Identification and characterization of biomarkers and their functions for docetaxel-resistant prostate cancer cells

LEIHONG DENG1, XIAOPENG GU2, TAO ZENG3, FANGHUA XU4, ZHIFENG DONG1, CHAO LIU1 and HAICHAO CHAO5

1Medical Department of The Graduate School, Nanchang University, Nanchang, Jiangxi 33006; 2Department of Orthopedics, Zhoushan Guhechuan Hospital, Zhoushan, Zhejiang 316000; 3Department of Urology, 4Pathology Department, 5Laboratory of Clinical Medicine, Jiangxi Provincial People's Hospital Affiliated to Nanchang University, Nanchang, Jiangxi 330006, P.R. China

Received November 3, 2018; Accepted June 13, 2019

DOI: 10.3892/ol.2019.10623

Abstract. Docetaxel treatment is a standard chemotherapy strategy for castration-resistant prostate cancer (CRPC), and patients with CRPC eventually develop resistance to treatment. However, little is understood regarding the underlying mechanism of resistance. The present study aimed to identify the underlying crucial genes and regulatory networks associated with docetaxel resistance in prostate cancer using bioinformatics analyses. For this purpose, one expression profile dataset (GSE33455), which included two docetaxel-sensitive and two docetaxel-resistant cell lines, was downloaded from the Gene Expression Omnibus database, and analyses of differential gene expression and function enrichment were performed. A protein-protein interaction (PPI) network was constructed, and the associated hub genes were investigated using the Search Tool for the Retrieval of Interacting Genes/Proteins and Cytoscape software. A total of 756 differentially expression genes (DEGs) were identified, including 509 downregulated and 247 upregulated genes. Enrichment analysis revealed that the DEGs were associated with the interferon-γ-mediated signaling pathway, protein binding, bicellular tight junctions and cancer pathways. Two modules were screened from the PPI network, and the corresponding genes were identified to be largely enriched in the interferon-γ-mediated signaling pathway and the negative regulators of the DExD/H-Box helicase 58/interferon induced with helicase C domain 1 signaling pathway, and enriched in cell-cell adhesion and the Rap1 signaling pathway. Among the ten hub genes, epidermal growth factor receptor, spleen tyrosine kinase (SYK), intracellular adhesion molecule 1 (ICAM1), interleukin (IL)6, CXC motif chemokine ligand 8 (CXCL8), cyclin dependent kinase 1 and CD44 molecule (CD44) were significantly differentially expressed in prostate cancer tissues compared with healthy tissues based on The Cancer Genome Atlas data. The Gene Expression Profiling Interactive Analysis database revealed that ICAM1 was positively associated with IL6 and CXCL8, and epidermal growth factor receptor was positively associated with CD44 and SYK. Additionally, ten hub genes, which were identified to be associated with the drug resistance of docetaxel in prostatic carcinoma in the present study, were predominantly associated with tumor progression and metastasis. Reverse transcription-quantitative PCR analysis performed on docetaxel-sensitive and docetaxel-resistant prostate cancer cell lines demonstrated that certain hub genes, including CDK1, 2'-5'-oligoadenylate synthetase 3, CXCL8 and CDH1, were highly expressed in the docetaxel-resistant cell lines, which confirmed the bioinformatics results. In conclusion, the present study identified a number of important genes that are associated with the molecular mechanism of docetaxel resistance by integrated bioinformatical analysis, and these genes and regulatory networks may assist with identifying potential gene therapy targets for CRPC. Further functional analyses are required to validate the current findings.

Introduction

Prostate cancer (PCa), which exhibits complicated pathogenesis and treatment difficulties, is the most common malignancy of the male reproductive system worldwide, accounting for ~29,430 deaths in the USA in 2018 (1). PCa is a global public issue that threatens human health and life, with increasing morbidity and mortality rates each year (2). Metastatic PCa is commonly treated with androgen deprivation therapy; however, resistance can still develop quickly, which leads to castration-resistant PCa (CRPC) (3). Docetaxel is widely used as the standard first-line chemotherapy treatment for patients with CRPC (3). The majority of patients with CRPC who receive docetaxel chemotherapy develop resistance to this treatment. Additionally, with increasing treatment times and doses, complications may occur (4). Therefore, further
investigation regarding the mechanism of docetaxel-resistant PCa may improve the prognosis of patients with PCa.

Although the mechanism underlying PCa drug resistance has been extensively studied, its cause and pathogenesis remain poorly understood. The current consensus is that the mechanism of docetaxel-resistant PCa is associated with multiple factors, including androgen receptor splice variant expression (5), changes in the expression of β-tubulin (6), multidrug resistance induced by abnormal expression of the ATP binding cassette (ABC) transporter family and abnormal expression of signaling pathway factors (7), including the PI3K/AKT/mTOR (8), Wnt (9) and NF-kB/interleukin (IL)6 pathways (10). Additionally, abnormal expression levels of EMT and stem-like cell markers have been detected in PCa cells resistant to docetaxel, which lead to a downregulation of cadherin 1 (CDH1) and an upregulation of vimentin, zinc finger E-box binding homeobox 1 and the stem-like cell marker CD44 molecule (CD44) (11). Taken together, these studies suggest that docetaxel resistance in PCa occurs due to alterations in numerous factors and/or genetic changes, rather than a single factor. Although these basic and clinical studies have investigated the resistance of docetaxel in PCa in the past few decades with the aim of revealing the potential underlying mechanisms, the effect of treatment remains unsatisfactory (5-11). Therefore, understanding the precise molecular mechanisms associated with the development of docetaxel resistance in PCa is essential for the improvement of effective diagnosis and treatment strategies. Microarray technologies, which have widely been used to investigate large scale gene expression simultaneously, presents an effective method to investigate the expression of tens of thousands of genes and identify the mechanisms of numerous diseases, particularly cancers. The integration and analysis of microarray data provide valuable information for the study of docetaxel resistance (12).

In this present study, the GSE33455 microarray dataset (13), which includes two docetaxel-sensitive and two docetaxel-resistant cell lines, was downloaded from the Gene Expression Omnibus (GEO) database, and differentially expressed genes (DEGs) between the two types of PCa cell lines were identified. Functional enrichment analyses and functional annotation were performed and a protein-protein interaction (PPI) network was constructed and analyzed to indicate a statistically significant result.

**Materials and methods**

**Data collection.** The microarray expression profile dataset GSE33455 (13) was downloaded from the GEO database (http://www.ncbi.nlm.nih.gov/geo), which is based on the GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array. The dataset contained 12 sets of data from four cell lines, including PCa cell lines DU-145 (docetaxel-sensitive), PC-3 (docetaxel-sensitive), DU-145R (docetaxel-resistant) and PC-3R (docetaxel-resistant).

**Analysis of DEGs.** The original expression data underwent background correction and quartile data normalization and was converted into gene expression measures using the robust multi-array average (14) in the R Affy package (release 3.9; http://www.bioconductor.org/packages/release/html/affy.html). The DEGs between docetaxel-sensitive and docetaxel-resistant samples were analyzed using the limma package (15) in Bioconductor (http://www.bioconductor.org), and a DEG was considered to be significant according to the following criteria: \( \log_{10}\text{fold-change (FC)}} > 2\) and false discovery rate (FDR) <0.05. Subsequently, a heatmap was constructed and the DEGs were identified using the pheatmap package of R software (16).

**Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses.** GO is a tool used to annotate genes, collect and analyze information according to cellular component (CC), biological process (BP) and molecular function (MF) terms following the criteria \( P < 0.05 \) (17). KEGG is an online database and analysis tool for integrating and interpreting large molecular datasets (18). Database for Annotation, Visualization and Integrated Discovery (DAVID; https://david.ncifcrf.gov) is a website composed of a comprehensive biological database and analysis tools that assist with the understanding of the biological meaning of gene lists (19). In the present study, DAVID and Metascape (https://metascape.org) were used for GO and KEGG pathway enrichment analyses of the DEGs. FDR<0.05 was considered to indicate a statistically significant result.

**Analysis of the PPI network.** The STRING database is an online biological database that collects comprehensive information on proteins to evaluate the PPI information (20). In the current study, significant gene pairs of the PPI network were visually represented using Cytoscape; a combined score >0.4 was considered as significant and the strength of an interaction was modelled by the number of lines (21). Cytoscape is a bioinformatics software used to perform computational analysis of cellular networks and merge experimental omics datasets together (22). The hub genes were selected using the CytoHubba network analyzer plug-in (23). In addition, analysis of the most important module was performed using the MCODE plug-in for Cytoscape. Subsequently, Metascape (http://metascape.org/gp/index.html) software was used for functional enrichment analysis of the module genes.

**Analysis of hub gene expression levels.** RNA-sequencing data of 497 PCa and 52 adjacent normal tissue samples were downloaded from The Cancer Genome Atlas (TCGA) database (https://cancergenome.nih.gov/) to examine the expression levels of the hub genes. Gene Expression Profiling Interactive Analysis (GEPIA; http://geopia2.cancer-pku.cn/#index, accessed on May 4th, 2019) is a newly developed interactive web server for analyzing the RNA-sequencing expression data of 9,736 tumor samples and 8,587 normal samples from TCGA and GTEx projects using a standard processing pipeline. GEPIA provides customizable functions, including tumor/normal differential expression analysis,
profiling according to cancer types or pathological stages, patient survival analysis, similar gene detection and correlation analysis (24). The present study used GEPIA to analyze the associations between the identified hub genes. GEPIA uses the non-log scale for calculation and uses the log-scale axis for visualization. This function of GEPIA performs pairwise gene expression correlation analysis for given sets of TCGA and/or GTEx expression data using a variety of methods, including Pearson, Spearman and Kendall analyses.

Cell lines. The human PCa cell lines DU-145 and PC-3, purchased from the Type Culture Collection of the Chinese Academy of Sciences were maintained in MEM (Gibco; Thermo Fisher Scientific, Inc.) or F12K (Gibco; Thermo Fisher Scientific, Inc.), respectively. The media were supplemented with 10% fetal calf serum (Gibco; Thermo Fisher Scientific, Inc.). The DU-145R and PC-3R cell lines were developed by docetaxel dose escalation, as previously described (25). Cells were cultured at 37°C in a 5% CO2 incubator.

RNA extraction and reverse transcription-quantitative PCR. Total RNA was extracted from cells using TRizol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.) and reverse transcribed into cDNA templates using PrimeScript® RT Reagent kit (Takara Biotechnology Co., Ltd.) according to the manufacturer's instructions. The mRNA expression levels were evaluated using SYBR® Green Master Mix (Takara biotechnology Co., Ltd) and a CFX96 PCR machine (Bio-Rad Laboratories, Inc.). The thermocycling conditions were as follows: 10 min at 95°C, 40 cycles of 15 sec at 95°C and 60 sec at 60°C, followed by 1 h at 4°C. β-actin was used as an internal reference for normalization. Compared with the control, the fold change in mRNA levels was calculated using the 2^ΔΔCq method (26). The specific PCR primers for the hub genes and β-actin as the housekeeping gene were designed with Primer Express version 2.0 (Applied Biosystems, Carlsbad, CA, USA) and are presented in the Table SI.

Statistical analysis. The PCR data were presented as the mean ± standard deviation and analyzed using SPSS 19.0 statistical software (IBM Corp.). Differences between the two types of PCa cell lines were analyzed using Student’s t-test. P<0.05 was considered to indicate a statistically significant difference.

Results

Identification of DEGs. The gene expression dataset GSE33455 was downloaded from the GEO database and included data for two docetaxel-sensitive PCa cell lines and two docetaxel-resistant PCa cell lines. Following differential expression analysis, 756 DEGs were identified between docetaxel-sensitive and docetaxel-resistant PCa, including 247 upregulated and 509 downregulated genes. A heatmap was constructed using the top 100 DEGs based on their FC (Fig. 1).

GO and pathway enrichment analyses. The biological functions of all identified DEGs were evaluated by GO and pathway enrichment analyses, which were performed using DAVID and Metascape. In the enrichment analysis of BPs, the DEGs were significantly enriched in ‘type I interferon signaling pathway’, ‘interferon-gamma-mediated signaling pathway’, ‘epidermis development’, ‘defense response to virus’ and ‘transforming growth factor beta receptor signaling pathway’ (Fig. 2A). In the MF analysis, the DEGs were significantly enriched in ‘protein binding’, ‘identical protein binding’, ‘cadherin binding involved in cell-cell adhesion’ and ‘actin binding’ (Fig. 2B). In the CC analysis, the DEGs were predominantly enriched in ‘bicellular tight junction’, ‘cytosol’, ‘extracellular exosome’ and ‘receptor complex’ (Fig. 2C). The top five GO terms of the DEGs are presented in Tables SII and SIII.

KEGG pathway analysis indicated that the DEGs were significantly enriched in ‘metabolic pathways’, ‘pathways in cancer’, ‘PI3K-Akt signaling pathway’ and other significant signaling pathways with the highest gene numbers (P<0.05; Table SIV; Fig. 3). The majority of these pathways are closely associated with the occurrence and progression of tumors.

PPI network analysis and module selection. The PPI network of the DEGs was constructed using the STRING online database and consisted of 324 nodes and 1,087 edges (Fig. 4A). The results were then transferred to Cytoscape software to analyze the interactions between the candidate DEGs in PCa. The Cytoscape cytoHubba Network Analyzer plug-in selected ten hub genes from the PPI network by identifying the top ten nodes ranked by degree. To investigate the significant modules in this PPI network, two significant modules were obtained by Cytotyper MCODE, with enrichment scores of 11.053 and 5.3, respectively, and all of the MCODE scores for the two significant modules were >5. The results of functional enrichment analysis indicated that module one consisted of 18 nodes and 105 edges (Fig. 4B), which were predominantly enriched in the ‘defense response to virus’, ‘interferon-gamma-mediated signaling pathway’ and ‘negative regulators of DDX58/IFIH1 signaling’ (Table I). Module two consisted of 19 nodes and 53 edges (Fig. 4C), which were predominantly associated with the ‘regulation of peptidyl-tyrosine phosphorylation’, ‘DNA replication’, ‘cell-cell adhesion’ and the ‘Rap1 signaling pathway’ (Table II).

The top ten DEGs with high degrees of connectivity were considered as the hub genes of resistant PCa, and a degree >28 was identified as the central node degree used to determine hub genes as the degree of the tenth gene was 29. These hub genes, ranked by node degree, including intercellular adhesion molecule 1 (ICAM1), Spleen-associated tyrosine kinase SYK, Cyclin-dependent kinase 1 (CDK1), 2′-5′-oligoadénylate synthetase-like (OASL), 2′-5′-oligoadénylate synthetase 3 (OAS3), CXC motif chemokine ligand 8 (CXCL8), CD44, CDH1, epidermal growth factor receptor (EGFR) and IL6, were identified as the key candidate genes, which may play crucial roles in cancer drug resistance (Fig. 4D). The degrees and functions of the top ten hub genes in the PPI network are presented in Table III, and these genes/proteins may be associated with the docetaxel resistance of PCa.

Hub gene validation using TCGA database. To validate the hub genes, the expression levels of the hub genes were analyzed using data from TCGA database. The results indicated that the expression levels of ICAM1 and CDK1 were significantly higher in PCa tissues compared with normal
tissues (Fig. 5A and C), whereas the expression levels of SYK, CXCL8, CD44, EGFR and IL6 were lower in PCa tissues compared with normal tissues (Fig. 5B, F, G, I and J).

However, there was no significant difference in the expression levels of OASL, OAS3 and CDH1 between PCa tissues and normal tissues (Fig. 5D, E and H).
Correlations among the expression of the ten hub genes. As significant differences were identified in the expression levels of EGFR, SYK, ICAM1 and CD44 in PCa compared with adjacent normal tissues, the GEPIA database was used in the present study to analyze the correlations among these genes. The results revealed that ICAM1 may be associated with IL6 and CXCL8. ICAM1 and CXCL8 were positively correlated (P<0.001; R=0.88), and ICAM1 and IL6 were positively correlated (P<0.001; R=0.52) (Fig. 6A and B). EGFR and CD44 were positively correlated (P<0.001; R=0.46), and EGFR and SYK were positively correlated (P<0.001; R=0.36) (Fig. 6D and E).

Expression of the hub genes in docetaxel-sensitive and docetaxel-resistant cell lines. To further validate the potential role of the hub genes in docetaxel-resistant PCa, their expressions in docetaxel-sensitive and docetaxel-resistant PCa cell lines were investigated by RT-qPCR, which demonstrated that the relative expression levels of ICAM1, CDK1, OAS3, CXCL8

Figure 2. Gene Ontology enrichment analysis of the differentially expressed genes. (A-C) The numbers of enriched genes according to the (A) biological process, (B) molecular function and (C) cellular component categories.
and CDH1 in DU-145 cells were significantly lower compared with those in DU-145R cells (Fig. 7A), whereas CDK1, OAS2, OAS3, CXCL8, CDH1 and IL6 expression levels in PC-3 cells were lower compared with those in PC-3R cells (Fig. 7B).

Discussion

In the present study, 756 DEGs were identified between two docetaxel-sensitive prostate cell lines and two docetaxel-resistant prostate cell lines by analysis of the GSE33455 dataset. The DEGs included 247 upregulated genes and 509 downregulated genes. The interactions among these DEGs were investigated with KEGG and GO enrichment analyses; the DEGs were predominantly enriched in the ‘interferon-gamma-mediated signaling pathway’ in the BP category. In addition, other notable enriched terms included ‘bicellular tight junction assembly’, ‘cell-cell adhesion’ and the ‘transforming growth factor beta receptor signaling pathway’, all of which are closely associated with tumor metastasis and drug resistance. In the MF category, the DEGs were associated with ‘protein binding’, ‘identical protein binding’, ‘cadherin binding involved in cell-cell adhesion’, ‘actin binding’ and ‘GTPase activity’; these data suggested that the DEGs may affect the binding of proteins, cadherin, actin and GTPase activity. In the CC category, the DEGs were mainly enriched in the ‘bicellular tight junction’, ‘cytosol’, ‘extracellular exosome’ and ‘receptor complex’; these data indicated that the DEGs were mainly involved in substance transfer and transport in the cytoplasm of cells.

According to the KEGG analysis, the DEGs were mainly enriched in ‘pathways in cancer’, ‘metabolic pathways’, the ‘PI3K-Akt signaling pathway’, the ‘Jak-STAT signaling pathway’, ‘proteoglycans in cancer’ and the ‘NF-κB signaling pathway’. Chen et al. (8) have demonstrated that upregulated inositol polyphosphate-4-phosphatase type II B induces apoptosis and enhances sensitivity to docetaxel via the PI3K/Akt signaling pathway in PC3-DR and DU-145-DR cells. NF-κB signaling serves a crucial role in regulating invasion, metastasis, proliferation, angiogenesis and drug resistance in tumor cells. A previous study reported that the NF-κB pathway may be a potential target for combination therapy during the advanced stages of thyroid cancer (27). In addition, NF-κB, pAkt, macrophage inhibitory cytokine-1 and EGFR, which are significantly overexpressed in PCa samples, induce caspase-dependent apoptosis and increase the sensitivity of cytotoxic effects caused by docetaxel in chemo-resistant SP WPE1-NB26 cells (28). This indicates the crucial roles of the
PI3K/Akt and NF-κB signaling pathways in PCa resistance to docetaxel.

In the present study, a PPI network was constructed using the DEGs with 324 nodes and 1,087 edges, and two notable...
modules termed module one and module two were obtained. Module one comprised 18 genes, including interferon induced protein 35, phospholipid scramblase 1, guanylate binding protein 1 and ubiquitin conjugating enzyme E2 L6, which were enriched in ‘defense response to virus’, ‘interferon-gamma-mediated signaling pathway’ and ‘negative regulators of DDX58/IFIH1 signaling’. These enrichments result in the interaction of multiple signal transduction pathways in effector cells and the expression of associated stimulatory genes, which have many biological functions, including...
antivirus, antitumor and immune regulatory functions (29). Module two consisted of 19 genes, including CDK1, cyclin B1, meiotic nuclear divisions 1, DNA primase subunit 1, checkpoint kinase 1, colony stimulating factor 2 and CDH1, which were mainly associated with ‘regulation of peptidyl-tyrosine phosphorylation’, ‘DNA replication’, ‘cell-cell adhesion’ and the ‘Rap1 signaling pathway’. It has been reported that these enrichment results are mainly involved in the processes of tumor adhesion, invasion, metastasis and drug resistance (30). The top ten DEGs with a degree of connectivity $>28$ were considered as the hub genes, including ICAM1, SYK, CDK1, OASL, OAS3, CXCL8, CD44, CDH1, EGFR and IL6, which may serve critical roles in docetaxel-resistance in PCa. Analysis using data from TCGA database demonstrated that the expression levels of ICAM1 and CDK1 were significantly higher in PCa tissues compared with normal tissues, whereas the expression levels of SYK, CXCL8, CD44, EGFR and IL6 were significantly lower. Tumor cells promote growth by avoiding or preventing the immune response (31). Therefore, it can be hypothesized that ICAM-1, a co-stimulatory molecule, may promote tumor survival by signaling to natural killer cells and cytotoxic T lymphocytes (32). Several studies have demonstrated that CXCL8 is associated with the migration and proliferation of various types of cancer cells, including PCa cells (33,34). CXCL8 promotes the proliferation and progression of cancer cells and increases the resistance to cytotoxic drugs in androgen-independent PCa by upregulating the expression of survival factors, which promotes the growth and development of tumors (35).

Correlation analysis of the hub genes identified in the present study revealed that the expression levels of ICAM1 and CXCL8 were positively correlated ($P<0.01$, $R=0.88$), suggesting that ICAM1 may serve an important role in docetaxel-resistance in PCa. Ghotra et al (36) demonstrated that the protein tyrosine kinase SYK may be a new therapeutic target for advanced PCa as it stimulates the growth and migration of PCa cells. CDK1 is essential for cell viability as it serves important roles in numerous biological events, including activating checkpoint proteins, repairing DNA damage and regulating the cell cycle (37). A previous study has indicated that abnormal activation of CDK1 promotes the proliferation and survival of PCa cells by phosphorylating and suppressing FOXO1 (38). Previous studies have demonstrated that 2′-5′-oligoadenylate synthetase (OAS) is induced by interferons when infected by viruses, as OAS-like (OASL) has a regulatory function in antiviral innate immunity via interferon signaling; the genetic variation of OAS may increase the risk of chronic lymphocytic leukemia (39,40). CD44 performs versatile functions as a cell membrane receptor, including cell adhesion, invasion and metastasis in tumor cells (41). CD44 has also been identified on cancer-initiating cells and stem cells (42). CD44 performs a tumor-promoter function by mediating the invasion, proliferation and migration of PCa PC-3 cells; inhibition of CD44 decreases the glucose consumption and increase the sensitivity to docetaxel of PC-3 cells. This suggests that CD44 exhibits a regulatory effect on the progression and drug resistance of PCa cells (43). Furthermore, Jiang et al (44) reported that a mutation of the CDH1 gene is associated with metastasis and invasion in numerous types of cancer, as it changes the transcriptional activity of epithelial cells. Epigenetic loss of CDH1 is associated with multidrug resistance in human hepatocellular carcinoma cells (44). Additionally, EGFR has been demonstrated to be a driver of tumorigenesis by promoting the proliferation and development of a number of different cancer types (45). Hour et al (46) have demonstrated a positive correlation between EGFR expression and resistance to docetaxel, which was mediated by EGFR via the Akt/ABCBI
pathway in PCa cells, and an increased susceptibility to docetaxel-based treatment while dealt with EGFR inhibition. These findings indicate that EGFR serves a crucial role in docetaxel-resistant PCa. IL6, an inflammatory factor associated with inflammation-driven cancer, performs an important role in the resistance to EGFR drugs. A recent study suggested that co-targeting EGFR and IL6 may exhibit potential as a new cancer treatment, as crosstalk between the EGFR and IL6 signaling pathways contributes to drug resistance (47). The present study demonstrated positive correlations between EGFR and CD44 and between EGFR and SYK expression levels.

In summary, a total of 756 DEGs and ten hub genes were identified in the current study. Bioinformatics analysis demonstrated that ICAM1, CXCL8, CD44, SYK, EGFR and IL6 were upregulated in the docetaxel-resistant PCa cell lines, and RT-qPCR analysis confirmed that a number of the hub genes, including CHK1, OAS3, CXCL8 and CDH1, were highly expressed in the docetaxel-resistant cell lines; these data suggested that these genes may be the core genes involved in
the mechanism of docetaxel resistance in PCa. The data from the present study suggested that these genes may be closely associated with carcinogenesis, progression, prognosis and drug resistance of PCa.

In conclusion, the present preliminary study revealed several hub genes associated with docetaxel resistance by comprehensive bioinformatics analysis, which may assist with improving the understanding of the underlying molecular mechanisms of docetaxel resistance. Combined targeted therapy of multiple genes and pathways is of great significance to investigate the mechanism of docetaxel-resistance. However, a limitation of the present study is that only a single platform based on docetaxel sensitivity and docetaxel resistance in PCa was analyzed. Furthermore, the current study was focused on
bioinformatics and the results only verified by RT-qPCR in cell lines; therefore, the conclusion remains to be confirmed by in vivo experiments. Studies involving experiments and larger sample sizes are required to further confirm the present results in the future.

Acknowledgements

Not applicable.

Funding

The present study was funded by the Project of Youth Science Foundation of Jiangxi Science and Technology Office (grant no. 20171BAB215015).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LD and XG contributed to the study design, data acquisition and analysis and drafted the manuscript. HC participated in the study design, data acquisition and revision of the manuscript. TZ, FX, ZD and CL assisted in the performance of the study design, data acquisition and analysis and drafted the manuscript. HC participated in the study design, data acquisition and analysis and drafted the manuscript. TZ, FX, ZD and CL assisted in the performance of the study design, data acquisition and analysis and drafted the manuscript. HC participated in LD and XG contributed to the study design, data acquisition and analysis and drafted the manuscript. HC participated in the study design, data acquisition and revision of the manuscript. TZ, FX, ZD and CL assisted in the performance of the statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References


39. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.