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Original Article

The prognostic significance of FMR1 expression and its immunomodulatory implications in esophageal carcinoma

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Abstract: Background: Esophageal carcinoma (ESCA) is deemed a highly lethal malignancy with a grim prognosis and stands as the fourth leading cause of cancer-related mortality. Recent research has revealed the potential crucial role of fragile X mental retardation 1 (FMR1) protein in tumor development and progression. However, the correlation between FMR1 and immune regulation in ESCA remains unclear. In this study, we aimed to assess the clinicopathological and prognostic significance of FMR1 expression, and its relationship with immune cell infiltration, immune biomarkers and the pathway involved in ESCA. Methods: The Cancer Genome Atlas (TCGA) pan-cancer data and the Gene Expression Omnibus (GEO) database were used to analyze the expression of FMR1. The correlation between FMR1 and cancer stage, time-dependent survival curve and receiver operating characteristic (ROC) curve were performed using R package. Immune cell infiltration was assessed using the samples found in TCGA. Functional enrichment analyses were performed to investigate the potential signaling pathway and biological functions. Results: FMR1 was upregulated in 7 tumors and downregulated in 4 tumors. Overexpression of FMR1 considerably associated with cancer stage and poor prognosis in ESCA. The ROC area was 0.745 and 0.830 for 3-year and 5-year respectively. FMR1 exhibited a positive correlation with common lymphoid progenitor and T cell CD4+ Th2, and a negative correlation with B cell memory, B cell plasma, endothelial cell, monocyte, neutrophil, T cell CD4+ Th1, and T cell CD4+ effector memory in ESCA. The enrichment analysis revealed FMR1 was primarily associated with cell development and predominantly enriched in immune-related pathways. Conclusion: FMR1 may act as a prognostic biomarker for ESCA and participate in immune regulation in ESCA.

Keywords: Esophageal carcinoma, prognosis, immune cell infiltration, immune regulation

Introduction

Esophageal carcinoma (ESCA), characterized by multiple causes, is deemed a highly lethal malignancy with a grim prognosis primarily due to late-stage diagnoses. It ranks as the fourth leading cause of cancer-related mortality, imposing a substantial burden on public health [1, 2]. The two primary histologic subtypes, esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EADC), exhibit widely varying risk factors that influence their incidence and distribution across different countries and populations [3]. In China, ESCC predominates as the primary subtype [4]. Despite notable advancements in the diagnosis and treatment of ESCC, the five-year survival rate hovers around 30% [5]. Consequently, there is an imperative need to delve into deeper insights into ECSA, with the aim of enhancing current diagnostic and therapeutic methodologies.

The fragile X mental retardation 1 (FMR1) gene, situated on the X chromosome, encodes the

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FMR1 protein (FMRP), an RNA-binding protein that impedes the translation of mRNA targets [6]. FMRP deficiency leads to fragile X syndrome (FXS), the most prevalent inherited form of intellectual disability [7]. FXS patients, in contrast to the general population, exhibit a decreased risk of cancer [8]. A case report has highlighted reduced glioblastoma invasion in patients with FXS [9]. Recent research has revealed the potentially crucial role of the FMRP in tumor development and progression. It undergoes up-regulation in various human tumors, functioning as a regulator within the tumor microenvironment's network of genes and cells, facilitating tumor survival through immune evasion [10]. This marks the first demonstration of FMRP's role in adaptive immunity [11]. Additionally, studies have shown a significant correlation between elevated FMR1 expression and unfavorable clinicopathological features in colorectal cancer patients. The upregulation of FMR1 can enhance the proliferation and migration of colorectal cancer cells [12]. Wei Li et al. discovered that overexpression of lncRNA FMR1-AS1 correlated with a poor clinical outcome in female ESCC patients, being packaged into exosomes released into the tumor microenvironment. Exosome FMR1-AS1 can boost cancer cell proliferation and invasion by mediating TLR7-NFκB signaling activation [13]. However, this study had limitations, including a small sample size and an exclusive focus on women in East China. Additionally, the immune status in the tumor microenvironment of ESCA remains unclear.

In our study, the objective was to assess the relationship between FMR1 expression and its clinicopathological and prognostic significance in ESCA patients. Furthermore, we sought to investigate its molecular mechanisms and potential functions utilizing bioinformatics. Our findings revealed FMR1 overexpression in ESCA, with high levels correlating with poorer survival in ESCA patients. Additionally, FMR1 was predicted to be associated with immune cell infiltration, participating in cytokine-cytokine interaction, IL-17 signaling pathway and interferon-gamma response. These results indicate that FMR1 may play a role in the tumor immunity of ESCA, providing novel insights into the pathogenesis of this malignancy.

Materials and methods

Data collection and analysis

FMR1 expression data in the Cancer Genome Atlas (TCGA) pan-cancer and Genotype-Tissue Expression project (GTEx) were retrieved from the UCSC Xena database (https://xenabrowser.net/datapages/). Tumor tissue samples were obtained from TCGA and normal tissue samples from TCGA and GTEx to assess differences in FMR1 expression according our previously reported methods [14, 15]. R packages "stats" and "car" were employed for statistical analysis, Log2(value+1) transformation and Wilcoxon rank sum test were conducted on the expression data in TPM format. In addition, UALCAN portal (http://ualcan.path.uab.edu/) was utilized to explore FMR1 promoter methylation levels in ESCA to identify differences between tumor and normal tissue.

Prognostic value of FMR1 in ESCA

Correlation between FMR1 expression and clinicopathologic features, including T stage, pathologic stage, histologic grade was explored using Wilcoxon test. Subsequently, Kaplan-Meier (KM) survival analysis of FMR1 for overall survival (OS), progress free interval (PFI) and disease specific survival (DSS) was conducted using R package "survival" and "survminer". To further explore the predictive ability of FMR1, time-dependent receiver operating characteristic (ROC) curve was conducted by R package "timeROC".

Immune cell infiltration analysis

As previously mentioned [16, 17], the correlation between FMR1 and immune cell infiltration was assessed in 33 tumors using the ssGSEA algorithm of the R package "GSVA" [18], and the results were visualized with correlation heatmaps using R package "ggplot2".

Functional enrichment analyses

The FMR1 mRNA expression median was used to divide ESCA samples into high- and low-expression groups, and the difference analysis between the two groups was performed using the DESeq2 package. DEGs were collected with the criteria of adjusted p-value < 0.05 and |logFC| >1. Correlation analysis between FMR1

and other mRNAs in ESCA was performed using TCGA data, and the Pearson correlation coefficient was calculated. The top 449 genes most positively associated with FMR1 were selected for enrichment analysis to reveal the role of FMR1. Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genomes (KEGG) analysis were performed using the EnrichGO function and EnrichKEGG function in the R package "clusterProfiler", respectively. Gene Set Enrichment Analysis (GSEA) was performed using the gseGO, gseKEGG, and gsePathway functions of the R package "clusterProfiler" [19]. The gene sets h.all.v7.5.1.symbols.gmt was chosen as the reference gene set.

Statistical analysis

All statistical analysis were performed using R software (version 4.2.1). Wilcoxon rank sum tests were performed for analysis of differences. Correlations were assessed using Spearman's correlation coefficients, and all data were visualized using package "ggplot2". $P < 0.05$ was considered statistically significant.

Results

Pan-cancer FMR1 expression analysis

We first assessed FMR1 expression in pan-cancer data from TCGA and GTEx. The analysis from TCGA revealed high level of FMR1 expression in 7 tumors, including CHOL, COAD, ESCA, HNSC, LIHC, READ and STAD. In contrast, low level expression in GBM, KIRC, KIRP and PRAD (**Figure 1A**). Subsequently, the combined analysis of TCGA and GTEx revealed high expression of FMR1 in 14 tumors, including CHOL, DLBC, ESCA, HNSC, KICH, LAML, LGG, LIHC, LUAD, PAAD, READ, STAD, TGCT and THYM, with low expression in ACC, KIRC, LUSC, OV, PRAD, THCA, UCEC and UCS (**Figure 1B**). Further analysis of FMR1 expression in ESCA was performed. The results confirmed that FMR1 was overexpressed in ESCA, including 173 unpaired samples from TCGA, 848 unpaired samples from TCGA and GTEx, and 8 paired samples (**Figure 1C-E**). In addition, the promoter methylation level of FMR1 in ESCA was lower than that in normal samples (**Figure 1F**). Furthermore, we assessed the diagnostic value of FMR1 in ESCA. The AUC of FMR1 for diagnosis was 0.815 (CI: 0.773-0.858) (**Figure 1G**).

Association between FMR1 expression and cancer patient prognosis

To evaluate the value of FMR1 in predicting the prognosis of cancer patients, the association between FMR1 expression and patient prognosis was analyzed in TCGA cohort. The results showed higher FMR1 expression in cancer patients across tumor stage (T1-T4), pathologic stage (Stage II-IV) and histologic grade (G1-G3) compared to normal group. However, there was no significant difference between T1 and T2-T4, stage I and normal group, G1 and G2-G3 (**Figure 2A-C**). Furthermore, elevated expression of FMR1 was significantly associated with reduced overall survival (OS) (P=0.01), progress free interval (PFI) (P=0.014) and disease specific survival (DSS) (P=0.01) (**Figure 3A-C**). AUC values were 0.745 and 0.830 for 3-year and 5-year respectively (**Figure 3D**).

Correlation between immune cell infiltration and FMR1

We further assessed the immune cell infiltration score in TCGA pan-cancer data, and found that the cell infiltration level of common lymphoid progenitor, T cell CD4+ Th2 was positive correction with FMR1 in ESCA. Conversely, the cell infiltration level of B cell memory, B cell plasma, endothelial cell, monocyte, neutrophil, T cell CD4+ Th1, T cell CD4+ effector memory showed a negative correction with FMR1 (**Figure 4**).

Correlation and enrichment analyses

To predict the function of FMR1, including associated pathways, we performed a correlation analysis between FMR1 and other genes in ESCA using TCGA data. The results showed that 10 gene terms were associated with the expression of FMR1, including PCDH11X, IRS4, FAM71F1, CYP1A1, CPLX2 up-regulation and MAGEC2, CRISP3, FOLR1, SLURP1, FTHL17 down-regulation (**Figure 5A**, **5B**).

Then, the top 449 genes most highly correlated with FMR1 were selected for enrichment analysis. We further explored the potential functional pathways based on the top 449 genes using the clusterProfiler R package. Functional enrichment and GO analysis revealed that FMR1 was primarily associated with cell development, including keratinocyte differentiation, keratinization, skin development, epidermis develop-

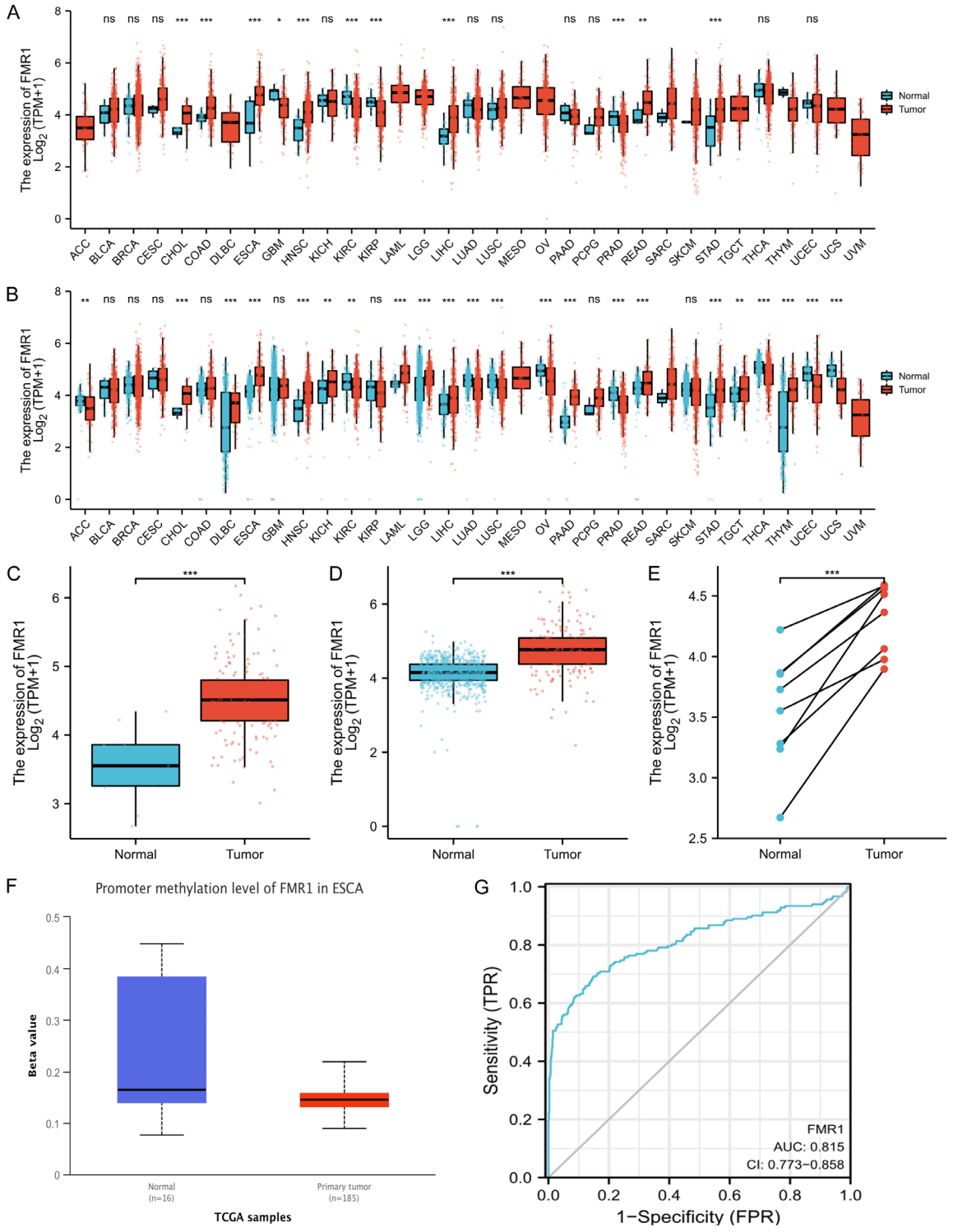

Figure 1. Pan-cancer analysis of FMR1 expression in primary tumor and normal tissues from TCGA data (A) or TCGA and GTEx data (B). FMR1 expression in ESCA and normal tissues from TCGA data (C) or TCGA and GTEx data (D). (E) FMR1 expression in paired cancer tissues of ESCA from TCGA data. (F) Promoter methylation level of FMR1 in ESCA and normal samples from TCGA data. (G) ROC curve of FMR1 for ESCA diagnosis.

ment, cornified envelope, anchored component of membrane, ion channel complex, cation channel complex, structural constituent of skin epidermis, ion channel activity, endopeptidase

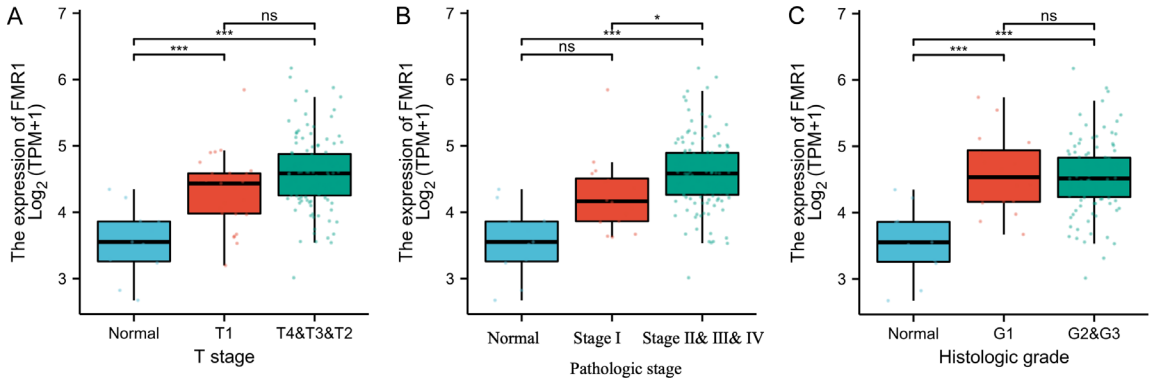

Figure 2. FMR1 expression in normal and cancer tissues of ESCA with different tumor stage (A) or different pathologic stage (B) or different histologic grade (C).

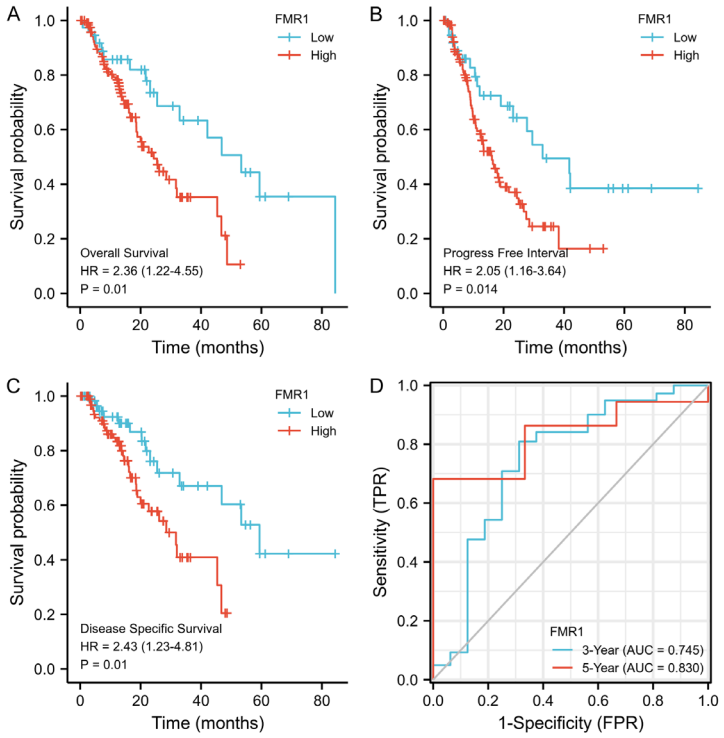

Figure 3. Association between FMR1 expression and tumor prognosis, including (A) overall survival, (B) progress free survival, (C) disease specific survival of ESCA patients in TCGA. (D) The area of ROC for 3-year and 5-year in ESCA patients.

inhibitor activity, cation channel activity (**Figure 5C**). KEGG pathway analysis indicated the top 449 genes were mainly enriched in arachidonic acid metabolism, cytokine-cytokine receptor interaction, linoleic acid metabolism, serotonergic synapse and IL-17 signaling pathway (**Figure 5D**). GSEA was used to search for KEGG and Reactome pathways, which revealed that interferon gamma response, P53 pathway, G2m checkpoint, epithelial mesenchymal transition and oxidative phosphorylation were significantly enriched (**Figure 5E**).

Discussion

Traditionally, FMR1 has been implicated in three syndromes, namely Fragile X syndrome, premature ovarian insufficiency, and Fragile X-associated tremor/ataxia syndrome [9]. However, recent studies have demonstrated its crucial role in the initiation and progression of tumors. The regulation of the stability of cancer-related mRNAs by FMR1, as reported by Xiong Chen et al., promoted the growth and metastasis in invasive mucinous lung adenocarcinoma [20]. FMR1 was also found to be negatively associated with tumor stages and overall survival in renal clear cell carcinoma [21]. Conversely, the role of FMR1 appears to be contradictory in some other tumors. Jianqiu Kong et al. demonstrated a significant positive correlation between FMRP expression and treatment outcome in advanced urothelial carcinoma, as it modulated m6A methylation, potentially influencing the survival of urothelial carcinoma cells [22]. The reason for such contradictory conclusions might be FMR1 differentially acted in different stages and locations of the tumors, because the expression of FMR1 varied in distinct parts of human body. High

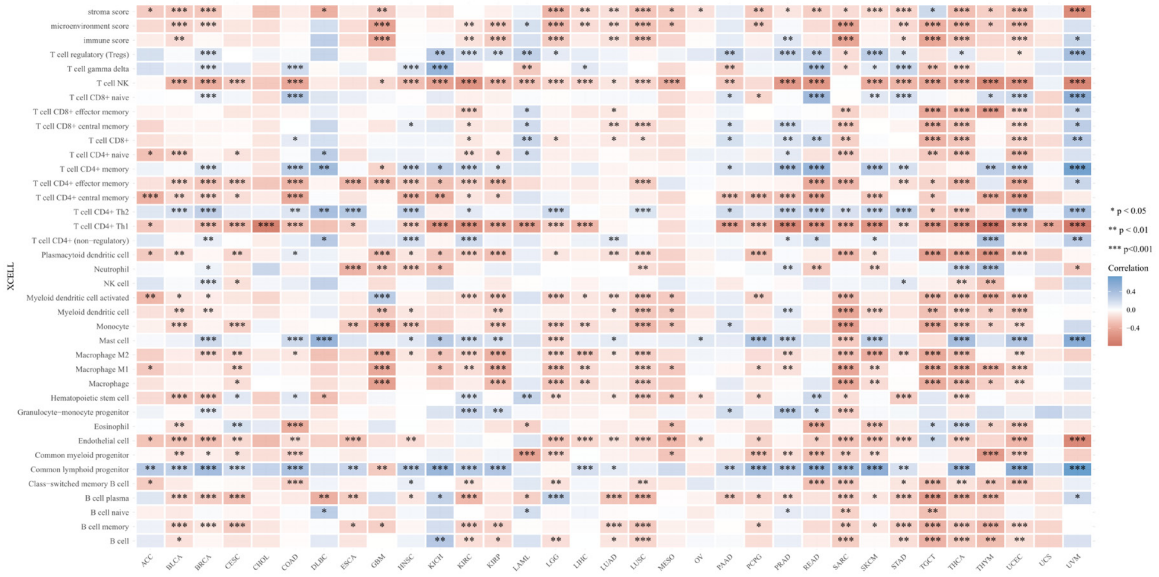

Figure 4. The top genes of most positively associated with FMR1 in different cancers.

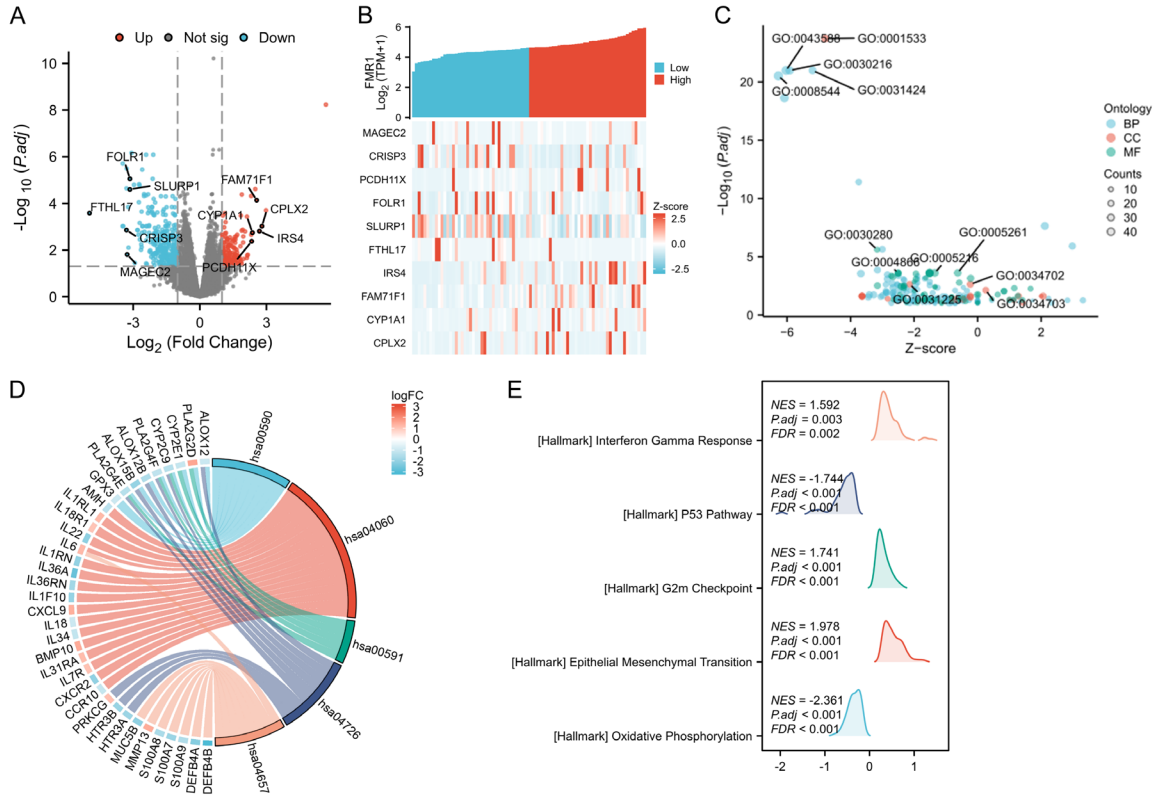

Figure 5. Function and pathway enrichment analysis of FMR1 in ESCA. A, B. Connection analysis between FMR1 and other genes in ESCA. C. Significant Gene Ontology terms of the top 449 genes most positively associated with FMR1, including biological processes (BP), molecular function (MF), and cell component (CC). D. Significant KEGG pathways of the top 449 genes most positively associated with FMR1. E. Significant GSEA results of the top 449 genes most positively associated with FMR1.

FMR1 expression was demonstrated in breast tumor with differential expression between different subtypes and metastatic sites [23]. Despite this, there are few researches investigating

the correlation between FMR1 and ESCA. Therefore, elucidating the role of FMR1 in ESCA is of great significance. Through the analysis of TCGA and GTEx data to assess the expression level and prognostic function of FMR1, our results unveiled a high expression in ESCA. FMR1 exhibited high expression not only in unpaired samples but also in paired samples of ESCA compared to normal tissues. These results indicated that FMR1 might participate in the occurrence and progression of ESCA. Moreover, the significant association between the overexpression of FMR1 and poor OS, PFI, and DSS in ESCA patients underscores its potential as a prognostic biomarker.

The Tumor Immune Microenvironment (TIME), primarily composed of cytokines and infiltrating immune cell populations, including both innate and adaptive immune cells, has been reported to play a crucial role in tumor immune suppression and was closely associated with the clinical prognosis of tumor patients [24, 25]. In this study, a correlation between FMR1 and various types of tumor-infiltrating immune cells in distinct cancers was unveiled. FMR1 exhibited a positive correlation with common lymphoid progenitor and T cell CD4+ Th2, and a negative correlation with B cell memory, B cell plasma, endothelial cell, monocyte, neutrophil, T cell CD4+ Th1, and T cell CD4+ effector memory in ESCA. CD4+ T cell, as the dominant immune cells infiltrated in tumor microenvironment, its reaction is an indicator reflecting the host immune response to tumor cells [26]. Th1 cells infiltration was positively associated with pathological complete response of ESCC patients [27]. Previous research revealed that overexpression of FMRP had the capability to limit CD8 and CD4 T cells recruitment, allowing solid tumors to evade immune destruction [11]. GO and KEGG pathway analyses revealed that genes associated with FMR1 were predominantly enriched in immune-related pathways, including cytokine-cytokine receptor interaction, IL-17 signaling pathway, and interferon-gamma response. IL-17 promoted neutrophil infiltration and activation to inhibit tumor growth in ESCC [28]. Meanwhile, IL-17A also promoted the migration of B cells and enhanced their cytotoxicity against tumor cells [29]. Th1 cells inhibited the proliferation of ESCC cells by upregulating interferon-gamma response signaling [22]. Tumors could reciprocally shape the tumor immune microenvironment into an immunosuppressive state to evade host immunity by influencing the balance between pro- and anti-tumor inflammatory mediators [30]. The hypothesis based on our results was that overexpression of FMR1 influenced IL-17 and interferon-gamma pathway to regulate diverse immune cells such as B cell, T cell, monocyte and neutrophil infiltration, which directly affected the development and prognosis of ESCA. Additionally, metabolic and biochemical components could also impact the tumor progress. For instance, arachidonic acid metabolism and its products were related to growth and invasiveness of tumor cells [31]. In colorectal cancer, raising arachidonic acid promoted tumor growth by metabolizing to prostaglandin E2 [32]. Adenosine inhibited the function of antitumor immune cells and facilitated immunosuppressive activity [33, 34]. Iron metabolism in the tumor microenvironment is notably related to antitumor immune response and affects tumor cell immunosurveillance [35, 36]. KEGG pathway analysis revealed the genes highly correlated with FMR1 enriched in many metabolism pathways, indicating it was another potential means for FMR1 influencing tumor growth of ESCA.

In summary, this study revealed that FMR1 is significantly associated with aggressive clinical features and immune cell infiltration in ESCA. It was enriched in immune-related pathways and acted as a regulator of tumor immunology by influencing the balance of various immune mediators. These findings verified the correlation between FMR1 and immune regulation in ESCA, and indicated the potential role of FMR1 as a prognostic biomarker or therapy target for ESCA. However, the mechanism of how FMR1 regulated tumor physiology in ESCA needed further clarification.

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Disclosure of conflict of interest

The authors state that they conducted the research without any commercial or financial

relationships that could be considered a potential conflict of interest.

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