FNDC3B is associated with ER stress and poor prognosis in cervical cancer

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Abstract. Currently, the occurrence and mortality rate of cervical cancer is high, particularly in low-to-middle-income countries. Therefore, the development of novel diagnostic and treatment strategies for cervical cancer is urgently required. The aim of the present study was to assess the prognostic significance of fibronectin type III domain containing 3B (FNDC3B) expression in patients with cervical cancer and to determine the underlying mechanism of FNDC3 in tumor development. Analysis of the ONCOMINE database revealed that FNDC3B was significantly upregulated in cervical cancer tissue compared with normal tissue. Additionally, FNDC3B expression data and the clinical characteristics of patients with cervical cancer were obtained from the cBioPortal database. Correlations between FNDC3B expression and overall survival were subsequently investigated. The results revealed that increased FNDC3B expression was significantly correlated with a lower overall survival in patients with cervical cancer. A co-expression network was subsequently constructed to elucidate the function of FNDC3B in cervical cancer. Co-expression genes for FNDC3B were obtained from the cBioPortal database and were subjected to Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analyses. The results demonstrated that the genes were enriched in pathways associated with migration, invasion, endoplasmic reticulum (ER) stress and the unfolded protein response (UPR). Furthermore, immunofluorescence results obtained from the Human Protein Atlas revealed that the FNDC3B protein was localized to the ER. The results revealed that upregulated FNDC3B expression may be a biomarker for poor prognosis for patients with cervical cancer. Additionally, the results revealed that FNDC3B may serve an oncogenic role in cancer development via ER stress, UPR, cell migration and invasion. However, further studies are required to determine the exact molecular mechanism of FNDC3B in the development of cervical cancer and to assess its potential as a novel therapeutic target for the treatment of this disease.

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Key words: fibronectin type III domain containing 3B, prognostic biomarker, endoplasmic reticulum stress, unfolded protein response, Gene Ontology, Kyoto Encyclopedia of Genes and Genomes

Introduction

Cervical cancer is the fourth most frequently diagnosed tumor and the fourth leading cause of cancer-associated mortalities in women worldwide. In 2018, ~570,000 females were diagnosed with cervical cancer and ~311,000 deaths were reported (1). The burden of this type of cancer remains heavy, particularly in low-to-middle-income countries. In fact, the number of cervical cancer deaths in developing countries accounted for ~90% of all cervical cancer deaths worldwide in 2015 (2). Cervical cancer ranks second in incidence and mortality in low- and middle-income countries (1). In high-income countries, the incidence and mortality rates of cervical cancer have decreased dramatically due to screening programs being made available in the mid-20th century (3). From 2006 to 2014 in the United States of America (USA), delay-adjusted cervical cancer incidence rates decreased at an average annual percentage rate of 0.3% (4). Mortality rates have also declined at an average annual rate of 0.8% between 2003 and 2014 (4). However, in 2018, ~13,240 women were diagnosed with invasive cervical cancer and 4,170 patients succumbed to the disease in the USA (5). Human papilloma virus infection is a risk factor for cervical cancer, but infection alone does not necessarily lead to the development of the disease (6). Thus, the identification of novel biomarkers with prognostic value is urgently required. Additionally, this may clarify the mechanism underlying tumorigenesis and aid the identification of novel therapeutic targets.

Fibronectin type III domain containing 3B (FNDC3B), also termed factor for adipocyte differentiation 104 (FAD104), was initially determined to be a regulator of adipocyte differentiation (7). A previous study used gene targeting to demonstrate that FNDC3B was involved in cell proliferation, adhesion, spreading and migration in FNDC3B-deficient mice (8). FNDC3B has been previously identified as an oncogene that promotes cell migration in hepatocellular carcinoma (3,9). However, to the best of the authors' knowledge, the prognostic value and function of FNDC3B in cervical cancer has not yet been elucidated.

Systematic biology comprehensively determines the underlying mechanism and allows the identification of new biomarkers in human disease on a global scale. Networks are practical graphical representations of complex interactions (10). The combination of systematic biology and networks is therefore useful to visualize complex biological activities and to annotate protein functions and predictions (11). Thus, the present study utilized systematic biology and network methods to predict the effect of FNDC3B expression on the prognosis of patients with cervical carcinoma and to annotate protein function.

The present study assessed the expression of FNDC3B mRNA in patients with cervical cancer using the ONCOMINE database. Subsequently, the association between FNDC3B expression and prognosis was investigated, and the biological function and mechanism of action of FNDC3B in patients with cervical cancer was explored using publicly accessible databases.

Materials and methods

Expression analysis of FNDC3B in cervical cancer. The expression value of FNDC3B mRNA in cervical cancer was analyzed using the ONCOMINE database (version 4.5; www.oncomine.org/resource/login.html) (12). Cancerous tissues and normal tissues obtained from healthy volunteers were subsequently compared according to the default settings of $P<1x10^{-4}$, fold-change >2 and gene ranking in the top 10% (13).

Survival analysis. FNDC3B gene expression data and the clinical characteristics of patients with cervical cancer were downloaded from The Cancer Genome Atlas (www.cbioportal.org) (14,15). The association between FNDC3B expression and patient overall survival (OS) was analyzed using the R package survival (version 2.43-3, https://cran.r-project.org/web/views/Survival.html) (16,17). Samples were then divided into high- and low-expression groups using the median expression level of FNDC3B mRNA as the cut-off point. The difference in OS between the two groups was assessed using Kaplan-Meier curves followed by a log-rank test.

Co-expression gene identification and protein-protein interaction network visualization. The cBioportal database (cbioportal.org) was used to assess and visualize cancer co-expression data (14), which was subsequently downloaded. FNDC3B co-expression genes with an absolute correlation coefficient of >0.4 and P<0.05 were obtained from cBioPortal. The Search Tool for the Retrieval of Interacting Genes/Proteins (STRING version 10.5, string-db.org) was used to perform protein-protein interaction (PPI) analysis (18). Data was subsequently downloaded and the PPI network was constructed using Cytoscape software (version 3.7.1) (19).

Gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) enrichment analysis. The clusterProfiler package (version 3.8.1, http://bioconductor.org/packages/release/bioc/html/clusterProfiler.html) (20) in R was used to identify and visualize the GO terms (geneontology.org) and KEGG pathways (www.genome.jp/kegg) associated with the FNDC3B co-expression genes. The P-value was adjusted using the Benjamini-Hochberg method. P<0.05 and q<0.05 were set as the cut-off criteria for significant enrichment.

Localization of FNDC3B in cells. The cellular localization of FNDC3B was determined using The Human Protein Atlas (version 18.1, www.proteinatlas.org) (21). The key word used for searching was 'FNDC3B'. The location of FNDC3B in cells was determined using the immunofluorescence with anti-FNDC3B antibodies (cat. no. HPA007859; Atlas Antibodies AB). Images were obtained from www.proteinatlas.org/ENSG00000075420-FNDC3B/cell#img.

Statistical analysis. Statistical analyses were performed using R software (version 3.5.1; R Foundation for Statistical Computing). The relative expression of FNDC3B was presented as the mean ± standard deviation. The differential expression of FNDC3B between cancerous and non-cancerous samples was compared using an independent Student's t-test. A total of 20 cancerous and eight non-cancerous samples from the multi-cancer dataset published by Pyeon *et al* (22) were selected for analysis in the present study. An additional 32 cancerous and 21 non-cancerous samples were selected from a dataset published by Scotto *et al* (23). Kaplan-Meier survival analysis was performed to estimate the survival distributions and the log-rank test was used to compare the survival curves. The correlation of gene expression was analyzed by Spearman's correlation test. P<0.05 was considered to indicate a statistically significant difference.

Results

FNDC3B expression is upregulated in cervical cancer. Analysis of the ONCOMINE database revealed that the level of FNDC3B mRNA was significantly increased in cervical cancer tissues compared with normal tissues. By contrast, no cervical cancer tissues with downregulated FNDC3B expression were identified (Fig. 1).

Survival prediction of FNDC3B in cervical cancer. Survival analysis was performed to investigate the association between upregulated FNDC3B expression and the clinical outcome of patients with cervical cancer. As presented in Fig. 2, upregulated FNDC3B expression was significantly associated with a lower OS in patients with cervical cancer. The results indicated that upregulated FNDC3B expression may serve as a biomarker of poor prognosis in patients with cervical cancer.

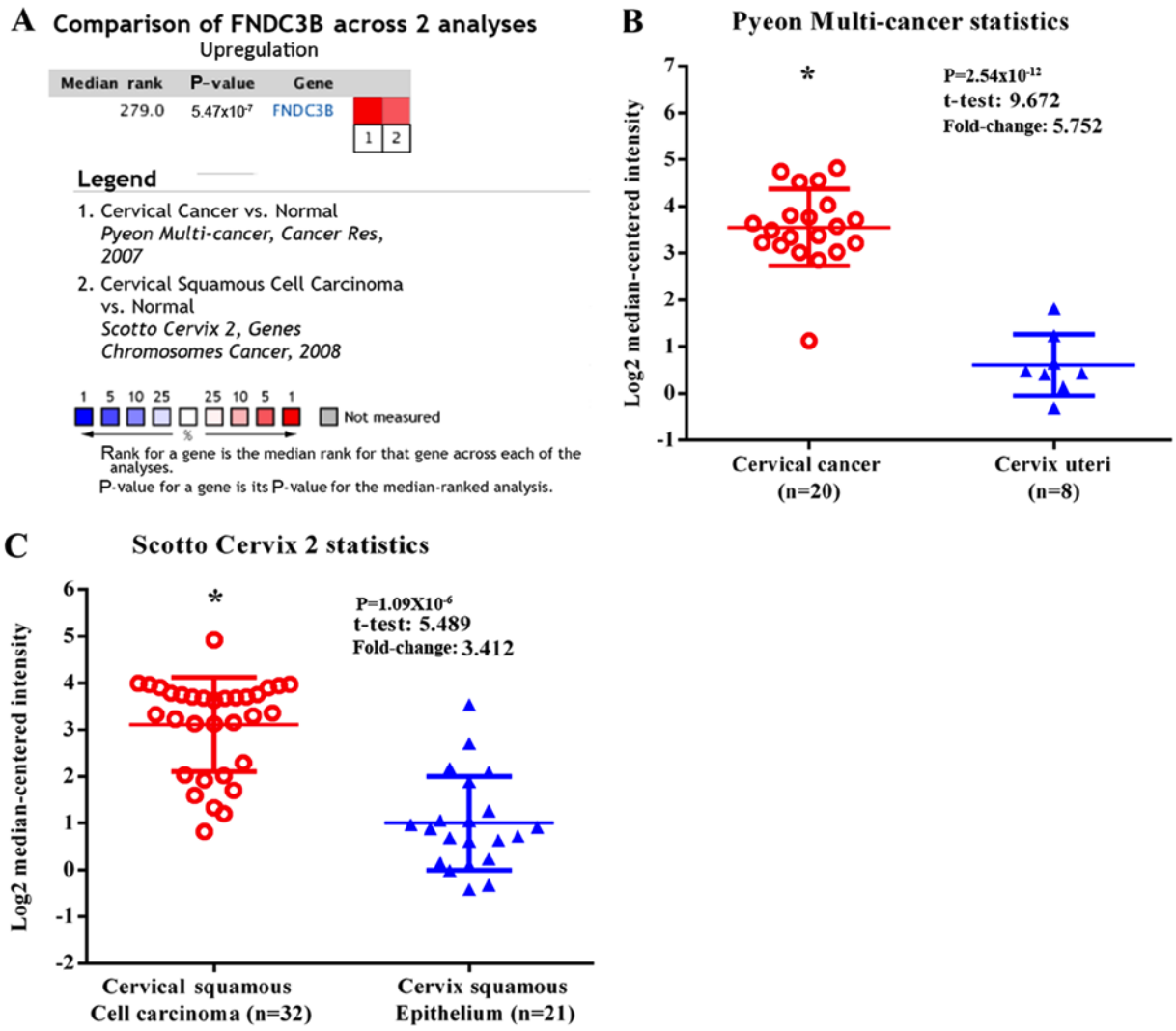

Figure 1. Validation of upregulated FNDC3B expression using the ONCOMINE database. FNDC3B mRNA expression in cancerous and corresponding normal tissue was determined using the ONCOMINE database. (A) The comparison of FNDC3B expression across two cervical cancer analyses is presented. Red and blue represent upregulated and downregulated expression, respectively. (B) FNDC3B expression in cervical cancer and normal tissue samples from the multi-cancer study by Pyeon *et al* (22) (normal tissues, 8 cases; cervical cancer tissues, 20 cases). (C) FNDC3B expression in cervical cancer and normal tissue samples from the cervical cancer study by Scotto *et al* (23) (normal tissues, 21 cases; cervical cancer tissues, 32 cases). Data are presented as the mean ± SD. *P<0.05 vs. the non-cancerous group. FNDC3B, fibronectin type III domain containing 3B.

Co-expression gene identification and PPI network visualization. Analysis of the cBioPortal database revealed that a total of 88 genes were significantly co-expressed with FNDC3B. Additionally, 79 co-expressed genes were positively correlated with FNDC3B and 9 co-expressed genes were negatively correlated with FNDC3B (Table I). A PPI network consisting of FNDC3B co-expression genes based on the STRING database was constructed using Cytoscape software. The co-expression network contained 66 nodes and 179 edges (Fig. 3).

Gene co-expression network analysis is associated with FNDC3B in cervical cancer. The results of GO enrichment analysis revealed that the co-expression genes were significantly enriched in 72 biological processes (BPs), 29 molecule functions (MFs) and 50 cellular components (CCs). The five top ranked BPs, MFs and CCs were as follows: 'Extracellular matrix organization', 'extracellular structure organization', 'protein folding', 'response to unfolded protein', 'response to topologically

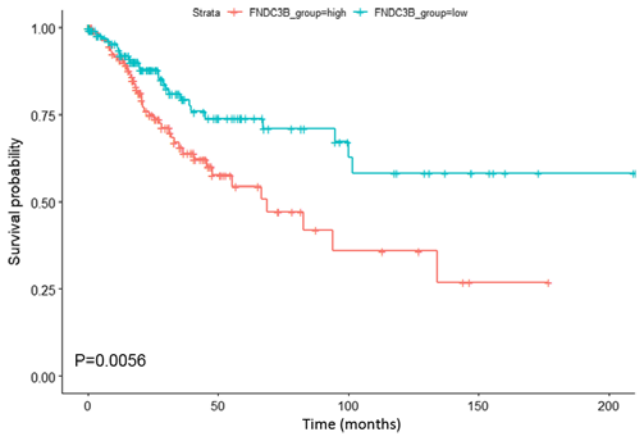

Figure 2. Overall survival analysis of FNDC3B with data obtained from The Cancer Genome Atlas database. Overall survival analysis of FNDC3B was assessed using Kaplan-Meier curves followed by a log-rank test. The blue and red lines represent patients with a low and FNDC3B expression, respectively. FNDC3B, fibronectin type III domain containing 3B.

Table I. Co-expressed genes associated with fibronectin type III domain containing 3B.

Correlated gene	Cytoband	Spearman's correlation coefficient	P-value
NCEH1	3q26.31	0.56	3.51×10^{-26}
B4GALT1	9p21.1	0.54	5.53×10^{-25}
CALU	7q32.1	0.54	7.49×10^{-25}
LAMC1	1q25.3	0.54	1.87×10^{-24}
ITGB1	10p11.22	0.52	4.80×10^{-23}
MCFD2	2p21	0.52	2.19×10^{-22}
TMED7	5q22.3	0.51	6.07×10^{-22}
COPB2	3q23	0.51	8.75×10^{-22}
SKIL	3q26.2	0.51	1.72×10^{-21}
UGGT1	2q14.3	0.50	3.66×10^{-21}
TMEM263	12q23.3	0.50	5.60×10^{-21}
HSPA5	9q33.3	0.50	2.20×10^{-20}
SEC62	3q26.2	0.49	4.63×10^{-20}
SUSD1	9q31.3-q32	0.49	1.62×10^{-19}
PLOD2	3q24	0.48	2.13×10^{-19}
TEAD1	11p15.3	0.47	2.76×10^{-18}
LMAN1	18q21.32	0.47	2.81×10^{-18}
HSP90B1	12q23.3	0.47	3.08×10^{-18}
FKBP14	7p14.3	0.47	6.05×10^{-18}
ITGB3	17q21.32	0.47	6.39×10^{-18}
CCDC50	3q28	0.47	6.82×10^{-18}
KIRREL1	1q23.1	0.47	6.89×10^{-18}
LPP	3q27.3-q28	0.47	7.66×10^{-18}
SLC39A14	8p21.3	0.46	1.04×10^{-17}
NCKAP5L	12q13.12	0.46	1.12×10^{-17}
ATP13A3	3q29	0.46	1.29×10^{-17}
EXT2	11p11.2	0.46	1.76×10^{-17}
LAMB1	7q31.1	0.46	2.85×10^{-17}
SLC33A1	3q25.31	0.46	2.99×10^{-17}
TTYH3	7p22.3	0.46	3.22×10^{-17}
FSTL1	3q13.33	0.46	4.40×10^{-17}
SSR3	3q25.31	0.46	4.76×10^{-17}
IKBIP	12q23.1	0.45	6.75×10^{-17}
SERPINH1	11q13.5	0.45	2.10×10^{-16}
PDIA6	2p25.1	0.44	4.18×10^{-16}
TMEM30A	6q14.1	0.44	4.84×10^{-16}
PLOD1	1p36.22	0.43	1.57×10^{-15}
PLBD2	12q24.13	0.43	1.63×10^{-15}
AGRN	1p36.33	0.43	1.75×10^{-15}
GNS	12q14.3	0.43	1.96×10^{-15}
ZNF281	1q32.1	0.43	2.00×10^{-15}
SLC41A2	12q23.3	0.43	3.07×10^{-15}
ADAM9	8p11.22	0.43	3.18×10^{-15}
TGFBR2	3p24.1	0.43	3.54×10^{-15}
HIF1A	14q23.2	0.43	3.80×10^{-15}
STC1	8p21.2	0.43	4.46×10^{-15}
DNAJC10	2q32.1	0.43	5.28×10^{-15}
ITGAV	2q32.1	0.43	7.41×10^{-15}
GANAB	11q12.3	0.42	9.71×10^{-15}
PAPSS2	10q23.2-q23.31	0.42	1.02×10^{-14}
RAB43	3q21.3	0.42	1.05×10^{-14}
TGOLN2	2p11.2	0.42	1.63×10^{-14}

Table I. Continued.

Correlated gene	Cytoband	Spearman's correlation coefficient	P-value
TMEM39A	3q13.33	0.42	$1.71x10^{-14}$
ITFG1	16q12.1	0.42	$2.29x10^{-14}$
BICC1	10q21.1	0.42	$2.66x10^{-14}$
ZBTB38	3q23	0.41	$3.83x10^{-14}$
ERLEC1	2p16.2	0.41	$5.09x10^{-14}$
SEC24D	4q26	0.41	$5.18x10^{-14}$
HSPA13	21q11.2	0.41	$5.49x10^{-14}$
LATS2	13q12.11	0.41	$5.53x10^{-14}$
MPDZ	9p23	0.41	$5.81x10^{-14}$
LAMC2	1q25.3	0.41	$5.85x10^{-14}$
OSMR	5p13.1	0.41	$6.70x10^{-14}$
RAI14	5p13.2	0.41	$7.52x10^{-14}$
HSPG2	1p36.12	0.41	$7.53x10^{-14}$
PDIA4	7q36.1	0.41	$7.92x10^{-14}$
ITGA1	5q11.2	0.41	$9.88x10^{-14}$
CMTM6	3p22.3	0.41	$1.02x10^{-13}$
SURF4	9q34.2	0.41	$1.25x10^{-13}$
TNS3	7p12.3	0.41	$1.29x10^{-13}$
CPD	17q11.2	0.41	$1.40x10^{-13}$
OSBPL10	3p23	0.41	$1.42x10^{-13}$
CD276	15q24.1	0.40	$2.47x10^{-13}$
GALNT1	18q12.2	0.40	$2.72x10^{-13}$
CKAP4	12q23.3	0.40	$2.91x10^{-13}$
GPX8	5q11.2	0.40	$2.97x10^{-13}$
NEDD9	6p24.2	0.40	$3.25x10^{-13}$
TGFB2	1q41	0.40	$3.30x10^{-13}$
PARVA	11p15.3	0.40	$3.37x10^{-13}$
NUDT8	11q13.2	-0.40	$3.28x10^{-13}$
NOL12	22q13.1	-0.40	$3.28x10^{-13}$
TIMM13	19p13.3	-0.40	$3.08x10^{-13}$
ENDOG	9q34.11	-0.40	$2.91x10^{-13}$
COQ4	9q34.11	-0.41	$1.41x10^{-13}$
VPS28	8q24.3	-0.41	$6.90x10^{-14}$
CYC1	8q24.3	-0.43	$4.54x10^{-15}$
COMTD1	10q22.2	-0.43	$3.48x10^{-15}$
NDUFS7	19p13.3	-0.43	$1.82x10^{-15}$

incorrect protein', 'unfolded protein binding', 'extracellular matrix binding', 'protein disulfide isomerase activity', 'intramolecular oxidoreductase activity, transposing S-S bonds', 'chemokine binding', 'endoplasmic reticulum (ER) lumen', 'melanosome', 'pigment granule', 'ER chaperone complex' and 'ER-Golgi intermediate compartment' (Fig. 4A-C). The results of KEGG pathway enrichment analysis demonstrated that the co-expression genes of FNDC3B were significantly enriched in four pathways, including 'protein processing in ER', 'extracellular matrix (ECM)-receptor interaction', 'focal adhesion' and 'PI3K-Akt signaling pathway' (Fig. 4D).

Cellular location of FNDC3B. The results of immunofluorescence analysis obtained from The Human Protein Atlas database are presented in Fig. 5. Co-localization of FNDC3B (green) and ER (yellow) was observed, indicating that FNDC3B was localized to the ER.

Discussion

The present study assessed the prognostic effect of FNDC3B and its potential underlying molecular mechanisms in cervical cancer using bioinformatics tools. FNDC3B is an important oncogenic driver gene that was identified in an oncogenomic screen for oncogenes in hepatocellular carcinoma (3). Lin *et al* (9) identified FNDC3B as a biomarker and therapeutic target for hepatocellular carcinoma metastasis. In the present study, FNDC3B expression was upregulated in cervical cancer

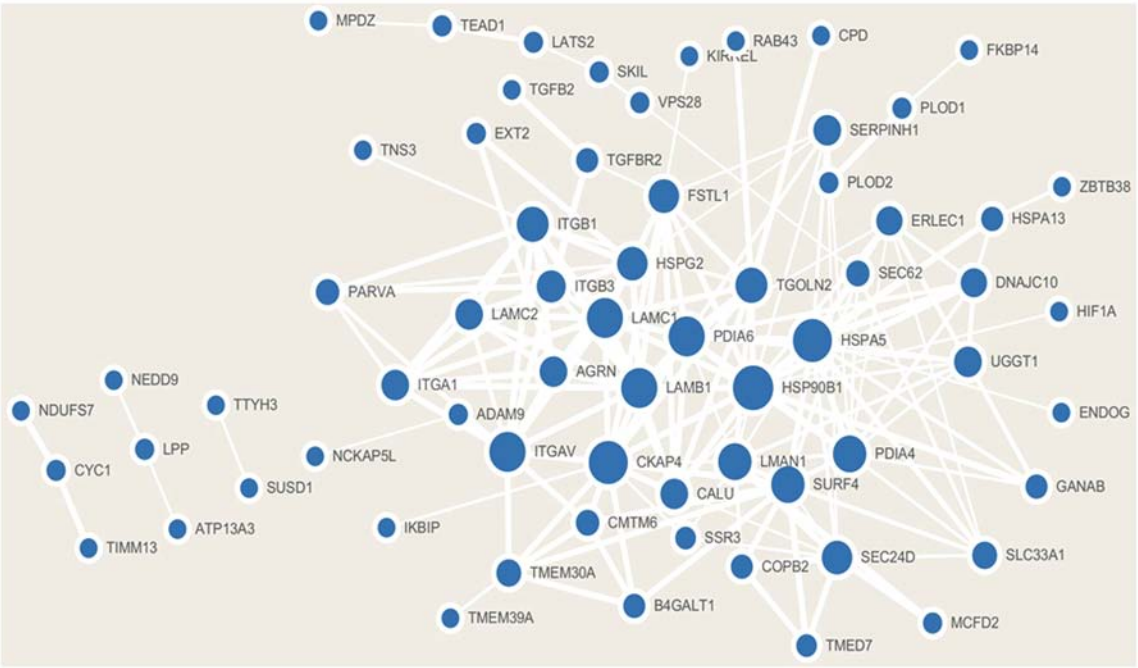

Figure 3. Visualization of the PPI network of FNDC3B co-expression. In the PPI, co-expressed genes are presented as nodes and the interactions between them are presented as edges. Label size indicates the degree value and the thickness of the lines represents the level of closeness between the two nodes. PPI, protein-protein interaction; FNDC3B, fibronectin type III domain containing 3B.

tissues and was associated with a poor prognosis. As the function of FNDC3B in cervical cancer is unknown, the present study investigated its potential functions by constructing a co-expression network. GO and KEGG enrichment analyses revealed that FNDC3B was associated with ER stress and UPR signaling. Furthermore, KEGG pathways analysis revealed that FNDC3B was enriched in 'protein processing in ER'. The ER is a subcellular organelle that is associated with protein synthesis, folding and quality control (24). Adequately folded proteins are subsequently transported to their destined sites, whereas terminally misfolded proteins are subjected to degradation via ER-associated degradation pathways (25). Certain biological processes including 'protein folding', 'response to unfolded protein' and 'response to topologically incorrect protein' were enriched in the present study and were associated with ER stress and UPR activation. The highest enrichment of MF and CC were 'unfolded protein binding' and 'ER lumen', respectively. These indicated that the function of FNDC3B may be associated with ER stress and UPR. The role of ER stress and UPR activation in the development of cancer has been previously revealed in various types of cancer, including cervical cancer (26-28). Tumor growth can produce several cell-intrinsic and extrinsic stresses (29). The effects induced by these stresses disrupt the ER protein-folding environment, resulting in protein misfolding and the accumulation of misfolded proteins, which is referred to as ER stress (26). Tolerable levels of ER stress promote tumor development by bolstering viability under hypoxia and nutrient deprivation, enhancing metastatic spread by supporting epithelial-mesenchymal transition (EMT), tumor cell dormancy and tumor-initiating cell function, thereby stimulating angiogenesis (29). ER stress can activate the UPR, which is mediated by three ER membrane localized stress sensing proteins: Inositol-requiring enzyme 1, activating transcription factor 6 and protein kinase RNA-like ER kinase (30). Additionally, UPR activation may be tumor-supportive or suppressive depending on the intensity and duration of ER stress (31). The UPR also acts to restore ER homeostasis for cancer cell survival (32). When corrective efforts are insufficient, the cell will undergo apoptosis (33). In the current study, FNDC3B was localized to the ER. The results of the present study may therefore indicate the function of FNDC3B in ER stress and UPR.

Although FNDC3B acts as an oncogenic gene, its target genes have not been identified. However, certain studies have indicated that FNDC3B may be involved in stress granule formation-mediated ER stress (34-36). Stress granules are dense aggregations that are composed of mRNAs and proteins under conditions of stress. FNDC3B is primarily composed of fibronectin type III domains (9). FNDC3B was identified as an RNA-binding protein candidate via the interactome capture of proliferating human HeLa cells (37). When cells were challenged with ER stress, stress granules were formed (35). FNDC3B has also been identified in stress granule proteomes (34). Stress granules recruit various mRNAs and signaling proteins, including receptor for activated C kinase 1/mitogen-activated protein kinase 14/JNK, integrated stress response/phosphorylated-eukaryotic translation initiation factor 2A, rapamycin and Rho GTPase signaling pathways, which modulate metabolism, growth and survival (36). However, the role of FNDC3B in stress granule formation requires further elucidation.

In congruence with the current study, a previous study has indicated that FNDC3B induces and activates the PI3K/Akt signaling pathway (3). The FNDC3B co-expression genes identified in the present study were enriched in the PI3K/Akt

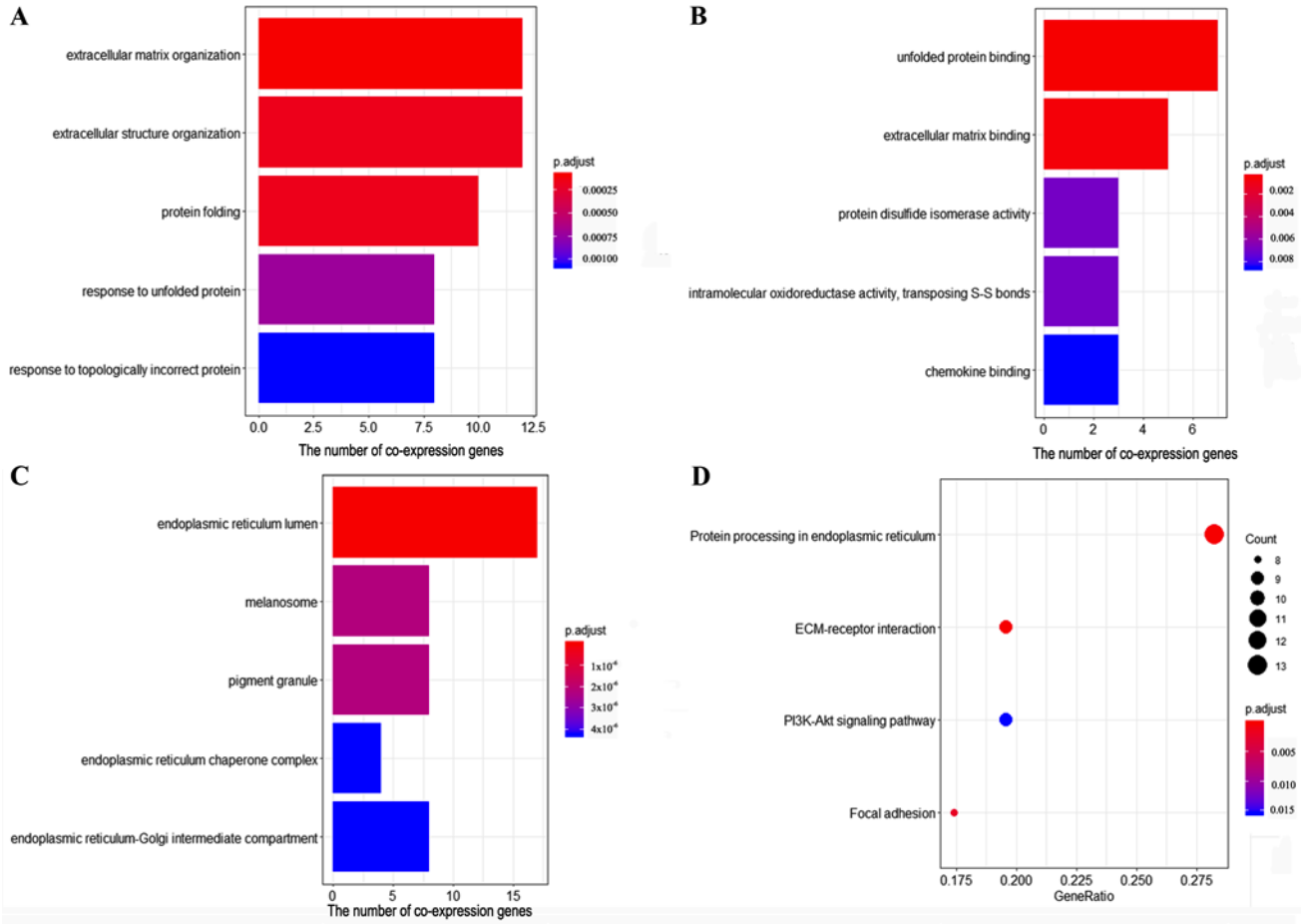

Figure 4. GO and KEGG enrichment analyses in co-expression genes associated with FNDC3B. GO terms and KEGG pathways were enriched and visualized using the clusterProfiler package in R. The P-value was adjusted using the Benjamini-Hochberg method. Enriched terms or pathways with a low or high significance are presented in blue and red, respectively. The horizontal axis in (A-C) was designed to indicate the number of co-expression genes enriched in each term, while the vertical axis indicates the enriched terms. The top five most enriched GO terms belonging to the category of (A) BP, (B) MF and (C) CC are presented. (D) Enriched KEGG pathways are presented. The label size represents the number of co-expression genes enriched in each pathway. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; FNDC3B, fibronectin type III domain containing 3B; BP, biological process; MF, molecule function; CC, cellular component.

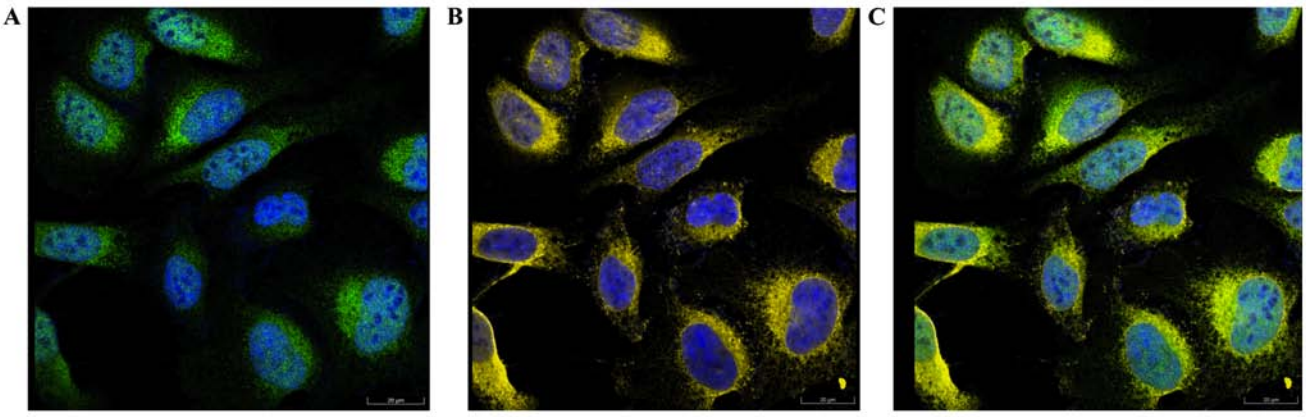

Figure 5. Cellular localization of FNDC3B determined via the Human Protein Atlas database. Immunofluorescence analysis results were obtained from the Human Protein Atlas database. FNDC3B and organelle probes are presented as different channels in the multicolor images. (A) FNDC3B was labeled with green fluorescence and nuclei were stained in blue. (B) ER was stained yellow and nuclei were stained blue. (C) Merged image of (A) and (B). FNDC3B, fibronectin type III domain containing 3B.

signaling pathway, which serves a pivotal role in tumor growth, proliferation, metabolism, motility, migration, invasion, angiogenesis, survival and autophagy (38). Considering the additional pathway enrichment of 'ECM-receptor interaction' and 'focal adhesion' determined in the current study, FNDC3B may be involved in migration and invasion.

In conclusion, the present study revealed that FNDC3B was upregulated in cervical cancer tissue compared with normal tissue. Furthermore, elevated FNDC3B levels were associated with poor OS. Therefore, it was determined that elevated FNDC3B may be a biomarker for poor prognosis in patients with cervical cancer. Coupled with the co-expression network analysis of the current study, it was inferred that FNDC3B may serve an oncogenic role in cancer development via ER stress, UPR, cell migration and invasion. However, further studies are required to determine the exact molecular mechanism of FNDC3B in the development of cervical cancer and its potential as a novel therapeutic target.

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Availability of data and materials

All datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JZ, JT and HW designed the present study. BH and JZ performed the experiments, analyzed the data and prepared the manuscript. All authors read and approved the final version of the manuscript.

Ethics statement and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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