Articles

Bioinformatics analysis and the clinical significance of TP73 in regulating the immune microenvironment and chemosensitivity of endometrial cancer

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Abstract

Objective: Endometrial cancer is among the most common malignant tumors of the female reproductive system. Most patients can achieve a favorable prognosis in the early stages, but some may experience tumor progression or treatment resistance, necessitating the search for new molecular markers to improve diagnosis and treatment. *TP73* plays a significant role in the development and progression of various tumors. This study aims to investigate the expression characteristics of the *TP73* gene in endometrial cancer and its associations with clinicopathological parameters, patient prognosis, the immune microenvironment, and chemotherapy sensitivity. Methods: Data from the TCGA and GTEx databases were obtained from UCSC Xena. UALCAN was used to analyze the correlation between TP73 expression and clinical features. The pROC package was used to plot ROC curves to evaluate diagnostic performance. STRING was used to construct a protein–protein interaction network, and KEGG enrichment analysis was performed using LinkedOmics. Immune infiltration analysis was conducted using CIBERSORT, GSVA, and the estimate package, while TISIDB was used to explore associations with immune molecules. CPADS and GSCA databases were used to analyze the IC50 values of chemotherapeutic drugs and identify potential targeted therapies. Results: TP73 was highly expressed in endometrial cancer tissues and significantly correlated with histological subtype, TP53 mutation status, and menopausal status ($P < 0.001$). The ROC curve showed an AUC of 0.895, indicating diagnostic potential. The coexpression network of TP73 was enriched primarily in pathways such as RNA transport and the proteasome. TP73 expression was positively correlated with immune cell infiltration (e.g., NK CD56bright cells) and negatively correlated with macrophages ($P < 0.05$) while also regulating the expression of various immune modulators. Its expression level influenced the IC50 values of chemotherapeutic agents such as cisplatin and docetaxel ($P < 0.05$). Conclusion: TP73 is highly expressed in endometrial cancer and has diagnostic and prognostic value. It may contribute to tumor progression by modulating the immune microenvironment and chemotherapy sensitivity, suggesting its potential as a target for precision therapy in this disease. However, this study is solely based on bioinformatics mining of public databases and has not conducted experimental validation, including in vitro cell experiments, in vivo animal experiments, or clinical sample verification. All the conclusions are predictive results and cannot confirm the actual biological functions of TP73 in regulating the immune microenvironment of endometrial cancer and chemotherapy sensitivity, which is the main limitation of this study.

Keywords: mRNA vaccine, glioblastoma multiforme (GBM), immune subtypes

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Introduction

Endometrial cancer is the most common gynecological tumor, and its incidence continues to increase globally[1]. The 1-year, 3-year, and 5-year survival rates for domestic patients are 96.8%, 89.9%, and 82.1%, respectively. Pathological type, histological grade, clinical stage, and cervical involvement have been confirmed as independent prognostic risk factors[2]. However, significant challenges remain in the early diagnosis and prognostic assessment of endometrial cancer, primarily because of the lack of early diagnostic biomarkers and insufficient prognostic evaluation indicators[3]. Therefore, new biomarkers are needed to improve the early diagnosis and prognostic evaluation of endometrial cancer.

TP73 belongs to the *TP53* gene family and produces N-terminal and C-terminal protein isoforms through alternative promoters, alternative translation initiation, and alternative splicing. Notably, p73 protein isoforms may contain a p53-like transactivation domain (TAp73 isoform) or lack this domain (ΔTAp73 isoform), and these variants have opposing or independent functions[4]. Multiple studies have shown that abnormal expression of *TP73* in various tumors is closely related to tumorigenesis and tumor progression. Meta-analyses have indicated that the *TP73* G4C14-A4T14 polymorphism significantly increases overall cancer risk, with a higher risk in patients with gynecological tumors[5]. In cervical cancer, the protein expression of *TP73* is significantly greater than that in normal cervical epithelium, and high expression is associated with early-stage disease, fewer lymph node metastases, and better overall survival[6]. The expression and functional regulation of the *TP73* gene are not mediated by a single molecule. Its transcription, splicing, and isoform balance are also precisely regulated by upstream and downstream regulatory molecules, among which epigenetic regulation by antisense long noncoding RNAs (lncRNAs) is among the key mechanisms. Owing to its natural genomic adjacency to *TP73*, the TP73-

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associated antisense lncRNA TP73-AS1 serves as a specific regulatory molecule for TP73 function. This lncRNA is located on chromosome 1p36.32 and has a tail-to-tail antisense transcription pattern relative to that of *TP73*. It can inhibit the methylation of the *TP73* promoter by binding to lysine demethylase 5A (KDM5A) while simultaneously interfering with the alternative splicing of *TP73* mRNA. This ultimately leads to a biased suppression of tumor-suppressive TAp73 isoform expression, directly reshaping the functional balance of *TP73* isoforms[7]. Consequently, TP73-AS1 is upregulated in various gynecological cancers, and its pro-oncogenic functions are closely linked to the regulation of *TP73* isoforms. In ovarian cancer, TP73-AS1 modulates *TP73* isoforms to regulate the expression of MMP2 and MMP9, promoting tumor cell invasion and metastasis[8]; in cervical cancer, this lncRNA exerts its procancer effects through the miR-329-3p/ARF1 axis, and ARF1, as a downstream target gene of *TP73*, is also indirectly regulated by the *TP73* isoform profile[9].

In this study, bioinformatics methods were used to analyze the total expression levels and mutation characteristics of the *TP73* gene in endometrial cancer tissues, explore its association with tumor development and patient prognosis, and systematically investigate the role of this gene in regulating the immune microenvironment of endometrial cancer and modulating chemotherapeutic drug sensitivity. Owing to the lack of standardized annotations and specific detection probes for *TP73* isoform-specific transcripts in the TCGA and GTEx databases used in this research, accurate quantification of TAp73 and ΔTAp73 isoform expression levels could not be achieved; hence, this study did not differentiate between the two for analysis. Current research on *TP73* in endometrial cancer remains in the preliminary exploratory stage, with unclear correlations between its total expression characteristics and patient clinicopathological parameters and prognosis, as well as undefined specific regulatory mechanisms in tumor immune microenvironment remodeling and chemotherapeutic drug response. These research gaps make it difficult to define the functional and clinical application value of *TP73* in endometrial cancer development.

This study relies on public databases such as TCGA and GTEx to conduct the first systematic analysis of the total expression level, gene mutation characteristics, protein interaction network, and downstream regulatory pathways of *TP73* in endometrial cancer. We also explored for the first time the correlation between its expression and tumor-infiltrating immune cells, immune molecule expression, and the half-maximal inhibitory concentration (IC50) values of commonly used clinical chemotherapeutic drugs, clarifying its diagnostic and prognostic value. This study proposes a core hypothesis: *TP73*, as a key regulatory molecule in endometrial cancer, participates in tumorigenesis, malignant progression, and therapeutic response regulation through a multidimensional synergistic mechanism involving remodeling of the tumor immune microenvironment infiltration landscape, regulation of chemotherapeutic drug cellular sensitivity, and the mediation of tumor-associated protein interactions and signaling pathway activation. Differences in its expression levels may lead to imbalances in these mechanisms, affecting tumor immune escape, chemotherapy resistance, and patient clinical outcomes, making *TP73* a potential target for endometrial cancer diagnosis and precision therapy. This research aims to fill existing gaps by clarifying the potential value of *TP73* as a diagnostic biomarker for endometrial cancer, deciphering its molecular characteristics in regulating the tumor immune microenvironment and chemotherapy sensitivity, and providing preliminary theoretical evidence for the use of total *TP73* expression as a diagnostic marker and therapeutic target. The differential functional roles of TAp73 and ΔTAp73 isoforms will be the focus of subsequent studies employing subtype-specific detection methods.

Materials and Methods

Pancancer, expression level, and diagnostic efficacy analysis

The standardized TCGA and GTEx expression data processed through the Toil pipeline were downloaded from the UCSC Xena database (https://xenabrowser.net/datapages/) for pancancer expression profile analysis[10]. In this study, the analysis of *TP73* gene expression levels was based on pansubtype detection data from the aforementioned database, using the gencode.v23 transcript, with the total expression level of all the isoforms of the *TP73* gene used as the basis for analysis. The UALCAN database was used to analyze the correlations between *TP73* expression levels and menopausal status, *TP53* gene mutation status, and tumor histological subtypes. The R packages pROC [1.18.0] and ggplot2 [3.4.4] were used to plot receiver operating characteristic (ROC) curves and calculate the area under the curve (AUC) to evaluate the diagnostic value of *TP73* in endometrial cancer. The above bioinformatics analyses were performed using the Xiantao Academic platform (https://www.xiantaozi.com/).

Construction of interaction networks for *TP73* and its associated protein molecules based on the STRING Database

The STRING database (https://STRING-db.org/) is a shared network platform that collects and integrates protein–protein interaction relationships. Using the STRING database, a *TP73* protein interaction network was constructed, in which different colored lines represent distinct types of interactions, categorized as those extracted from validated databases, experimental verification, gene neighborhood, coexpression, protein homology, and text mining.

Coexpression and enrichment analysis of *TP73* based on the LinkedOmics Platform

In the LinkedOmics database (http://www.linkedomics.org/), the gene sets significantly correlated with *TP73* expression in the transcriptomic data of endometrial cancer patients were analyzed. A Pearson correlation test was used to assess the degree of association between genes, calculate the false discovery rate (FDR), and perform Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. The GSEA enrichment method was employed, with the minimum gene number set to 3, and an FDR ≤ 0.05 was established as the criterion for pathway enrichment determination.

Analysis of *TP73* gene alterations in endometrial cancer using the

cBioPortal Database

This study utilized the cBioPortal visualization analysis platform and selected data from 1,526 samples across four endometrial cancer datasets (with sample sizes of 529, 81, 545, and 371 cases, respectively) to analyze the variation characteristics of the *TP73* gene and the impact of the *TP73* gene variation status on the prognosis of endometrial cancer patients from multiple perspectives.

Immune microenvironment analysis

Utilizing the 22 immune cell signature markers provided by CIBERSORTx (https://cibersortx.stanford.edu/), the R package GSVA [1.46.0] with the ssGSEA algorithm was employed to perform immune infiltration scoring on the basis of 24 immune cell markers. The R package estimate [1.0.13] was used to calculate the immune score and stromal score of the samples. The stats and car packages were used for Spearman correlation analysis, with the Benjamini–Hochberg correction method, to analyze the correlation between *TP73* expression levels and the immune infiltration matrix. Visualization of the results was accomplished using the ggplot2 package.All bioinformatics analyses in this study were implemented on the Xiantao Academic platform (https://www.xiantaozi.com/).

Leveraging the multiomics integration analysis function of the TISIDB database (http://cis.hku.hk/TISIDB/), a systematic evaluation of *TP73* gene expression levels was conducted from the perspectives of chemokine receptors, chemokines, immune inhibitors, immune activators, and major histocompatibility complex (MHC) molecules within the immune microenvironment.

Drug sensitivity analysis

Using the TCGA module in CPADS (https://smuonco.shinyapps.io/CADSP/), with a threshold of $P < 0.05$, *TP73* samples were divided into high- and low-expression groups on the basis of the median. The Wilcoxon test was applied to compare the half-maximal inhibitory concentration (IC50) of commonly used chemotherapeutic drugs in endometrial cancer samples between the high-expression and low-expression groups. The IC50 value represents the drug concentration required to inhibit 50% of cell growth.

Potential drug screening

Using the GSCA platform (https://guolab.wchscu.cn/GSCA/) to analyze the relationship between *TP73* expression levels and drug sensitivity, potential drugs for treating *TP73* were identified. Pearson correlation analysis was employed to assess the correlation between gene expression and drug IC50.

Result

TP73 expression levels and prognostic analysis

Pancancer analysis revealed that the *TP73* gene is highly expressed in various tumor tissues. The expression level of *TP73* in endometrial cancer tissues was significantly greater than that in normal endometrial tissues (Figure 1A). Stratified analysis revealed that patients with endometrioid adenocarcinoma had higher *TP73* expression levels than those with mixed serous carcinoma did ($P<0.001$); *TP73* expression levels were higher in patients with nonmutated *TP53* genes than in those with mutated *TP53* ($P<0.001$), and perimenopausal patients had higher *TP73* expression levels than postmenopausal patients did ($P<0.001$) did (Figure 1B). Receiver operating characteristic (ROC) curve analysis demonstrated that the *TP73* expression level is effective for the diagnosis of related diseases, with an area under the curve (AUC) of 0.895 (95% CI: 0.854–0.936), indicating that *TP73* has potential as a diagnostic biomarker (Figure 1C). The expression characteristics of *TP73* mentioned above did not directly correlate with the degree of malignancy of endometrial cancer subtypes, suggesting that its biological function may not be related to total expression levels but could be related to the expression ratio of TAp73/ΔNp73 isoforms. High expression of *TP73* might involve primarily the ΔNp73 isoform with dominant-negative effects, and its specific regulatory mechanisms will be further analyzed in the discussion section.

Protein interaction network of *TP73*

In the STRING database, the interaction network for *TP73* and its interacting factors was filtered, resulting in 11 nodes and 45 edges, with an average node degree of 8.18, an average local clustering coefficient of 0.848, and a PPI enrichment p value of 7.72E-08. The results revealed that proteins associated with *TP73*, including *TP63*, *YAP1*, *TP53*, *TP53BP2*, and *BCL2L1*, participate in diverse biological processes, primarily involving transcription repressor complexes, transcription regulator complexes, protein domain-specific binding, p53 binding, and p53-mediated apoptosis pathways (Figure 2). Here, *TP73* forms heterodimers with *TP53* to regulate the transcription of downstream apoptotic target genes, serving as a core component of the tumor-suppressive effects mediated by the p53 family in endometrial cancer. Additionally, the interaction between *TP73* and YAP1, a key molecule in the Hippo pathway, is a critical regulatory node for the DNA damage response and chemotherapy sensitivity in endometrial cancer cells. Furthermore, KEGG pathway enrichment analysis revealed that TP73-related genes were significantly enriched in multiple tumor-related pathways. Among these pathways, the p53 signaling pathway (FDR=4.0×10^{-8}; signal=3.5) exhibited the highest enrichment level, followed by the miRNAs in the cancer pathway (FDR=4.0×10^{-8}; signal=3.0). Additionally, pathways such as the cell cycle, platinum drug resistance, and chronic myeloid leukemia were significantly enriched, suggesting that *TP73* may participate in the development of endometrial cancer and the regulation of chemotherapy sensitivity by modulating the p53 pathway, noncoding RNAs, and cell cycle progression. GO functional enrichment analysis further revealed that TP73-related genes are primarily localized in the nucleus at the cellular component level and are significantly enriched in transcriptional repressor complexes and transcriptional regulatory complexes. At the molecular function level, the core enrichment term was p53 binding (FDR=1.0×10^{-11}; signal=5.0), along with MDM2/MDM4 family protein binding and DNA-binding transcription factor binding. In terms of biological processes, the genes were highly focused on p53 class mediator-mediated signal transduction (FDR=3.0×10^{-10}; signal=4.2) and endogenous apoptotic signaling pathways related to the DNA damage response.

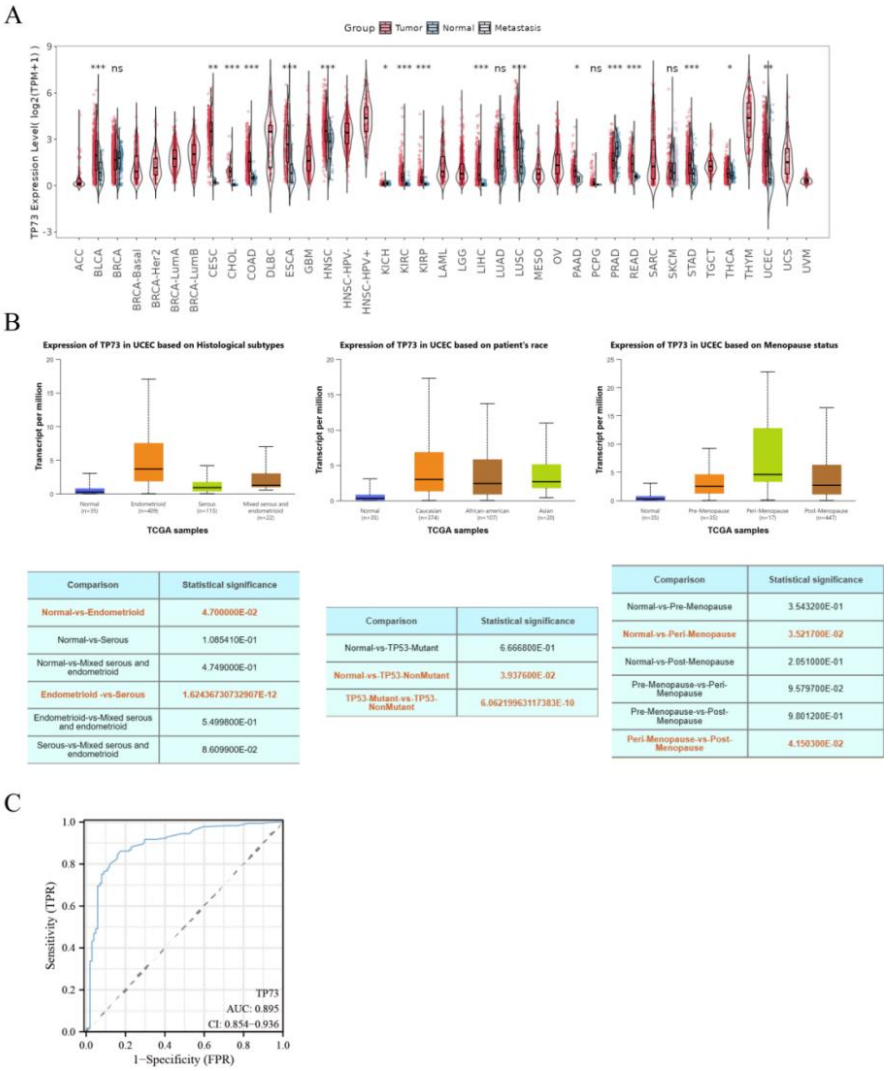

Figure 1. Analysis of *TP73* expression characteristics, clinical correlations, and diagnostic efficacy across cancers and endometrial cancer. (A) Differences in the expression of *TP73* in tumor versus normal tissues across the pancancer cohort. (B) Association and statistical test results of *TP73* expression with metastatic status, *TP53* mutation status, and histological subtypes in endometrial cancer. (C) Diagnostic potential of *TP73* expression for endometrial cancer.

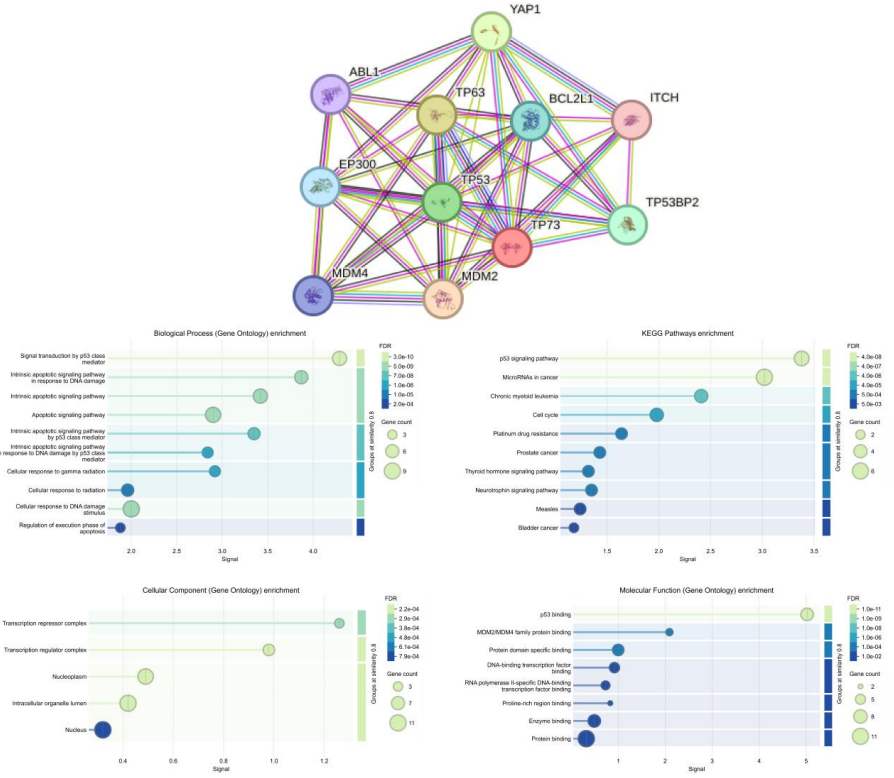

Figure 2. Protein−protein interaction network and its GO/KEGG enrichment.

Expression variants and biological significance of *TP73* in endometrial cancer

Using the LinkedOmics platform, KEGG enrichment analysis was performed on gene sets significantly associated with *TP73* in the transcriptomic data of endometrial cancer patients. The pathways were enriched in RNA transport, proteasome, ECM-receptor interaction, and ribosome biogenesis.

Genomic mutations of *TP73* in endometrial cancer

In this study, *TP73* gene mutations in 1,532 endometrial cancer samples with complete gene sequence and copy number variation information were analyzed through the cBioPortal database. Among them, 56 samples had *TP73* gene mutations, with a total mutation rate of 4% (56/1,532). The mutation types included 9 amplification mutations, 7 deletion mutations, 7 truncation mutations, 2 splice mutations, and 31 missense mutations (Figure 4A). Gene variant characteristic analysis revealed that the main *TP73* gene mutation types were amplification mutations and missense mutations.

In the cancer type summary analysis module, four endometrial cancer-related datasets were selected. The mutation frequency of the *TP73* gene in each dataset, as well as the composition ratio of mutation types such as mutations, amplifications, and deep deletions, are shown in Figure 5B. Among them, in the Uterine Corpus Endometrial Carcinoma (TCGA, PanCancer Atlas) dataset with 529 cases, *TP73* gene alterations accounted for 5.86%; in the Endometrial Carcinoma (CPTAC, Cell 2020) dataset with 81 cases, *TP73* gene alterations accounted for 3.7%; in the Uterine Corpus Endometrial Carcinoma (TCGA, Firehose Legacy) dataset with 545 cases, *TP73* gene alterations accounted for 2.57%; and in the Uterine Corpus Endometrial Carcinoma (TCGA, Nature 2013) dataset with 371 cases, *TP73* gene alterations accounted for 2.16% (Figure 4B).

The survival analysis module of the cBioPortal database was used to further explore the relationship between *TP73* gene alterations and the clinical characteristics of endometrial cancer patients. The results revealed that the *TP73* gene alteration status significantly affected the overall survival of endometrial cancer patients (P=0.0386) (Figure 4C).

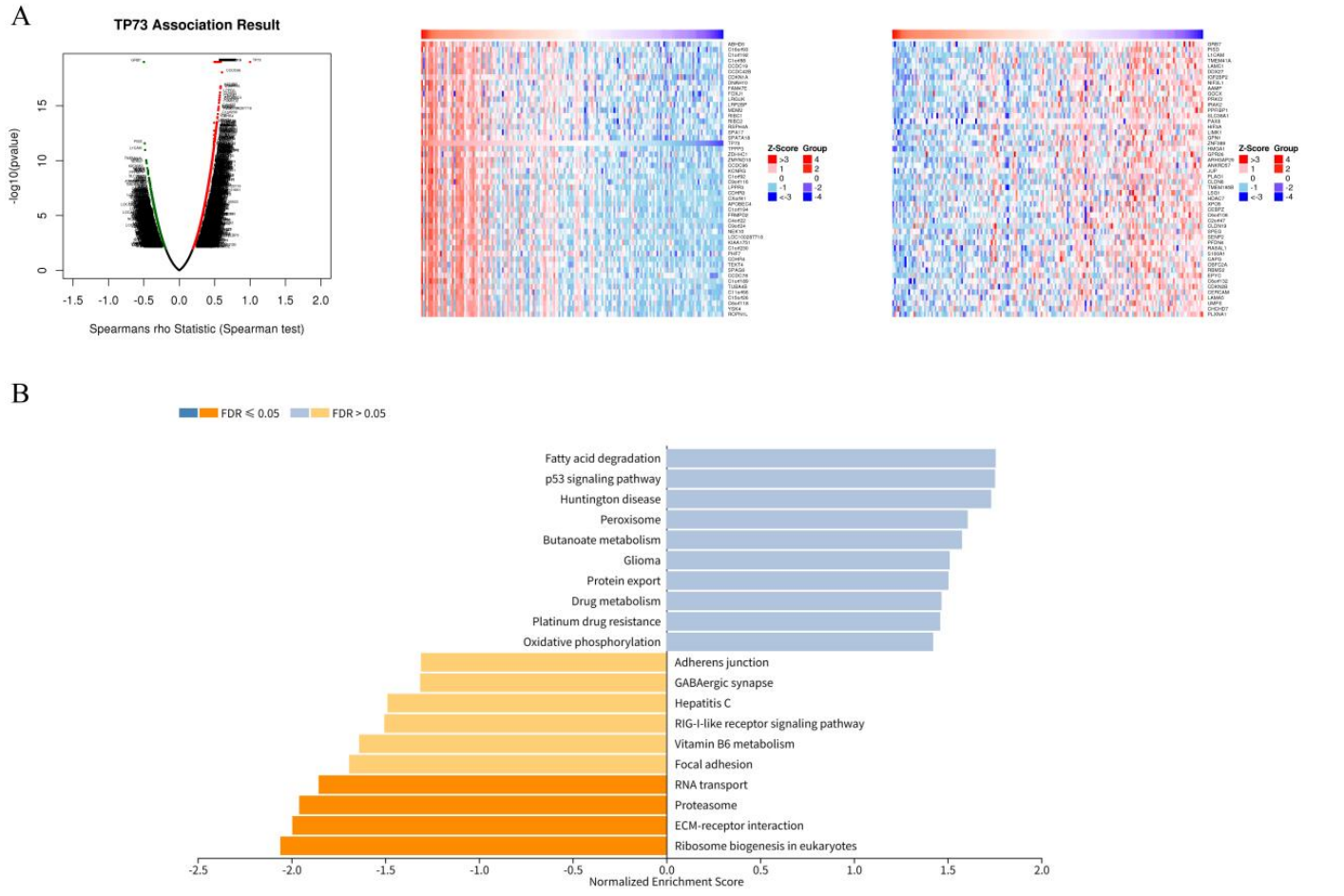

Figure 3. Coexpression network of *TP73* in endometrial cancer based on the Linked Omics platform. (A) Genes associated with GOLM1 in endometrial cancer. (B) Kyoto Encyclopedia of Genes and Genomes pathway analysis of the associated genes.

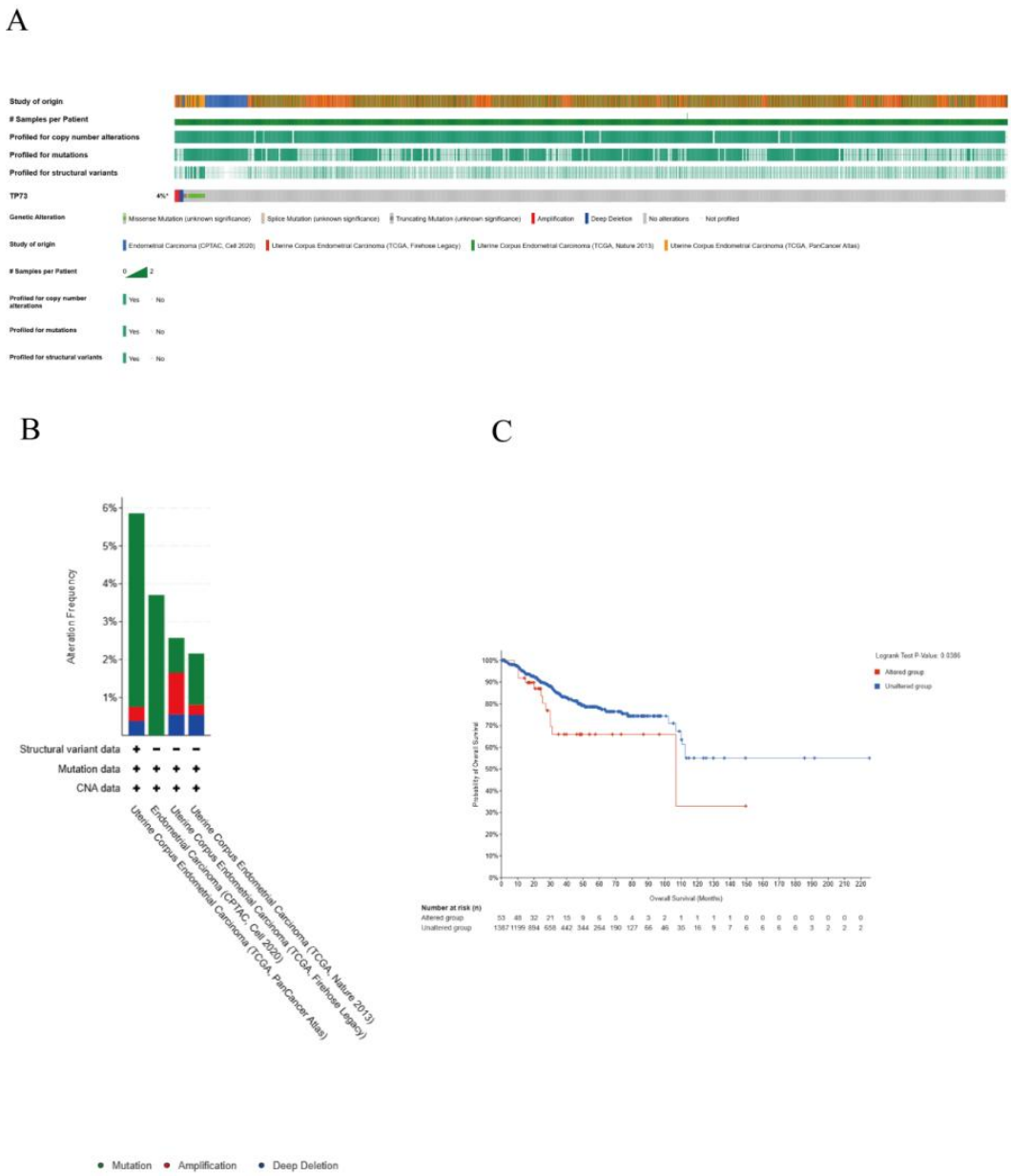

Figure 4. Analysis of the *TP73* mutation status. (A) Genetic variation landscape of *TP73*. (B) Stacked bar chart of *TP73* genetic variations. (C) KM survival curves of *TP73* variant groups.

Association analysis between *TP73* expression and the immune microenvironment in endometrial cancer

The stromal score and immune score of endometrial cancer tissues were analyzed. The results revealed that the stromal score and ESTIMATE score were significantly greater in the low-TP73 expression group than in the high-TP73 expression group ($P < 0.05$) (Figure 5A). Patients were divided into high and low *TP73* expression groups, and immune cell infiltration characteristics were compared. The results revealed that in the high-TP73 expression group, the infiltration levels of four immune cells — γ δ T cells (gamma delta T cells), M1 macrophages (M1 macrophages), activated dendritic cells (dendritic cells activated), and resting mast cells (resting mast cells)—were significantly decreased ($P < 0.05$). In contrast, the infiltration levels of six immune cells, including $CD8^+$ T cells (CD8 T cells) and activated NK cells (activated NK cells), significantly increased ($P < 0.05$) (Figure 5B). Analysis of the data from the TCGA database revealed that *TP73* expression levels were significantly negatively correlated with the degree of macrophage infiltration (r = -0.242; $P < 0.01$) but significantly positively correlated with the infiltration levels of NK CD56bright cells (r =0.267), eosinophils (Eosinophils; r = 0.187), and Th17 cells (r = 0.144) ($P < 0.001$) (Figure 5C). Notably, the reduced stromal score in the high *TP73* expression group was associated with altered immune cell infiltration patterns in this group. Changes in the proportions of tumor microenvironment components may affect the detection of immune cell infiltration. Further investigation is needed to explore the possibility that the altered immune cell infiltration patterns in the high *TP73* expression group are caused by a "proportional effect" rather than an "absolute abundance effect".

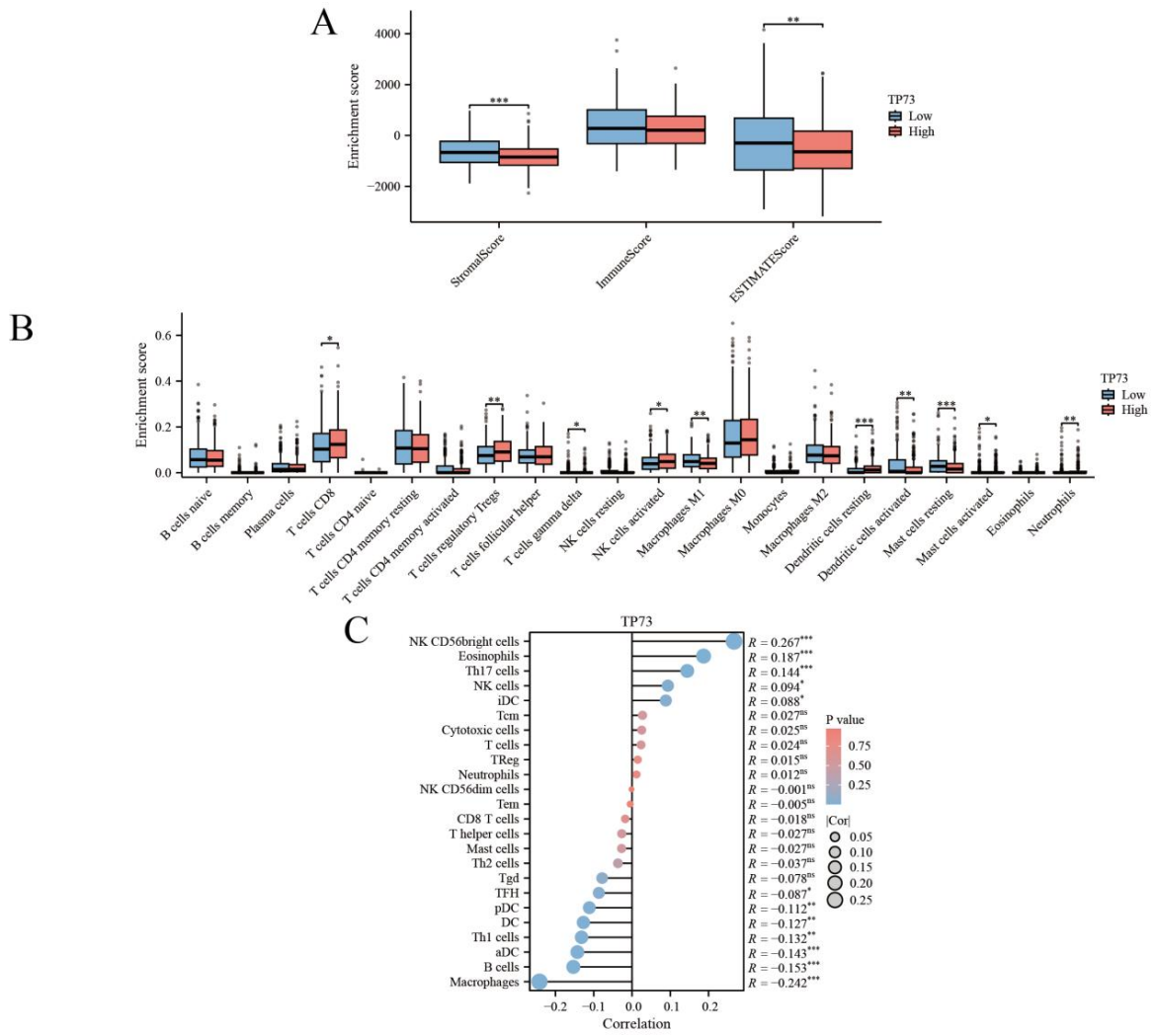

Figure 5. Association analysis of *TP73* with the immune microenvironment of endometrial cancer. (A) Low expression of *TP73* significantly reduces stromal and ESTIMATE scores in the tumor microenvironment. (B) low expression of *TP73* decreases the infiltration of most immune cells. (C) correlation analysis between *TP73* expression levels and the extent of infiltration of different immune cells.

Analysis of the relationship between *TP73* and immune molecule expression in endometrial cancer based on the TISIDB Database

Using the TISIDB database for analysis, it was found that in endometrial cancer, increased *TP73* levels can lead to the upregulation of the abundance of various immunomodulatory molecules, such as Eosinophil, *HLA-G*, *RAETE1*, *NT5E*, and *HLA-DQA2*, while increased *TP73* levels can also lead to the downregulation of the abundance of various immunomodulatory molecules, such as Tmem *CD4*, *IL10*, *TGFBR1*, *CD40*, *CCL8*, *CCL7*, and *CCR3* (Figure 6).

The impact of TP73 expression levels on chemotherapy drug sensitivity in endometrial cancer patients

Analysis of chemotherapy drug sensitivity through the CPADS drug database revealed significant differences in the IC_{50} values of cisplatin, cyclopamine, docetaxel, paclitaxel, and other chemotherapy drugs between endometrial cancer samples with high and low *TP73* expression ($P<0.05$). Cisplatin, cyclopamine, and paclitaxel are more effective at treating endometrial cancer patients with low *TP73* expression, whereas docetaxel shows better therapeutic efficacy in patients with high *TP73* expression.

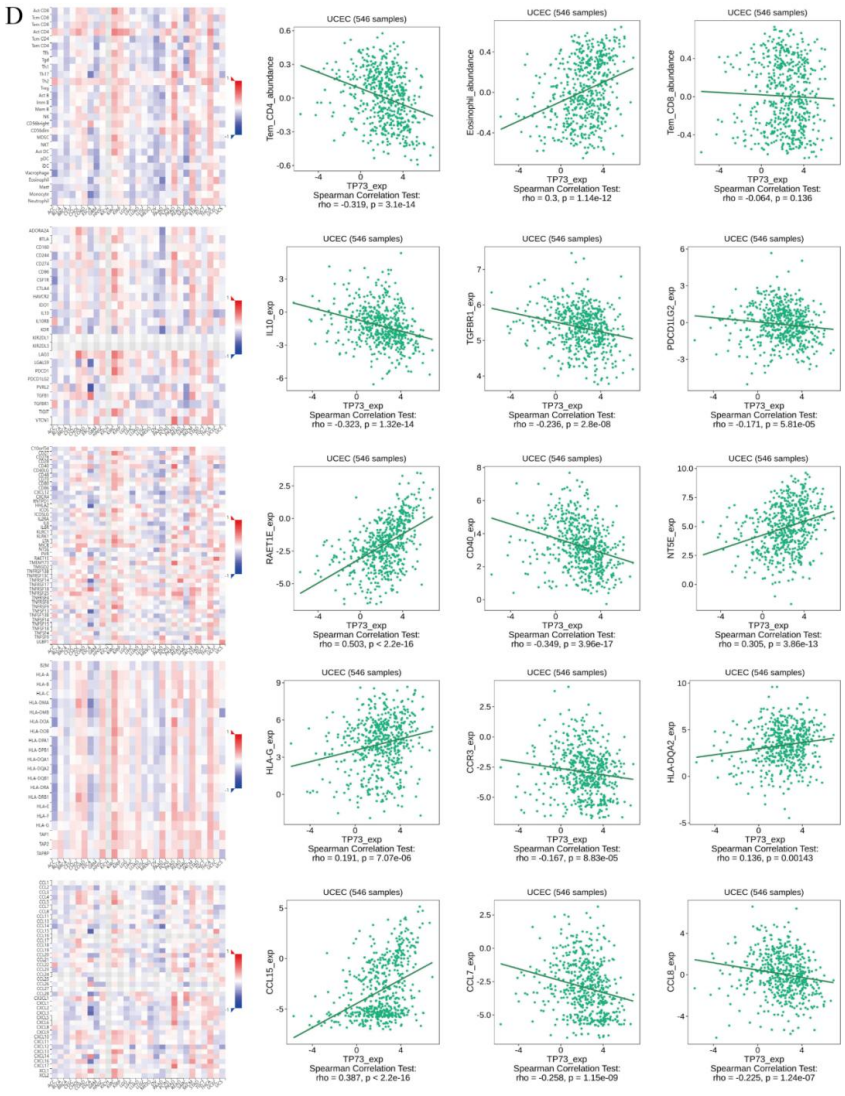

Figure 6. *TP73* and immune molecule expression in endometrial cancer.

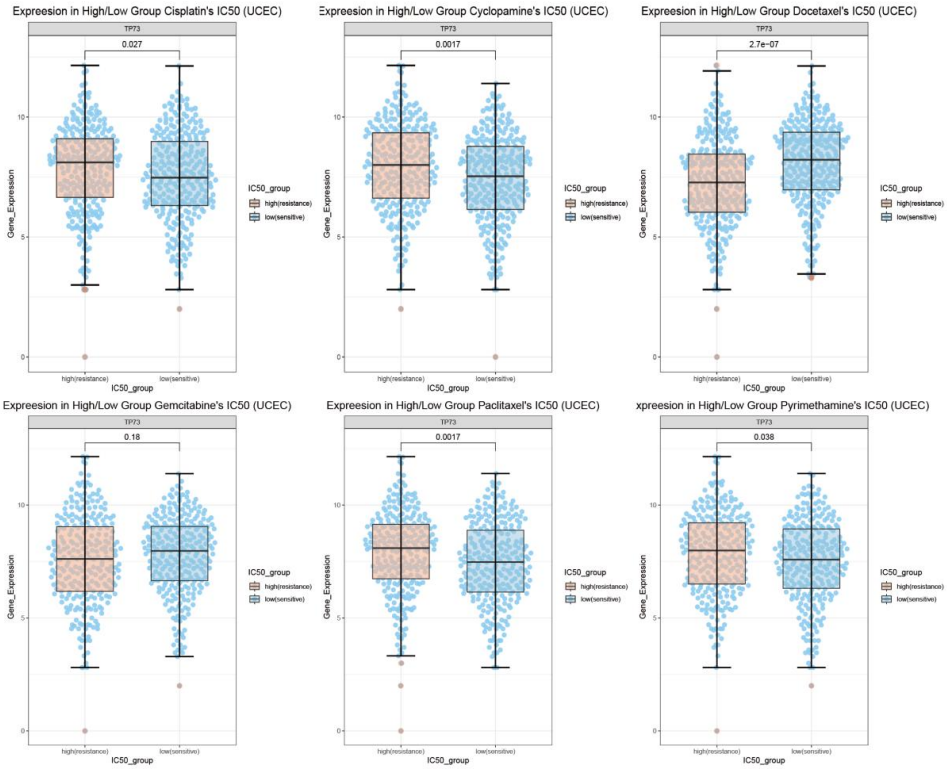

Figure 7. Analysis of *TP73* expression and the half-maximal inhibitory concentration (IC50) of various chemotherapeutic drugs in UCEC.

Screening of potential drugs targeting *TP73*

Analysis of the top 30 most sensitive drugs in the CTRP database revealed that *TP73* expression levels were positively correlated with the IC50 values of 5 drugs and negatively correlated with the IC50 values of 25 drugs (FDR <0.05). In the GDSC database, *TP73* expression was positively correlated with the IC50 of 19 of the top 30 drugs and negatively correlated with the IC50 of 11 drugs (FDR <0.05).

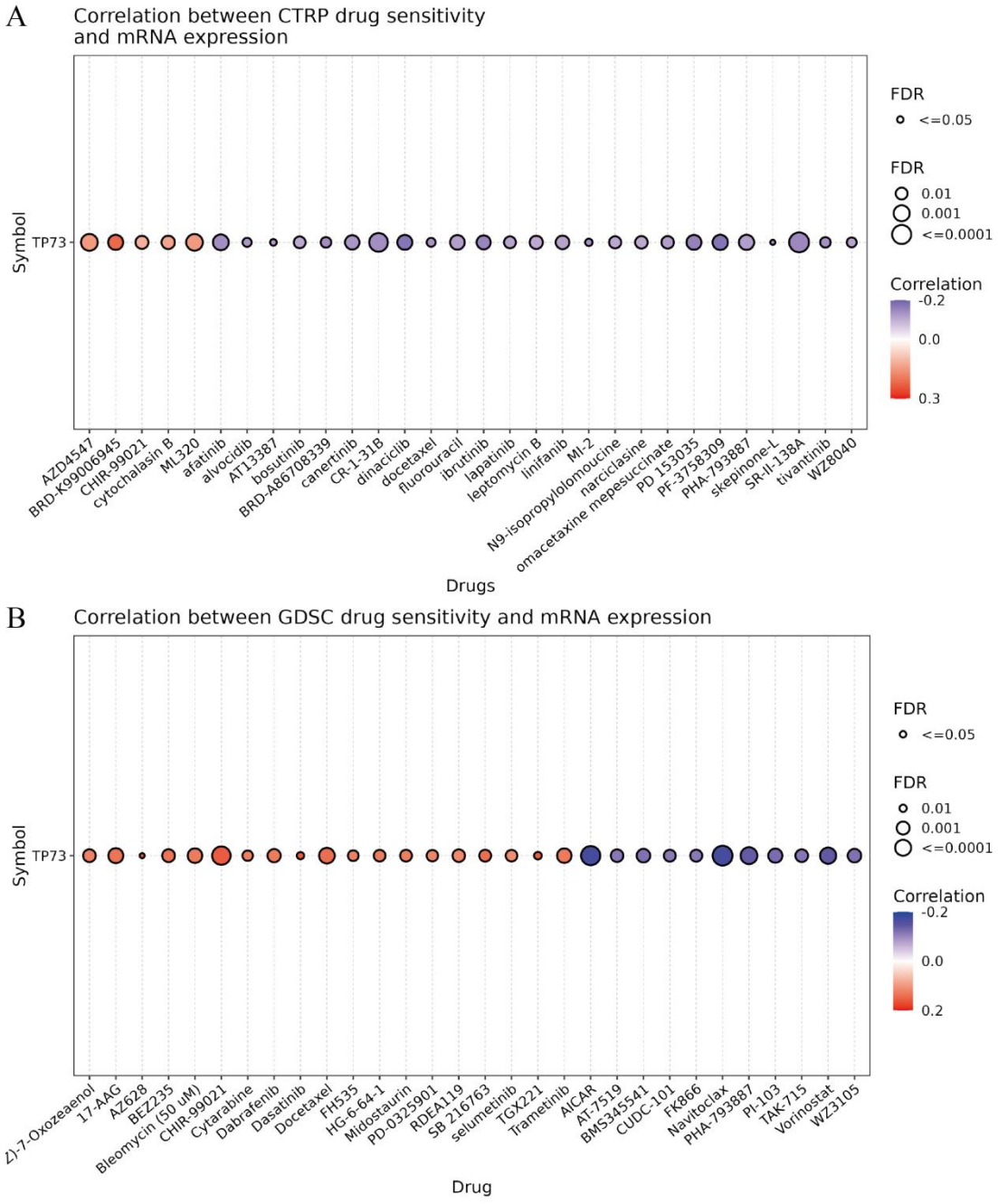

Figure 8. Screening of potential drugs targeting TP73.

Discussion

Changes in modern lifestyles and an increase in average life expectancy have led to a yearly increase in the incidence of endometrial cancer, with a trend toward younger age groups. In some developed cities in China, the incidence rate of endometrial cancer has already ranked first among gynecological malignancies[11]. Current main treatment options for advanced endometrial cancer include surgical therapy combined with radiotherapy and chemotherapy supplemented by endocrine therapy[12]. *TP73*, also known as p73, is an important member of the *TP53* gene family. Proteins encoded by genes in this family typically have two isoforms, TA and DN, where the TA isoform has tumor-suppressive functions and the DN isoform has procancer activity. The biological role of the *TP73* gene in the body is primarily determined by the expression level of the DN isoform and the ratio of TA to DN isoform expression. TA-p73 can inhibit cancer development and progression by regulating autophagy, suppressing angiogenesis, interfering with tumor cell drug resistance, and promoting tumor cell apoptosis. However, under certain conditions, it may also promote tumor progression by increasing oxidative stress responses, upregulating rate-limiting enzyme expression, and aiding tumor cells in serine metabolism and proliferation[13].

P73 is highly expressed in various tumor tissues, where it promotes cell proliferation, accelerates cell aggregation, and inhibits apoptosis alongside the p53 protein, thereby driving tumorigenesis and progression[14].

This study revealed that the expression level of *TP73* is significantly elevated in endometrial cancer tissues and that the expression level of *TP73* is associated with various clinicopathological features. This conclusion is consistent with the expression pattern of *TP73* in other gynecological malignancies. High expression of *TP73* is related to early tumor stage and fewer lymph node metastases6. Additionally, the expression level of *TP73* significantly differed among patients with different histological subtypes, *TP53* mutation statuses, and menopausal statuses. In this study, the phenomenon of high *TP73* expression in the *TP53* nonmutated group and endometrioid adenocarcinoma, seemingly contradictory to the characteristics of high-malignancy subtypes such as serous carcinoma and the TP53-mutated type, is actually the combined effect of functional specificity of the *TP73* subtype, antagonistic regulation within the p53 family, and molecular heterogeneity among endometrial cancer subtypes. The function of *TP73* is not determined by its total expression level but is dominated by the TAp73/ΔNp73 subtype ratio. As a dominant-negative subtype, ΔNp73 can form heterodimers with wild-type *TP53* and TAp73, blocking tumor-suppressive pathways mediated by both proapoptosis and cell cycle arrest[15]. Endometrioid adenocarcinoma is predominantly *TP53* wild-type, and tumor cells selectively upregulate the ΔNp73 subtype to escape its tumor-suppressive function, thereby increasing total *TP73* expression. In contrast, highly malignant subtypes, such as serous carcinoma, are mostly TP53-mutated, where *TP53* function is lost, eliminating the need for ΔNp73-mediated antagonistic regulation. Additionally, mutant *TP53* can directly perform pro-oncogenic functions, ultimately leading to the downregulation of total *TP73* expression[16]. This also explains how differences in its expression levels reflect heterogeneity in tumor biological behavior. ROC curve analysis revealed that the AUC value of *TP73* for the diagnosis of endometrial cancer was 0.895, indicating that *TP73* has good diagnostic performance and could serve as a potential diagnostic biomarker. The *TP73* gene mutation rate is only 4%, but patients with mutations have significantly shorter survival periods. However, in this study, only the correlation between *TP73* and overall survival of patients at the level of overall genetic alterations was analyzed, and stratified survival analysis was not conducted on the basis of specific genetic alteration types, such as amplification, truncating mutations, or missense mutations. Considering the low mutation rate of *TP73* (only 4%), its significant association with survival is more likely driven by relatively common gene amplification. The lack of stratified analysis by genetic alteration type makes it difficult to precisely distinguish the independent regulatory effects of different variants on endometrial cancer prognosis. Subsequent studies could clarify the regulatory mechanisms of various *TP73* genetic alteration types through stratified analysis.

Protein interaction network analysis revealed close interactions between *TP73* and tumor-related proteins such as *TP53*, *TP63*, and *YAP1*. As a member of the p53 family, *TP73* can form homodimers or heterodimers with *TP53* and *TP63* to regulate the transcription of downstream target genes, which together participate in tumor suppression-related biological processes such as cell cycle arrest and apoptosis initiation. This interaction pattern has been confirmed in various malignant tumors[17]. *YAP1* is a key effector molecule of the Hippo pathway that is abnormally activated in endometrial cancer. Its interaction with *TP73* serves as a specific regulatory mechanism for the DNA damage response in endometrial cancer cells. Under DNA damage stress induced by chemotherapeutic agents such as cisplatin or ionizing radiation, *YAP1* in endometrial cancer cells is phosphorylated at Y357, after which it subsequently forms a stable functional complex with *TP73*. This complex selectively binds to the promoter regions of pro-apoptotic genes downstream in endometrial cancer cells, activating their transcription and further triggering the mitochondrial apoptosis pathway, thereby enhancing the sensitivity of endometrial cancer cells to DNA damage-inducing therapeutic agents[18]. In TP53-mutant endometrial serous carcinomas with a defective p53-mediated DNA damage response, the YAP1-TP73 complex becomes the primary compensatory pathway for DNA damage-induced apoptosis, serving as a critical molecular basis for the chemotherapy response in highly malignant endometrial cancers. This dual role regulates tumor progression and guides clinical treatment. *TP73* can also form a regulatory network with p53 and early growth response factor 1 (Egr1), continuously activating apoptosis-related signaling pathways through feedback loops to enhance growth inhibition in tumor cells[19], suggesting that *TP73* may participate in the development of endometrial cancer by forming a multidimensional regulatory network through synergy or interaction with the aforementioned proteins.The KEGG pathway enrichment analysis in this study revealed that TP73-related genes were significantly enriched in multiple tumor-related pathways, with the p53 signaling pathway showing the greatest enrichment (FDR=4.0×10^{-8}; signal=3.5), followed by cancer-associated microRNA pathways. Additionally, pathways such as the cell cycle and platinum drug resistance pathway were significantly enriched, suggesting that *TP73* may participate in endometrial cancer progression and the regulation of chemotherapy sensitivity by modulating the p53 pathway, noncoding RNAs, and the cell cycle. GO functional enrichment analysis further revealed that TP73-related genes are primarily localized in the nucleus and enriched in transcriptional regulatory complexes, with molecular functions centered on p53 binding (FDR=1.0×10^{-11}; signal=5.0). Biological processes were highly enriched in p53-mediated signal transduction and DNA damage response-related intrinsic apoptotic pathways. These results suggest that *TP73* primarily mediates transcriptional regulation through the p53 signaling pathway, which is involved in key biological processes such as apoptosis, DNA damage repair, and the cell cycle. Notably, *YAP1*, a key effector of the Hippo pathway, is abnormally activated in endometrial cancer. Its interaction with *TP73* constitutes a specific regulatory mechanism for the DNA damage response. Under DNA damage stress induced by chemotherapeutic agents such as cisplatin, *YAP1* is phosphorylated at the Y357 site and forms a stable functional complex with *TP73*, specifically binding to pro-apoptotic gene promoters and activating the mitochondrial apoptotic pathway, thereby enhancing tumor cell sensitivity to DNA-damaging agents[20]. Additionally, *TP73* can form a multidimensional regulatory network with p53 and Egr1, continuously activating apoptotic signals through feedback loops and thereby enhancing the growth inhibitory effect on tumor cells[19].

Enrichment analysis revealed that genes related to the expression of *TP73* are enriched primarily in RNA transport, proteasome activity, ECM-cytokine receptor interactions, and ribosome biogenesis. The enrichment of the ECM–receptor interaction pathway suggested that *TP73* can regulate the synthesis and remodeling of the extracellular matrix, thereby

influencing tumor cell adhesion, invasion, and distant metastasis. Abnormal expression of *TP73* has been confirmed to be associated with malignancies such as head and neck squamous cell carcinoma[21]. Additionally, the enrichment of RNA transport and proteasome pathways reflects the multidimen- sional regulatory role of *TP73* in the occurrence and development of endometrial cancer, which is closely associated with its known core functions and the specific biological characteristics of endometrial cancer. As a key transcriptional regulatory factor in the p53 family, *TP73* performs its transcriptional regulatory functions by mediating the nucleocytoplasmic transport of RNA molecules and the precise splicing of precursor mRNA[15]. The enrichment of the RNA transport pathway suggested that *TP73* can regulate the posttranscriptional processing of key genes related to endometrial cancer progression (such as hormone receptor genes and cell cycle regulatory genes) through this pathway, thereby influencing the hormone sensitivity and abnormal proliferation characteristics of endometrial cancer cells. The proteasome pathway is central to intracellular protein degradation and is closely linked to the regulation of apoptosis and cell cycle progression. *TP73* can bind to the HECT-type ubiquitin ligase Itch. Itch selectively binds and ubiquitinates *TP73* without acting on *TP53*, leading to rapid proteasome-dependent degradation of *TP73*. Under DNA damage stress, the expression of Itch is downregulated, resulting in elevated p73 protein levels and increased activity of its corresponding functions. In summary, *TP73* interacts with key molecules such as p53 and *YAP1* to form a complex regulatory network that participates in the occurrence and development of endometrial cancer, remodeling of the immune microenvironment, and regulation of chemotherapy sensitivity, providing a reliable molecular mechanism explanation for the bioinformatics results of this study[22]. *TP73* can regulate the activity of the ubiquitin–proteasome system through this enriched pathway, modulating the degradation of antiapoptotic proteins and cell cycle checkpoint proteins and thereby promoting apoptosis and cell cycle arrest in endometrial cancer. Moreover, the proteasome pathway is a critical therapeutic target in endometrial cancer chemotherapy. The interaction between *TP73* and this pathway may also serve as an important molecular basis for regulating the sensitivity of endometrial cancer cells to proteasome inhibitors and DNA damage-inducing chemotherapeutic agents.

The remodeling of the tumor immune microenvironment is a critical factor in tumor development and treatment response and is a key component of tumor microenvironment (TME)-related carcinogenic mechanisms[23]. Tumor cells can influence the process of apoptosis by modulating the tumor microenvironment, thereby promoting cancer progression and the development of treatment resistance[24]. In this study, *TP73* expression levels were significantly correlated with the degree of infiltration of various immune cells. The infiltration of macrophages and other cells was negatively correlated with *TP73* expression, whereas the infiltration of NK CD56bright cells, eosinophils, and Th17 cells was positively correlated with TP73 expression. Previous studies have confirmed that TAp73 can suppress NF-κB pathway activity, reduce *CCL2* secretion, and block the migration of monocytes into tumor-associated macrophages. Low *TP73* expression is closely associated with $CD163^+$ macrophage enrichment[25], suggesting that the regulatory effect of *TP73* on macrophage infiltration may be conserved across tumor types. In patients with high *TP73* expression, the infiltration of classical antitumor immune cells such as $CD8^+$ T cells and activated NK cells significantly increased, whereas the infiltration of immune cells such as γδ T cells and M1 macrophages markedly decreased. Stromal and ESTIMATE scores also decreased significantly. Increased infiltration of $CD8^+$ T cells and activated NK cells indicates enhanced immune-killing capacity in tumor tissues. The stromal score directly reflects the relative content of stromal components in tumor tissue. The low-TP73 group had a higher stromal score, indicating a richer stromal component and a relatively lower proportion of tumor cells in the tissue microenvironment. In contrast, the high-TP73 group had a reduced stromal score, suggesting that decreased stromal deposition led to a relative increase in the tumor cell proportion. This shift in the relative proportion of tumor cells to stromal components may have triggered proportional changes in immune cell infiltration in the high-TP73 group, rather than reflecting true alterations in the absolute abundance of immune cells. Such proportional effects represent a potential bias in transcriptome-based immune infiltration analyses[26,27]. Therefore, the altered immune cell infiltration patterns in the high-TP73 group cannot be simply attributed to active recruitment or depletion of immune cells by *TP73*. The potential interference from proportional effects caused by differences in the stromal score must also be fully considered. This study analyzed only the infiltration characteristics of total macrophages and M1-type macrophages and did not further explore the infiltration levels of M2-type macrophages or the association between M1/M2 polarization ratios and *TP73* expression. Consequently, whether *TP73* participates in remodeling the immune microenvironment of endometrial cancer by regulating macrophage polarization balance rather than merely altering total cell numbers remains unclear, which is a significant limitation of this research. M1/M2 macrophage polarization is a critical aspect of tumor immune regulation. Future studies could further investigate the regulatory role and molecular mechanisms of *TP73* in macrophage polarization. Additionally, analysis of the TISIDB database revealed that *TP73* expression levels are closely associated with the expression of numerous immune regulatory molecules. High *TP73* expression upregulates the expression of molecules such as *HLA-G* and *NT5E* while downregulating the expression of molecules such as *IL10* and *TGFBR1*. *IL10* and *TGFBR1* are key molecules in typical immunosuppressive pathways, and their downregulation can inhibit the formation of an immunosuppressive microenvironment. *HLA-G* is a critical immune checkpoint molecule; tumor cells upregulate its expression to suppress antitumor immune responses. The specific mechanism involves interactions with immune cell surface receptors, modulating the activation states of immune cells such as T cells and natural killer (NK) cells, ultimately aiding tumor cells in evading immune surveillance[28]. Therefore, *TP73* can regulate immune checkpoint molecules and cytokine networks, participate in the remodeling of the endometrial cancer immune microenvironment, and provide new insights for the selection of immunotherapy targets.

Drug sensitivity analysis revealed that the expression level of *TP73* can significantly affect the response of endometrial cancer patients to chemotherapeutic drugs, which is consistent with the functional characteristics of *TP73* as a tumor suppressor gene in the p53 family[13]. Through selective promoter selection and alternative splicing mechanisms, *TP73* can generate TAp73 isoforms with transcriptional activation functions and ΔNp73 isoforms with dominant-negative regulatory functions. The balance of the expression of different isoforms can directly regulate the chemotherapeutic response mechanisms of tumor cells[29]. Common chemotherapeutic drugs such as cisplatin and paclitaxel have lower IC_{50} values in patients with low *TP73*

expression, suggesting that these patients are more sensitive to the aforementioned drugs. Previous studies have demonstrated that TAp73 can activate the GADD45α/MKK4/JNK signaling pathway, promoting cisplatin-induced tumor cell apoptosis, whereas *TP73* deficiency or functional inhibition weakens the apoptotic pathway and reduces the threshold of chemotherapeutic drug efficacy[30]. Conversely, docetaxel is more effective in patients with high *TP73* expression, which may be related to TAp73-mediated cell cycle arrest under high *TP73* expression. This study, while exploring the association between *TP73* and chemotherapy sensitivity, focused primarily on the pro-apoptotic function of TAp73 and did not fully consider the dominant negative effect of ΔNp73 and the potential impact of tumor heterogeneity on chemotherapy sensitivity. ΔNp73 can form heterodimers with TAp73, blocking the activation of its pro-apoptotic pathway, while differences in the expression ratios of *TP73* isoforms induced by tumor heterogeneity may further alter the drug response patterns of tumor cells. Additionally, the results of this study revealed that the sensitivity to paclitaxel and docetaxel, two chemotherapeutic agents with similar mechanisms of action, tended to be opposite that to *TP73* expression (Figure 7). This discrepancy is hypothesized to be related to the selective regulation of *TP73* isoforms by the two drugs and differences in their synergistic effects on microtubule-associated signaling pathways, which require further experimental validation. Moreover, a GSCA database analysis revealed that *TP73* expression levels are associated with sensitivity to multiple potential therapeutic drugs, providing clues for the screening of novel targeted agents. The results of this study suggest that targeting *TP73* and its related signaling pathways is a promising novel therapeutic strategy for endometrial cancer. However, *TP73* has complex isoform-specific functions and is involved in physiological processes such as apoptosis and transcriptional regulation in normal tissues. Directly targeting the overall *TP73* molecule is likely to face feasibility challenges and potential toxicity risks: the TAp73 isoform possesses tumor-suppressive functions, and direct targeting may disrupt its normal physiological regulatory role, leading to weakened tumor-suppressive effects. Additionally, *TP73* is relatively highly expressed in normal reproductive, hematopoietic, and other tissues, and nonspecific targeting may cause damage to normal cells, increasing treatment-related toxicity. Therefore, directly targeting *TP73* is not the optimal strategy. Targeting the cancer-promoting ΔNp73 isoform of *TP73* by inhibiting ΔNp73 expression or blocking its heterodimer formation with TAp73 and *TP53* can restore the normal functions of tumor-suppressive isoforms while avoiding interference with these isoforms and normal tissues. Alternatively, targeting specific downstream effector molecules of *TP73*, such as key molecules in the RNA transport and proteasome pathways enriched in this study, as well as immune regulation-related molecules and chemotherapy sensitivity-associated GADD45α/MKK4 pathway molecules, can indirectly intervene in TP73-mediated procancer signaling through the regulation of downstream targets. This approach preserves normal physiological functions while precisely blocking tumor-related regulatory pathways.

This study is solely based on multidatabase integrated analysis and lacks experimental validation with clinical samples. Some mechanistic analyses remain at the level of bioinformatics prediction. In the future, cell experiments, animal model establishment, and clinical sample validation are needed to determine the molecular mechanisms through which *TP73* regulates the development and progression of endometrial cancer. Additionally, the relationships between *TP73* and the immune microenvironment as well as chemotherapy sensitivity should be explored. Furthermore, the functional differences among different *TP73* isoforms and their expression characteristics in endometrial cancer have not yet been elucidated. Subsequent research could investigate the roles and regulatory networks of different isoforms to identify more specific targets for precise targeted therapy.

Although this study systematically analyzed the potential role of *TP73* in endometrial cancer through various bioinformatics methods, several limitations remain. The analysis in this study was based on data from public databases, and further in vitro or in vivo experiments to validate the related conclusions are lacking. Second, the sample sources of the databases used in this study may have some selection bias, which could influence the research results. Therefore, future studies still need to integrate more clinical samples and functional experiments to further verify the specific mechanisms of *TP73* in the development and progression of endometrial cancer. This study has several limitations. All analyses are based on bioinformatics mining of public databases, and no in vitro cell experiments, in vivo animal experiments, or clinical sample validations have been performed. Therefore, the conclusions drawn are merely predictive and cannot yet confirm the true biological role of *TP73* in regulating the immune microenvironment and chemotherapy sensitivity in endometrial cancer. In addition, although *TP73* was found to be significantly associated with the infiltration of immune cells such as macrophages and NK CD56bright, it remains unclear through which cytokines, chemokines, or immune checkpoint molecules it mediates regulation; only differential molecules are listed, and the inter-molecular interaction network and the direct/indirect regulatory relationship with *TP73* have not been systematically constructed.Future plans include the collection of clinical endometrial cancer tissues and paired adjacent normal tissues to validate *TP73* expression levels using qRT-PCR, Western blotting, and immunohistochemistry. Endometrial cancer cell lines will be used to construct *TP73* knockdown and overexpression models. Combined with CCK-8, colony formation, and flow cytometry, the effects on cell proliferation and apoptosis will be assessed. Chemotherapy sensitivity will be evaluated by measuring cell IC50 values after treatment with cisplatin and docetaxel. Additionally, the expression of immune-related molecules was detected to preliminarily explore the potential mechanisms underlying the regulatory effect of *TP73* on the immune microenvironment. Furthermore, combined with TISIDB analysis results and cell experiments, we will strengthen the screening of core immune molecules and the discussion of mechanisms, so as to provide a clear direction for subsequent mechanism research, thereby providing experimental evidence to support the conclusions of this study.

Conclusions

Through systematic bioinformatics analysis, this study revealed that *TP73* is highly expressed in endometrial cancer and is closely associated with patient clinical characteristics, the tumor immune microenvironment, and chemotherapy drug sensitivity. *TP73* may play a significant regulatory role in the pathogenesis and progression of endometrial cancer by interacting with various tumor-related proteins, modulating immune cell infiltration, and regulating signaling pathway activity. It also holds promise as a potential diagnostic biomarker and a target

for precision therapy. This study provides new theoretical foundations for further exploration of the mechanistic role of *TP73* in endometrial cancer. However, this study relies solely on public databases and bioinformatics predictions and has not conducted experimental research, such as in vitro cell experiments, in vivo animal experiments, or clinical sample validation, which presents certain limitations. Therefore, these conclusions are favorable and cannot confirm the actual biological functions of *TP73* in regulating the immune microenvironment of endometrial cancer and chemotherapy sensitivity. In the future, qRT-PCR, Western blot, and immunohistochemical experiments will be performed to validate the expression levels of *TP73* in clinical endometrial cancer tissues and adjacent normal tissues; *TP73* knockdown and overexpression cell models will be constructed to assess its effects on cell proliferation, apoptosis, and sensitivity to cisplatin and docetaxel, and changes in the expression of immune-related molecules will be detected to preliminarily explore its regulatory mechanisms in the tumor immune microenvironment. Subsequent studies will combine TISIDB analysis results with cell experiments to strengthen the screening of core immune molecules and the discussion of mechanisms. This study provides new theoretical foundations for further investigations into the role and mechanisms of *TP73* in endometrial cancer.

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Data Availability Statement

The data supporting the findings of this study are available from public databases. The gene expression and clinical data used in this study were sourced from the UCSC Xena platform (https://xenabrowser.net/datapages/), which includes the TCGA and GTEx datasets. Additional analyses were conducted using publicly available tools, including UALCAN (http://ualcan.path.uab.edu/), STRING (https://string-db.org/), LinkedOmics (http://www.linkedomics.org/), cBioPortal (https://www.cbioportal.org/), CIBERSORTx (https://cibersortx.stanford.edu/), TISIDB (http://cis.hku.hk/TISIDB/), CPADS (https://smuonco.shinyapps.io/CADSP/), and GSCA (https://guolab.wchscu.cn/GSCA/). This study did not generate new, unpublished raw datasets. All the processed data can be obtained from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Author Contributions: Conceptualization, methodology, writing—original draft preparation, and writing—review and editing, Jia Lu; conceptualization, methodology, visualization, and writing—original draft preparation, Tongyan Yang; investigation, data curation, and software, Junjie Ye; investigation, formal analysis, and visualization, Yunyi Chen; investigation, validation, and technical support, Dejun Nong; resources, supervision and project administration, Lingzhang Meng; resources, supervision, project administration, and funding acquisition, Jiangtao Fan. All authors have read and agreed to the published version of the manuscript.

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