

Differential Effect of ITE on the Aryl Hydrocarbon Receptor Signaling in Breast Cancer Tissue: A Histopathological Study

Efecto Diferencial de ITE en la Señalización del Receptor de Hidrocarburo de Arilo en Tejido de Cáncer de Mama: Un Estudio Histopatológico

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SUMMARY: Aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that is highly expressed in various types of cancers including breast cancer. However, the role of AhR with its endogenous ligand 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) on the progression of breast cancer remains poorly understood. We aimed to investigate cell proliferation and migration states in breast cancer after activating AhR with the endogenous ligand ITE. Breast cancer tissue was evaluated by cell lines, immunohistochemistry, reverse transcription-polymerase chain reaction, cell proliferation, flow cytometry, migration assays and western blot techniques. We found that AhR was widely expressed in breast cancer tissues and metastasis lymph node tissues, but not in normal tissues. The expression AhR was independent between the age, grades and TNM classifications for breast cancer tissues. ITE treatment significantly induced the activation of AhR in a time-dependent manner in both MCF-7 and T47D breast cancer cell lines. Meanwhile, ITE did not affect the cell migration but significantly suppressed the cell proliferation in estrogen receptor positive (ER+) MCF-7 and T47D cells, which probably attribute to the induction of cell cycle arrest in G1 phase and shortened S phase. Further mechanism study showed that ERK1/2 and AKT signaling were required for the activation of AhR in MCF-7 cells. These data suggest that AhR is a potential new target for treating patients with breast cancer. ITE may be more potentially used for therapeutic intervention for breast cancer with the kind of ER(+).

KEY WORDS: ITE; Aryl hydrocarbon receptor; Breast cancer; Estrogen receptor.

INTRODUCTION

Aryl hydrocarbon receptor (AhR) plays an important role in regulation of gene expression in metabolic machinery and detoxification systems. Recently, the relationship between AhR and tumorigenesis is gaining more and more attention. As a transcription factor, AhR can be activated by either exogenous or endogenous AhR ligands, where the endogenous ligands is critical for normal physiologic responses such as cancer development, cell cycle regulation, and immune function (Ide *et al.*, 2017). AhR ligands are also proved to have therapeutic effects on treating diseases caused by abnormal immune function and certain cancers (Guarnieri, 2020). Moreover, another study demonstrated that AhR agonists can cause regression of existing chemical-induced tumors and inhibit the growth of human cancer cells (Zhao *et al.*, 2019). These promising evidence suggests that AhR modulation is useful in controlling primary tumor growth and may be an attractive

therapeutic method for breast cancer treatment (Narasimhan *et al.*, 2018).

To date, several published *in vitro* studies have addressed the effect of AhR agonists on breast cancer, which suggested that 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD) and other AhR ligands could alleviate the proliferation, invasion, motility, and colony formation of breast tumor cells (Romagnolo *et al.*, 2017; Yang *et al.*, 2018). AhR activation has been reported to suppress the growth of pancreatic and liver cancers (Safe *et al.*, 2017; Masoudi *et al.*, 2019). Recently, a lot of endogenous AhR ligands have been discovered, for example, 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (Dolciemi *et al.*, 2018), which was first isolated from porcine lungs (Abron *et al.*, 2018). According to the activity of ITE on the dioxin responsive element, the biological potency of ITE was

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approximately 100-fold lower than that of TCDD (Piwarski *et al.*, 2020). Meanwhile, the estimated Kd value for ITE in mouse hepatoma cells was approximately 5 to 6 fold greater than that of TCDD (Nugent *et al.*, 2013). Thus, given its naturally producing feature and specific binding to AhR, ITE could potentially be used for interfering breast cancer growth, particularly due to the lack of toxicity (Dolciami *et al.*, 2018; Abron *et al.*, 2018; Bian *et al.*, 2019).

In the current study, we tested the effect of ITE exposure on mammary tumor growth and metastasis by using estrogen receptor-positive (ER+) MCF-7 and ER-negative (ER-) MDA-MB-231 breast cancer cells, respectively. We investigated the cell proliferation and migration states in breast cancer after activating AhR by its endogenous ligand ITE. To explore new ideas for the clinical development of anti-breast cancer drugs or endocrine therapy in breast cancer treatment, we also examined the expression of AhR in different clinical phenotypes of breast cancer specimens.

MATERIAL AND METHOD

Ethical permission. The study was approved by the Scientific and Ethical Committee of the Shanghai First Maternity and Infant Hospital affiliated with Tongji University (No. KS20142) and informed consent was taken from all the patients.

Cell lines. Four human breast adenocarcinoma cell lines (MDA-MB-231, MDA-MB-468, MCF-7 and T47D) were obtained from ATCC (American Type Culture Collection, Manassas, VA). All cells were cultured in RPMI 1640 (DMEM, SIGMA) medium containing 10 % FBS, and 1 % penicillin/streptomycin (P/S) (designed as the complete growth media). Each cell line was maintained in a humidified atmosphere containing 5 % CO₂ at 37 °C.

Immunohistochemistry. Immunolocalization of AhR was performed using the human breast cancer tissue microarray purchased from Chaoying, Shanxi, China (cat#BR1008) as described (Moorthy *et al.*, 2015; Dolciami *et al.*, 2018). The tissue microarray contained 50 cases of breast carcinoma, 40 cases of metastatic lymph node from breast invasive ductal carcinoma, 10 breast tissues of benign diseases. Major cancer histotypes include invasive ductal carcinoma (IDC; n = 46), medullary carcinoma (MC; n = 3), neuroendocrine carcinoma (NEC; n = 1), in which all were classified as molecule markers and grade. The stage of tumors was assessed according to the 6th ed. of TNM Classification of Malignant Tumors. Two microarrays were run in parallel: one was probed with AhR anti-body AhR (1: 500; Enzo Life Sciences Inc., Farmingdale, NY, USA) and the other was probed with IgG control. The brief processes were performed as following immunohistochemistry (IHC) methods.

The sections were incubating in a 10 mM citrate buffer solution (pH 6.0) in a microwave for 10 min for antigen retrieval. Endogenous peroxidase activity was quenched by immersing the tissue sections in 3 % H₂O₂ in methanol for 10 min. After blocking the non-specific binding with 1 % horse serum albumin for 20 min, the tissue sections were probed with a rabbit anti-AhR antibody (1: 2000, Chemicon International, Billerica, MA). Rabbit IgG was used as the negative control. The intensity of immunohistochemical reactions was estimated independently by two pathologists. In doubtful cases a reevaluation was performed using a double-headed microscope and staining was discussed until a consensus was achieved. Thus, in order to evaluate the AhR expression, the Remmele scale (IRS) were applied according to Immunoreactive Score by Remmele and Stegner (Table I). In IRS scale the intensity of color reaction and percentage of positive cells were taken into account. The score represented a product of points given for the evaluated characters and it ranged from 0 to 12. Cases with expression

Table I. Correlation of AhR expression with clinical characteristics of breast cancers.

		AhR expression		P value
		Total (n = 89)	High (> 3.6) (n = 41)	
Age	≤ 50		28	0.332
	> 50		20	
Pathology	breast carcinoma		22	0.685
	metastatic lymph node		20	
Grade	1		0	0.359
	2		19	
	3		15	
TNM Stage	I		2	0.579
	II		15	
	III		3	
	IV		0	

of 0 to 3 in IRS scale and with score 0 to 1+ according to Hofmann *et al.* (2008) criteria were treated as cases without overexpression.

Reverse transcription-polymerase chain reaction (RT-PCR). Total RNA from cells before and after treated with ITE (0.1-10 µM, Tocris Bioscience, San Diego, CA) was isolated with Trizol Reagent according to manufacturer’s protocol (Sigma-Aldrich). RNA was quantified by UV absorption measure and was reverse transcribed to cDNA. The reverse transcription (RT) was carried out using Prime Script RT reagent Kit (TaKaRa, Dalian, China) for 15 min at 37 °C, 5 s at 85 °C in a 20 mL reaction volume. RT-PCR was performed using SYBR Premix Ex Taq (TaKaRa) according to the manufacturer’s instruction. Primer sequences were ordered from Sangon (Shanghai, China) (Table II). The real-time PCR cycling condition for GAPDH, CYP1A1, CYP1B1, ERα is 30 s at 95 °C for incubation, 40 cycles of 15 s at 95 °C, and 20 s at 60 °C.

Cell proliferation. Cell proliferation assay was as described as follow: after 16 h of seeding in 96-well plates (5000 cells/well, 6 wells/dose), cells were treated with different concentration of ITE or DMSO (0.1 % v/v) in the complete growth media up to 2 days with daily change of media containing ITE or dimethyl sulfoxide (DMSO, the vehicle control). At the end of treatment, the number of cells per well was determined using a crystal violet method. Briefly, following removal of media, wells were rinsed (2X) with PBS (5 mM phosphate, 145 mM NaCl, 5 mM KCl, pH 7.5), fixed in methanol for 15 min, air-dried for 5 min and stained with 0.1 % (w/v) crystal violet for 5 min. After staining, wells were rinsed with distilled water, and air dried again. Once dry, cells were solubilized with 2 % (w/v) sodium deoxycholate solution for 30 min with gentle agitation. Absorbance was measured at 570 nm on a microplate reader (BioRad). Wells containing known cell numbers (0, 2500, 5000, 10000 and 20000 cells/well; n = 6/cell density) were treated in the similar fashion to establish standard curves for each individual cell line.

Flow cytometry. Cells were seeded at a density of 2 × 10⁵ cells per well on a 6-well plate and cultured overnight in growth medium for cell cycle analysis. Baicalein (28 µg/mL final concentration) was then added, and the cells were

incubated for an additional 48 h at 37 °C. The cells were then collected, fixed in ice-cold ethanol (70 %), and stored at -20 °C for overnight. Next, the ice-cold ethanol was removed by centrifugation, and the cells were incubated with 0.5 % Triton X-100 containing 100 µg/mL RNase A at 37 °C for 30 min. Cells were then incubated for 15 min with 25 µg/mL propidium iodide in PBS in the dark at room temperature and immediately analyzed using a BD FACSCanto II flow cytometer as indicated by the manufacturer (BD Biosciences). After 48 h of treatment, cells were labeled with PI and analyzed by flow cytometry. The data indicate the percentage of cells in each phase of the cell cycle.

Migration assays. Cell migration was evaluated using a 24-Multiwell BD Falcon FluoroBlok Insert System (8.0 µm pores; BD Biosciences, San Jose, CA, USA) as described. Cells were treated with 1 µM ITE or 0.1 % DMSO for 24 h. Cell suspensions (5 × 10³ cells per well) were added to the top chamber of Transwells (BD Biosciences). The bottom chamber contained RPMI medium with 10 % FBS and 1 µM ITE or DMSO. Cells were incubated for 24 h at 37 °C, at which time cells remaining in the insert were removed with a cotton swab. 24 h latter, the two cells that migrated to the bottom of the inserts were stained with calcein AM (0.2 mg/mL, Invitrogen) for 30 min, examined, and recorded by an inverted microscope mounted with a CCD camera. After serum starvation for 24 h, 30,000 cells were seeded in the insert (topside of membrane) and cultured in serum-free media. Migrated cells on the bottom of the filters were fixed with methanol and stained with crystal violet. The numbers of cells in five adjacent fields of view were counted under 100 magnification. The cells were then trypsinized and resuspended in fetal bovine serum (FBS)-free media containing 0.1 % bovine serum albumin and 1 µM ITE or DMSO vehicle. The numbers of migrated cells were counted using the MetaMorph image analysis software (Molecular Devices).

Western blot analysis. After serum starvation for 16 h, cells were treated without or with 1 µM of ITE for 0, 0.5, 2, 8, 24, or 48 h. The protein was subjected to Western blotting as described. For each set of samples, at least two gels were run simultaneously. One membrane was blotted with a phospho-ERK1/2 antibody, followed by reblotting

Table II. RT-PCR primers used in this study.

Target genes	Sense (5' to 3')	Antisense (5' to 3')
GAPDH(372 bp)	F: TCTTCTTTTGCGTCGCCAG	R: AGCCCCAGCCTTCTCCA
AhR (368 bp)	F: CATGCTTTGGTCTTTTATGC	R: TTCCCTTTCTTTTCTGTCC
CYP1A1 (596)	F: TCTTTCTCTTCCCTGGCTATC	R: CTGTCTCTTCCCTTCACT
CYP1B1 (360)	F: AACGTCATGAGTGCGTGTG T	R: GGCCGGTACGTTCTCCAAA TC
ERα (291 bp)	F: AGCACCCAGTGAAGCTACT	R: TGAGGCACACAAACTCCT

with a total ERK1/2 antibody (both were at 1: 2,000). All of the antibodies were purchased from Cell Signaling Technology, Beverly, MA, USA. The membranes were also reprobed with a mouse GAPDH (1: 10,000; H00002597; Abnova, Walnut, CA, USA). Proteins were visualized using chemiluminescence reagents (Amersham, Piscataway, NJ, USA). Changes in total and phospho-ERK1/2 protein levels were quantified by a densitometer. Data on phospho-ERK1/2 were normalized to total ERK1/2. Data on total ERK1/2 were normalized to GAPDH. ITE-exposed cells at 2×10^5 cells were seeded into each well of 6-well plates and cultured for 48 h. Cells were then pre-incubated with the ERK inhibitor PD98059 (Cell Signaling Technology, Danvers, MA) at different concentrations for 2 h prior to subjecting to Western blot assays.

Statistics analysis. Data were analyzed using one-way ANOVA using the SigmaStat software (Jandel Co, San Rafael, CA). When an F-test was significant, data were compared with their respective control by the Bonferroni's multiple comparison test or Student t-test. $P < 0.05$ was considered statistically significant. The value for ITE-inhibited proliferation of the two breast cancer cells was estimated using an origin data analysis and graphing software (Version 8.1) (OriginLab Corporation Northampton, MA).

RESULTS

Immunolocalization of AhR in human breast cancer tissues. IHC assay showed that AhR were localized primarily in cytoplasm (**Fig. 1A**). The semi-quantitative analysis revealed that, compared with normal tissues, the immunoreactivity of AhR was higher in cancer tissues and mammary metastasis lymph node tissues, while no significant difference was found in the latter two (Fig. 1B). Moreover, there was no significant difference in AhR staining intensity between the age, grades, stages, and TNM classifications in each histotype of breast cancer (Table I).

ITE initiated mRNA levels of CYP1A and CYP1B1 but not estrogen receptor alpha (Era). To assess whether ITE has functional roles in the regulation of CYP1A1, CYP1B1 and Era mRNA expression in breast cancer cell lines (MDA-MB-231, MDA-MB-468, MCF-7 and T47D), ITE at a concentration of $1 \mu\text{M}$ was used and treated for 0 to 48 h. The RT-PCR analysis showed that AhR downstream genes of CYP1A1 and CYP1B1 were initiated by ITE treatment in all the cells, while ERA expression was not changed in MDA-MB-231 and MDA-MB-468 cells (Fig. 2) (Table II).

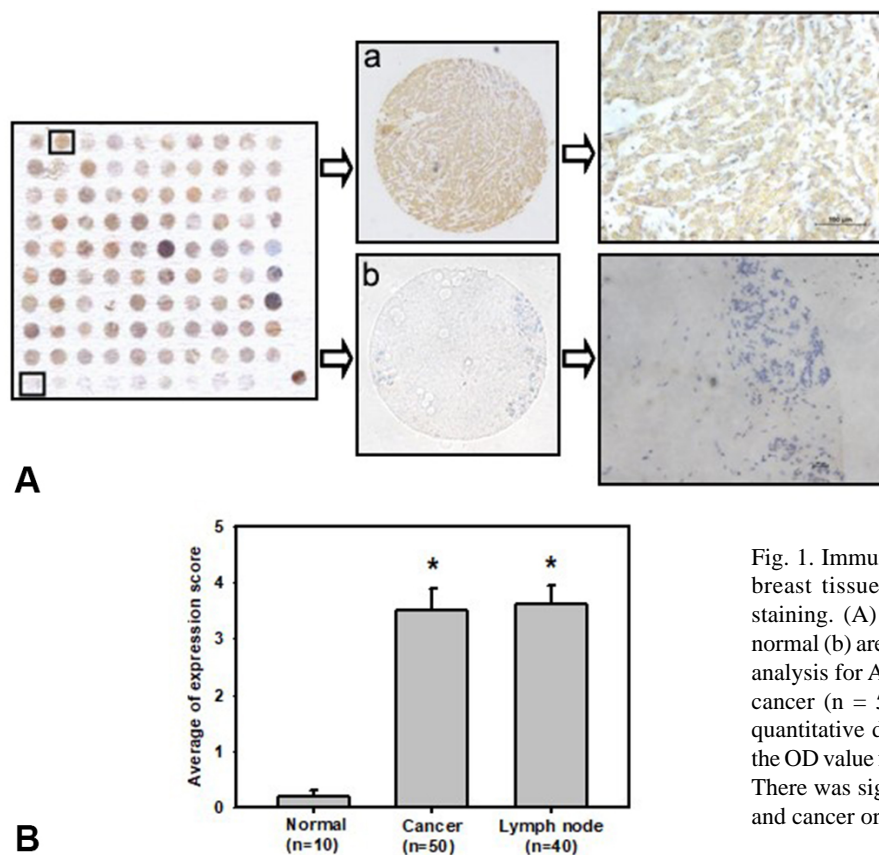


Fig. 1. Immunohistochemical analysis of AhR in human breast tissues. Reddish color indicates positive AhR staining. (A) Representative images for cancer (a) and normal (b) are shown. Bar, $100 \mu\text{m}$. (B) Semi-quantitative analysis for AhR staining intensities for normal ($n = 10$), cancer ($n = 50$), metastasis lymph node ($n = 40$). Semi-quantitative data are expressed as means \pm SEM fold of the OD value from normal. *Differ from normal ($P \leq 0.05$). There was significant difference in normal breast tissues and cancer or metastatic lymph node.

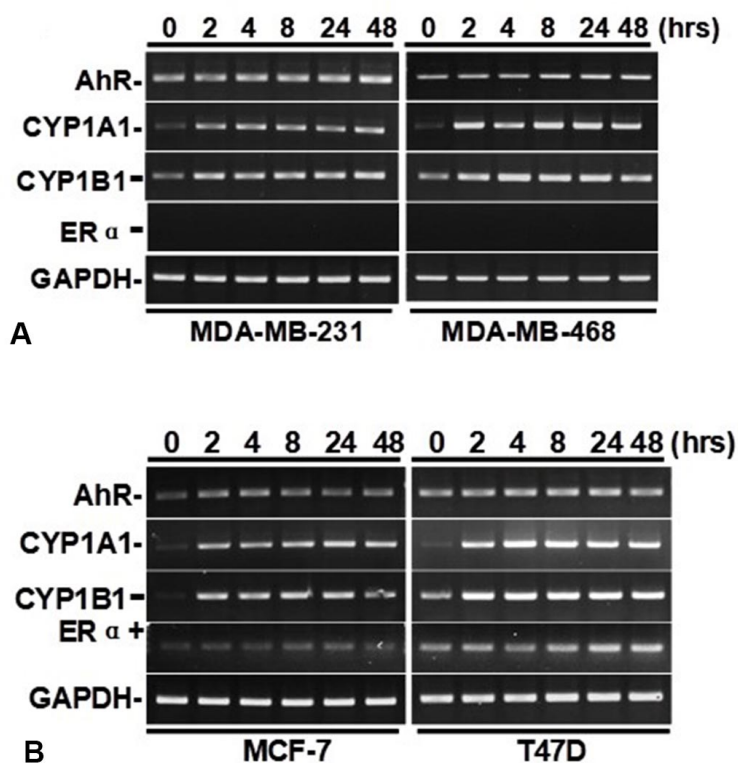


Fig. 2. RT-PCR showed the effects of ITE on the mRNA expression of AhR, CYP1A1, CYP1B1 and Era in human breast cancer cell lines. (A) MDA-MB-231 and MDA-MB-468. (B) MCF-7 and T47D.

ITE inhibited MCF-7 and T47D cell proliferation. Compared to the vehicle control, ITE dose- and time-dependently inhibited cell proliferation in MCF-7 and T47D breast cancer cell lines on Day 2. The maximal inhibitory effect of ITE on the proliferation of these two cells was observed at doses from 1 μM to 10 μM (Fig. 3).

AhR induced G1 phase arrest in ER(+) breast cancer cell lines. To investigate the role of AhR in ITE-treated cells, the four breast cancer cells were treated with ITE for 24 h and cell cycle distribution was analyzed by flow cytometry. Cell-cycle analysis of the two grouped cells (ER(+) for MCF-7 and T47D; ER(-) for MDA-MB-231 and MDA-MB-468) showed that ITE treated MCF-7 and T47D cells induced G1 phase arrest with shorted S phase compared to the control group (Fig. 4), while the tendency was not significant in MDA-MB-231 and MDA-MB-468 (data not shown), indicating that AhR has a more stronger effect on ER(+) breast cancer cell lines. The phenomena was in agreement with the inhibiting effect of proliferation occurred in ER(+) MCF-7 cells (Fig. 3).

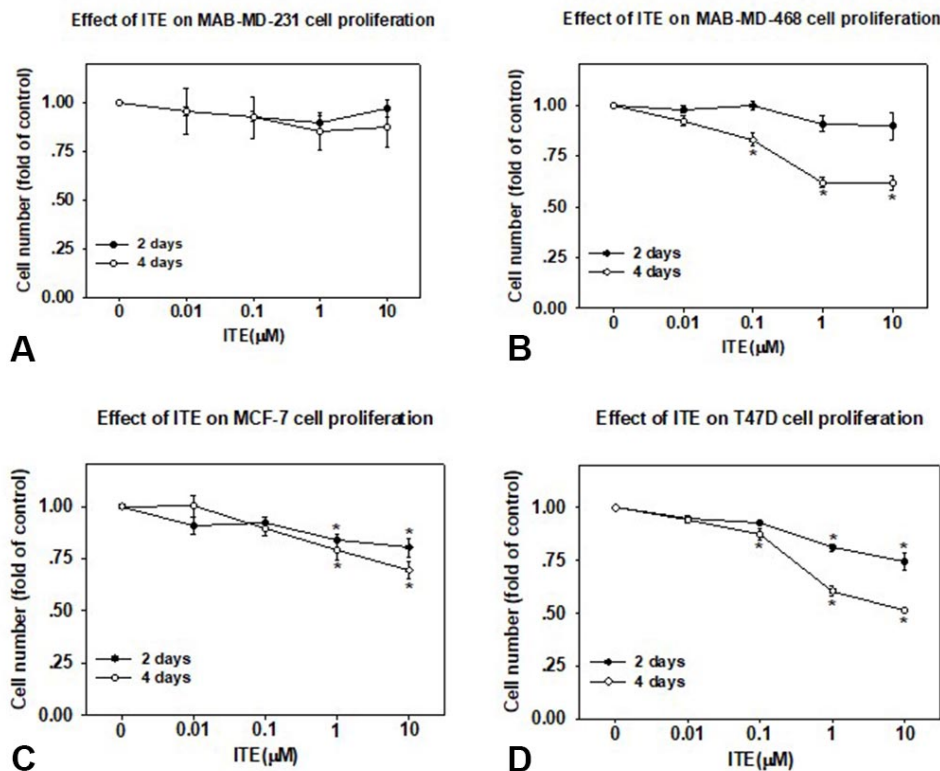
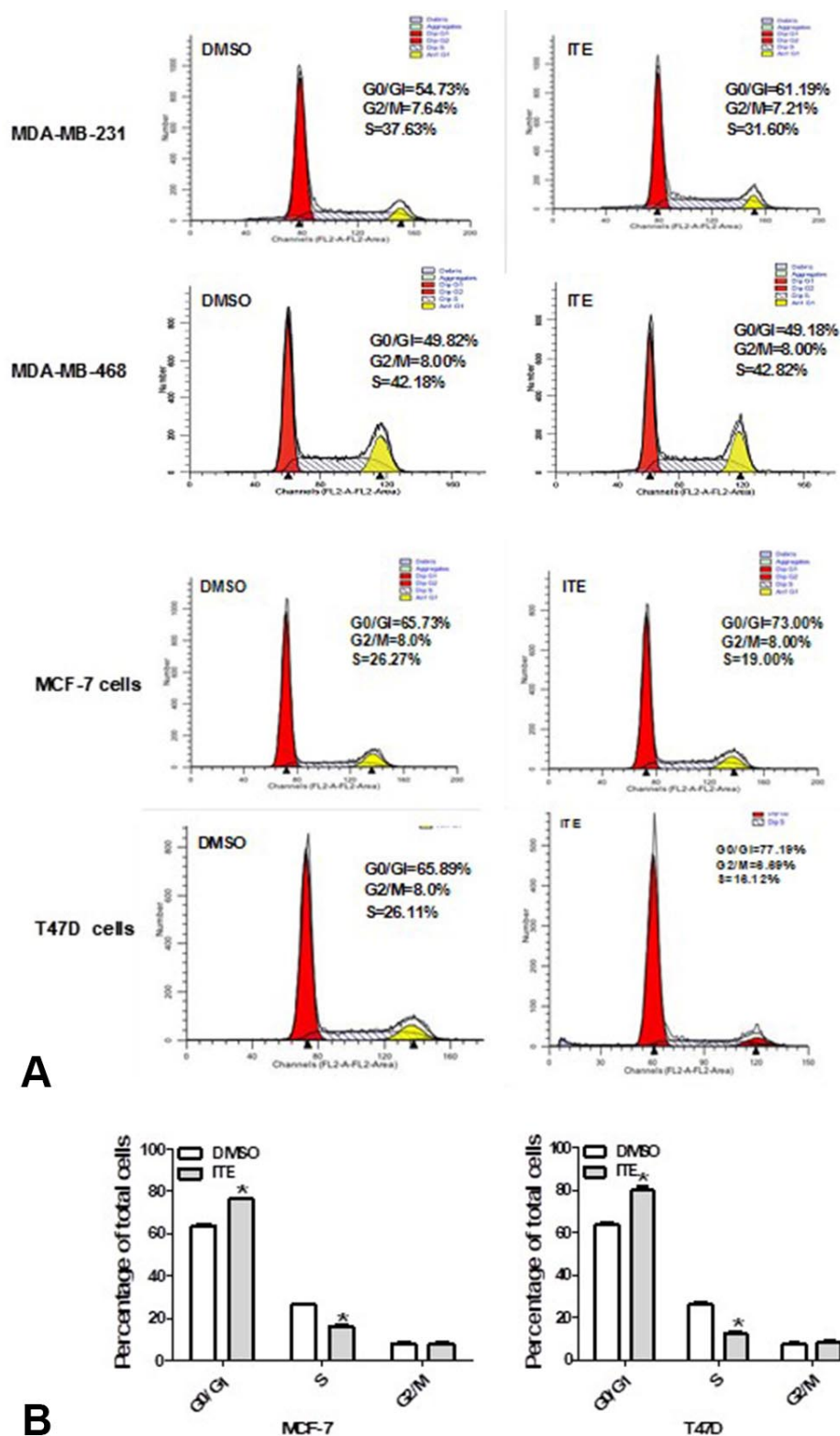


Fig. 3. Effects of ITE on breast cells proliferation. Cells were treated with or without ITE at different doses for up to 48 or 96 hours. *P < 0.05 was considered significant. (A) MDA-MB-231. (B) MDA-MB-468. (C) MCF-7. (D) T47D.



ITE exposure *in vitro* does not alter migration of MCF-7 and T47D. Cell migration of the two cells before and after ITE treated were examined (Fig. 5A). None of these endpoints were affected by exposure to 1 μ M ITE, neither MCF-7, nor T47D (Fig. 5B).

ERK1/2 and AKT signaling were required for the activation of AhR in ER(+) MCF-7 cells. Considering the importance of AKT and ERK signaling pathways in cell proliferation regulation, we examined the effects of ITE on the activation of AKT and ERK. MCF-7 and MDA-MB-231 cells were exposed to 1 μ M ITE for 0, 0.5, 2, 8, 24 and 48 h. It, however, was noted that gradual increases of pERK1/2 was only observed in MCF-7 cells, with no change in MD-MBA-231 cells. Meanwhile, pAKT was decreased in MCF-7 cells but not MD-MBA-231 cells (Fig. 6A). The results suggested that ERK1/2 and AKT pathways probably involved in AhR mediated ITE-inhibited cell proliferation in ER (+) MCF-7 cells (Fig. 6B).

Fig. 4. Flow cytometry analysis of cell cycle distribution after treatment with 1 mM of ITE in breast cancer cells. (A) Flow cytometry analysis of the four cells. (B) Changes in cell cycle distribution were quantified.

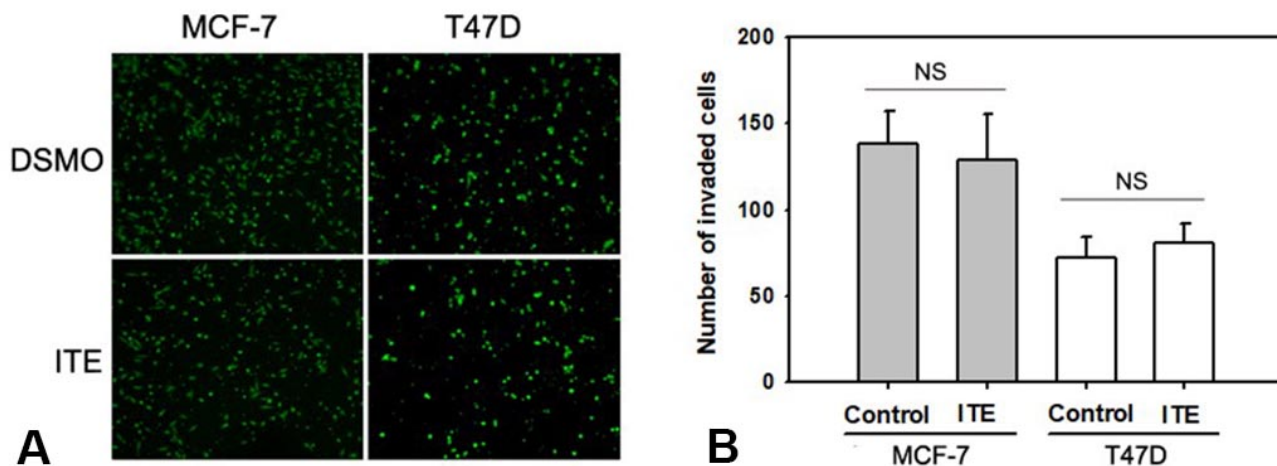


Fig. 5. Effects of ITE on breast cancer cell migration. (A) Cells were treated with 1 μ M of ITE for up to 48 hours, and then migration of cells were determined by Transwell assay. Representative images are shown. (B) Changes in cell migration were quantified.

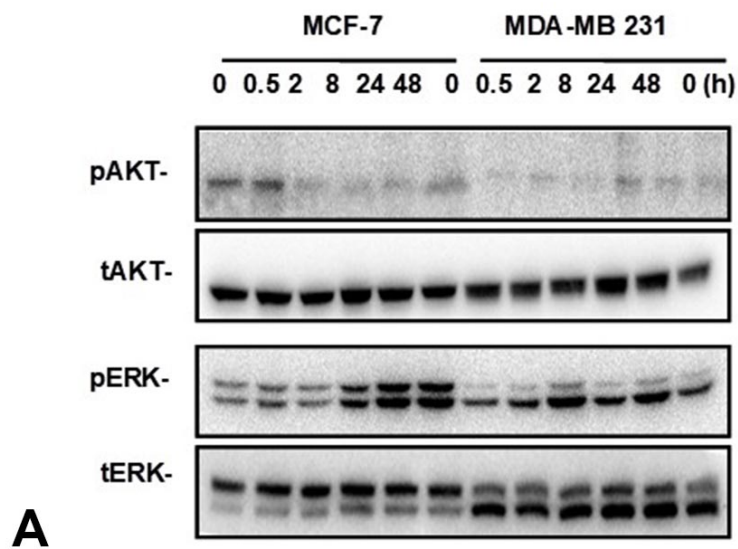


Fig. 6. Representative Western blot images of the effects of ITE on phosphorylation of ERK1/2 in MCF-7 and MD-MBA-2311 cells. (A) Gradual increase/decrease of pERK1/2 or pAKT stainings in MCF-7 and MDA-MB 231 cells. (B) Summary schematic depicting AhR-mediated molecular mechanisms on proliferation in breast cancer cells with different ER phenotypes.

DISCUSSION

As breast cancer is still the most common cancer in women worldwide, more strategies are needed for prevention and treatment of breast cancer. To date, little is known about

the roles of AhR in human breast cancer growth and development. Herein, we examined the expression of AhR in human normal and malignant (metastatic) breast tissues

and examined its potential role in regulating the proliferation and migration of human breast cancer cells. We demonstrated that AhR was highly expressed in a variety of histotypes of breast cancers regardless of cancer grades, stages, and TNM grading, which are consistent with previous reports in human lung and ovarian cancers (Yu *et al.*, 2018; Deuster *et al.*, 2019). Moreover, AhR expression was not associated with breast tumor invasion and lymph node metastasis (Fig. 1). In addition to human breast cancer, increased expression of AhR has also been found in human lung cancer, liver cancer, and prostate cancer (Deuster *et al.*, 2019; Baker *et al.*, 2020). Similar to other study, as the AhR staining is almost negative inside the normal breast tissue; relatively high levels of AhR expression inside the breast cancer could be used as potential marker for breast cancers (Spink *et al.*, 2015). Additionally, AhR gene polymorphisms was reported to be closely related to the increased risk of lung and breast cancers (Aftabi *et al.*, 2016; Vacher *et al.*, 2018), further study regarding this expression pattern of breast cancer is needed to confirm the observations.

ITE, as an endogenous ligand of AhR, was first isolated from porcine and exhibits high affinity to AhR and TCDD both in vivo and *in vitro* (Dolciami *et al.*, 2018). In this study, we observed that ITE significantly inhibited the ER(+), but not ER(-) breast cancer cell lines through activation of AhR. However, we did not find any effects of ITE on breast cancer cell migration. Importantly, ITE significantly prolonged G1 and shortened S phase in ER(+) breast cancer cell, which in turn suppressed cell proliferation. These observations indicate that the potential inhibition of DNA synthesis by ITE is specific to human ER(+) breast cancer cells. Recent animal and human data suggested that AhR is involved in various cell signaling pathways that are critical to cell cycle regulation. Dysregulation of these pathways is contributed to events such as tumor initiation, promotion, and progression (Vacher *et al.*, 2018). Whereas treatment with exogenous ligands activates AhR induced cell cycle arrest (Bock, 2019). In cultured cells, ITE shows marked inhibitory effects on the proliferation of breast cancer cells and AGS cells via induction of growth arrest at the G1-S phase.

Finally, we explore the molecular mechanisms in relation to AhR-inhibited proliferation of breast cancer cells. Extracellular signal-regulated kinase (ERK) pathway has been proved to associate with cell proliferation (Moreno-Marín *et al.*, 2018). Here, our data showed that ITE significantly activated ERK signaling in ER(+) MCF-7 cell, suggesting the positive correlation between AhR activation and ERK signaling pathway. Also, we observed ITE robustly suppressed AKT activation in ER(+), but not in ER(-) breast cancer cells. Taken together, our findings indicated that

ERK1/2 and AKT might participate in AhR mediated ITE-inhibited cell proliferation in MCF-7 cells. However, it is unclear whether ITE-inhibited breast cell proliferation is mediated partially via interfering the ER signaling, although estrogen receptors are ligand-activated transcription factors and members of the nuclear receptor and bHLH-PAS super-families similar to AhR (Dunlap *et al.*, 2017).

CONCLUSION

In summary, we show that activation of ITE/AhR could suppress breast cancer cell proliferation, suggesting ITE can potentially be used as a therapeutic drug for treating at least a subset of human breast cancer. The *in vitro* data indicates that ITE possesses potent anti-breast cancer activity dependent on AhR and ER. Moreover, further dissecting out signaling pathways which mediate ITE-induced different cell responses between different breast cancer cells might assist us to design more optimal strategies for therapeutic intervention of human breast cancer. In addition, clarifying the AhR-independent mechanism of ITE to breast cancer cells may provide us a novel strategy for breast cancer chemotherapy.

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LI, Z.; CHENG, X.; ZHUANG, Z. & WANG, K. Efecto diferencial de ITE en la señalización del receptor de hidrocarburo de arilo en tejido de cáncer de mama: Un estudio histopatológico. *Int. J. Morphol.*, 41(5):1348-1356, 2023.

RESUMEN: El receptor de hidrocarburo de arilo (AhR) es un factor de transcripción activado por ligando que se expresa en gran medida en varios tipos de cáncer, incluido el cáncer de mama. Sin embargo, el papel de AhR con su ligando endógeno 2-(1H-indol-3'-carbonil)-tiazol-4-ácido carboxílico metil éster (ITE) en la progresión del cáncer de mama sigue siendo poco conocido. Nuestro objetivo fue investigar la proliferación celular y los estados de migración en el cáncer de mama después de activar AhR con el ligando endógeno ITE. El tejido de cáncer de mama se evaluó mediante líneas celulares, inmunohistoquímica, reacción en cadena de la polimerasa con transcriptasa inversa, proliferación celular, citometría de flujo, ensayos de migración y técnicas de transferencia Western. Descubrimos que AhR se expresó ampliamente en tejidos de cáncer de mama y en linfonodos con metástasis, pero no en tejidos normales. La expresión AhR fue independiente entre la edad, grados y clasificaciones TNM para tejidos de cáncer de mama. El tratamiento con ITE indujo significativamente la activación de AhR de manera dependiente del tiempo en las líneas celulares de cáncer

de mama MCF-7 y T47D. Mientras tanto, ITE no afectó la migración celular, pero suprimió significativamente la proliferación celular en células MCF-7 y T47D con receptor de estrógeno positivo (ER+), lo que probablemente se atribuye a la inducción de la detención del ciclo celular en la fase G1 y la fase S acortada. Un estudio adicional del mecanismo mostró que las señales de ERK1/2 y AKT eran necesarias para la activación de AhR en las células MCF-7. Estos datos sugieren que AhR es un nuevo objetivo potencial para el tratamiento de pacientes con cáncer de mama. ITE puede ser utilizado más potencialmente en la intervención terapéutica para el cáncer de mama con el tipo de ER (+).

PALABRAS CLAVE: ITE; Receptor de hidrocarbano de arilo; Cáncer de mama; Receptor de estrógeno.

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