Original Article

Role of BCAR4 in prostate cancer cell autophagy

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Background: Increased autophagy of prostate cancer (PC) cells contributes to their resistance to chemotherapy. Recently, we reported that a long non-coding RNA (lncRNA)—breast-cancer anti-estrogen resistance 4 (BCAR4)—is highly expressed in PC and contributes to castration resistance through activation of GLI2 signaling. However, the role of BCAR4 in the regulation of PC cell autophagy is unknown and is the subject of the current study.

Methods: BCAR4 and Beclin-1 levels and the alteration in autophagy pathway genes were assessed in PC using a public database and in our own clinical specimens. The correlation between BCAR4 and Beclin-1 levels in PC and PC cell lines was determined and their regulatory relationship was assessed by overexpression and knockout assay. The final effect on autophagy was measured by microtubule-associated protein 1A/1B-light chain 3 (LC3) levels. The mechanism that underlies the control of Beclin-1 by BCAR4 was analyzed by cancer database and gain-of-function and loss-of-function approaches.

Results: BCAR4 and Beclin-1 were both upregulated in PC and were positively correlated. BCAR4 directly activated Beclin-1 at transcriptional level, which subsequently increased the ratio of LC3 II to LC3I to augment PC cell autophagy. Beclin-1 did not control levels of BCAR4. Mechanically, BCAR4 and Beclin-1 shared several targeting microRNAs, among which miR-15 and miR-146 appeared to be the mediators of the effects of BACR4 on Beclin-1.

Conclusions: BCAR4 may enhance PC cell autophagy through altering miRNA-regulated Beclin-1 expression in PC.

Keywords: Long noncoding RNA (lncRNA); breast-cancer anti-estrogen resistance 4 (BCAR4); autophagy; prostate cancer (PC); microRNAs

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Introduction

Prostate cancer (PC) is a prevalent cancer in aged men (1). Autophagy is a catabolic pathway widely used by organisms to degrade, recycle, and reuse biological cellular compartments to improve cell survival, especially in harsh environments (2). Microtubule-associated protein 1A/1B-light chain 3 (LC3) is a soluble cellular protein, while its cytosolic form (LC3-I) forms membrane-bound LC3-phosphatidylethanolamine conjugate (LC3-II) to generate autophagosomes that engulf cytoplasmic components to fulfill the autophagy. Thus, levels of autophagic activity are often quantified by the ratio of LC3-II to LC3-I (2-4). Autophagy-associated protein 6 (Atg6, or Beclin-1) is the most important autophagy-associated protein that coordinates the occurrence of

autophagy (5). Importantly, many cancer cells use autophagy to improve their survival at rest or when they are exposed to a radiotherapy or chemotherapy to antagonize apoptotic cell death. Thus, it is important to understand the regulation of PC cell autophagy.

There are two categories of non-coding RNAs (ncRNAs): small non-coding RNA (small molecular RNA, also known as microRNAs), and long non-coding RNA (lncRNA) (6). Although lncRNAs typically do not translate into proteins, they have many biological functions such as interaction with miRNAs or mRNAs to regulate gene expression (6). In the past, some lncRNAs have been shown to play roles in the carcinogenesis of PC (7,8). We recently showed that breast-cancer anti-estrogen resistance 4 (BCAR4), a critical lncRNA functioning in tamoxifen-resistant breast cancer, activates GLI2 signaling in PC to contribute to castration resistance (9). However, the role of BCAR4 in the regulation of PC cell autophagy is unknown and is the subject of the current study.

We found that BCAR4 and Beclin-1 were both upregulated in PC and were positively correlated. BCAR4 directly activated Beclin-1 at transcriptional level, which subsequently increased the ratio of LC3 II to LC3I to augment PC cell autophagy. Beclin-1 did not control levels of BCAR4. Mechanically, BCAR4 and Beclin-1 shared several targeting microRNAs, among which miR-15 and miR-146 appeared to be the mediators of the effects of BACR4 on Beclin-1.

We present the following article in accordance with the MDAR reporting checklist (available at https://dx.doi.org/10.21037/tau-21-929).

Methods

Protocols and patient specimens

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Shanghai Changzheng Hospital (JS-254). Use of specimens was approved by donors (no number) who returned signed informed consent.

We evaluated ninety PC tissues with matched adjacent normal prostate tissues (NT) without prior chemotherapy or radiotherapy in male patients aged from 45 to 78 years. Samples were histologically diagnosed independently by two experienced pathologists and extracted RNA was kept in −70 ℃ before proceeding. Proper randomization and blinding method were used, and the 5-year survival of patients was followed.

Cell culture

Human PC cell lines (PC346, LNCap, MDAPC1 2a/b, C4-2, PC3, and DU145) were obtained from the American Type Culture Collection (Catalog number CRL-2876, CRL-1740, CRL-2242, CRL-3314, CRL-1435, and HTB-81, respectively, ATCC, Rockville, MD, USA). Human PC cell line (BPH1) was obtained from Accegen Biotechnology (Catalog number ABC-TC454S, Fairfield, NJ, USA). All lines were maintained in DMEM (Invitrogen, Rockville, MD, USA) suppled with 5% fetal bovine serum (FBS; Sigma-Aldrich, Rockville, MD, USA) in a humidified incubator at 37 ℃ with a 5 % CO_2 atmosphere.

Plasmids and transfection

The BCAR4 and siRNA-BCAR4 plasmids have been previously described (9). The plasmids that express recombinant Beclin-1, siRNA, or a scrambled sequence for Beclin-1 (si-Beclin-1; scrambled), or express miR-15, miR-105, miR-146, and antisense for miR-15 (as-miR-15), as-miR-105, and as-miR-146 under a CMV promoter were all purchased from GenePharma and Santa Cruz (Beijing, China). The sequence for si-BCAR4 was 5'-GGGACTTGAGTTATGTTGGTGGCTA-3' and the sequence for the scrambled sequence was 5'-TGAGTTGGCGCGACTG-3'. Scrambled shRNAs were used as negative controls. Transfection was performed with 1.5 μg plasmids using Lipofectamine 3000 (Invitrogen) for 24 hours.

RNA extraction and quantitative real-time polymerase chain reaction (RT-qPCR)

Total RNA, including ncRNAs, was extracted with the miRNeasy Kit (Qiagen, Shanghai, China) following the manufacturer's protocol. cDNA was generated with a RT Synthesis Kit (Qiagen) which was used as the template in RT-qPCR with a commercial SYBR Green PCR Kit (Qiagen, Shanghai, China) and designed primers from Qiagen. The RT-qPCR reactions were performed in duplicate. The levels of gene expression were quantified with the $2^{-\Delta\Delta Ct}$ method and presented as relative values after sequential normalization to α-tubulin and the experimental controls.

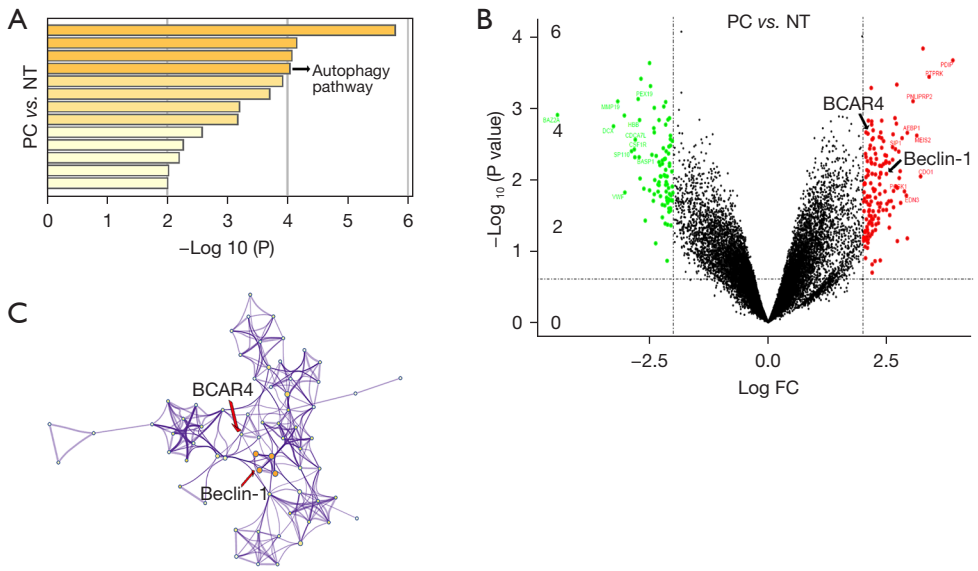

Figure 1 Analysis of public databases shows enhanced autophagy pathway and Beclin-1 levels in PC. PC data from public databases were obtained and the online tool GEO2R was used to screen associated genes and pathways. (A) Pathway enrichment analysis were assessed by the Metascape online tool, showing that the enriched pathways included autophagy; (B) a volcano map to show that both BACR4 and Beclin-1 were upregulated in PC; (C) protein-protein interaction network demonstrated a close, although not direct, interaction between BACR4 and Beclin-1. BCAR4, breast-cancer anti-estrogen resistance 4; PC, prostate cancer.

Western blot

The protein was obtained through RIPA buffer containing protease and phosphatase inhibitors (cOmplete ULTRA Tablets, Roche, Nutley, NJ, USA) mediated cell lysis, and the protein quantification was performed using NanoDrop microvolume spectrophotometers. The proteins were next subjected to an SDS-PAGE and then transferred to nitrocellulose membranes. After blocking with 5% non-fat milk, the membranes were probed with rabbit anti-LC3, rabbit-anti-Beclin-1, or rabbit-anti-α-tubulin (Catalog number 4599, 3495 and 5335, respectively, Cell Signaling Technology, Danvers, MA, USA). Secondary antibodies used HRP-conjugated antibodies against rabbit (Jackson ImmunoResearch Labs, West Grove, PA, USA). Protein levels were presented as relative values after sequential normalization to α-tubulin, and the experimental controls and densitometry of Western blots was quantified with NIH ImageJ software.

Bioinformatics and statistical analysis

The public database from the Gene Expression Omnibus (GEO) was used in the current study (10). Several gene expression profiles in PC (GSE161304, GSE134171, GSE134170, GSE134168, and GSE134073) were used for GEO2R online analysis for detecting the differentially expressed genes (DEGs), after which the P value, adjusted P value, and logFC were calculated. Pathway enrichment analyses of DEGs were performed at Metascape (11), and the data were statistically analyzed with GraphPad Prism 6 (GraphPad, Chicago, IL, USA). Student's T test was performed to compare the data of two groups and the values were expressed as mean ± standard deviation (SD). When $P<0.05$, the data was considered as significant. Bivariate correlations were calculated by Spearman's Rank Correlation Coefficients, and Kaplan-Meier curve was applied to record the overall survival of included patients. Experiments were repeated 3–4 times.

Results

Analysis of a public database shows enhanced autophagy pathway and Beclin-1 levels in PC

To evaluate the role of BCAR4 in PC autophagy, we first obtained data from a public database and used the online tool GEO2R to screen DEGs between PC and adjacent NT. Pathway enrichment analysis was analyzed using the Metascape online tool and showed autophagy pathway as a major altered pathway in PC (*Figure 1A*). Among

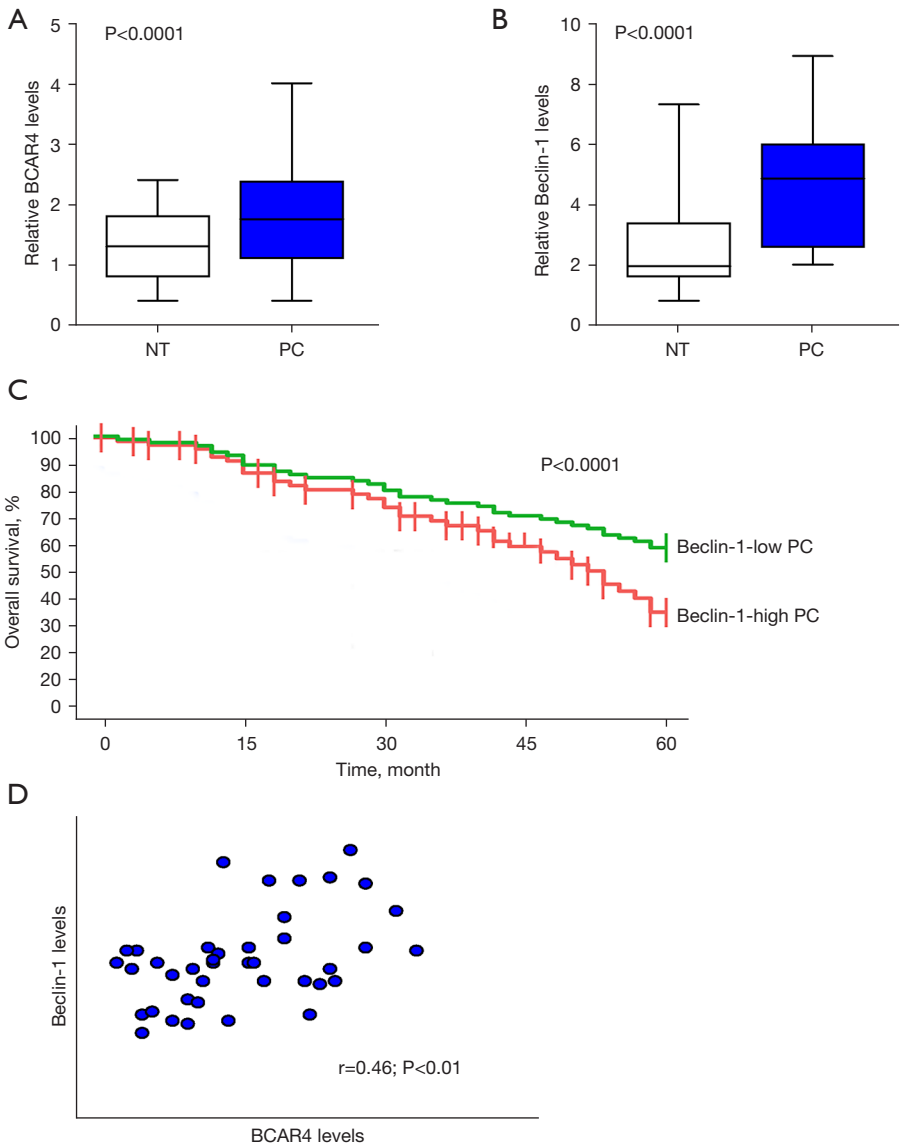

Figure 2 Analysis of our clinic samples shows a positive correlation between BACR4 and Beclin-1/autophagy in PC. (A,B) BCAR4 (A) and Beclin-1 (B) levels were examined in PC and paired adjacent normal prostate tissues (NT) by RT-qPCR. (C) The PC tissues were classified into two groups (Beclin-1-low and Beclin-1-high) using the median value of Beclin-1 in all cases as the cutoff point. A Kaplan-Meier curve showed patients' overall survival. (D) A correlation test for BACR4 and Beclin-1 levels in PC specimens. N=50. BCAR4, breast-cancer anti-estrogen resistance 4; PC, prostate cancer.

all DEGs, significantly downregulated and upregulated genes were detected, and interestingly, both BACR4 and Beclin-1 were found significantly upregulated in PC (*Figure 1B*). Moreover, protein-protein interaction network demonstrated a close, although not direct, interaction between BACR4 and Beclin-1 (*Figure 1C*). These data suggest a possible relationship between BACR4 and Beclin-1/autophagy in PC.

Analysis of clinic samples shows a positive correlation between BACR4 and Beclin-1/autophagy in PC

To further provide evidence for a possible relationship between BACR4 and Beclin-1/autophagy in PC, we analyzed our clinic samples as previously described (9), and found significant increases in both BACR4 (*Figure 2A*) and Beclin-1 (*Figure 2B*) in PC, compared to NT. The PC

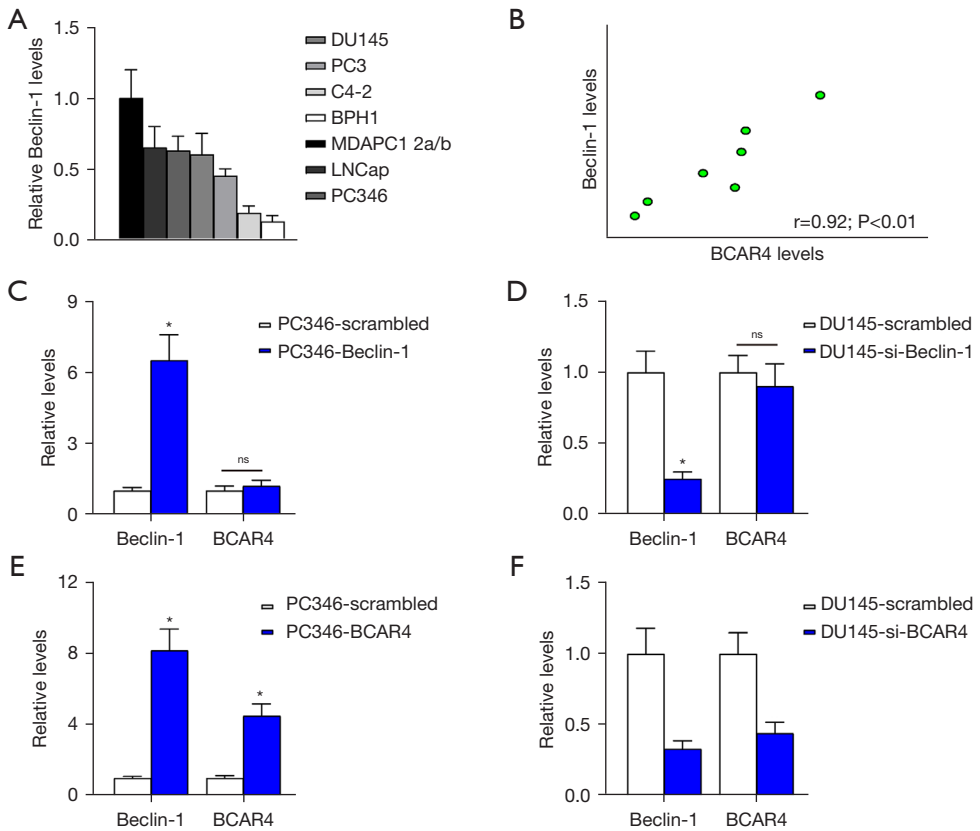

Figure 3 BCAR4 regulates Beclin-1 expression in PC cells. (A) RT-qPCR for Beclin-1 levels in seven commonly used PC cell lines. (B) A correlation test for BACR4 and Beclin-1 levels in the seven PC cell lines. (C,D) Low-Beclin-1-expressing PC346 cells were transfected with either scrambled or Beclin-1 plasmids, while high-Beclin-1-expressing DU145 cells were transfected with either scrambled or si-Beclin-1 plasmids. RT-qPCR for Beclin-1 and BCAR4 levels in transfected PC346 cells (C) and in transfected DU145 cells (D). (E,F) Low-BCAR4-expressing PC346 cells were transfected with either scrambled or BCAR4 plasmids, while high-BCAR4-expressing DU145 cells were transfected with either scrambled or si-BCAR4 plasmids. RT-qPCR for BCAR4 and Beclin-1 levels in transfected PC346 cells (E) and in transfected DU145 cells (F). *, P<0.05. NS, non-significant. N=5. BCAR4, breast-cancer anti-estrogen resistance 4; PC, prostate cancer.

specimens were grouped into a Beclin-1-high and Beclin-1-low group, respectively, using the median value of all cases as the cutoff point, and the results showed overall survival was significantly better in those with low Beclin-1 levels, shown in a Kaplan-Meier curve (P<0.0001, *Figure 2C*). Moreover, the BACR4 and Beclin-1 level in each individual patient exhibited a strong positive correlation (r=0.46; P<0.01; *Figure 2D*). These data suggest a regulatory relationship between BACR4 and Beclin-1/autophagy in PC.

BCAR4 regulates Beclin-1 expression in PC cells

We then tried to prove this relationship in PC cells. First, we examined seven commonly used PC cell lines and found that PC346 expressed the least level of Beclin-1, while DU145 expressed the highest level (*Figure 3A*). Interestingly, we have previously shown that PC346 expressed the least level of BCAR4, while DU145 expressed the highest level of BCAR4 (9). Thus, a correlation test for BACR4 and Beclin-1 levels in the seven lines was performed, and, surprisingly, showed a very strong positive correlation (r=0.92; P<0.01; *Figure 3B*). We then assessed whether alteration in either BACR4 or Beclin-1 could change the levels of the other by transfecting low-Beclin-1-expressing PC346 cells with either scrambled or Beclin-1 plasmids, while high-Beclin-1-expressing DU145 cells were

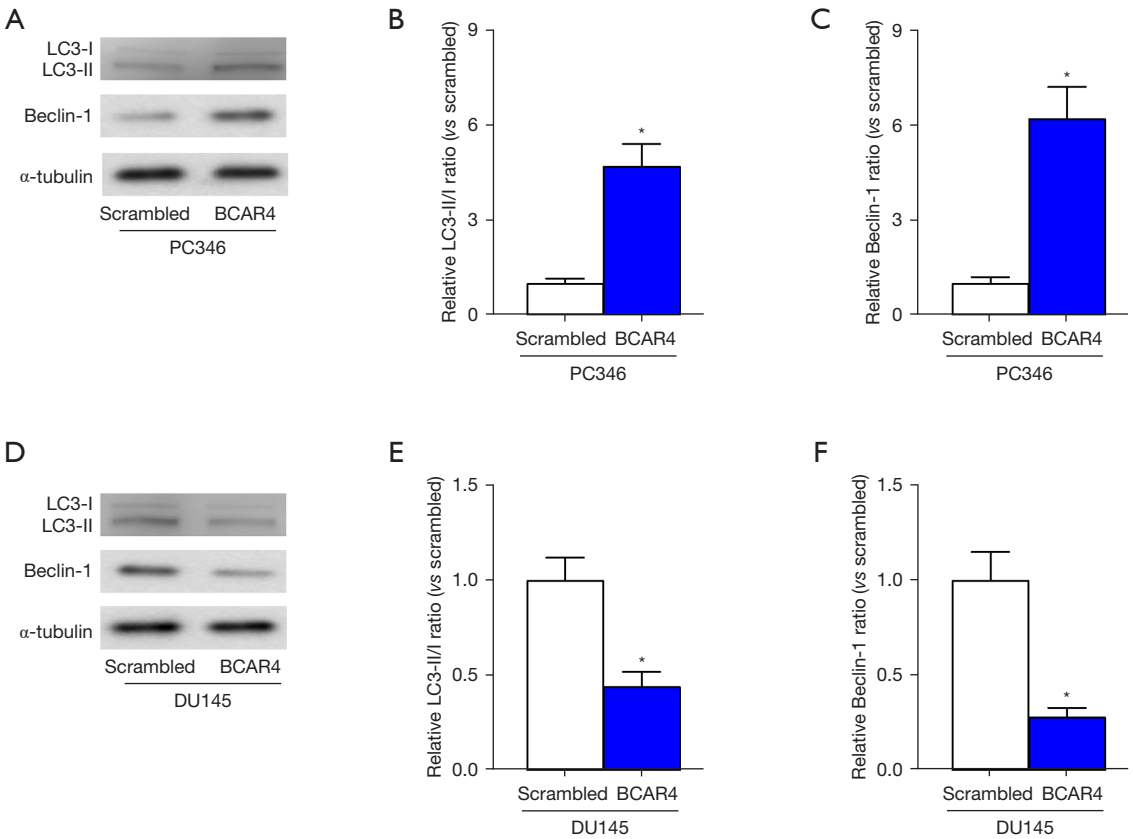

Figure 4 Regulation of Beclin-1 by BCAR4 alters PC cell autophagy. (A,B) Immunoblots for autophagy-associated genes LC3 and Beclin-1 in transfected PC346 cells, shown by representative blots (A), and by quantification for ratio LC3-II *vs.* I (B) and Beclin-1 (C). (D-F) Immunoblots for LC3 and Beclin-1 in transfected DU145 cells, shown by representative blots (D), and by quantification for ratio LC3-II *vs.* I (E) and Beclin-1 (F). *, P<0.05. N=5. BCAR4, breast-cancer anti-estrogen resistance 4; PC, prostate cancer; LC3, light chain 3.

transfected with either scrambled or si-Beclin-1 plasmids. The results showed that transfection with Beclin-1 significantly increased Beclin-1 levels in PC346 cells without altering BCAR4 levels (*Figure 3C*), while transfection with si-Beclin-1 significantly decreased Beclin-1 levels in DU145 cells without altering BCAR4 levels (*Figure 3D*). This indicated Beclin-1 does not regulate BCAR4. In another set of experiments, low-BCAR4-expressing PC346 cells were transfected with either scrambled or BCAR4 plasmids, while high-BCAR4-expressing DU145 cells were transfected with either scrambled or si-BCAR4 plasmids. We found that transfection with BCAR4 significantly increased both BCAR4 and Beclin-1 levels in PC346 cells (*Figure 3E*), while transfection with si-BCAR4 significantly decreased both BCAR4 and Beclin-1 levels in DU145 cells (*Figure 3F*). Thus, BCAR4 appears to regulate Beclin-1 levels in PC cells.

Regulation of Beclin-1 by BCAR4 alters PC cell autophagy

Next, we analyzed whether the regulation of Beclin-1 by BCAR4 altered PC cell autophagy by analyzing the changes in Beclin-1 levels and LC3-II/I ratio as an indicator for autophagy levels in transfected cells. We found that transfection of BCAR4 in low-BCAR4-expressing PC346 cells not only significantly increased the levels of Beclin-1, but also significantly increased the levels of LC3-II/I ratio, shown by representative immunoblots (*Figure 4A*), and by quantification (*Figure 4B,4C*). On the other hand, transfection of si-BCAR4 in high-BCAR4-expressing DU145 cells not only significantly decreased the levels of Beclin-1, but also significantly decreased the levels of LC3-II/I ratio, shown by representative immunoblots (*Figure 4D*), and by quantification (*Figure 4E,4F*). Together, these data suggest that the BCAR4-mediated increases in Beclin-1

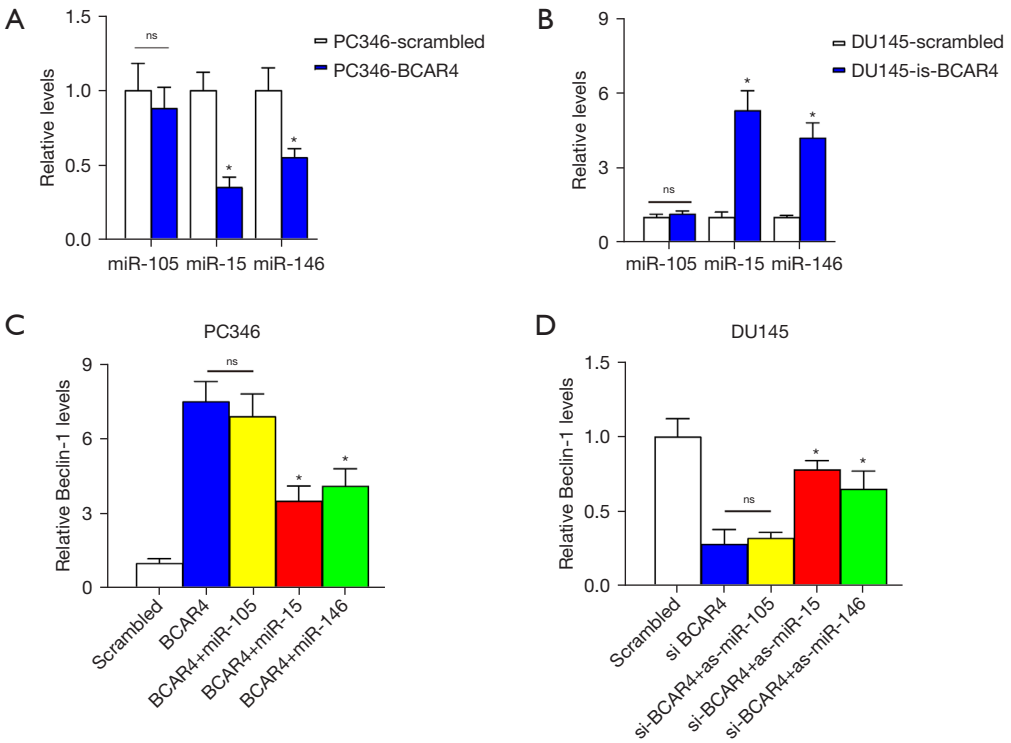

Figure 5 BCAR4 likely regulates Beclin-1 through miR-15 and miR-146 in PC cells. (A,B) RT-qPCR for the levels of miR-105, miR-15, and miR-146 in BCAR4/scrambled-transfected PC345 cells (A) and in si-BCAR4/scrambled-transfected DU145 cells (B). (C,D) RT-qPCR for the levels of Beclin-1 in PC345 cells transfected with scrambled or BCAR4 or combined BCAR4 with either miR-105, miR-15, or miR-146 (C), and in DU145 cells transfected with scrambled or si-BCAR4 or combined si-BCAR4 with either as-miR-105, as-miR-15, or as-miR-146 (D). *, P<0.05. NS, non-significant. N=5. BCAR4, breast-cancer anti-estrogen resistance 4; PC, prostate cancer.

promote PC cell autophagy.

BCAR4 likely regulates Beclin-1 through miR-15 and miR-146 in PC cells

Finally, we studied the mechanisms underlying the regulation of Beclin-1 in PC by BCAR4. As a lncRNA, BCAR4 typically regulates gene expression through its interaction with miRNAs, which must have complementary sequences with both targeting lncRNA and the 3'-UTR for the mRNA of the targeting gene, here as BCAR4 and Beclin-1, respectively. Therefore, we used the online miRcode tool to predict all Beclin-1 (Table S1; 36 candidates obtained) and BCAR4 (Table S2; 53 candidates obtained) targeting miRNAs, among which nine groups were shared (miR-7, miR-105, miR-138, miR-146, miR-15, miR-150, miR-17, miR-216, and miR-29). The miRCancer online tool was then used to examine the miRNAs among these nine groups that have been reported to be downregulated in PC (available online: https://cdn.amegroups.cn/static/public/tau-21-929-01.pdf) (12), and miR-105, miR-15, and miR-146 were obtained as final candidates to be tested. We then tested whether levels of these three miRNAs could be altered in BCAR4/si-BCAR4-transfected PC cells and found transfection of BCAR4 in low-BCAR4-expressing PC346 cells did not significantly alter the levels of miR-105, but significantly decreased the levels of miR-15 and miR-146 (*Figure 5A*). On the other hand, transfection of si-BCAR4 in high-BCAR4-expressing DU145 cells did not significantly alter the levels of miR-105, but significantly increased the levels of miR-15 and miR-146 (*Figure 5B*). Moreover, transfection with miR-15 and miR-146, but not with miR-105, significantly attenuated the effects of altered BCAR4 on Beclin-1 levels in both PC346 cells (*Figure 5C*) and DU145 cells (*Figure 5D*). These data suggest that BCAR4 likely regulates Beclin-1 through miR-15 and miR-146 in PC cells.

Discussion

Beclin-1 is the mammalian orthologue of yeast ATG6, and plays a pivotal role in the regulation of autophagy, in which Beclin-1 has crosstalk with a number of autophagy cofactors, including ATG14L, Rubicon, Ambra1, UVRAG, nPIST, VMP1, Bif-1, SLAM, IP3R, HMGB1 and PINK, to initiate the process of autophagy (13). A previous study has demonstrated the importance of Beclin-1 in the tumorigenesis of PC by showing it likely regulates the malignant transformation of prostate tissue and promotes PC cell differentiation, progression, and aggressive potential (14).

Interestingly, Beclin-1 has been shown to be controlled by miRNAs (15,16) in PC and by lncRNAs in other cancers (17-20). However, a role of BCAR4 in the regulation of Beclin-1 and autophagy has not been reported before now. BCAR4 is a lncRNA, which typically regulates gene expression through its interaction with miRNAs which further regulate protein translation of certain target genes through their complementary sequence binding to the 3'-UTR for the mRNA (21). Moreover, the interaction between lncRNA and miRNAs is also through complementary sequence binding. The lncRNA negatively regulates the level of the target miRNA while miRNA negatively regulates the translation of the target gene (21). Therefore, such a regulatory pair is characteristic in that the direction of the changed expression level of lncRNA, and the gene is typically the same, but different with the miRNAs (21).

Based on these criteria, we screened all candidate miRNAs and found miR-105, miR-15, and miR-146, to meet all these requirements. However, only miR-15 and miR-146 passed the gain-of-function and loss-of-function tests, suggesting they may be the mediators for the regulation of Beclin-1 by BCAR4. In contrast, MiR-105 did not seem to be involved in this regulation, which may be due to the expression level, assess to the control point, or other mechanisms. Interestingly, miR-146 has been shown to regulate cell autophagy in PC (22,23), and miR-15 has been reported to control PC progression through interacting with a number of genes (24). However, a direct crosstalk between Beclin-1 and miR-15/miR-146 has not been shown before.

Thus, to the best of our knowledge, our study not only showed a novel role of BCAR4 in the regulation of autophagy in PC, but also showed a possible innovative mechanism by which Beclin-1 can be regulated by miR-15 and miR-146. Further studies may evaluate the possible presence of this regulatory axis in other cancers, and these approaches may help to better characterize this molecular pathway and its importance in cancer cell autophagy.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://dx.doi.org/10.21037/tau-21-929

Data Sharing Statement: Available at https://dx.doi.org/10.21037/tau-21-929

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tau-21-929). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Shanghai Changzheng Hospital (JS-254). Use of specimens was approved by donors (no number) who returned signed informed consent.

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