UHRF1 modulates breast cancer cell growth via estrogen signaling

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Abstract
The ubiquitination process, which involves that binding of an ubiquitin protein to certain substrates, regulates several human biological processes and human cancers. Several studies report that the abnormal expression of quite a few E3 ubiquitin ligases could play critical role in carcinogenic process and cancer progression. In our current study, we identify UHRF1 (Ubiquitin Like with PHD And Ring Finger Domain 1) is an important regulator for breast cancer growth. UHRF1 depletion significantly decreases breast cancer growth in vitro and in vivo. Clinical data analysis reveals that UHRF1 is dramatically elevated in breast cancer, compared to normal breast tissue. UHRF1 correlates with poor survival in luminal type of breast cancer patients, but not in ER-negative groups. The molecular biological studies show that UHRF1 localizes in the nuclear and interact with ERα via its SRA domain, which subsequently inhibits K48-linked ubiquitination of ERα and enhances ERα stability. Our study provides a novel function of UHRF1 in regulation estrogen signaling in breast cancer and a promising target for breast cancer therapeutics.

Keywords UHRF1 · ERα · Breast cancer · Ubiquitin · Stability

Background
The ubiquitin–proteasome system is one of the critically important post-translational modifications in controlling tissue homeostasis and various signaling pathways in eukaryotic cells [1]. The ubiquitination process is the attachment of ubiquitin to certain substrate proteins to modify several biological processes [2], which are mediated by three different groups of ubiquitin enzymes, including Ub-activation enzymes E1, Ub-conjugating enzymes E2 and E3 ubiquitin ligases. Among them, E3 ubiquitin ligases are regarded to play important roles in mediating thousands of substrates...
The E3 ligases are mainly composed of two types according to the catalytic domains: the HECT (Homologous to E6AP C-terminus) type and the RING (Really Interesting New Gene) type. According to the current knowledge, there are about 700 RING family proteins identified in human genome, but most of them are not well studied [3]. Recent studies demonstrate that several RING finger protein E3 ubiquitin ligases are elevated in human cancers and facilitate tumor progression [4]. Among human malignancies, breast cancer is the most common women cancer worldwide, which causes 20% of cancer-related death in women malignancies [5]. According to the molecular classification of breast cancer, it can be separated into luminal type breast cancer (positive for estrogen receptor or progesterone receptor), HER2-positive type, and triple-negative type (negative of estrogen receptor, progesterone receptor, and HER2) [6, 7]. The luminal type of breast cancer accounts to 70% of all breast cancers, which could be effectively regulated by endocrine therapy, such as tamoxifen. Yet, approximately 50% of tamoxifen-treated patients will eventually develop endocrine therapy resistance, making it an urgent clinical problem [8–10]. Thus, decoding the potential mechanisms to overcome endocrine resistance is essential for the therapeutics treatment of breast cancer.

As the majority of breast cancers, the luminal type of breast cancer is ERα positive, while the dys-regulation of estrogen signaling is the main driver for the carcinogenic process [11, 12]. Since ERα is activated by estrogen, it translocates transferred to the nucleus and binds to the certain promoter regions of its target genes, which facilitates ERα target gene expression and breast cancer growth [13]. In clinics, ERα is elevated in breast tumors compared with normal breast tissues. Since there are several confirmed and possible explanations for tamoxifen resistance, the mechanism is still not totally understood [14, 15]. Recent studies indicated that several E3 ubiquitin ligases were elevated in breast cancer and correlates with the activity of estrogen signaling [16]. In our current study, we identified that UHRF1 was a critical factor in modulating estrogen signaling activity and breast cancer progression. UHRF1 was widely elevated in human malignancies and was reported to play important roles in histone modification and genomic hypomethylation [17]. Our study provided a novel link between UHRF1 and ERα signaling, which could be a novel therapeutic target for luminal type of breast cancers.

Materials and methods

Cell lines

Human breast cancer cell lines MCF-7, T47D, and human embryonic kidney cell HEK293T were obtained from the American Type Cell Culture Collection. All cell lines were maintained with Dulbecco’s modified Eagle’s medium (DMEM, Gibco) supplemented with 10% fetal bovine serum (FBS, BI). For adding E2 assays, cells were cultured in charcoal-stripped FBS (Gibco, 12676-029) treated with phenol red-free DMEM (Gibco, 11330-057). The cells were incubated at 5% CO2 with 37 °C. All cell lines have the characteristics of cell line certification. The cell line authentication via short tandem repeat (STR) is performed via PowerPlex 21 system.

siRNA and plasmids transfection

For siRNA transfection, cells were inoculated the day before transfection. According to the manufacturer’s instructions, Lipofectamine RNAiMAX (Invitrogen 13778-075) was used for transfection when it was about 50–60% fused. UHRF1 silencing was performed in MCF-7 and T47D cells using small interfering RNA (siRNA, GenePharma, China). Target sequences for human UHRF1 small interfering RNA were as listed: 5-GGTTTCCAACCAGGGGTAA-3, 5-GGC GTGGTCCAGATGAACTCC-3. The siControl sequence is GGTTCACACCAGGGGTAA-3, which was the random sequence independent of UHRF1 mRNA. Lipofectamine 2000 (Invitrogen, 1662298) was used for plasmid transfections following the manufacturer’s instructions. The Myc-UHRF1 plasmid was acquired from the Addgene. The Flag-ERα, HA-Ub, HA-K48, and HA-K63 Ubi plasmids were obtained from Ting Zhuang [18]. The HA-K48R and HA-K63R plasmids were obtained from Bo Yang [19].

Quantitative real-time PCR (qRT-PCR)

Total RNA was isolated from cells using Trizol (Thermo) and reverse transcribed to cDNA using the PrimeScript™ First-Strand cDNA Synthesis Kit (TaKaRa, China). The mRNA expression was detected by SYBR green qPCR assay (TaKaRa, China). 36B4 was used for internal control. The primer sequences were shown here. UHRF1 F: GCCATA CACCTTCTCGACTACG, R: GCCCCAATTCGGTCTCAT CC; GREB1 F: CGT GTG GTG ACT GGA GTA GC, R: ACC TCT TCA AAG CGT GTC GT; ER F: GCT ACG AAC TGG GAA TGA TGA AAG, R: TCT GGC GCT TGT GTT TCA AC; PS2 F: TGG GCT TCA GCT CCT TC, R: TTC ATA GTG AGA GAT GGC CGG. 36B4 F: GCC GACCTGGAAAGTCACACT; R: CCATCAGCACCAAG CCTTC. The data were analyzed using the 2-△△Ct method with 36B4 serving as a standard gene for normalization.

Western blot

The protein was separated and transferred to the nitrocellulose membrane (Millipore) by SDS/PAGE gel. The
nitrocellulose membrane with protein was cropped according to the target protein molecular weight. The following antibodies were used at the following concentrations for experiment: anti-HA (901514, BioLegend, 1:5000), anti-Myc (ab32, Abcam, 1:2000), anti-Flag (ab205606, Abcam, 1:3000), anti-UHRF1 (D6G8E, Cell Signaling Technology, 1:2000), anti-ERα (DSH8, Cell Signaling Technology, 1:5000), and anti-β-actin (SAB4502631, Sigma, 1:5000). Secondary antibodies were as follows: anti-Mouse IgG (A0216, Beyotime, 1:5000) and anti-Rabbit IgG (A0208, Beyotime, 1:5000). After final washing with TBST, the membranes were developed by using ECL and visualized using BD-Rad ChemiDoc (American).

**Quantification of cell viability**

MCF-7 and T47D cell viability was measured using CCK8 analysis (C0038, Beyotime, 1:100) according to the manufacturer’s protocol. Cells transfected with siControl or siUHRF1 were seeded in 96-well plate with 4000 cells per well. The number of live cells was measured at 0 h, 24 h, 48 h, and 72 h. The absorbance was detected at 450 nm through Thermo Scientific™ Multiskan™ FC.

**Cell cycle analysis**

For cell cycle analysis, MCF-7 and T47D cells were transfected with 30 nM siUHRF1 or siControl. After 48 h, the cells were fixed with 70% ethanol for 1 h at 4 °C, and then stained with propidium iodide. A BD LSR flow cytometer was used to measure the fluorescence intensity.

**Dual-luciferase reporter assay**

For dual-luciferase reporter assay, cells transfected with siControl or siUHRF1 were seeded in 24-well plate; when the cells were 70–80% confluent, 0.01 μg Renilla and 0.5 μg of the ERE luciferase reporter were transfected using Lipofectamine Reagent 2000 (Invitrogen). The luciferase activity was performed using Dual-Luciferase Reporter Assay System (Promega, America).

**Xenograft tumor model**

Four-week-old female BALB/c nude mice were purchased from the Beijing Vital River Laboratory Animal Technology Co., Ltd. shControl or shUHRF1 T47D cells were resuspended and injected into the right flank of each mouse (4 × 10^6 cells/mouse) subcutaneously. The tumor sizes are measured every seven day, and tumor volume was measured and calculated by using the following formula: Volume (mm^3) = length x width^2/2. All animals were raised in a specific pathogen free (SPF) and free access to water and food with 12 h of light.

**Lentivirus transduction**

For lentiviral transduction, the lentiviral shUHRF1 vectors were generated into pLVX lentiviral vector using T4 DNA ligase (NEB, American). The sense strand of the nucleotide sequence encoding shRNA targeting UHRF1 was 5’-GGT GTC AGG GTG ACG CGG AA-3’. The packaging of lentivirus was performed with 4 μg PLVX-shUHRF1, 3 μg psPAX2, and 1 μg pMD2.G plasmid into HEK293T cells using Lipofectamine 2000, according to the manufacturer’s protocol. After 48 h, the culture supernatant was collected and filtered through a 0.45 μM filter. T47D cells in 6-well plates were transduced with 1 ml viral supernatant supplemented and 1 mL fresh 10% FBS DMEM with 8 μg/ml Polybrene (Solarbio, China). Stably transfected cells were cultured in the 10% FBS DMEM with puromycin 1 μg/ml (Beyotime, China).

**Statistical analysis**

Statistical analyses were carried out using GraphPad Prism 8 software. The statistical difference was determined using two-tailed Student’s t-test. *P* value < 0.05 was considered to be statistically significant.

**Results**

**UHRF1 is required for breast cancer growth in vitro and in vivo**

We firstly investigated the effect of UHRF1 in breast cancer phenotypes. We utilized MCF-7 and T47D cells as the cell line model via depletion UHRF1 expression (Fig. 1A, B). The CCK8 assays showed that UHRF1 silencing inhibited breast cancer cell growth in MCF-7 and T47D cells (Fig. 1C, D). In the EdU incorporation assay, we could observe that UHRF1 depletion significantly reduced the EdU-positive cells in MCF-7 and T47D cells (Fig. 1E, F). We further explored the impact of UHRF1 in cell cycle. The flowcytometry analysis showed that UHRF1 depletion increased the proportion of cells in G1 phase but reduced the proportion of cells in S phase (Fig. 1G, H). This indicated that UHRF1 might be required for G1-S cell phase transition. Finally, we further investigated the role of UHRF1 in vivo by xenograft mice model. Our data showed that UHRF1 depletion inhibit the tumor growth speed in vivo (Fig. 1I–K).
UHRF1 is elevated in breast cancer and correlates with poor survival in luminal type of breast cancer

Since UHRF1 plays such important roles in breast cancer proliferation, we further analyzed its expression in clinical database. From the TCGA database, we could observe that UHRF1 was dramatically elevated in breast tumors compared with normal tissues (fold change = 12.5; Fig. 2A), while its expression in each subtype was significantly higher than normal tissue (Fig. 2B). Besides, we further investigated the prognostic impact of UHRF1 in breast cancers. Interestingly, the expression of UHRF1 correlated with poor survival in all breast cancer patients and luminal A type groups (P < 0.001, Fig. 2C, D). However, the expression of UHRF1 failed to correlate with survival in luminal B type, HER2 type, and triple-negative type of breast cancer patients (Fig. 2E–G, P = 0.068; P = 0.17; P = 0.37, respectively).

UHRF1 depletion inhibits ERα signaling in breast cancer

Based on the prognostic correlation between UHRF1 and luminal A type of breast cancers, we proposed that UHRF1 might exert its function via ERα signaling. We further depleted UHRF1 expression in MCF-7 and T47D cells. The immunoblotting data showed that UHRF1 depletion inhibits
ERα protein level in both vehicle and E2-treated conditions in MCF-7 and T47D cells (Fig. 3A, B). We further investigated if UHRF1 depletion could affect ERα transcriptional function. We tested estrogen-response element (ERE) luciferase activity in both MCF-7 and T47D cells. The data showed that UHRF1 depletion decreased ERE luciferase activity in both MCF-7 and T47D cells (Fig. 3C, D). Accordingly, UHRF1 depletion could significantly decrease ERα target gene expression in MCF-7 and T47D cells under both vehicle and E2 conditions (Fig. 3E, F).

To further investigate the regulation of estrogen receptor signaling pathway by UHRF1, we overexpressed UHRF1 in MCF-7. The immunoblotting data showed that overexpression of UHRF1 promoted the expression of ERα proteins (Fig. S1A). We also investigated whether overexpression of UHRF1 could affect the transcriptional function of ERα. We tested the luciferase activity of estrogen response element (ERE) in MCF-7 cells. The data showed that overexpression of UHRF1 enhanced ERE luciferase activity in MCF-7 cells (Fig. S1B). In addition, overexpression of UHRF1 could
also upregulate the expression level of ERα target genes in MCF-7 cells (Fig. S1C).

**UHRF1 associates with ERα in breast cancer cells**

We further investigated the localization of UHRF1 and ERα in breast cancer cells. The immuno-staining data showed that UHRF1 was localized in the cytosol and nuclear, while ERα was mainly located in the nuclear (Fig. 4A). The immunoprecipitation assay showed that UHRF1 could associate with ERα in MCF-7 cells (Fig. 4B). We further identified the interaction domains between UHRF1 and ERα. ERα contains three functional domains: AF1 domain, DNA binding domain, and AF2 domain, while UHRF1 is composed of several functional domains, including UBL domain, TTD domain, PHD domain, and SPA domain (Fig. 4C, D). The further immunoprecipitation data showed that AF1 was required for ERα to associate with UHRF1, while the SRA domain of UHRF1 was necessary for UHRF1 to interact with ERα (Fig. 4E, F). However, overexpression of UHRF1 full length or variants together with ERα in HEK293 cells showed that the intact UHRF1 was necessary for its effect to stabilize ERα (Fig. 4G).

**UHRF1 enhances ERα stability and inhibits ERα K48-linked poly-ubiquitination**

We performed that protein stability assay and observed that UHRF1 could enhance ERα stability in MCF-7 cells (Fig. 5A). In the presence of MG132, which is a
proteasome inhibitor, the stabilization effect of UHRF1 could not further increase ERα protein level, indicating UHRF1 could inhibit proteasome-dependent degradation (Fig. 5B). The ubiquitin-based immunoprecipitation assay showed that UHRF1 could inhibit the global poly-ubiquitination of ERα (Fig. 5C). In order to confirm the ubiquitination manner affected by UHRF1, we utilized the ubiquitin plasmids with only lysine 48 or 63 sites available. Further investigations indicated that UHRF1 mainly inhibited K48-linked poly-ubiquitination of ERα, but no effect on K63-linked poly-ubiquitination (Fig. 5D, E). This is further confirmed in the rescue assay by the ubiquitin plasmids with lysine 48 or 63 mutations. The mutation at K48 site of ubiquitin could rescue the decreased poly-ubiquitination level of ERα caused by UHRF1, but not K63 mutation at the ubiquitin (Fig. 5F, G).

**Discussion**

Our study demonstrated that the RING finger protein UHRF1 associate with and stabilizes ERα, possibly through inhibiting K48-linked ubiquitination, which subsequently promoted ERα signaling and breast cancer cell progression (Fig. 6). Interestingly, UHRF1 was dramatically increased in mammary malignancies and correlated with poor survival only
in luminal A type of breast cancer patients. Our research elaborated a novel regulatory mechanism for non-genomic control of ERα stability. Based on these findings, we can propose that selective modulators or inhibitors that regulate UHRF1 activity or expression may be a promising strategy for clinical luminal breast cancer treatment.

The relationship between ERα and breast cancer was identified more than 30 years [20]. ERα consists of three functional domains: AF1 domain, the DNA binding domain, and AF2 domain [21]. In the absence of ligand binding, the AF1 domain can activate transcriptional function. DNA binding domain could combine to estrogen response elements (ERE) directly in human genome, and AF2 domain is a ligand-dependent trans-activation domain [22, 23]. When ERα is stimulated by estrogen, it could trans-locate into the nucleus and bind to cis-regulatory DNA of target genes and subsequently increase gene transcription [24]. Since 60%-70% of breast cancers have elevated ERα expression, targeting ERα signaling has been proved as an effective treatment for luminal type of breast cancer patients. Several confirmed and hypothetical
studies on endocrine resistance have been reported [25, 26]. In addition to the low percentage of ESR1 gene amplification or mutation, endocrine resistance is mainly related to two potential mechanisms [27]. For example, estrogen signaling may be cross-linked with several other signaling pathways, such as HER2 [28] and NF-KB signaling [29, 30], which could promote cell proliferation and tamoxifen resistance. ERα could associate with HER2 protein and promote the activation of MAPK signaling, and the MAPK pathway could also promote the phosphorylation of ERα and enhance the signaling activity of ERα [31]. Clinically, the binding of ERα and HER2 provided an explanation for the lower efficacy of tamoxifen in luminal B type patients with HER2 overexpression [32]. In addition, the modification of ERα signaling could affect the efficacy of endocrine therapy through some mechanisms [26]. ERα protein function could be modified by post-translational modifications, such as phosphorylation and acetylation. For example, P300 promoted the acetylation of ERα at the hinge structure and subsequently increased the activity of ER signaling [33]. In addition, phosphorylation of ERα at certain sites could alter estrogen signaling activity and tamoxifen inhibition efficacy, such as the phosphorylation at Y537 site [34].

UHRF1 is also reported as inverted CCAAT box binding protein of 90 kDa, which acquired a lot of research interests due to its high expression in several human cancers [35–37]. One of the important findings is that UHRF1 is a critical factor in modulating epigenetic process in human genome [38]. UHRF1 could interact with several methylation factors, such as DNA methyltransferases (DNMTs) and regulate several DNA methylations patterns and histone methylation status [36]. Besides, as the family members of RING finger protein, UHRF1 exhibits the E3 ubiquitin ligase on histone proteins. For example, UHRF1 was found to promote the ubiquitination of Histone 3 at the lysine 23 sites, which marked the regions for replication foci targeting sequence [39]. Recent studies showed that the SRA domain (The Unique Set and Ring-Associated Domain) was responsible for recognition of ubiquitin targets [40, 41]. In our current study, we observe that SRA domain is responsible for UHRF1–ERα interaction and promotes ERα stability. Since very few studies report the E3 ubiquitin ligase function of UHRF1 in modulating certain signaling pathway, we provide a novel insight in UHRF1 function, which modulates estrogen signaling and breast cancer growth. Further clinical or pre-clinical studies might be beneficial to discover certain inhibitors which could block UHRF1–ERα interaction for breast cancer therapy.

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Author contributions HJ Y and GS L conceived the designed that study. GS L and QH L performed the molecular and cellular biology of the study. M Y and TS W performed the cellular phenotype assays. ZP L and YF Z performed the bioinformatics data analysis. ZG N and JH L wrote the manuscript and approved the manuscript. ZG N and JH L offered the funding support and project supervision during the revision stage.

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Data availability Expression analysis in luminal, HER2-positive, and Triple-negative breast cancer tissues and normal tissues was performed by GraphPad Prism 8 from TCGA (PanCancer Atlas). Analysis of UHRF1 with clinical prognosis was carried out through KMPLLOT database (https://kmplot.com). The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest There is no competing interest to declaim.

Ethical approval All animal experiments involved in this study were approved by the Ethics Committee of Xinxiang Medical University. All methods were carried out in accordance with relevant guidelines and regulations. The study is reported in accordance with ARRIVE guidelines.

Consent for publication Not applicable.

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