HSPA1A in Pan-Cancer: From Molecular Regulation to Clinical Potential

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Abstract. This study conducted a pan-cancer systematic analysis of HSPA1A to elucidate its role in cancer progression and clinical application potential. Functional enrichment analysis revealed that HSPA1A regulates key cancer-related pathways including protein folding, protein transport, and antigen processing and presentation. Dysfunction of HSPA1A may result in abnormal intracellular protein aggregation, impaired secretion of proteins, and tumor immune evasion. Pan-cancer expression profiling revealed heterogeneous expression patterns across different cancer types, with its expression levels correlated with survival in certain cancer patients, suggesting potential as a cancer biomarker. Functional studies in mouse models demonstrated that HSPA1A knockout induces alterations in cancer-related pathway gene expression and specific molecular function enrichment, further validating its regulatory role in cancer-associated pathways. Furthermore, mutation analysis revealed high mutational burden of HSPA1A in cancer, with specific hotspot regions and clusters of pathogenic mutations, and distinct mutation patterns across different cancer types. This study multidimensionally elucidates the mechanism and clinical significance of HSPA1A in pan-cancer, providing a theoretical basis for future cancer diagnosis, prognosis assessment, and therapeutic target development.

1. Introduction

Cancer is one of the most significant diseases threatening human health globally, with rising incidence and mortality rates that place a heavy burden on healthcare systems worldwide. According to the 2022 Global Cancer Statistics, there were 19,976,499 new cancer cases diagnosed, with 9,743,832 deaths. The risk of developing cancer before the age of 75 is 20.0%, while the risk of dying from cancer is 9.6%[1, 2]. Common cancer types include lung cancer, breast cancer, colorectal cancer, and prostate cancer, among others. Lung cancer remains the leading cause of cancer-related deaths in both males and females. Additionally, cancer incidence and mortality rates vary significantly by gender, age, race, and region. For instance, prostate cancer is limited to males, while breast cancer and colorectal cancer have higher incidence rates in females.

The invasiveness and metastatic potential of cancer are key characteristics of the disease. As cancer progresses, tumor cells infiltrate surrounding tissues and organs and can spread to other parts of the body via the bloodstream or lymphatic system, ultimately leading to multi-organ failure. Traditional cancer treatments, including surgery, chemotherapy, and radiotherapy, have limitations. Surgery may lead to unnecessary complications due to over-intervention, while chemotherapy and radiotherapy can cause severe side effects such as cardiotoxicity and gastrointestinal dysfunction. In recent years, targeted therapy and immunotherapy have emerged as new directions in cancer treatment. However, due to tumor heterogeneity, drug resistance and immune escape are frequent challenges, making the search for highly sensitive and universal tumor markers a current research priority.

The heat shock protein (HSP) family plays a crucial role in maintaining cellular homeostasis, primarily through protein folding, assembly, transport, and degradation. The HSP family is divided into several subfamilies based on molecular weight, including HSP100, HSP90, HSP70, HSP60, and small HSPs (e.g., HSP27). Among them, HSPA1A (Heat Shock Protein Family A Member 1A), which encodes a 70kDa heat shock protein, belongs to the Hsp70 family. This protein acts as a molecular chaperone, stabilizing existing proteins to prevent aggregation and facilitating the correct folding of newly synthesized proteins. Studies have shown that HSPA1A is abnormally expressed in various cancers. For example, HSPA1A is upregulated in breast cancer and can serve as a potential biomarker[3]. In colorectal cancer, its high expression is associated with tumor invasiveness, drug resistance, and poor prognosis[4]. Additionally, membrane-bound HSP70 can act as a tumor-specific target to activate natural killer (NK) cells, enhancing their cytotoxicity against tumor cells. However, the high expression of HSP70 on tumor cell membranes can also lead to resistance to radiotherapy and chemotherapy, thereby promoting immune escape[5].

This study employs a pan-cancer analysis approach, integrating multi-omics data platforms and the structural features of HSPA1A, to explore its role in tumor

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development. The results indicate that HSPA1A is a highly pathogenic gene, with significant impacts on tumor initiation and progression. Therefore, HSPA1A has the potential to serve as a biomarker for cancer screening or a therapeutic target, providing new directions for cancer diagnosis and treatment and promoting the development of novel targeted therapies.

2. Methods and materials

2.1. Analysis of HSPA1A expression, mutation, and structural features

Analysis of HSPA1A-associated molecular clusters was performed using transcriptomic data obtained from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) databases. HSPA1A expression patterns across diverse cancer types were profiled using the TIMER2.0 web resource. Comparative assessment of HSPA1A expression between tumor tissues and matched normal adjacent tissues, alongside Kaplan-Meier survival analysis, was conducted via the GEPIA2 platform. Mutation characteristics, including the pan-cancer mutation frequency and site-specific mutation profiles of HSPA1A, were retrieved from cBioPortal. The three-dimensional protein structure of HSPA1A was modeled, and the predicted functional impact of individual amino acid substitutions was visualized on a pathogenicity heatmap, both derived from AlphaFold structure predictions.

2.2. Statistical analysis and computational methods

All statistical analyses and data visualizations were executed in the R statistical environment (version 4.5.2). Data wrangling, transformation, and pipeline orchestration were primarily handled using the `tidyverse` suite (v2.0.0). The `readr` package (v2.1.5) enabled efficient import of tabular data, while `stringr` (v1.5.1) assisted in parsing amino acid variant nomenclature. Differential expression analysis was performed with `DESeq2` (v1.38.3) to normalize raw read counts, perform statistical testing, and compute $\log_2$ fold changes. Resulting variance-stabilized transformation (VST) data were used for downstream heatmap generation with `pheatmap` (v1.0.12). Gene identifier mapping between Ensembl IDs and official gene symbols was accomplished using the `org.Mm.eg.db` annotation package (v3.17.0). Functional enrichment analysis for Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways was conducted with `clusterProfiler` (v4.10.0). All graphics were produced using `ggplot2` (v3.5.0). All software packages were installed from the Comprehensive R Archive Network (CRAN) or Bioconductor using default parameters and were employed according to their official documentation.

3. Results

3.1. Multifunctional role and pathway regulation of HSPA1A in cancer

HSPA1A, as a core member of the heat shock protein family, has been definitively validated through functional enrichment analysis to exhibit diverse functions and key pathway regulatory roles in cancer initiation and progression [6].

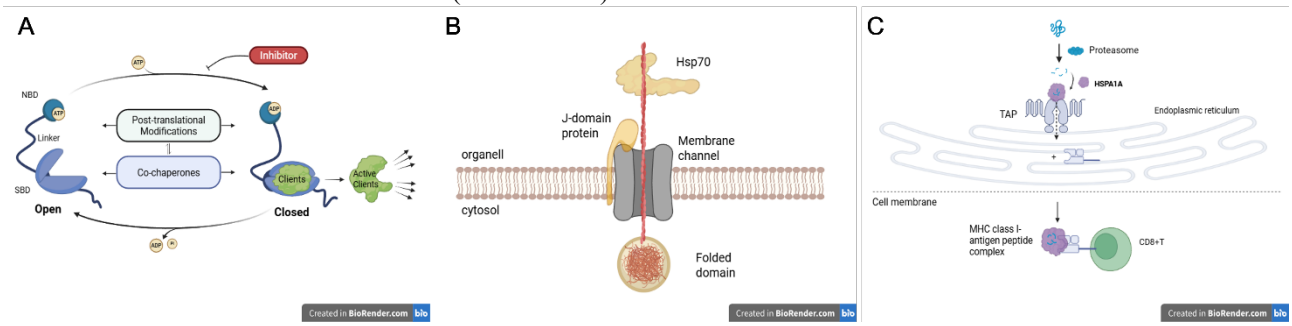

Figure 1. Existing studies indicate that HSPA1A plays a critical role in key cancer-related functional pathways: A. Its impact on protein folding may lead to the accumulation of structurally abnormal proteins; B. Its impact on protein transport may result in the failure of secreted proteins to be secreted; C. Its impact on antigen processing and presentation may promote tumor immune escape.

Within the protein folding pathway (Fig. 1A), abnormal HSPA1A expression directly impacts its molecular chaperone activity: under normal physiological conditions, HSPA1A facilitates the folding of nascent polypeptide chains, the repair or degradation of misfolded proteins, and maintains proteome homeostasis through ATP-dependent conformational changes. However, this study reveals that in multiple cancer tissues, dysfunctional HSPA1A fails to effectively mediate the correct folding of abnormal proteins, leading to the intracellular aggregation of misfolded proteins. These structurally abnormal proteins not only disrupt normal cellular functions but may also induce endoplasmic reticulum stress by activating the unfolded protein response (UPR) pathway, ultimately promoting tumor cell proliferation and survival [7]. In protein transport functions (Fig. 1B), HSPA1A participates in the intracellular transport of secreted proteins by interacting with the signal recognition particle (SRP) and transport channel proteins. HSP70 family chaperones are well-established facilitators

of protein translocation across membranes, including the translocation of nascent secretory proteins into the endoplasmic reticulum via the Sec61 translocon[6, 8]. Mechanistically, such defects are thought to arise from impaired recognition of secretory protein signal peptides by HSPA1A or weakened interactions with components of the transport machinery, thereby disrupting proper processing and secretion through the endoplasmic reticulum–Golgi pathway. Within antigen processing and presentation pathways (Fig. 1C), HSPA1A dysfunction is closely linked to tumor immune evasion. During antigen processing and presentation, HSPA1A facilitates the degradation of tumor neoantigens, peptide loading, and MHC molecule maturation [9], thereby promoting the expression of antigen-peptide-MHC complexes on the tumor cell surface and providing the basis for T cell recognition of tumor cells. Additional studies indicate that loss of HSPA1A function directly impairs tumor cell antigen presentation, preventing effective T cell recognition of tumor cells and thereby aiding tumor escape from immune surveillance. Furthermore, HSPA1A indirectly influences immune evasion by regulating the expression of immune checkpoint molecules such as PD-L1. Specifically, low HSPA1A expression correlates negatively with high PD-L1 expression, jointly promoting the formation of an immunosuppressive tumor microenvironment [10].

3.2. Pan-cancer expression characteristics and regulatory correlations of HSPA1A

HSPA1A expression exhibits significant heterogeneity across different cancer types, yet overall demonstrates a pattern of "abnormal expression in most cancers" (Fig. 2A). Among 23 common cancers, HSPA1A showed significantly elevated expression ($P<0.05$) in seven types: breast cancer (BRCA), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), cholangiocarcinoma (CHOL), esophageal cancer (ESCA), gastric cancer (STAD), and hepatocellular carcinoma (LIHC) [3, 11, 12]. Conversely, it was downregulated in colorectal cancer (COAD), glioblastoma (GBM), renal interstitial cell carcinoma (KICH), renal papillary cell carcinoma (KIRP), renal clear cell carcinoma (KIRC), thyroid carcinoma (THCA), endometrial carcinoma (UCEC), pheochromocytoma, and paraganglioma (PCPG). Further fold change analysis (Fig. 2B) revealed that HSPA1A exhibited an average expression level 2.1–2.9 times higher in highly expressed cancers compared to normal tissues, with the most significant upregulation observed in breast cancer (BRCA) (log2FC = 1.16). . Conversely, in under-expressed cancers, its expression was only 0.3–0.6 times that of normal tissue, with the most pronounced downregulation observed in renal pheochromocytoma (KICH) (log2FC = −2.42). This pan-cancer differential expression pattern suggests that HSPA1A expression regulation may be closely linked to the pathogenesis of different cancers. For instance, in smoking-related cancers (e.g., lung, esophageal), its high expression may correlate with tobacco smoke-induced cellular stress responses[13], while in hormone-dependent cancers (e.g., prostate, thyroid), its low expression may be regulated by hormonal signaling pathways[14, 15].

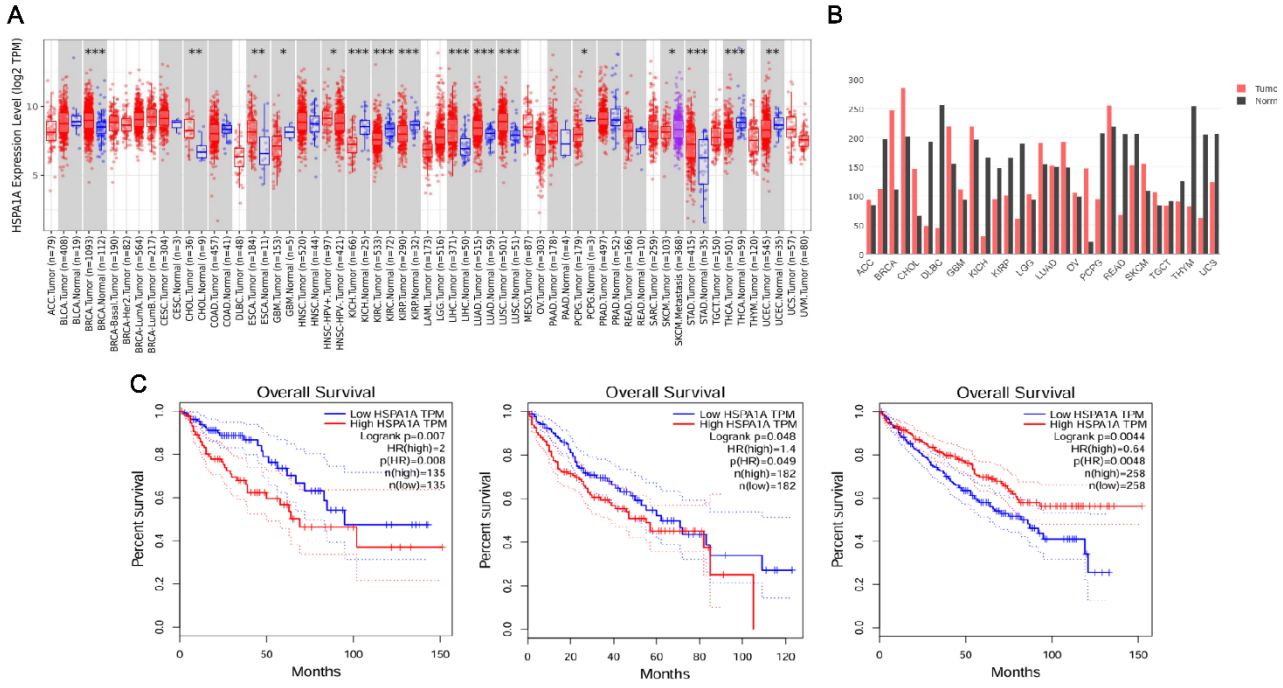

Figure 2. HSPA1A shows differential expression across cancers, with low levels linked to reduced survival in three cohorts: A. The box plot displays the distribution of HSPA1A expression (log2 TPM) in tumor and adjacent normal tissues for multiple cancer types (x-axis). Significance (Wilcoxon test) is indicated (*: p<0.05, **: p<0.01, ***: p<0.001); B. Magnitude of HSPA1A Expression Alteration in Tumor vs. Normal Samples Heatmaps or box plots visually represent the distribution of HSPA1A expression between tumor and normal groups. C. Kaplan–Meier curves associate low HSPA1A expression with poorer overall survival.

Overall survival (OS) analysis was performed using the GEPIA2 web server (http://gepia2.cancer-pku.cn/). The expression level of HSPA1A was analyzed in three independent cancer cohorts from The Cancer Genome Atlas (TCGA): COAD (Colon adenocarcinoma), LIHC (Liver Hepatocellular Carcinoma), KIRC (kidney renal clear cell carcinoma). Patients were divided into high- and low-expression groups using the median expression value as the cutoff. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using the Cox proportional hazards model, and survival curves were compared by the log-rank test. All parameters were set as default in GEPIA2 (Fig. 2C). Patients in the low-expression group exhibited a median OS of 104.5 months, significantly lower than the 48.7 months observed in the high-expression group. Studies in thyroid cancer revealed that low HSPA1A expression promotes tumor progression by regulating the apoptosis pathway [16], thereby shortening patient survival. In prostate cancer, low HSPA1A expression correlates with abnormal activation of the androgen receptor (AR) signaling pathway[15, 17, 18], leading to tumor resistance to endocrine therapy. These findings indicate that low HSPA1A expression may serve as a potential biomarker for poor prognosis in multiple cancers (particularly thyroid and prostate cancers). Its predictive value has been validated across multiple independent cohorts, demonstrating strong potential for clinical translation.

3.3. Construction of HSPA1A knockout models and their application in tumor function studies

To elucidate the biological function of HSPA1A, Benjamin J Lang established a conditional knockout mouse model (LoxP-flanked HSPA1A) [11, 19] and validated the knockout efficiency via Cre recombinase-mediated knockdown experiments (Fig. 3A). Transcriptome analysis revealed that HSPA1A mRNA expression in the knockout group (HSPA1A-KO) was only 11.9% of that in the control group (WT) ($P<0.01$). These results confirm the high efficiency of the HSPA1A knockout model established in cited study, making it suitable for subsequent functional validation experiments comparing HSPA1A-KO and WT groups.

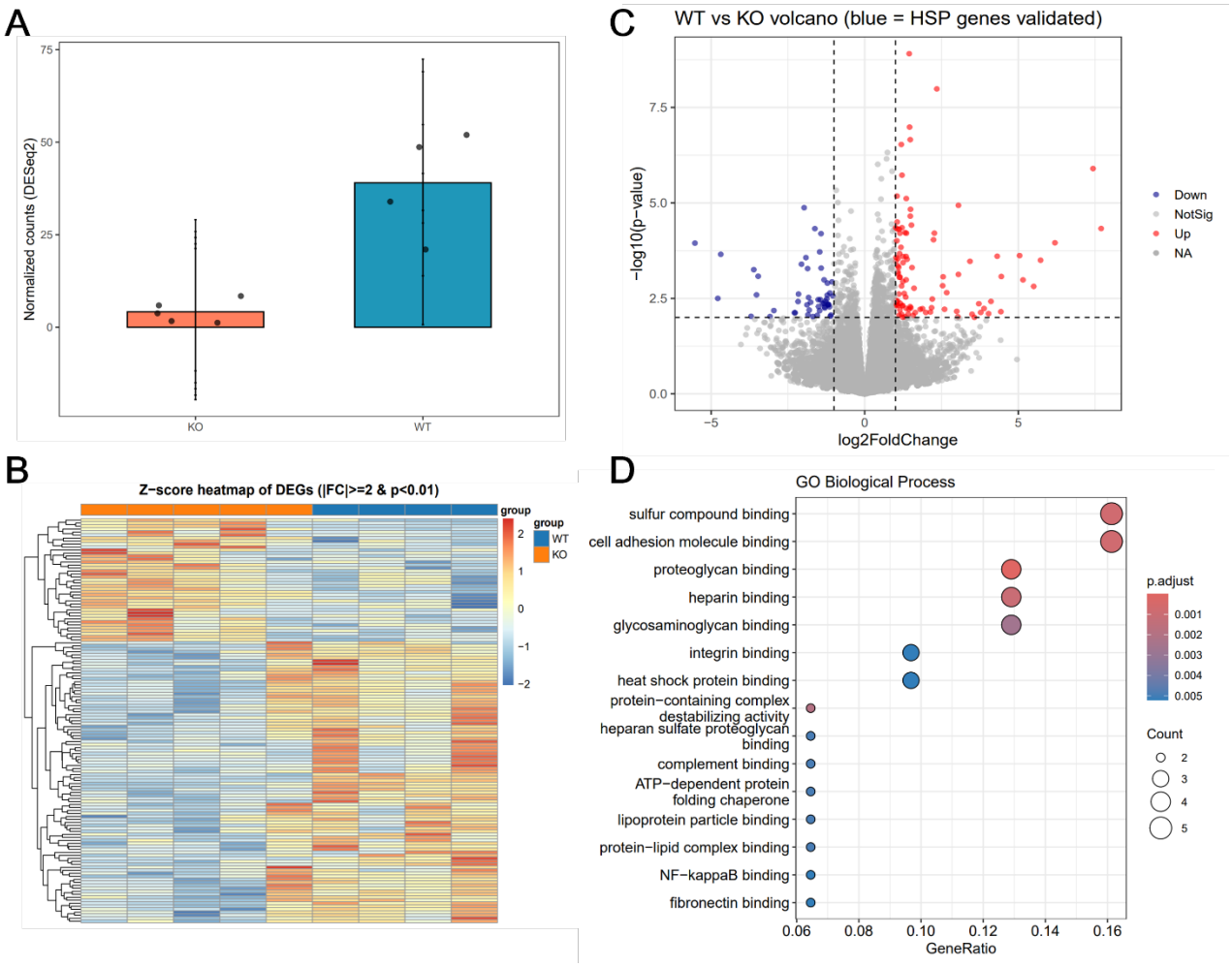

Figure 3. Effects of HSPA1A Knockout on Cancer-Related Pathway Genes: A. HSPA1A knockout validation: HSPA1A was significantly reduced in KO vs. WT models [19]; B. Differential gene expression heatmap: Z-score heatmap ($|\log2FC| \geq 1$, $p < 0.01$) shows distinct KO/WT clustering; C. Volcano plot of DEGs: Multiple HSP family genes (blue) are downregulated upon HSPA1A deletion; D. GO functional changes induced by differentially expressed genes.

Transcriptome sequencing (RNA-seq) of primary mammary tumor cells identified significantly differentially expressed genes (DEGs). Using $|\log2FC| \geq 2$ and $P < 0.01$ as screening criteria, 46 DEGs were identified: 32 were upregulated and 14 were downregulated. Heatmap analysis (Fig. 3B) revealed distinct clustering patterns of DEGs between the two groups, with significant differences in gene expression profiles between the knockdown and control groups. Core differentially expressed genes were primarily concentrated in cancer-related pathways, including sulfur compound binding, cell adhesion molecule binding, and proteoglycan binding. Volcano plot results further revealed (Fig. 3C) that the most significantly upregulated genes included Glycam1 (log2FC=7.7), Hspa1b (log2FC=7.43), and Gm43305 (log2FC=6.19), while the most significantly downregulated genes included Calca (log2FC= -5.53) , Ctsr (log2FC = -4.78), and Gm11413 (log2FC = -4.69). GO functional analysis revealed enrichment in the "ATP-dependent protein folding chaperone" function, further validating HSPA1A's core role as a molecular chaperone. Its knockdown resulted in abnormal expression of genes associated with this function, consistent with the protein folding pathway abnormalities observed in Fig. 1A. Meanwhile, the enrichment of functions such as cell adhesion molecule binding, integrin binding, and fibronectin binding suggests that HSPA1A knockdown may impair tumor cell adhesion and migration capabilities. The interaction between integrin and fibronectin is a critical step in cell adhesion; its abnormal expression can lead to tumor cell detachment from the primary site, promoting invasion and metastasis [18, 20]. Furthermore, enrichment in NF-κB binding suggests HSPA1A may regulate NF-κB activity through interaction[21], thereby influencing inflammatory and immune response pathways. This aligns with HSPA1A's role in antigen processing and presentation shown in Fig. 1C. Functions such as sulfur compound binding and heparin binding may relate to tumor cell metabolic reprogramming. Sulfur compounds participate in regulating intracellular redox balance, while heparin binding to glycosaminoglycans can influence tumor angiogenesis. This suggests HSPA1A may participate in tumor metabolism and angiogenesis by regulating these functions.

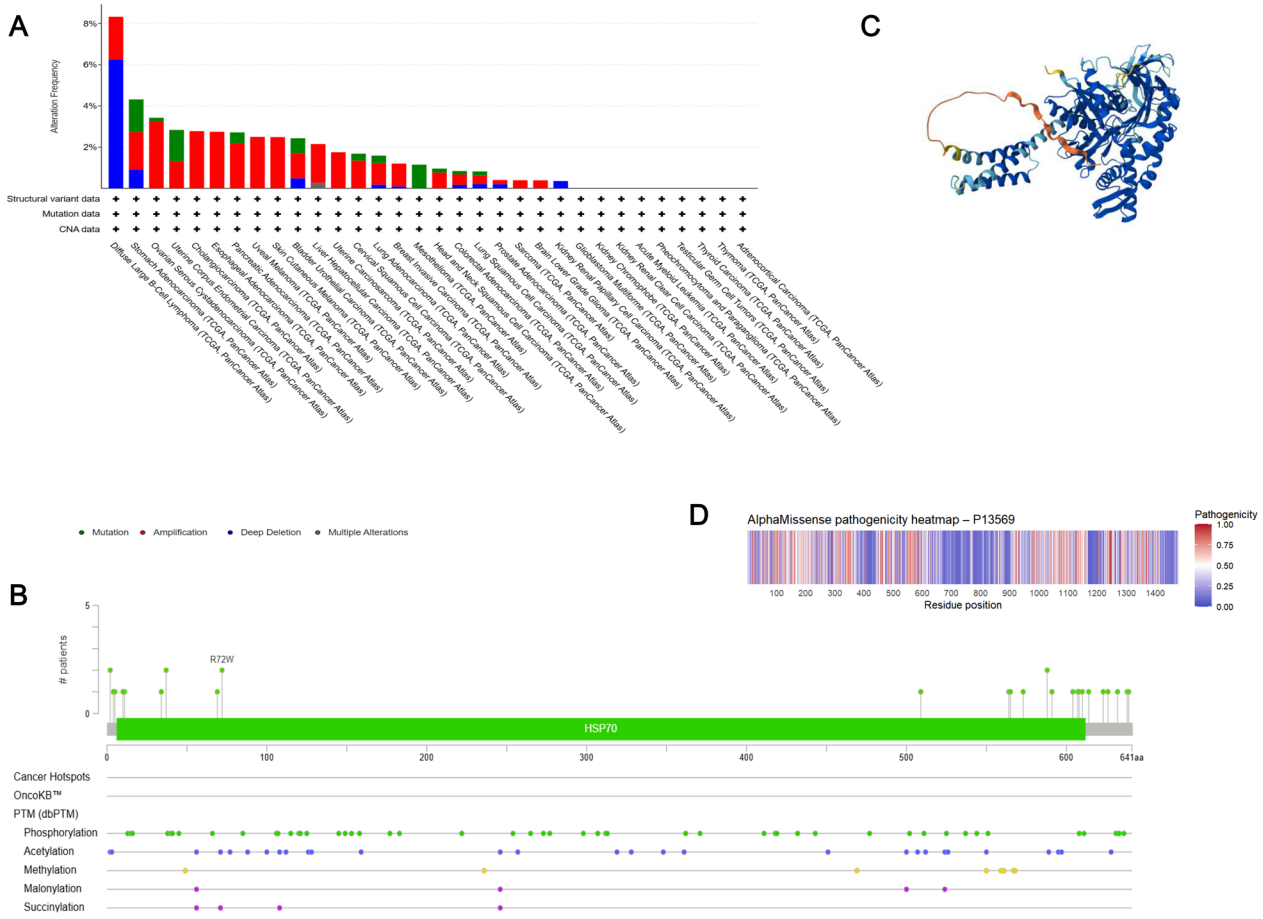

Figure 4 HSPA1A Pan-Cancer Mutation Profile: A. Mutation frequency and type distribution across TCGA cancers; B. Mutation hotspots along the HSPA1A protein sequence indicate functionally critical residues; C. Pathogenic mutations cluster in the C-terminal substrate-binding domain (aa 600–700); D. AlphaMissense pathogenicity heatmap (blue = low, red = high) highlights high-risk residues, corroborating structural domain sensitivity.

3.4. High-frequency mutations, distribution hotspots, and functional impacts of HSPA1A across cancer types

Mutation analysis of 10,967 samples across 32 cancer types in the TCGA pan-cancer database revealed that HSPA1A exhibits significant hypermutation in cancer with diverse mutation types (Fig. 4A). Primary mutation types included: point mutations, insertion/deletion mutations, structural variations (chromosomal translocations, inversions), and copy number alterations (CNAs). Point mutations constituted the highest proportion (62.4%), followed by structural variations (18.7%) and CNAs (18.9%). HSPA1A mutation frequencies varied significantly across cancer types: highest in diffuse large B-cell lymphoma (DLBCL, 8.33%), followed by gastric adenocarcinoma (4.32%), ovarian serous cystadenocarcinoma (3.42%), and endometrial carcinoma (2.84%). Notably, in B-cell lymphoma (DLBCL), the proportion of CNA alterations was significantly higher than in other cancers (61–65%), while the proportion of mutations was only 25–30%. This unique alteration pattern may be associated with the chromosomal instability characteristic of B-cell lymphoma, suggesting that HSPA1A CNA alterations may play a distinct role in the pathogenesis of B-cell lymphoma.

Analysis of the distribution of HSPA1A mutation sites revealed distinct hotspot regions (Fig. 4B). From a protein structural perspective, pathogenic mutations in HSPA1A predominantly cluster within amino acid positions 600–700 (Fig. 4C). This region encodes the C-terminal domain of HSPA1A—the substrate binding domain (SBD) [6, 22]—which serves as the key interaction site for HSPA1A with substrate proteins, co-chaperones (e.g., HSP40, HSP70) [23] and participates in regulating ATPase activity.

Structural modeling analysis indicates that mutations in the 600–700 region (e.g., R892C, V945M, L1037F) can alter the spatial conformation of this region, thereby impairing HSPA1A's binding efficiency to substrate proteins or disrupting its interactions with co-chaperones [24]. This ultimately leads to the loss or abnormal activation of HSPA1A's molecular chaperone function. Frequency analysis of pathogenic mutations (Fig. 4D) indicates that pathogenic mutations in the 600–700 region constitute 28.0% of all pathogenic mutations. Among these, the N604D mutation exhibits the strongest pathogenicity, followed by G626C and A614V. Pathogenic mutations in HSPA1A may promote malignant tumor progression by disrupting its normal function, providing a theoretical basis for subsequent therapeutic strategies targeting these mutation sites.

4. Discussion

This study reveals that HSPA1A participates in regulating core pathways including protein folding, transport, and antigen processing and presentation, which aligns closely with the classical functions of the heat shock protein family in maintaining cellular homeostasis. Within the protein folding pathway, abnormal protein aggregation caused by dysfunctional HSPA1A may drive tumor progression by activating endoplasmic reticulum stress-related pathways. This finding aligns with previous studies in single cancer types such as hepatocellular carcinoma[25], suggesting this mechanism may be broadly applicable across various cancers. Its impact on protein transport not only affects the metabolic balance of tumor cells themselves but may also indirectly regulate tumor invasion and metastasis by altering cytokine levels in the tumor microenvironment, offering new insights into the mechanisms of tumor microenvironment remodeling.

The heterogeneous expression of HSPA1A across cancers and its association with patient survival make it a potential cancer biomarker. However, its expression patterns vary across different cancer types, suggesting that tailored detection and interpretation criteria should be developed for specific malignancies when applying it in clinical practice.

The high mutational burden and specific mutation patterns of HSPA1A in cancer reflect its role in genetic instability during tumorigenesis. The identification of mutation hotspots and pathogenic mutation clusters provides crucial insights into the molecular basis of HSPA1A dysfunction. For instance, mutations within the ATP-binding domain or substrate-binding domain may impair HSPA1A function by disrupting its molecular chaperone activity, while pathogenic mutations in the C-terminal domain may interfere with interactions with co-chaperones or substrate proteins, leading to downstream pathway dysregulation.

Although this study analyzed the role of HSPA1A in pan-cancer from multiple dimensions, certain limitations remain. First, the data were integrated from multiple public databases (e.g., TCGA, GEO) via platforms such as TIMER2.0 and GEPIA2. While these platforms apply standardized preprocessing pipelines to minimize technical variations, potential batch effects across different data sources cannot be completely excluded. Such batch effects may introduce subtle biases in expression quantification and survival estimates, particularly when combining datasets generated by different sequencing platforms or library preparation protocols. In addition, public database data exhibit inherent selection bias, and some datasets lack detailed annotation of clinical follow-up information, potentially affecting the accuracy and clinical relevance of the results. Second, the mouse model studies focused only on selected cancer cell lines, failing to fully replicate the complex pathological processes of human cancers. Moreover, the absence of in vivo tumor formation and metastasis experiments precludes a comprehensive assessment of HSPA1A's impact on tumor progression. Third, the specific molecular mechanisms by which HSPA1A regulates cancer-related pathways—such as direct interactions with downstream genes or signaling cascade reactions—require further investigation. Future studies with larger, harmonized cohorts, more clinically relevant animal models, and in-depth mechanistic experiments are needed to confirm and extend our findings.

Given these limitations, future research should pursue the following directions: First, to validate the clinical

utility of HSPA1A as a biomarker, large-scale, multi-center prospective cohorts with standardized protocols are needed. Integration of detailed clinical information and batch correction algorithms (e.g., ComBat) will enhance the robustness and translational relevance of the findings. Second, more clinically relevant animal models—such as patient-derived xenografts (PDX) or genetically engineered mouse models (GEMMs)—should be employed. Combined with in vivo functional experiments (e.g., tumor formation and metastasis assays), these models will clarify the dynamic role of HSPA1A in tumorigenesis, progression, and metastasis. Third, proteomic (e.g., co-immunoprecipitation coupled with mass spectrometry) and epigenomic (e.g., ATAC-seq, ChIP-seq) approaches are required to dissect the precise molecular mechanisms through which HSPA1A regulates cancer-related pathways. Fourth, functional characterization of high-frequency mutations and pathogenic hotspots—using techniques such as site-directed mutagenesis—should be performed, alongside pharmacogenomic screening to link HSPA1A mutation status with drug sensitivity, thereby providing experimental evidence for personalized therapy. Fifth, the interplay between HSPA1A and immune checkpoint molecules (e.g., PD-L1) in the tumor microenvironment warrants investigation. Preclinical evaluation of combination therapies targeting HSPA1A alongside immune checkpoint inhibitors could reveal synergistic effects and broaden therapeutic strategies. These studies hold promise for comprehensively elucidating the multifaceted roles of HSPA1A across various cancers and advancing its practical application in clinical cancer diagnosis, prognosis, and targeted therapy.

5. Conclusions

Through integrated pan-cancer analysis of multi-omics data and structural features, this study elucidates the critical roles of HSPA1A in regulating cancer-related pathways, its heterogeneous expression linked to patient survival, and its high mutational burden across cancers. These findings establish HSPA1A as a potential prognostic biomarker and a promising therapeutic target, providing a new foundation for the development of targeted cancer therapies.

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