Pathology - Research and Practice 240 (2022) 154198

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

In silico characterization of competing endogenous RNA network in castration-resistant prostate cancer cells in presence of the natural compound atraric acid using RNA-seq analysis

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ARTICLE INFO

Keywords:
LncRNA
Castration-resistant prostate cancer cells
Atraric acid

ABSTRACT

Atraric acid (AA) is a natural compound used for treatment of benign prostate hyperplasia. This agent has an anti-androgen receptor (AR) activity suppressing androgen-mediated neo-angiogenesis. In the current study, we have analyzed the transcriptome data of prostate cancer cells treated with AA (GSE172205) to find differentially expressed genes (DEGs) with an especial focus on lncRNAs and miRNAs. Then, we assessed expression of the differentially expressed lncRNAs (DElncRNAs) in available online sources to validate their association with prostate cancer and their importance in the determination of survival of patients with this type of cancer. We obtained 1871 DEGs, including 914 down-regulated DEGs (such as DAB1 and CD200) and 957 up-regulated DEGs (such as CHRNA2 and TRGC1), and 25 DElncRNAs, including 15 down-regulated DElncRNAs (such as LINC00639 and HOTTIP) and 10 up-regulated DElncRNAs (such as LINC00844 and LINC00160), and one up-regulated DEmiRNA (MIR29B1). The main pathways for the down-regulated genes and the up-regulated genes were Axon Guidance and Steroid BioSynthesis, respectively. Taken together, AA has been found to affect expression of several lncRNAs which are possibly involved in the pathoetiology of prostate cancer.

1. Introduction

Atraric acid (AA) is a natural compound extracted from the African tree *Pygeum africanum*. This agent is used as a medication for treatment of benign prostate hyperplasia [4]. Moreover, it has been shown to be an androgen receptor (AR) antagonist [20]. More recently, AA has been found to suppress androgen-mediated neo-angiogenesis through a VEGF-independent mechanism that involves angiopoietin 2 [5]. Besides, this compound could inhibit cell growth of castration-resistant prostate cancer (CRPC) [5]. Mechanistically, AA not only suppresses activity of the wild-type AR, but also inhibits AR mutants that facilitate resistance to other antagonists of AR possibly though inhibition of the binding of androgens to AR [5]. Furthermore, transcriptome analysis of a CRPC cell line has shown differential expression of a number of genes upon treatment treated with AA. Detailed analyses have shown the regulatory effect of AA on the retinoblastoma protein (pRb) pathway. In addition, AA could alter expression signature of genes in the reverse way of androgen [5].

AR has functional interactions with a number of non-coding RNAs (ncRNAs) with different sizes ranging from microRNAs (miRNAs) to long ncRNAs (lncRNAs) [23]. These interactions are functionally involved in the pathophysiology of human disorders, particularly prostate cancer [23]. In the current study, we have re-analyzed the transcriptome data of prostate cancer cells treated with AA (GSE172205) to find differentially expressed genes (DEGs) with an especial focus on lncRNAs and miRNAs. Then, we assessed expression of the differentially

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https://doi.org/10.1016/j.prp.2022.154198
Received 18 August 2022; Received in revised form 31 October 2022; Accepted 1 November 2022
Available online 7 November 2022

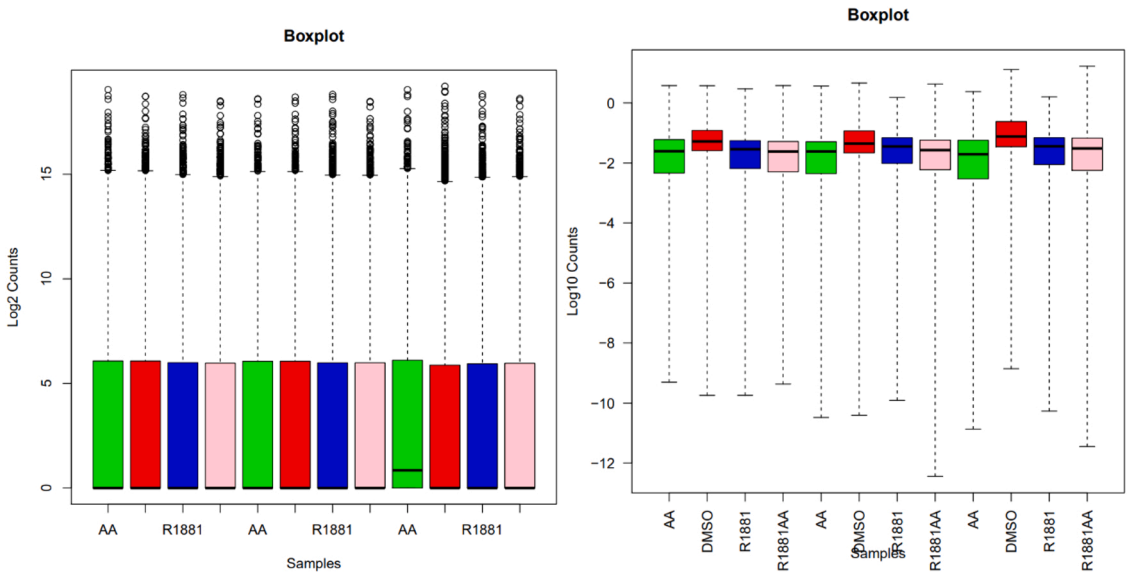

Fig. 1. Boxplot of normalized data and Cook's distance measured for each sample.

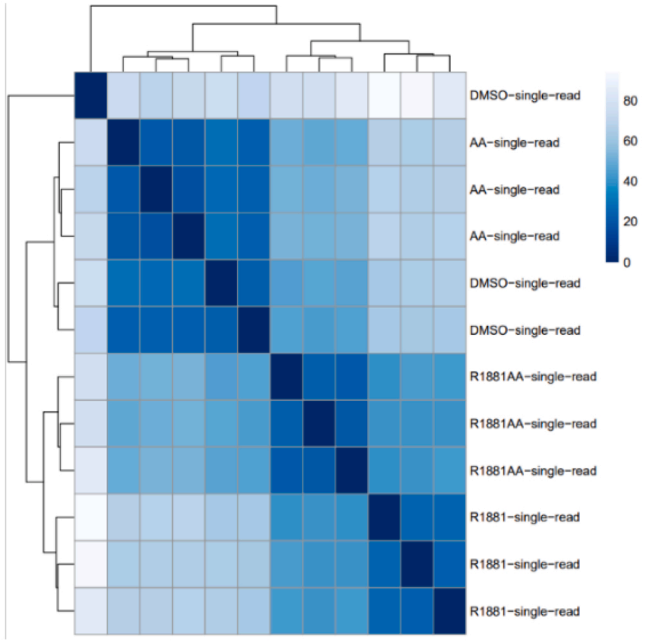

Fig. 2. Euclidean distances between the samples as calculated from the regularized log transformation.

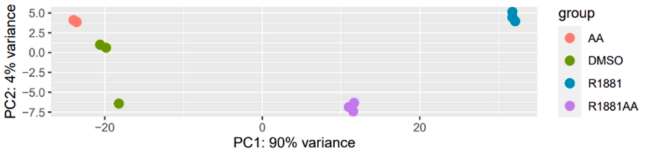

Fig. 3. PCA plot of 12 samples are shown in the 2D plane spanned by their first two principal components.

expressed lncRNAs (DElncRNAs) in available online sources to validate their association with prostate cancer and their importance in the determination of survival of patients with this type of cancer.

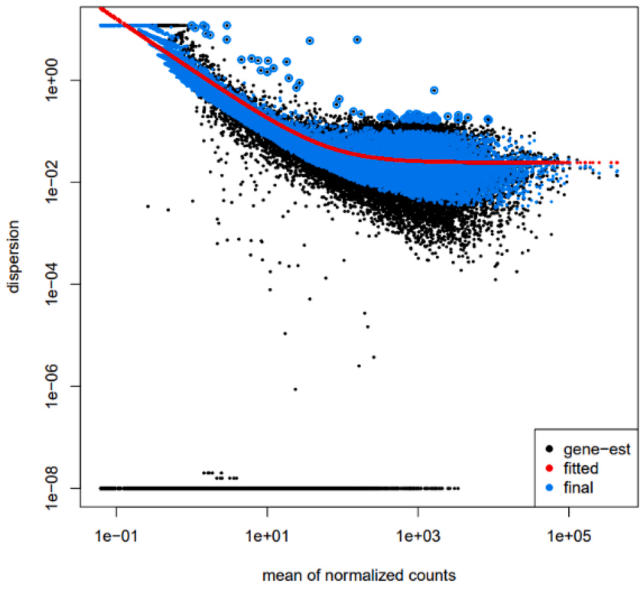

Fig. 4. Dispersion estimate plot. Gene-wise estimates, the fitted values and the final maximum a posteriori estimates used in testing are shown in black, red and blue, respectively.

2. Methods

2.1. RNA-seq data collection

We used the Gene Expression Omnibus (GEO; http://www.ncbi.nlm.nih.gov/geo/) to find the RNA-seq raw counts of GSE172205 (Illumina NextSeq 500 (Homo sapiens)), which contained 12 samples. Three R1881 (1 nm) samples and three AA samples were chosen for further study.

2.2. Dataset quality assessment

In Rstudio software (version 4.0.4), we imported the dataset and assessed its quality. This step involves examining the Euclidean distance of the samples using the Pheatmap package, performing principal

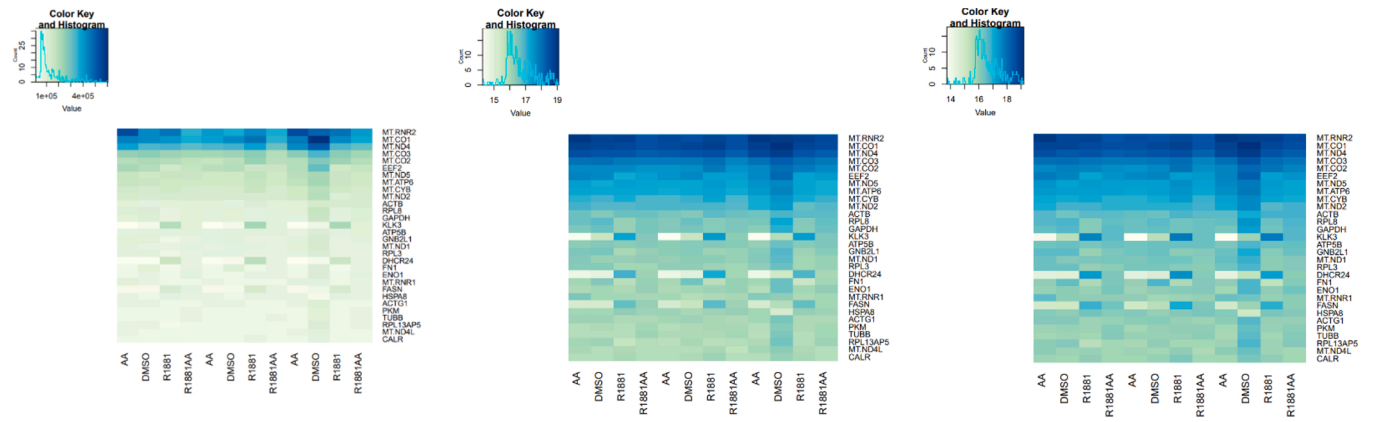

Fig. 5. Heatmaps displaying expression data of the 30 most highly expressed genes. The data is of raw counts (left), from regularized log transformation (center) and from variance stabilizing transformation (right).

Table 1
The top 10 up- and down-regulated DEGs between R1881 and AA samples (R1881 vs. AA).

Down-regulated			Up-regulated		
DEG	**Log FC**	**Adjusted *P* value**	**DEG**	**Log FC**	**Adjusted P value**
DAB1	-7.535166	1.683171e-07	**CHRNA2**	10.295103	1.129825e-139
CD200	-7.523300	5.639075e-07	**TRGC1**	9.504317	3.367003e-27
PLA2G2A	-6.439443	4.497049e-52	**STEAP4**	9.226566	6.393554e-65
SI	-6.421207	7.563954e-10	**CCDC141**	9.202280	1.806347e-24
UGT2B17	-6.347837	1.307757e-46	**ORM2**	8.881877	6.221102e-12
CYP7A1	-6.259775	5.972063e-05	**ORM1**	8.789585	3.338562e-11
UNC13C	-5.992429	5.989688e-06	**ADAM7**	8.704370	2.900305e-11
CAMK2N1	-5.982837	2.378889e-285	**PTCRA**	8.33322	5.595144e-11
CDH10	-5.838935	9.143251e-04	**ADH1C**	8.322429	5.951366e-14
FST	-5.645249	5.782776e-06	**GP2**	7.961415	3.288838e-09

Table 2
The significantly up- and down-regulated DElncRNAs between R1881 and AA samples (R1881 vs. AA).

Down-regulated			Up-regulated		
DEG	**Log FC**	**Adjusted *P* value**	**DEG**	**Log FC**	**Adjusted P value**
LINC00639	-5.210061	0.0021232	**LINC00844**	7.043368	1.739964e-09
HOTTIP	-4.424055	1.747729e-11	**LINC00160**	6.183482	9.759476e-05
COLCA1	-3.674422	8.515328e-43	**LINC01088**	5.608908	1.19901e-07
LINC00365	-2.490563	0.0053309	**LINC00964**	5.256506	0.003953163
LINC00940	-2.108542	2.301298e-15	**LINC00668**	4.953758	0.002328603
LINC00511	-1.888252	9.203472e-17	**PART1**	3.73564	1.087848e-21
HCP5	-1.753821	5.685447e-06	**RFPL1S**	3.459246	6.071452e-14
LINC00648	-1.670406	2.774731e-06	**UCA1**	2.754571	0.0179697
FAM201B	-1.640159	0.0019664	**LINC00930**	2.418421	1.806347e-24
LINC00887	-1.639043	0.0187391	**TP53TG1**	1.018093	1.533181e-07
LINC00900	-1.605906	0.0006550			
LINC00574	-1.588727	0.0165464			
LINC00933	-1.566320	0.0046505			
LINC00886	-1.468178	6.371638e-10			
RN7SL2	-1.189063	0.0011673			

Table 3
The significantly up- DEmiR between R1881 and AA samples (R1881 vs. AA).

Down-regulated			Up-regulated		
DEG	Log FC	Adjusted *P* value	DEG	Log FC	Adjusted P value
			MIR29B1	3.077267	2.878807e-06

component analysis, investigating normalized counts boxplot and cook's distance boxplot and investigating dispersion estimate plot for each sample.

2.3. The dataset preprocessing and DEGs analysis

We analyzed raw counts data using DESeq2 package [14] and got DEGs. Furthermore, Bonferroni in the stats package was used to adjust the P value into the FDR. We applied the FDR < 0.02 and $|\log2\ FC| = > 1$ as the cutoff criteria for DEGs and DElncRNAs.

2.4. Gene Ontology (GO) enrichment analyses

With the intention of exploring the functions of the obtained considerably down-regulated and up-regulated DEGs, we performed Gene Ontology (GO) enrichment analysis using the clusterProfiler R package. We set Benjamini-Hochberg corrected p-value < 0.05 as the thresholds of the functional categories.

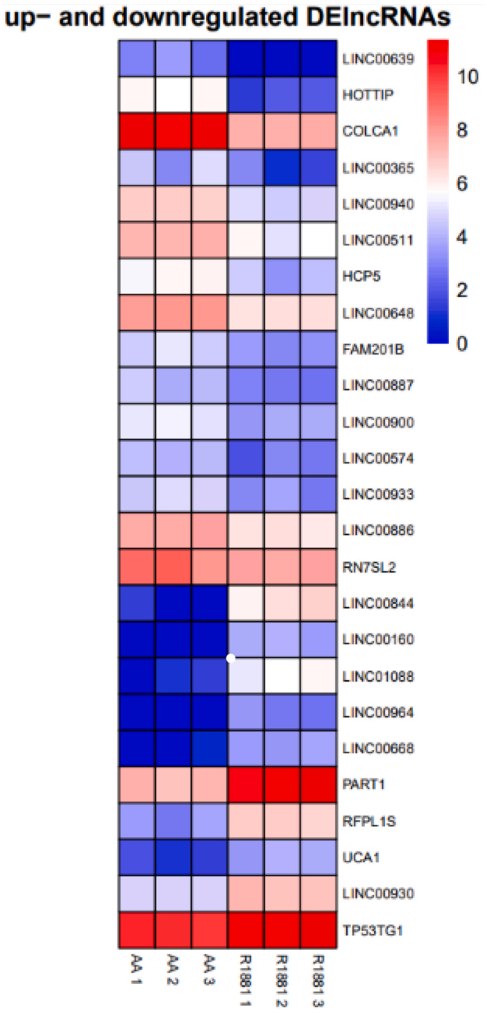

Fig. 6. Heatmap of differentially expressed lncRNAs. The horizontal axis displays the names of six samples. The vertical axis displays the lncRNAs names.

2.5. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis

KEGG pathway analysis of considerably down-regulated and up-regulated DEGs was performed to determine the potential functions of these genes that contributed to the pathways based on the KEGG database.

2.6. Survival analysis

High-throughput experimental data with survival profile of prostate cancer patients was retrieved from the TCGA database. The associations between lncRNAs expressions and overall survival of prostate cancer patients were appraised by using log rank test, with *P*-values less than 0.05 accepted as statistically significant.

3. Results

3.1. Dataset quality assessment

Fig. 1. shows the boxplot of normalized data and Cook's distance measured for each sample.

Fig. 2 shows the Euclidean distances between the samples as calculated from the regularized log transformation (rlog).

In PCA plot (Fig. 3), the selected 12 samples are shown in the 2D plane spanned by their first two principal components (PC1 and PC2).

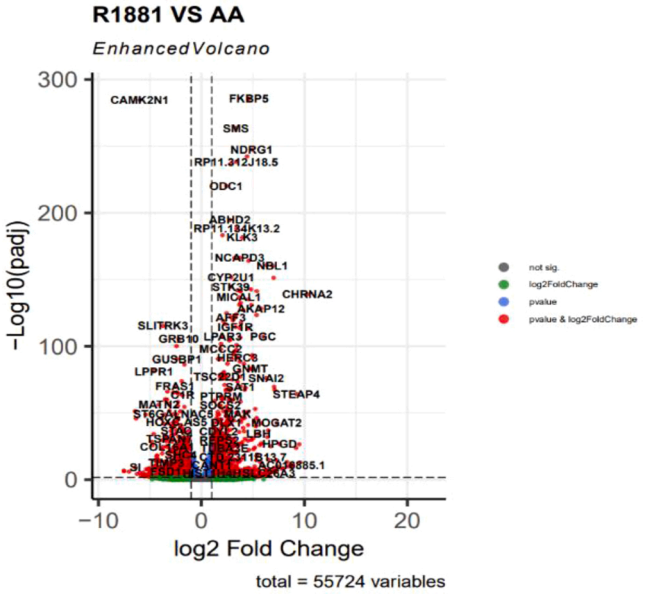

Fig. 7. The volcano plot of differentially expressed genes (DEGs); horizontal axis, log2(FC); vertical axis, -$\log_{10}$(adjusted P value). Up-regulated and down-regulated genes are clustered on the right and left parts of the plot, respectively. The x-axis shows the fold change in genes expressions, and the y-axis shows the statistical significance of the differences.

According to this plot, the AA samples and R1881 samples have the highest variation relative to each other.

The dispersion estimate plot (Fig. 4) shows the gene-wise estimates, the fitted values, and the final maximum a posteriori estimates used in testing. This plot shows that the data is a good fit for the DESeq2 model.

Heatmap of the count Table is shown in Fig. 5.

3.2. DEGs analysis

Based on the RNA-seq data analysis between R1881 and AA samples by DESeq2, we obtained 1871 DEGs, including 914 down-regulated DEGs (such as DAB1 and CD200) and 957 up-regulated DEGs (such as CHRNA2 and TRGC1), and 25 DElncRNAs, including 15 down-regulated DElncRNAs (such as LINC00639 and HOTTIP) and 10 up-regulated DElncRNAs (such as LINC00844 and LINC00160), and one up-regulated DEmiRNA (MIR29B1). Table 1 lists the top 10 markedly down-regulated and up-regulated DEGs.

Table 2 lists the markedly down-regulated and up-regulated lncRNAs.

Detailed statistics of the only DEmiRNA is shown in Table 3.

Expressions of these DElncRNAs are shown in Fig. 6. The variations of lncRNA and mRNA expression between R1881 and AA samples are visualized and assessed using volcano plot (Fig. 7).

3.3. GO enrichment analysis of DEGs

The considerably down-regulated DEGs (LogFC<−1 and adjusted P value<0.05) were enriched in 73 GO terms. In addition, the considerably up-regulated DEGs (LogFC>1 and adjusted P value<0.05) were primarily enriched in 62 GO terms. We used Clusterprofiler package [25] to perform analysis. Fig. 8 shows the barplots of function enrichment analysis.

3.4. Pathway analysis

Using Pathview [15] and gage [16] packages in R, KEGG pathways analysis [10,11] of 914 down-regulated and 957 up-regulated DEGs were executed to recognize the potential functional genes (Fig. 9). The

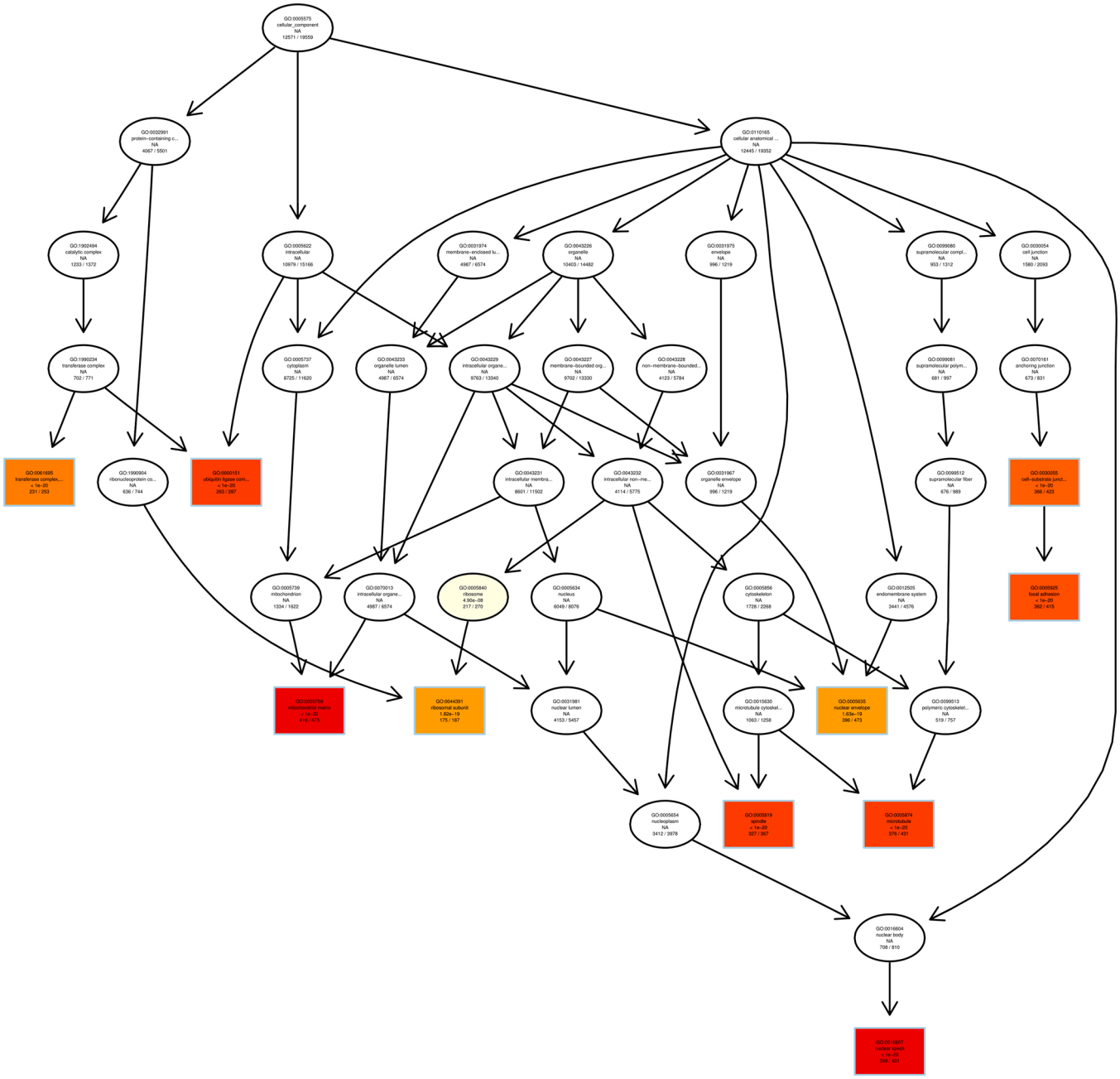

Fig. 8. a. GO enrichment analysis of down-regulated DEGs. b. GO enrichment analysis of up-regulated DEGs.

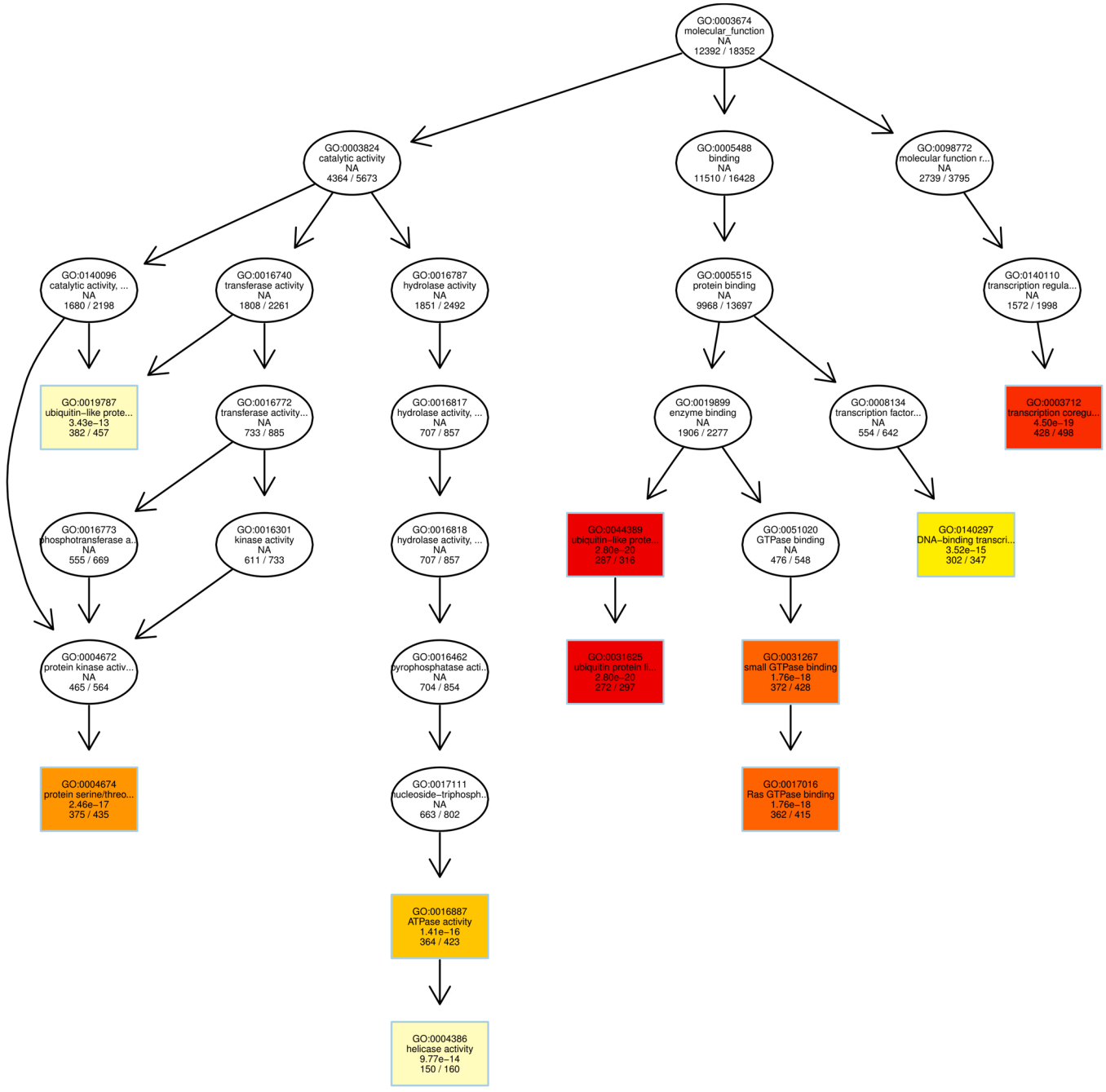

Fig. 8. (*continued*).

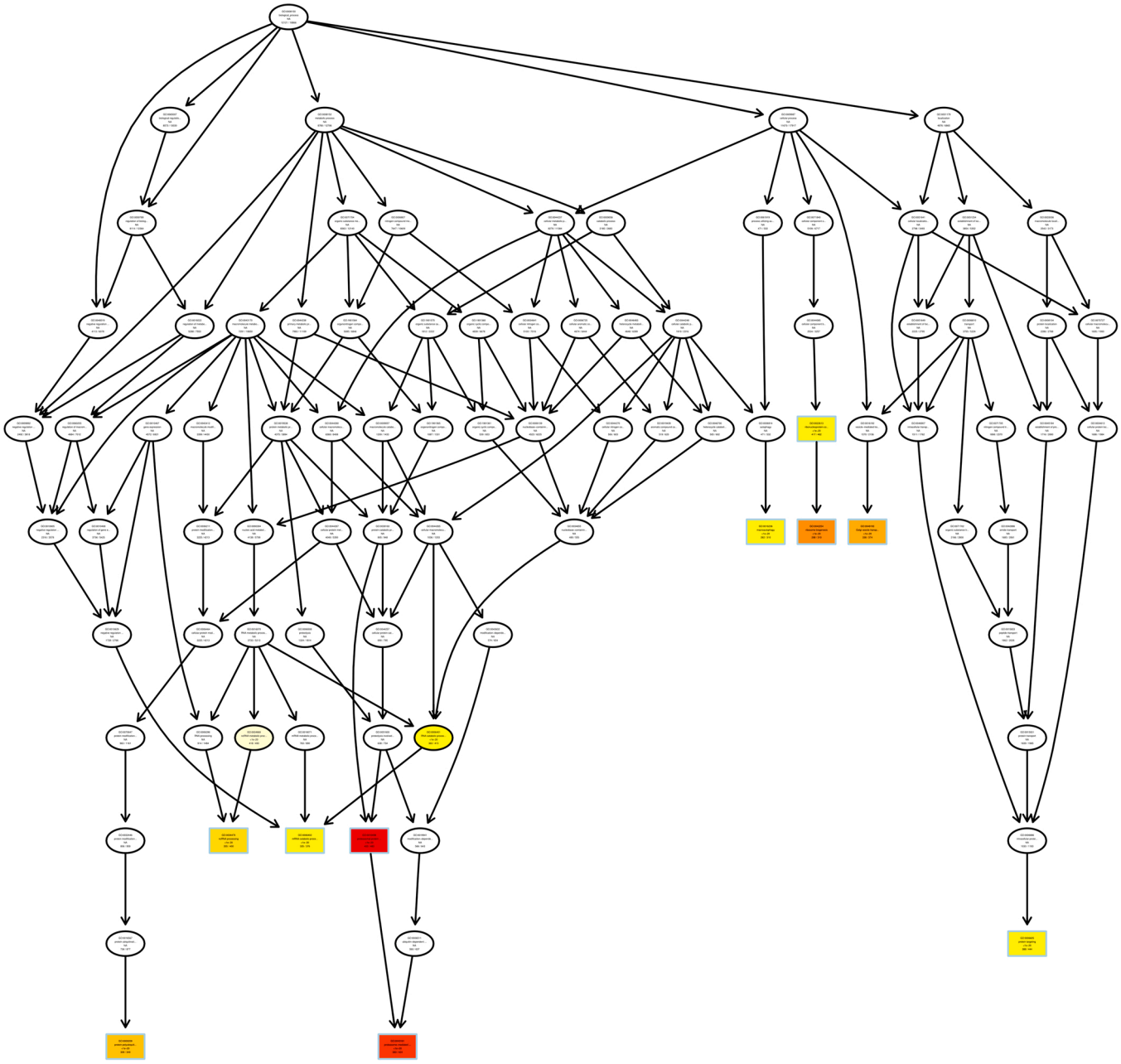

Fig. 8. (*continued*).

main pathways for the down-regulated genes and the up-regulated genes are Axon Guidance and Steroid BioSynthesis, respectively (Table 4).

3.5. Survival analysis

In this section, we retrieved RNA-seq data of prostate cancer from TCGA. Survival analysis was based on the Kaplan-Meier curve analysis using Survival package in R [2,24]. We performed survival analysis based on the DElncRNAs. The difference was statistically significant with log-rank $P < 0.05$. Results showed that LINC00668, LINC00887 and LINC00900 were significantly correlated with poor survival time in patients with prostate cancer (Fig. 10).

4. Discussion

AR signaling has an important oncogenic effect in prostate cancer. In fact, the core approaches for treatment of this malignancy are based on controlling AR activity [1]. Acquired resistance to androgen deprivation therapy is the main obstacle in the treatment of this kind of cancer resulting in significant mortality and morbidity [19]. Therefore, identification of the molecular mechanisms of resistance to androgen deprivation therapy would facilitate design of novel therapeutic targets for these patients.

Next generation sequencing methods have facilitated identification of numerous ncRNAs with functional relation with AR activity and development or progression of prostate cancer [28]. We have used a series of *in silico* methods for identification of differentially expressed ncRNAs in CRPC cells treated with AA compound.

Our analysis led to identification of 1871 DEGs and 25 DElncRNAs, including 15 down-regulated DElncRNAs (such as LINC00639, HOTTIP, COLCA1, HCP5 and FAM201B) and 10 up-regulated DElncRNAs (LINC00844, LINC00160, LINC01088, LINC00964, LINC00668, PART1, RFPL1S, UCA1, LINC00930 and TP53TG1). Moreover, we found one up-regulated DEmiRNA (MIR29B1).

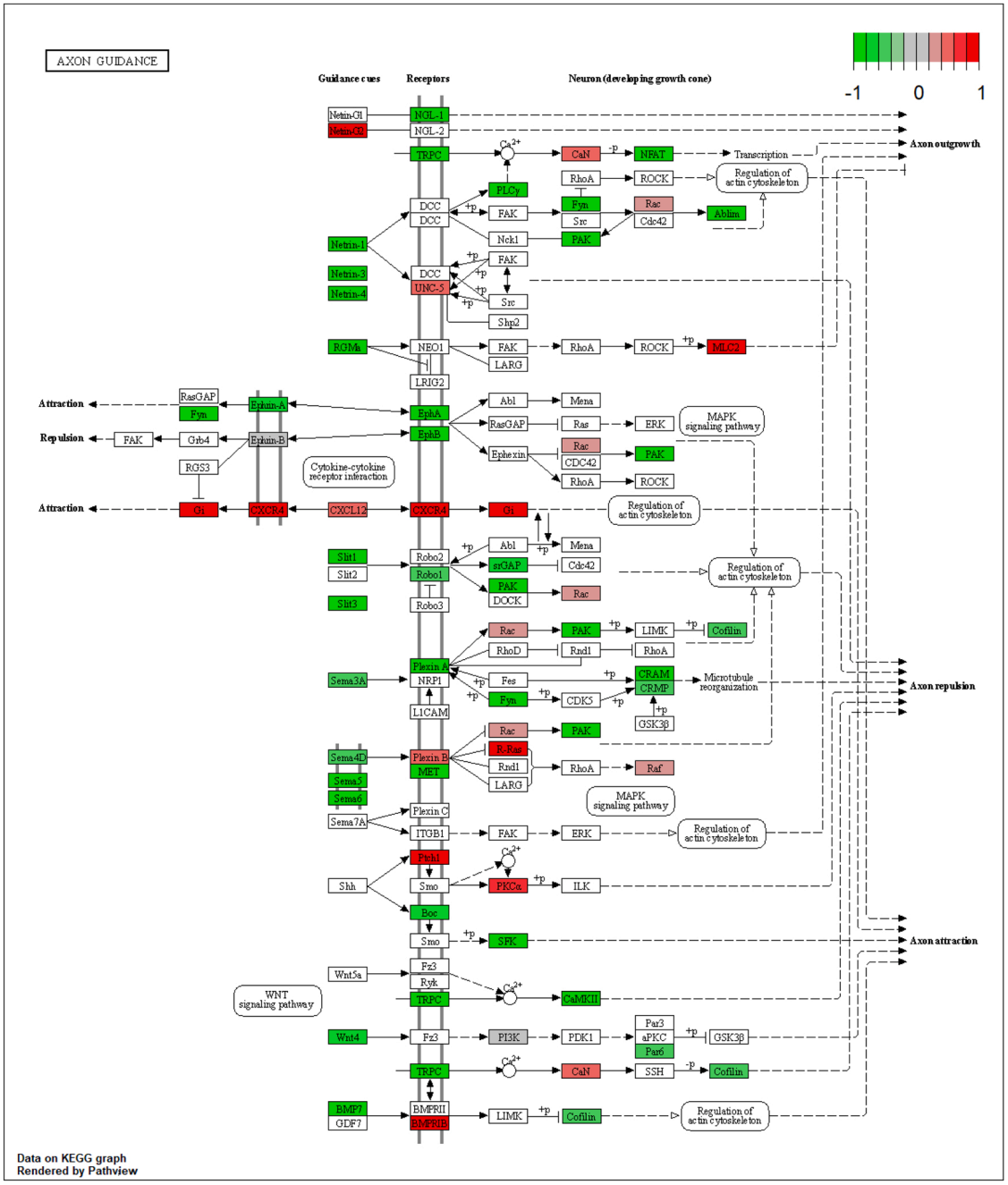

Fig. 9. Visualization of Axon Guidance and Steroid BioSynthesis pathways. Green boxes are down-regulated genes and Red boxes are up-regulated genes.

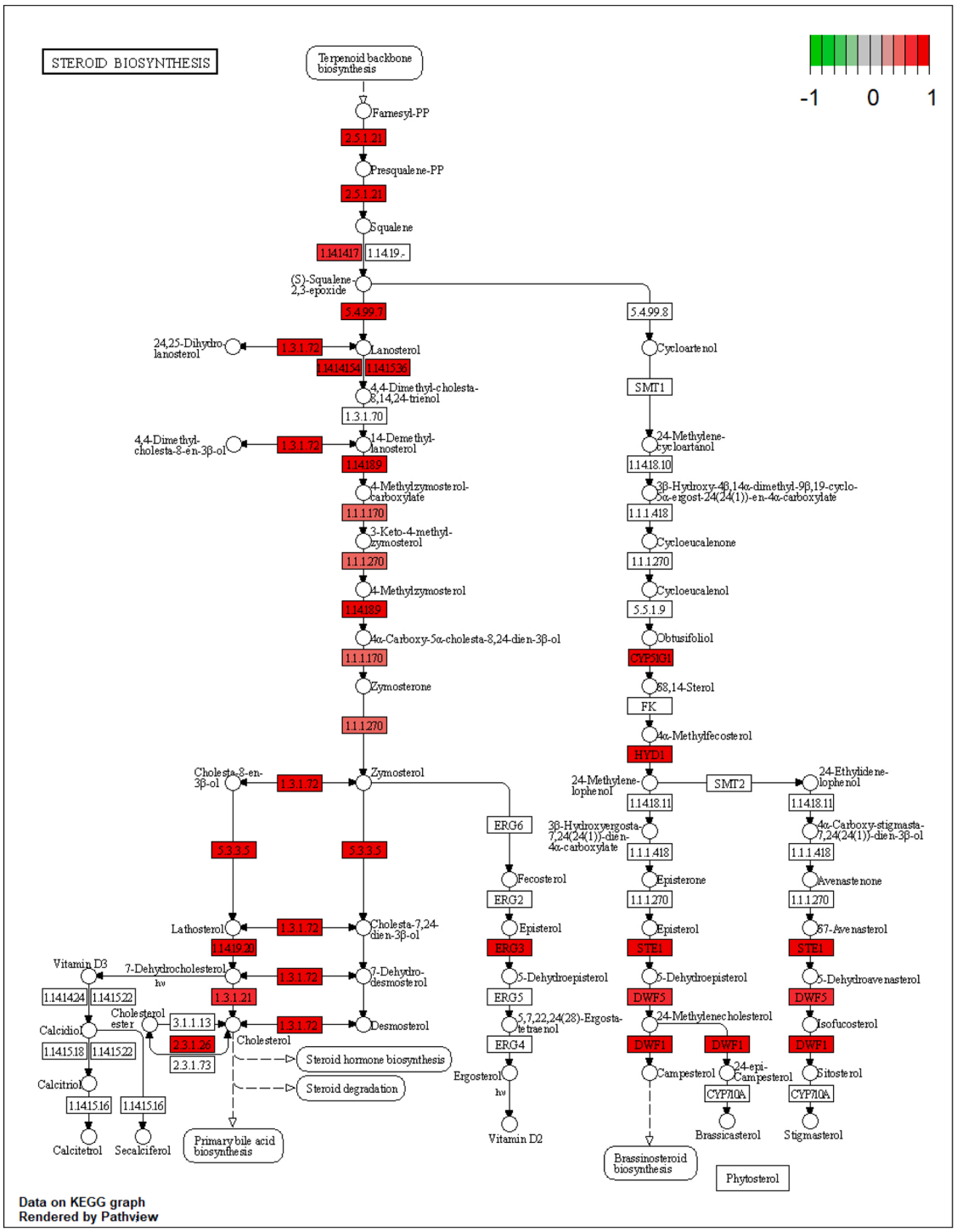

Fig. 9. (*continued*).

Table 4
Main pathways of up-regulated and down-regulated genes.

Down-regulated		Up-regulated	
Pathway	P value	Pathway	P value
Axon Guidance	0.01	Steroid BioSynthesis	0.05

LINC00639 has been among lncRNAs whose expression profiles have been associated with progression of lung cancer [26]. HOTTIP has been shown to promote proliferation of prostate cancer cells and their migratory potential through sequestering miR-216a-5p [27]. Besides, HOTTIP can establish a complex with TWIST1 and with WDR5 to induce expression levels of HOXA9 through induction of alterations in chromatin structure leading to aggressive cellular phenotypes [17]. HOTTIP binding with WDR5 is also implicated in induction of cancer stem cell features and enhancement of activity of Wnt/β-catenin pathway [6]. HCP5 is another down-regulated lncRNA by AA. This lncRNA has been shown to promote proliferation of prostate cancer cells through sequestering miR-4656 and modulating expression of CEMIP [9]. FAM201A has been reported to be involved in the radioresistance phenotype of lung cancer through increasing expression of EGFR via

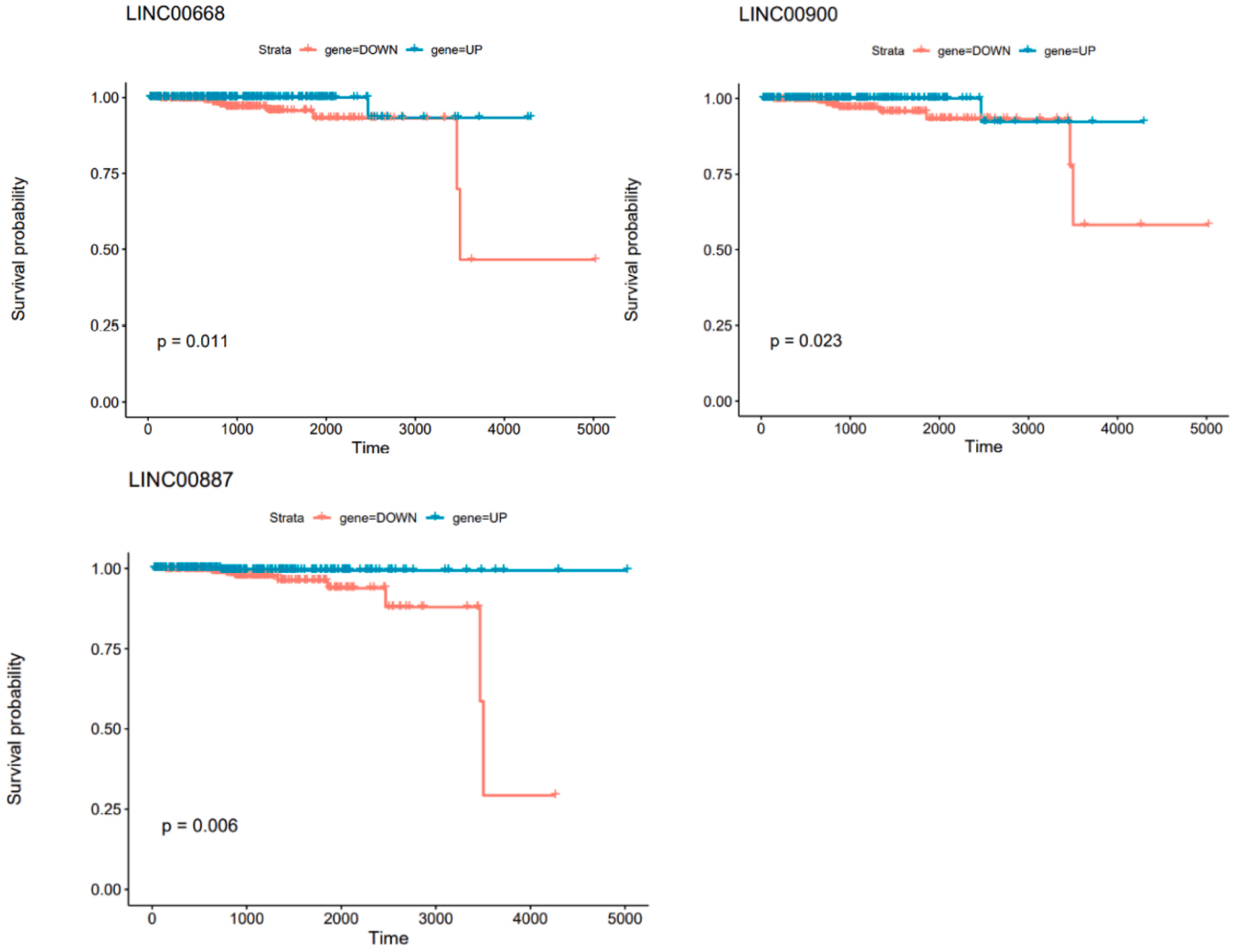

Fig. 10. Kaplan–Meier survival curves of DElncRNAs associated with overall survival of patients with prostate cancer.

miR-370 [7]. COLCA1 is among candidate susceptibility genes for colorectal cancer which have been identified via assessment of eQTL [3].

Among the up-regulated lncRNAs by AA was PART1. This lncRNA is a prostate-specific androgen-regulated gene [12] being up-regulated in prostate cancer [21,29]. Moreover, AA could enhance expression of the oncogenic lncRNA UCA1 in prostate cancer cells. This lncRNA has been reported to act as a ceRNA for miR-134, thus promoting progression of prostate cancer [30]. Future studies are needed to find the functional consequences of up-regulation of these lncRNAs by AA.

miR-29b has been shown to inhibits prostate cancer growth and induces apoptosis through enhancing expression of Bim [22]. Therefore, up-regulation of this miRNA by AA might represent a possible mechanism for anti-cancer effect of AA.

The main pathways for the down-regulated genes and the up-regulated genes are Axon Guidance and Steroid BioSynthesis, respectively. The relevance of these DEGs with Axon Guidance can be explained by the previous finding showing induction of axon guidance processes in the bone or bone marrow stroma by osteolytic cancer cells [8]. The Steroid BioSynthesis is explicitly implicated in the prostate cancer through modulation of androgen levels.

Survival analysis showed that LINC00668, LINC00887 and LINC00900 were significantly correlated with reduced survival time in patients with prostate cancer. LINC00668 has an established role in the enhancement of progression of breast cancer through inhibition of apoptosis and induction of cell cycle transition [18]. LINC00887 is an oncogenic lncRNA in nasopharyngeal carcinoma that influences cell proliferation through miR-203b-3p/NUP205 axis [31]. LINC00900 has been among TLR-related lncRNAs whose expressions are associated with survival esophageal cancer patients [13].

Taken together, our study shows altered expression of several cancer-related lncRNAs in prostate cancer cells upon treatment with AA. Functional consequences of these alterations should be assessed in future studies.

Conflict of interest

The authors declare they have no conflict of interest.

Acknowledgement

The authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, cooperation and assistance throughout the period of study.

Author's statement

SGF wrote the draft and revised it. MT designed and supervised the

study. AS, FR and BMH performed the bioinformatic analysis and designed the figure and tables.

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