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Identification of prognosis biomarkers of prostatic cancer in a cohort of 498 patients from TCGA

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ABSTRACT

Objective: Prostatic cancer (PCa) is the first common cancer in male, and the prognostic variables are beneficial for clinical trial design and treatment strategies for PCa. This study was performed to identify more potential biomarkers for the prognosis of patients with PCa.

Methods and results: The transcriptome data and survival information of a cohort including 498 subjects with PCa were downloaded from TCGA. A total of 4293 differentially expressed genes (DEGs), including 1362 prognosis-related DEGs, were identified in PCa tissues compared with normal tissues. Upregulated genes, including serine/arginine-rich splicing factors (SRSFs; such as *SRSF2, SRSF5, SRSF7* and *SRSF8*), and ubiquitin conjugating enzyme E2 (UBE2) members (such as *UBE2D2, UBE2G2, UBE2J1* and *UBE2E1*), were identified as negative prognostic biomarkers of PCa, as the high expression of them correlated with poor overall survival of PCa patients. Several downregulated Golgi-ER traffic mediators (such as *SEC31A, TMED2,* and *TMED10*) were identified as positive prognostic biomarkers of PCa, as the high expression of them correlated with good overall survival of PCa patients.

Conclusions: These genes were of great interests in prognosis of PCa, and some of them may be constructive for the augmentation of clinical trial design and treatment strategies for PCa.

ARTICLE INFO

Keywords: Prostatic cancer; Prognosis; Biomarkers; TCGA

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Introduction

Prostatic cancer (PCa), the first common cancer in men, is the third cause of cancer-related death. The lethal metastasis of PCa is the dominant factor of PCa-related death,[1] especially in the 10% patients with metastatic castration resistance PCa, the 5-year mortality of it is over 80%.[1,2]

There were numerous and increasing variables including mRNAs and noncoding RNAs (lncRNAs and miRNAs) have been identified to be as potent clinical biomarkers for the diagnosis, prognosis, and therapeutic targets of PCa. Prostate-specific antigen (PSA) is the only widely used circulating biomarker for PCa,[3,4] and the diagnosis of PCa at early stage increased to over 80% due to the usage of PSA biomarker.[5,6] Another 2 PCa specific biomarker are prostate cancer antigen 3 (PCA3) and fusion transcript of v-ets erythroblastosis virus E26 oncogene homolog (ERG, also known as TMPRSS2-ERG) gene, which are recently identified in urine.[4,7-9] Of these aforementioned biomarkers, TMPRSS2-ERG showed prognostic value.[4]

Given the fact that diagnostic biomarkers guarantee the diagnosis of human cancer at early stage, both prognostic and diagnostic biomarkers augment clinical trial designs and treatment strategies for cancer. For instance, the interleukin 10 (IL-10) concentration in cerebrospinal fluid is an effective diagnostic biomarker of diffuse B-cell primary central nervous system lymphoma (PCNSL), and a potent prognostic biomarker for negative impact of treatment on PCNSL patients' survival.[10] Sun et al showed that the high expression of phosphoglycerate kinase-1 (PGK1), a potent biomarker in pancreatic cancer,[11] in breast cancer was related with higher histologic grade and worse overall survival in patients underwent paclitaxel chemotherapy,[12] suggesting a requirement of a specific clinic trial for patients with PGK1 positive breast cancer. The prospective elucidation of variables correlated with the survival outcomes of patient with PCa may be constructive for the augmentation of clinical trial design and treatment strategies for PCa.

To identify more and potential biomarkers for the prognosis of PCa patients, we performed this bioinformatics study using a cohort of 498 PCa subjects with survival information in TCGA. The potential prognostic biomarkers were identified, the prognostic values and molecular mechanism in disease progression would be elucidated. These biomarkers may shed lights on the clinical trial design and prognosis assessment.

Materials and methods

TCGA data

Transcriptome data of TCGA drostate adenocarcinoma (PRAD) cohort (including 498 PCa tumor samples and 52 normal adjacent tissues, with available survival information) were downloaded from TCGA data portal in UCSC Xena database (https://xenabrowser.net/datapages/) in October, 2018. The protein coding genes in human genome was filtered with annotation in Gencode database (v25, https://www.gencodegenes.org/),[13] and the mRNA matrix was obtained and used for further analysis.

Identification of significantly altered genes

The differentially expressed genes (DEGs) in PCa samples in confront of the normal tissues were identified using the R LIMMA package (v3.10.3; http://www.bioconductor.org/packages/2.9/bioc/html/limma.html).[14] Altered genes with adjust.P.value < 0.05 were regarded as DEGs in current study. Clustering analysis of these DEGs were conducted using pheatmap in R.[15] The overall survival analysis of DEG expression was performed using survival analysis in R package (v2.42-6; https://cran.r-project.org/web/packages/survival/index.html)[16] with extracted information of survival from TCGA. The median expression value of each gene was set as threshold for low and high expression. P value of log-rank test < 0.05 was considered as significantly

different. DEGs significantly correlated with survival of patients with PCa were screened as prognosis-related genes and were used for further analysis.

Enrichment analysis for PCa prognosis-related genes

To examine the molecular functions of PCa prognosis-associated DEGs, we identified the DEG-related Gene Ontology (GO) biological processes (BP) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. The GO-BP terms and KEGG pathways significantly related to prognosis-related DEGs were identified from DAVID tool (v6.8; https://david-d.ncifcrf.gov/). Pathways involved at least 2 genes with $P < 0.05$ were selected.

Protein-protein interaction (PPI) network analysis for prognosis-related genes

To identify DEGs with high potential positions in PCa prognosis, we acquired and constructed the PPI network for all prognosis-related DEGs with interviewing STRING database (v10.0; http://string-db.org/)[17]. Higher node score indicates more important location of the node in the PPI network. Interactions with combined score > 0.9 (highest confidence) were identified and subjected to Cytoscape software (v3.2.0; http://www.cytoscape.org/) for visualization of PPI network.[18] Based on the MCODE plug-in[19] in Cytoscape software, the significant network modules were screened, with the threshold of score ≥ 10. Topology features of the nodes (gene products; without weight) in the network was analyzed using CytoNCA plugin in Cytoscape software. Important modules in the PPI network were identified using MCODE plugin in Cytoscape software (v1.4.2; http://apps.cytoscape.org/apps/MCODE),[20] with the threshold of score ≥10.

Transcription factors (TF) and miRNAs regulatory analysis

For gene set enrichment analysis in PPI network, the TF-target and miRNA-mRNA pairs among DEGs in PPI network were predicated using webgestal tool (http://www.webgestalt.org/option.php)[21] with Overrepresentation Enrichment Analysis (ORA) methods. Accordingly, TF-miRNA-target axes were predicated. Cytoscape was employed for visualizing of regulatory axes.

Results

DEGs analysis and clustering

A total of 4293 DEGs, including 2405 upregulated and 1888 downregulated DEGs, were identified from the 498 PCa tumor samples comparing to 52 normal adjacent tissues. According to the median expression value of these DEGs, tumor and normal samples were obviously distanced by hierarchical clustering analysis (Fig 1).

DEGs related to prognosis of PCa patients

All the 4293 DEGs were subjected for survival analysis and 1362 DEGs were identified to be significant prognosis-related genes, including 967 upregulated and 395 downregulated DEGs. Of these DEGs, higher expression of *SRSF2, SRSF5, SRSF7, SRSF8, UBE2D2, UBE2B, UBE2I, POLR2H, TMPRSS5* and *TMPRSS9* and were related with poor survival of PCa patients, and yet low expression of *MAPK1, FBXO8, CDK6, EGF, MTOR, TMED10* and *MAP2K4* were related with poor survival (Data not shown).

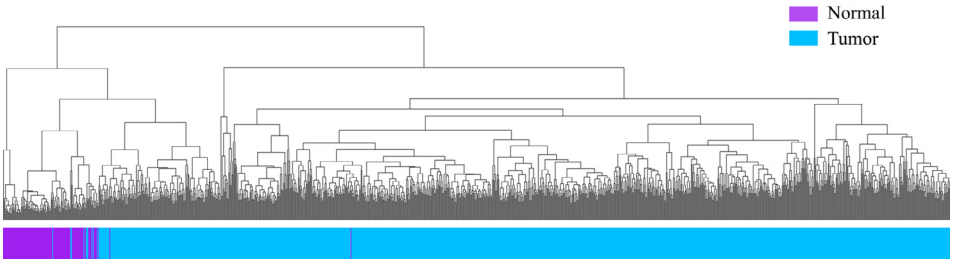

Fig. 1. Hierarchical clustering analysis for differentially expressed genes in PCa. Tumor and normal controls samples were mainly distinct. (Color version of figure is available online.)

Enrichment analysis of PCa prognosis-related DEGs

GO BP enrichment analysis using DAVID online tool showed the upregulated DEGs associated with PCa prognosis were enriched into 31 biological processes, including GO:0000398~mRNA splicing, via spliceosome (27 DEGs), GO:0006281~DNA repair (24 DEGs), GO:0051301~cell division (28 DEGs), GO:0007067~mitotic nuclear division (20 DEGs) and GO:0000722~telomere maintenance via recombination (6 DEGs, Table S1) and 14 KEGG pathways including Spliceosome (15 DEGs), mRNA surveillance pathway (10 DEGs), Nucleotide excision repair (8 DEGs), DNA replication (*LIG1, MCM7, RFC2, RFC4, RPA2, RPA3* and *RNASEH2C*) and Apoptosis-multiple species (*BBC3, HTRA2, DIABLO* and *BIRC7*; Fig 2 and Table S2). These enrichment results showed the upregulated DEGs in PCa were associated with cell cycle and apoptosis via regulating mitosis, DNA repair and nuclear division.

The downregulated DEGs were involved in 36 GO BP terms including GO:0036498~IRE1-mediated unfolded protein response (9 DEGs), GO:0006886~intracellular protein transport (16 DEGs), GO:0034976~response to endoplasmic reticulum (ER) stress (6 DEGs), GO:0006888~ER to Golgi vesicle-mediated transport (10 DEGs) and GO:0006470~protein dephosphorylation (8 DEGs, Table S1), and 13 KEGG pathways including protein processing in ER (20 DEGs), N-Glycan biosynthesis (6 DEGs), lysosome (8 DEGs), ErbB signaling pathway (*EGF, ERBB3, MTOR, MAPK1,* and *MAP2K4*), pancreatic cancer (*CDK6, EGF, MAPK1* and *STAT3*) and glioma (*CDK6, EGF, MTOR* and *MAPK1*; Fig 2 and Table S2). These results showed downregulated DEGs were associated with pathways-mediated PCa pathogenesis mainly by regulating intracellular protein transport and response in ER.

PPI network analysis for PCa prognosis-related DEGs

The PPI network of the PCa prognosis-related DEGs was constructed in our study. The network consisted of 428 nodes (gene products) and 1580 lines (interactions, Figure S1). Two modules module a (score = 26.566) and b (score = 10.235) were identified using MCODE with the threshold of score $\geq$10. Module a was comprised of 54 nodes and 704 lines and module b was comprised of 18 nodes and 87 lines (Fig 3). Of the 54 nodes in module a, 47 DEGs (87.04%) were upregulated and only 7 DEGs (12.97%) were downregulated in PCa tissues compared with normal tissues. POLR2H had the highest interaction degree of 59, followed with CFSF1 (degree = 39), SRSF2 (degree = 37), SRSF7 (degree = 37), and U2AF1L4 (degree = 35). Several other DEGs, including ARIH2, UBE2G2, FBXO44 and KBTBD7, had the lowest degree of 23.

Eight of 18 DEGs (44.44%) in module b were upregulated DEGs and the other 10 were downregulated (55.56%). The interaction degrees of DEGs in module b were relative lower than genes in module a, with a little range from 19 (DYNC1H1) to 7 (COL7A1, CNIH2 and SEC22A; Fig 3 and Table 1).

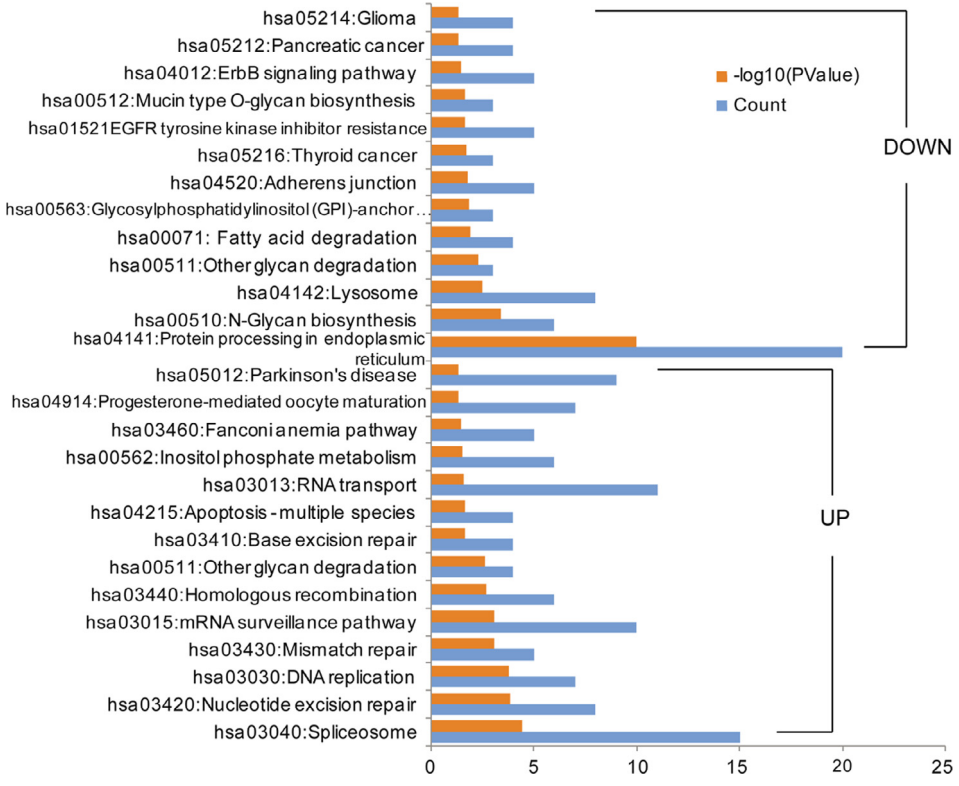

Fig. 2. The KEGG pathways involves differentially expressed genes (DEGs) in PCa. Pathways associated with downregulated DEGs (upper) and upregulated DEGs (lower). (Color version of figure is available online.)

Functional annotation of genes in modules

To elucidate the molecular features of the DEGs in module a and b, genes in 2 modules were separately subjected to DAVID online tool and the corresponding terms were obtained. DEGs in module a were classified into 27 GO BP terms including GO:0000398~mRNA splicing, via spliceosome (25 DEGs, including *POLR2H, SNRPD1, HNRNPA1, SRSF2, SRSF5, SUGP1, SRSF7* and *HNRNPH1*), GO:0016567~protein ubiquitination (13 DEGs, including *RNF130, UBE2D2, KBTBD7, UBAC1, UBE2B*, and *UBE2E1*), GO:0006406~mRNA export from nucleus (6 DEGs; *SRSF2, SRSF5, SRSF7, MAGOH, HNRNPA2B1* and *CPSF1*) and GO:0008543~fibroblast growth factor receptor (FGFR) signaling pathway (*POLR2H, HNRNPM, HNRNPH1*, and *HNRNPA1*; Table S3); and were involved into 3 KEGG pathways including hsa03040:Spliceosome (including *SNRPD1, HNRNPA1, SRSF2, SRSF5* and *SRSF7*), hsa04120:Ubiquitin mediated proteolysis (including *ANAPC2, UBE2D2, TCEB1, CDC26, UBE2B*, and *UBE2E1*) and hsa04141:Protein processing in ER (including *UBE2D2, UBE2G2, UBE2J1* and *UBE2E1*). These results suggested that DEGs in module a were related with mRNA splicing and transportation from nucleus via ER-protein ubiquitination and proteolysis (Table 2).

DEGs in module b were classified into 13 GO BO terms, including GO:0006888~ER to Golgi vesicle-mediated transport (13 DEGs, including *ARFGAP1, SEC31A, TMED2, COL7A1, SPTBN5* and *TMED10*), GO:0006890~retrograde vesicle-mediated transport, Golgi to ER (7 DEGs, including *ARFGAP1, KDELR3, TMED2, ARCN1* and *TMED10*), GO:0048208~COPII vesicle coating (6 DEGs, including, *TMED2, COL7A1, SEC31A* and *TMED10*), GO:0007030~Golgi organization (*TMED2, SPTBN5* and *TMED10*), GO:0048205~COPI coating of Golgi vesicle (*TMED2* and *TMED10*),

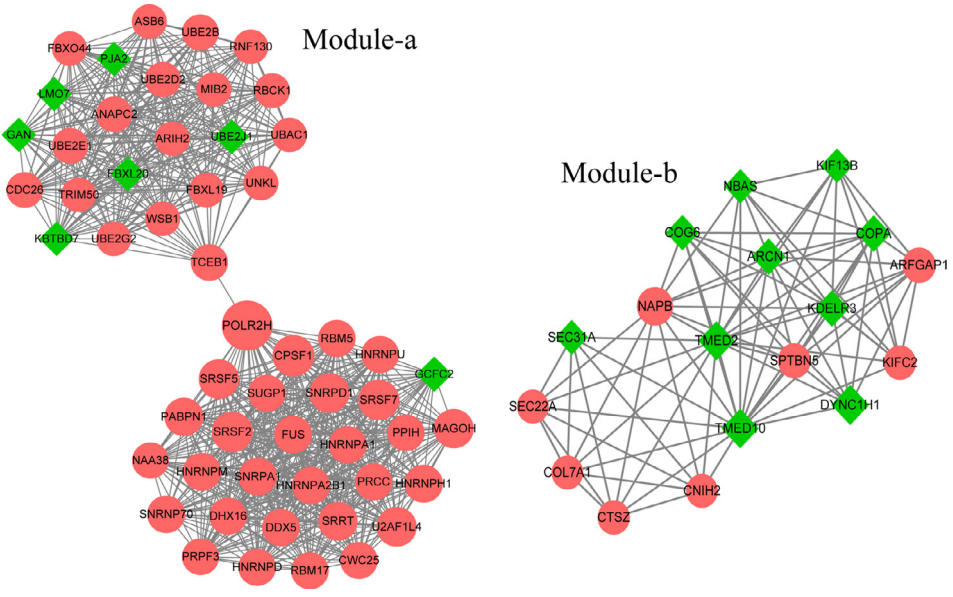

Fig. 3. The 2 modules in the protein-protein interaction network of the prognosis-related differentially expressed genes (PPI) in PCa. Modules were identified using MCODE in Cytoscape software. Module a, score = 26.566; Module b, score = 10.235. Red and green nodes are upregulated and downregulated DEGs, respectively. The larger the node, the higher the interaction degree is. (Color version of figure is available online.)

Table 1
The list of gene and interaction degree of nodes in module a and b.

Module-a						Module-b		
Nodes	Deg.	U/D	Nodes	Deg.	U/D	Nodes	Deg.	U/D
POLR2H	59	Up	PPIH	28	Up	DYNC1H1	19	Down
CPSF1	39	Up	TCEB1	28	Up	TMED10	18	Down
SRSF2	37	Up	NAA38	27	Up	TMED2	17	Down
SRSF7	37	Up	UBE2B	27	Up	NAPB	16	Up
U2AF1L4	35	Up	CDC26	26	Up	KDELR3	12	Down
SRSF5	35	Up	UBE2E1	26	Up	COPA	12	Down
SNRPD1	35	Up	ANAPC2	26	Up	ARCN1	12	Down
MAGOH	34	Up	GCFC2	25	Down	COG6	10	Down
SRRT	33	Up	UBE2D2	25	Up	ARFGAP1	10	Up
PABPN1	32	Up	RBCK1	24	Up	SEC31A	9	Down
HNRNPH1	31	Up	UBE2J1	24	Down	SPTBN5	9	Up
HNRNPM	31	Up	UBAC1	23	Up	NBAS	8	Down
SNRPA1	31	Up	ARIH2	23	Up	KIF13B	8	Down
SNRNP70	30	Up	WSB1	23	Up	KIFC2	8	Up
HNRNPA1	30	Up	UNKL	23	Up	CTSZ	8	Up
HNRNPA2B1	30	Up	UBE2G2	23	Up	COL7A1	7	Up
FUS	30	Up	PJA2	23	Down	CNIH2	7	Up
PRCC	29	Up	RNF130	23	Up	SEC22A	7	Up
HNRNPU	29	Up	TRIM50	23	Up			
CWC25	29	Up	FBXO44	23	Up			
RBM17	29	Up	FBXL20	23	Down			
SUGP1	29	Up	LMO7	23	Down			
RBM5	29	Up	FBXL19	23	Up			
HNRNPD	29	Up	GAN	23	Down			
DHX16	29	Up	ASB6	23	Up			
DDX5	29	Up	MIB2	23	Up			
PRPF3	28	Up	KBTBD7	23	Down			

Deg., degree. U/D, up/down.

Table 2
Three KEGG pathways involve genes in module a.

Term	Count	*P* value	Genes
hsa03040:Spliceosome	16	5.02E-19	*SNRPA1, MAGOH, SNRPD1, PRPF3, DDX5, U2AF1L4, HNRNPA1, HNRNPU, SRSF2, HNRNPM, SRSF5, PPIH, SRSF7, DHX16, SNRNP70, RBM17*
hsa04120:Ubiquitin mediated proteolysis	8	1.12E-06	*ANAPC2, UBE2D2, UBE2G2, UBE2J1, TCEB1, CDC26, UBE2B, UBE2E1*
hsa04141:Protein processing in endoplasmic reticulum	4	0.032963499	*UBE2D2, UBE2G2, UBE2J1, UBE2E1*

and GO:0035459~cargo loading into vesicle (*TMED2* and *TMED10*), revealing the important roles of these DEGs in intracellular Golgi and ER organization and transportation. No significant KEGG pathway involved those DEGs in module b.

TF/miRNA-mRNA regulatory analysis

Four TFs (*ZBTB33, ATF3, ELK1* and *YY1*) and 5 miRNAs (miR-495, miR-519e, miR-515-5p, miR-217 and miR-433) with more than one target DEGs in PPI network were predicated using webgestal tool. Accordingly, the TF/miRNA-mRNA regulatory network was comprised of 4 TFs, 5 miRNAs and 218 DEGs (including 137 upregulated and 81 downregulated DEGs) and 336 lines. *ZBTB33, ATF3, ELK1* and *YY1* regulates 112, 87, 72 and 22 DEGs; *miR-495, miR-519e, miR-515-5p, miR-217* and miR-433 targets to 12, 8, 8, 8, and 7 DEGs (Fig 4). We noted that *SRSF2* and *SRSF5* are regulated by TF *YY1; UBE2D2* targeted by *miR-433; UBE2B* is respectively *miR-515-5p* and *miR-519e; CDK6, HNRNPH1, SNRPD1* and *SRSF5* is target of *miR-495; UBE2I* is regulated by *SBTB33* and *miR-217; MAPK1* is a target of *miR-217*. Our afore analysis showed that the higher expression of *SRSF2, SRSF5, HNRNPH1, UBE2D2, UBE2B* and *UBE2I* were related with poor survival of PCa patients, whereas *CDK6* and *MAPK1* expression was associated with good survival of PCa patients (Fig 5).

Discussion

Surprising in our study was the identification of 1362 prognosis-related genes in the 498 PCa cohort. The high/low expression of these genes was significantly associated with the poor overall survival of the 498 PCa subjects. Of the 1362 prognosis-related genes, 71.0% (967/1362) were upregulated and the high expression of them was correlated with poor survival of PCa patients. Interesting was that the upregulated gene sets were mostly associated mRNA splicing, mitosis, and apoptosis via involving in DNA repair and nuclear, and the downregulated genes were associated with the transport, dephosphorylation, and response of intracellular proteins.

Among the upregulated prognostic biomarkers, several serine/arginine-rich splicing factors (SRSFs), including *SRSF2, SRSF5, SRSF7* and *SRSF8* were upregulated in PCa and identified as negative prognostic biomarkers of overall survival in PCa. We annotated that these factors were associated with mRNA export from nucleus and mRNA splicing via spliceosome (Table S3). Upregulation, metastatic feature, diagnostic and prognostic potential of *SRSF2, SRSF5* and *SRSF7* in several human cancer had been reported so far, including in small-cell lung cancer,[22] oral squamous cell carcinoma,[23] and hepatocellular carcinoma.[24] SRSFs are RNA-binding factors in alternative and constitutive splicing of mRNA precursors.[25-27] Human papillomavirus (HPV), especially HPV16, is a risk factor for cervical cancer, PCa, and bladder cancer.[27-30] The E6/E7 viral oncoproteins, which are essential for HPV oncogenesis, are induced by SRSF2/3-mediated alternative splicing.[27] After HPV infection, SRSF2/3 is activated, E6/E7 expression and stability are enhanced and E6/E7 splice isoforms are formed, implicating the oncogenic process of HPV-associated tumor.[27,31] The depletion of SRSF2/3 decreased expression of E6/E7, E6-regulated p53 proteins and cervical cancer cell

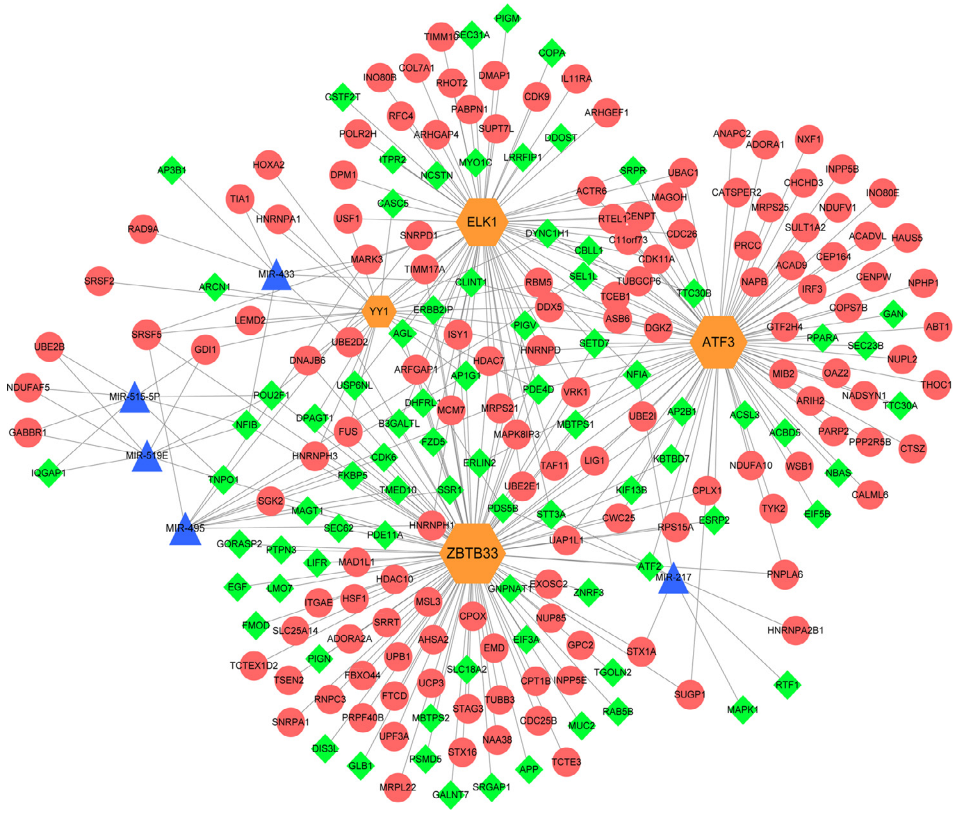

Fig. 4. The TF/miRNA-mRNA regulatory network of the prognosis-related differentially expressed genes (DEGs) in PCa. Red circles and green rhombi are upregulated and downregulated DEGs, respectively. Triangles and hexagons are miRNAs and TFs, respectively. The larger the node, the higher the interaction degree is (Color version of figure is available online.)

apoptosis, and reduced cervical cancer cell proliferation and colony formation.[27] In addition, the inhibition of SRSF7 suppressed cancer cell proliferation and tumor development via enhancing apoptosis.[32] Our present study showed that *SRSF2, SRSF5, SRSF7,* and *SRSF8* were upregulated in PCa tissues from a 498 cohort from TCGA comparing with 52 normal adjacent tissues. Additional survival analysis showed these genes were associated with poor survival of PCa patients, thus identified as potential negative prognostic biomarkers of PCa patients.

Another upregulated gene cluster in PCa is ubiquitin conjugating enzyme E2 (UBE2) members, including *UBE2D2, UBE2G2, UBE2J1* and *UBE2E1*. These genes, as *SRSF* genes, were defined as negative prognostic biomarkers of PCa cohort, as high expression of UBE2 genes were correlated with poor survival of PCa patients. These genes were related with protein ubiquitination, ubiquitin-mediated proteolysis, and protein processing in ER. The *UBE2D* and *UBE2E* factors modulate the ubiquitination and degradation of epidermal growth factor receptor (EGFR) by Cbl RING finger protein.[33,34] However, UBE2E usually acts as a positive modulator of EGFR by competing with *UBE2D2* for Cbl combination, and thus prevents Cbl-meditated EGFR downregulation and ubiquitination,[33,34] and instead the inhibition of *UBE2E* increased EGFR ubiquitination and degradation.[34] The upregulation of *EGFR* in PCa has been reported in previous reports,[35,36] and *EGFR* promoted PCa cell metastasis.[37] However, the downregulations of *EGF* and *EGFR* were confirmed in PCa tissues in confront of the normal adjacent tissues in our study, and *EGF* expression was defined as a positive prognostic biomarker of survival in PCa as the *EGF* high expression was correlated with good overall survival (Data not shown). These suggested that both UBE2

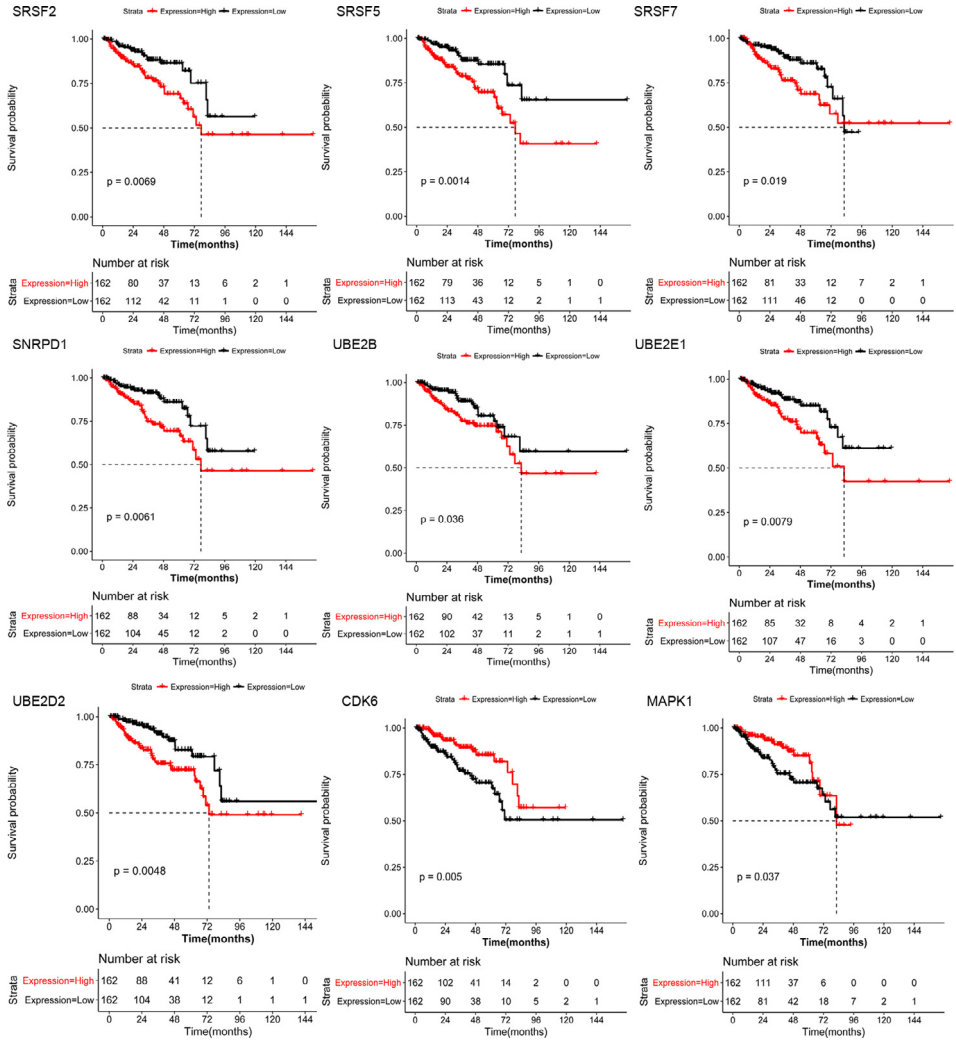

Fig. 5. Survival analysis of several prognosis-related differentially expressed genes. (Color version of figure is available online.)

members and EGF signaling play important roles in the development of PCa via multiple pathways, the association between EGF signaling and UBE2-mediated ubiquitination may be of great interests in PCa prognosis and treatments.

In our present study, we identified both *SRSF5* and *SRSF3* are targets of *miR-495* and *miR-433*, respectively. The downregulations of *miR-495* and *miR-433* have been confirmed in gastric cancers and other cancers,[38-40] suggesting the tumor suppressor roles of these 2 miRNAs in tumor development. These results were inconsistent with our results that both *SRSF5* and *SRSF3* were upregulated in PCa tissues. These regulatory interactions of the miRNA, TF, and mRNAs suggested the complex and great roles of these molecules in PCa development, prognosis and also may in treatment.

The significantly altered genes in PCa included a cluster of genes involved in ER and Golgi organization, ER to Golgi or retrograde Golgi to ER vesicle-mediated transport, and cargo loading

into vesicle. These genes included downregulated *SEC31A, TMED2* and *TMED10* and upregulated *COL7A1*. ER stress and Golgi fragmentation deterioration are involved in pathological changes of tissues.[41] SEC31 is a component of the outer layer of coat protein II (COPII)-coated vesicles.[42] COPI and COPII complex mediates Golgi to ER traffic and ER-to-Golgi traffic, respectively.[41] Transmembrane emp24-like trafficking-protein 10 (*TMED10* or p24δ1) is required for the gp40-mediated retention of major histocompatibility complex (MHC) class I in the ER, the suppression of TMED10 or TMED2 induced retain of MHC class I and increased fragmented Golgi apparatus.[42] The deletion or loss of function of *TMED2/10* is correlated with dilated ER membrane, increased ER-stress and unfolded protein response.[42,43] Our current study identified both *TMED2* and *TMED10* were downregulated in PCa tissues comparing with normal control tissues, and were positive prognostic biomarkers as higher expression of them were associated with good overall survival of PCa patients, revealing the potential roles of *SEC31A, TMED2* and *TMED10* genes in PCa development, prognosis and treatment.

Conclusion

In conclusions, we demonstrated that these significantly altered genes in PCa tissues relative to normal control tissues, such as SRSFs (including *SRSF2, SRSF5, SRSF7* and *SRSF8*) and UBE2 members (including *UBE2D2, UBE2G2, UBE2J1* and *UBE2E1*). These 2 gene sets were upregulated in PCa tissues and identified as negative prognostic biomarkers of PCa, as high expression of them related with poor survival of PCa patients. Several Golgi-ER traffic mediators (including *SEC31A, TMED2* and *TMED10*) were identified as positive prognostic biomarkers of PCa, as high expression of them related with good overall survival. These genes are of great interests. More experiments should be conducted prior to clinical trial design.

Funding Information

None.

Compliance with Ethical Standards

This article does not contain any studies with human participants or animals performed by any of the authors, the authors have no ethical conflicts to declare.

Declaration of Competing Interest

All authors declare that there is no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2019.100503.

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