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Original Article

PGC1α as a downstream effector of KDM5B promotes the progression of androgen receptor-positive and androgen receptor-negative prostate cancers

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Abstract: PPARγ coactivator-1α (PGC1α), as a co-activator, is known to optimize the action of several transcription factors, including androgen receptor (AR). However, the precise functions of PGC1α in prostate cancer, particularly those via the non-AR pathways, remain poorly understood. Meanwhile, our bioinformatics search suggested that PGC1α could be a direct downstream target of lysine-specific demethylase 5B (KDM5B/JARID1B/PLU1). We herein aimed to investigate how PGC1α induced prostate cancer outgrowth. Immunohistochemistry in radical prostatectomy specimens showed that the levels of PGC1α expression were significantly higher in prostatic adenocarcinoma [H-score (mean ± SD): 179.0 ± 111.6] than in adjacent normal-appearing tissue (16.7 ± 29.9, $P<0.001$) or high-grade prostatic intraepithelial neoplasia (79.0 ± 94.7, $P<0.001$). Although there were no strong associations of PGC1α expression with tumor grade or stage, outcome analysis revealed that patients with high PGC1α (H-score of ≥200) tumor had a significantly higher risk of postoperative biochemical recurrence even in a multivariable setting (hazard ratio 5.469, $P=0.004$). In prostate cancer LNCaP and C4-2 cells, PGC1α silencing resulted in considerable reduction in the levels of prostate-specific antigen expression. Interestingly, PGC1α silencing inhibited the cell viability of not only AR-positive LNCaP/C4-2/22Rv1 lines but also AR-negative PC3/DU145 lines. Chromatin immunoprecipitation assay further revealed the binding of KDM5B to the promoter region of *PGC1α* in these lines. Additionally, treatment with a KDM5 inhibitor KDM5-C70 considerably reduced the expression of PGC1α and prostate-specific antigen, as well as the cell viability of all the AR-positive and AR-negative lines examined. PGC1α silencing or KDM5-C70 treatment also down-regulated the expression of phospho-JAK2 and phospho-STAT3 in both AR-positive and AR-negative cells. These findings suggest the involvement of PGC1α, as a downstream effector of KDM5B, in prostate cancer progression via both AR-dependent and AR-independent pathways. KDM5B-PGC1α is thus a potential therapeutic target for both androgen-sensitive and castration-resistant tumors. Meanwhile, PGC1α overexpression may serve as a useful prognosticator in those undergoing radical prostatectomy.

Keywords: Androgen receptor, KDM5B, PGC1α, prostate cancer

Introduction

Prostate cancer has represented one of the most commonly diagnosed malignancies, while the number of cancer-related deaths throughout the world appears to be considerably increasing (*e.g.* 307,500 in 2012 [1], 375,304 in 2020 [2]). Although definitive therapy, such as radical prostatectomy, often offers a cure in most patients with localized disease, they have a risk of developing recurrent disease for which adjuvant therapy is required [3, 4]. More critically, those with advanced hormone-naïve prostate cancer who are usually sensitive to androgen deprivation therapy eventually develop castration-resistant disease for which treatment options are currently limited [5, 6]. Meanwhile, the activity of androgen receptor (AR), a member of the nuclear receptor superfamily, is well known to be associated with the outgrowth of even castration-resistant prostate cancer [5-7].

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As its name indicates, PPARγ coactivator-1α (PGC1α) has originally been identified as a co-activator of PPARγ [8, 9]. Subsequent studies have indicated that PGC1α interacts with other nuclear receptors, such as estrogen receptor-α, estrogen receptor-β, estrogen-related receptor-α, glucocorticoid receptor, mineralocorticoid receptor, and retinoid X receptors, and transcriptionally activates them [9-12]. It has also been documented that PGC1α induces the growth of prostate cancer cells via functioning as an AR coactivator which enhances AR N/C-terminal interactions and DNA binding to the androgen response elements in the promoters of target genes, including *prostate-specific antigen* (*PSA*) [13]. However, it remains uncharacterized how PGC1α promotes prostate cancer progression, particularly via the pathways other than AR.

Lysine-specific demethylase 5B (KDM5B; also known as JARID1B or PLU1), a histone demethylase, has been implied to involve prostate tumorigenesis [14]. Interestingly, our bioinformatics search suggested that PGC1α could represent a direct downstream target of KDM5B. The present study aimed to further investigate how PGC1α induced prostate cancer progression.

Materials and methods

Prostate tissue microarray (TMA) and immunohistochemistry

Two sets of TMA (75 cases in each set) consisting of retrieved prostate tissue specimens [*i.e.* adjacent normal-appearing prostate, high-grade prostatic intraepithelial neoplasia (HGPIN), prostatic adenocarcinoma] obtained by radical prostatectomy performed at the University of Rochester Medical Center in 2007 were constructed previously upon appropriate approval from the Institutional Review Board, including the request to waive the documentation of informed consent from the patients [15, 16]. None of the patients had received therapy with radiation, hormonal agents, and/or other anticancer drugs pre-operatively or post-operatively prior to clinical/biochemical recurrence defined as a single PSA level of ≥0.2 ng/mL or the introduction of adjuvant therapy.

Immunohistochemical staining was performed on the 5-μm sections, using a primary antibody to PGC1α (clone PA5-38021, dilution 1:200; Thermo Fisher Scientific), as we described previously [16-18]. All stains were manually assessed by two pathologists (Y.T. & Z.Y.) who were blinded to sample identify. The H-score (0-300) [19] was calculated by multiplying the staining intensity (0/1/2/3) by the percentage of immunoreactive cells for each intensity.

Cell lines

Human prostatic carcinoma cell lines, LNCaP, C4-2, 22Rv1, DU145, and PC3, were originally obtained from the American Tissue Type Collection (ATCC) and then authenticated by the institutional core facility. The following ATCC-recommended cell culture media (all from Thermo Fisher Scientific) were used: Roswell Park Memorial Institute 1640 medium for LNCaP and 22Rv1; Dulbecco's modified Eagle's medium for C4-2 and DU145; and Ham's F-12K for PC3. Gene silencing was achieved by transfection of PGC1α-small interfering RNA (siRNA) (sc-38884, Santa Cruz Biotechnology) or non-targeting control-siRNA (sc-37007, Santa Cruz Biotechnology), using Lipofectamine™ 3000 (Thermo Fisher Scientific), as described previously [16, 20].

Chemicals and antibodies

We obtained a KDM5 inhibitor, KDM5-C70, from Xcess Biosciences. Primary antibodies purchased were: PGC1α (dilution for western blotting 1:500); KDM5B (clone 7H3D7, 1:200; Santa Cruz Biotechnology); AR (clone 441, 1:1000; Santa Cruz Biotechnology); PSA (clone 3E6, 1:500; Thermo Fisher Scientific); JAK2 (clone D2E12, 1:1000; Cell Signaling Technology); phospho-JAK2 (Tyr1007/1008, 1:1000; Cell Signaling Technology); STAT3 (clone 124H6, 1:1000; Cell Signaling Technology); phospho-STAT3 (Tyr705 or Ser727, 1:1000; Cell Signaling Technology); and GAPDH (clone 6C5, 1:5000; Santa Cruz Biotechnology).

Western blotting

Total proteins were extracted from the cells collected with RIPA buffer supplemented with a protease and phosphatase inhibitor cocktail (Halt™; Thermo Fisher Scientific), and the DC Protein Assay kit (Bio-Rad) was used for the determination of protein concentration. Equal

amounts of proteins (30 μg) obtained from the cell extracts were separated in 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis, transferred to polyvinylidene difluoride membrane electronically, blocked, and incubated with a primary antibody at 4°C overnight and a HRP-linked secondary antibody (Cell Signaling Technology) for 1 hour at room temperature. Chemiluminescent signals were generated by a Clarity Western ECL Subtrate (Bio-Rad) and detected by ChemiDoc™ MP (Bio-Rad).

Chromatin immunoprecipitation (ChIP) assay

We first performed a bioinformatic search (LASAGNA-Search 2.0 available online at https://biogrid-lasagna.engr.uconn.edu/lasagna_search/[21]) for potential KDM5B binding sites in the promoter of PGC1α. A ChIP assay was then performed, using the Magna ChIP kit (Sigma-Aldrich) according to the manufacturer's recommended protocol with minor modifications, as we described recently [18, 22]. Briefly, cells were cross-linked with 1% formaldehyde for 10 minutes at room temperature, and the lysates were sonicated in nuclear buffer (four 30-s pulses, output 3.0, duty cycle 30% in ice with 120-s rest between pulses; Branson Sonifier 450). Soluble chromatin was immunoprecipitated with an anti-KDM5B antibody or normal mouse IgG (sc-2025, Santa Cruz Biochemistry) directly conjugated with Protein A Magnetic beads (Thermo Fisher Scientific). Immunoprecipitated DNA was eluted and reverse cross-linked, and DNA was extracted and purified using a spin filter column (Thermo Fisher Scientific). DNA samples were eventually analyzed by PCR, using the following primer set: forward, 5'-GTCATCATAGGACAGAAATCAC-3'; reverse, 5'-CCACAATAGGGCACAAATC-3'. The PCR products electrophoresed were visualized using Gel Doc XR+ (Bio-Rad).

MTT (3-(4,5-dimethylthiazol-2-yl)-2,5diphenyltetrazolium bromide) assay

We used the MTT assay to assess cell viability and drug response. Cells (1-5 × 10^3) seeded in 96-well plates were cultured for up to 48 hours in the absence or presence of KDM5-C70, and then incubated with 0.5 mg/mL of MTT (Sigma-Aldrich) in 100 μL of medium for 4 hours at 37°C. MTT was dissolved by 150 μL of dimethyl sulfoxide, and the absorbance was measured at a wavelength of 570 nm with background subtraction at 630 nm.

Statistical analysis

Student's *t*-test and chi-square test were used to evaluate numerical data and categorized variables, respectively. Time-to-event estimates of recurrence-free survival were calculated by the Kaplan-Meier method and compared by the log-rank test. The Cox proportional hazards model was also used to determine the statistical significance of prognostic factors in a multivariable setting. All statistical analyses were performed, using EZR software [23] (R version 4.0.2; The R Foundation for Statistical Computing) or Prism version 10.2.3 (GraphPad Software). A *P* value of less than 0.05 was considered to be statistically significant.

Results

Expression of PGC1α in surgical specimens

We stained immunohistochemically for PGC1α in sets of prostate TMA consisting of a total of 150 radical prostatectomy specimens. Positive signals were detected predominantly in the cytoplasm of non-neoplastic and neoplastic epithelial cells (**Figure 1A**).

The expression levels of PGC1α expression were significantly higher in prostatic adenocarcinomas than in corresponding non-neoplastic normal-appearing prostate ($P<0.001$) or HGPIN ($P<0.001$) tissues (**Table 1**), while the difference between normal and HGPIN tissues was statistically significant ($P<0.001$). When PGC1α levels in prostate cancer were dichotomized at the median H-score (*i.e.* 200), there were no significant differences in clinicopathologic features of the patients, including preoperative PSA, tumor grade, pT or pN staging category, and surgical margin status, between the two groups (**Table 2**).

We then performed Kaplan-Meier analysis coupled with the log-rank test to assess the prognostic value of PGC1α expression. Patients with high PGC1α tumor had a significantly higher risk of biochemical recurrence after radical prostatectomy, compared to those with low PGC1α tumor ($P=0.023$; **Figure 1B**). To further determine if PGC1α immunoreactivity is an independent predictor of postoperative recur-

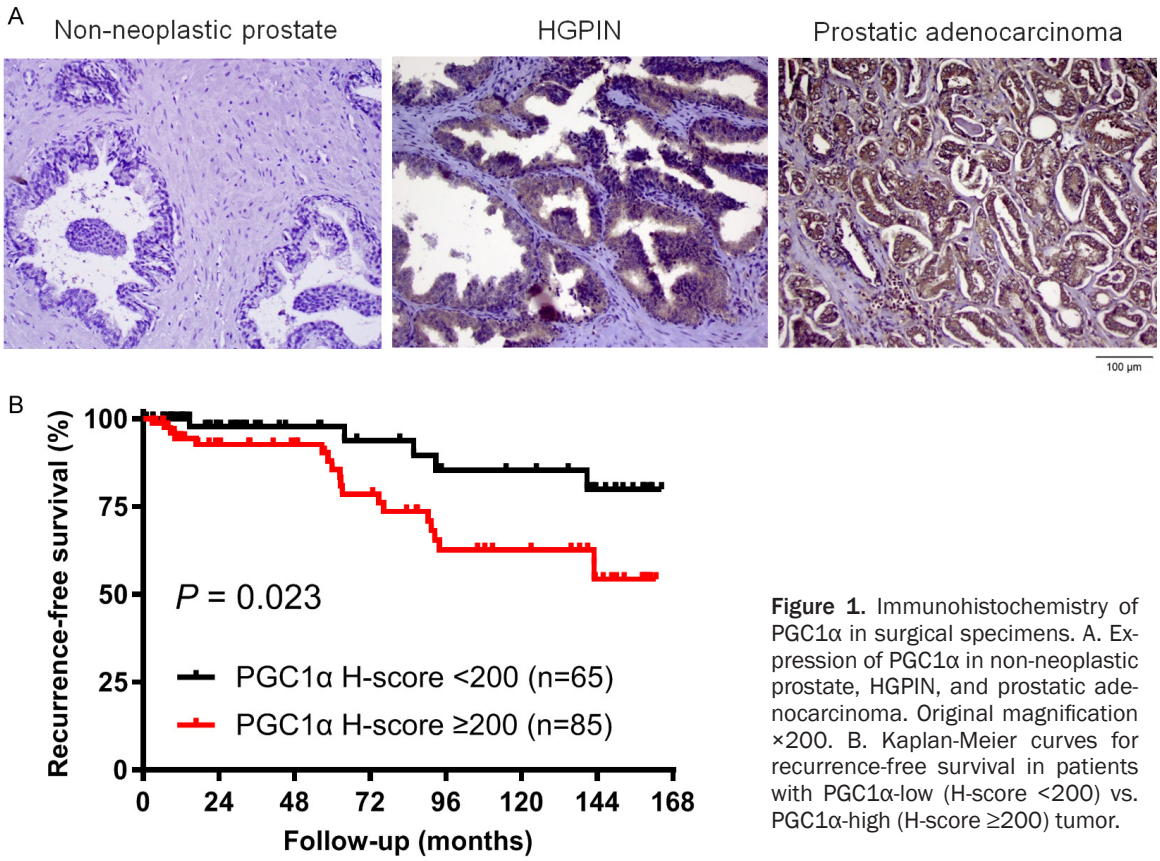

Figure 1. Immunohistochemistry of PGC1α in surgical specimens. A. Expression of PGC1α in non-neoplastic prostate, HGPIN, and prostatic adenocarcinoma. Original magnification ×200. B. Kaplan-Meier curves for recurrence-free survival in patients with PGC1α-low (H-score <200) vs. PGC1α-high (H-score ≥200) tumor.

Table 1. H-scores of immunostaining for PGC1α in radical prostatectomy specimens

Tissue	*n*	H-score [median (IQR)]	H-score (mean ± SD)	*P* (vs. carcinoma)
Non-neoplastic prostate	150	0 (0-20)	16.7 ± 29.9	<0.001
High-grade prostatic intraepithelial neoplasia	145	50 (0-100)	79.0 ± 94.7	<0.001
Prostatic adenocarcinoma	150	200 (100-300)	179.0 ± 111.6	

rence, multivariable analysis of clinicopathologic factors was performed. In the Cox regression model, PGC1α overexpression showed significantly worse recurrence-free survival (hazard ratio 5.469, 95% confidence interval 1.725-17.34, *P*=0.004; **Table 3**).

Impact of PGC1α on cell growth

We first examined the expression of PGC1α in 5 human prostate cancer lines, and western blotting detected its signals in all the cell lines. We next confirmed the silencing of PGC1α by transfection of its siRNA in LNCaP and C4-2, and assessed its effects on the expression of AR and PSA (**Figure 2A**). In both cell lines, PGC1α silencing resulted in considerable reduction in the levels of PSA expression, but not AR expression. We also confirmed the down-regulation of PGC1α expression in other 3 lines with PGC1α-siRNA (**Figure 2B**).

Then, the MTT assay was performed to assess the impact of PGC1α on the proliferation of prostate cancer cells. In all the 5 cell lines examined, PGC1α silencing resulted in significant reduction in the cell viability (**Figure 3**).

Impact of KDM5B on cell growth

A bioinformatics-driven search identified a putative KDM5B binding site in the promoter regions of *PGC1α*. We therefore investigated whether KDM5B could regulate the expression of PGC1α, using a ChIP assay. DNA fragments from LNCaP, C4-2, and 22Rv1 cells immuno-

Table 2. Clinicopathologic features of patients according to the expression of PGC1α

	H-score (mean ± SD)	H-score		*P* (<200 vs. ≥200)
		<200	≥200	
n		65	85	
Age (mean ± SD, year)		60.2 ± 6.9	60.1 ± 6.9	0.942
Preoperative PSA (mean ± SD, ng/mL)		6.03 ± 3.84	6.72 ± 5.22	0.250
Grade Group				0.686
1	180.4 ± 110.5	21 (32%)	30 (35%)	
2	175.7 ± 112.8	32 (49%)	36 (42%)	
3	169.2 ± 123.4	6 (9%)	7 (8%)	
4	212.5 ± 100.3	3 (5%)	9 (11%)	
5	158.3 ± 128.1	3 (5%)	3 (4%)	
pT				0.677
2	178.3 ± 113.4	52 (80%)	63 (74%)	
3a	180.8 ± 107.8	10 (15%)	16 (19%)	
3b	183.3 ± 111.8	3 (5%)	6 (7%)	
pN				0.076[a]
0	181.1 ± 113.3	41 (63%)	54 (64%)	
1	250.0 ± 50.0	0 (0%)	5 (6%)	
X	168.0 ± 111.5	24 (37%)	26 (31%)	
Surgical margin				0.425
Negative	177.2 ± 112.0	60 (92%)	74 (87%)	
Positive	193.8 ± 110.9	5 (8%)	11 (13%)	

PSA, prostate-specific antigen. [a]pN0 *vs.* pN1.

Table 3. Multivariable analysis of clinicopathologic factors for recurrence-free survival

	HR	95% CI	*P*
PSA	0.983	0.883-1.094	0.755
Grade Group			
1	Reference		
2	4.383	0.941-20.41	0.060
3	8.086	1.193-54.80	0.032
4	25.44	4.074-158.9	<0.001
5	73.64	8.428-643.4	<0.001
pT			
2	Reference		
3a	2.366	0.834-6.715	0.106
3b	0.925	0.211-4.058	0.918
Lymph node metastasis	2.946	0.376-23.07	0.304
Surgical margin	1.286	0.335-4.936	0.714
PGC1α	5.469	1.725-17.34	0.004

CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen.

precipitated with an anti-KDM5B antibody or normal IgG were amplified by PCR with a set of primers specific for the promoter of *PGC1α*. The PCR products could be visualized from those precipitated by the KDM5B antibody, but not control precipitants (**Figure 4**), indicating the interaction of KDM5B with the *PGC1α* promoter.

We next assessed the effects of a KDM5 inhibitor on the proliferation of prostate cancer cells. In MTT assay, KDM5-C70 treatment significantly reduced the cell viability of LNCaP in a dose-dependent manner (**Figure 5A**). Similarly, KDM5-C70 significantly inhibited the viability of C4-2, 22Rv1, PC3, and DU145 cells (**Figure 5B**). However, in LNCaP or PC3 cells transfected with PGC1α-siRNA, no significant inhibitory effects of KDM5-C70 on their viability were seen (**Figure 5C**).

Involvement of KDM5B-PGC1α in JAK-STAT signaling

To explore downstream signaling of KDM5B-PGC1α, we examined some of signal transduction pathways known to involve prostate cancer progression and castration resistance [24], including JAK/STAT (**Figure 6**). In both LNCaP

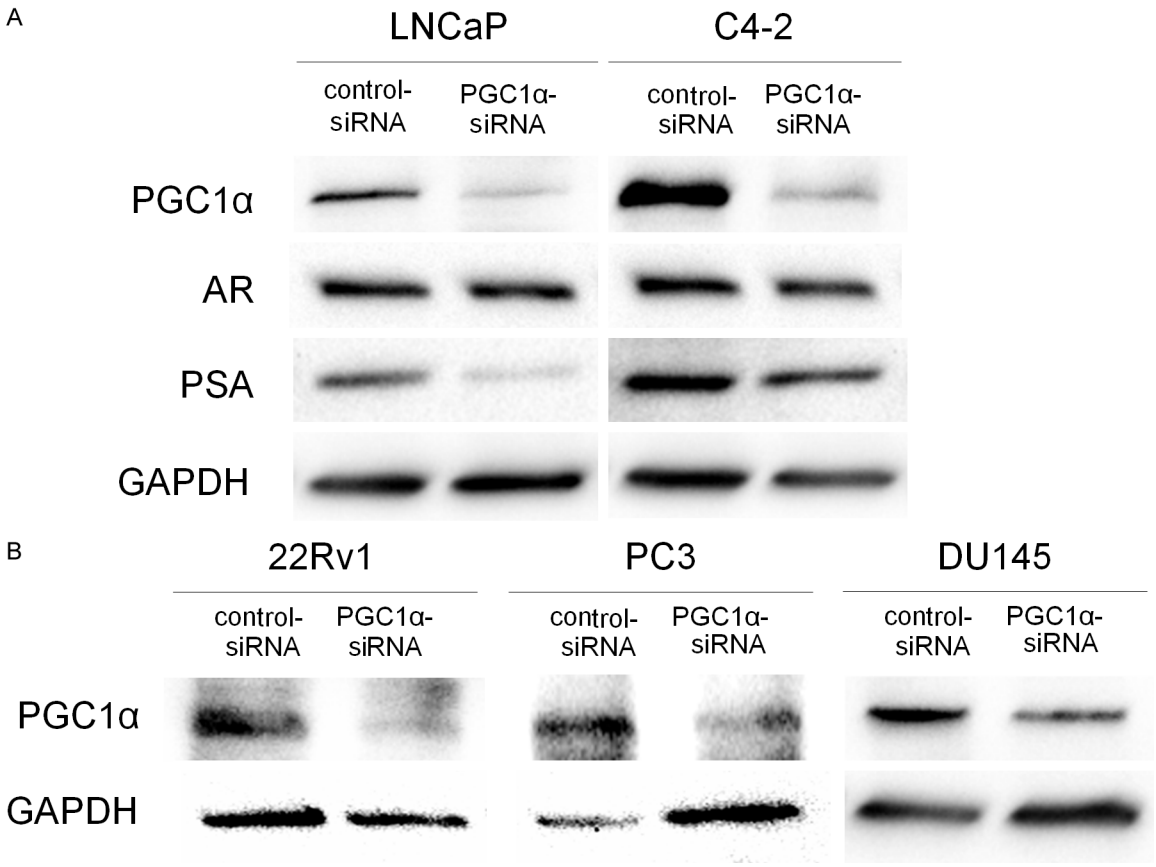

Figure 2. Effects of PGC1α silencing in prostate cancer cells. A. Western blotting of PGC1α, AR (full-length), and PSA in LNCaP and C4-2 cells transfected with control-siRNA vs. PGC1α-siRNA. B. Western blotting of PGC1α in 22Rv1, PC3, and DU145 cells transfected with control-siRNA vs. PGC1α-siRNA. GAPDH served as a loading control.

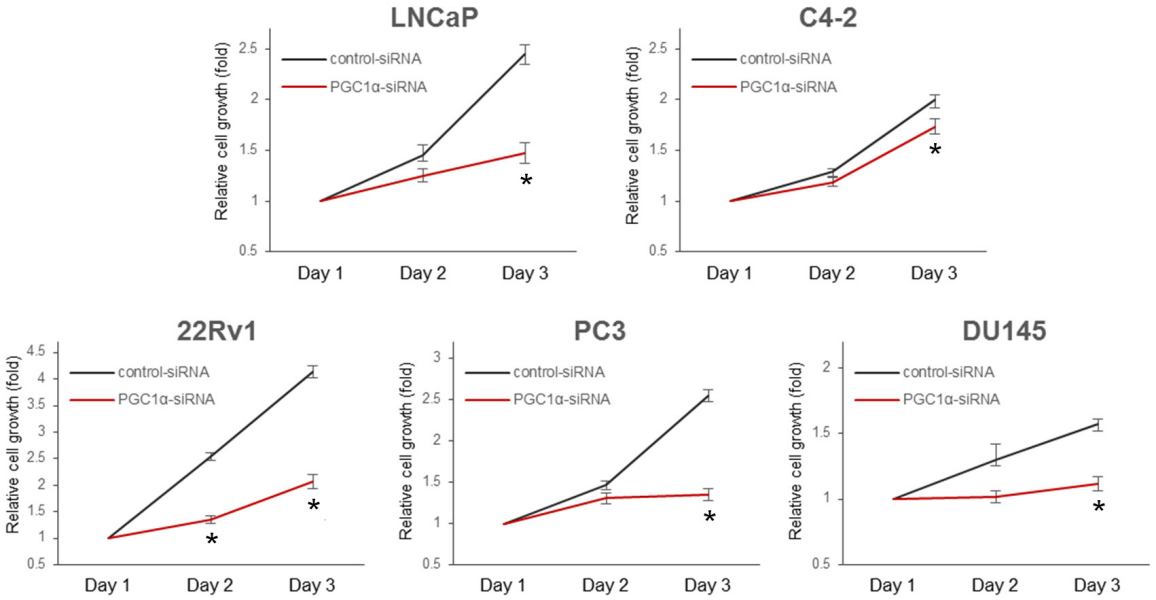

Figure 3. Effects of PGC1α silencing on the proliferation of prostate cancer cells. The MTT assay in LNCaP, C4-2, 22Rv1, PC3, and DU145 cells transfected with control-siRNA vs. PGC1α-siRNA and cultured for additional 24-48 hours. Cell viability representing the mean (± SD) from 3 independent experiments is presented relative to that of each line/transfection on day 1. *P<0.05 (vs. control-siRNA).

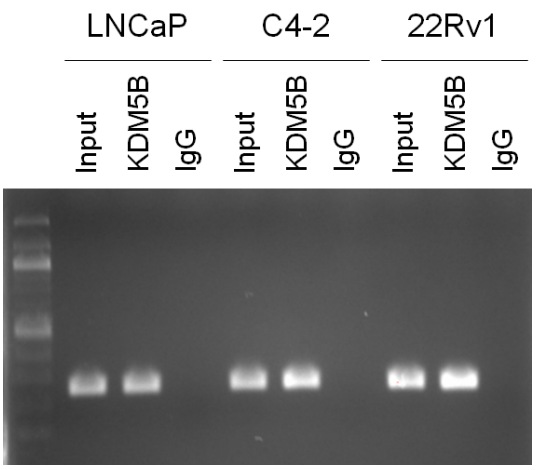

Figure 4. Binding of KDM5B to the *PGC1α* promoter in prostate cancer cells. The ChIP assay, using LNCaP/C4-2/22Rv1 cell lysates immunoprecipitated with an anti-KDM5B (or IgG as a negative control). The DNA fragments were PCR amplified with a set of primers specific for the promoter of *PGC1α*, and the PCR products were electrophoresed on 1% agarose gel and stained with ethidium bromide. Fractions of the mixture of protein-DNA complex (*i.e.* 1% of total cross-linked, reserved chromatin prior to immunoprecipitation) were used as "input" DNAs.

and DU145 cells, PGC1α expression was down-regulated by PGC1α-siRNA and KDM5-C70, whereas KDM5B expression was down-regulated by KDM5-C70, but not by PGC1α-siRNA. In LNCaP cells, the levels of PSA expression were reduced by not only PGC1α-siRNA but also KDM5-C70. Additionally, in both cell lines, PGC1α-siRNA and KDM5-C70 reduced the expression levels of phospho-JAK2 and phospho-STAT3.

Discussion

It is extremely well known that AR activation is associated with the progression of prostate cancer, even castration-resistant disease [5-7]. Meanwhile, the roles of PGC1α [13, 25-28] and KDM5B [14, 29, 30] in prostate cancer have been separately studied. However, their involvement particularly via the non-AR pathways remains largely unknown. Moreover, to the best of our knowledge, the relationship between PGC1α and KDM5B has never been tested. The present study thus aimed to investigate the functional role of PGC1α and KDM5B in the growth of AR-positive and AR-negative prostate cancers.

As aforementioned, PGC1α was identified as a transcriptional coactivator which could particularly regulate the genes involving energy metabolism including mitochondrial biosynthesis [8, 31]. Conflicting data on the functions of PGC1α in prostate cancer progression exist. PGC1α was initially reported to interact with the N-terminus of AR, enhance the transcription of AR target genes, and promote the growth of androgen-sensitive LNCaP cells as well as its castration-resistant derivatives [13]. In addition, androgen treatment in LNCaP and VCaP cells induced the levels of PGC1α mRNA and protein expression, while PGC1α knockdown reduced the growth of C4-2 cells [25]. Conversely, there has been *in vitro* [26] and *in vivo* [27] evidence indicating a suppressive role of PGC1α in the cell invasion and metastasis of prostate cancer. Meanwhile, promoter methylation of *PGC1α* has been linked to the risk of developing prostate cancer [28].

KDM5B has been more extensively studied in non-prostate malignancies [32], such as breast cancer [33]. In prostate cancer, up-regulation of KDM5B expression and its correlation with metastatic disease have been documented [29, 30]. Additionally, in a conditional mouse model, KDM5B knockout resulted in hyperplastic changes within the prostate [14]. KDM5B has also been found to interact with the AR and activate its target genes [29, 30]. Moreover, combined treatment with a KDM5 inhibitor, CPI-455, and a KDM1A inhibitor significantly retarded the growth of LNCaP and C4-2 cells [30].

In line with some of previous observations [13, 25], we herein demonstrated that PGC1α silencing via a commercially available siRNA product consisting of a pool of 3 target-specific 20-25 nt siRNAs reduced the expression levels of an AR target, PSA, without considerably altering those of AR, as well as the viability of AR-positive cells. Similarly, KDM5-C70 treatment inhibited the expression of PSA and the viability of AR-positive cells. Interestingly, the inhibitory effects of PGC1α silencing and KDM5-C70 treatment on the cell growth were similarly seen in AR-negative lines. Because no significant growth suppression by KDM5-C70 was observed in the cell lines with PGC1α-siRNA, the effect of KDM5 inhibition might likely be mediated via PGC1α. However, the inhibi-

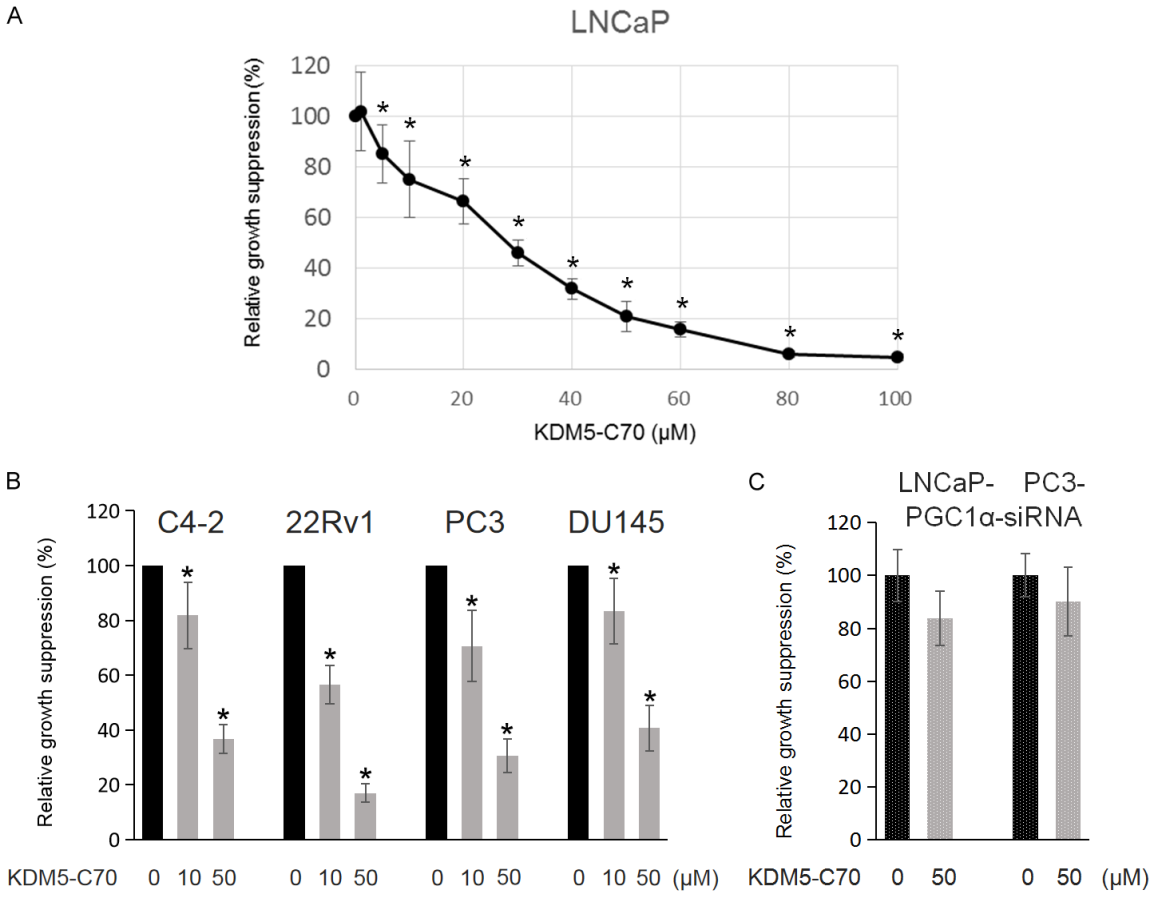

Figure 5. Effects of a KDM5 inhibitor on the proliferation of prostate cancer cells. The MTT assay in LNCaP cultured for 48 hours with 0-100 μM KDM5-C70 (A), as well as C4-2, 22Rv1, PC3, and DU145 cultured for 48 hours with 0-50 μM KDM5-C70 (B) or LNCaP and PC3 transfected with PGC1α-siRNA and cultured for 48 hours with 0-50 μM KDM5-C70 (C), as indicated. Cell viability representing the mean (± SD) from 3 independent experiments (A, B) or triplicate experiments (C) is presented relative to that of mock treatment in each line. *P<0.05 (vs. mock treatment).

tory effects of KDM5-C70, as a pan-KDM5 histone demethylase inhibitor, seemed to be more evident in, for example, C4-2 (especially at 50 μM) than those of PGC1α silencing, implying the involvement of the non-KDM5B/PGC1α pathway in the growth inhibition by KDM5-C70. Moreover, a ChIP assay in prostate cancer cells revealed the interactions of KDM5B with *PGC1α* at its promoter region, indicating the direct regulation of PGC1α expression by KDM5B. These findings suggest that PGC1α represents a downstream effector of KDM5B and promotes prostate cancer progression in both the AR-dependent and AR-independent pathways.

Signal transduction pathways downstream of KDM5B/PGC1α in prostate cancer cells remain unrecognized, while the link between PGC1α and JAK2/STAT3 signaling has been suggested in non-neoplastic cells, such as hepatocytes following ischemia-reperfusion injury [34]. We found that inhibition of KDM5 or PGC1α in both AR-positive and AR-negative prostate cancer cells was associated with inactivation of JAK2 and STAT3. **Figure 7** illustrates the potential downstream signaling pathways of KDM5B/PGC1α in prostate cancer cells, which ultimately induces tumor progression. Meanwhile, the involvement of JAK2/STAT3 in AR signaling in prostate cancer cells has previously been suggested [35].

The increased expression of PGC1α in prostate cancer has been documented [25]. Using sets of TMA consisting of radical prostatectomy specimens, we immunohistochemically demonstrated that PGC1α expression was significant-

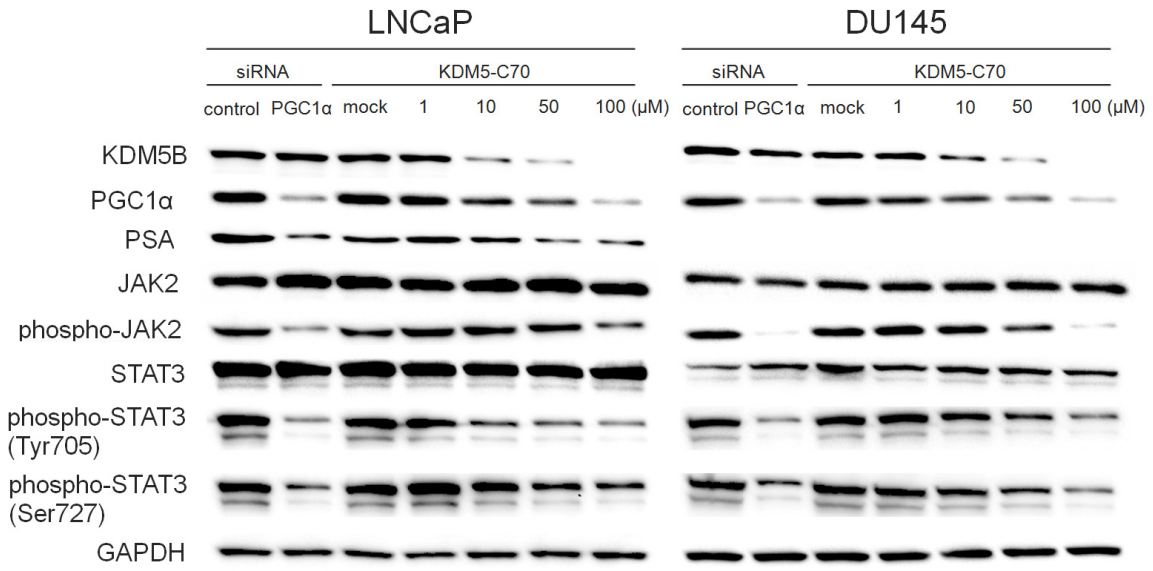

Figure 6. Effects of PGC1α silencing and KDM5 inhibitor treatment on signal transduction pathways in prostate cancer cells. Western blotting of KDM5B, PGC1α, PSA, JAK2, phospho-JAK2, STAT3, and phospho-STAT3 in LNCaP or DU145 transfected with control-siRNA vs. PGC1α-siRNA or cultured for 24 hours with ethanol (mock) vs. 1-100 μM KDM5-C70. GAPDH served as a loading control.

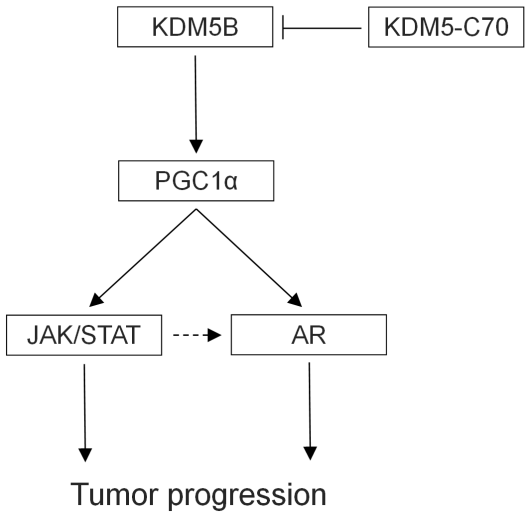

Figure 7. Potential signaling pathway involving prostate cancer progression. In prostate cancer cells, KDM5B up-regulates the expression of PGC1α, leading to the activation of AR and JAK2/STAT3 pathways.

ly elevated in prostatic adenocarcinoma, compared with adjacent normal-appearing prostate or HGPIN. Additionally, when its levels were dichotomized at the median score, there were no significant associations between PGC1α expression in prostate cancer and its histopathology including tumor grade and stage. Nevertheless, the elevated expression of PGC1α, as an independent prognosticator, was associated with a significantly higher risk of postoperative recurrence. These findings in surgical specimens further support our data in cell lines indicating that PGC1α induces the progression of prostate cancer.

In conclusion, we identified that PGC1α, as a downstream effector of KDM5B, could promote prostate cancer progression presumably via both AR-dependent and AR-independent pathways. KDM5B-PGC1α may thus represent a therapeutic target for not only advanced androgen-sensitive prostate cancers but also castration-resistant tumors including AR-negative cases. In addition, PGC1α overexpression in prostate cancer may serve as a useful prognosticator in men undergoing radical prostatectomy.

Disclosure of conflict of interest

None.

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