

Evaluating the Carcinogenic Potential and Molecular Mechanisms of 6PPDQ in the Human Stomach Using Organoids and Bulk Sequencing Data: A Multi-Machine Learning Approach Combined with Computational Simulation

Ke Yan

Shaanxi Provincial People's Hospital

Cheng Li

Shaanxi Provincial People's Hospital

Jia Ma

Shaanxi Provincial People's Hospital

Yujie Liu

Shaanxi Provincial People's Hospital

Xulong Zhu

Shaanxi Provincial People's Hospital

Youfu Tian

Shaanxi Provincial People's Hospital

Jianfei Zhang

dr_feifei@163.com

Shaanxi Provincial People's Hospital

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Abstract

Background: The environmental contaminant 6PPD-quinone (6PPDQ), a tire rubber antioxidant derivative, has emerged as a potential health hazard, yet its association with gastric cancer (GC) remains unexplored. This study investigates the molecular mechanisms underlying 6PPDQ-induced GC using network toxicology.

Methods: 6PPDQ targets were retrieved from PharmMapper and SwissTargetPrediction databases. GC-related datasets (GSE33335, GSE19826, GSE63089) were obtained from GEO for differential expression analysis and model construction, with GSE112369 (organoid) for validation. Weighted Gene Co-expression Network Analysis (WGCNA) identified disease modules and hub genes, combined with GeneCards screening. Intersection of 6PPDQ and GC targets yielded 19 cross-targets undergoing GO/KEGG enrichment and Protein-Protein Interaction (PPI) analysis. Machine learning algorithms (LASSO, Random Forest, SVM-RFE) and topological methods (DMNC, MCC, Degree, EPC) identified core targets, validated by molecular docking.

Results: The 19 cross-targets were enriched in cell cycle regulation (G2/M transition), chromosomal organization, and kinase activity. KEGG analysis highlighted p53, PI3K-Akt, Ras, MAPK signaling pathways, and cancer metabolism. Multi-dimensional screening identified PLAU, MET, and CDK2 as core targets. The three-gene risk model showed robust predictive performance. Molecular docking confirmed strong 6PPDQ binding affinities: -8.3 kcal/mol (MET), -8.1 kcal/mol (CDK2), and -6.7 kcal/mol (PLAU).

Conclusion: PLAU, MET, and CDK2 represent core targets in 6PPDQ-induced GC. 6PPDQ promotes tumorigenesis through metabolic reprogramming, hormone metabolism disruption, tumor microenvironment modulation, and PI3K-AKT-CDK2 axis activation. These findings elucidate 6PPDQ's oncogenic mechanisms and provide therapeutic targets for GC prevention.

1. Introduction

Gastric cancer ranks among the malignancies with the highest morbidity and mortality rates globally[1, 2], and its development represents a complex pathological process involving multiple genes, signaling pathways, and multi-stage evolution[3, 4]. In recent years, with the acceleration of industrialization and increasing environmental pollution, research on the association between environmental pollutants and tumorigenesis has emerged as a critical frontier in cancer etiology. Among these, N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine-quinone (6PPDQ), an emerging contaminant derived from tire and road wear particles (TRWPs), has garnered increasing attention in public health and oncology research due to its widespread environmental distribution and potential biological toxicity[5–7].

6PPDQ represents the primary oxidative transformation product of the rubber antioxidant 6-PPD (N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine) in the environment[8]. Since Tian et al. reported the acute lethal toxicity of 6PPDQ to coho salmon in Science in 2021, this compound has been recognized as the second most toxic emerging pollutant to aquatic organisms[9]. Studies have demonstrated that 6PPDQ

can be widely distributed in water bodies, sediments, atmospheric dust, and crops through atmospheric deposition, surface runoff, and soil infiltration, ultimately entering the human body through bioaccumulation in the food chain[10]. Recent toxicological studies have further revealed that 6PPDQ exposure can induce multi-organ toxicity in mammals, including hepatic lipid metabolism disorders, neurodegenerative lesions, intestinal barrier damage, and reproductive system dysfunction[11, 12]. Notably, 6PPDQ has been confirmed to be rapidly absorbed and distributed in human liver, brain tissue, and placenta, with detectable levels in human serum, urine, and cerebrospinal fluid, indicating potential human health risks[12–15]. However, research on the association between 6PPDQ and human digestive system tumors, particularly gastric cancer, and its molecular mechanisms remains unexplored.

From a molecular toxicological perspective, the carcinogenic potential of 6PPDQ may be closely related to its induction of oxidative stress, DNA damage, mitochondrial dysfunction, and apoptosis. Existing studies have shown that 6PPDQ can trigger cytotoxicity through mechanisms including reactive oxygen species (ROS) generation, endoplasmic reticulum homeostasis disruption, and inflammatory cascade activation[16–18]. In *Caenorhabditis elegans* models, 6PPDQ exposure can induce germ cell apoptosis, ferroptosis, and transgenerational lipid accumulation[19]; in mammalian models, it can interfere with lipid and glucose metabolism and induce non-alcoholic fatty liver disease-like pathological changes by regulating key molecules such as PPAR γ , TNF- α , and IL-6[20, 21]. These toxic effects involve signaling pathways that significantly overlap with classical pathways in tumorigenesis (such as PI3K/AKT, MAPK, NF- κ B, and p53), suggesting that 6PPDQ may participate in the malignant transformation process of gastric cancer by regulating these key nodes[22].

Network toxicology, as an emerging research paradigm integrating systems biology, computational toxicology, and big data mining, provides powerful technical support for elucidating the complex toxicity mechanisms of environmental pollutants. This approach systematically identifies key molecular targets and core regulatory modules of toxic effects by constructing compound-target-disease interaction networks combined with topological analysis and enrichment algorithms. Meanwhile, computational simulation technologies, including molecular docking and machine learning prediction models, can precisely resolve the interaction patterns between compounds and biological macromolecules at the atomic level, providing high-resolution structural biological evidence for mechanism elucidation. In recent years, the combined application of network toxicology and multi-omics technologies has successfully revealed key targets (such as P53, MAPK1, Casp8, Traf6, etc.)[23] and core pathways (TNF, NF- κ B) in 6PPDQ-induced hepatotoxicity, demonstrating the reliability and effectiveness of this method in environmental pollutant mechanism research.

In summary, given the environmental ubiquity, bioaccumulation potential, and multi-target toxicity characteristics of 6PPDQ, in-depth investigation of its molecular association with gastric cancer development holds significant scientific value and practical implications. This study employs a strategy combining network toxicology and computational algorithm simulation to systematically screen potential targets of 6PPDQ in gastric cancer, construct compound-target-pathway interaction networks, and validate core binding patterns through molecular docking and dynamics simulation, aiming to

elucidate the key molecular mechanisms of 6PPDQ in gastric carcinogenesis from a systems biology perspective and provide theoretical basis for assessing the tumor risk of this emerging pollutant and developing targeted prevention strategies.

2. Methods

2.1 Data Collection and Preprocessing

Batch RNA sequencing data from three independent gastric cancer cohorts (GSE33335, GSE19826, and GSE63089; $n = 167$) were downloaded from the NCBI Gene Expression Omnibus (GEO) database. Batch effects were removed using the sva R package (version 3.44.0) before merging. Another transcriptome dataset (GSE52194; $n = 42$) was used as an external validation cohort. All Affymetrix microarray data underwent $\log_2$ transformation before merging to ensure scale consistency. Batch labels strictly annotated sample collection time and sequencing batch information. Ensembl gene IDs (v104) served as the primary anchor identifiers.

The toxicity of 6PPDQ was predicted using ProTox 3.0 - Prediction Of Toxicity Of Chemicals (<https://tox.charite.de/>), with results shown in (Supplementary File 1). Putative human targets of 6PPDQ were retrieved from PharmMapper (<http://www.lilab-ecust.cn/pharmmapper/>) and SwissTargetPrediction (<http://www.swiss-targetprediction.ch/>).

2.2 Identification of 6PPDQ and GC Cross-Targets

Differential expression analysis was performed using the limma package (v3.52.4) with thresholds set at $|\log_2 \text{fold-change}| > 0.585$ and false discovery rate (FDR) < 0.05 . Weighted Gene Co-expression Network Analysis (WGCNA, v1.72) was applied to the merged training set to identify biologically relevant modules. The optimal soft-thresholding power $\beta = 4$ was selected (scale-free $R^2 = 0.80$), and the topological overlap matrix (TOM) was calculated with a minimum module size of 80 genes. Module-trait relationships were assessed through Pearson correlation, with genes defined as hub genes when $|\text{module membership}| > 0.6$ and $|\text{gene significance}| > 0.6$.

2.3 Functional Enrichment and Protein-Protein Interaction (PPI) Network Analysis

To explore the potential molecular mechanisms of 6PPDQ-induced gastric carcinogenesis, functional enrichment analysis and protein-protein interaction (PPI) network analysis were performed on candidate target genes.

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were conducted based on the DAVID database (<https://david.ncifcrf.gov>). GO enrichment analysis covered three categories: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF). Fisher's exact test was used to assess the enrichment significance of target genes in GO

terms and KEGG pathways, with $P < 0.05$ as the screening criterion to identify significantly enriched biological functions and signaling pathways.

The STRING database (<https://string-db.org/>) was utilized to retrieve protein-protein interaction relationships among candidate target genes. The obtained interaction data were imported into Cytoscape software for network visualization to reveal interaction patterns and potential regulatory mechanisms among target genes.

2.4 Machine Learning-Based Core Target Prioritization

To screen the most influential genes from the 19-gene signature, we employed an ensemble approach of three algorithms: Least Absolute Shrinkage and Selection Operator (LASSO), Random Forest (RF) algorithm, and Support Vector Machine Recursive Feature Elimination (SVM-RFE). Genes retained by all three methods were defined as core targets.

2.5 Core Target Pathway Mapping

Classical signal transduction cascades involving the final two gene sets were analyzed through the KEGG pathway database (<https://www.kegg.jp/kegg/kegg2.html>) and graphically superimposed onto GC-specific maps to generate mechanistic hypotheses.

2.6 Molecular Docking

First, protein information of target genes was retrieved from three-dimensional conformation data of small molecular compounds sourced from PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) and RCSB Protein Data Bank (<https://www.rcsb.org/>). Docking was performed using CB-Dock2 software (<https://cadd.labshare.cn/cb-dock2/index.php>) with grid dimensions of 100×100×100, 50 docking runs, and maximum iterations of 20,000.

3. Results

3.1 Screening of GC Characteristic Genes

Batch correction was performed on the included GC samples and their control sequencing data. Sample correlation plots before and after batch correction are shown in Figure S1.A,B, and principal component analysis results are shown in Figure S1.C,D. Subsequently, differential expression analysis was performed on the GC group and normal control group using the limma package, with screening criteria set at $|\log_2FC| > 1$ and $FDR < 0.05$. The results showed that compared with the NC group, a total of 359 genes were significantly differentially expressed (DEGs) in the GC group (Figure 1A).

Subsequently, to identify gene modules closely associated with gastric cancer occurrence, weighted gene co-expression network analysis (WGCNA) was performed on the training set data. First, the pickSoftThreshold function was used to evaluate a range of soft-thresholding powers β . Based on the scale-free topology fit index, the optimal soft-thresholding power $\beta = 4$ was selected (Figure 1B) to

construct the weighted adjacency matrix, which was further converted to the topological overlap matrix (TOM) for quantifying co-expression similarity between genes. Subsequently, hierarchical clustering analysis was performed based on the TOM dissimilarity matrix, combined with the dynamic tree cut algorithm, with minimum module gene number set to 60, deepSplit parameter set to 3, and module merge dissimilarity threshold set to 0.25. Ultimately, 10 gene co-expression modules with different expression patterns were identified, and the correspondence between modules and gene dendrograms is shown in Figure 1C. Among these, the blue module showed high positive disease correlation, and 941 hub genes highly associated with GC were identified (Figure 1D). Significant differences were observed between different modules (Figure 1E). These hub genes showed high connectivity within their respective modules and significant association with disease phenotypes, suggesting their potential important roles in GC pathogenesis.

Furthermore, the GeneCards database was used to explore GC-related targets, yielding 639 GC-related target genes. Finally, the 941 WGCNA hub genes, 359 differentially expressed genes, and 978 GeneCards genes were subjected to Venn diagram intersection analysis. Genes appearing in any two screening methods were defined as GC-related target genes, ultimately yielding 199 disease-related genes that met the criteria simultaneously (Figure 1F).

3.2 Confirmation of Cross-Target Genes and Enrichment Analysis

To systematically identify 6PPDQ action targets, this study retrieved human genes related to 6PPDQ from two databases, PharmMapper and SwissTargetPrediction. After integration and deduplication, 258 potential 6PPDQ-related target genes were ultimately obtained (Figure 2A). Subsequently, intersection analysis was performed between GC-related genes and 6PPDQ targets, yielding 19 cross-target genes (Figure 2B). GO and KEGG functional enrichment analyses were performed on these 19 common targets using the DAVID database to explore the specific molecular mechanisms involved in 6PPDQ-induced gastric cancer. GO analysis results showed that these genes were mainly involved in biological processes including cellular component disassembly, regulation of G2/M transition of mitotic cell cycle, and regulation of cell cycle G2/M phase transition; cellular components including condensed chromosome, chromosomal region, and spindle microtubule; and molecular functions including protein serine kinase activity, endopeptidase activity, and protein serine/threonine kinase activity (Figure 2C). KEGG enrichment analysis revealed that these genes were mainly enriched in the p53 signaling pathway, PI3K-Akt signaling pathway, Ras signaling pathway, MAPK signaling pathway, Cell cycle, and Central carbon metabolism in cancer (Figure 2D).

3.3 Construction of Diagnostic Models

Subsequently, based on the 19 cross-targets, 113 machine learning methods and their combinations were used to train diagnostic models. The batch-effect-removed data collection served as the training set, while the three pre-batch-correction GC sequencing datasets (GSE33335, GSE19826, and GSE63089) were used as independent validation sets. Additionally, organoid sequencing data (GSE112369) was downloaded from the GEO database as an independent test set. As shown in Figure 3A, the

"Lasso+XGBoost" algorithm demonstrated the highest diagnostic efficacy, showing high diagnostic performance in both validation and test sets. The diagnostic efficacy in validation and test sets was further visualized in Figures 3B-F. To more effectively evaluate this model, confusion matrices were used for validation, which also indicated high diagnostic efficacy (Figures 3G-K).

3.4 SHapley Additive exPlanations Analysis

Subsequently, expression analysis was performed on the 12 modeling genes under the "Lasso+XGBoost" algorithm, with results shown in Figure 4A. The diagnostic efficacy of each modeling gene for GC is shown in Figure 4B, demonstrating that all modeling genes showed generally high diagnostic efficacy for GC.

SHapley Additive exPlanations (SHAP) analysis calculates the marginal contribution of each feature to model predictions, ensuring fair allocation and additivity of feature attribution while providing interpretability for individual predictions. To improve the interpretability and reliability of the risk prediction model, this study employed SHAP analysis to analyze modeling features. First, the importance of each gene feature's contribution to model prediction results was analyzed, with genes ranked according to SHAP importance as shown in Figure 4C. The GC prediction model based on 12 modeling genes showed robust performance across five algorithms, with RF achieving the highest AUC value (0.965; 95% CI 0.948-0.981) (Figure 4D). The SHAP summary plot (Figure 4E) indicated that AURK1 individually contributed the highest explanatory power to the model (mean $|\text{SHAP}| = 0.134$), followed by KIF11 (0.083), with other genes decreasing sequentially. The waterfall plot example (Figure 4F) demonstrated how these modeling genes played key roles in pushing prediction results from the baseline value (0.646) to the final value (0.952) in a single sample, with increased AURK1 expression contributing the most to the increase in individual sample prediction probability, followed by SPARC, with contributions from other genes decreasing sequentially, corroborating the predictive reliability of the modeling genes.

3.5 Screening of Core Targets

To further clarify the core targets of 6PPDQ action in gastric cancer, the protein-protein interaction (PPI) network of the 19 cross-targets was constructed (see Figure S2). Subsequently, this PPI network was imported into Cytoscape, and four topological algorithms (MNC, MCC, Degree, and EPC) in the CytoHubba plugin were used to extract the top 10 genes ranked by each algorithm (Figures 5A-D). Multiple topological dimension core proteins were screened, and intersection analysis yielded 8 core proteins (Figure 5E).

Subsequently, the SVM-RFE algorithm was used to screen the 19 cross-targets, yielding 4 core targets (Figure 5F); LASSO was used for further screening, and when 12 variables were retained, model performance peaked, thus ultimately yielding 12 feature targets (Figure 5G). Then, the Random Forest (RF) algorithm was used to screen the 19 cross-targets, retaining the top five cross-targets according to convention when $n\text{Tree} = 61$ (Figures 5H,I). Intersection analysis of cross-targets obtained from the three

machine learning methods yielded 4 core targets (Figure 5J). Then, intersection analysis was performed between the core proteins obtained from the four topological algorithms and the core targets obtained from the two machine learning screening methods, ultimately yielding 3 core targets: PLAU, MET, and CDK2 (Figure 5K).

3.6 Construction and Validation of Risk Prediction Model

Using the 3 screened core characteristic genes of 6PPDQ-induced gastric cancer (PLAU, MET, and CDK2), a risk prediction model was constructed. The nomogram model showed that upregulated expression of PLAU, MET, and CDK2 were risk factors for gastric cancer occurrence (Figure 6A). To validate the efficacy of the nomogram, calibration curves were used for validation, with results indicating high fitting between the prediction curve and standard trend, suggesting high predictive performance of the nomogram model (Figure 6B). Subsequently, Decision Curve Analysis (DCA) was plotted to assess the clinical net benefit of this model for patients, with results indicating moderate predictive efficacy of the model (Figure 6C). Clinical impact curves were also plotted, with results showing close proximity between the prediction curve and actual curve, similarly indicating good clinical benefit of this model (Figure 6D).

3.7 Molecular Docking Prediction of 6PPDQ Action on GC Core Targets

To validate the direct binding capacity between 6PPDQ and gastric cancer core target proteins, molecular docking analysis was performed between 6PPDQ and PLAU, MET, and CDK2. 6PPDQ showed favorable binding affinity with all 3 target proteins, with binding energies of -8.1 kcal/mol (CDK2), -6.7 kcal/mol (PLAU), and -8.3 kcal/mol (MET), suggesting that 6PPDQ may form stable complexes with these proteins. The 6PPDQ-CDK2 docking results indicated that the 6PPDQ pose docked in a region containing residues GLU8, LYS9, ILE10, GLY11, GLU12, GLY13, THR14, VAL18, LYS20, ALA31, LYS33, VAL64, PHE80, GLU81, PHE82, LEU83, HIS84, GLN85, ASP86, LYS88, LYS89, LYS129, GLN131, ASN132, LEU134, ALA144, ASP145, GLU162, VAL163, VAL164, THR165, etc. (Figure 7A). The 6PPDQ-PLAU docking results indicated that the 6PPDQ pose docked in a region containing residues ARG35, TYR40, VAL41, CYS42, HIS57, CYS58, ASP60, TYR60, THR97, LEU97, HIS99, TYR151, ASP189, SER190, CYS191, GLN192, GLY193, ASP194, SER195, VAL213, SER214, TRP215, GLY216, ARG217, GLY219, CYS220, PRO225, GLY226, VAL227, etc. (Figure 7B). The 6PPDQ-MET docking results indicated that the 6PPDQ pose docked in a region containing residues PHE1089, VAL1092, ALA1108, LYS1110, LEU1112, ARG1114, ILE1115, GLU1120, GLN1123, PHE1124, GLU1127, GLY1128, MET1131, LEU1140, LEU1142, ILE1145, VAL1155, LEU1157, PRO1158, MET1160, HIS1202, ASP1204, MET1211, ALA1221, ASP1222, etc. (Figure 7C). These results preliminarily validate the direct interactions between 6PPDQ and core target proteins at the molecular level.

3.8 Exploration of Core Target Signaling Pathways

We further utilized the KEGG PATHWAY Database (<https://www.kegg.jp/kegg/kegg2.html>) to explore the signaling pathways of the 3 core differentially expressed genes in cancer. The results indicated that

CDK2 is located downstream of the PI3K-AKT signaling pathway and participates in the "cell cycle" process, potentially playing an important role in the process of 6PPDQ-induced gastric cancer. The hypothesized regulatory mechanism is shown in Figure 8.

4. Discussion

This study systematically analyzed the molecular association between the environmental emerging contaminant 6PPDQ and gastric cancer development through the integration of network toxicology and computational algorithm simulation, successfully identifying three core targets: PLAU, MET, and CDK2, and constructing a carcinogenic mechanism hypothesis based on the PI3K-AKT-CDK2 axis. This discovery not only fills the gap in 6PPDQ human tumor toxicity research but also provides a new perspective for understanding the molecular patterns of environmental pollutant-induced digestive tract tumors.

PLAU (plasminogen activator, urokinase), as a target screened in this study, its core role in gastric cancer invasion and metastasis has been confirmed by multiple studies. PLAU creates physical conditions for tumor cells to break through the basement membrane barrier by activating the conversion of plasminogen to plasmin, thereby degrading fibrin and laminin in the extracellular matrix[24]. Notably, the carcinogenic effect of PLAU extends far beyond its proteolytic function—its binding to the receptor uPAR can activate downstream Src, PI3K/AKT[25], and MAPK signaling cascades[26, 27], forming a positive feedback loop that continuously promotes cell proliferation and anti-apoptosis. Recent studies have shown that high PLAU expression is significantly associated with gastric cancer peritoneal metastasis and poor prognosis, and the FOXM1-PLAU synergistic axis can drive tumor progression by regulating TGF- β , DNA repair, and drug resistance-related pathways[28]. The strong binding affinity between 6PPDQ and PLAU (-6.7 kcal/mol) identified in this study suggests that this pollutant may abnormally activate the uPA-uPAR signaling axis by directly occupying the PLAU active site or allosterically regulating its conformation, thereby breaking the dynamic balance between extracellular matrix degradation and remodeling, and paving the way for local infiltration and distant dissemination of gastric cancer cells.

MET (mesenchymal-epithelial transition factor), as a member of the receptor tyrosine kinase family[29], its abnormal activation is an important research direction in gastric cancer targeted therapy[30]. The high binding energy of -8.3 kcal/mol between 6PPDQ and MET in this study suggests that the two may form a stable ligand-receptor complex. The carcinogenic mechanism of MET mainly stems from ligand-independent activation of hepatocyte growth factor (HGF), leading to sustained activation of downstream PI3K/AKT, RAS/MAPK, and STAT3 pathways, ultimately promoting cell proliferation, epithelial-mesenchymal transition (EMT), and angiogenesis. Clinical studies have shown that MET gene amplification occurs in approximately 1.5%-6% of gastric cancers[31], and although the proportion is not high, these patients show significant therapeutic responses to MET tyrosine kinase inhibitors (such as Crizotinib, Savolitinib). More meaningfully, MET amplification often co-amplifies with other receptor tyrosine kinases (such as HER2, EGFR, FGFR2), forming the molecular basis for driving tumor heterogeneity and targeted therapy resistance[32]. 6PPDQ may induce receptor dimerization and

autophosphorylation by mimicking HGF conformational features or directly binding to the MET extracellular domain, thereby initiating carcinogenic signal transduction without ligand dependence. This mechanism shares similarities with the pattern of heavy metal cadmium inducing abnormal MET signal activation through oxidative stress, suggesting that environmental pollutants may share certain strategies for perturbing carcinogenic signaling pathways.

CDK2 (cyclin-dependent kinase 2) is a key regulator of the G1/S phase transition in the cell cycle, and its activity is precisely regulated by Cyclin E and Cyclin A[33, 34]. The binding energy of -8.1 kcal/mol between 6PPDQ and CDK2 in this study, and molecular docking showing its stable binding to the active site near the ATP-binding pocket. CDK2 promotes cell entry into the DNA synthesis phase by phosphorylating downstream substrates (such as Rb protein, E2F transcription factor) to relieve cell cycle arrest. In gastric cancer, excessive CDK2 activation is closely associated with cell cycle dysregulation, increased genomic instability, and chemotherapy resistance. Notably, CDK2 does not function in isolation—it is located downstream of the PI3K/AKT pathway, and AKT can indirectly promote CDK2 activation by inhibiting the activity of CDK inhibitors p21 and p27, forming the "PI3K-AKT-CDK2" carcinogenic axis[35]. The KEGG enrichment analysis in this study showed that cross-targets were significantly enriched in Cell cycle, p53 signaling pathway, and Central carbon metabolism in cancer pathways, which highly matches the functional characteristics of CDK2. 6PPDQ may lead to excessive phosphorylation of CDK2 substrates and accelerated cell cycle progression by directly binding to CDK2 and mimicking the reverse effect of ATP-competitive inhibitors (i.e., stabilizing its active conformation), or indirectly through PLAU/MET-mediated sustained activation of PI3K/AKT, thereby weakening the surveillance function of DNA damage checkpoints[36, 37].

The 19 cross-targets screened in this study were enriched in core carcinogenic pathways including p53 signaling pathway, PI3K-Akt signaling pathway, Ras signaling pathway, and MAPK signaling pathway. These pathways do not exist in isolation but form signaling networks through complex cross-talk. The PI3K/AKT pathway is at the central node of this network—it can be directly activated by MET receptors or indirectly activated by PLAU-uPAR complexes, thereby regulating cell survival, metabolic reprogramming, and protein synthesis by phosphorylating downstream effector molecules such as GSK-3 β , FOXO transcription factors, and mTOR. More importantly, AKT can weaken cellular response to DNA damage by inhibiting p53 transcriptional activity and promoting MDM2-mediated p53 degradation; simultaneously, AKT can relieve negative regulation of CDK2 by inhibiting p21 expression, accelerating cell cycle progression. This multi-level regulatory network of "PI3K-AKT-p53-CDK2" precisely explains why 6PPDQ can simultaneously affect multiple biological processes including cell cycle regulation (G2/M transition), DNA damage repair, and metabolic reprogramming.

From an environmental toxicology perspective, the carcinogenic potential of 6PPDQ may be closely related to its ability to induce oxidative stress and DNA damage. Existing evidence shows that 6PPDQ can cause lipid peroxidation, protein oxidation, and DNA adduct formation through reactive oxygen species (ROS) generation, and oxidative stress is a classic stimulus for initiating p53 signaling pathway and DNA damage response. Under normal physiological conditions, p53 induces cell cycle arrest to

allow DNA repair time by activating p21 to inhibit CDK2 activity; however, under conditions of sustained 6PPDQ exposure, abnormal activation of the PI3K/AKT pathway may inhibit p53 transcriptional function by phosphorylating p53 at Ser315 and Ser392 sites, leading to "cell cycle checkpoint escape" and accumulation of genomic instability. Furthermore, 6PPDQ-induced ROS can directly activate MAPK and Ras signaling pathways, promoting the release of inflammatory factors (such as IL-6, TNF- α) through AP-1 and NF- κ B transcription factors, forming a vicious cycle of "oxidative stress-inflammation-tumor".

The findings of this study show high consistency with previous research on environmental pollutant carcinogenic mechanisms. Components in air pollutant PM_{2.5} such as polycyclic aromatic hydrocarbons and heavy metals (such as lead, cadmium, arsenic) [38] have been confirmed to increase gastric cancer risk by inducing oxidative stress and DNA damage, with mechanisms involving ROS-mediated 8-hydroxydeoxyguanosine (8-OHdG) formation, inhibition of base excision repair systems, and epigenetic modification changes[39]. Particularly noteworthy is that epidemiological surveys of rubber workers have shown that workers with long-term exposure to talc and asbestos have significantly elevated gastric cancer mortality, suggesting that rubber industry-related chemicals (including 6PPD and its transformation product 6PPDQ) may have underestimated digestive tract tumor risks[40]. This study provides theoretical support for this epidemiological observation from the molecular mechanism level—6PPDQ may directly target key molecules such as PLA α , MET, and CDK2, simulating or amplifying the signal perturbation effects of traditional carcinogens.

At the targeted therapy level, the core targets identified in this study have important clinical translational value. Targeted drugs against MET (such as Crizotinib, Cabozantinib) have shown significant efficacy in MET-amplified gastric cancer patients, while CDK4/6 inhibitors (such as Palbociclib, Ribociclib) have successful applications in breast cancer[37], providing reference for CDK-targeted therapy in gastric cancer[41, 42]. Although selective CDK2 inhibitors are still in the development stage, the binding mode analysis of 6PPDQ and CDK2 in this study can provide structural templates for developing competitive antagonists. More prospectively, the combined application of PLA α -uPAR axis inhibitors (such as Serpin molecules) with MET or CDK inhibitors may produce synergistic anti-tumor effects by simultaneously blocking extracellular matrix degradation and intracellular proliferation signals. The risk prediction model constructed in this study (based on PLA α , MET, and CDK2) showed good diagnostic efficacy (AUC = 0.965), suggesting that these three genes can serve as a potential biomarker combination for early gastric cancer screening and prognosis assessment, particularly applicable to precision monitoring of high-exposure risk populations such as those exposed to 6PPDQ.

Although this study strives for rigor, several limitations remain. First, network toxicology analysis relies on prediction algorithms from public databases. Although 6PPDQ target prediction has been cross-validated through multiple databases, direct experimental evidence (such as drug affinity responsive target stability analysis DARTS or cellular thermal shift analysis CETSA) is lacking. Second, molecular docking only provides static binding mode information, failing to fully simulate dynamic biological processes such as cell membrane microenvironment, protein post-translational modifications, and allosteric effects. Future research should utilize gastric cancer organoid models to simulate the chronic

exposure effects of 6PPDQ, parsing tumor heterogeneity evolution trajectories; subsequently employ gene editing technologies (such as CRISPR-Cas9) to knock out PLAU, MET, and CDK2 separately in gastric cancer cell lines to verify the target dependence of 6PPDQ carcinogenic effects; furthermore construct 6PPDQ-induced gastric cancer animal models (such as transgenic mice or humanized PDX models) to evaluate the intervention effects of targeted inhibitors; finally, conduct prospective cohort studies to detect dose-response relationships between serum 6PPDQ levels and gastric cancer incidence in high-risk populations (such as rubber industry workers, traffic police), providing epidemiological evidence for establishing occupational exposure limits.

5. Conclusion

This study, based on network toxicology and computational algorithm simulation, systematically elucidated for the first time the key molecular mechanisms of the environmental emerging contaminant 6PPDQ in gastric carcinogenesis. The study identified three core targets: PLAU, MET, and CDK2, revealing that 6PPDQ may drive malignant transformation of gastric cancer through mechanisms including activation of the PI3K-AKT-CDK2 signaling axis, disruption of cell cycle regulation, and promotion of tumor microenvironment remodeling. Molecular docking validation demonstrated strong binding affinities between 6PPDQ and the three core target proteins, providing structural biological evidence for the hypothesis that environmental pollutants directly target human key carcinogenic molecules.

Declarations

Clinical trial number

Not applicable.

Ethics, Consent to Participate, and Consent to Publish declarations

Not applicable.

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Data availability

The data used in this study were obtained from the GEO ([https:// www.ncbi.nlm.nih.gov/geo/](https://www.ncbi.nlm.nih.gov/geo/)) database, both of which are available in publicly available databases. This study complies with its data use and publication rules.

Author contributions

YK and LC contributed equally. YK, LC, MJ, LY, TY, ZX, and ZJ participated in the conception and design of the study. YK, LC and ZJ organized the database and statistical analysis. MJ, LY, ZJ, ZX, YK and LC divided the work and participated in the picture drawing. YK and LC wrote the first draft of the manuscript. YK, LC and ZJ participated in the revision of the manuscript. All authors read and agreed to the final manuscript and authorship arrangement.

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Figures

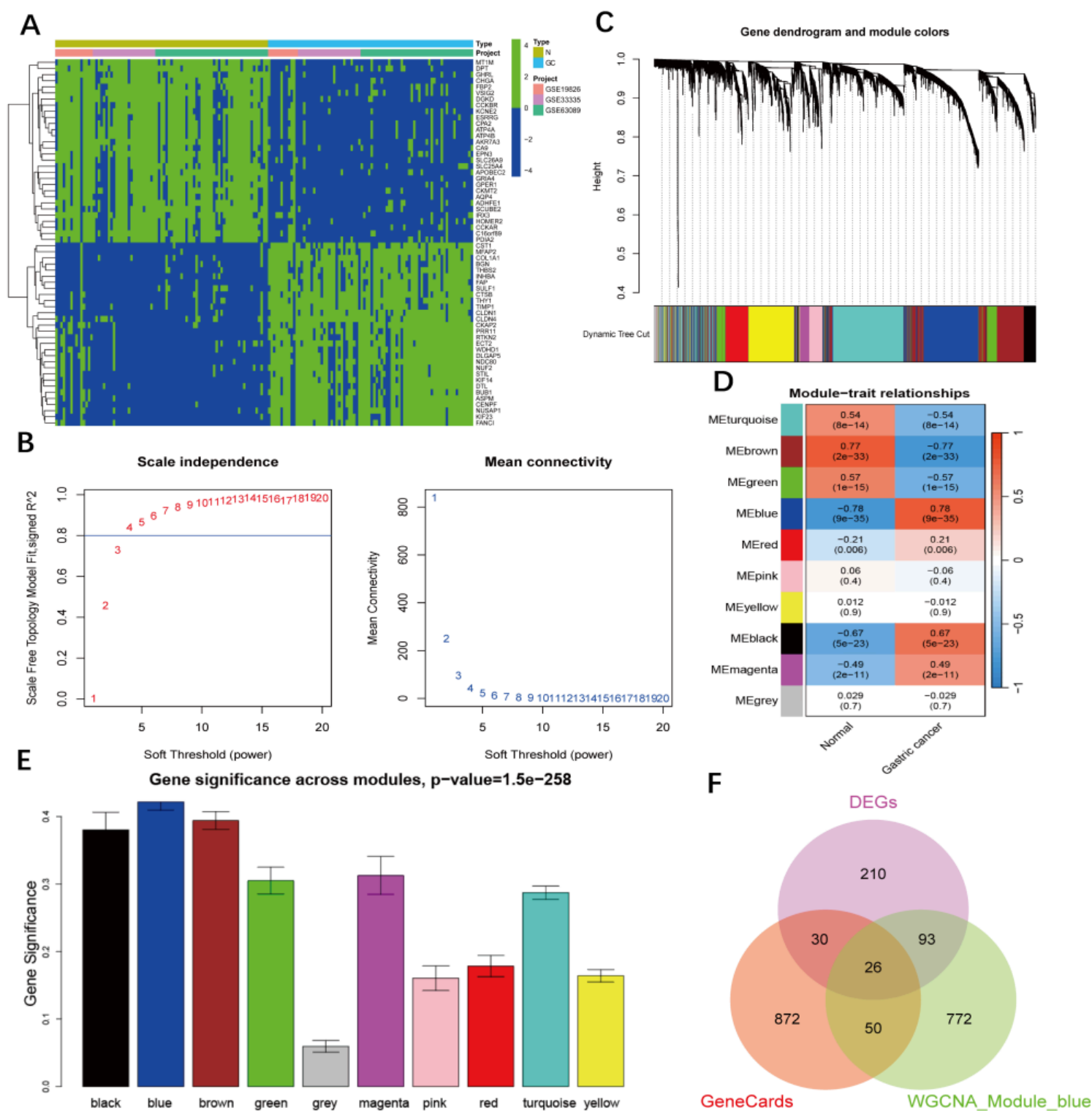


Figure 1

Screening of GC characteristic genes.

(A) Heatmap of differential expression analysis results of included GC mRNA sequencing data after batch correction; (B) Soft-threshold selection: left panel shows scale-free topology fit index R^2 , right panel shows mean connectivity, with red marking $R^2 = 0.8$ threshold; (C) Gene clustering dendrogram: different color bars represent different co-expression modules; (D) Module-trait correlation heatmap:

values are correlation coefficients, with P values in parentheses, and colors indicating correlation strength; (E) Differential analysis between different modules; (F) Venn diagram: showing intersection of DEGs, GeneCards target genes, and WGCNA hub genes, with genes appearing in any two screening methods defined as GC-related target genes.

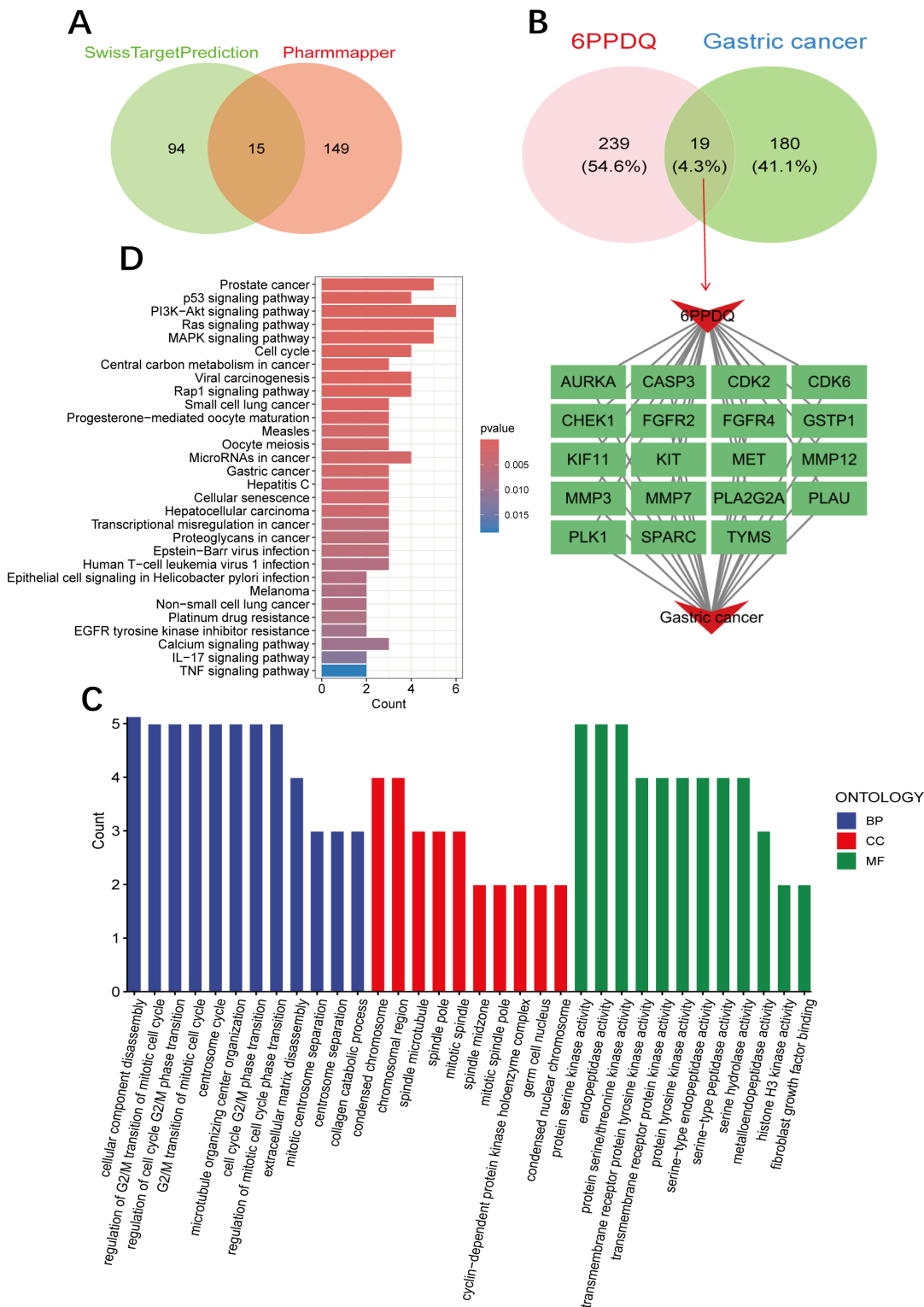


Figure 2

Confirmation of cross-target genes and enrichment analysis.

(A) Screening of 6PPDQ-related targets; (B) Intersection analysis between GC-related genes and 6PPDQ targets, yielding 19 cross-target genes; (C) GO functional enrichment analysis of cross-targets; (D) KEGG functional enrichment analysis of cross-targets.

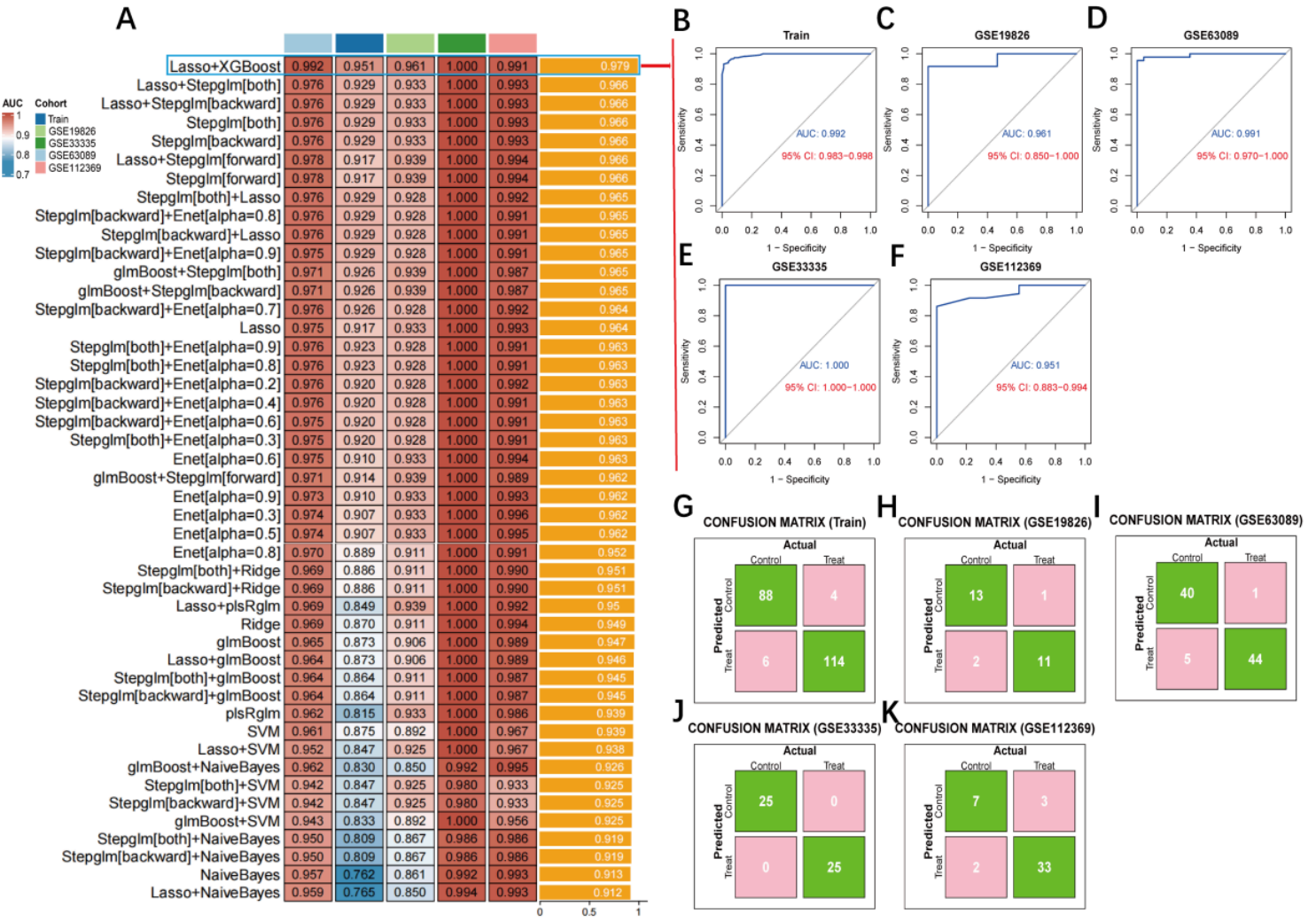


Figure 3

Diagnostic models based on 113 machine learning screening methods.

(A) Heatmap of diagnostic model training cohort, validation cohort, and test cohort under different machine learning combinations; (B-E) Diagnostic ROC curves of validation and test cohorts under Lasso+Stepglm[forward] algorithm; (F-I) Confusion matrices of validation and test cohorts under Lasso+Stepglm[forward] algorithm for model validation; (J) Box plots of differential expression analysis of GC modeling genes; (K) Diagnostic ROC curves of GC modeling genes for GC.

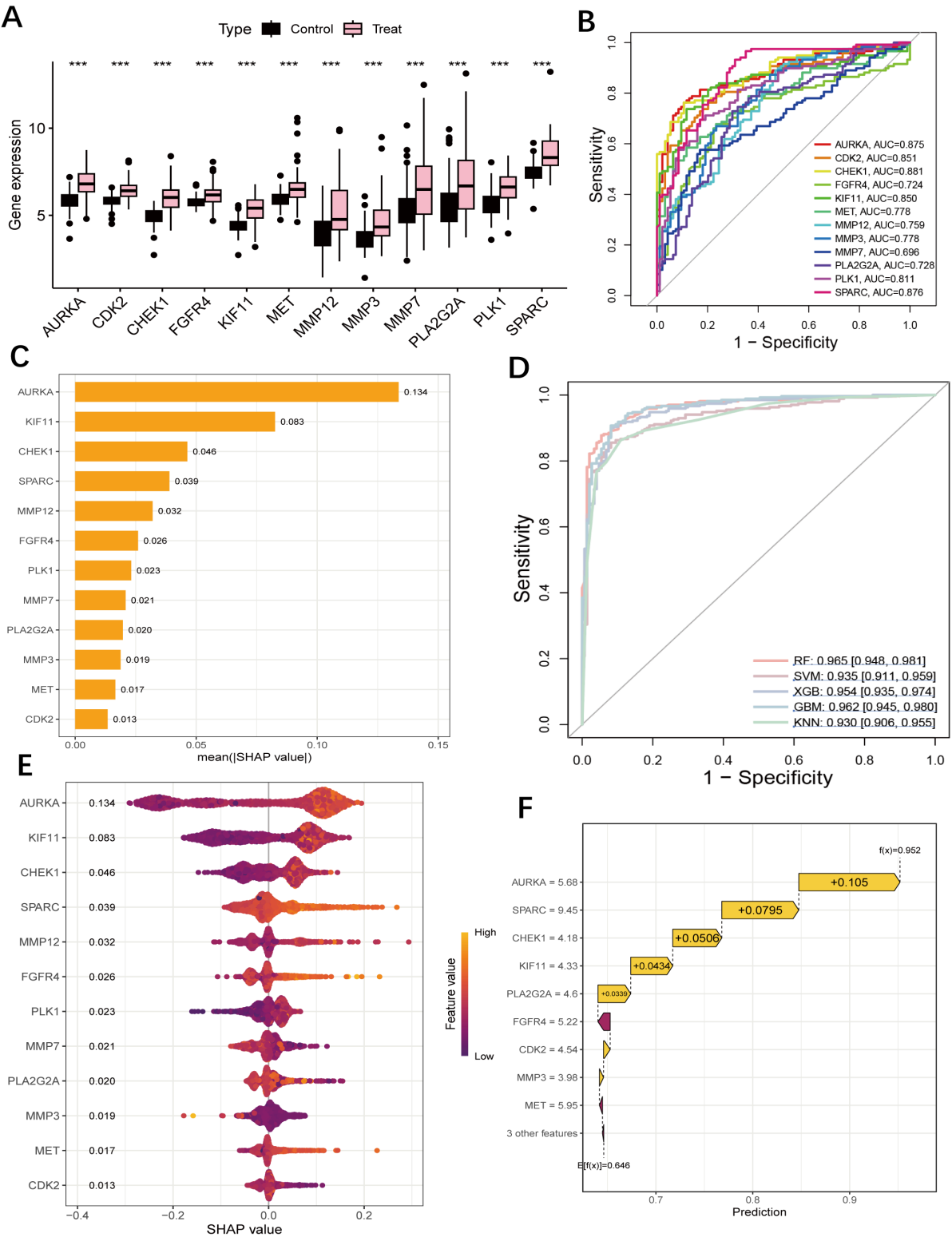


Figure 4

SHAP analysis.

(A) Expression of modeling genes; (B) Diagnostic efficacy analysis of modeling genes for GC; (C) Grouped SHAP feature importance bar plot of modeling genes; (D) Validation set ROC curves: systematic evaluation of discriminative performance of different machine learning models in gastric

cancer diagnosis through comparison of multiple algorithms; (E) SHAP value feature importance plot (SHAP summary plot) showing contribution of modeling genes to the model; (F) SHAP single-sample explanation plot (force plot), showing departure from baseline 0.646 at lower left, with each feature sequentially "adding" or "subtracting" portions (SHAP values), ultimately reaching the prediction value for this sample ($f(x) = 0.952$) at upper right, indicating high predictive efficacy.

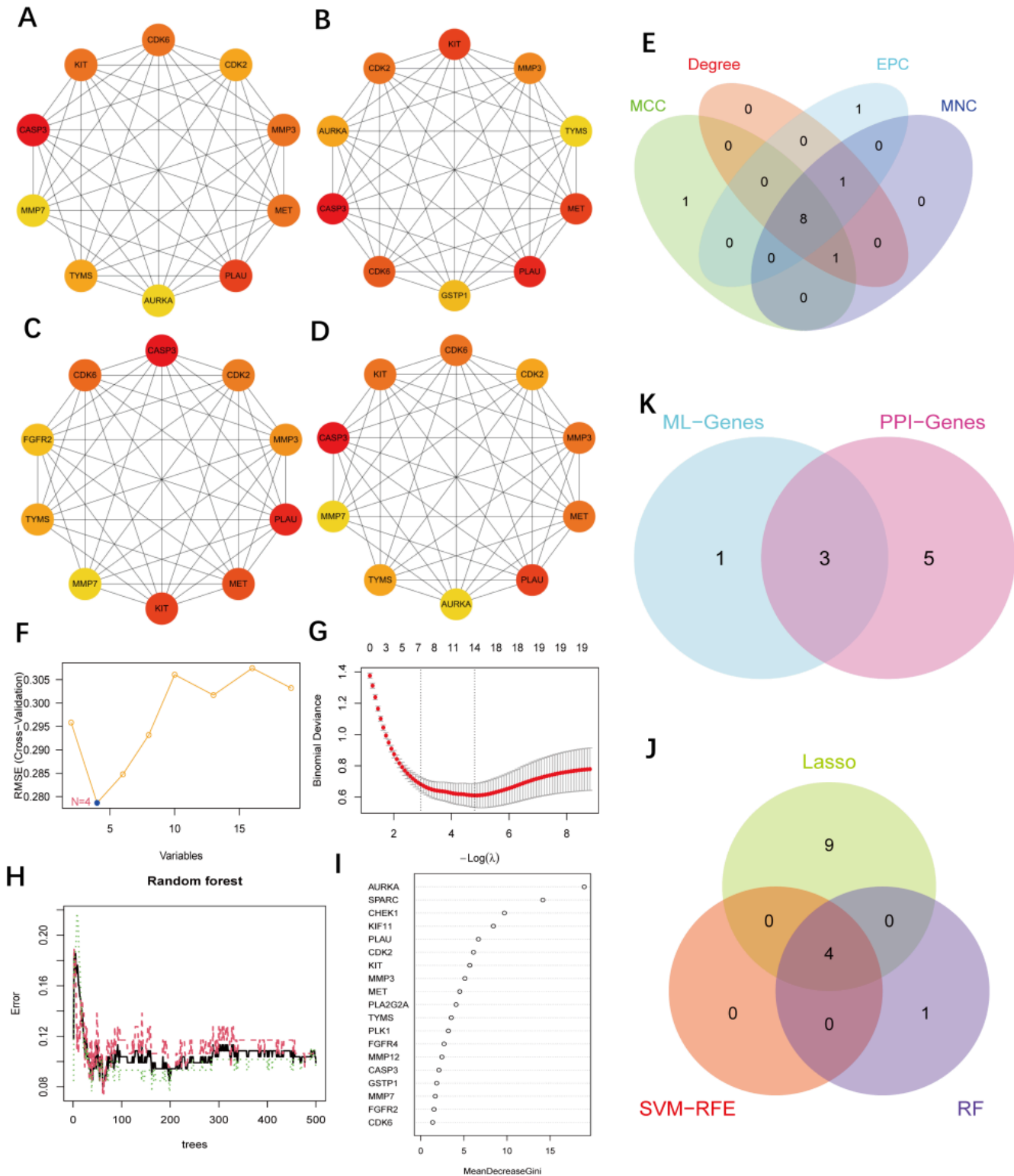


Figure 5

Screening of key target genes.

(A-D) Top 10 key genes by DMNC algorithm, top 10 key genes by MCC algorithm, top 10 key genes by Degree algorithm, and top 10 key genes by EPC algorithm, with node colors ranging from red to yellow indicating scores from high to low; (E) Venn diagram of four algorithm screening results: showing 8 core target genes commonly identified by the four algorithms; (F) Core target gene screening based on SVM-RFE analysis; (G) Core target gene screening based on LASSO regression analysis; (H,I) Core target gene screening based on RF analysis; (J) Intersection of three machine learning method screening results yielding 4 core targets; (K) Intersection of core targets obtained from topological algorithms and machine learning yielding the final 3 core targets.

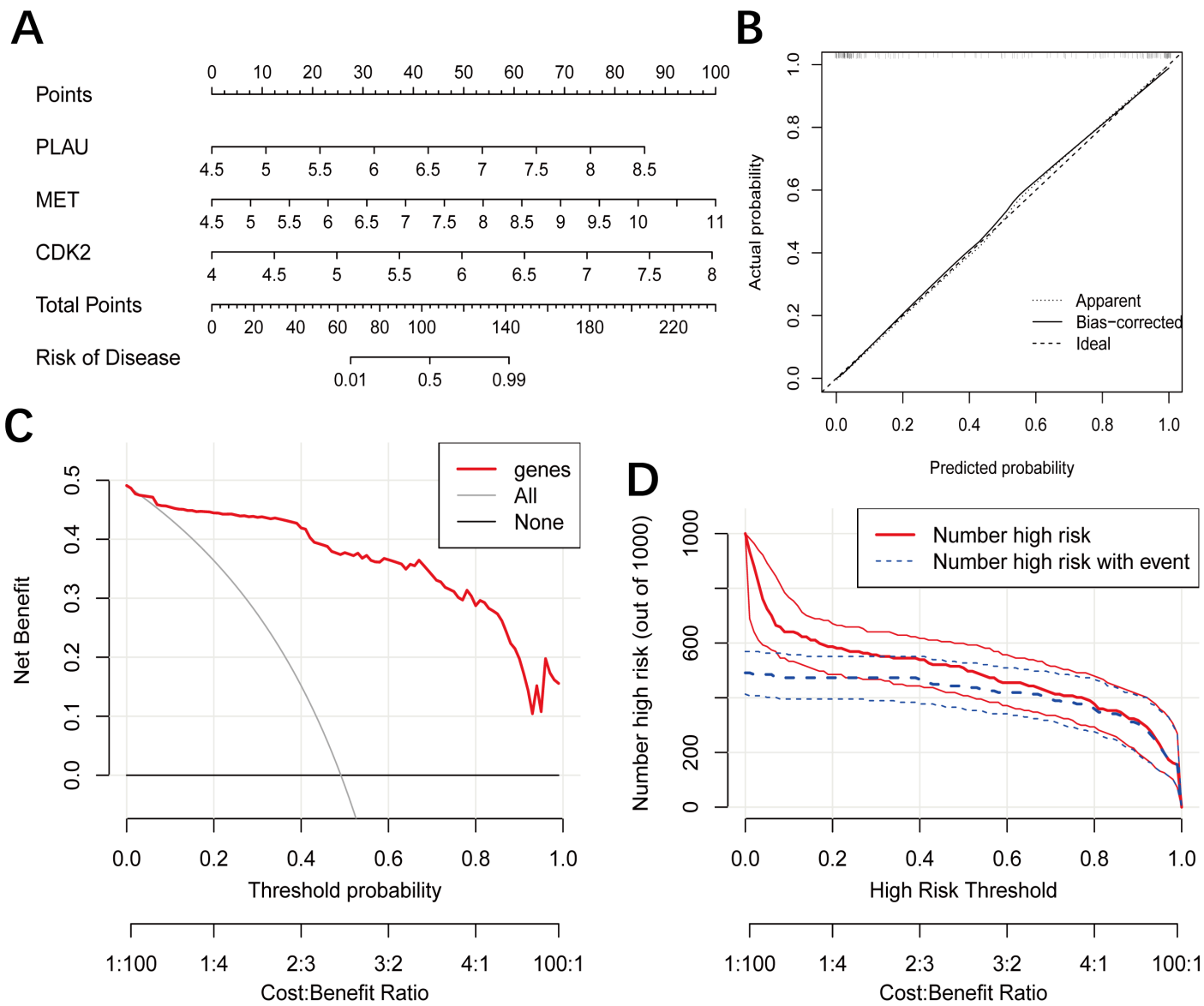


Figure 6

Construction and validation of 6PPDQ-induced GC risk model.

(A) Nomogram of risk prediction model based on 3 core cross-target genes; (B) Calibration curve; (C) Decision curve; (D) Clinical impact curve.

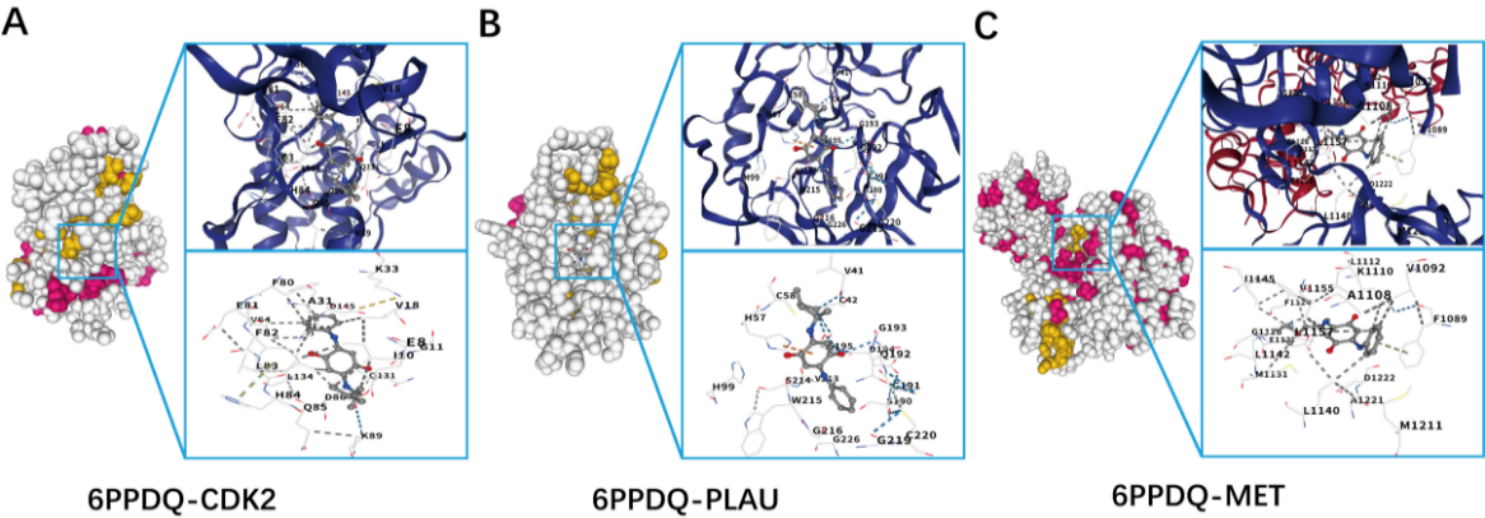


Figure 7

Molecular docking results.

(A) Molecular docking results of 6PPDQ with CDK2; (B) Molecular docking results of 6PPDQ with PLAU; (C) Molecular docking results of 6PPDQ with MET.

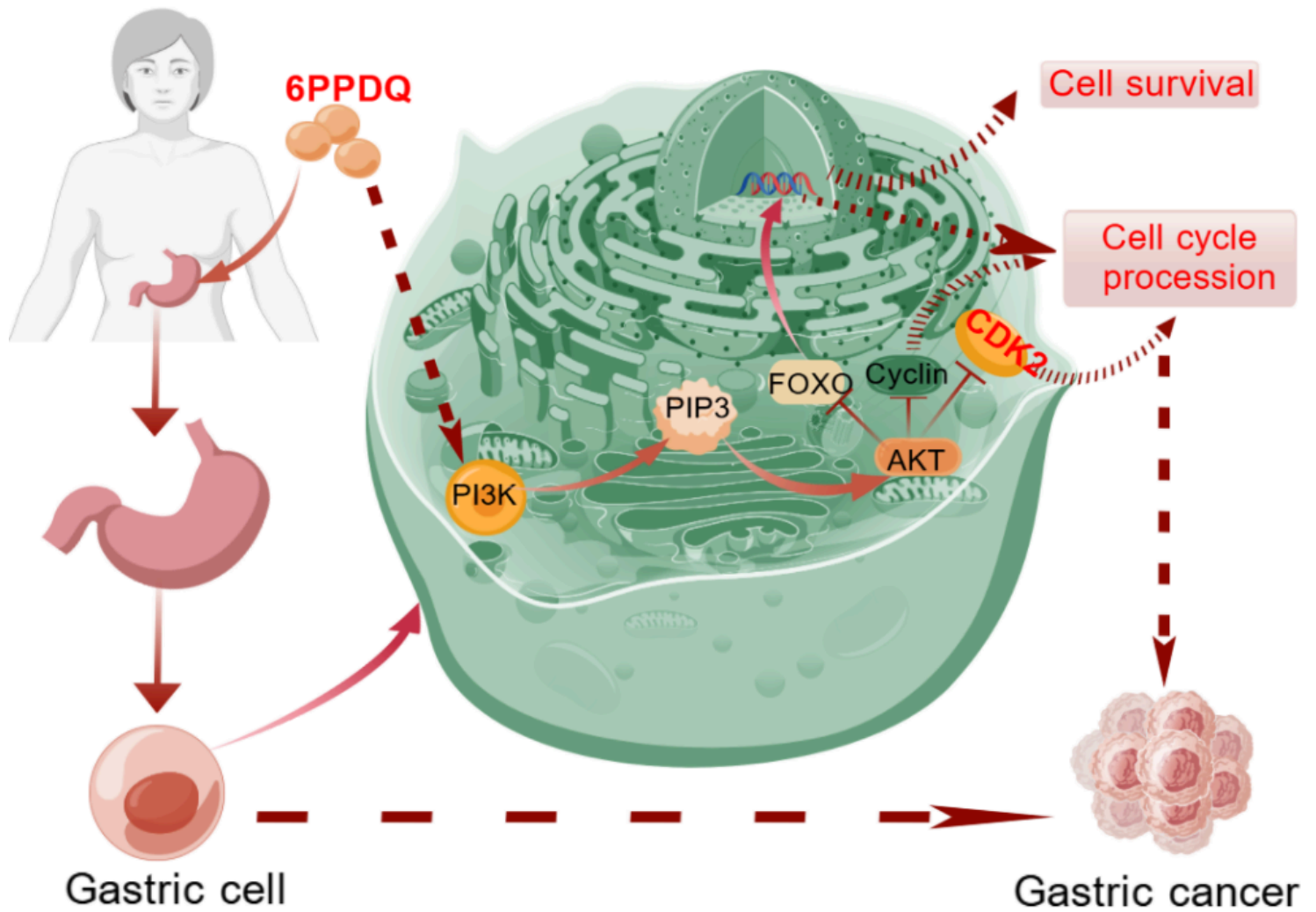


Figure 8

Hypothetical mechanism diagram of 6PPDQ-mediated gastric cancer occurrence through the PI3K-AKT-CDK2 signaling pathway.

Supplementary Files

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