Systematic Review And Meta-Analysis

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FANCI may serve as a prognostic biomarker for cervical cancer

A systematic review and meta-analysis

Xiaoling Liu, MM[a,b,*], Xiqin Liu, MM[a,b], Xia Han, MD[a]

Abstract

Background: DNA damage is a fundamental process that plays a considerable role in generating protein diversity. *FANCI*, loaded on the altered chromatin, plays a vital role in DNA damage. Abnormal *FANCI* expression is potentially associated with carcinogenesis. However, the biological role of *FANCI* in cervical cancer is yet to be determined.

Methods: We analyzed *FANCI* expression via multiple gene expression databases. Genes co-expressed with *FANCI* and its regulators were identified using LinkedOmics. The correlations between *FANCI* and cancer immune infiltrates were investigated via Tumor Immune Estimation Resource (TIMER).

Results: *FANCI* was found upregulated with amplification in tumor tissues of multiple cervical cancer cohorts. High *FANCI* expression was associated with poorer overall survival (OS). Functional network analysis suggested that *FANCI* regulates spliceosome, DNA replication, and cell cycle signaling via pathways involving several cancer-related kinases and the E2F family. In additional, *FANCI* expression was positively correlated with infiltrating levels of CD4+ T and CD8+ T cells, and neutrophils. *FANCI* expression also showed strong correlations with diverse immune marker sets in cervical cancer.

Conclusion: These findings suggested that *FANCI* is correlated with prognosis of and immune infiltration in cervical cancer, laying a foundation for further study of the immune regulatory role of *FANCI* in cervical cancer.

Abbreviations: OS = overall survival, TCGA = the cancer genome atlas, TIMER = tumor immune estimation resource, GSEA = gene set enrichment analysis, GSEA = gene set enrichment analysis.

Keywords: biochemical tumor marker, gene expression regulation, prognosis, uterine cervical neoplasms

1. Introduction

Cervical cancer is one of the most common malignancies of the female genital tract. It is the fourth leading cause of cancer-related death in females, with an estimated 311,365 deaths worldwide in 2018.[1] The risk of death in females with cervical cancer is higher in low-income countries (0.9%) than in high-income countries (0.3%).[2]

Despite a series of advances in the prevention, screening, and treatment of cervical cancer (e.g., modern radiotherapy techniques and targeted therapy), treatment against cervical cancer has not significantly improved.[3,4] In China, the overall morbidity and mortality associated with cervical cancer have steadily increased from 1991 to 2013, and it is predicted to rise continually in future.[5] In addition to metastasis or recurrence, the disease is linked to poor prognosis, with a 5-year relative survival rate of 66.3% (Based on data from 2011–2017), and distant stage with a 5-year relative overall survival (OS) rate of only 17.6%.[6] Hence, identifying novel therapeutic targets and survival-associated biomarkers is essential to enhance the therapeutic effect in cervical cancer.

DNA damage is a fundamental process that plays a considerable role in generating protein diversity. DNA damage is also the key to the pathology of numerous diseases, especially cancers.[7] The connection between cancer biology and DNA damage is of primary importance to understand the mechanisms leading to disease and also to improve the development of therapeutic approaches.[8] Upon DNA damage, *FANCI* and FANCD2 can be phosphorylated by ATM and ATR kinases. This complex holds a E3 ubiquitin ligase activity via *FANCI*, which collaborates with the UBE2T ubiquitin-conjugating enzyme.[9] After DNA damage, *FANCI* and FANCD2 proteins are loaded on the altered chromatin.[10] Both partners are required for their reciprocal mono-ubiquitination by the FA core complex.[10–12]

It is also known that *FANCI*, complexed with FANCD2, suppresses the fanconi anemia pathway in the absence of DNA damage.[13] One study indicated that the expression of FANCI is changed in prostate cancer.[14] However, the biological function

Editor: Balaji Thas Moorthy.

The authors report no conflicts of interest.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Supplemental Digital Content is available for this article.

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How to cite this article: Liu X, Liu X, Han X. FANCI may serve as a prognostic biomarker for cervical cancer: A systematic review and meta-analysis. Medicine 2021;100:51(e27690).

Received: 10 June 2021 / Received in final form: 24 September 2021 / Accepted: 18 October 2021

http://dx.doi.org/10.1097/MD.0000000000027690

of *FANCI* in cervical cancer remains to be determined. Here, we investigated *FANCI* expression and mutations in data from patients with cervical cancer in The Cancer Genome Atlas (TCGA) and various public databases. Using multi-dimensional analysis, we evaluated genomic alterations and functional networks related to *FANCI* in cervical cancer and explored its role in tumor immunity. Our results could potentially reveal new targets and strategies for cervical cancer diagnosis and treatment.

2. Materials and methods

2.1. Databases description

2.1.1. Oncomine database analysis. The expression level of the *FANCI* gene in cervical cancers was examined in the Oncomine 4.5 database (https://www.oncomine.org/).[15] Oncomine is a cancer microarray database and web-based data-mining platform. The threshold was determined according to the following values: *P* value of .05, fold change of 1.5, and gene ranking of all.

2.1.2. UALCAN database analysis. UALCAN (http://ualcan.path.uab.edu) uses TCGA level 3 RNA-seq and clinical data from 31 cancer types,[16] allowing analysis of relative expression of genes across tumor and normal samples, as well as in various tumor sub-groups based on individual cancer stages, tumor grade, or other clinicopathological features.

2.2. Kaplan–Meier survival curve analysis

Kaplan–Meier Plotter (http://kmplot.com/analysis), an online survival analysis tool, was used to assess the effects of genes on the survival rates in cancers, including 371 CERVICAL CANCER.[17] The correlation between *FANCI* expression and cervical cancer patients OS was analyzed using Kaplan–Meier Plotter.

2.2.1. LinkedOmics database analysis. The LinkedOmics database (http://www.linkedomics.org/admin.php) is a web-based platform for analyzing 32 TCGA cancer-associated multi-dimensional datasets.[18]

FANCI co-expression was analyzed statistically using Pearson's correlation coefficient, presenting in volcano plots, heat maps, or scatter plots. The Function module of LinkedOmics analyzes Gene Ontology (GO) biological process (GO_BP), Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, kinase-target enrichment, miRNA-target enrichment, and transcription factor-target enrichment by the gene set enrichment analysis (GSEA). The rank criterion was FDR < 0.05, and 1000 simulations were performed.

2.2.2. TIMER database analysis. *TIMER* is a comprehensive resource for systematic ally analyzing immune infiltrates across diverse cancer types from TCGA (https://cistrome.shinyapps.io/timer/), which includes 10,897 samples across 32 cancer types.[19] TIMER applies a deconvolution method to infer the abundance of tumor-infiltrating immune cells (TIICs) from gene expression profiles. We analyzed *FANCI* expression in cervical cancer, and the correlation of *FANCI* expression with the abundance of immune infiltrates, including B cells, $CD4^+$ T cells, $CD8^+$ T cells, neutrophils, macrophages, and dendritic cells, as well as the tumor purity.

2.3. Statistical analysis

The *t* test $P < .05$ was utilized to determine the statistical significance between groups with different expression levels of *FANCI*. We compared the OS of cervical cancer patients separated by the median expression level of specific genes. Kaplan–Meier curves were used to compare the survival time differences. The log-rank test $P < .05$ was used to indicate the significance of survival time differences.

3. Results

3.1. Elevated expression of FANCI in cervical cancer

We initially evaluated the *FANCI* transcription levels in multiple cervical cancer studies from TCGA. Data in the Oncomine database indicated that the mRNA expression of *FANCI* was significantly higher in cervical cancer tissues than in the adjacent normal tissues (Fig. 1). In addition, results from the UALCAN database showed that the *FANCI* expression was significantly higher in tumor tissues than in the normal tissue (Fig. 2A). Further sub-group analysis of multiple clinic-pathological features of TCGA cervical cancer samples in UALCAN database consistently showed elevated transcription levels of *FANCI*. The expression of *FANCI* was significantly higher in cervical cancer patients than normal controls in subgroup analysis based on weight, age, ethnicity, disease stages, and tumor grade (Fig. 2B–F). Thus,

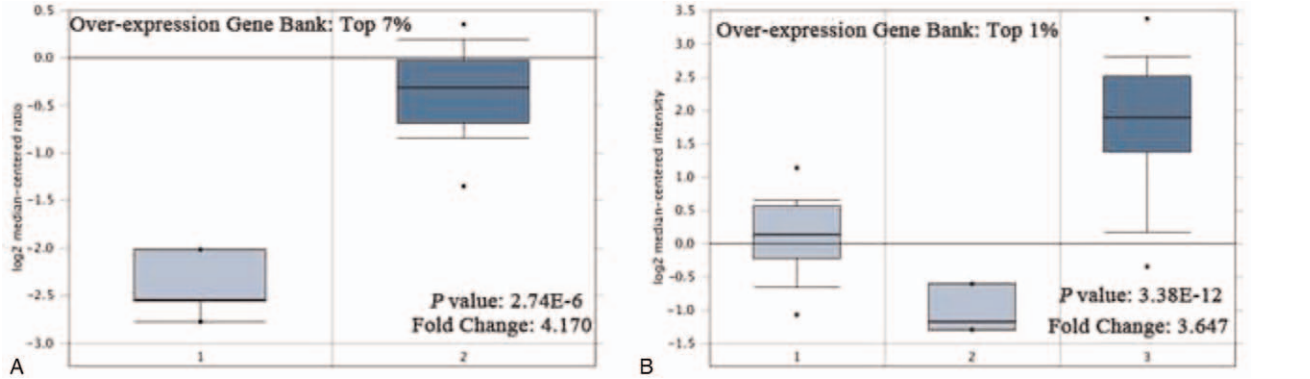

Figure 1. *FANCI* expression in cervical cancer according to public databases. (A,B) Box plot showing *FANCI* mRNA levels in cervical cancer specimens (dark blue) and their normal controls (light blue) according to datasets from Biewenga Cervix and Scotto Cervix 2, respectively.

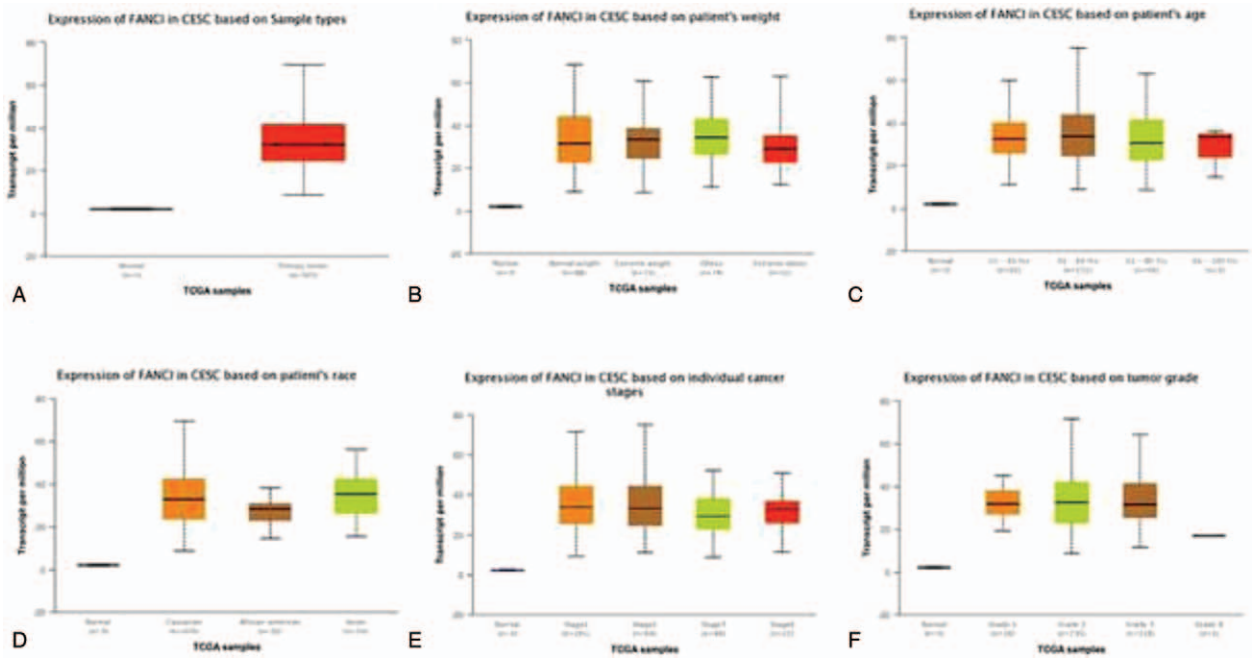

Figure 2. *FANCI* transcription in cervical cancer based on TCGA database. (A) Boxplot showing relative expression of *FANCI* in normal individuals or cervical cancer patients. (B) Boxplot showing relative expression of *FANCI* in normal individuals or cervical cancer patients with average weight, extreme weight, obesity, or extreme obesity. (C) Boxplot showing relative expression of *FANCI* in normal individuals of any age or cervical cancer patients aged 21–40, 41–60, 61–80, or 81–100 yr. (D) Boxplot showing relative expression of *FANCI* in normal individuals of any ethnicity or cervical cancer patients of Caucasian, African-American, or Asian ethnicity. (E) Boxplot showing relative expression of *FANCI* in normal individuals or cervical cancer patients with stage 1, 2, 3, or 4 tumors. (F) Boxplot showing relative expression of *FANCI* in normal individuals or cervical cancer patients with grade 1, 2, 3, or 4 tumors. Figures (A–F) conducted using UALCAN.

FANCI expression may serve as a potential diagnostic indicator in cervical cancer.

3.2. FANCI expression is survival-associated

Kaplan–Meier survival curves were used to assess the association between *FANCI* expression and the survival outcomes of cervical cancer cohorts with survival information available. The patients were separated into 2 groups according to the median value of *FANCI* expression level in each cohort. Generally, the high *FANCI* expression group had significantly shorter OS (log-rank test, $P < .05$), compared with the low expression group in the cervical cancer cohort (Fig. 3).

3.3. FANCI co-expression networks in cervical cancer

To gain an insight into the biological function of *FANCI* in cervical cancer, the function modu of LinkedOmics was used to examine *FANCI* co-expression mode in cervical cancer cohort. As shown in Figure 4A, 3558 genes (dark red dots) were shown significant positive correlations with *FANCI*, whereas 1891 genes (dark green dots) were shown to have significant negative correlations (false discovery rate, FDR < 0.01). The top 50 significant genes positively and negatively correlated with *FANCI* were shown in the heat map (Fig. 4B,C). A total description of the co-expressed genes was detailed in Supplementary Table 1, http://links.lww.com/MD/G558.

FANCI expression showed a strong positive association with expression of *BLM* ($r = 0.7281$, $P = 6.727\text{E-}43$), *PRC1* ($r = 0.7148$, $P = 1.049\text{E-}40$), and *C15orf42* ($r = 0.6365$, $P = 4.951\text{E-}30$), *RCCD1* ($r = 0.626$, $P = 7.941\text{E-}29$), *CCNB2* ($r = 0.5992$, $P = 6.007\text{E-}26$), etc (Fig. 5).

Significant Gene Ontology (GO) term annotation by gene set enrichment analysis (GSEA) showed that *FANCI* co-expressed genes participate primarily in chromosome segregation, mitotic cell cycle phase transition, double-strand break repair, and mRNA processing, while the activities like fatty acid metabolic

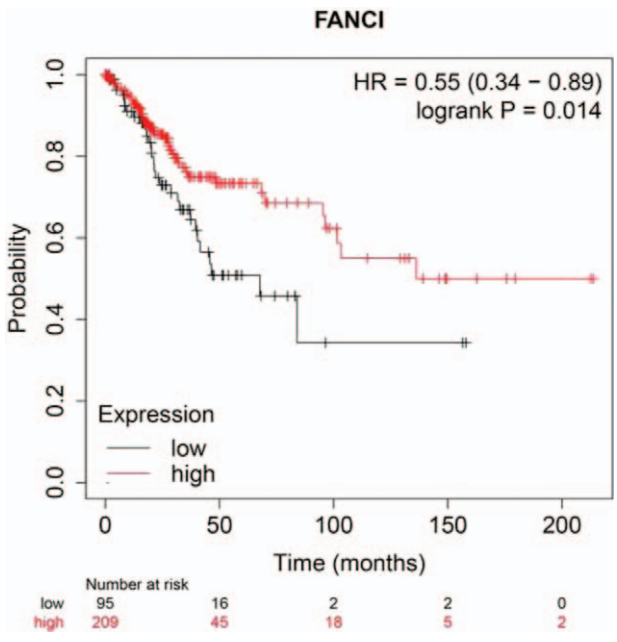

Figure 3. Survival curve analyses showing the correlation between *FANCI* mRNA expression and overall survival in patients with cervical cancer.

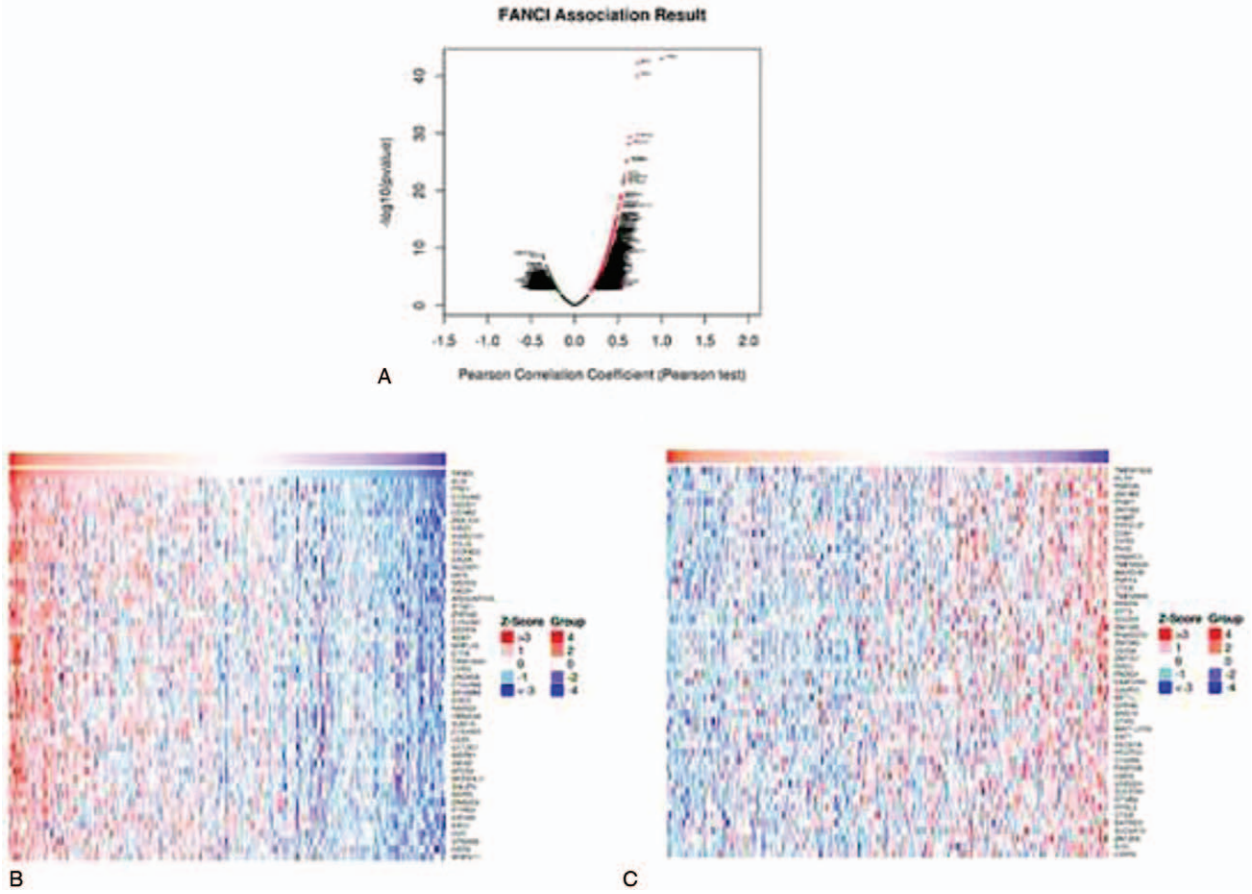

Figure 4. Genes differentially expressed in correlation with *FANCI* in cervical cancer (LinkedOmics). (A) Pearson test used to analyze correlations between *FANCI* and genes differentially expressed in cervical cancer. (B–C) Heat maps showing genes negatively and positively correlated with *FANCI* in cervical cancer (TOP 50).

process, peroxisomal transport, and multiple metabolic processes were inhibited (Fig. 6 and Supplementary Table 2, http://links.lww.com/MD/G559). Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis showed enrichment in the spliceosome, fanconi anemia pathway, RNA transport, and nucleotide excision repair pathways, etc (Fig. 6 and Supplementary Table 3, http://links.lww.com/MD/G560). These results suggest that a widespread impact of *FANCI* on the global transcriptome.

3.4. Regulators of FANCI networks in cervical cancer

To further explore the regulators of *FANCI* in cervical cancer, we analyzed the kinases, miRNAs, and transcription factors' (TF) enrichment of *FANCI* co-expressed genes. The top 5 most significant kinases related primarily to the cyclin-dependent kinase 1 (*CDK1*), polo like kinase 1 (*PLK1*), ATM serine/threonine kinase (*ATM*), cyclin- dependent kinase 2 (*CDK2*), and checkpoint kinase 1 (*CHEK1*) (Table 1 and Supplementary Table 4, http://links.lww.com/MD/G561). In addition, the top 5 correlated miRNA-target networks were (CACGTTT) MIR-302A, (TATCTGG) MIR-488, (CCTGAGT) MIR-510,

(CAGGTCC) MIR-492, and (ATAACCT) MIR-154 (Table 1 and Supplementary Table 5, http://links.lww.com/MD/G562). Moreover, the enrichment of transcription factors was related mainly to the *E2F* transcription factor family (Supplementary Table 6, http://links.lww.com/MD/G563), including V$E2F_Q4, V$E2F_02, V$E2F_Q6, V$E2F1DP1_01, and V$E2F4DP2_01. One recent study, using combinatorial mapping of chromatin occupancy and transcriptome profiling, identified an *E2F*-driven transcriptional program that was associated with cervical cancer development and progression.

ANCI is related with tumor purity and immune infiltration level in cervical cancer. Therefore, we investigated whether *FANCI* expression was correlated with immune infiltration levels in cervical cancer from TIMER database. The results show that *FANCI* expression has significant correlations with tumor purity ($r=0.129$, $P=3.17E-02$) and significant correlations with the dominant immune cells infiltration levels (Fig. 7A). Particularly, *FANCI* CNV has significant correlations with infiltrating levels of CD8+ T cells and dendritic cells (Fig. 7B). Moreover, multivariable hazards models were used to evaluate the impacts of *FANCI* expression in the presence of varying immune cells.

4. Discussion

DNA damage is emerging as a critical step in abnormal phenotypic heterogeneity. Moreover, DNA damage is expected to be a major potential factor for untapped molecular targets in precision oncology and cancer disparities.[20] FANCI, a core component of the FANCD2-FANCI complex, is involved in multiple steps of DNA damage. To gain more detailed insights

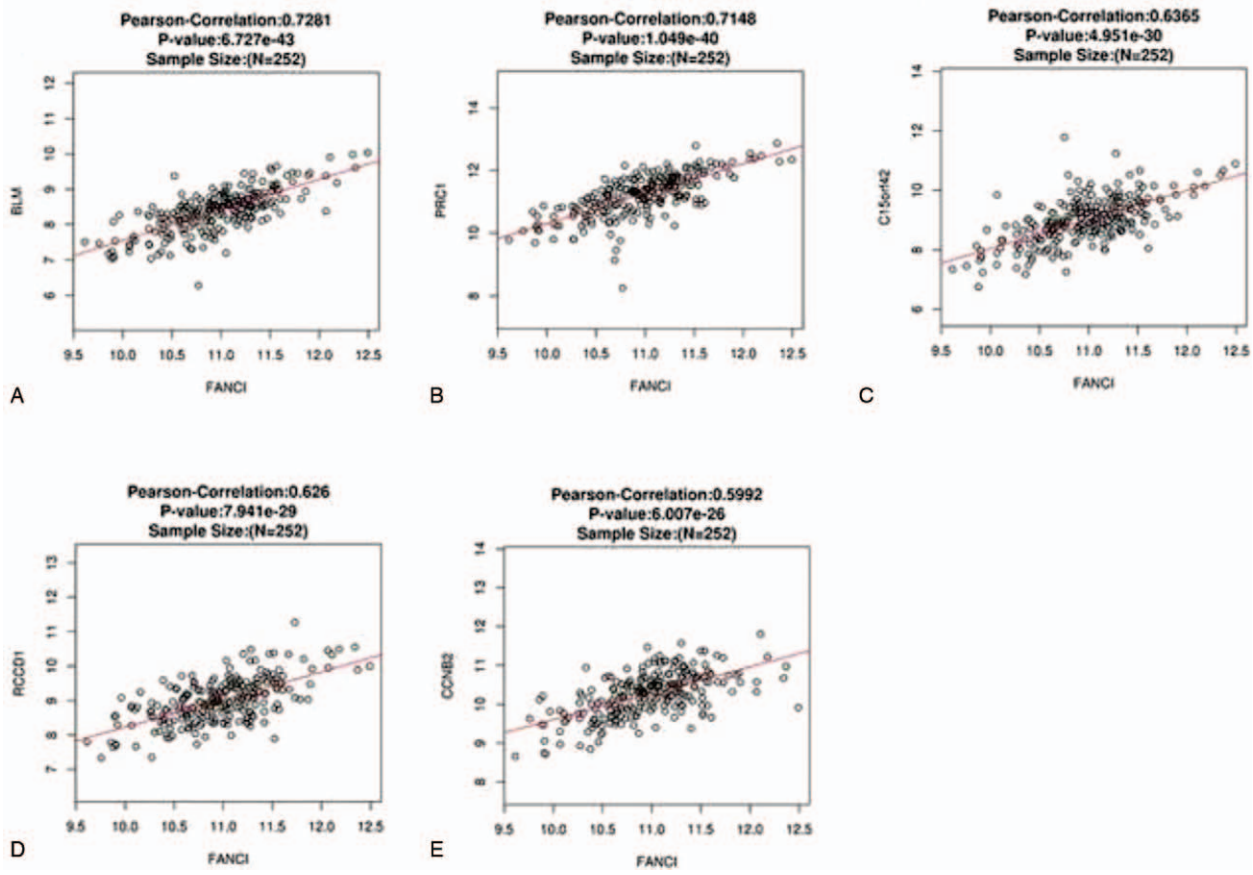

Figure 5. Overall survival (OS) of the top 5 positive genes correlated with *FANCI*. (A-E) All of these genes were significantly correlated with OS in cervical cancer.

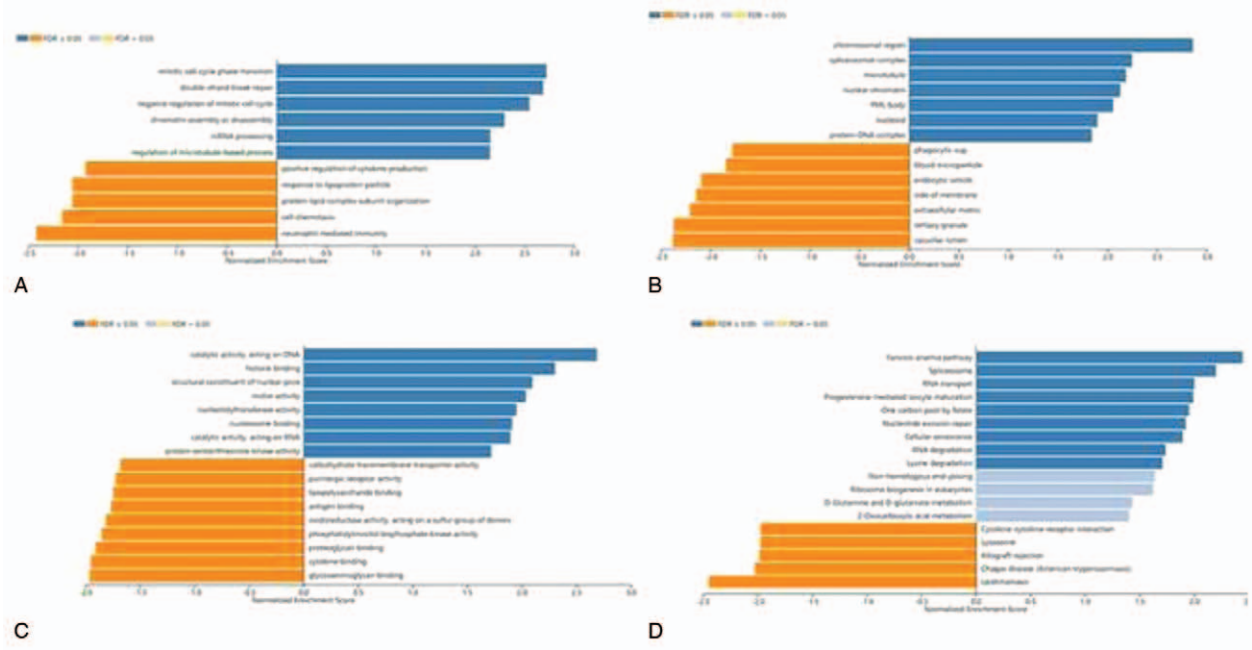

Figure 6. Genes co-expressed with *FANCI* in cervical cancer (LinkedOmics). Significantly enriched GO annotations and KEGG pathways of *FANCI* in cervical cancer cohort.

Table 1

The kinase, miRNA, and transcription factor-target networks of FANCI in cervical cancer (LinkedOmics).

Enriched category	Geneset	LeadingEdgeNum	*P*
Kinase Target	Kinase_ CDK1	88	0
	Kinase_ PLK1	34	0
	Kinase_ATM	42	0
	Kinase_CDK2	88	0
	Kinase_CHEK1	44	0
MiRNA Target	ATAGGAA, MIR-302A	8	0
	ATGTACA, MIR-488	3	0
	ATAAGCT, MIR-510	6	.020548
	ATAACCT, MIR-492	11	.003413
	TTGGAGA, MIR-154	25	.02027
Transcription Factor Target	V$E2F1_Q4	104	0
	V$E2F1_02	85	0
	V$E2F1_Q6	104	0
	V$E2F1DP1_01	84	0
	V$E2F4DP2_01	84	0

into the potential functions of *FANCI* in cervical cancer and its regulatory network, we performed the bioinformatics analysis of public data to guide future research in cervical cancer.

Analysis of transcriptome from more than 3400 clinical samples comprising 6 geographic regions and ethnic cervical cancer studies confirmed that *FANCI* mRNA levels are significantly higher in cervical cancer than in normal tissue. In addition, high expression of *FANCI* was significantly to improve poor survival in cervical cancer patients. Thus, our results suggested that *FANCI* upregulation occurs in many cases of cervical cancer and deserves further clinical validation as a potential diagnostic and prognostic marker.

For mining regulators potentially responsible for *FANCI* dysregulation, we found that *FANCI* in cervical cancer is associated with a network of kinases, including *CDK1*, *PLK1*, *ATM*, *CDK2*, and *CHEK1*. These kinases regulated genomic stability, mitosis, and the cell cycle, and showed differential expression and survival prognosis in cervical cancer. *CDK1* participates in the regulation of mitosis, self-renewal, differentiation, and somatic reprogramming. Various inhibitors of *CDK1* have been developed, and some have entered phase I and II clinical trials to treat a variety of solid tumors and hematologic malignancies.[21] As a critical driver gene, a causal link has recently been established between *PLK1* and cervical cancer.[22]- *FANCI* may regulate DNA replication, repair, and cell cycle progression via interacted kinases in cervical cancer.

Next, the *E2F* family constitutes the main transcription factors for *FANCI* dysregulation. *E2F1* is one of the critical links in the cell cycle regulatory network. Activated *E2F* oncogenic signaling was always seen in the progression of typical cancer, and studies have shown that dosage-dependent copy number gains in *E2F1* and *E2F3* drive cervical cancer.[23] Our results suggest that *E2F1* is an essential regulator of *FANCI* and that *FANCI* might act through this factor to regulate the cell cycle and proliferation capacity of cervical cancer. Further studies are needed to test this hypothesis. Our study did not identify any miRNA that was significantly associated with *FANCI*, possibly because *FANCI* is involved in mRNA splicesome and has no role in regulation of miRNA cellular machinery.

To probe the signaling events in controlling abnormal *FANCI* expression, we tested the *FANCI* co-expression network. Our results suggested that the functional consequence of *FANCI* mainly include spliceosome, DNA repair, DNA replication, and cell cycle, while it inhibits the metabolic processes, such as fatty acid, lipid, antibiotic, nucleoside bisphosphate, and cellular

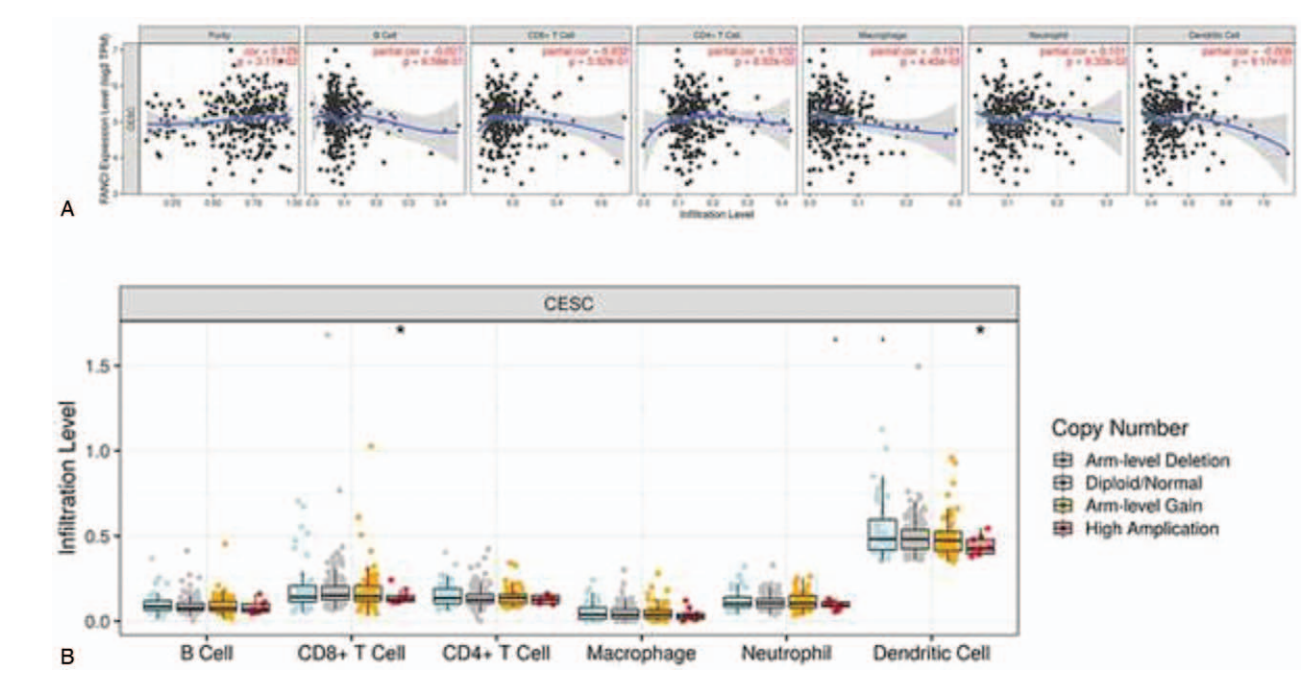

Figure 7. Correlations of *FANCI* expression with immune infiltration level in cervical cancer. (A) *FANCI* expression is significantly related to tumor purity and has significant positive correlations with infiltrating levels of $CD8^+$ T cells, $CD4^+$ T cells, macrophages, neutrophils, and dendritic cells in cervical cancer. (B) *FANCI* CNV affects the infiltrating levels of $CD8^+$ T cells, macrophages, neutrophils, and dendritic cells in cervical cancer.

modified amino acid metabolic process. These findings are consistent with the molecular pathways implicated in cervical cancer.[24]

The tumor microenvironment is the non-cancerous cells present in and around a tumor, have a strong influence on the genomic analysis of tumor samples.[25] As gene dynamics are known to influence belowground genetic diversity and microenvironment processes, co-occurrence analysis was performed. Most genes co-occurring with *FANCI* CNV were distributed in the 1q21 locus. Further, a gene-level network representing the co-occurrence of genes across cervical cancer genomes was built, giving the clues of the role of *FANCI* in regulating the immune response.

Herein, by tumor purity analysis, the network of *FANCI* alterations is involved in the tumor purity and tumor immunity. Our findings provide a detailed characterization of the association between *FANCI* and immune marker sets in cervical cancer patients. Further studies need to be done to elucidate whether *FANCI* is a crucial factor in mediating T-cell therapy.

In conclusion, this study provides multilevel evidence for the role of *FANCI* in immune response and its potential as a biomarker in cervical cancer. Our results suggest that *FANCI* upregulation in cervical cancer may likely have far-reaching effects in RNA splicing and genomic stability, and at multiple cell cycle steps. Further, our results suggest a potential novel immune regulatory role of *FANCI* in tumor immunity. These findings call for large-scale cervical cancer genomics research and subsequent functional studies. And further clinical research, as well as convincing validations in cell lines and animal models are necessary.

Author contributions

Data curation: Xiaoling Liu, Xiqin Liu, Xia Han.
Formal analysis: Xiaoling Liu, Xiqin Liu.
Methodology: Xiaoling Liu.
Project administration: Xiaoling Liu.
Software: Xiaoling Liu.
Supervision: Xiaoling Liu, Xia Han.
Validation: Xia Han.
Writing – original draft: Xiaoling Liu, Xia Han.
Writing – review & editing: Xiaoling Liu.

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