Screening of potential therapy targets for prostate cancer using integrated analysis of two gene expression profiles

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Abstract. The aim of the present study was to analyze potential therapy targets for prostate cancer using integrated analysis of two gene expression profiles. First, gene expression profiles GSE38241 and GSE3933 were downloaded from the Gene Expression Omnibus database. Differentially expressed genes (DEGs) between prostate cancer and normal control samples were identified using the Linear Models for Microarray Data package. Pathway enrichment analysis of DEGs was performed using Gene Ontology and the Kyoto Encyclopedia of Genes and Genomes. Furthermore, protein-protein interaction (PPI) networks of DEGs were constructed, on the basis of the Search Tool for the Retrieval of Interacting Genes/Proteins database. The Molecular Complex Detection was utilized to perform module analysis of the PPI networks. In addition, transcriptional regulatory networks were constructed on the basis of the associations between transcription factors (TFs) and target genes. A total of 529 DEGs were identified, including 129 upregulated genes that were primarily associated with to the cell cycle. Additionally, 400 downregulated genes were identified, which were principally enriched in the pathways associated with vascular smooth muscle contraction and focal adhesion. Cell Division Cycle Associated 8, Cell Division Cycle 45, Ubiquitin Conjugating Enzyme E2 C and Thymidine Kinase 1 were identified as hub genes in the upregulated sub-network. Furthermore, the upregulated TF E2F, and the downregulated TF Early Growth Response 1, were identified to be critical in the transcriptional regulatory networks. The identified DEGs and TFs may have critical roles in the progression of prostate cancer, and may be used as target molecules for treating prostate cancer.

Introduction

Prostate cancer is a malignancy that occurs in the prostate epithelial cells and it is the most common type of reproductive system cancer in males worldwide (1,2). Cancer statistics in 2016 revealed that prostate cancer accounts for ~20% novel cancer cases in males in the USA (3). Radical prostatectomy is an effective treatment to improve patient survival time (4), but it is only suitable for ~10% of all cases (5). A number of other therapies, including radiotherapy, hormonal therapy, chemotherapy and immunotherapy, have been developed for prostate cancer treatment (6); however, there is limited information regarding the long-term survival rate, and the mortality rate of patients with prostate cancer remains high (7). Therefore, investigations into novel treatment strategies for patients with prostate cancer are required.

Gene therapy and small molecule drugs are novel strategies for cancer treatment, and have received increasing attention over the past few decades (8). Recently, a number of studies have been conducted to reveal the underlying molecular mechanisms and identify treatment targets for prostate cancer (9-20). Specific genes involved in the DNA damage response, including breast cancer 1, breast cancer 2 and tumor protein 53 genes, are mutated during the progression of prostate cancer (9-11). A number of activated carcinogenic signaling pathways, including c-Myc, protein kinase B and Ras, induce the replication and genomic instability of prostate cancer cells (12-14). The histone-lysine N-methyltransferase gene is overexpressed in prostate cancer and may act as a therapeutic target (15). Previous studies have primarily focused on a certain gene or pathway; therefore, it is necessary to explore the underlying molecular mechanisms and therapy targets for prostate cancer using other methods.

Identification and analysis of differentially expressed genes (DEGs) is an effective method to acquire multiple novel targets for the treatment of diseases (16,17). An expression profiling analysis for prostate cancer has been studied previously (18). In addition, DNA methylation alterations in prostate cancer have been analyzed using the gene expression profile GSE38241 (19), and clinically relevant subtypes, including subgroups I (the clinically least aggressive subclass) and subgroups II/III (clinically aggressive tumor subclasses), of prostate cancer have been studied using the gene expression profile GSE3933 (20). However, DEGs and their regulatory
factors between prostate cancer and normal samples were not analyzed as part of the present study.

In the present study, the expression-profiling data GSE38241 and GSE3933 were integrated to identify DEGs between prostate cancer samples and normal samples. The functions of DEGs were analyzed using Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis. Furthermore, protein-protein interactions (PPIs) of DEGs were investigated and hub genes, genes identified to be key genes, in the PPI network were identified. In addition, transcriptional regulatory networks were constructed on the basis of the associations between transcription factors (TFs) and DEGs. The results of the present study may identify the underlying molecular mechanisms of prostate cancer and provide targets for the treatment of prostate cancer.

Materials and methods

mRNA expression profiles of prostate cancer. The datasets of prostate cancer gene expression profiling by array with large sample size and high data quality were searched in the Gene Expression Omnibus database (www.ncbi.nlm.nih.gov/geo). Prostate cancer and normal control samples were included in the eligible dataset, and samples were not treated by additional treatments such as drugs and radiation. As a result, two prostate cancer expression profiling datasets were chosen for analysis, GSE38241 (18) and GSE3933 (19). Data of 39 samples (18 prostate cancer samples and 21 normal samples) in GSE38241 were produced using platform GPL4133 Agilent-014850 Whole Human Genome Microarray 4x44K G4112F. Data of 112 samples in GSE3933 were produced using three platforms, consisting of GPL2695 SHBB (26 samples), GPL3044 SHCQ (45 samples) and GPL3289 SHBW (41 samples). In the dataset GSE3933, only the data of 45 samples (29 prostate cancer samples and 16 normal samples) obtained from platform GPL3044 were selected for additional analysis, since gene probes detected by platform GPL3044 overlapped more with those from platform GPL4133. Data and probe annotation files were downloaded for analysis.

Data preprocessing. Subsequent to obtaining the raw data, probe IDs of the matrix data were first translated into corresponding gene symbols. If one gene symbol was matched by a number
of probe IDs, the mean expression value was selected as the expression level of this gene. In order to obtain reliable results, only the common genes in the two datasets were selected for the following analysis.

During the process of merging the two different datasets, batch errors (21) were removed using the ComBat command of sva package in R language (http://www.bioconductor.org/packages/release/bioc/html/sva.html; version 3.5) (22). Subsequently, quantile normalization of genes was performed by preprocessCore package in R (http://www.bioconductor.org/packages/release/bioc/html/preprocessCore.html; version 1.38.1) and an expression profile matrix was generated consisting of 12,621 genes.

Identification of DEGs. The linear models for microarray data package (http://www.bioconductor.org/packages/release/bioc/html/limma.html; version 3.22.7) (23), a widely-used tool for the identification of DEGs, was applied to identify DEGs between prostate cancer samples and normal samples. The raw P-value for each gene was calculated and subsequently adjusted into the false discovery rate (FDR) using

| ID          | Term                                              | Count | P-value          |
|-------------|---------------------------------------------------|-------|------------------|
| G0007517    | muscle organ development                          | 23    | 2.94x10-9       |
| G0005556    | extracellular region                              | 90    | 4.38x10-11      |
| G00031012   | extracellular matrix                              | 29    | 3.94x10-9       |
| G0005578    | proteinaceous extracellular matrix                | 26    | 5.96x10-9       |
| G0043292    | contractile fiber                                 | 16    | 8.23x10-9       |
| G0046870    | cadmium ion binding                               | 7     | 3.11x10-8       |
| G0003779    | actin binding                                     | 27    | 5.32x10-8       |
| G0008092    | cytoskeletal protein binding                       | 34    | 9.74x10-8       |
| G0005507    | copper ion binding                                | 12    | 5.45x10-7       |
| G0005198    | structural molecule activity                       | 33    | 3.76x10-5       |

DEGs, differentially expressed genes; count, number of DEGs; BP, biological process; CC, cell component; MF, molecule function; ATP, adenosine 5'-phosphate; GO, Gene Ontology.
the Benjamini-Hochberg method (24). Only the genes that met the threshold criteria of \(|\log_2\text{fold change}| > 1\) and FDR < 0.05 were identified as DEGs.

### Functional enrichment analysis of DEGs

To reveal the biological functions of DEGs, GO and KEGG pathway enrichment analysis was performed using the Database for Annotation, Visualization and Integrated Discovery (27,28). This provided a number of functional annotation tools to reveal the biological function of genes. Functional terms with \(P < 0.05\) were considered to indicate a statistically significant difference.

### PPI networks and module analysis

PPIs of DEGs were searched in the Search Tool for the Retrieval of Interacting Genes/Proteins database (29), which integrates a number of known and predicted associations between proteins. The PPI network was visualized using Cytoscape (30), an open source software for integrating biomolecular networks. In the network, ‘node’ represents a gene or protein, and ‘line’ represents an interaction between two nodes. The degree of each node is equal to the number of nodes that the node interacted with. The node degree represents its topological importance; the higher the degree, the more important the node is (31). Hub genes were identified on the basis of the degree of genes in the PPI network. Molecular Complex Detection (MCODE) (32) is a tool used to determine the dense connections in large PPI networks, which may represent molecular complexes. In the present study, MCODE was utilized to screen the modules from the PPI network with a network aggregation score >10.

### Results

#### Identified DEGs

Prior to normalization, the medians of gene expression in each sample were markedly distinct (Fig. 1A). However, the medians became consistent and were at a similar level following normalization (Fig. 1B and C), suggesting that the normalization process was successful and the normalized data may be used for additional analysis.

On the basis of the threshold criteria, a total of 529 DEGs were obtained, including 129 upregulated and 400 downregulated genes in prostate cancer samples, compared with normal samples.

#### Enrichment analysis of DEGs

To reveal the biological functions of DEGs, GO and KEGG pathway enrichment analysis was performed using the Database for Annotation, Visualization and Integrated Discovery (27,28). This provided a number of functional annotation tools to reveal the biological function of genes. Functional terms with \(P < 0.05\) were considered to indicate a statistically significant difference.

### Constructing the transcriptional regulatory networks

TFs targeting DEGs were identified from DEGs on the basis of information in the TRANSFAC database (http://gene-regulation.com/pub/databases.html; version 7.0) (33), which provided data on eukaryotic transcription factors, consensus binding sequences (positional weight matrices), experimentally proven binding sites and regulated genes. Transcription regulatory networks were visualized using Cytoscape, as aforementioned, in order to observe the interactions between TFs and target DEGs.
analyses were performed for the up- and downregulated genes. Upregulated genes were primarily enriched in cell cycle-associated GO terms, including cell cycle phase, spindle and adenosine 5’-phosphate binding (Table I). Downregulated genes were identified to be significantly involved in a set of GO terms including muscle organ development, negative regulation of cell proliferation and cell adhesion (Table I).

According to KEGG pathway enrichment analysis, upregulated genes were significantly associated with cell cycle and oocyte meiosis signaling pathways (Table II). Downregulated DEGs were principally implicated in vascular smooth muscle and focal adhesion signaling pathways (Table II).

PPI networks construction and MCODE analysis. To investigate interactions between the DEGs, PPI networks for the DEGs were constructed. There were 69 nodes and 180 edges in the PPI network of the upregulated genes (Fig. 2A). According to the degrees of nodes, four genes were selected as the hub nodes of the PPI network, cell division cycle associated 8 (CDC8A), cell division cycle associated 5 (CDC8A5), ubiquitin-conjugating enzyme E2C (UBE2C) and thymidine kinase 1 (TK1). These four DEGs interacted with >45 nodes in the PPI network, suggesting the four DEGs served crucial roles in the PPI network. One sub-network was selected from the upregulated PPI network (network aggregation score, 19.366), containing 41 nodes and 794 edges (Fig. 2B). Enrichment analysis of genes in the sub-network revealed that genes in the sub-network were primarily associated with cell cycle and cell division (Tables III and IV). Furthermore, 257 nodes and 594 edges were included in the PPI network of the downregulated genes (Fig. 3). However, no significant module was screened with the threshold of network aggregation score >10.

Table III. Top 5 most significant genes within the sub-network of upregulated genes from GO analysis of 3 categories including BP, CC and MM.

| Category          | Term                                      | Count | P-value       |
|-------------------|-------------------------------------------|-------|---------------|
| GOTERM_BP_FAT     | GO:0000279-M phase                        | 23    | 4.23x10^-27  |
| GOTERM_BP_FAT     | GO:0022403-cell cycle phase               | 24    | 1.82x10^-26  |
| GOTERM_BP_FAT     | GO:0007067-mitosis                        | 20    | 3.12x10^-25  |
| GOTERM_BP_FAT     | GO:0000280-nuclear division               | 20    | 3.12x10^-25  |
| GOTERM_BP_FAT     | GO:0000087-M phase of mitotic cell cycle  | 20    | 4.44x10^-25  |
| GOTERM_CC_FAT     | GO:0005819-spindle                        | 11    | 4.94x10^-13  |
| GOTERM_CC_FAT     | GO:0000775-chromosome, centromeric region | 10    | 4.83x10^-12  |
| GOTERM_CC_FAT     | GO:0000777-condensed chromosome kinetochore| 8     | 3.94x10^-11  |
| GOTERM_CC_FAT     | GO:0015630-microtubule cytoskeleton       | 14    | 5.31x10^-11  |
| GOTERM_CC_FAT     | GO:0000779-condensed chromosome, centromeric region | 8     | 1.01x10^-10  |
| GOTERM_MF_FAT     | GO:0005524-ATP binding                    | 13    | 3.65x10^-9   |
| GOTERM_MF_FAT     | GO:0032559-adenyl ribonucleotide binding  | 13    | 4.17x10^-9   |
| GOTERM_MF_FAT     | GO:0030554-adenyl nucleotide binding      | 13    | 7.02x10^-5   |
| GOTERM_MF_FAT     | GO:0001883-purine nucleoside binding      | 13    | 8.15x10^-5   |
| GOTERM_MF_FAT     | GO:0001882-nucleoside binding             | 13    | 8.72x10^-5   |

Count, number of differentially expressed genes; GO, Gene Ontology; BP, biological process; CC, the cell component; MF, molecule function; count, number of differentially expressed genes; ATP, adenosine 5’-phosphate.

Table IV. KEGG pathway analysis of the sub-network of upregulated genes.

| Category   | Term                                      | Count | P-value       |
|------------|-------------------------------------------|-------|---------------|
| KEGG_PATHWAY | hsa04110: Cell cycle                      | 5     | 1.48x10^-4   |
| KEGG_PATHWAY | hsa04114: Oocyte meiosis                 | 4     | 1.88x10^-3   |

Count, number of differentially expressed genes; KEGG, Kyoto Encyclopedia of Genes and Genomes; hsa, human.

Discussion

Prostate cancer is the most common type of reproductive system cancer in males (1,2), particularly in men over 65 years of age. In the present study, analysis of GSE38241 and GSE3933 gene expression profiles identified a total of
529 DEGs (129 up- and 400 downregulated DEGs) between the prostate cancer and normal samples. Integrative analysis of two microarray data enhanced the reliability of the present study. Enrichment analysis of the upregulated genes predicted the cell cycle to be the primary biological process in the GO function and the KEGG pathway analyses. In addition, focal adhesion pathway was identified as a significant pathway of downregulated genes. The results of the present study were consistent with those of previous studies, which demonstrated that the cell cycle and focal adhesion are required for the progression of cancer (35,36).

A total of four genes, consisting of CDCA8, CDCA5, UBE2C and TK1, exhibited a high degree of interaction in the upregulated PPI network. All four genes were involved in cell cycle-associated biological processes and signaling pathways. In the sub-network, CDCA8 interacted with pituitary tumor-transforming gene-1 (PTTG1), which was upregulated in prostate cancer. There is evidence that knockdown of PTTG1 suppresses the proliferation and invasive potential of prostate cancer cells (37). Therefore, it was hypothesized that CDCA8 may be used as a target for prostate cancer treatment, and that the interaction between CDCA8 and PTTG1 may have a role in the progression of prostate cancer. In addition, UBE2C belongs to the ubiquitin-conjugating enzyme family and participates in the process of cell mitosis (38). A previous study identified that UBE2C, as an androgen receptor target gene, was involved in the progression of prostate cancer (39). Furthermore, serological TK1 protein concentration was used as a reliable marker for the risk assessment of pre/early cancerous progression (40). However, to the best of our knowledge, there is no evidence that TK1 is a target for cancer treatment. It was hypothesized that CDCA8, CDCA5, UBE2C and TK1 may be associated with the progression of prostate cancer, and these genes were expected to be used as potential treatment targets for prostate cancer. Limited information is known about the roles and underlying molecular mechanisms of these four genes in prostate cancer; therefore, the present study may provide novel insights into the study of treatment targets for prostate cancer.

In addition to the hub genes in the PPI network, TFs targeting DEGs were identified on the basis of the transcriptional regulatory network analysis. TFs are well known to regulate the
Figure 4. Transcriptional regulatory networks. (A) Transcriptional regulatory network of the upregulated genes. Blue nodes represent transcription factors of the upregulated genes and red nodes represent upregulated genes. (B) Transcriptional regulatory network of the down-regulated genes. Blue nodes represent transcription factors of the downregulated genes and yellow nodes represent downregulated genes.
transcription of a number of genes involved in distinct signaling pathways and biological processes (34). In the present study, the upregulated TF, E2F2, and the downregulated TF EGR1 regulated a number of DEGs. E2F2 regulates genes by binding the target sequence 5'-TTTSSGC-3' (S=C/G) (41). In the transcriptional regulatory network, DEGs, including CDC6 and RAD51, which contain the aforementioned sequence, may be bound by E2F2 (42). CDC6 is a protein that is required for the initiation of DNA replication and has been previously identified to be deregulated in prostate cancer (43). RAD51, a protein that catalyzes DNA repair via homologous recombination, is highly expressed in cancer cells (44). Additionally, overexpression of E2F2 leads to uncontrolled proliferation of ovarian cancer cells (45) and EGR1 regulates gene expression by binding the target sequence 5'-GGCG(G/T)GGGGC-3' (46). The downregulated gene Dickkopf WNT Signaling Pathway Inhibitor 3 (DKK3) contained this sequence and was predicted to be regulated by EGR1. DKK3 promotes the proliferation and differentiation of fibroblasts and has a function in the pathogenic stromal remodeling of prostate cancer (47). Therefore, the TFs, E2F2 and EGR1, may have marked roles in the progression of prostate cancer.

The cell cycle signaling pathway may be closely associated with prostate cancer. A total of four genes (CDCA8, CDC5, UBE2C and TK1) and two TFs (E2F2 and EGR1) were selected, and may have important roles in the progression of prostate cancer. The selected DEGs and TFs may be used as gene targets for the treatment of prostate cancer and, although they were identified using bioinformatics, the specific roles and underlying molecular mechanisms in prostate cancer require further confirmation.

References

1. Bosetti C, Bertuccio P, Chatenoud L, Negri E, La Vecchia C and Levi F: Trends in mortality from urologic cancers in Europe, 1970-2004. Eur J Cancer 40: 1-15, 2011.
2. Chung BH: The role of radical prostatectomy in high-risk prostate cancer. Prostate Int 1: 95-101, 2013.
3. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2016. CA Cancer J Clin 66: 7-30, 2016.
4. Dell'Oglio P, Kames RJ, Joniau S, Garcia-Solano J, Garza-Aquino F, Turpin Mdel C, Trujillo-Santos J, Torres-Moreno D, Oviedo Ramirez I, Carbonell-Muñoz R, Muñoz-Delgado E and Rodríguez-Braun E: Expression profiling shows differential molecular pathways and provides potential new diagnostic biomarkers for colorectal serrated adenocarcinoma. Int J Cancer 132: 297-307, 2013.
5. Wu C, Zhu J and Zhang X: Network-based differential gene expression analysis suggests cell cycle related genes regulated by E2F1 underlie the molecular difference between smoker and non-smoker lung adenocarcinoma. BMC Bioinformatics 14: 365, 2013.
6. Li Y, Vongsangnak W, Chen L and Shen B: Integrative analysis reveals disease-associated genes and biomarkers for prostate cancer progression. BMC Med Genomics 7 (Suppl 1): S3, 2014.
7. Ayree MJ, Liu W, Engelmann JC, Nuhn P, Garel M, Haffner MC, Esopi D, Irazarry RA, Getzenberg RH and Nelson WG: DNA methylation alterations exhibit intratumoral stability and interindividual heterogeneity in prostate cancer metastases. Sci Transl Med 5: 169ra10, 2013.
8. Lapointe J, C, Higgins JP, van der Rijn M, Bair E, Montgomery K, Ferrari M, Egevad L, Rayford W and Bergerheim U: Gene expression profiling identifies clinically relevant subtypes of prostate cancer. Proc Natl Acad Sci USA 101: 811-816, 2004.
9. Johnson WE, Li C and Rabinovic A: Adjusting batch effects in microarray expression data using empirical Bayes methods. Biostatistics 8: 118-127, 2007.
10. Leek JT and Storey JD: A general framework for multiple testing dependence. Proc Natl Acad Sci USA 105: 18718-18723, 2008.
11. Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W and Smyth GK: limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res 43: e47, 2015.
12. Pounds S and Morris RW: Estimating the occurrence of false positives and false negatives in microarray studies by approximating and partitioning the empirical distribution of P-values. Bioinformatics 19: 1236-1242, 2003.
13. Shoop E, Casaeas P, Onsongo G, Lesnelt L, Petursdottir EO, Duktor EK, Tkach D and Cosimini M: Data exploration tools for the gene ontology database. Bioinformatics 20: 3442-3454, 2004.
14. Kanehisa M, Goto S, Kawashima S, Okuno Y and Hattori M: The KEGG resource for deciphering the genome. Nucleic Acids Res 32: D277-280, 2004.
15. Huong da W, Sherman BT and Lempicki RA: Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nature Protoc 4: 44-57, 2009.
16. Huong da W, Sherman BT and Lempicki RA: Bioinformatics enrichment tools: Paths toward the comprehensive functional analysis of large gene lists. Nucleic Acids Res 37: 1-13, 2009.
17. Frankel GM, Frankel MG, Liao J, Hattori M, Roth A, Lin J, Minquez P, Bork P, von Mering C and Jensen LJ: STRING v9.1: Protein-protein interaction networks, with increased coverage and integration. Nucleic Acids Res 41: D808-D815, 2013.
18. Kohlb M, Wiese S and Warscheid B: Cytoscape: Software for visualization and analysis of biological networks. Methods Mol Biol 696: 291-303, 2011.
19. Albert R, Albert I and Nakarado GL: Structural vulnerability of the North American power grid. Physical Review E 69: 025103, 2004.
20. Barreiro GD and Houghton CW: An automatic method for finding molecular complexes in large protein interaction networks. BMC Bioinformatics 4: 2, 2003.
21. Matys V, Kel-Margoulis OV, Frische I, Liebich I, Land S, Barre-Dirrie A, Reuter I, Chekmenev D, Krull M and Hitzig M: TRANSFAC and its module TRASCouple: Transcriptional regulation gene in eukaryotes. Nucleic Acids Res 34: D108-110, 2006.
34. Chen K and Rajewsky N: The evolution of gene regulation by transcription factors and microRNAs. Nat Rev Genet 8: 93-103, 2007.
35. Seong J, Wang N and Wang Y: Mechanotransduction at focal adhesions: From physiology to cancer development. J Cell Mol Med 17: 597-604, 2013.
36. Fu LJ and Wang B: Investigation of the hub genes and related mechanism in ovarian cancer via bioinformatics analysis. J Ovarian Res 6: 92, 2013.
37. Huang SQ, Liao QI, Wang XW, Xin DQ, Chen SX, Wu QJ and Ye G: RNAi-mediated knockdown of pituitary tumor-transforming gene-1 (PTTG1) suppresses the proliferation and invasive potential of PC3 human prostate cancer cells. Braz J Med Biol Res 45: 995-1001, 2012.
38. Summers MK, Pan B, Mukhyala K and Jackson PK: The unique N terminus of the UbcH10 E2 enzyme controls the threshold for APC activation and enhances checkpoint regulation of the APC. Mol Cell 31: 544-556, 2008.
39. Chen Z, Zhang C, Wu D, Chen H, Rorick A, Zhang X and Wang Q: Phospho-MED1-enhanced UBE2C locus looping drives castration-resistant prostate cancer growth. EMBO J 30: 2405-2419, 2011.
40. Huang S, Lin J, Guo N, Zhang M, Yun X, Liu S, Zhou J, He E and Skog S: Elevated serum thymidine kinase 1 predicts risk of pre/early cancerous progression. Asian Pac J Cancer Prev 12: 497-505, 2011.
41. Slansky JE and Farnham PJ: Introduction to the E2F family: Protein structure and gene regulation. Curr Top Microbiol Immunol 208: 1-30, 1996.
42. Bracken AP, Ciro M, Cocito A and Helin K: E2F target genes: Unraveling the biology. Trends Biochem Sci 29: 409-417, 2004.
43. Liu Y, Gong Z, Sun L and Li X: FOXM1 and androgen receptor co-regulate CDC6 gene transcription and DNA replication in prostate cancer cells. Biochim Biophys Acta 1839: 297-305, 2014.
44. Mason JM, Logan HL, Budke B, Wu M, Pawlowsk M, Weichselbaum RR, Kozikowski AP, Bishop DK and Connell PP: The RAD51-stimulatory compound RS-1 can exploit the RAD51 overexpression that exists in cancer cells and tumors. Cancer Res 74: 3546-3555, 2014.
45. Reimer D, Sadr S, Wiedemair A, Concin N, Hofstetter G, Marth C and Zeimet AG: Heterogeneous cross-talk of E2F family members is crucially involved in growth modulatory effects of interferon-gamma and EGF. Cancer Biol Ther 5: 771-776, 2006.
46. Liu C, Rangnekar VM, Adamson E and Mercola D: Suppression of growth and transformation and induction of apoptosis by EGR-1. Cancer Gene Ther 5: 3-28, 1998.
47. Zenzmaier C, Sampson N, Plas E and Berger P: Dickkopf-related protein 3 promotes pathogenic stromal remodeling in benign prostatic hyperplasia and prostate cancer. Prostate 73: 1441-1452, 2013.