

The Critical Role of PTEN Mutation in Cellular Process and Drug Selection of Endometrial Cancer

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Research article

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Abstract

Background: Phosphatase and tensin homolog (PTEN) is a frequently mutated genes found in endometrial cancer (EC), making it a potential biomarker for individualized treatment opinions. In this study, a method was designed to evaluate the role of the PTEN mutation in the prognosis and drug selection of EC. We identified the potential alterations in pathways and genes related to the mechanism.

Methods: cBioPortal database was used to analyze the PTEN mutation status for EC patients. Kaplan-Meier was used to analyze the prognosis of PTEN mutation in EC patients. GDSC dataset was used to identified the drugs that sensitive to cell lines with PTEN mutation. DEGs between PTEN mutation and wide type group were identified using the edgeR package. GO and KEGG analysis were carried out using the DAVID database. GSEA v3.0 were used to dig out the differences in gene mRNA levels of biological function annotation and pathways between PTEN mutation and wide type patients. PPI network of DEGs was performed using STRING and then visualized using Cytoscape software (3.7.2).

Results: Our results showed that PTEN mutation was carried in 68% of EC patients. The mRNA expression level of PTEN was lower in patients with PTEN mutation than that with wide type. Prognosis analysis showed that there were favorable overall survival and progression free survival in EC patients with PTEN mutation. Moreover, it is more sensitive to AKT inhibitor (Afuresertib and AZD5363), and Mcl-1 inhibitor (MIM1) on EC cell lines with PTEN mutation than that with wide type. A total of 216 genes were identified as DEGs. GO analysis showed that DEGs significantly enriched in chemical synaptic transmission, extracellular region, etc.. KEGG analysis suggested that DEGs significantly enriched in categories associated with metabolic progression. GSEA analysis identified signaling pathways including fatty acid metabolism, fructose and mannose metabolism, etc.. PPI network analysis identified top 10 genes and top three clusters.

Conclusions: Multiple genes and pathways may play an important role in EC patients with PTEN mutation. These results provide a potential target and therapeutic strategies for patients with PTEN mutation.

Introduction

Endometrial cancer (EC) is one of the most common malignancies of the female reproductive system [1–3]. The incidence of endometria cancer is still increasing as a consequence of the populations increasing life expectancy and the overall prevalence of obesity and metabolic syndromes [4]. The number of new cases and deaths is expected to increase by 17.4 and 20.3 percent by 2025, respectively [5]. The five years overall survival rate of EC patients is approximately 82% [6]. Mortality of EC patients is associated with poor prognosis factors. Prognostic prediction of EC patients relies on histological stage, tumor grade, depth of myometrial invasion, cervical involvement, tumor size and lymph node status, but they are not always reliable [5, 6]. Recently, next-generation sequencing results reveal many genetic mutations in EC, including CTNNB1, FGFR2, HER2, P53, etc. [2, 7, 8]. These different mutation types result in drug

resistance and poor prognosis of EC patients. Therefore, to identify potential biomarkers that effectively predict prognosis and response to drug therapy appears extremely urgent.

Phosphatase and tensin homolog (PTEN) located in 10q22.3, is one of tumor suppressor genes [9]. PTEN is a dual specificity protein and lipid phosphatase that involved in multiple cellular process and signal pathways, such as cell cycle, cell differentiation, migration and tumor invasion [10]. PTEN functions can be either dependent or independent on the negative regulation of the phosphatidylinositol-3- kinase B pathway [11]. PTEN mutation has been found in many cancers, including ovarian cancer, endometrial cancer, gastric cancer and breast cancer [12–15]. PTEN mutation may affect cancer development, cancer progression, disease prognosis and treatment strategies [16, 17], and results in poor prognosis and natural resistance or sensitivity to treatment in patients. Therefore, to explore the alterations in cell process and signal pathways will provide more evidence for individualized treatment in EC patients with PTEN mutation.

In this study, we analyzed the RNA sequencing data of uterine corpus endometrial carcinoma (UCEC) based on The Cancer Genome Atlas (TCGA) to identify the key genes and pathways associated with the PTEN mutation. The Genomic of Drug Sensitivity in Cancer (GDSC) was used to evaluate the role of PTEN mutation in drug selection of EC. The aim is to uncover the potential biomarker on prognostic prediction and individualized treatment of EC patients with PTEN mutation.

Methods

TCGA data

Gene expression data and corresponding clinical information were downloaded from TCGA database (<https://tcga.xenahubs.net>). PTEN mutation data was obtained from cBioPortal for Cancer Genomics (<https://www.cbioportal.org>) [18]. The mRNA data was provided by TCGA which are public and open-ended, and therefore does not require the approval of a local ethics committee.

Identification of differential expressed genes

Downloaded mRNA data were analyzed to obtain differentially expressed genes (DEGs) at genes levels between wide type and PTEN mutation using Edger software package. Fold changes ($|\log_2FC| \geq 1$, both P-value and FDR (false discovery rate) < 0.05 were set as the cut-off value.

Function and Pathway enrichment

To determine the function of the DEGs, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment were implemented using the Database for Annotation,

Visualization and Integrated Discovery (DAVID) website (<https://david.ncifcrf.gov/>) [19, 20]. A P-value <0.05 was set as the cut-off value.

Correlation between PTEN mutation and drug response

The relation between PTEN mutation and drug response was analyzed using the Genomics of Drug Sensitivity in Cancer (GDSC) (<https://www.cancerrxgene.org>) [21]. For this analysis, the status of PTEN mutation in UCEC was correlated with drug sensitivity data by an analysis of variance (ANOVA). This includes coding variants and copy number alterations. We first searched genetic feature 'PTEN' and selected the 'PTEN mut' in UCEC cell lines, and then searched for compounds with significant selectivity for the PTEN mutation in UCEC cell lines. Scatter plots were generated and computed via the GDSC online platform.

Gene Set Enrichment Analysis (GSEA)

The association between status of PTEN and biological processes was analyzed using GSEA v3.0 (<https://www.gsea-msigdb.org/gsea/downloads.jsp>). GSEA calculates a gene set Enrichment Score (ES) that estimates whether genes in pre-defined gene set are enriched in the PTEN mutation/wide type groups. $|ES| > 1$, $p < 0.05$, and $FDR < 0.25$ were considered to be statistically significant.

Protein-Protein Interaction Network

Protein-protein interaction (PPI) network analysis of DEGs was performed by the Search Tool for Retrieval of Interacting Genes (STRING) database (<https://string-db.org/>). Confidence of 0.4 was set as the minimum required interaction score. Simple tabular text output was generated from STRING, then visualized by Cytoscape software (3.7.2). We used the Cytoscape plugin Molecular Complex Detection (MCODE) plugin for screening the intersected clusters from the PPI network. The cluster determining extremities was charted, such as Kappa score (K-core) fixed to five, Degree Cutoff fixed to two, Max. Depth fixed to 100, and Node score Cutoff fixed to 0.2, which constraints the cluster size for coexpressing networks.

Statistical analysis

All statistical analysis was conducted by R. Wilcox analysis was used to compare the mRNA levels of PTEN between PTEN mutation and wide type group. Kaplan-Meier method with log-rank test was used to analyze the prognosis of PTEN mutation in EC patients. FDR in edgeR and GSEA were adjusted for multiple testing with the Benjamini-Hochberg procedure to control FDR, respectively. $P < 0.05$ and $FDR < 0.25$ were considered to be statistically significant.

Results

PTEN mutation in EC patients

PTEN mutation information was downloaded from cBioPortal website, and there were 347 (68%) (Figure 1A) with PTEN mutation in UCEC patients. Mutation types are included inframe mutation, missense mutation, truncating mutation, fusion, amplification and deep deletion (Figure 1B).

Prognosis of PTEN mutation in EC patients

In order to effect identification of PTEN mutation on process and prognosis in EC patients, we compared the mRNA expression level of PTEN between PTEN mutation and wide type group, the result showed that mRNA expression of PTEN was downregulated in EC patients with PTEN mutation ($P=0.049$, Figure 2A). We further analyzed the relationship between PTEN status and prognosis in EC patients. The result revealed that it was a favorable overall survival ($P=8.273e-4$, Figure 2B) and progression free survival ($P=0.715e-4$, Figure 2C) in EC patients with PTEN mutation. These results indicated that PTEN mutation may influent the progression in EC patients.

Drug selection to EC patients with PTEN mutation

We then investigated the role of PTEN mutation in EC therapy by GDSC website. The results showed that AKT inhibitor (Afuresertib and AZD5363) (Figure 3A ,3B), Mcl-1 inhibitor (MIM1) (Figure 3C) exhibited sensitivity for EC cell lines harboring the PTEN mutation in the GDSC website, it indicated that these compounds were potential for individualized treatment of EC patients with PTEN mutation.

Identification of DEGs

To identify the key genes and pathways associated with the PTEN mutation, we analyzed the differences between PTEN mutation and wide type group using edgeR software package. $|\log_2FC| \geq 1$, both P-value and $FDR < 0.05$ was set as the cut-off value, and a total of 216 genes were identified as DEGs, these DEGs include 64 upregulated genes and 152 downregulated genes, the volcano plot of the DEGs and heatmap of top 50 upregulated genes and downregulated genes were shown in Figure 4.

Functional and Pathway enrichment

To determine the function of the DEGs, GO and KEGG pathway enrichment of all 216 DEGs were implemented using DAVID website, the GO analysis of DEGs showed significant enrichment in chemical synaptic transmission, extracellular region, negative regulation of endopeptidase activity, neurotransmitter transport, serine-type endopeptidase inhibitor activity, serotonin receptor signaling

pathway, GABA-A receptor complex, defense response to Gram-negative bacterium, neurotransmitter: sodium symporter activity, chloride channel activity, GABA-A receptor activity, voltage-gated potassium channel activity, and neurotransmitter receptor activity (Figure 5A). KEGG pathway analysis suggested significant enrichment in neuroactive ligand-receptor interaction, retinol metabolism, drug metabolism cytochrome P450, metabolism of xenobiotics by cytochrome P450, chemical carcinogenesis, GABAergic synapse, morphine addiction, retrograde endocannabinoid signaling, nicotine addiction, serotonergic synapse and cAMP signaling pathway (Figure 5B).

GSEA

We further analyzed the influence of PTEN mutation on cellular process. GSEA was performed to identify signaling pathways that activated in EC patients. It was found that fatty acid metabolism, fructose and mannose metabolism, p53 signaling pathway, terpenoid backbone biosynthesis and alpha linolenic acid metabolism were significantly enriched. These results indicated that multiple pathways and metabolism were activated which were involved in progression of EC patients with PTEN mutation (Figure 6).

Establishment of PPI network and module analysis

Finally, we constructed the PPI network of DEGs using STRING, the PPI network was involved in 186 nodes and 132 edges. The top 10 genes ranked by degree were CYG13, CT45A1, NPY, GABRA5, HTR2C, MAGEC1, PASD1, MAGEC2, SSX4 and NXF2B (Figure 7). Regions interlinked closely from the network were identified by cytoscape MCODE plugin in the form of clusters. It showed that the top three clusters were significant in the PPI network (Figure 8).

Discussion

PTEN is a multifunctional tumor suppressor gene, which is mutated in large number of cancers at different frequency. PTEN alterations are more frequent in glioblastoma (30%-60%) [22, 23], breast cancer(11%-15%) [24, 25], prostate cancer (17%-21%) [26, 27]. PTEN mutation is thought to be an early step in the development and progression of EC patients [28, 29]. It is reported that PTEN mutation is in 30–50% of EC cases [30] [31]. We found that 68% of EC patients harbored PTEN mutation in the present study. These findings suggested that PTEN is strongly involved in the development and progression of EC patients.

The role of PTEN mutation in prediction of prognosis varies in different cancer types. Previous study reported that PTEN mutation have a significantly poorer prognosis of survival and disease recurrence in clear cell renal cell carcinoma (ccRCC) patients [17]. Recent research showed that low expression of PTEN is of limited value in predicting the prognosis of patients with ccRCC for overall survival and progression free survival, but it is significantly associated with an unfavorable disease-specific survival [32]. However, it is also reported that PTEN mutation was correlated with a favorable prognosis for EC

patients [9]. In addition, it is indicated that PTEN mutation only outside exons 5–7 was significantly associated with better survival [33]. Consistently, our results showed that PTEN mutation have a favorable overall survival and progression free survival in EC patients.

PTEN mutation contributes to natural resistance or sensitivity to chemotherapy. It is found that somatic mutations of PTEN were associated with resistance to immune checkpoint inhibitors in patients with glioblastomas [34]. Moreover, PTEN loss contributes to hyperactivation of the PI3K pathway and to drug resistance in breast cancer [35], and PTEN deletion is closely related to acquired resistance to EGFR-TKIs [36]. Conversely, it was found that GSK690693, a AKT inhibitor, selectively inhibited on ccRCC with PTEN mutation [17]. Our results revealed that PTEN mutation are more sensitive to AKT inhibitor (Afuresertib and AZD5363) in EC cell lines than that in wide type, also Mcl-1 inhibitor (MIM1) does. These results provide evidence for the potential individualized therapy of EC patients with PTEN mutation.

PTEN, a dual specificity protein and lipid phosphatase, is inactivated by PTEN enzymatic activity which leads to induction of cell proliferation and inhibition of cell death, causing cancer development and progression [35]. PTEN can be secreted into the extracellular environment and works as a tumor suppressor in a cell non-autonomous manner [36]. Role of PTEN has recently been established in metabolic reprogramming, including drug metabolism and lipid metabolism. PTEN mutation may affect the expression or activity of cytochrome P450, suggesting the potential role of PTEN in drug response or resistance. Consistently, our results showed that DEGs related to extracellular region, neurotransmitter transport, GABA-A receptor activity, drug metabolism-cytochrome P450, metabolism of xenobiotics by cytochrome P450, chemical carcinogenesis, GABAergic synapse, serotonergic synapse and cAMP signaling pathway in EC patients with PTEN mutation. These results further explain why are more sensitive to AKT inhibitor (Afuresertib and AZD5363) and Mcl-1 inhibitor (MIM1) in EC cell lines with PTEN mutation than that with wide type.

GSEA analysis suggests that PTEN mutation is significantly associated with multiple cancers related fatty acid metabolism, fructose and mannose metabolism, p53 signaling pathway, terpenoid backbone biosynthesis and alpha linolenic acid metabolism. Features of cancer cell reprogramming are increased in glucose uptake and fermentation of glucose to lactate. Evidence suggested that inactivation of PTEN leads to fatty acid accumulation in cancer cells [37]. Furtherly, loss of PTEN resulting in p53 increase can counteract tumor growth by activating an effective fail-safe mechanism of cellular senescence in prostate cells [38]. Therefore, it is suggested that PTEN mutation is associated with cellular progression and signal pathways.

Overall, our results provide a potential therapeutic targets and strategies for EC patients with PTEN mutation. However, our results should be verified by molecular biology experiments even though we investigated the role of PTEN mutation in cellular process and in progression of EC patients by bioinformatic analysis, Additionally, we only analyzed the role of PTEN mutation in drug selection of EC cell lines, it also should be validated by animal experiments, clinical researches and cohort studies.

Conclusions

Our results confirmed that mutation rate of PTEN is approximately 68% in EC patients. mRNA expression level of PTEN was lower in patients with PTEN mutation than that with wide type. Moreover, PTEN mutation have a favorable overall survival and progression free survival in EC patients. Cell lines are more sensitive to AKT inhibitor (Afuresertib and AZD5363) and Mcl-1 inhibitor (MIM1) than that with wide type in EC with PTEN mutation. Multiple genes and pathways may play an important role in EC patients with PTEN mutation. These results offer a potential target and strategies for patients with PTEN mutation.

Abbreviations

EC: Endometrial cancer; PTEN: Phosphatase and tensin homolog; UCEC: Uterine corpus endometrial carcinoma; TCGA: The Cancer Genome Atlas; GDSC: The Genomic of Drug Sensitivity in Cancer; GO: Gene ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; GSEA: Gene set enrichment analysis; DAVID: Database for Annotation, Visualization and Integrated Discovery; PPI: Protein-protein interaction; DEGs: differentially expressed genes; FDR: false discovery rate; FC: Fold changes; EC: Enrichment Score; STRING: Search tool for retrieval of interacting genes; MCODE: Molecular Complex Detection; ccRCC: Clear cell renal cell carcinoma;

Declarations

Acknowledgements

Not applicable.

Authors' contributions

LY, ZJT, and SDH participated in the study design. LY and ZJT performed most of the microarray and RNA-seq analyses. NPG, CRH and ZFX performed function and pathway enrichment analyses. DJ, LW and ZXP performed PPI network analyses. LY and ZJT drafted the paper. LY, ZJT and SDH participated in the final preparation and revision of the paper. All authors read and approved this final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from TCGA database (<https://portal.gdc.cancer.gov/>) and GDSC database (<https://www.cancerrxgene.org>), which are all publicly available.

Ethics approval and consent to participate

This study does not involve animal and/or human tissue/individual data/participants, there is no ethics related issues. No permissions were required to use any repository data involved in the present study.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures



Figure 1

PTEN mutation in EC patients. (A) Mutation frequency, (B) Mutation types.

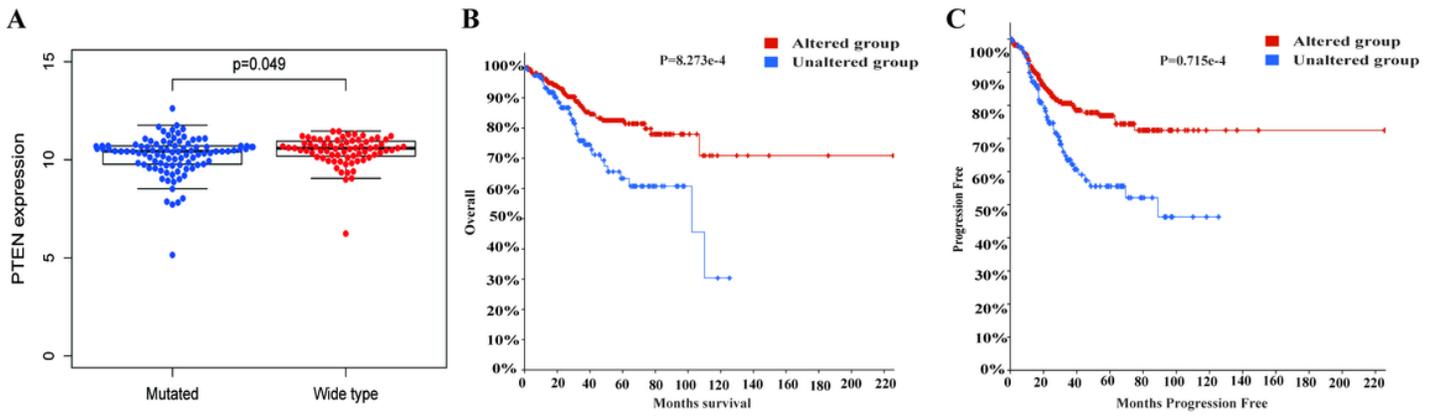


Figure 2

Relationship between PTEN mutation and prognosis of EC. (A) Correlation between PTEN mRNA expression and mutation, (B) Kaplan-Meier survival curves were stratified by the PTEN mutation for EC patients, (C) Progression free curves for EC stratified by the PTEN mutation.

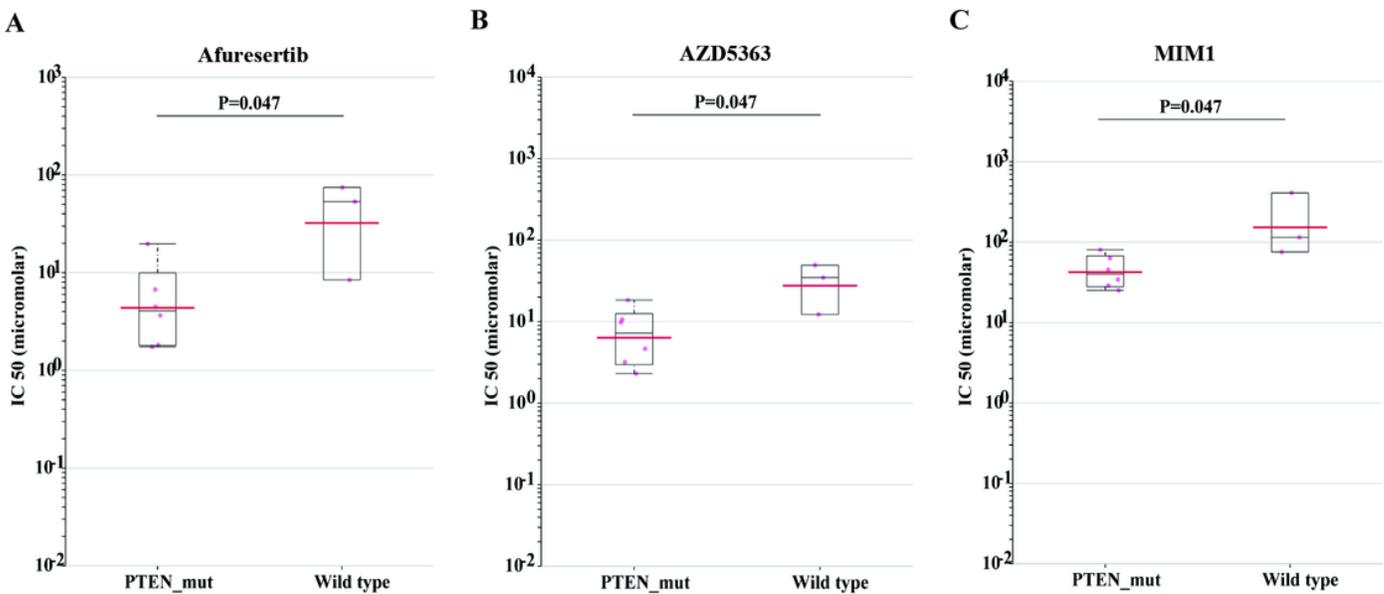


Figure 3

Drugs sensitive to cell lines with PTEN mutation. (A) Afuresertib, (B) AZD5363, (C) MIM1.

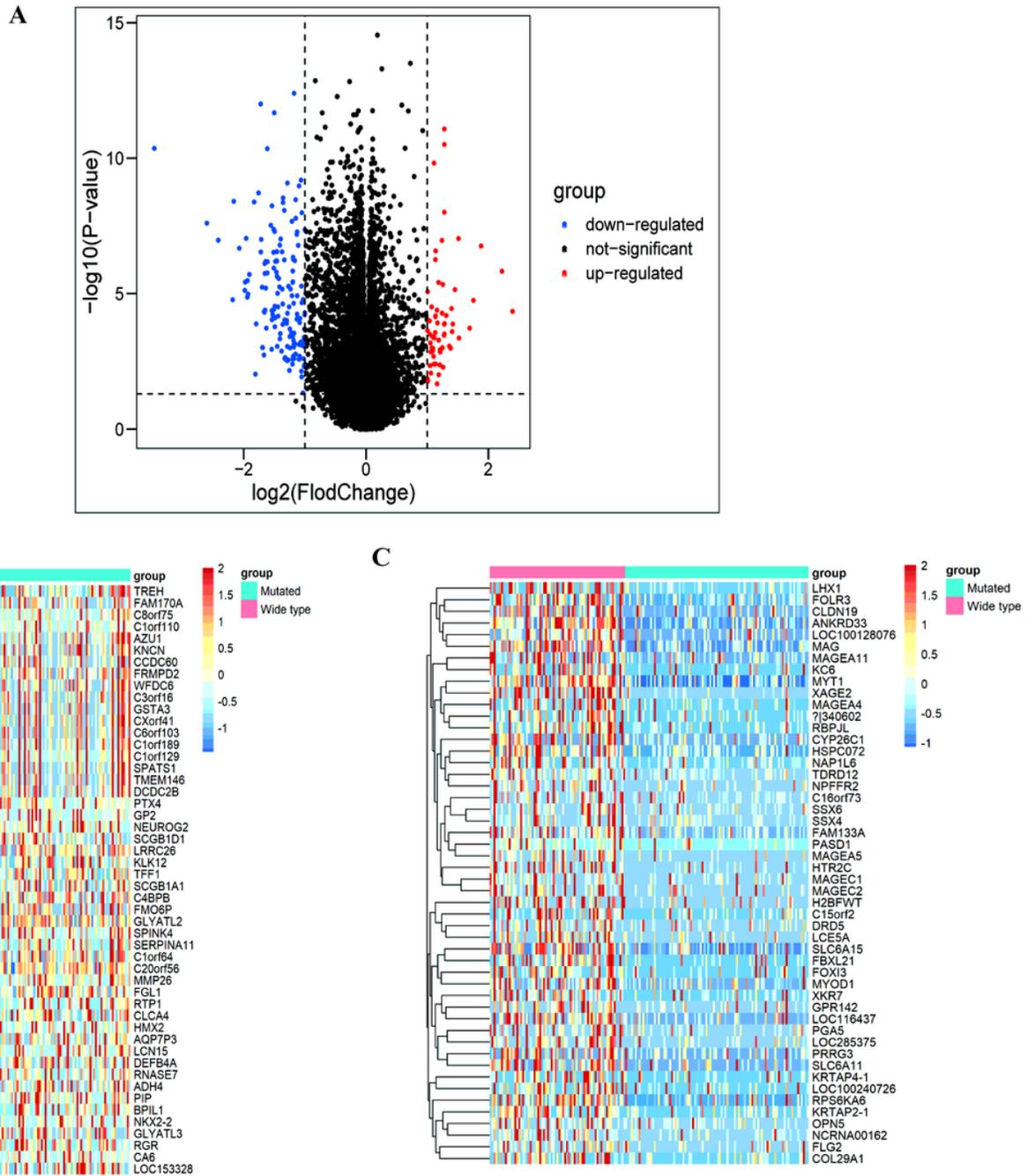


Figure 4

Differences analysis between wide type and PTEN mutation in EC patients. (A) Volcano plot for DEGs, (B) Top 50 upregulated genes, (C) Top 50 downregulated genes.

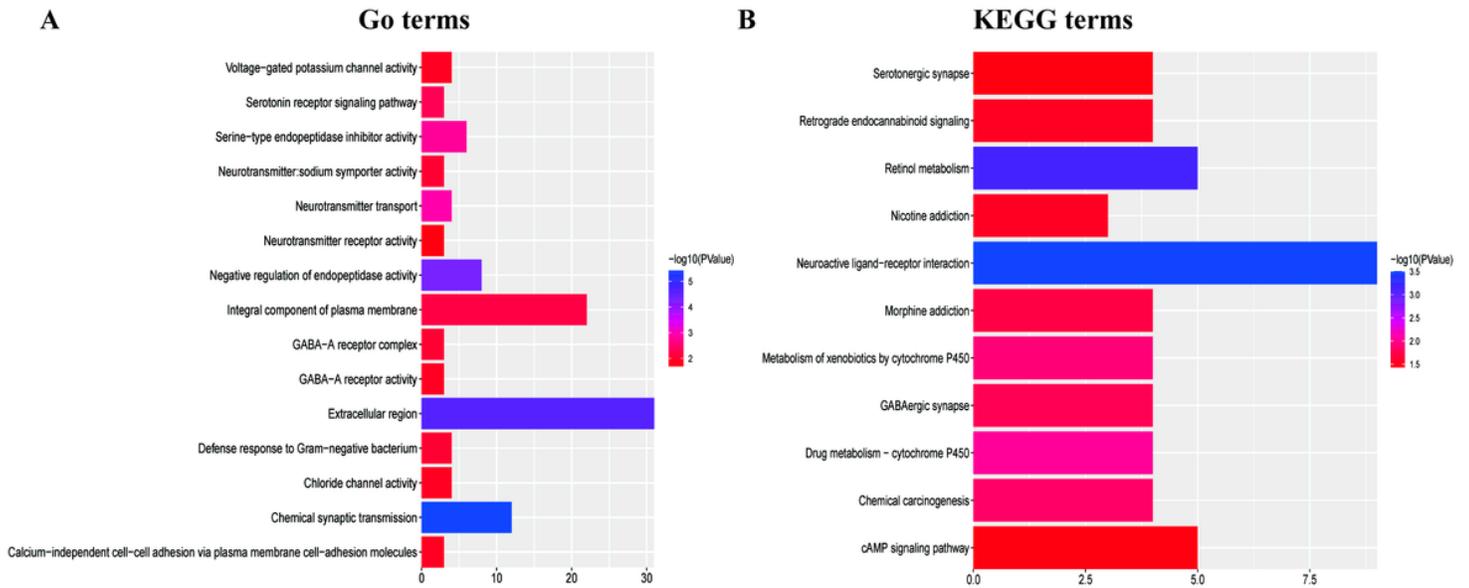


Figure 5

DAVID enrichment of DEGs. (A) The GO term of DEGs, (B) The KEGG term of DEGs.

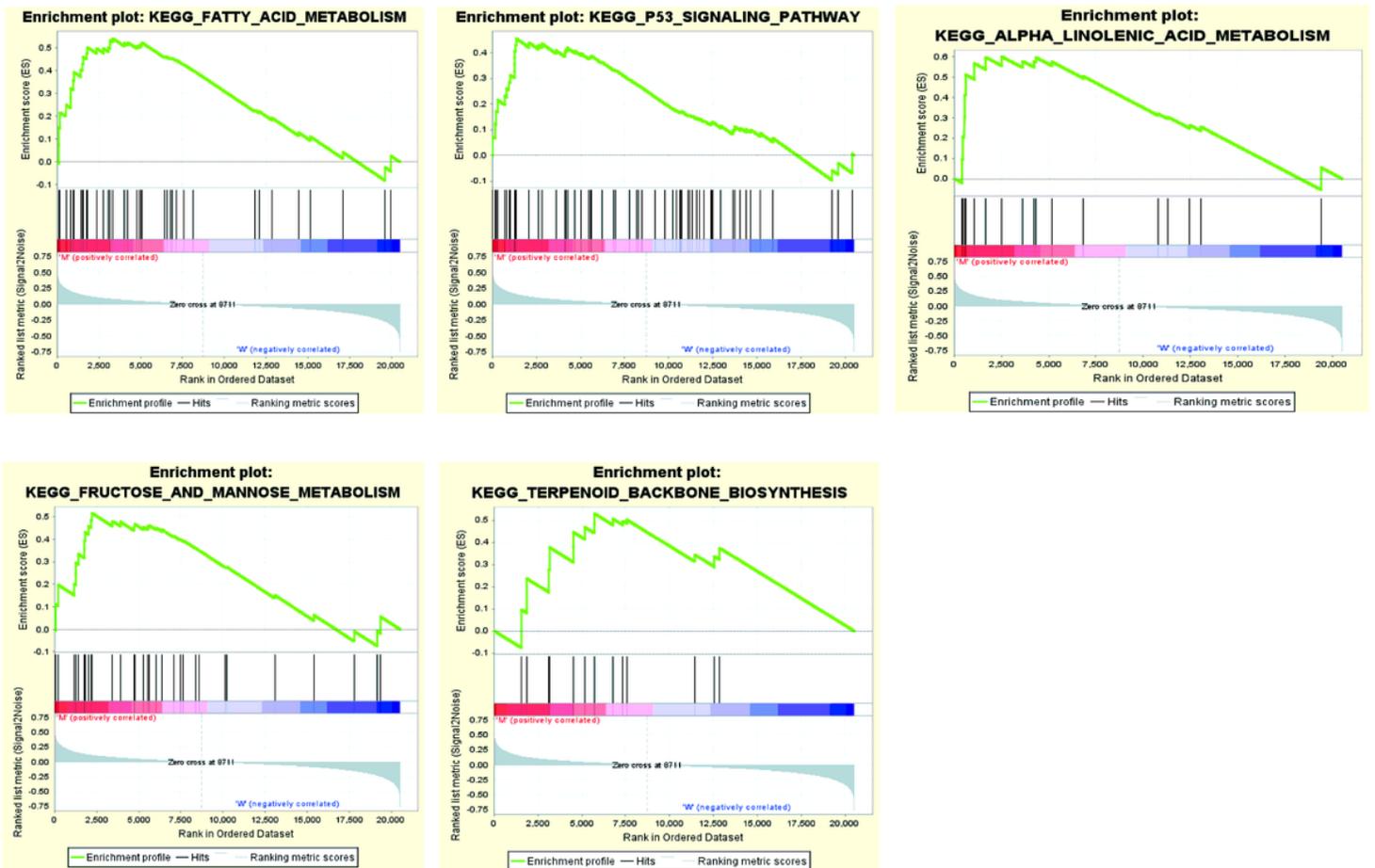


Figure 6

GSEA results of the PTEN mutation in EC patients.

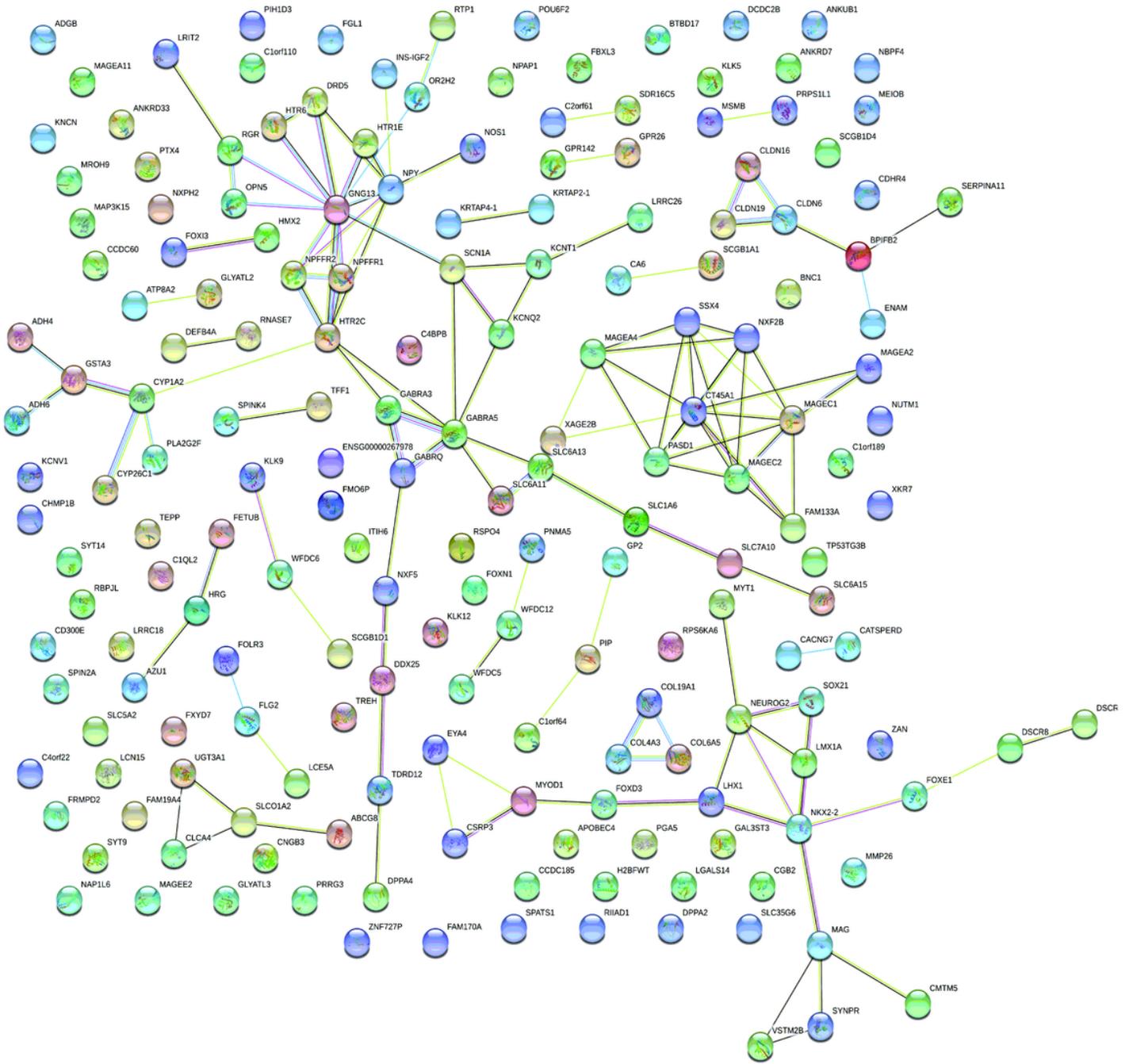


Figure 7

PPI networks show the interaction of DEGs. Nodes and edges are retrieved from the STRING website.

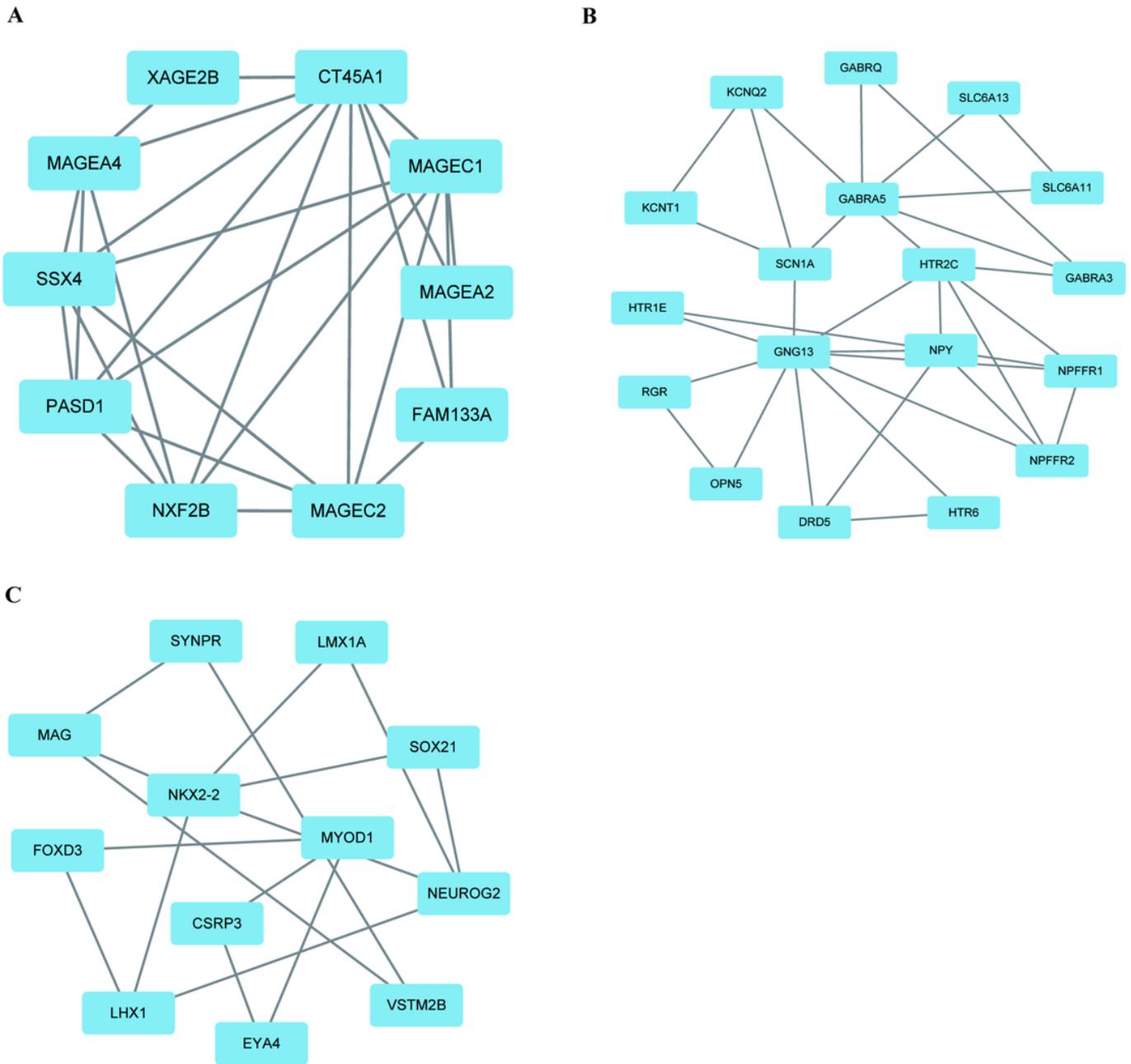


Figure 8

Top three clusters in the PPI network.