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Original Article

KAT5 and KAT6B are in positive regulation on cell proliferation of prostate cancer through PI3K-AKT signaling

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Abstract: Histone modifications play important roles in the tumorigenesis and progression of prostate cancer (PCa) and genes involved in histone modifications are seemed as ideal targets for treatment of PCa patients. However, clinical trials have shown that those existing drugs exert the minimal antitumor activity and excess adverse effects on PCa patients. Therefore, it is of great interest to figure out novel specific biomarkers to guide the development of new drugs. In present study, an RNAi screening with 44 genes involved in histone modifications was applied to a PCa cell line, Du145. The results showed that nine genes were in positive regulation of Du145 cell growth. Then four selected genes (KAT2B, KAT5, KAT6B and HDAC1) were found to exert this effect by a gene-specific manner when silenced. And then KAT5 or KAT6B silenced cells were subjected to DNA microarray analysis. The common differentially expressed genes were analyzed by Ingenuity Pathway Analysis (IPA) and found that PDEF signaling, EIF2 signaling and PI3K signaling was suppressed following by KAT5 or KAT6B silencing. Subsequent immunoblotting assay showed that AKT signaling was inhibited, which suggested that KAT5 or KAT6B regulates cancer cell growth through PI3K-AKT signaling. Together with our published data [31] that AURKA inhibitoin increased drug sensitivity of DU145, our work demonstrated the underlying mechanism that how the acetylation enzyme regulates cancer cells survial and might provide potential therapeutic targets for prostate cancer patients in future epigenetic drug development.

Keywords: Prostate cancer, histone modifications, RNAi screening, KAT5, KAT6B, PI3K-AKT signaling

Introduction

Epigenetic modifications are implicated in development and progression of various cancers, including prostate cancer, the most common noncutaneous malignancy and the second leading cause of cancer death among men in the United States [1]. Epigenetic modifications are comprised of DNA methylation, histone modifications (including acetylation, methylation, ubiquitinylation, phosphorylation, poly-ADP ribosylation, sumoylation, carbonylation and glycosylation), nucleosome remodeling and RNA-associated silencing, and growing evidences suggest that there are interplay between these four means of modifications and that they may compose of a complex machinery to regulate gene function. Histone modifications play roles in regulation of not only gene expression but also alternative splicing of pre-mRNA [2]. Furthermore, Chromatin organization, mediated by histone modifications, is a major influence on regional mutation rates in human cancer cells [3]. These suggest the importance of histone modifications in tumor cells and the possibility that genes linked to histone modifications are therapeutic targets for cancer.

Prostate cancer is proposed to be a model of 'epigenetic catastrophe', in which epigenetic changes that occur during the earliest stages of tumor initiation are maintained throughout disease progression [4]. In prostate cancer, histone acetylation seems to be closely involved in regulating the activity of the androgen receptor. Most co-activators (such as KAT2B, KAT5, NCOA1 and EP300) and co-repressors (such as HDAC1, HDAC2, HDAC3 and SIRT1) of the androgen receptor influence transcriptional activity by regulating the acetylation of either

androgen-responsive genes or the androgen receptor itself, via their respective histone acetyl transferase (HAT) or histone deacetylase (HDAC) activities [5-10]. Profiles of histone modifications (especial histone methylation) are altered in prostate cancer and may be used to predict disease outcome [11]. Histone H3K4m1, H3K9m2, H3K9m3 and acetylation of both H3 and H4 are all considerably reduced in prostate cancer compared with nonmalignant tissue, whereas H3K4m1, H3K4m2 and H3K4m3 are markedly increased in tissue from patients with castration-resistant prostate cancer (CRPC) [12]. Furthermore, overexpression of histone-modifying enzymes has also been linked to prostate cancer progression. Overexpression of HDAC1 and HDAC2 conveys poor prognosis and has a highly significant negative prostate-specific antigen (PSA) relapse-free survival [13, 14]. High levels of lysine-specific demethylase 1A (KDM1A) correlate with an increased risk of relapse in patients with primary prostate cancer [15]. Enhancer of zeste homolog 2 (EZH2), a subunit of Polycomb repressive complex 2 (PRC2), silences gene expression via its histone methyltransferase activity. EZH2 expression is dysregulated in various cancers, including prostate cancer, and is associated with metastasis [16, 17]. EZH2 are also upregulated in CRPC patients [18].

Epigenetic drugs, mainly DNA methyltransferase (DNMT) or HDAC inhibitors have demonstrate their antitumor activity in vitro. However, the excess toxicity [19, 20] or minimal clinical activity [21] of HDAC inhibitors hinder the further evaluation in clinical trials. The main obstacle may lie in the non-specific inhibition of inhibitors to HDACs, which may subsequently activate some unwanted genes, such as transposable elements contributing to tumorigenesis or some oncogenes. Therefore, it is worth to investigating systematically the effect of genes involved in histone modifications on proliferation of prostate cancer cells.

In this work, a high throughput RNAi screening with genes involved in histone modifications was applied to DU145 cells. 9 histone modifications-related genes were found to be in positive control of Du145 cell growth, then four of them were selected and found that they played the role by a gene-specific manner. Finally the underlying mechanisms by which KAT5 or KAT6B regulated the cell proliferation were examined by DNA microarray analysis and immunoblotting experiments. The candidate genes we found might provide potential targets for prostate cancer therapy. Moreover, our previously published data that AURKA inhibition increasing the drug sensitivity in prostate cancer cell line [31] would suggest a powerful combination therapy strategy, although it needs to be addressed more *in vitro* and *in vivo*.

Materials and methods

Cell culture

Du145 (American Type Culture Collection, Rockville, Md.) were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS), penicillin (100 IU/ml) and Streptomycin (100 μg/ml) (Life Technologies) in a humidified atmosphere containing 5% CO_2 at 37°C. Cells in the exponential growth phase were used for all the experiments.

shRNA construction and lentivirus infection

44 genes involving histone modifications were subjected to shRNA primer design and eight distinct shRNA fragments for each gene were constructed into lentivirus vector (Invitrogen, BLOCK-iT™ Lentiviral RNAi Expression System, K4944-00), the eight shRNA plasmids for each gene were separated into two groups (A-D and E-H), four plasmids in each group were mixed with equal amount and the mixtures were applied to shRNA lentivirus package and the obtained lentivirus were titered in HEK293T cells according to the manufacturer's protocol. The obtained two shRNA pools for each gene were used for RNAi screening. Du145 cells were infected with shRNA lentivirus at MOI of 10 in the presence of polybrene (8 μg/ml).

MTS cell proliferation assay

The tetrazolium compound (MTS) cell proliferation assay is a quantitative colorimetric assay for mammalian cell survival and proliferation. Du145 cells (4×10^3) were grown in 100 μl of culture medium containing serum per well in a 96-well plate. After 24 h, the cells were treated by shRNA lentivirus for 96 h. Every treatment for each cell line was triplicate in the same experiment. Then 20 μl of MTS (CellTiter 96 AQueous One Solution Reagent; Promega) was added to each well for 1 to 4 h at 37°C. After

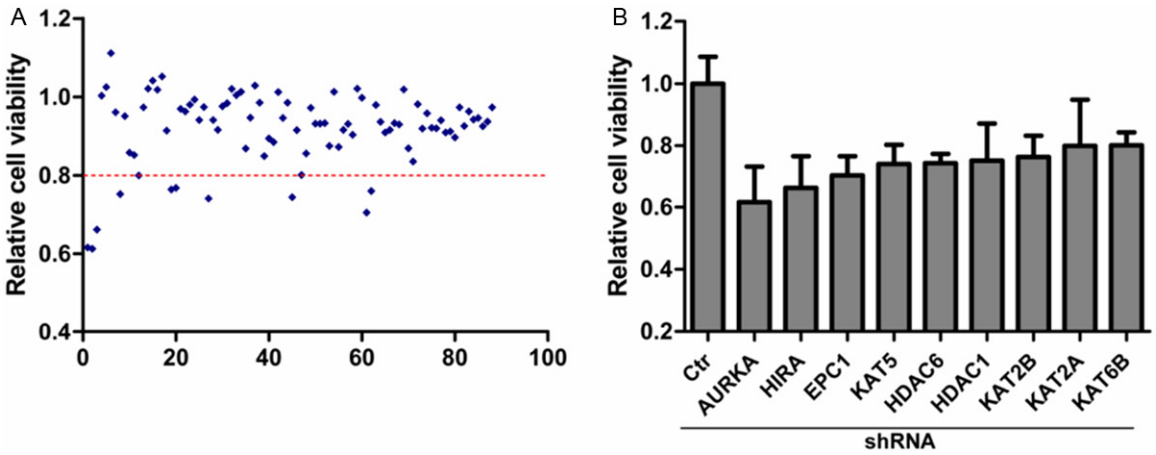

Figure 1. RNAi screening in Du145 cells. A: Primary screening results. shRNA library of 44 genes involved in histone modifications was applied to Du145 cells, the cell viability was detected by MTS assay and plotted. The red line in figure represented the relative cell viability was 0.8; dots under the red line represented the positive hits in screening. B: Histogram shown the relative cell viability of the positive hits.

incubation, the absorbance was read at a wavelength of 490 nm according to the manufacturer's protocol.

Quantitative PCR

Du145 cells were infected with lentiviral shRNA under condition above mentioned. After 24 h, the culture medium was refreshed. RNA was extracted 72 h later and cDNA was synthesized using PrimeScript RT reagent kit with gDNA Eraser (Takara, RR074A) for RT-PCR with oligo-dT. Real-time qPCR was performed on CFX-96 (Bio-lab), with endogenous control Actb. Gene expression was calculated relative to expression of hActb endogenous control and adjusted relative to expression in shControl-infected cells. The primers for qPCR validation were as follows: Actb: forward (F): 5'-GCATCCCCCAAAGTTCACAA-3', reverse (R): 5'-GGACTTCCTGTAACAACGCATCT-3'; KAT2B: F: 5'-GTTACTGCAACGTGCCACAGTT-3', R: 5'-TGAAGACCGAGCGAAGCAAT-3'; KAT5: F: 5'-GACGGAAGCGAAAATCGAATTG-3', R: 5'-GCTGACGGTATTCCATCAGAG-3'; KAT6B: F: 5'-GACTCCATTGGGCTGTAATCAGT-3', R: 5'-TTTGTGTCCCCCTGTTGTTGT-3'; HDAC1: F: 5'-TGACAAGCGCATCTCGATCT-3', R: 5'-CTTCAGAATCGGAGAACTCTTCCT-3'.

DNA microarray

Du145 cells in 12-well plate were left untreated or treated with KAT5 or KAT6B shRNA pool for 96 h. All the samples were homogenized with 0.5 ml Trizol (Invitrogen, Life Technologies) and total RNAs were extracted according to the manufacturer's instruction. 500 ng total RNA was used to synthesize double-strand cDNA and in vitro transcribed to cRNA, purified 10 μg cRNA was used to synthesize 2nd-cycle cDNA and then hydrolyzed by RNase H and purified. Above steps were performed with Ambion WT Expression Kit. 5.5 μg 2nd-cycle cDNA was fragmented and the single-stranded cDNA was labeled with GeneChip2 WT Terminal Labeling Kit and Controls Kit (Affymetrix, PN 702880). About 700 ng fragmented and labeled single-stranded cDNA were hybridized to an Affymetrix GeneChip Human Gene 1.0 ST array, which was washed and stained with GeneChip2 Hybridization, Wash and Stain kit (Affymetrix). Functional annotation was performed to the differential expression genes with Ingenuity Pathway Analysis (IPA) online software.

Protein isolation and western blotting

Cell pellets were resuspended in 1×SDS loading buffer (1 mmol·L^{-1} Na_3VO_4, 10 mmol·L^{-1} NaF, 1 mmol·L^{-1} PMSF) containing protease inhibitors. Lysates (20 μg each lane) were applied to SDS-PAGE. Immunoblotting of Abs specific for GAPDH (Abmart, 080922), AKT (Santa Cruz, sc-8312) and p-AKT (Santa Cruz, SC-7985-R) were detected using HRP-conjugated anti-mouse (Promega) or anti-rabbit (Promega) and visualized by chemiluminescence detection system (Millipore, WBKLS0500).

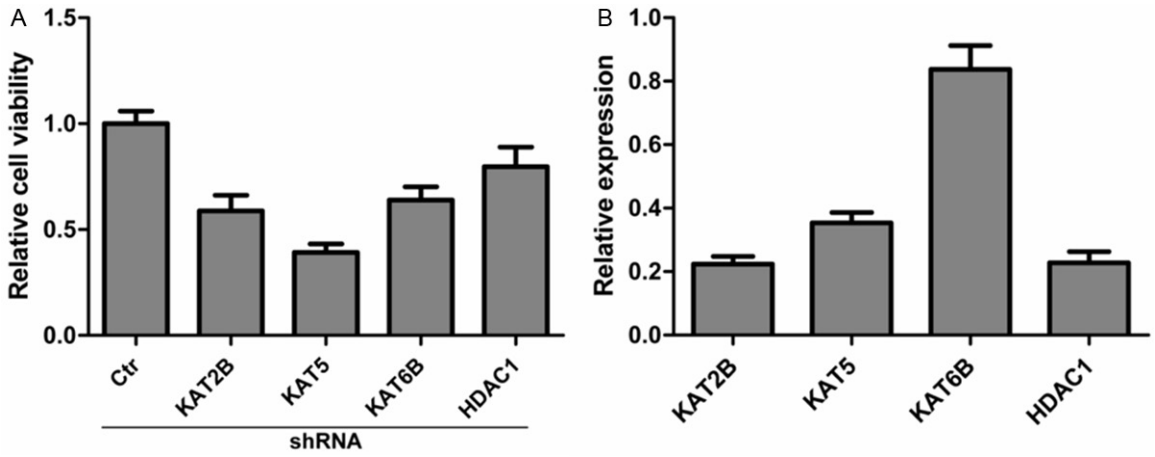

Figure 2. Four genes-specific knockdown inhibits the growth of Du145 cells. A: Cell viability following each gene silencing. B: Relative expression of each gene after it was silenced by the corresponding shRNAs.

Results

RNAi screening showed that several HAT and HDAC genes are in positive regulation of Du145 cell proliferation

shRNA library for 44 genes involving histone modifications was applied to Du145 cells to screen genes that play roles in proliferation of prostate cancer cells (**Figure 1A**). The screening results showed that RNAi of 9 genes (corresponding to 12 pools of shRNA) significantly ($p<0.05$) inhibited Du145 proliferation by higher than 20% (**Figure 1B**). The 9 genes are AURKA, HIRA, EPC1, KAT2A, KAT2B, KAT5, KAT6B, HDAC1 and HDAC6. AURKA is a cell cycle-regulated kinase and has been proposed to regulate H3ser10 phosphorylation and hence to play critical roles in mouse oocyte meiosis [22]. HIRA encodes a histone chaperone that preferentially places the variant histone H3.3 in nucleosomes. EPC1 protein, a member of the polycomb group family, is a component of the NuA4 histone acetyltransferase complex and can act as both a transcriptional activator and repressor. KAT2A, KAT2B, KAT5 and KAT6B genes all encode HATs, while HDAC1 and HDAC6 proteins are typical HDACs.

Silencing of HAT and HDAC genes specifically inhibits Du145 cell proliferation

And then, four genes (KAT2B, KAT5, KAT6B and HDAC1) were selected to validate the primary screening. The inhibition to cell proliferation (**Figure 2A**) and gene knockdown efficacy (**Figure 2B**) following shRNA treatment were assayed by MTS and qPCR, respectively. The results showed that silencing of these four genes inhibited Du145 cell viability by 41%, 61%, 36% and 20% respectively, the knockdown efficacy was 78%, 65%, 16% and 77% respectively. These data suggest that silencing of these four genes specifically inhibits Du145 cell proliferation.

Microarray data showed that PI3K signaling was inhibited by KAT5 or KAT6B knockdown

To elucidate the mechanism by which HATs regulate proliferation of prostate cancer cells, cell samples silencing of KAT5 or KAT6B were applied to DNA microarray chips. The common expression-altered (upregulated by higher than 50% or downregulated to lower than 80%, $p<0.05$) genes between KAT5 knockdown and KAT6B knockdown were as follows: 32 upregulated genes and 280 downregulated genes. Then these 312 genes were applied to Ingenuity pathway analysis (IPA). IPA results showed that PDEF signaling, EIF2 signaling and PI3K signaling were all inactivated following KAT5 or KAT6B knockdown. PIK3CA, the core component of these pathways, was downregulated to 0.72 and 0.73 of that in untreated cells, respectively, following KAT5 or KAT6B silencing. And hence the downstream signaling, including AKT, ERK and NF-κB signaling, was predicted to be inhibited (**Figure 3**). Furthermore, HDAC1 expression was decreased to 0.74 and 0.30 of that in untreated cells, after KAT5 or KAT6B knockdown.

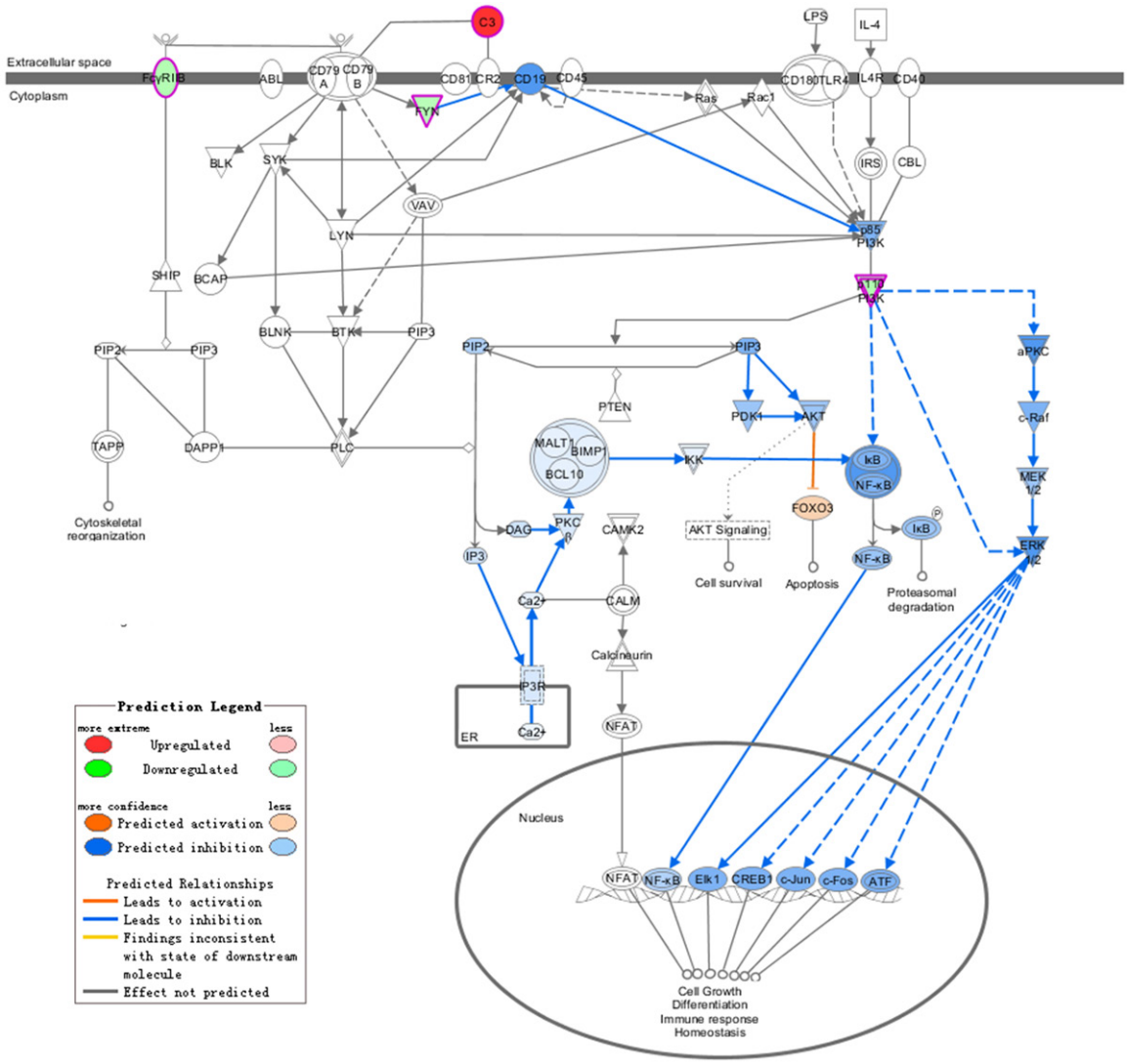

Figure 3. PI3K signaling was predicted to be suppressed following KAT5/KAT6B silencing. Based on the downregulation of PIK3CA when KAT5/KAT6B silenced, IPA predicted that the downstream AKT, ERK and NF-κB signaling were all inhibited, and hence repressed Du145 cell growth.

AKT/ERK signaling was suppressed by KAT5 or KAT6B knockdown

To validate the prediction by IPA, western blotting was performed for cell samples treated with KAT5 or KAT6B shRNA. The results showed that with KAT5 or KAT6B knockdown, p-AKT proteins were both dramatically reduced in Du145 cells (**Figure 4**), suggesting that the upstream signaling of AKT, possible PI3K signaling, is inhibited.

Discussion

The everlasting progression of prostate cancer makes it urgent to develop new strategies and novel drugs to kill the cancer cells. It seems likely that epigenetic drugs may meet the demand because the crucial roles of epigenetic modifications on tumorigenesis and progression of prostate cancer. However, the clinical trials showed that the non-specific HDAC inhibitors exert the minimal activity and adverse effect on patients with prostate cancer [19-21]. Therefore, it would be very valuable to identify histone modifications-related genes that play roles in growth of prostate cancer cells.

In this work, an RNAi screening with genes involved in histone modifications was applied to Du145 cells. The results showed that not only HDAC genes (HDAC1 and HDAC6), but also

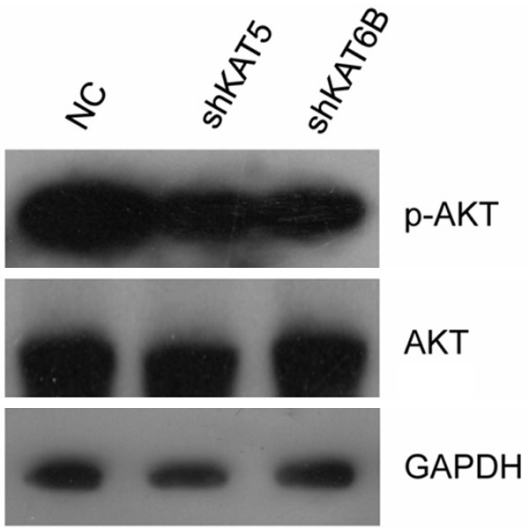

Figure 4. Immunoblotting of AKT/p-AKT for KAT5/KAT6B silenced cells. Proteins from cells treated with negative control (NC) shRNAs or KAT5/KAT6B shRNAs were used to investigate the protein expression of phosphorylation of AKT. The total AKT protein and GAPDH were used as loading control.

HAT genes (EPC1, KAT2A, KAT2B, KAT5 and KAT6B) and other genes (AURKA and HIRA) are in positive control of Du145 cell growth, indicating the possibility that all or partial of these genes may be in a complex machinery to coordinately control the expression and function of some gene(s) and hence to control the cell growth. This hypothesis can be further supported by the microarray data, in which HDAC1 was downregulated when KAT5 or KAT6B was silenced.

The four genes (KAT2B, KAT5, KAT6B and HDAC1) were shown to specifically inhibit Du145 cell growth. Malatesta et al reported recently that KAT2B is required for Hedgehog-Gli-dependent transcription and cancer cell proliferation of brain tumors and that KAT2B may be a potential therapeutic target for the treatment of patients with medulloblastoma and glioblastoma [23]. KAT5, a coactivator of androgen receptor, is involved in multiple cellular processes including transcriptional regulation, DNA damage repair and cell signaling. It is proposed that KAT5 promotes prostate cancer cell proliferation by translocation of androgen receptor into the nucleus [24] and that KAT5 is overexpressed in aggressive prostate cancers and may be partial reason for CRPC initiation [25]. KAT6B can induce the expression of Brahma (BRM), a novel anticancer gene, which is frequently inactivated in a variety of tumor types [26]. In addition, KAT6B interacts with ING5, members of the ING family of tumor suppressors [27]. HDAC1, a gene that is frequently overexpressed in many types of cancer, is required for cancer cell proliferation and growth of prostate cancer and exocrine pancreatic cancer [28, 29] and is involved in the expression regulation of p53 and SIRT1 [30]. Our results are consistent with these previous studies. Moreover, our screening result that AURKA as a positive hit was also consistent with our published data that AURKA inhibition induces the DU145 apoptosis and therefore enhances the sensitivity to drug treatment [31].

DNA microarray data were analyzed by IPA. IPA results showed that PI3K signaling was inhibited by KAT5 or KAT6B silencing, and the downstream AKT, ERK and NF-κB signaling was predicted to be inhibited, too. The subsequent immunoblotting experiments showed that AKT signaling was really repressed by KAT5 or KAT6B silencing, suggesting that KAT5 or KAT6B positively regulate cell growth of prostate cancer cells through PI3K-AKT signaling. Meanwhile, the status of ERK and NF-κB signaling needed to be further validated. In addition, previous studies suggest that KAT5 silencing suppressed the growth of prostate cancer cells by inducing cell-cycle arrest at the G1 phase [24]. The alterations on cell cycle fraction with KAT5 or KAT6B silencing also need to be further examined.

In summary, our work might provide potential therapeutic targets for prostate cancer patients. With the development of novel drugs specifically targeted to these genes, the adverse effect of existing drugs (such as non-specific HDAC inhibitors) may be avoided and the antitumor activity may be improved. Moreover, the mechanism by which some histone modification-related genes (such as KAT5 or KAT6B) regulate the growth of prostate cancer cells was elucidated.

Disclosure of conflict of interest

None.

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