene sets that were significantly positively and negatively correlated with FAM83A (Fig. 6A). The statistical scatter plot of a single gene showed that the expression of FAM83A was correlated with LOC100131726 (Pearson correlation = 0.9182, P = 1.657e-119), SERPINB4 (Pearson correlation = 0.7043, P = 7.425e-47) and GNA15 (Pearson correlation = 0.6932, P = 7.539e-45) (Fig. 6B).
There were 4,106 genes that were significantly positively correlated with FAM83B (dark red dots), and 5,459 genes that were significantly negatively correlated with FAM83B (dark green dots; FDR < 0.01) (Fig. 6C). The heat map showed the top 50 gene sets that were significantly positively and negatively correlated with FAM83B (Fig. 6C). The statistical scatter plot of a single gene showed that the expression of FAM83B was correlated with DSP (Pearson correlation = 0.7682, $P = 1.928\times 10^{-60}$), DENND2C (Pearson correlation = 0.7085, $P = 1.233\times 10^{-47}$) and FAM83G (Pearson correlation = 0.7017, $P = 2.249\times 10^{-46}$) (Fig. 6D).

There were 2,294 genes that were significantly positively related to FAM83H (dark red dots), and 5,317 genes that are significantly negatively related to FAM83H (dark green dots; FDR < 0.01) (Fig. 6E). The heat map showed the top 50 gene sets that were significantly positively and negatively correlated with FAM83H (Fig. 6E). The statistical scatter plot of a single gene showed that the expression of FAM83H is related to PLEC (Pearson correlation = 0.6789, $P = 2.005\times 10^{-42}$), PLEKHN1 (Pearson correlation = 0.6599, $P = 2.22\times 10^{-39}$) and PKP3 (Pearson correlation = 0.6532, $P = 2.337\times 10^{-38}$) (Fig. 6F).

**Functional and pathway enrichment analysis of FAM83A/B/H in patients with cervical cancer**

GO and KEGG enrichment analysis of FAM83A, FAM83B, and FAM83H and their associated genes were performed by Metascape. GO showed that FAM83A and its related genes were mainly located in cell-substrate junction, membrane raft, desmosome, and basal part of the cell, and these molecules could bind cadherin and participate in biological processes, such as skin development, regulation of peptidase activity, inflammatory response, wound healing and cell junction organization (Fig. 7A and Table 2). KEGG enrichment analysis showed that the signaling pathways involved in FAM83A and its related genes include axon guidance, regulation of actin cytoskeleton, pathways in cancer, estrogen signaling pathway, NOD-like receptor signaling pathway, and MAPK signaling pathway (Fig. 7B and Table 3). GO results showed that FAM83B and its related genes are mainly located in cell-cell junction, desmosome, and polymeric cytoskeletal fiber. They could participate in lipid binding, epidermis development, wound healing, establishment of skin barrier, and involved in biological processes, such as desmosome and cell junction organization (Fig. 7C and Table 4). KEGG enrichment analysis showed that the signaling pathways involved in FAM83B and its related differential genes include adherens junction, pathways in cancer, Rap1 signaling pathway, Hippo signaling pathway, and central carbon metabolism in cancer (Fig. 7D and Table 5). GO results showed that FAM83H and its related differential genes were mainly located in cell-cell junctions, and involved in cadherin-binding and calcium-dependent protein-binding and participated in biological process including epidermis development, regulation of endopeptidase activity, intermediate filament cytoskeleton, and desmosome organization (Fig. 7E and Table 6). KEGG enrichment analysis showed that the signaling pathways involved in FAM83H and its related differential genes included axon guidance, MAPK signaling pathway, estrogen signaling pathway, pathogenic infection, and regulation of actin cytoskeleton (Fig. 7F and Table 7). The above-mentioned signaling pathways can participate in the occurrence and development of a variety of tumors including cervical cancer.
| Category                      | Description                                                      | InTerm_InList | Log($P$)  | Log($q$-value) |
|-------------------------------|------------------------------------------------------------------|---------------|-----------|----------------|
| GO Biological Processes       | skin development                                                 | 57/415        | -32.97    | -28.62         |
| GO Molecular Functions        | cadherin binding                                                 | 38/333        | -19.15    | -15.76         |
| GO Biological Processes       | regulation of peptidase activity                                 | 42/458        | -17.56    | -14.25         |
| GO Biological Processes       | inflammatory response                                            | 50/778        | -14.44    | -11.25         |
| GO Biological Processes       | wound healing                                                    | 41/538        | -14.35    | -11.20         |
| GO Biological Processes       | myeloid cell activation involved in immune response              | 40/550        | -13.34    | -10.25         |
| GO Cellular Components        | cell-substrate junction                                          | 32/426        | -11.14    | -8.31          |
| GO Biological Processes       | multicellular organismal homeostasis                             | 35/516        | -10.88    | -8.06          |
| GO Biological Processes       | response to bacterium                                            | 42/728        | -10.68    | -7.87          |
| GO Biological Processes       | cell junction organization                                       | 40/701        | -10.05    | -7.31          |
| GO Cellular Components        | membrane raft                                                    | 26/325        | -9.74     | -7.04          |
| GO Cellular Components        | desmosome                                                        | 9/25          | -9.62     | -6.95          |
| GO Biological Processes       | positive regulation of cell motility                            | 35/574        | -9.61     | -6.95          |
| GO Biological Processes       | intermediate filament cytoskeleton organization                  | 11/50         | -9.04     | -6.42          |
| GO Biological Processes       | cellular response to external stimulus                           | 24/303        | -8.95     | -6.35          |
| GO Biological Processes       | epithelial cell proliferation                                    | 29/439        | -8.84     | -6.26          |
| GO Biological Processes       | cellular response to lipid                                       | 33/556        | -8.80     | -6.22          |
| Category                      | Description                              | InTerm_InList | Log(\(P\)) | Log(\(q\)-value) |
|-------------------------------|------------------------------------------|---------------|-------------|------------------|
| GO Cellular Components        | basal part of cell                       | 22/260        | -8.79       | -6.22            |
| GO Biological Processes       | positive regulation of hydrolase activity | 39/779        | -8.20       | -5.65            |
| GO Biological Processes       | positive regulation of cellular protein localization | 22/295        | -7.78       | -5.27            |

**Table 3**
Significantly KEGG enrichment analysis of genes correlated with FAM83A in cervical cancer

| Category                      | Description                              | InTerm_InList | Log(\(P\)) | Log(\(q\)-value) |
|-------------------------------|------------------------------------------|---------------|-------------|------------------|
| KEGG Pathway                  | Axon guidance                            | 15/175        | -6.26       | -3.66            |
| KEGG Pathway                  | Regulation of actin cytoskeleton          | 16/212        | -5.90       | -3.60            |
| KEGG Pathway                  | Pathways in cancer                       | 22/395        | -5.61       | -3.41            |
| KEGG Pathway                  | Estrogen signaling pathway               | 11/146        | -4.23       | -2.40            |
| KEGG Pathway                  | Endocytosis                              | 15/260        | -4.18       | -2.40            |
| KEGG Pathway                  | NOD-like receptor signaling pathway      | 11/170        | -3.64       | -2.05            |
| KEGG Pathway                  | Bacterial invasion of epithelial cells   | 7/76          | -3.41       | -1.86            |
| KEGG Pathway                  | Pancreatic secretion                     | 8/103         | -3.32       | -1.80            |
| KEGG Pathway                  | MAPK signaling pathway                   | 13/255        | -3.19       | -1.71            |
| KEGG Pathway                  | Apoptosis                                | 9/138         | -3.11       | -1.68            |
| KEGG Pathway                  | Hepatitis C                              | 10/169        | -3.06       | -1.68            |
| KEGG Pathway                  | Fluid shear stress and atherosclerosis   | 9/142         | -3.02       | -1.68            |
| KEGG Pathway                  | Central carbon metabolism in cancer      | 6/65          | -3.00       | -1.68            |
| KEGG Pathway                  | Inflammatory bowel disease (IBD)         | 6/65          | -3.00       | -1.68            |
| KEGG Pathway                  | Renal cell carcinoma                     | 6/65          | -3.00       | -1.68            |
| KEGG Pathway                  | Phospholipase D signaling pathway        | 9/146         | -2.93       | -1.64            |
| KEGG Pathway                  | Calcium signaling pathway                | 10/182        | -2.82       | -1.56            |
| KEGG Pathway                  | Amoebiasis                               | 7/96          | -2.81       | -1.56            |
| KEGG Pathway                  | Renin secretion                          | 6/73          | -2.74       | -1.52            |
| KEGG Pathway                  | Galactose metabolism                     | 4/31          | -2.69       | -1.49            |
| Category                          | Description                              | InTerm_InList | Log($P$) | Log($q$-value) |
|----------------------------------|------------------------------------------|---------------|----------|----------------|
| GO Biological Processes          | epidermis development                    | 68/463        | -41.28   | -36.93         |
| GO Cellular Components           | cell-cell junction                        | 48/485        | -21.39   | -18.00         |
| GO Cellular Components           | desmosome                                | 12/25         | -14.47   | -11.20         |
| GO Biological Processes          | wound healing                             | 40/538        | -13.62   | -10.39         |
| GO Biological Processes          | establishment of skin barrier             | 10/24         | -11.38   | -8.17          |
| GO Biological Processes          | peptide cross-linking                     | 11/35         | -10.88   | -7.74          |
| GO Biological Processes          | desmosome organization                    | 7/10          | -10.23   | -7.14          |
| GO Biological Processes          | cell junction organization                | 40/701        | -10.02   | -6.95          |
| GO Biological Processes          | regulation of epidermis development       | 13/69         | -9.66    | -6.64          |
| GO Biological Processes          | keratinocyte proliferation                | 11/49         | -9.13    | -6.13          |
| GO Biological Processes          | regulation of endopeptidase activity      | 29/429        | -9.05    | -6.06          |
| GO Biological Processes          | molting cycle                             | 14/105        | -8.30    | -5.40          |
| GO Biological Processes          | plasma membrane bounded cell projection morphogenesis | 35/659 | -8.03 | -5.14 |
| GO Biological Processes          | positive regulation of hydrolase activity | 38/779        | -7.68    | -4.88          |
| GO Cellular Components           | polymeric cytoskeletal fiber              | 37/747        | -7.66    | -4.87          |
| GO Biological Processes          | cell-substrate adhesion                   | 24/360        | -7.48    | -4.70          |
| GO Biological Processes          | tissue morphogenesis                      | 33/638        | -7.33    | -4.57          |
| Category                        | Description                        | InTerm_InList | Log(\(P\)) | Log(\(q\)-value) |
|--------------------------------|------------------------------------|---------------|-------------|------------------|
| GO Biological Processes        | epithelial cell development        | 18/212        | -7.31       | -4.57            |
| GO Cellular Components         | intermediate filament              | 18/215        | -7.22       | -4.51            |
| GO Molecular Functions         | lipid binding                      | 37/783        | -7.14       | -4.45            |
| Category                  | Description                                      | InTerm_InList | Log(P)  | Log(q-value) |
|--------------------------|--------------------------------------------------|---------------|---------|--------------|
| KEGG Pathway             | Adherens junction                                | 10/72         | -6.27   | -3.73        |
| KEGG Pathway             | Pathways in cancer                               | 23/395        | -6.15   | -3.73        |
| KEGG Pathway             | Rap1 signaling pathway                           | 14/210        | -4.61   | -2.32        |
| KEGG Pathway             | Hippo signaling pathway                          | 12/174        | -4.18   | -2.13        |
| KEGG Pathway             | Central carbon metabolism in cancer              | 7/65          | -3.83   | -1.97        |
| KEGG Pathway             | Endocytosis                                      | 14/260        | -3.62   | -1.85        |
| KEGG Pathway             | Cell cycle                                       | 9/124         | -3.44   | -1.74        |
| KEGG Pathway             | ErbB signaling pathway                           | 7/86          | -3.08   | -1.48        |
| KEGG Pathway             | thyroid hormone signaling pathway                | 8/123         | -2.81   | -1.25        |
| KEGG Pathway             | Arrhythmogenic right ventricular cardiomyopathy  | 6/72          | -2.77   | -1.25        |
| KEGG Pathway             | Choline metabolism in cancer                     | 7/99          | -2.72   | -1.24        |
| KEGG Pathway             | inflammatory mediator regulation of trp channels | 7/104         | -2.60   | -1.14        |
| KEGG Pathway             | Sphingolipid signaling pathway                   | 7/118         | -2.30   | -0.99        |
| KEGG Pathway             | Amoebiasis                                       | 6/96          | -2.15   | -0.92        |
| KEGG Pathway             | Phosphatidylinositol signaling system            | 6/97          | -2.12   | -0.92        |
Table 6
Significantly GO enrichment analysis of genes correlated with FAM83B in cervical cancer

| Category                        | Description                                      | InTerm_InList | $\log(P)$ | $\log(q$-value) |
|--------------------------------|--------------------------------------------------|---------------|-----------|-----------------|
| GO Biological Processes        | epidermis development                            | 62/463        | -35.13    | -30.78          |
| GO Molecular Functions         | cadherin binding                                 | 39/333        | -19.99    | -16.60          |
| GO Biological Processes        | regulation of endopeptidase activity             | 35/429        | -13.13    | -9.86           |
| GO Biological Processes        | intermediate filament cytoskeleton organization   | 12/50         | -10.27    | -7.17           |
| GO Biological Processes        | desmosome organization                            | 7/10          | -10.23    | -7.16           |
| GO Biological Processes        | wound healing                                    | 34/538        | -9.71     | -6.73           |
| GO Biological Processes        | keratinocyte proliferation                       | 11/49         | -9.12     | -6.19           |
| GO Biological Processes        | cell-cell junction organization                   | 20/211        | -8.87     | -5.97           |
| GO Biological Processes        | peptide cross-linking                             | 9/35          | -8.13     | -5.33           |
| GO Molecular Functions         | calcium-dependent protein binding                | 12/84         | -7.53     | -4.80           |
| GO Biological Processes        | molting cycle                                    | 13/105        | -7.35     | -4.63           |
| GO Biological Processes        | regulated exocytosis                             | 37/780        | -7.16     | -4.47           |
| GO Biological Processes        | intrinsic apoptotic signaling pathway            | 20/283        | -6.72     | -4.09           |
| GO Biological Processes        | inflammatory response                            | 36/778        | -6.72     | -4.09           |
| GO Cellular Components         | cell-substrate junction                           | 25/426        | -6.68     | -4.06           |
| GO Biological Processes        | cellular response to external stimulus           | 20/303        | -6.25     | -3.68           |
| GO Biological Processes        | chemotaxis                                       | 30/644        | -5.75     | -3.24           |
| Category                  | Description                                | InTerm_InList | Log($P$) | Log($q$-value) |
|---------------------------|--------------------------------------------|---------------|----------|----------------|
| GO Biological Processes   | multicellular organismal homeostasis       | 26/516        | -5.67    | -3.19          |
| GO Biological Processes   | response to bacterium                      | 32/728        | -5.57    | -3.09          |
| GO Biological Processes   | establishment of skin barrier              | 6/24          | -5.52    | -3.06          |
### Table 7
Significantly KEGG enrichment analysis of genes correlated with FAM83B in cervical cancer

| Category           | Description                                         | InTerm_InList | Log(P) | Log(q-value) |
|--------------------|-----------------------------------------------------|---------------|--------|--------------|
| KEGG Pathway       | Axon guidance                                       | 14/175        | -5.51  | -2.91        |
| KEGG Pathway       | MAPK signaling pathway                              | 14/255        | -3.70  | -1.40        |
| KEGG Pathway       | Estrogen signaling pathway                          | 10/146        | -3.55  | -1.35        |
| KEGG Pathway       | Pathogenic Escherichia coli infection               | 6/55          | -3.38  | -1.33        |
| KEGG Pathway       | Regulation of actin cytoskeleton                    | 11/212        | -2.83  | -1.11        |
| KEGG Pathway       | Adherens junction                                   | 6/72          | -2.76  | -1.09        |
| KEGG Pathway       | Pathways in cancer                                  | 16/395        | -2.71  | -1.09        |
| KEGG Pathway       | Bacterial invasion of epithelial cells              | 6/76          | -2.64  | -1.04        |
| KEGG Pathway       | Pancreatic secretion                                | 7/103         | -2.62  | -1.04        |
| KEGG Pathway       | Sphingolipid signaling pathway                      | 7/118         | -2.29  | -0.87        |
| KEGG Pathway       | Inositol phosphate metabolism                       | 3/22          | -2.18  | -0.84        |
| KEGG Pathway       | Amoebiasis                                          | 6/96          | -2.14  | -0.84        |
| KEGG Pathway       | Drug metabolism - other enzymes                     | 4/46          | -2.06  | -0.84        |
| KEGG Pathway       | PPAR signaling pathway                              | 5/72          | -2.05  | -0.84        |
| KEGG Pathway       | Arrhythmogenic right ventricular cardiomyopathy (ARVC) | 5/72      | -2.05  | -0.84        |

Correlation analysis between the expression of FAM83A/B/H and immune molecules in cervical cancer

The TISIDB database was used to analyze the relationship between the expression of FAM83A, FAM83B, and FAM83H, and tumor-infiltrating lymphocytes (TILs) and immunomodulators by Spearman's
correlation (Fig. 8). The results showed the expression of FAM83A was correlated with TILs (Fig. 8A). Additional file: Figure S1A showed the top 3 TILs with the strongest correlation with FAM83A, including neutrophils (rho = 0.425, P < 2.2e-16), Tcm_CD4 (rho = 0.422, P = 6.77e-16), Tcm_CD8 (rho = 0.42, P = 4.85e-15). Figure 8B–D showed the relationship between FAM83A and immunomodulators (immunoinhibitors, immunostimulators, and major histocompatibility complex (MHC) molecules). The results showed that the immunoinhibitors with the strongest correlation with FAM83A included TGFβ1 (rho = 0.448, P < 2.2e-16), CD274 (rho = 0.395, P = 9.34e-13), and TGFBR1 (rho = 0.335, P = 2.64e-09) (Additional file: Figure S1B). The immunostimulators with the strongest correlation with FAM83A included RAET1E (rho = 0.566, P < 2.2e-16), C10orf54 (rho = 0.474, P = P < 2.2e-16), and TNFSF9 (rho = 0.44, P < 2.2e-16) (Additional file: Figure S1C). The MHCs with the strongest correlation with FAM83A included TAP2 (rho = 0.442, P < 2.2e-16), TAP1 (rho = 0.326, P = 6.62e-09), and B2M (rho = 0.317, P = 1.8e-08) (Additional file: Figure S1D).

Figure 8E–H showed that the expression of FAM83B was correlated with TILs, immunoinhibitors, immunostimulators, and MHCs. TILs with the strongest correlation with FAM83B included Tcm_CD4 (rho = 0.268, P = 2.16e-06), Th2 (rho = 0.268, P = 2.14e-06), and Tcm_CD8 (rho = 0.266, P = 2.58e-06) (Additional file: Figure S2A). The immunoinhibitors with the strongest correlation with FAM83B included CD274 (rho = 0.364, P = 7.08e-11), TGFBR1 (rho = 0.338, P = 1.67e-09), and TGFβ1 (rho = 0.258, P = 5.33e-06) (Additional file: Figure S2B). The immunostimulators with the strongest correlation with FAM83B included RAET1E (rho = 0.537, P < 2.2e-16), IL6R (rho = 0.42, P = 4.97e-15), and TNFSF9 (rho = 0.249, P = 1.11e-05) (Additional file: Figure S2C). The MHCs with the strongest correlation with FAM83B included TAP2 (rho = 0.228, P = 5.75e-05), HLA-E (rho = 0.114, P = 0.0461) (Additional file: Figure S2D).

Figure 8I–L showed that the expression of FAM83H was correlated with TILs, immunoinhibitors, immunostimulators, and MHCs. TILs with the strongest correlation with FAM83B included Tcm_CD4 (rho = 0.306, P = 5.52e-08), neutrophils (rho = 0.23, P = 5.07e-05), and CD56bright (rho = 0.201, P = 3.87e-04) (Additional file: Figure S3A). The immunoinhibitors with the strongest correlation with FAM83H included TGFβ1 (rho = 0.283, P = 5.62e-07), TGFBR1 (rho = 0.202, P = 3.76e-04), and CD274 (rho = 0.165, P = 3.82e-03) (Additional file: Figure S3B). The immunostimulators with the strongest correlation with FAM83H included RAET1E (rho = 0.503, P < 2.2e-16), TNFSF9 (rho = 0.394, P = 1.16e-12) TNFRSF25 (rho = 0.386, P = 3.77e-12), and (Additional file: Figure S3C). The MHCs with the strongest correlation with FAM83H included TAP2 (rho = 0.316, P = 1.92e-08), TAP1 (rho = 0.182, P = 1.44e-03) and HLA-E (rho = 0.122, P = 0.0327) (Additional file: Figure S3D).

Discussion

In recent years, many studies have shown that FAM83 family members are potential oncogenes, which are abnormally expressed in a variety of tumors, and affect the occurrence and development of tumors through different signaling pathways, such as EGFR, MAPK, and PI3K-AKT\textsuperscript{7,9,30}. Abnormal expression or activation of FAM83 family members is a common phenomenon in malignant tumors, and is associated with tumor occurrence or progression. However, the expression and mechanism of different FAM83
family members in cervical cancer are still unclear. In this study, we investigated the expression, prognostic value, immune infiltration, and potential molecular functions of different FAM83 family members in cervical cancer for the first time.

FAM83A is the smallest protein in the FAM83 family, which was initially considered as a potential tumor biomarker\[^{31}\]. Researchers have found that FAM83A mRNA is highly expressed in circulating tumor cells of patients with lung adenocarcinoma by PCR\[^{31}\]. High expression of FAM83A was correlated with poor prognosis of patients in breast cancer\[^{32}\]. Several studies have shown that FAM83A is highly expressed in lung cancer and liver cancer, and related to advanced stages and poor prognosis, and also can promote the proliferation and invasion of lung cancer cells\[^{33\text{--}36}\]. In this study, we found that the expression of FAM83A mRNA were upregulated in cervical cancer, while methylation levels of FAM83A gene decreased. The OS of cervical cancer patients with high expression of FAM83A was shortened and significantly related to poor prognosis. The above results are consistent with those from Liu et al. and Rong et al\[^{15,32}\]. However, other studies have shown that high expression of FAM83A was negatively correlated with shortened survival time in patients with cervical cancer, and that FAM83A has a tumor-suppressing effect on cervical cancer by inhibiting integrin expression\[^{38}\], which may be due to the number of cervical cancer patient samples and the interaction of other related factors. Nonetheless, the above studies are sufficient to show that FAM83A has important value in the occurrence, development, and prognosis evaluation of cervical cancer.

FMA83B is another important member of the FAM83 family. Jackson et al. first discovered that FAM83B can act as a driving factor and induce malignant transformation for human breast epithelial cells\[^9\]. Many studies have reported that FAM83B is overexpressed in several malignant tumors, including endometrial cancer, lung cancer, pancreatic cancer, and ovarian cancer\[^{39\text{--}41,13}\], and promotes tumor proliferation, invasion, and migration. Studies have shown that FAM83B reversed the inhibitory effect of 14-3-3 protein on CRAF and promotes cell membrane localization of CRAF, thereby activating the MAPK signaling pathway and promoting tumor growth\[^9\]. The interaction between FAM83B and EGFR was necessary to promote the activation of EGFR and phospholipase D1\[^{42}\]. In this study, we found for the first time that the expression level of FAM83B mRNA in cervical cancer was increased and correlated with tumor stages, while the OS in cervical cancer patients with high expression of FAM83A was shortened, which was significantly related to poor prognosis, indicating that FAM83B plays an important role in the occurrence, development, invasion, metastasis, and prognosis of cervical cancer.

At present, there are few studies on FAM83C, and only a few have shown that FAM83C is highly expressed in lung cancer and is related to poor prognosis\[^{43}\]. Thus, relevant experimental confirmation is still lacking. Researchers have performed proteomics to determine that FAM83G can participate in the BMP signaling pathway and affect the expression and function of SMAD1\[^{44}\]. In addition, FAM83G can form a complex with Axin1, CK1\(\alpha\), and GSK3\(\beta\) in the \(\beta\)-catenin degradation complex to promote the phosphorylation of CK1\(\alpha\) and GSK3\(\beta\), thereby activating Wnt signaling\[^{45}\]. Brown et al. found that FAM83G could interact with Smad2 and Smad3 to regulate the TGF-\(\beta\) signaling pathway by mass
The present study found that the expression of FAM83C and FAM83G gene were upregulated in cervical cancer and correlated with tumor stages, but has no correlation with prognosis of patients with cervical cancer. However, additional experiments are still necessary for further confirmation of these research.

FAM83D was originally thought to be a protein correlated with the spindle, which can interact with proteins in the spindle, such as chromokinesin, dynein light chain 1, and HMMR. Recent studies have shown that FAM83D was highly expressed in pancreatic cancer, lung cancer, and ovarian cancer and involved in regulating tumor cell proliferation, apoptosis, invasion, and metastasis. Furthermore, FAM83D could promote tumor cell proliferation by regulating multiple signaling pathways, such as MAPK and Notch, indicating that FAM83D played an important role in the occurrence and development of malignant tumors. There were also reports in the literature that the high expression of FAM83E in pancreatic cancer was related to the shortened survival time. However, relevant experimental evidence is lacking. It has been shown that FAM83F enhanced its stability by inhibiting the ubiquitination and degradation of p53. FAM83F could activate the MAPK signaling pathway by interacting with BRAF and RAF in thyroid cancer. Studies have shown that miR-1827 and miR-940 inhibited the malignant progression of lung cancer by targeting FAM83F. The present study revealed for the first time that the expression levels of FAM83D, FAM83E, and FAM83F in cervical cancer were upregulated and correlated with tumor stages, while the high expression of FAM83D and FAM83F were negatively correlated with the shortened OS in cervical cancer patients, showing that FAM83D, FAM83E, and FAM83F played a potentially important role in the occurrence, development, and prognosis values of cervical cancer, although the specific functions and mechanisms need to be further explored.

Abnormal expression of FAM83H was initially confirmed to be related to calcium-deficient enamel hypoplasia. FAM83H mutants can destroy the subcellular structure of tooth enamel and related proteins. Recent studies have reported that FAM83H was overexpressed in a variety of malignant tumors, including gastric cancer, osteosarcoma, and renal clear cell carcinoma, and associated with the shortened survival time, and regulated the malignant biological behaviors. Kim et al. reported that FAM83H was highly expressed in liver cancer cells and correlated with the shortened OS in patients, and could promote the expression of CCND1 and CCNE1 and inhibit the expression of P53, thereby affecting the proliferation and invasion of liver cancer cells. In our study, we found that the expression level of FAM83H mRNA in cervical cancer was increased, while the OS in cervical cancer patients with high expression of FAM83H was shortened and related to poor prognosis. The above results were consistent with the research by Chao et al. This shows that FAM83H is also significantly associated with the occurrence, development, and prognosis values of cervical cancer.

The above research showed that the high expression of FAM83A/B/H in cervical cancer had important value in the occurrence, development, and prognosis evaluation of cervical cancer. In recent years, many studies have shown that FAM83A/B/H can activate MAPK, Wnt, and PI3K/AKT/mTOR signaling pathways in lung and pancreatic cancers and regulate tumor occurrence, development,
and biological behavior. In order to better clarify the molecular mechanism, biological function, and related signal regulation network of FAM83A/B/H in cervical cancer, GO enrichment analysis on FAM83A/B/H and their closely related genes was performed, which revealed that the above genes were involved in the formation of cell-substrate junction, membrane raft, desmosome, and regulated various biological behaviors, including lipid binding, cadherin, and calcium-dependent protein binding, and regulating skin and epidermis development, inflammatory response and cell junction organization. At the same time, KEGG enrichment analysis results showed that FAM83A/B/H and their closely related genes were significantly enriched in cancer pathways, estrogen signaling pathway, MAPK signaling pathway, Rap1 and Hippo signaling pathway. We speculate that FAM83A/B/H can regulate the occurrence, development, and malignant biological behavior of cervical cancer by regulating the above-mentioned tumor-related pathways. This study provides more supporting evidences for FAM83A/B/H and the related signaling pathways and provides clues for the rational development of FAM83A/B/H-mediated multi-target therapy.

The main cause of cervical cancer is HPV infection, a very small number of infected people will develop immune tolerance and tumors, and the immunogenicity of tumor patients may be higher. Therefore, immunotherapy plays a very important role in the pathogenesis and disease progression of cervical cancer. In recent years, the treatment of cervical cancer has not been limited to mature surgical treatment or radiotherapy or chemotherapy. Immunotherapy has also become a new type of treatment for advanced and recurrent cervical cancer, mainly including PD1/PD-L1 immune checkpoint suppression (Pembrolizumab), adoptive T lymphocyte therapy, and therapeutic tumor vaccines. Immune infiltration in the tumor has important value in the survival, prognosis, and immunotherapy of patients with cervical cancer. In the present study, we assessed the relationship between FAM83A/B/H and immune infiltration in cervical cancer using the TISIDB database. The results showed that FAM83A/B/H were significantly correlated with lymphocytes (neutrophils, Tcm_CD4, and Tcm_CD8), immunoinhibitors (TGFB1, TGFBR1, and CD274), immunostimulators (RAET1E and TNFSF9), and MHCs (TAP1, TAP2, and HLA-E). Studies have shown that the high expression of FAM83A in lung cancer was negatively correlated with the level of B cells and dendritic cell infiltration. In pancreatic cancer, FAM83H was associated with the infiltration of CD8+ T cells, gamma delta T cells, and CD4+ T cells and immunomodulators. Therefore, the above research shows that FAM83A/B/H has important value in the immunoregulatory response of cervical cancer and is expected to become a new target for improving the prognosis of cervical cancer patients.

However, there exist some limitations in our research. All of the data came from different online databases, which may cause background heterogeneity, therefore, a larger clinical sample size is necessary to further confirm the above research. Furthermore, in vitro and in vivo experiments are necessary to validate the present study and explore the underlying mechanisms.

**Conclusion**
In summary, with various bioinformatics tools, we determined that the high expression of FAM83A/B/H in cervical cancer were correlated with shortened OS and poor prognosis, indicating that FAM83A/B/H were involved in the occurrence and development of cervical cancer and played an important role in prognosis assessment. The gene regulatory network, tumor-related signaling pathways, and immune infiltration of FAM83A/B/H were also illuminated, which will help to clarify the function and mechanism of FAM83A/B/H in cervical cancer. Therefore, FAM83A/B/H can potentially be identified as tumor biomarker for cervical cancer and is valuable in the pathogenesis, early diagnosis, prognostic evaluation, and immunotherapy of cervical cancer. However, the specific functions and molecular mechanisms of FAM83A/B/H in cervical cancer warrant further confirmation.

**Abbreviations**

CESC: Cervical Squamous Cell Carcinoma; FAM83: The Family with sequence similarity 83; TIMER: Tumor Immune Estimation Resource, GEPIA: Gene Expression Profiling Interactive Analysis, HPA: Human Protein Atlas, TCGA: The Cancer Genome Atlas; OS: overall survival; PPI: protein-protein interaction; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes.

**Declarations**

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**Authors’ contributions**

YQ designed and analyzed the study, drafted the manuscript, participated in data acquisition and analysis and data interpretation, YW critical review and manuscript revision. All authors participated in manuscript editing and approved the final version of the manuscript.

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**Availability of data and materials**

The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

**Ethics approval and consent to participate**

No ethical approval nor informed consent was required in this study due to the public-availability of the data used.

**Consent for publication**
All authors consent to publication.

Competing interests

The authors declare that there are no conflicts of interest.

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Figures
| Analysis Type by Cancer       | Cancer vs. Normal | Cancer vs. Normal | Cancer vs. Normal | Cancer vs. Normal | Cancer vs. Normal | Cancer vs. Normal | Cancer vs. Normal | Cancer vs. Normal |
|-------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                               | FAM 83A           | FAM 83B           | FAM 83C           | FAM 83D           | FAM 83E           | FAM 83F           | FAM 83G           | FAM 83H           |
| Bladder Cancer                |                   |                   |                   |                   |                   |                   |                   |                   |
| Brain and CNS Cancer          |                   |                   |                   |                   |                   |                   |                   |                   |
| Breast Cancer                 | 2                 | 1                 |                   |                   |                   |                   |                   |                   |
| Cervical Cancer               |                   |                   |                   |                   |                   |                   |                   |                   |
| Colorectal Cancer             | 2                 | 3                 | 3                 |                   |                   |                   |                   |                   |
| Esophageal Cancer             | 2                 | 1                 | 2                 |                   |                   |                   |                   |                   |
| Gastric Cancer                |                   |                   |                   |                   |                   |                   |                   |                   |
| Head and Neck Cancer          | 2                 |                   |                   |                   |                   |                   |                   |                   |
| Kidney Cancer                 |                   |                   |                   |                   |                   |                   |                   |                   |
| Leukemia                      |                   |                   |                   |                   |                   |                   |                   |                   |
| Liver Cancer                  |                   |                   |                   |                   |                   |                   |                   |                   |
| Lung Cancer                   | 4                 |                   |                   |                   |                   |                   |                   |                   |
| Lymphoma                      |                   |                   |                   |                   |                   |                   |                   |                   |
| Melanoma                      |                   |                   |                   |                   |                   |                   |                   |                   |
| Myeloma                       |                   |                   |                   |                   |                   |                   |                   |                   |
| Other Cancer                  | 2                 |                   |                   |                   |                   |                   |                   |                   |
| Ovarian Cancer                |                   |                   |                   |                   |                   |                   |                   |                   |
| Pancreatic Cancer             | 2                 |                   |                   |                   |                   |                   |                   |                   |
| Prostate Cancer               |                   |                   |                   |                   |                   |                   |                   |                   |
| Sarcoma                       |                   |                   |                   |                   |                   |                   |                   |                   |
| Significant Unique Analyses   | 16                | 3                 | 4                 | 8                 | 58               | 12               | 6                 | 12               |
| Total Unique Analyses         | 297               | 230               | 238               | 287               | 341              | 254              | 132               | 290               |

**Figure 1**

The mRNA levels of FAM83 family members in cervical cancer and normal tissues (Oncomine). Correlation between FAM83 family members and tumor stages, promoter methylation in patients with CESC (GEPIA and UALCAN)
The expression of FAM83 family members in patients with CESC patients (GEPIA and UALCAN) A-H: The gene expression of FAM83A (A), FAM83B (B), FAM83C (C), FAM83D (D), FAM83E (E), FAM83F (F), FAM83G (G) and FAM83H (H) between CESC and normal tissues derived from gene expression data for GEPIA. I-P: The gene expression of FAM83A (I), FAM83B (J), FAM83C (K), FAM83D (L), FAM83E (M),
FAM83F (N), FAM83G (O) and FAM83H (P) in patients with CESC derived from UALCAN. * P< 0.05, ** P< 0.01, *** P< 0.001.

Figure 3

Correlation between FAM83 expression and tumor stage, promoter methylation in CESC patients (UALCAN) (A-H) The gene expression of FAM83A (A), FAM83B (B), FAM83C (C), FAM83D (D), FAM83E (E), FAM83F (F), FAM83G (G) and FAM83H (H) in different tumor stages in patients with CESC derived from UALCAN. (I-P) The promoter methylation of FAM83A (I), FAM83B (J), FAM83C (K), FAM83D (L), FAM83E (M), FAM83F (N), FAM83G (O) and FAM83H (P) in patients with CESC derived from UALCAN. * P< 0.05, ** P< 0.01, *** P< 0.001.
Figure 4

Genomic alteration and interaction analysis of FAM83 family members in patients with cervical cancer (cBioPortal and GeneMANIA) A-B: Genes expression and mutation analysis of FAM83 family members in patients with cervical cancer. C: Co-expression and interaction analysis of FAM83 family members in patients with cervical cancer.
Figure 5

The prognostic value of FAM83 family members in CESC patients (Kaplan-Meier plotter). A: The prognosis of FAM83 family members in patients with CESC shown by survival significance map with GEPIA. B: The prognosis of FAM83 family members in patients with CESC shown by forest plot. C-J: Relationship between the expression of FAM83A (C), FAM83B (D), FAM83C (E), FAM83D (F), FAM83E (G), FAM83F (H), FAM83G (I) and FAM83H (J) and prognosis of patients with CESC.
Figure 6

Differentially expressed genes correlated with FAM83A/B/H in CESC. A: Genes positively and negatively correlated with FAM83A in CESC with volcano map and heat maps (TOP 50). B: Correlation between FAM83A and expression of LOC100131726, SERPINB4 and GNA15 with Pearson test in the scatter plot. C: Genes positively and negatively correlated with FAM83B in CESC with volcano map and heat maps (TOP 50). D: Correlation between FAM83B and expression of DSP, DENND2C and FAM83G with Pearson test in the scatter plot. E: Genes positively and negatively correlated with FAM83H in CESC with volcano map and heat maps (TOP 50). F: Correlation between FAM83H and expression of PLEC, PLEKHN1 and PKP3 with Pearson test in the scatter plot.
Figure 7

Significantly (Gene Ontology) GO enrichment analysis and KEGG pathways of FAM83 A/B/H and related genes in CESC (Metascape). A: GO terms enrichment of genes correlated with FAM83A with bar graph colored by P-values. B: KEGG enriched terms of genes correlated with FAM83A with bar graph colored by P-values. C: GO terms enrichment of genes correlated with FAM83B with bar graph colored by P-values. D: KEGG enriched terms of genes correlated with FAM83B with bar graph colored by P-values. E: GO terms enrichment of genes correlated with FAM83H with bar graph colored by P-values. F: KEGG enriched terms of genes correlated with FAM83H with bar graph colored by P-values.
Correlation analysis between the expression of FAM83A/B/H and immune molecules in cervical cancer A-D: Correlation between TILs, immunoinhibitors, immunostimulators, MHCs and the expression of FAM83A shown by heatmap. E-H: Correlation between TILs, immunoinhibitors, immunostimulators, MHCs and the expression of FAM83B shown by heatmap. I-L: Correlation between TILs, immunoinhibitors, immunostimulators, MHCs and the expression of FAM83H shown by heatmap. Positive and negative correlations colored by red and blue, respectively. The color intensity is proportional to correlations. TILs: tumor-infiltrating lymphocytes, MHC: major histocompatibility

**Supplementary Files**

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