

RESEARCH COMMUNICATION

Expression and Significance of Microsomal Prostaglandin Synthase-1 (mPGES-1) and Beclin-1 in the Development of Prostate Cancer

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Abstract

The aim of this study was to investigate the expression and significance of microsomal prostaglandin synthase-1 (mPGES-1) and Beclin-1 in the development of prostate cancer (PCa). Immunohistochemistry was performed on paraffin-embedded sections with rabbit polyclonal against mPGES-1 and Beclin-1 in 40 PCa, 40 benign prostatic hyperplasia (BPH) and 10 normal prostate specimens for this purpose. Quantitative real-time polymerase chain reaction (qRT-PCR) was applied for mRNA expression of mPGES-1 and Beclin-1, while MTT assays were used to ascertain the best working concentration of the mPGES-1 inhibitor (CAY10526). The effect of CAY10526 treatment on expression of Beclin-1 in DU-145 cells was studied using Western blot analysis. Localization of Beclin-1 and mPGES-1 was in endochylema. Significant differences in expression was noted among PCa, BPH and normal issues ($P < 0.05$). Beclin-1 expression inversely correlated with mPGES-1 expression in PCa tissue ($P < 0.05$). CAY10526 could significantly block mPGES-1 expression and the proliferation of DU-145 cells ($P < 0.05$), while increasing Beclin-1 levels ($P < 0.05$). Overexpression of mPGES-1 could decrease the autophagic PCa cell death. Inhibiting the expression of mPGES-1 may lead to DU-145 cell death and up-regulation of Beclin-1. The results suggest that inhibition of mPGES-1 may have therapeutic potential for PCa in the future.

Keywords: Microsomal prostaglandin-E synthase-1 - Beclin-1 - prostatic neoplasms

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Introduction

For the past few years, the incidence of PCa has a rising trend and it remains the most common cause of death among urologic malignance. Majority of PCa patients manifested androgen dependent prostate cancer (ADPC) in prophase of pathogenesis. However, most patients will develop AIPC after the initiation of androgen deprivation. This development could account for most of the morbidity and mortality associated with this disease. There is no any effective therapy for this disease today, so identification of a new effective biology based therapy is therefore mandatory (Hellerstedt and Pienta, 2002; Wingo et al., 2003). Prostaglandin E2 (PGE2) which converted from arachidonic acid has been shown to play important roles in development and progression of PCa (Jain et al., 2008; Jia et al., 2008; Myung and Kim, 2008). Inhibition of PGE2 production could be achieved by blocking the cyclooxygenases (COX) with COX inhibitors such as celecoxib and etoricoxib, respectively. And the trials have showed promising results to some extent. Unfortunately, recently released data has disclosed a significant increase in the incidence of cardiovascular adverse events among users of COX-2 inhibitors (Smith et al., 2006; Srivastava

et al., 2009). So it is especially important to find other new drugs that target arachidonic acid metabolism and inhibit carcinogenesis.

Jakobsson has confirmed that PGE synthase (PGES) participant in converting PGH2 into PGE2 (Jakobsson et al., 1999). There are three PGESs presenting in human cells: microsomal prostaglandin-E synthase-1 (mPGES-1), microsomal prostaglandin synthase-2 (mPGES-2) and cytosolic PGES (cPGES). mPGES-1 is a very important inducible enzyme, which is functionally coupled with COX-2 and has a predominantly responsible for PGE2 generation in neoplastic tissues. The other two isoforms are constructive expression, and thought to be less important in cancer (Samuelsson et al., 2007; Banning et al., 2008; Kawata et al., 2010). Takasu et al. (2008) has reported that, in vitro mice trials, over-expression of mPGES-1 have been detected in gastric carcinogenesis and may contribute to progression of this carcinogenesis, Katarina (Rask et al., 2006) also found this phenomenon in ovarian epithelial cancer. Supporting that mPGES-1 is of importance for malignant transformation and progression. Hanaka has demonstrated that there also was a significant high expression of mPGES-1 in PCa cells and high expression of mPGES-1 can promote growth and survival

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in the cancer cells (Hanaka et al., 2009). These results implied us that inhibition of mPGES-1 is a therapeutic option for cancers that express this enzyme.

Wu et al. (2009) had reported deletion of mPGES-1 played a protective role in cardiac ischemia in mice trials. Wang et al. (2006) also found that mPGES-1 deletion in mice rarely occurred atherogenesis and inhibition of mPGES-1 could avoid cardiovascular risks of COX-2 inhibitor. Beales et al. (2010) had found that mPGES-1 inhibitor can block proliferation of oesophageal adenocarcinoma cells. The effectiveness and advantages of mPGES-1 inhibitor prompted us that mPGES-1 inhibitor may be an ideal therapeutic measure for cancers.

Beclin-1 is considered a very important factor for modulating autophagy and appear significant down-regulation in many tumor cells including PCa (Gao et al., 1995; Chen and Karantzis-Wadsworth, 2009). Moreover, there was also a negative correlation with pathological, clinical characteristics, such as stage, grade and so on the more malignant and higher stage, the lower-expression Beclin-1 is (Miracco et al., 2007). mPGES-1 also could up-regulate Bcl-2 expression to promote anti-apoptosis of cancer cells. In the meantime, Bcl-2 could inhibit autophagy mediated low-expression of Beclin-1 in cancer cells (Lalier et al., 2007; Ciechomska et al., 2009; Lian et al., 2010). In AIPC cells, Beclin-1 was also low-expresses and this may be related to anti-apoptosis mechanism of AIPC cells (Bhutia et al., 2010; Lian et al., 2011). But, till now, we do not know whether or not mPGES-1 involve in regulating Beclin-1 in AIPC.

We therefore sought to determine the expression of mPGES-1 and Beclin-1 in a series of surgically resected different prostate tissues and DU-145 cell line to examine the associations between these two factors and their impact on PCa.

Materials and Methods

Tissues specimen

All prostate tissues included in this study were from 40 adenocarcinoma of prostate cases, 40 benign prostatic hyperplasia (BPH) cases and 10 health men who have accepted medical examination that were diagnosed by two pathologists between 2000 and 2005. The median age of the PCa patients and BPH patients was 67 years (rang from 55 to 81 years) and 65 years (ranged from 53 to 82 years). History, transrectal ultrasound, computed tomography, magnetic resonance imaging and isotope scanning of the skeleton were combined to decide the clinical staging of PCa patients. Every PCa patients has received needle-biopsy. Tissue samples were obtained from 17 PCa patients whose clinical tumor staging were T1 or T2 and from other 23 PCa patients who had lost the opportunity to prostatectomy received neoadjuvant complete androgen ablation therapy based on luteinizing hormone-releasing hormone agonist and an anti-androgen treatment for 15 to 30 months (average 20.8 months). 9 PCa cases Gleason scores were ≤ 7 , and 31 patients Gleason scores were > 7 . Every BPH patient has accepted transurethral resection of the prostate (TURP). All patients were followed up 5 years after therapy: 14 patients who accepted radical

prostatectomy did not have metastases and maintained very low PSA levels (below 0.5 ng/mL), with no relapse; and 3 patients who had had a radical prostatectomy had biochemical recurrences (average PSA level 1.7 ng/mL). Antiandrogen therapy was given intermittently to these 3 patients for a short period. We considered these 17 cases to be androgen dependent prostate cancer (ADPC). The other 23 patients who presented with rises in PSA levels or bone metastases were determined hormone independent PCa. The study was conducted with the approval of the ethical committee of Nanjing Medical University (Nanjing, China).

Immunohistochemistry

mPGES-1(Cayman Chemical Company, Michigan, USA) and Beclin-1 (Epitomics Company, Burlingame, CA, USA) expression were analyzed in paraffin embedded tumor specimens and BPH from 40 patients respectively. Sections (4 μ m) were incubated overnight at 4°C with the following anti-bodies (100:1 per slide): mPGES-1 rabbit polyclonal IgG (1:250 dilution) and Beclin-1 rabbit monoclonal antibody (1:250 dilution). Following a phosphate buffered saline (PBS) wash, secondary antibody was applied (mPGES-1: biotinylated bovine anti-rabbit IgG/B at a dilution of 1:400 in PBS with 0.1% bovine serum albumin; Beclin-1:biotinylated bovine anti-rabbit whole immunoglobulins at a dilution of 1:400) and slides incubated for 30min (room temperature, RT) prior to a PBS wash. Avi-din-biotin complex (ABC) solution (100:1) was applied to each slide (incubated for 30 min RT). Slides were mounted with a xylene-based mounting medium.

Specimen interpretation

Semi-determination of mPGES-1 and Beclin-1 expression was judged on the basis of the staining intensity and ratio of positive cells in five randomly selected fields under the high power lens. Stand for staining intensity, Integral Optical Density (IOD) was evaluated on a 3-point scale: 0 (no coloring), 1 (yellow), 2 (brown). The scoring criteria for the proportion of positive substances were as follows: 0 (less than 10% of positive cells), 1 (10%-40% of positive cells), 2 (40%-70% positive cells), 3 (more than 70% of positive cells). Sums of the two kind of the scores were defined as - (0 or 1), + (2), ++ (3 or 4) and +++ (5 or 6). Image Pro plus 6.0 software package was used for image analysis.

Cell culture

DU-145 cell lines (American Type Culture Collection, Rockville, MD, USA) were routinely cultured in RPMI 1640-maintained media containing 10% fetal calf serum, 25 U/mL penicillin and 25 μ g/mL streptomycin. In certain experiments, cells were treated with mPGES-1 inhibitors (CAY10526, Cayman Chemical Company, USA) All experiments were repeated at least three times.

Quantitative real-time polymerase chain reaction

Total RNA from PCa and BPH issues was extracted using TRIzol (Gibco, Gaithersburg, MD, USA). QRT-PCR testing was performed using a qRT-PCR system according

to the manufacturer's instructions (Takara, Shiga, Japan). The primers of mPGES-1 were as follows: up 5'-GAAGAAGGCCTTTGCCAAC-3' and down 5'-GGAAGACCAGGAAGTGCATC-3', and the length of the production was 200bp. The primers of Beclin-1 were as follows: up 5'-CTGAGGGATGGAAGGGTC-3' and down 5'-TGGGCTGTGGTAAGTAATG-3', and the length of the production was 159bp. Thirty-five cycles of amplification were performed under the following conditions: melting at 95°C; annealing at 56°C; and extension at 72°C. The result was analyzed by 7500 Real Time PCR System (Applied Biosystems company, California, USA).

MTT assay

DU-145 cells were cultured till mid-log phase to obtain a stock cell suspension containing 1×10^5 cells/L. The stock cell suspension (100 μ L) was then added to the wells of a 96-well plate. After 24h, the cells were treated with CAY10526 at various concentrations (1, 10, 20, 50 μ M), then incubated at 37°C in a 5% CO₂ for 12h. Simultaneously, zero group and control group were established. After incubation, 20 μ L MTT stock solution (5 mg/mL in PBS) was added to each well. The cells were further incubated at 37°C for 4h. The supernatant was discarded and 150 μ L DMSO was added and the culture medium was shaken for 10 min in the darkness. Six replicates were established per group. Similar results were found in at least three repeat experiments. Finally, the optical density (OD) values were detected on a microplate reader (Biotech Instruments μ Quant, USA) at a wavelength of 490 nm. The OD values were positively correlated with the cell viability.

Western blotting

Total cell lysates were obtained from the DU-145 cells. The cell lines were incubated with complete medium (CM), serum-free medium (SF) and intervened with CAY10526 (10 μ M, 20 μ M) for 12h in serum unsupplemented conditions. Equal amounts (35 μ g) of protein were resolved by 5% and 10% SDS-PAGE and transferred onto PVDF membranes which was incubated with the appropriate rabbit polyclonal mPGES-1 antibodies (Cayman) with 1:5000 dilution and Beclin-1 antibodies (Epitomics) with 1:500 followed by incubation with peroxidase-conjugated secondary antibodies. The level of β -actin expression was used as the internal control for equal loading. The bands were compared by

Table 1. The Table Shows that mPGES-1 and Beclin-1 Expressed in Three Different Prostate Tissues

GROUP	n	mPGES-1 IOD	Beclin-1 IOD	
PCa	40	87.3±91.9	20.3±21.6	p=0.005
BPH	40	2.28±3.91	48.3±51.1	p=0.001
Normal	10	1.28±2.90	47.4±18.9	p=0.001
		P=0.001	P=0.03	

There was significant difference in the mPGES-1 and Beclin-1 expression between the Pca and benign tissues (BPH and Normal), respectively (P=0.001, P=0.03). In the same tissues, there was significant different between mPGES-1 and Beclin-1 (P<0.05)

densitometry of Western blotting using an Eastman Kodak Co. Image Station 440CF, and the data were analyzed using Kodak ID V.3.5.4 (Scientific Imaging System).

Statistical analysis

SPSS 13.0 software packages were used for statistical analysis. Independent-sample t test was employed to analyze the results of immunohistochemical staining and western blotting. Analysis of variance (ANOVA) was used to analyze the results of MTT assay. Pearson's χ^2 -test was used to analyze mPGES-1, Beclin-1 and associations with age and clinical-pathological stage and Gleason scores. Kendall test was used to demonstrate the rank correlation of the two variables. P value less than 0.05 was considered to be statically significant.

Results

MpGES-1 immunostaining

The cinnamomeous staining mean positive. In our study, intense staining was seen 72.5% in PCa which were predominantly in endochylema. mPGES-1 was also seen in BPH (21%) and normal tissues (10%). There was significant difference in the mPGES-1 expression between the three groups (P=0.001) (Table 1). A significant association was observed between mPGES-1 expression and higher Gleason scores (p<0.05) and tumor stage (P<0.05). However, there was no significant association between mPGES-1 expression and age (P>0.05) (Table 2).

There were 9 and 20 mPGES-1 positive expression specimens in ADPC and AIPC respectively. And the positive rate of mPGES-1 in AIPC was significantly higher than that in ADPC (P<0.05) (Table 3).

Beclin-1 immunostaining

27 PCa specimens (67.5%), 30 BPH specimens (75%) and 10 normal tissues (100%) were negative for Beclin-1 expression. This different was observed between the three groups (P<0.05) (Table 1). A significant association was observed between Beclin-1 expression and lower Gleason scores (P < 0.05) and tumor stage (P < 0.05), the **Table 2. The Rate of mPGES-1 and Beclin-1 Positive Expression in PCa Tissues, and the Relationship of mPGES-1 and Beclin-1 Positive Expression with Different Ages and Gleason Scores, Clinical Stages, PSA Values**

GROUP	mPGES-1		P	Beclin-1		P
	+	-		+	-	
AGE						
>60	19	6	P>0.05	7	18	P>0.05
≤60	10	5		6	9	
TNM grade						
≤T2	9	8	P<0.05	10	7	P<0.05
>T2	20	3		3	20	
Gleason scores						
>7	27	4	P<0.05	6	25	P<0.05
≤7	2	7		7	2	
PSA value						
≤10ng/mL	8	8	P<0.05	8	8	P<0.05
>10ng/mL	21	3		5	19	

Table 3. The ^ΔCT value of mPGES-1 and Beclin-1 in three different prostate tissues**

GROUP	mPGES-1	Beclin-1
Normal	27.6±2.56	7.29±0.48
BPH	24.9±0.87**	11.2±0.54**
PCa	24.9±0.87**	30.0±0.58##

There was no significant difference between BPH and Normal group (P>0.05)##; There was significant difference between PCa and Normal group (P<0.05)

Table 4. The Positive/Negative Rate of mPGES-1 in ADPC and AIPC

	n	mPGES-1(+)(29)	mPGES-1(-)(11)	P
ADPC	17	9	8	P<0.05
AIPC	23	20	3	

The positive rate of mPGES-1 in AIPC was significantly higher than that in ADPC (P<0.05)

Table 5. This Table Shows that the Correlation Between mPGES-1 and Beclin-1 in PCa

mPGES-1	Beclin-1			
	-	+	++	+++
-	6	1	2	2
+	2	0	2	1
++	3	3	1	0
+++	16	1	0	0

r=-0.427; P<0.05

Beclin-1 expression has no significant association with age (P>0.05) (Table 2).

Relationship between mPGES-1 and Beclin-1 expression

All in all, the expression of mPGES-1 in both RNA and protein level was significantly higher than the expression of Beclin-1 in PCa group (P<0.05), conversely, the expression of mPGES-1 was significantly lower than Beclin-1 in BPH and normal group (P<0.05) (Table 1) (Figure 1, 2).

21 (67.5%) PCa were positive for mPGES-1 expression meanwhile negative for Beclin-1 expression. There was obviously negative correlation between mPGES-1 and Beclin-1 in PCa (r=-0.427 P<0.05) (Table 4).

Inhibitory effects of CAY10526 on DU-145 cell proliferation

The cytotoxicity of CAY10526 (0, 1, 10, 20, 50 μM) to DU-145 cells was calculated from the loss of cell viability by using MTT assay. The OD values is 0.41±0.18, 0.34±0.08, 0.22±0.04, 0.08±0.02, 0.06±0.01 according the grouping respectively. CAY10526 inhibited the growth of DU-145 cells in a concentration dependent manner. In different CAY10526 concentration groups (0, 1, 10, 20 μM), significant difference was found among 0, 1, 10, 20 μM groups (P<0.05). However, no significant different was found between 20 μM and 50 μM group (P>0.05) (Figure 3).

We used western blotting to analyze the expression of mPGES-1 and Beclin-1 after intervening by CAY10526 in DU-145 cells. The result revealed that the expression of mPGES-1 down-regulated in a concentration dependent

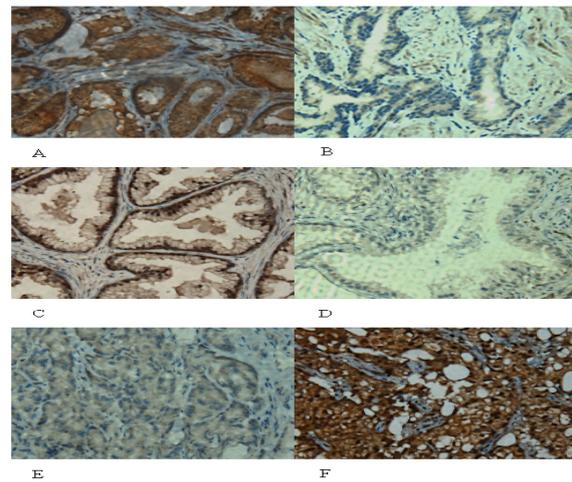


Figure 1. Immunohistochemical Patterns of Staining for mPGES-1 and Beclin-1 in PCa and BPH and Normal Tissues (brown denotes positive, × 400). A: Beclin-1 positive staining in NORMAL. B: mPGES-1 positive staining in NORMAL. C: Beclin-1 positive staining in BPH. D: mPGES-1 positive staining in BPH. E: Beclin-1 positive staining in PCa. F: mPGES-1 positive staining in PCa

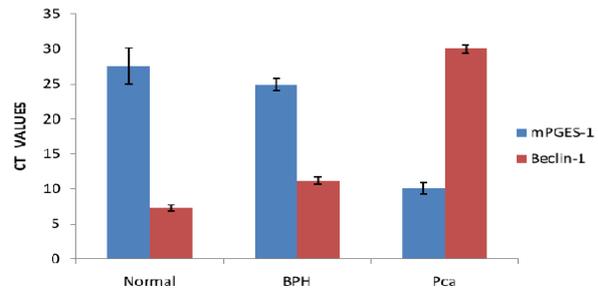


Figure 2. The RNA of mPGES-1 and Beclin-1 in Normal and BPH and PCa Tissues by qRT-PCR

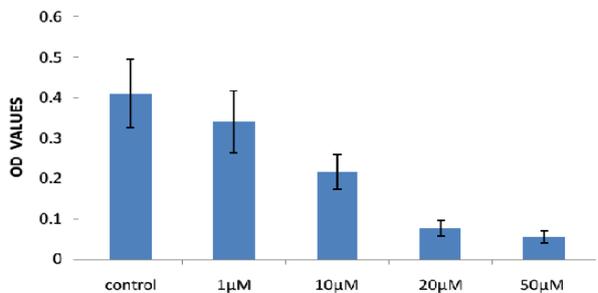


Figure 3. DU-145 Cells were Treated with CAY10526 (1 μM, 10 μM, 20 μM, 50 μM) for 12h. There were no serum in control group. Cell viability decreased significantly after CAY10526 stimulation (P<0.05). There was no significant different between 20 μM and 50 μM group, also between control group and 1 μM group (P>0.05)

manner.

There was no significant different of mPGES-1 expression between CM and SF group (P>0.05). The expression of Beclin-1 in the SF group was higher than that in the CM group (P<0.05). And there was a decrement of Beclin-1 expression following the increasing concentration of CAY10526. Furthermore, mPGES-1 was associated with Beclin-1 down-regulation in DU-145 cells. In addition, inhibition of mPGES-1 could efficiently up-regulate Beclin-1 expression and decrease the viability of DU-145 cells (Figure 4).

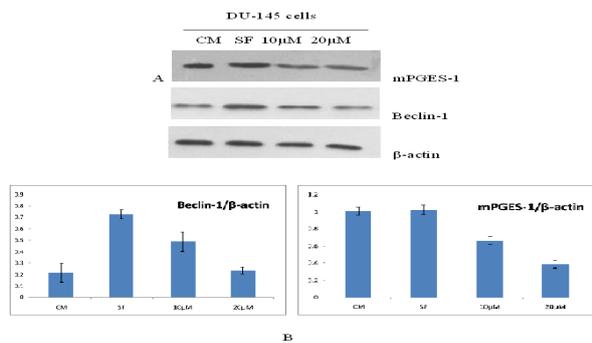


Figure 4. A: DU-145 cells were treated with CAY10526 (10 μ M, 20 μ M). CM, complete medium group; SF, serum free group. Whole cell lysates were analyzed by Western blot using a specific antibody that recognized Beclin-1 and mPGES-1, respectively. B: mPGES-1 and Beclin-1 and β -actin bands were subject to densitometry on an Eastman Kodak Co. Image Station 440 CF, and the ratio of mPGES-1 and Beclin-1 and β -actin were plotted for quantification of the blots. Representative results of three independent experiments

Discussion

mPGES-1, as the terminal enzyme of synthesizing PGE₂, was found coupled with COX-2 and over-expressed in many cancers including PCa (Nakanishi et al., 2010). So inhibiting the expression of mPGES-1 may be a potential therapeutic target in clinical practice (Murakami et al., 2000). Nakanishi has demonstrated that genetic deletion of mPGES-1 could suppress intestinal and lung tumorigenesis in vivo animal trials (Nakanishi et al., 2008; Pecchi et al., 2008). Cheng et al. (2006) has reported that mPGES-1 inhibitor could block PGE₂ and make therapeutic effects in many diseases instead of nonsteroidal anti-inflammatory drugs (NSAIDs), meanwhile, no obvious side effects were observed. Recently, Hanaka et al. (2009) has focused on the role of mPGES-1 in PCa. He found that mPGES-1 over-expressed in both PCa tissues and human PCa cell lines. In addition, xenograft tumors deriving from the mPGES-1 knockdown cells performed delayed tumor development and growth. In our study, we have found that mPGES-1 expression was higher in PCa than that in BPH and normal control group. It also has significant association with higher Gleason scores and tumor stage in PCa tissues. Madaan et al. (2000) has reported that there was significantly greater expression of COX-2 in PCa than that in BPH and normal prostate tissues. Lee et al. (2001) also did some researches in above three prostate tissues and indicated that COX-2 correlated with cancer stage. These results provided us that mPGES-1, likewise COX-2, is a major factor in PCa. In our previous trials, mediated COX-2 had a association with the process of ADPC transforming to AIPC (Jia et al., 2008). In this data, mPGES-1 positive rate in AIPC was also significantly higher than that in ADPC (P<0.05). Implying that mPGES-1 may play an important role in androgen independent transformation and progression of PCa.

Autophagy, just like apoptosis, is an important way of cell death. Both of them interacted in many cancers (Cheng et al., 2009; Liu et al., 2009). As a representative of autophagy, Beclin-1 was identified as a protein that

interacts with Bcl-2 (Liang et al., 1998; Pattingre and Levine, 2006). In AIPC cells, there is an increment of Beclin-1 with the decrease of Bcl-2 (Lian et al., 2010). In the mean time, Lalier has reported that mPGES-1 could up-regulate Bcl-2 expression in glioblastoma multiforme (Lalier et al., 2007). In our study, we found that Beclin-1 expression was significantly higher in BPH and normal tissues than that in PCa (P<0.05). Meanwhile, a significant association was observed among Beclin-1 expression, lower Gleason scores and tumor stage. The expression of mPGES-1 in PCa was higher than Beclin-1, conversely in BPH and normal group. mPGES-1 has a negative correlation with Beclin-1 in PCa tissues. Inhibiting mPGES-1 could make Beclin-1 up-regulation to mediate the death of AIPC cells. Suspecting that mPGES-1 and Beclin-1 may have a key function in the AIPC.

Lau has reported that mPGES-1 was relatively high expression in DU145 (Lau et al., 2000). So we selected the DU-145 cells for our study exclusively, meantime, applied CAY10526, a specific mPGES-1 inhibitor, to interfere the DU-145 cell lines. The results has showed that the DU-145 cells cytoactive descended with the does of CAY10526 increasing from 10 to 20 μ M although there is a plateau phase beyond 20 μ M. There was a little different from Beales results that the optimal inhibition concentration of CAY10526 was 10 μ M in esophageal cancer (Beales et al., 2010). Thus, we considered that CAY10526 at 10 to 20 μ M could inhibit mPGES-1 predominantly and this can be the consult for our subsequent research.

In mammalian cells, the autophagic process can be initiated by nutrient starvation, inflammation and neoplasm (Qu et al., 2003). In our research, Beclin-1 expression was higher in SF group than that in CM group. Conforming that, in starve circumstances, Beclin-1 expression could up-regulated to maintain DU-145 cells growth. After being intervened by CAY10526 at 10 μ M, Beclin-1 expression down-regulated, however, the expression of Beclin-1 remained higher than that in control group (P<0.05). This demonstrated that inhibiting mPGES-1 could up-regulate Beclin-1 expression to mediate DU-145 cells death to a certain degree. Nevertheless, with the cytoactive decreasing, mPGES-1 and Beclin-1 both down-regulated significantly (P<0.05). Owing to the cell viability gradually eclipsing, all kinds of protein would low-express in this process. We inferred that Beclin-1 expression associated with not only interaction by mPGES-1 but also cells survival condition. Taken together, these results indicate that mPGES-1 plays an important role in the mediation of Beclin-1 in DU-145 cells.

In summary, this is the first study to examine the relationship between mPGES-1 and Beclin-1 in different prostate tissues and vitro AIPC cell lines. To a certain degree, inhibiting targeted mPGES-1 could up-regulate Beclin-1 expression to induce autophagic death increases of AIPC cells. mPGES-1 may be a new promising effective treatment target in the future.

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