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Deciphering the role of FSCN family genes in cancer: a pan-cancer bioinformatics study

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Author contributions

W.Z. performed data analysis and original draft writing; W.Z. and D.R. performed original draft writing; X.L. reviewed and edited the manuscript; X.L. performed the study concept and design; X.L. is the guarantor of this work and takes responsibility for the integrity of the data and accuracy of the data analysis. All the authors have read and approved the final manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

FSCN, Fascin; TCGA, The Cancer Genome Atlas; OS, overall survival; CNVs, copy number variations; TMB, tumor mutational burden; MSI, microsatellite instability; GTEx, Genotype-Tissue Expression; FC, fold changes.

Citation

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Abstract

Background: The Fascin (FSCN) family, comprising actin-bundling proteins, plays vital roles in cytoskeletal reorganization and cell migration. FSCN1, FSCN2, and FSCN3 are implicated in cancer progression through cell motility, invasion, and metastasis. However, their specific contributions across different cancer types remain unclear. **Methods:** We conducted a pan-cancer bioinformatics analysis of FSCN genes using data from The Cancer Genome Atlas. This included differential expression patterns, copy number variations (CNVs), mutations, methylation status, and correlations with tumor mutational burden, microsatellite instability, and immune checkpoint molecule expression. Differential expression was analyzed using DESeq2, while CNV and mutation analyses utilized GISTIC2.0 and MuTect2. Methylation data were assessed using the Illumina Human Methylation 450K BeadChip. **Results:** FSCN1 and FSCN2 showed significant differential expression in multiple cancers, often correlating with poor prognosis. FSCN3 exhibited less variability but a protective role in certain contexts. CNV analysis indicated frequent gene gains in FSCN genes, correlating with increased expression. FSCN3 had a higher mutation rate, suggesting genetic instability. Methylation analysis showed hypomethylation of FSCN1 and FSCN2 in tumors compared to normal tissues, whereas FSCN3 had minor changes. Significant associations were found between FSCN gene expression and tumor mutational burden, microsatellite instability, and immune checkpoint molecules, suggesting their involvement in tumor immunogenicity and the immune microenvironment. **Conclusions:** This pan-cancer analysis highlights the multifaceted roles of FSCN genes in cancer biology, emphasizing their potential as biomarkers and therapeutic targets. FSCN1 and FSCN2 are associated with poor prognosis and aggressive phenotypes, while FSCN3 shows protective roles in specific contexts. These findings offer new avenues for cancer diagnosis and treatment, particularly in personalized medicine. Future studies should validate these findings and explore the underlying mechanisms to fully harness the clinical potential of FSCN family proteins in oncology.

Keywords: Fascin family; pan-cancer analysis; gene expression; copy number variation; tumor mutational burden

Introduction

The Fascin (FSCN) family, comprising highly conserved actin-bundling proteins, plays crucial roles in the reorganization of the cytoskeleton and the promotion of cell migration. The three main members of this family, FSCN1, FSCN2, and FSCN3, have been implicated in various cellular processes that are essential for cancer progression, including cell motility, invasion, and metastasis [1–3]. Despite their biological importance, the specific contributions and regulatory mechanisms of FSCN family proteins in different cancer types remain incompletely understood.

Previous studies have demonstrated that FSCN1 is often overexpressed in several cancers, such as breast cancer, colorectal cancer, and gastric cancer, and is associated with poor prognosis [4, 5]. FSCN2 and FSCN3, while less studied, have also been implicated in cancer progression through similar mechanisms involving actin cytoskeleton modulation [6, 7]. However, a comprehensive pan-cancer analysis that systematically investigates the expression patterns, genomic alterations, epigenetic modifications, and their clinical implications across a wide range of cancer types has not been thoroughly conducted.

In this study, we aim to fill this gap by conducting a detailed bioinformatics analysis of FSCN family genes using data from The Cancer Genome Atlas (TCGA). The objectives are to characterize the differential expression of FSCN1, FSCN2, and FSCN3 across various cancer types, identifying significant changes in expression levels between tumor and normal tissues, and understanding their impact on overall survival (OS) across different cancers. Furthermore, we assess the genomic alterations of FSCN family genes, including copy number variations (CNVs) and mutations, to determine the prevalence and impact of these alterations on gene expression and cancer progression. We also investigate the methylation status of FSCN family genes by comparing the methylation levels between tumor and normal tissues to understand the epigenetic regulation of these genes and its effect on their expression. Additionally, we explore the correlation of FSCN family gene expression with tumor mutational burden (TMB), microsatellite instability (MSI), and immune checkpoint molecule expression to elucidate the broader implications of FSCN gene expression on tumor immunogenicity and the immune landscape. This provides insights into their potential roles in cancer immunity and therapy.

Through this comprehensive analysis, we aim to shed light on the multifaceted roles of FSCN family genes in cancer biology, highlighting their potential as biomarkers and therapeutic targets. The results of this study could pave the way for novel strategies in cancer diagnosis and treatment, particularly in the context of personalized medicine.

Methods

Data collection and cleaning

Data for this study were obtained from TCGA and the Genotype-Tissue Expression (GTEx) databases, which together provide comprehensive genomic profiles for both cancerous and normal tissues [8]. The dataset included mRNA expression levels, CNV data, methylation profiles, and mutation data for the FSCN family genes (FSCN1, FSCN2, FSCN3) across multiple cancer types. Clinical information, including OS data, was also retrieved from TCGA.

Data were accessed through the Genomic Data Commons Data Portal and the GTEx Portal. We specifically downloaded RNA-seq, CNV, methylation, and mutation data for various cancer types from TCGA, and normal tissue RNA-seq data from GTEx to increase the sample size for normal tissues [9]. Clinical data, including patient survival information, were obtained to correlate genetic features with clinical outcomes. CNV data were downloaded as segmented copy number profiles. Methylation data were retrieved as beta values from the Illumina Human Methylation 450K BeadChip. Mutation data were acquired as variant call format files.

For RNA-seq data, raw count data were pre-processed to remove any non-expressed genes (genes with zero counts across all samples were excluded). Normalization was performed using the DESeq2 median of ratios method to account for differences in sequencing depth and RNA composition. CNV segments were filtered to retain only those with significant copy number changes, categorized into gains and losses using the GISTIC2.0 tool. Quality control steps included removing samples with high levels of noise or low-quality segments. For methylation data, beta values were filtered to remove probes with missing values in more than 10% of the samples. Batch effects were corrected using the ComBat function in the Chip Analysis Methylation Pipeline package to ensure consistency across different batches. Mutation data were cleaned by filtering variant calls to exclude common germline polymorphisms based on their presence in dbSNP. Only somatic mutations with high-confidence calls (as determined by the MuTect2 algorithm) were included in the analysis. Immune cell infiltration data were estimated using the CIBERSORT algorithm, which uses gene expression profiles to deconvolute the proportion of 22 immune cell types in the tumor microenvironment [10]. Data were filtered to remove outliers, and batch effects were corrected to maintain consistency across different samples.

Differential expression analysis

To analyze the differential expression of FSCN family genes between tumor and normal tissues, we utilized the DESeq2 package in R [11]. The raw RNA-seq count data were normalized using the DESeq2 median of ratios method to account for differences in sequencing depth and RNA composition. Log2 fold changes (FC) were calculated to determine the upregulation or downregulation of each gene. The Wald test was applied to estimate the significance of the observed changes, and the Benjamini-Hochberg procedure was used to control the false discovery rate at 5%. Genes with an adjusted P-value < 0.05 and $|\log2FC| > 1$ were considered significantly differentially expressed. The results were visualized using bar plots and heatmaps to illustrate the expression patterns across different cancers.

CNV analysis

CNV data for FSCN family genes were extracted from the TCGA database. The GISTIC2.0 tool was employed to identify significant CNVs, categorizing them into gains and losses [12]. The CNV data were then correlated with gene expression levels using Pearson correlation analysis to understand the impact of CNVs on gene expression. The results were visualized through bar plots and scatter plots to display the relationship between CNVs and gene expression.

Mutation analysis

Mutation data for FSCN family genes were obtained from TCGA and analyzed using the MuTect2 algorithm [13]. The frequency and types of mutations (missense, nonsense, splice site, frame shift) were calculated for each gene across different cancers. Waterfall plots were generated to illustrate the distribution and frequency of mutations in the FSCN genes.

Methylation analysis

Methylation profiles for FSCN family genes were analyzed using the Illumina Human Methylation 450K BeadChip data available in TCGA. Differential methylation analysis between tumor and normal tissues was performed using the R package Chip Analysis Methylation Pipeline. The beta values, representing methylation levels, were compared, and differences were visualized using heatmaps. Correlation analysis between methylation levels and gene expression was conducted using Pearson correlation.

Correlation with TMB and MSI

To explore the relationship between FSCN gene expression and TMB, we calculated TMB for each cancer type as the number of mutations per megabase of genomic sequence. MSI status was obtained from TCGA. Correlation analyses were performed using Pearson correlation to assess the relationship between FSCN gene expression and

Medical Data Mining 2024;7(4):22. https://doi.org/10.53388/MDM202407022

TMB/MSI. Radar plots were used to visualize these correlations.

Correlation with immune checkpoint molecules

The expression levels of immune checkpoint molecules (e.g., PDCD1, CD274, CTLA4) were retrieved from TCGA. Correlation analysis between FSCN gene expression and immune checkpoint molecule expression was conducted using Pearson correlation. Heatmaps were generated to illustrate the strength and direction of these correlations across different cancer types.

Statistical analysis

All statistical analyses were performed using R software. Correlation analyses were conducted using Pearson correlation coefficients, and statistical significance was determined at a threshold of $P < 0.05$.

Results

Differential expression of FSCN family genes in pan-cancer

To explore the expression patterns of FSCN family genes across various cancer types, we conducted a differential expression analysis using combined TCGA and GTEx datasets. The integration of GTEx data provided a more comprehensive baseline for normal tissue expression, addressing the issue of relatively few normal samples in TCGA. Figure 1A illustrates the differential expression of FSCN1, FSCN2, and FSCN3 across various cancers. The top section of Figure 1A shows the number of genes that are either upregulated (red) or downregulated (green) in different cancers. The lower section presents the expression changes of these genes, with red indicating upregulation and green indicating downregulation. Our results indicate that FSCN1 and FSCN2 exhibit significant expression changes in multiple cancer types, while FSCN3 shows less variability. These results highlight the potential involvement of FSCN1 and FSCN2 in cancer progression and the distinct role of FSCN3 in different cancer contexts.

To understand the prognostic significance of these genes, we analyzed their impact on OS. Figure 1B shows the association between FSCN family gene expression and OS in different cancers. Red indicates that higher gene expression is associated with worse outcomes (Risky), while blue indicates a protective effect. The analysis reveals that high expression of FSCN1 and FSCN2 is associated with poor prognosis in several cancers, whereas FSCN3 shows a protective role in certain cancers.

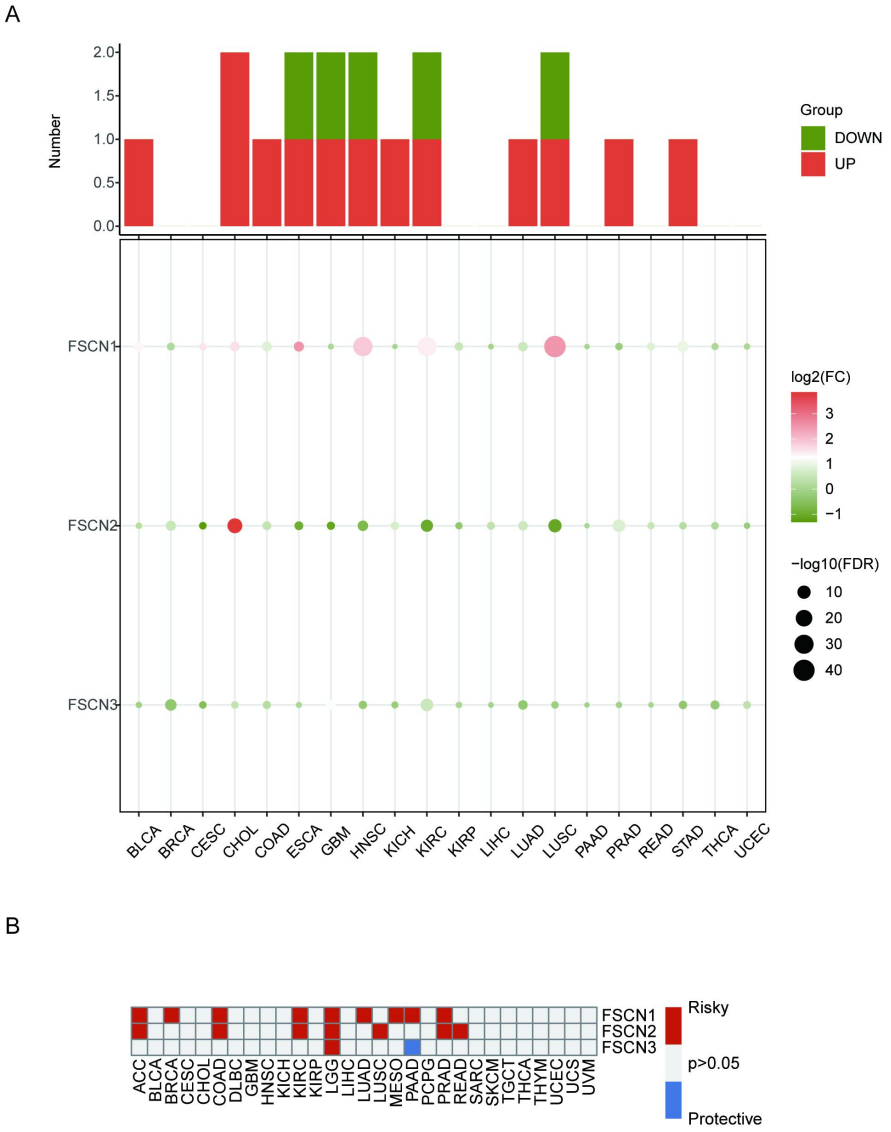

Figure 1 Differential expression of FSCN family genes in pan-cancer. (A) Differential expression of FSCN1, FSCN2, and FSCN3 across various cancer types. The top section shows the number of genes that are either upregulated (red) or downregulated (green) in different cancers. The lower section presents the expression changes of these genes, with red indicating upregulation and green indicating downregulation. (B) Association between FSCN family gene expression and overall survival across different cancers. Red indicates that higher gene expression is associated with worse outcomes (Risky), while blue indicates a protective effect. FSCN, Fascin; FC, fold changes; FDR, false discovery rate.

Medical Data Mining 2024;7(4):22. https://doi.org/10.53388/MDM202407022

CNV analysis of FSCN family genes in pan-cancer

In order to understand the genomic alterations of FSCN family genes, we performed a CNV analysis across various cancer types. This analysis aimed to identify the prevalence of gene gains and losses and their correlation with gene expression levels. Figure 2A shows the CNV status of FSCN1, FSCN2, and FSCN3 across different cancers. Positive values represent gene gains, while negative values represent gene losses. The results indicate significant gene gains for the FSCN family in many cancer types. We further investigated the correlation between CNV and gene expression. Figure 2B demonstrates that CNV is significantly correlated with the expression levels of FSCN genes in multiple cancers, with red indicating a positive correlation. This suggests that CNV plays a crucial role in regulating FSCN gene expression. Additionally, we analyzed the mutation frequency of FSCN genes. Figure 2C shows that FSCN3 has a higher mutation rate across various cancers compared to FSCN1 and FSCN2. Figure 2D provides a detailed view of mutation types in FSCN genes, with FSCN3 exhibiting a higher number of alterations, highlighting its genetic instability in numerous cancers.

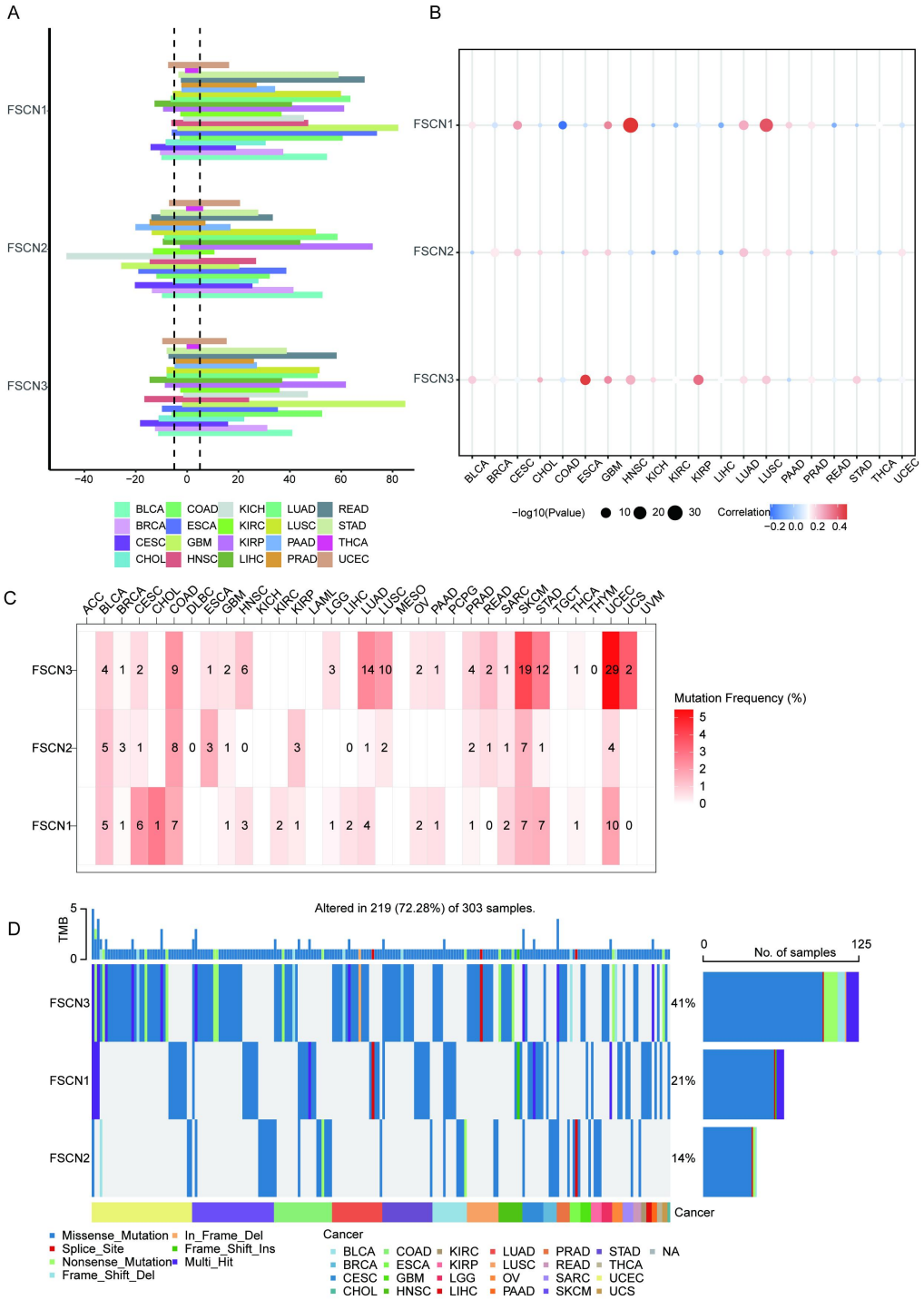

Figure 2 CNV analysis of FSCN family genes in pan-cancer. (A) CNV status of FSCN1, FSCN2, and FSCN3 across different cancers. Positive values represent gene gains, while negative values represent gene losses. (B) Correlation between CNV and gene expression levels of FSCN family genes in multiple cancers. Red indicates a positive correlation. (C) Mutation frequency of FSCN genes in different cancers, with FSCN3 showing a higher mutation rate. (D) Waterfall plots illustrating the distribution and frequency of mutations in FSCN genes, highlighting the genetic instability of FSCN3 in numerous cancers. CNV, copy number variation; FSCN, Fascin; TMB, tumor mutational burden.

Medical Data Mining 2024;7(4):22. https://doi.org/10.53388/MDM202407022

Methylation analysis of FSCN family genes in pan-cancer

To investigate the epigenetic regulation of FSCN family genes, we examined the methylation status of these genes in tumor and normal tissues. This analysis aimed to understand how methylation changes might affect gene expression in different cancers. Figure 3A compares the methylation levels of FSCN genes between tumor and normal tissues. Red indicates increased methylation in tumors, while blue indicates decreased methylation. The results show significant hypomethylation of FSCN1 and FSCN2 in several cancers compared to normal tissues, whereas FSCN3 shows minor variations. We also analyzed the correlation between gene methylation and expression levels. Figure 3B reveals that FSCN3 methylation is positively correlated with its expression in several cancers, suggesting that methylation might be an important regulatory mechanism for FSCN3 expression.

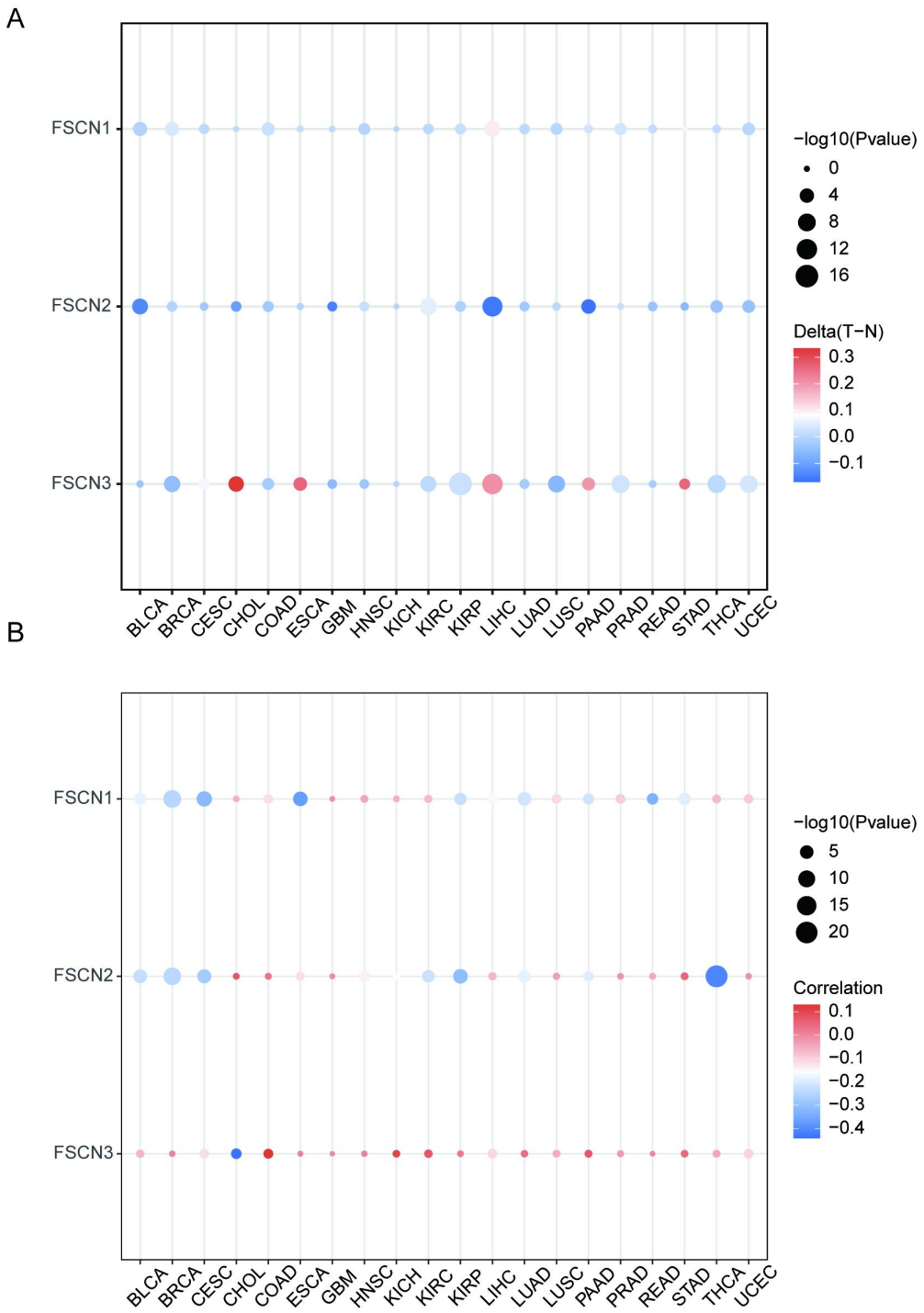

Figure 3 Methylation analysis of FSCN family genes in pan-cancer. (A) Comparison of methylation levels of FSCN genes between tumor and normal tissues. Red indicates increased methylation in tumors, while blue indicates decreased methylation. (B) Correlation between gene methylation and expression levels of FSCN family genes. The analysis shows that FSCN3 methylation is positively correlated with its expression in several cancers. FSCN, Fascin.

Medical Data Mining 2024;7(4):22. https://doi.org/10.53388/MDM202407022

Correlation of FSCN family genes with TMB, MSI, and immune checkpoint molecules

To explore the broader implications of FSCN family gene expression, we examined their correlation with TMB, MSI, and the expression of immune checkpoint molecules. This analysis aimed to understand the potential role of FSCN genes in influencing tumor immunogenicity and immune response. Figures 4A–4C depict the correlation between FSCN1, FSCN2, and FSCN3 expression and TMB across different cancers. Significant correlations are marked in green. The analyses reveal positive correlations between FSCN gene expression and TMB in multiple cancers, suggesting that higher expression of these genes may be associated with increased mutational load. Figures 4D–4F illustrate the correlation between FSCN1, FSCN2, and FSCN3 expression and MSI, with significant correlations also marked in green. The results indicate a positive correlation between FSCN gene expression and MSI in certain cancers, suggesting a role in regulating microsatellite instability. Figures 4G–4I show the correlation between FSCN family genes and the expression of conventional immune checkpoint molecules (such as PDCD1, CD274, and CTLA4). The heatmaps indicate significant correlations, highlighting the potential involvement of FSCN genes in modulating the tumor immune microenvironment.

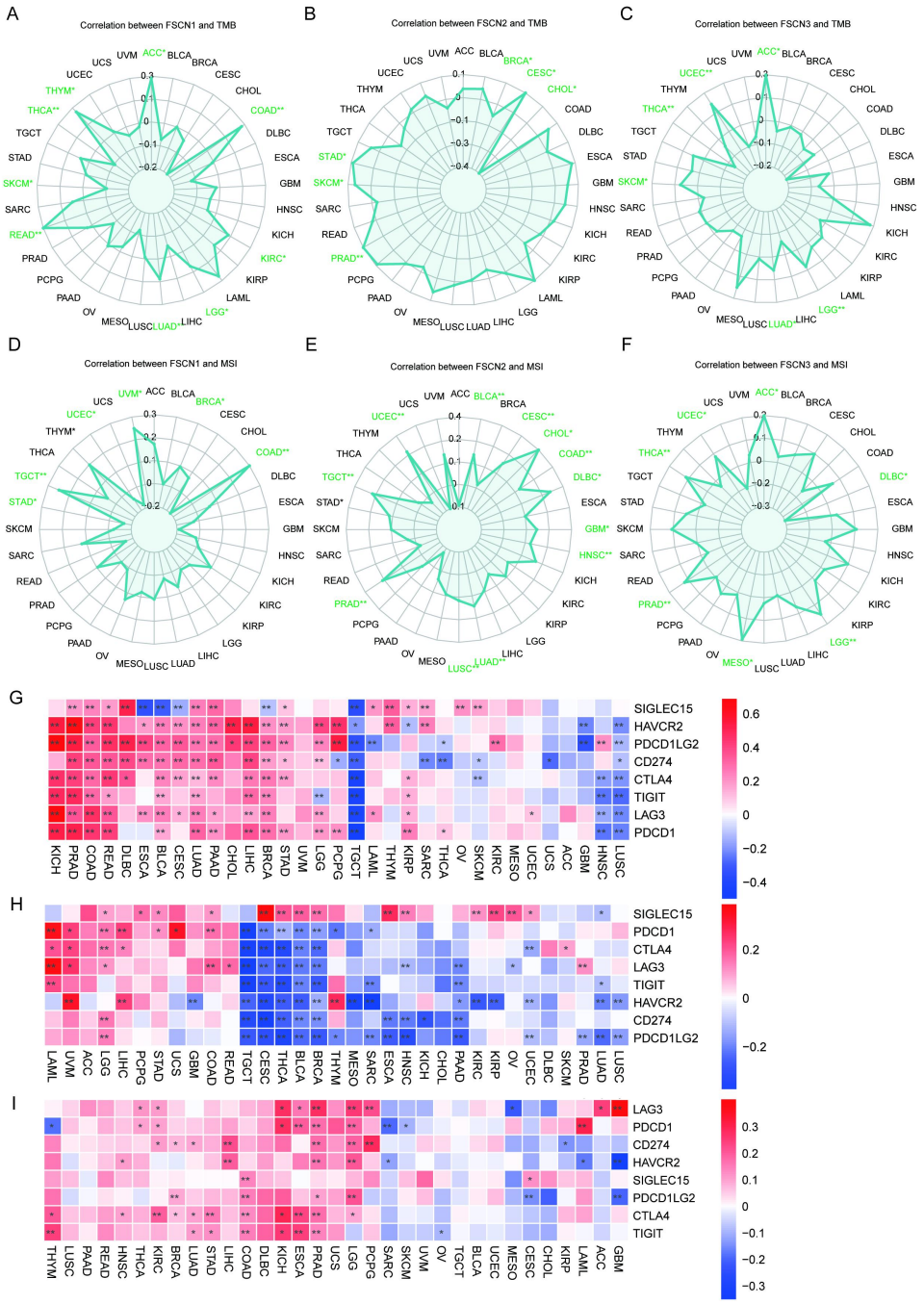

Figure 4 Correlation of FSCN family genes with TMB, MSI, and immune checkpoint molecules. (A–C) Correlation between FSCN1, FSCN2, and FSCN3 expression and TMB across different cancers. Significant correlations are marked in green. (D–F) Correlation between FSCN1, FSCN2, and FSCN3 expression and MSI. Significant correlations are marked in green. (G–I) Correlation between FSCN family genes and the expression of conventional immune checkpoint molecules (e.g., PDCD1, CD274, CTLA4). Heatmaps indicate the strength and direction of these correlations across different cancer types. FSCN, Fascin; TMB, tumor mutational burden; MSI, microsatellite instability.

Correlation of FSCN family genes with immune cell infiltration

To further explore the relationship between FSCN family genes and tumor immunity, we examined the correlation between FSCN gene expression and various types of immune cell infiltration using the CIBERSORT algorithm. This analysis aimed to understand how FSCN genes might influence the immune microenvironment in various cancers.

Figures 5 depict the correlation between FSCN1, FSCN2, and FSCN3 expression and the infiltration levels of 22 different immune cell types, including $CD8^+$ T cells, $CD4^+$ T cells, macrophages, neutrophils, and dendritic cells across different cancers. Significant correlations are highlighted. The analyses reveal that higher expression of FSCN1 and FSCN2 is positively correlated with increased infiltration of specific immune cells in several cancers, suggesting that these genes might play a role in modulating the immune response. In contrast, FSCN3 shows variable correlations depending on the type of immune cell and cancer context.

These findings suggest that FSCN family genes not only influence cancer progression through their effects on cell motility and invasiveness but also potentially modulate the tumor immune microenvironment, impacting the infiltration and function of various immune cells. This interaction could have implications for the effectiveness of immunotherapies and patient outcomes.

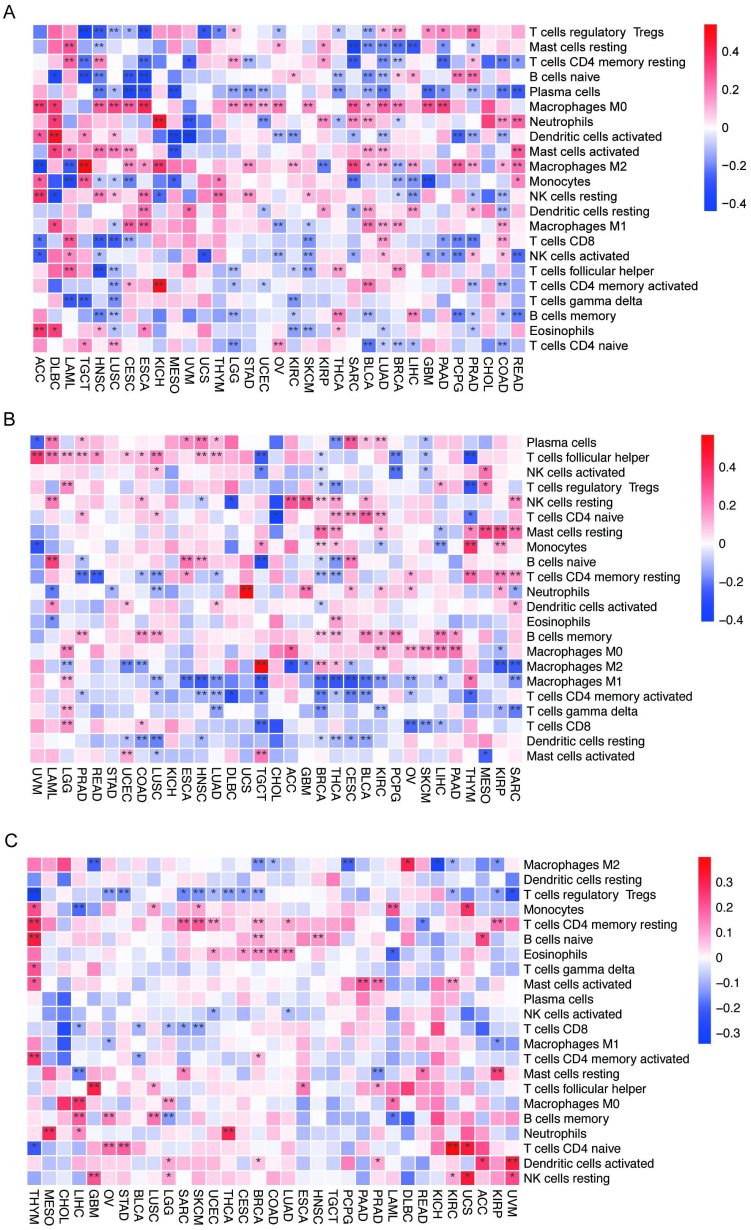

Figure 5 Correlation of FSCN family genes with immune cell infiltration. (A) Correlation between FSCN1 expression and the infiltration levels of 22 different immune cell types, including $CD8^+$ T cells, $CD4^+$ T cells, macrophages, neutrophils, and dendritic cells across different cancers. The heatmap shows significant correlations, highlighting how higher expression of FSCN1 is positively correlated with increased infiltration of specific immune cells in several cancers. (B) Correlation between FSCN2 expression and the infiltration levels of 22 different immune cell types, including $CD8^+$ T cells, $CD4^+$ T cells, macrophages, neutrophils, and dendritic cells across different cancers. The heatmap indicates significant correlations, demonstrating that FSCN2 expression is positively correlated with the infiltration of various immune cells, suggesting its role in modulating the immune microenvironment. (C) Correlation between FSCN3 expression and the infiltration levels of 22 different immune cell types, including $CD8^+$ T cells, $CD4^+$ T cells, macrophages, neutrophils, and dendritic cells across different cancers. The heatmap shows variable correlations, where FSCN3 expression has a more context-dependent relationship with immune cell infiltration, indicating diverse roles in different cancer types. FSCN, Fascin.

Discussion

This study presents a comprehensive pan-cancer analysis of the FSCN family genes, revealing significant insights into their roles and regulatory mechanisms across various cancer types. Our primary findings indicate that FSCN1 and FSCN2 exhibit significant differential expression in multiple cancers, often correlating with poor prognosis, while FSCN3 shows less variability but demonstrates a protective role in certain contexts. Additionally, we observed that the FSCN family genes frequently undergo CNVs, with gene gains being prevalent in numerous cancers. FSCN3, in particular, shows a higher mutation frequency, highlighting its genetic instability. Moreover, our analysis of methylation status revealed that FSCN1 and FSCN2 are generally hypomethylated in tumors compared to normal tissues, whereas FSCN3 exhibited minor changes. Lastly, the correlation of FSCN gene expression with TMB, MSI, and immune checkpoint molecules underscores their potential involvement in modulating tumor immunogenicity and the immune landscape.

The differential expression of FSCN1 and FSCN2 across various cancers and their association with poor prognosis suggest these genes may play crucial roles in promoting cancer progression. FSCN1 is known to enhance cell motility and invasiveness by bundling actin filaments, facilitating metastatic dissemination [14]. The upregulation of FSCN1 observed in our study aligns with previous findings that link FSCN1 overexpression to increased metastatic potential and poor clinical outcomes in breast, colorectal, and gastric cancers. FSCN1's ability to remodel the actin cytoskeleton enhances the formation of cellular protrusions such as filopodia, which are essential for cancer cell migration and invasion. FSCN1 also interacts with other cytoskeletal proteins and signaling molecules, integrating various pathways that regulate cell adhesion, migration, and survival. This makes FSCN1 a potential therapeutic target, as inhibiting its function could impair the invasive capabilities of cancer cells, reducing metastasis and improving patient outcomes. Similarly, FSCN2, while less extensively studied, appears to function in parallel pathways, contributing to cytoskeletal dynamics and cell migration. The overexpression of FSCN2 in cancers like glioblastoma suggests its role in enhancing cell motility and invasiveness, akin to FSCN1. Moreover, FSCN2's involvement in neurodevelopmental processes hints at its potential role in the nervous system's tumors, where its dysregulation could contribute to oncogenic transformations.

The frequent CNVs in FSCN genes, particularly gene gains, further support their involvement in oncogenesis. Gene gains can lead to overexpression, enhancing the aggressive behavior of cancer cells. The significant correlation between CNVs and gene expression in our analysis reinforces the notion that genomic alterations drive the dysregulation of FSCN genes in cancer. For instance, the amplification of FSCN1 and FSCN2 could enhance their expression, thus promoting oncogenic pathways that lead to tumor progression. These CNVs might also interact with other genomic alterations, creating a network of dysregulated pathways that contribute to cancer development and progression. The mutation analysis revealed that FSCN3 has a higher mutation rate in several cancers, suggesting it may undergo selection pressures that confer a growth advantage or resistance to apoptosis. These mutations could potentially disrupt normal cytoskeletal functions, leading to altered cell morphology and behavior, which are hallmarks of cancer cells [7]. Mutations in FSCN3 could affect its binding affinity to actin filaments or other regulatory proteins, altering its normal function and contributing to the malignant phenotype. The high mutation rate in FSCN3 also suggests it might be involved in adaptive responses to the tumor microenvironment, helping cancer cells survive under stressful conditions such as hypoxia or chemotherapy.

Epigenetically, the hypomethylation of FSCN1 and FSCN2 in tumors compared to normal tissues indicates that demethylation may be a mechanism that upregulates these genes in cancer. Hypomethylation can reactivate gene expression, contributing to the aberrant overexpression seen in tumors. For FSCN3, the positive correlation between its methylation status and expression suggests that methylation could be a regulatory mechanism that maintains its expression levels within a functional range, preventing detrimental overexpression or silencing.

The correlations between FSCN gene expression and TMB/MSI highlight the potential role of these genes in influencing the genomic stability of cancer cells. Higher TMB and MSI are associated with increased neoantigen load, which can enhance the immunogenicity of tumors. The positive correlation between FSCN expression and these features suggests that FSCN genes might contribute to a mutagenic environment, promoting genetic diversity and tumor evolution. The significant correlations between FSCN genes and immune checkpoint molecules suggest that FSCN family proteins might influence the immune evasion strategies of tumors. By modulating the expression of immune checkpoints such as PDCD1, CD274, and CTLA4, FSCN genes could affect the tumor-immune microenvironment, potentially impacting the effectiveness of immunotherapies.

While this study provides valuable insights, several limitations should be acknowledged. The analysis relies on data from TCGA, which, while comprehensive, may not capture all genetic and epigenetic variations present in diverse populations or less common cancer types. Additionally, the study is predominantly computational and lacks functional validation through experimental assays. The correlations observed need to be substantiated by in vitro and in vivo studies to confirm the mechanistic roles of FSCN genes. Furthermore, the cross-sectional nature of the data limits our ability to infer causal relationships. Longitudinal studies are required to understand the temporal dynamics of FSCN gene alterations and their impact on cancer progression and treatment response.

In conclusion, our pan-cancer analysis of FSCN family genes reveals their significant involvement in cancer biology through differential expression, genomic alterations, epigenetic modifications, and interactions with key clinical features such as TMB, MSI, and immune checkpoint molecules. FSCN1 and FSCN2 are predominantly associated with poor prognosis and aggressive cancer phenotypes, while FSCN3 exhibits protective roles in specific contexts. The findings highlight the potential of FSCN family genes as biomarkers and therapeutic targets, offering new avenues for personalized cancer treatment strategies. Future studies should aim to validate these findings and explore the underlying mechanisms further to fully harness the clinical potential of FSCN family proteins in oncology.

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