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Aromatic hydrocarbon receptor inhibits lysophosphatidic acid-induced vascular endothelial growth factor-A expression in PC-3 prostate cancer cells

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ABSTRACT

Lysophosphatidic acid (LPA) is a lipid growth factor with multiple biological functions and has been shown to stimulate cancer cell secretion of vascular endothelial growth factor-A (VEGF-A) and trigger angiogenesis. Hypoxia-inducible factor-1 (HIF-1), a heterodimer consisting of HIF-1α and HIF-1β (also known as aromatic hydrocarbon receptor nuclear translocator (ARNT)) subunits, is an important regulator of angiogenesis in prostate cancer (PC) through the enhancement of VEGF-A expression. In this study, we first confirmed the ability of LPA to induce VEGF-A expression in PC-3 cells and then validated that LPA-induced VEGF-A expression was regulated by HIF-1α and ARNT through phosphatidylinositol 3-kinase activation. Aromatic hydrocarbon receptor (AHR), a receptor for dioxin-like compounds, functions as a transcription factor through dimerization with ARNT and was found to inhibit prostate carcinogenesis and vanadate-induced VEGF-A production. Since ARNT is a common dimerization partner of AHR and HIF-1α, we hypothesized that AHR might suppress LPA-induced VEGF-A expression in PC-3 cells by competing with HIF-1α for ARNT. Here we demonstrated that overexpression and ligand activation of AHR inhibited HIF-1-mediated VEGF-A induction by LPA treatment of PC-3 cells. In conclusion, our results suggested that AHR activation may inhibit LPA-induced VEGF-A expression in PC-3 cells by attenuating HIF-1α signaling, and subsequently, suppressing angiogenesis and metastasis of PC. These results suggested that AHR presents a potential therapeutic target for the prevention of PC metastasis.

1. Introduction

Prostate cancer (PC) is the most frequently diagnosed cancer and second leading cause of cancer death in American men [1]. It usually originates as an uncontrolled and abnormal growth within the glandular tissue of the prostate gland, which is referred to as prostatic adenocarcinoma. Androgens are the main regulators of PC growth and survival by both stimulating cellular proliferation and inhibiting apoptosis [2]. Hormone therapy for androgen deprivation or ablation can effectively slow or inhibit PC proliferation [3]. Although hormone therapy can temporarily successfully control PC progression, PC often relapses, transforms to an androgen refractory tumor or androgen-independent cell-type, and becomes more aggressive and metastatic [4,5].

Lysophosphatidic acid (LPA) is a bioactive lysophospholipid that affects diverse cellular and pathological processes, such as cell proliferation and cancer progression [6,7], and is mainly stored in platelets and released upon an inflammatory response. The estimated concentrations of active, albumin-bound LPA in normal human serum are within the range of 1–5 μM [8]; however, in cancer patients, serum levels may increase to 80 μM [9]. LPA binds to a family of G protein-coupled receptors, termed LPA_1–LPA_5, to regulate cellular functions [10]. In PC, LPA regulates cancer cell proliferation, migration, invasion, and survival [11–14]. Moreover, LPA is known to stimulate cancer cells to secret vascular endothelial growth factor-A (VEGF-A) and trigger angiogenesis.

Hypoxia-inducible factor 1 (HIF-1) is a heterodimer consisting of two subunits: HIF-1α and HIF-1β, which is also known as aryl hydrocarbon receptor nuclear translocator (ARNT) [15]. HIF-1α is tightly regulated in response to hypoxia [15] and significantly overexpressed in PC [16]. Furthermore, HIF-1 was shown to

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participate in LPA-induced VEGF-A expression in PC-3 cells [17]. These results strongly suggest that LPA stimulates VEGF-A production, and therefore, induces angiogenesis through HIF-1 signaling pathways in PC cells.

The aromatic hydrocarbon receptor (AHR) is a member of the basic helix-loop-helix/per-arnt-sim family of transcription factors. AHR binds to a wide variety of chemicals and is activated by the environmental contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which leads to AHR nuclear localization, heterodimerization with ARNT [15], and subsequent binding to aryl hydrocarbon receptor enhancer elements located in the promoters of AHR-responsive genes. Reportedly, AHR and ARNT might regulate the carcinogenic process of PC [18,19]. Recent reports further suggested that AHR inhibits prostate carcinogenesis and VEGF-A production in transgenic adenocarcinoma of the mouse prostate (TRAMP) [20,21]. Since ARNT is a common dimerization partner of AHR and HIF-1α, it was hypothesized that AHR signaling may suppress VEGF-A expression by competing with HIF-1α for ARNT, thereby inhibiting angiogenesis and tumor growth in PCs. The aim of this study was to determine whether AHR could sequester ARNT from HIF-1α and subsequently reduce VEGF-A expression in PC-3 cells.

2. Materials and methods

2.1. Cell culture

The human PC-3 cell line was purchased from the American Type Culture Collection (ATCC; Manassas, VA) and maintained in RPMI-1640 medium supplemented with 10% FBS. Cell cultures were incubated at 37 °C in a humidified atmosphere of 5% CO_2.

2.2. Lentiviral production and transduction

To package the viruses, 293T cells were co-transfected with 7.5 μg of pLKO.1 lentiviral vectors, 1.9 μg of the envelope plasmid pMD.G, and 5.6 μg of the packaging plasmid pCMVΔR8.91. Viral solutions were collected 24 and 48 h after transfection and condensed using PEG8000 solution. The viral titer was determined before use. For transduction, an appropriate volume of the viral solution was combined with PC-3 cells in growth medium, which was replaced after 24 h of incubation. Then, 48 h after viral transduction, total RNA was extracted and subjected to real-time PCR.

2.3. LPA stimulation

LPA (Sigma–Aldrich, St. Louis, MO, USA) was prepared in chloroform and methanol (1:9) and stored at −20 °C. The PC-3 cells were cultured to 70–80% confluence in 9.5-cm^2 wells with complete medium, washed with PBS, and starved in serum-free RPMI-1640 medium for 16 h. After starvation, LPA was added into serum-free RPMI-1640 culture medium with 0.005% fatty acid-free bovine serum albumin as a carrier.

2.4. RNA isolation and reverse transcription

Total RNA was isolated from PC-3 cells using the TRIzol reagent (Invitrogen Corp., Carlsbad, CA, USA) according to the manufacturer's protocol. The reverse transcription of isolated total RNA (1 μg) was performed in a 20-μL reaction mixture containing M-MuLV reverse transcriptase (Thermo Fisher Scientific, Waltham, MA, USA) and oligo-dT primers.

2.5. Real-time PCR

Real-time PCR was performed using the iCycler iQ Real-Time detection system (Bio-Rad, Hercules, CA, USA) with SYBR Green I as the fluorescent dye, which enabled real-time detection of PCR products. cDNA was real-time PCR-amplified using the primer pairs listed below under cycling conditions of 95 °C for 3 min, followed by 40 cycles of 95 °C for 30 s, 60 °C for 30 s, and 72 °C for 60 s. For quantification, the target gene was normalized to the internal standard gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and the fold increase between the control and treatment groups was calculated using the following equation: increase fold = $2(CT_T - CT_S)$ of Tr − $(CT_T - CT_S)$ of Co, where CT_T is the threshold cycle of the target gene, CT_S is the threshold cycle of the standard gene, Co represents the control groups, and Tr represents the treatment groups. Oligonucleotide primers for PCR were designed using Beacon Designer2 software (Premier Biosoft International, Palo Alto, CA, USA). cDNA was then subjected to PCR amplification with the following primer sets for AHR, ARNT, HIF-1α, VEGF-A, and GAPDH: AHR forward, 5′-TCC CCA TAC CCC ACT ACT TC-3′; AHR reverse, 5′-GCT TGG AAT TAC AGG AAT CCA C-3′; ARNT forward, 5′-GGA ACA AGA TGA CAG CCT AC-3′; ARNT reverse, 5′-CAG AAA GCC ATC TGC TGC C-3′; HIF-1α forward, 5′-TCC ATG TGA CCA TGA GGA AA-3′; HIF-1α reverse, 5′-TAT CCA GGC TGT GTC GAC TG-3′; VEGF-A forward, 5′-CTA CCT CCA CCA TGC CAA GT-3′; VEGF-A reverse, 5′-ATC TGC ATG GTG ATG TTG GA-3′; GAPDH forward, 5′-CAT CTT CCA GGA GCG AGA-3′; and GAPDH reverse, 5′-CTG CTT CAC CAC CTT CTT GAT-3′.

2.5.1. Statistical analysis

Data were analyzed for statistical significance by one-way analysis of variance followed by the Fisher's protected least-significant difference test using StatView software (Abacus Concept, Berkeley, CA, USA). Each result was obtained from at least three independent experiments and expressed as mean ± standard deviation. $p < 0.05$ was considered statistically significant for all tests.

3. Results

3.1. HIF-1α is required in LPA-induced VEGF-A expression

Previous studies have suggested that LPA stimulates VEGF-A expression in PC cells [22,23]. In this study, we further confirmed that 5 μM LPA efficiently up-regulated VEGF-A mRNA expression in PC-3 cells (Fig. 1B). VEGF-A is one of the best-characterized target genes regulated by HIF-1α [23]; therefore, we used RNA interference as a strategy to determine whether HIF-1α mediates LPA-induced VEGF-A expression in PC-3 cells. Briefly, PC-3 cells were transduced with lentiviral control vectors or lentiviral HIF-1α shRNA and then incubated with LPA. Total RNA was isolated, subjected to real-time PCR to analyze mRNA expression, and then reverse-transcribed into cDNA. As shown in Fig. 1A, HIF-1α shRNA transduced using the lentiviral system significantly suppressed HIF-1α mRNA expression. Moreover, LPA-induced VEGF-A mRNA expression was blocked by HIF-1α shRNA (Fig. 1B). These results strongly suggested that HIF-1α was required for LPA-induced VEGF-A expression.

3.2. HIF-1β (ARNT) is required in LPA-induced VEGF-A expression

HIF-1β (ARNT) was suggested as an essential dimerization partner of HIF-1α to form the HIF-1 complex, which acts as a transcription factor to regulate VEGF-A expression under hypoxic conditions [24]. Under LPA stimulation, we found that HIF-1α was required in the regulation of VEGF-A expression. Therefore,

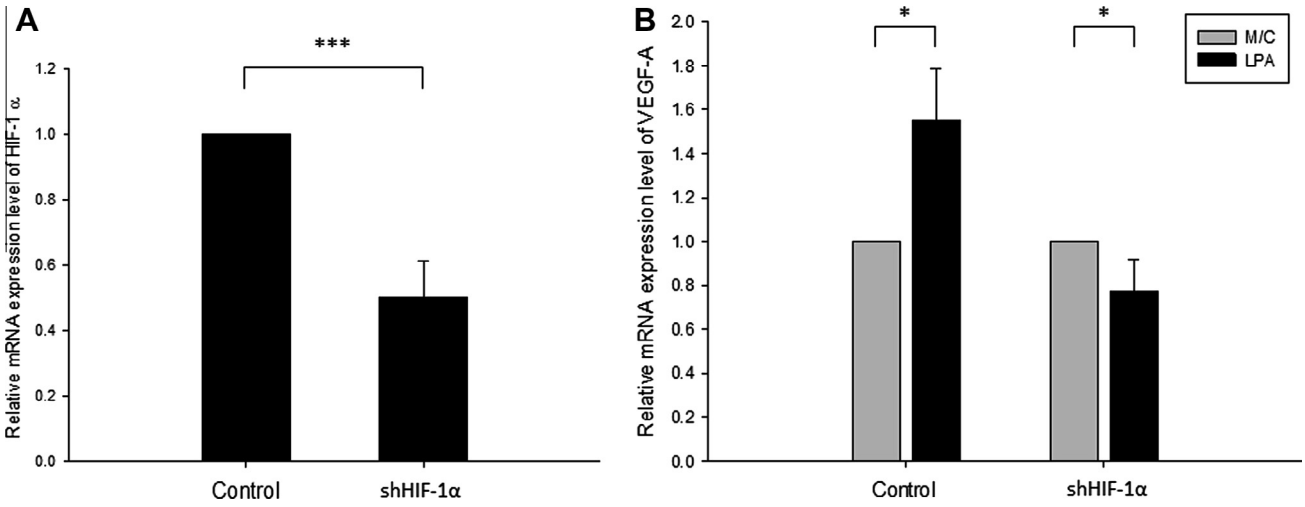

Fig. 1. The role of HIF-1α in LPA-induced VEGF-A expression in PC-3 cells. (A) PC-3 cells were transfected with HIF-1α shRNA or a control vector for 48 h. The relative HIF-1α mRNA levels were measured by real-time PCR. (B) After HIF-1α shRNA transfection, cells were starved for 12 h and then incubated with 5 μM of LPA or methanol–chloroform for 2 h. The relative mRNA levels of VEGF-A were analyzed using real-time PCR. $^{*}p < 0.05$; $^{***}p < 0.005$.

we subsequently overexpressed HIF-1β (ARNT) shRNA to determine whether HIF-1β (ARNT) regulated LPA-induced VEGF-A expression. Real-time PCR analysis showed that HIF-1β (ARNT) shRNA efficiently suppressed HIF-1β (ARNT) expression (Fig. 2A) and subsequently inhibited LPA-induced VEGF-A mRNA transcription (Fig. 2B). In contrast, LPA-induced VEGF-A expression was further enhanced by HIF-1β (ARNT) overexpression (Fig. 2D). These results demonstrated that HIF-1β (ARNT) was an important factor in regulation of LPA-induced VEGF-A expression in PC-3 cells.

3.3. Phosphatidylinositol 3-kinase (PI3K) regulation of HIF-1α and LPA-induced VEGF-A expression

Our results demonstrated that both components of the HIF-1 complex (HIF-1α and HIF-1β) were involved in the regulation of LPA-induced VEGF-A expression and previous reports suggested that PI3K may act as an upstream regulator of HIF-1α expression in PC cells [25–30]. Furthermore, PI3K has been suggested to mediate the effect of LPA in several cancers [31–33]. Therefore, we hypothesized that PI3K signaling was required for HIF-1-mediated VEGF-A expression in PC-3 cells. To determine whether PI3K signaling mediates LPA-induced HIF-1α expression in PC-3 cells, serum-starved cells were pretreated with either dimethyl sulfoxide (DMSO) or 10 μM LY294002, a potent inhibitor of P13K, and then treated with LPA. HIF-1α expression was then subjected to real-time PCR. As shown in Fig. 3A, LY294002 inhibited LPA-induced HIF-1α expression, which suggested that PI3K was required for LPA-induced HIF-1α expression. Moreover, LPA-induced VEGF-A expression was also significantly suppressed by blockage of PI3K activity (Fig. 3B). These results suggested that PI3K was an upstream regulator of HIF-1α signaling and mediated LPA-induced VEGF-A expression.

3.4. Activation of AHR inhibits LPA-induced VEGF-A expression in PC-3 cells

AHR was previously reported to participate in inhibition of vanadate-induced VEGF-A production and prostate carcinogenesis [20,21]. Herein, we attempted to determine whether AHR signaling activation suppressed LPA-induced VEGF-A transcription in PC-3 cells. Using a lentiviral transduction system, we successfully overexpressed human AHR in PC-3 cells (Fig. 4A). Ectopic AHR expression elicited a ligand-independent effect and significantly diminished LPA-induced VEGF-A expression (Fig. 4B). Furthermore, activation of the AHR signaling pathway by the AHR agonist 3-methylcholanthrene (3-MC) also efficiently suppressed LPA-induced VEGF-A mRNA expression (Fig. 4C). These results demonstrated that activation of AHR signaling inhibited LPA-induced VEGF-A expression in PC-3 cells.

4. Discussion

LPA has been implicated in regulation of cell proliferation, migration, invasion, and survival in PC [11–14]. In this study, we demonstrated that LPA-induced VEGF-A expression was regulated by HIF-1α, HIF-1β (ARNT), and PI3K in PC-3 cells, which plays roles in angiogenesis in PC. LPA was suggested to promote PC progression. Although LPA was initially shown to be released by activated platelets, more recent studies established that LPA is produced by a wide variety of mammalian cells, including PC cells, which reportedly serves as an autocrine/paracrine mediator to affect the functions of both cancer and neighboring cells [34]. Thus, LPA-induced VEGF-A expression might also act through autocrine/paracrine signaling to promote PC progression.

The HIF-1α protein has been indicated to degrade under normoxic conditions by the ubiquitin–proteasome system, whereas hypoxic conditions induced HIF-1α stabilization and transactivation [35,36]. Furthermore, HIF-1α has been indicated to dimerize with HIF-1β (ARNT) to form the HIF-1 complex, which then activates VEGF-A expression by directly binding to the VEGF-A promoter in response to hypoxic conditions [35]. These findings suggested that HIF-1α and HIF-1β were involved in hypoxia-induced VEGF-A expression. In the present study, we first demonstrated that LPA-induced VEGF-A expression was HIF-1α- and HIF-1β-dependent. Reportedly, reactive oxygen species (ROS) mediated LPA-induced signaling [37]. ROS are generated under hypoxic conditions and activate protective responses, including HIF activation, in diverse cell types [38–41]. Taken together, we speculated that LPA might induce ROS production to activate HIF-1 signaling and subsequently promote VEGF-A expression, similar to the hypoxic response. However, the specific mechanism of LPA-induced HIF-1 expression requires further investigations.

AHR is a ligand-activated transcription factor that requires heterodimerization with ARNT to function. ARNT is also a dimerization partner of HIF-1α in hypoxia-induced signaling. Therefore,

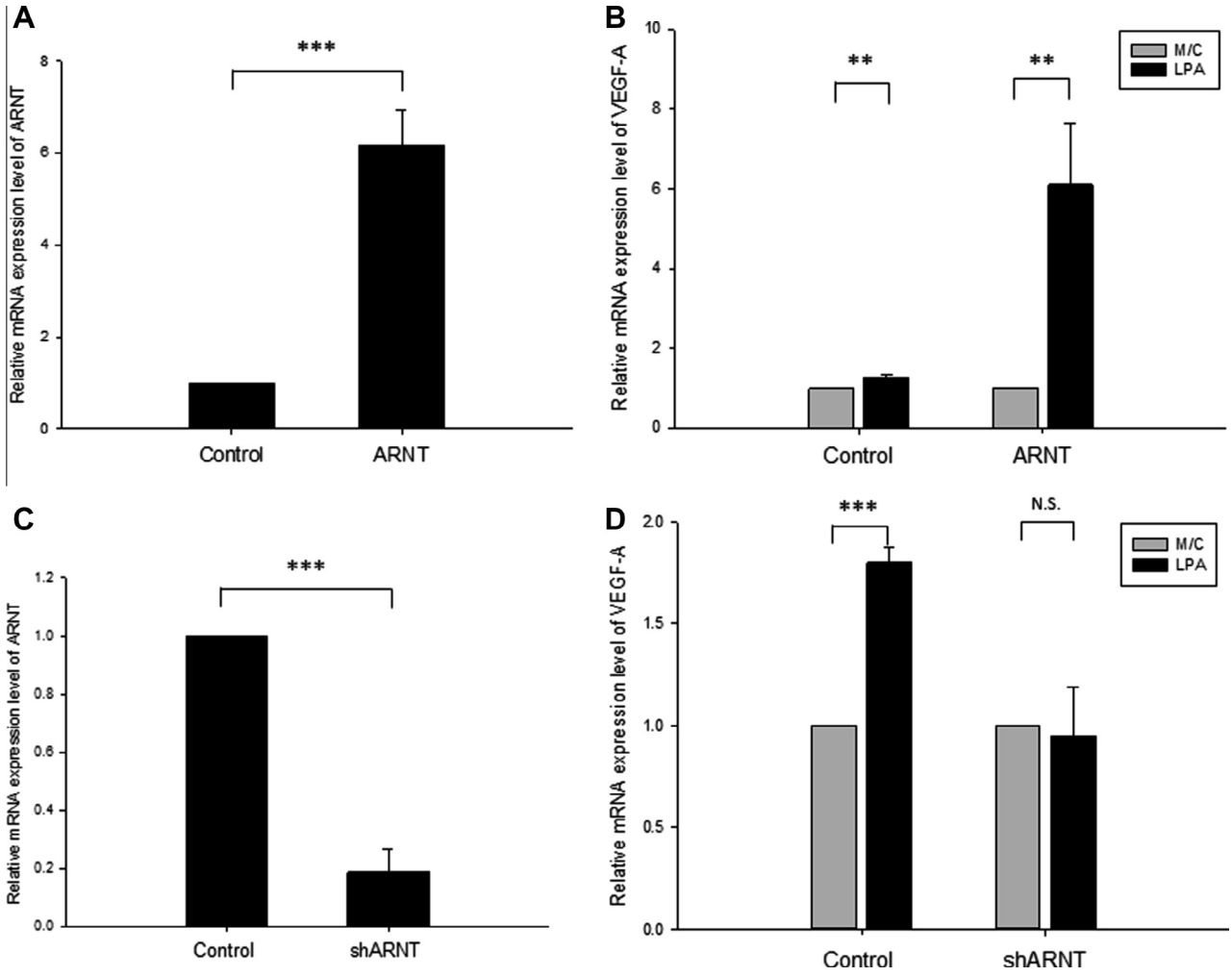

Fig. 2. ARNT regulation of LPA-induced VEGF-A expression in PC-3 cells. (A) PC-3 cells were transfected with ARNT expression vectors or control vectors for 48 h using a lentiviral transduction system. The relative ARNT mRNA expression levels were measured by real-time PCR. (B) After ARNT overexpression, the cells were starved for 24 h and then incubated with 5 μM of LPA or methanol–chloroform. The relative VEGF-A mRNA expression levels were measured by real-time PCR. (C) PC-3 cells were transfected with ARNT shRNA or control vector for 48 h using the lentiviral transduction system. The relative ARNT mRNA expression levels were measured by real-time PCR. (D) After ARNT shRNA transfection, the cells were starved for 24 h and incubated with 5 μM of LPA or methanol–chloroform. The relative VEGF-A mRNA expression levels were measured by real-time PCR. NS, non-significant; $^{**}p < 0.01$; $^{***}p < 0.005$.

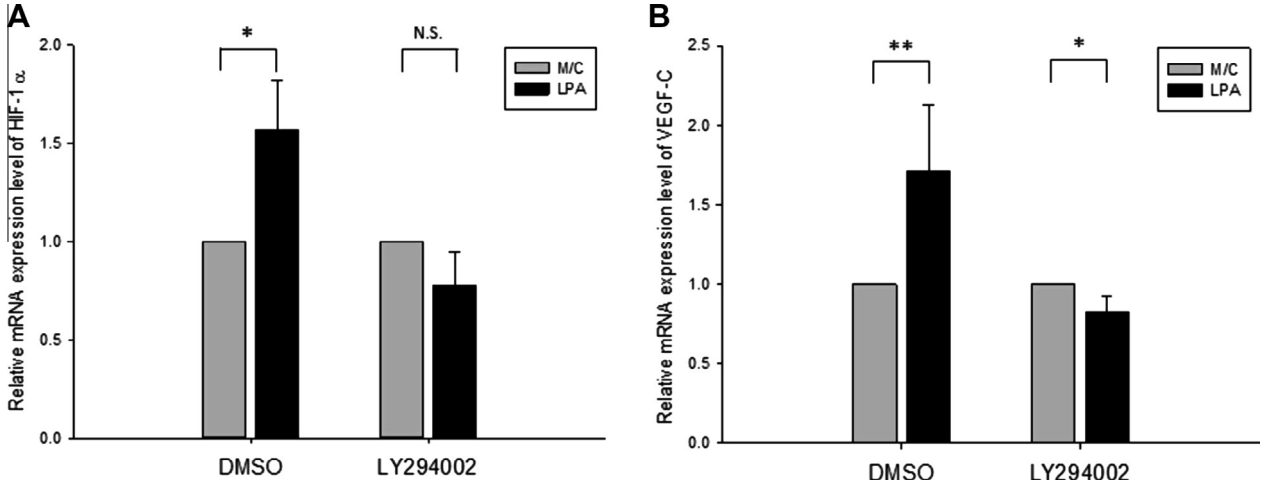

Fig. 3. Effects of PI3K on LPA-induced HIF-1α and VEGF-A expression in PC-3 cells. (A) and (B) Serum-starved PC-3 cells were pretreated with 10 μM of LY294002 or the solvent control DMSO for 1 h and then treated with 5 μM of LPA or methanol–chloroform for 2 h. The relative HIF-1α and VEGF-A mRNA expression levels were determined by real-time PCR. NS, non-significant; $^{*}p < 0.05$; $^{**}p < 0.01$.

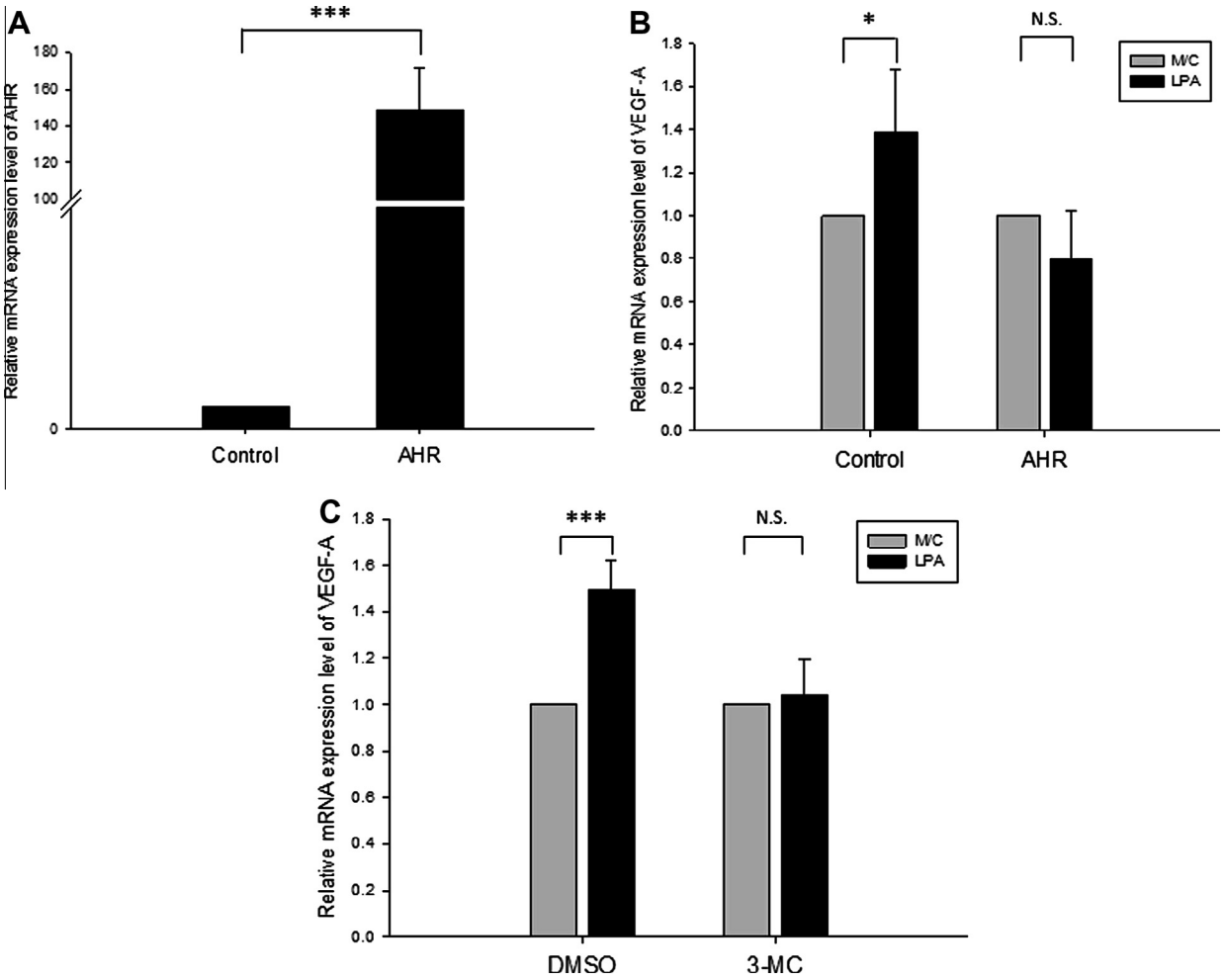

Fig. 4. AHR overexpression and activation inhibits LPA-induced VEGF-A expression in PC-3 cells. (A) PC-3 cells were transduced with AHR expression vectors or control vectors. AHR mRNA levels were measured by real-time PCR. (B) After viral transduction, cells were starved and then incubated with 5 μM LPA or methanol–chloroform as a control. The relative VEGF-A mRNA expression levels were analyzed by real-time PCR. (C) Serum-starved PC-3 cells were pretreated with 1 μM of the selective AHR modulator, 3-methylcholanthrene (3-MC), or the solvent control, DMSO, for 6 h and then treated with LPA or methanol–chloroform for 2 h. The relative VEGF-A mRNA expression levels were determined by real-time PCR. NS, non-significant; $^{*}p < 0.05$; $^{***}p < 0.005$.

ARNT is a common dimerization partner of both AHR and HIF-1α. Collectively, these results suggested that reciprocal crosstalk may occur between AHR and hypoxia signaling pathways. Furthermore, it was demonstrated that hypoxia inhibited AHR activity in an ARNT-dependent manner in topminnow hepatocarcinoma cells [42]. The hypoxic response was also suggested to decrease TCDD-induced responses in zebrafish embryos [43]. Reciprocally, ectopic expression of constituted, activated, truncated AHR (CΔ553) blocked hypoxia-induced signaling in breast cancer [44]. Moreover, the results in this study suggested that overexpression and ligand activation of AHR suppressed LPA-induced VEGF-A expression, which is HIF-1α- and ARNT-dependent. Collectively, this evidence supported the presence of crosstalk between ARNT-dependent pathways. Therefore, activation of this ARNT-dependent pathway may inhibit the activation of other pathways that depend on ARNT. Here, we clearly demonstrated that AHR sequestered ARNT from HIF-1α in PC-3 cells and subsequently reduced LPA-induced VEGF-A expression.

Vanadate is a potent mitogenic agent and was shown to induce HIF-1 activation and VEGF-A production in DU145 human prostate carcinoma cells [45]. AHR was suggested to sequester HIF-1β (ARNT), thereby decreasing interaction with HIF-1α in the inhibition of vanadate-induced VEGF-A production in TRAMP prostates [20]. Moreover, activation of AHR inhibits prostate tumor metastasis in TRAMP mice [46]. In our present study, we showed that overexpression and activation of AHR inhibited LPA-induced VEGF-A expression in PC-3 cells, suggesting a role of AHR as a tumor suppressor in PC, similar to the effect previously reported in heart [47] and breast cancers [48]. Therefore, AHR ligand treatment may be a potential strategy for PC therapy. Reportedly, less toxic dioxin alternatives were used to successfully hinder breast cancer progression [48]. These less toxic alternatives are collectively referred to as selective AHR modulators (SAHRMs), which includes 3-MC and 6-methyl-1,3,8-trichlorodibenzofuran. SAHRMs share the common ability with dioxin to activate AHR signaling, but they are distinguished from dioxin by their weakened toxicity [49]. In addition to inhibiting proliferation of human LNCaP cells, SAHRMs have been indicated to inhibit VEGF-A expression as well as to reduce pelvic lymph node metastasis in TRAMP mice [50]. It was also shown in this study that one of the SAHRMs, 3-MC, efficiently inhibited LPA-induced VEGF-A production. Thus, novel toxicity-free SAHRMs warrant further exploration for future PC treatments.

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