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Original Article

Estrogen Induces CK2α Activation via Generation of Reactive Oxygen Species

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The protein kinase CK2α (formerly Casein Kinase II) is implicated in tumorigenesis and transformation. However, the mechanisms of CK2α activation in breast cancer have yet to be elucidated. This study investigated the mechanisms of CK2α activation in estrogen signaling. Estrogen increased reactive oxygen species (ROS) production, CK2α activity, and protein expression in estrogen receptor positive (ER^+) MCF-7 human breast cancer cells, which were inhibited by the antioxidant N-acetyl-L-cysteine. H_2O_2 enhanced CK2α activity and protein expression. Human epidermal growth factor (EGF) increased ROS production, CK2α activity and protein expression in EGF receptor 2 (HER2)-overexpressing MCF-7 (MCF-7 HER2) cells, but not in MCF-7 cells. Estrogen induced the phosphorylation of p38 mitogen-activated protein kinase (MAPK). The p38 inhibitor, SB202190, blocked estrogen-induced increases in ROS production, CK2α activity and CK2α protein expression. The data suggest that ROS/p38 MAPK is the key inducer of CK2α activation in response to estrogen or EGF.

Key Words: Estrogen, CK2α, ROS, P38 MAPK

INTRODUCTION

Breast cancer is the most common cause of cancer death among women (Ferlay et al., 2010), and is characterized by molecular and cellular heterogeneity (Perou et al., 2000). The etiology of breast cancer is multifactorial, with major risk factors including age, early menarche, delayed menopause, use of contraceptives or oral medications, hormone therapy, family history, history of benign breast disease, and obesity; estrogen is a major risk factor for breast carcinogenesis and growth of breast cancer cells (Yager and Liehr, 1996; Clemons and Goss, 2001).

Reactive oxygen species (ROS) act as potent mutagens, increasing genomic instability and initiation as well as the progression of cancer (Carew and Huang, 2002). Oxidative stress is one of the mechanisms underlying the carcinogenic effect of estrogen in breast cancer. Genotoxic estrogen metabolites such as catechols and estrogen-semi-quinones generated during estrogen metabolism are known to produce ROS (Roy et al., 2007; Okoh et al., 2011). Mitochondria are the main source of estrogen-induced ROS in breast cancer cells (Felty et al., 2005; Parkash et al., 2006).

Protein kinase CK2α (formerly Casein Kinase 2 or II) is a highly conserved and ubiquitous serine/threonine kinase, which is localized in the cell nucleus and cytoplasm. CK2α is a tetrameric complex composed of catalytic (α or α') and regulatory (β) subunits with a $\alpha_2\beta_2$, $\alpha\alpha'\beta_2$, or $\alpha'_2\beta_2$ structure

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(Allende and Allende, 1995). CK2α modulates 300 potential substrates in the cell, as well as a wide range of pathways related to cell growth, proliferation and apoptosis (Litchfield, 2003; Duncan and Litchfield, 2008). CK2α is implicated in tumorigenesis and transformation. CK2α inhibits the activity and stability of tumor suppressor proteins (p53 and phosphatase and tensin homolog deleted on chromosome 10 (PTEN)), promotes cell survival signaling via up-regulation of proto-oncogenic products (c-Myc, c-Myb, and c-Jun) and transcriptional activators (α-catenin and Max) (Singh and Ramji, 2008). Overexpression of CK2α has been observed in many human cancers, including breast cancers (Filhol et al., 2015; Chua et al., 2017). However, the underlying mechanisms of CK2α expression in breast cancers remain elusive.

The molecular mechanism underlying the activation of CK2α is mediated via ROS (Kim et al., 2014). Therefore, it is of interest to investigate whether a similar mechanism occurs in estrogen signaling. In this study, we found that estrogen increased CK2α activation and expression via ROS /p38 mitogen activated protein kinase (MAPK) in estrogen receptor-positive (ER^+) cell lines.

MATERIALS AND METHODS

Cell cultures

MCF-7 and T47D, MBA-MB-231 human breast cancer cells (American Type Culture Collection, ATCC, Manassas, VA, USA Rockville, MD, USA) were cultured in Dulbecco's Modified Eagle's Medium (DMEM) or RPMI1640 medium (GIBCO Invitrogen, Carlsbad, CA, USA) supplemented with 10% (volume/volume) fetal bovine serum (GIBCO Invitrogen, Carlsbad, CA, USA) at 37℃ in a humidified atmosphere of 5% CO_2 and 95% air. MCF-7 overexpressing HER2 (MCF-7 $HER2^+$) and vector control (MCF-7 vec) cells were kindly provided by professor Ko, and were described elsewhere (Seo et al., 2012).

Antibodies and reagents

The following antibodies were used for Western blot analysis. Anti-phospho-CK2 (Thr306, Ser362) (Sigma-Aldrich, St Louis, MO, USA), anti-CK2α, anti-phospho-p38 mitogen activated protein kinase (MAPK) (Thr180, Tyr182), anti-phospho-JNK anti-phospho-ERK were purchased from Cell Signaling Technology (Beverly, MA, USA). Anti-GAPDH, anti-normal rabbit IgG were from Santa Cruz Biotechnology (Santa Cruz, CA, USA). The antioxidant, N-Acetyl-L-Cysteine (Sigma-Aldrich), p38 inhibitor (SB202190, 5 mg/kg), JNK inhibitor (SP600125, 12.5 mg/kg) or ERK inhibitor (PD-98059, 12.5 mg/kg) were purchased from Calbiochem Merck (Darmstadt, Germany).

Measurement of intracellular ROS

The oxidation-sensitive fluorescent probes CM-H_2DCF-DA were used to monitor the production of hydrogen peroxide. Cells in each well were treated with estrogen and/or reagents for 3 hr, after which they were incubated with 5 μM CM-H_2DCF-DA (DCF) (Sigma-Aldrich) for the detection of cytosolic ROS for 30 min at 37℃ in the dark. Fluorescence was read with excitation at 485 nm and emission at 530± 30 nm with an automated microplate reader (Ininite^{TM} M200 (Tecan, AG, Switzerland).

CK2α activity assay

Cells were homogenized in lysis buffer (50 mM Tris-HCl, pH 7.5, 150 mM NaCl, 1% Triton X-100, 0.5% sodium deoxycholate, 0.1% SDS, 1 mM EGTA, 1 mM EDTA, 10 mM sodium fluoride, 1 mM sodium orthovanadate, 1 mM dithiothreitol and 1 mM PMSF). The phosphotransferase activity of CK2α was measured using a CK2α assay kit (Millipore, Temecula, CA, USA) in accordance with the manufacturer's recommendations. Briefly, cell lysates, substrate peptide, protein kinase A inhibitor cocktail, and γ-[^{32}P] ATP in the assay dilution buffer were incubated for 10 min at 30℃. The phosphorylated substrate was then separated on P81 phosphocellulose paper and quantified with a scintillation counter.

Western blot analysis

Whole cell extracts were prepared using PhosphoSafe Extraction Reagent (Novagen Merck, Darmstadt, Germany) with phenylmethylsulfonyl fluoride protease inhibitor (Sigma-Aldrich, St Louis, MO, USA). Equal amounts of cell lysates were separated on 10% SDS-polyacrylamide gel under reducing conditions, and electrophoretically transferred onto

Protran Nitrocellulose Transfer Membranes (Whatman, Dassel, Germany). The membranes were blocked by 30 min of incubation at room temperature (RT) in 5% BSA in Tris-buffered saline (TBS)-0.1% Tween 20, followed by 2 hr incubation at 4℃ with primary antibodies in 5% BSA in TBS-0.1% Tween 20. The blots were washed for 30 min with three changes of TBS-0.1% Tween 20 solution, followed by incubation for 1 hr at RT with horseradish peroxidase-conjugated anti-rabbit IgG antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA). The blots were again washed three times for 30 min each, and finally developed in Lumi-GLO reagent (ECL, GE Health Care UK Limited Cell Signaling Technology, Beverly, MA, USA). GAPDH was used as a loading control. The density of each band was determined using the densitometry Fluor-STM Imager (Bio-Rad, Muncher, Germany).

Statistical analysis

Data are expressed as means ± SE Statistical significance was determined via one-way analysis of variance (StatView; Abacus Concepts Inc., Berkeley, CA, USA). All experiments were conducted at least twice. Reproducible results were obtained and representative data are, therefore, provided in the figures.

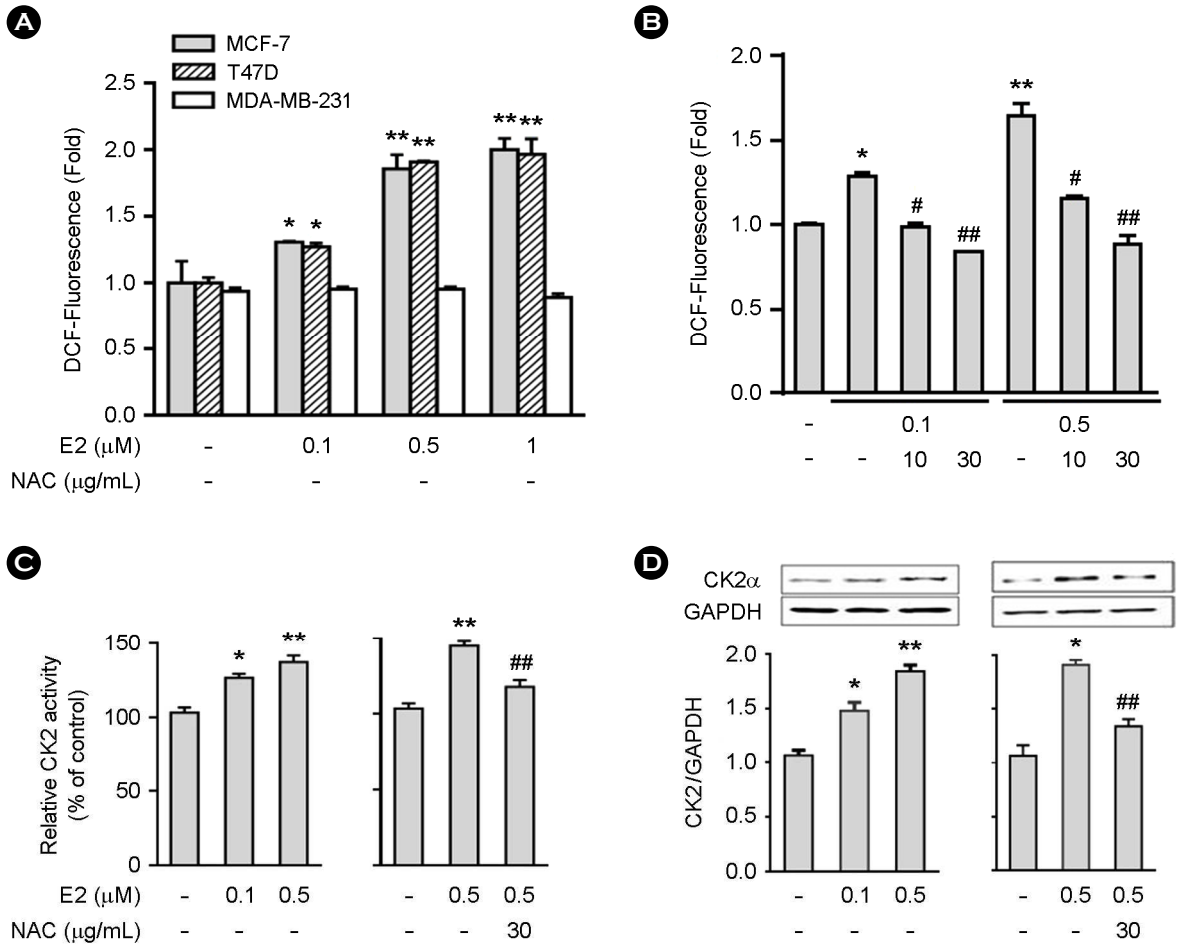

Fig. 1. Estrogen increases ROS production in ER$^+$ MCF-7 and T47D cells. A and B, Cells (4×10^3) were treated for 3 hr with varying concentrations of estrogen for the measurement of ROS. B, MCF-7 cells (4×10^3) were treated for 3 hr with varying concentrations of estrogen NAC (10 or 30 μg/mL) was added 30 min before estrogen (0.1 or 0.5 μM) treatment (B). C and D, Cells (1×10^6) were treated with NAC and/or estrogen for the measurement of CK2 activity (C) and protein expression (D). Data represent the mean ± SE of two to three independent experiments with three to five samples per experiment. $^*P < 0.01$ versus control group. $^{**}P < 0.001$ versus control group. $^{\#}P < 0.01$ versus estrogen-treated group. $^{\#\#}P < 0.001$ versus estrogen-treated group.

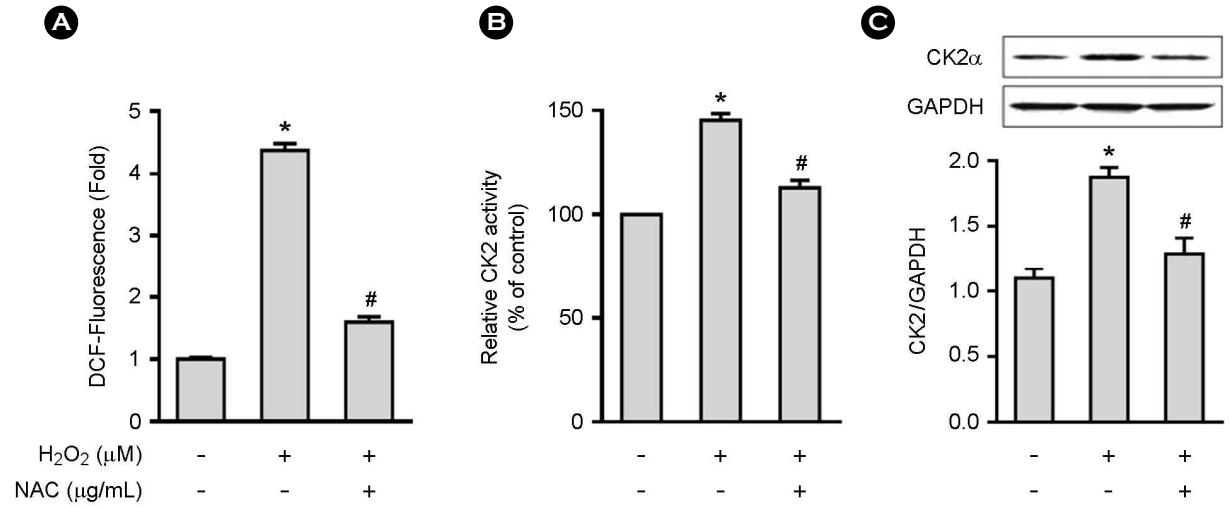

Fig. 2. H_2O_2 increases CK2 activity and protein expression in MCF-7 cells. A, Cells (4×10^3/well for A; 2×10^6/well for B and C) were pretreated with NAC (30 μg/mL) for 30 min followed by H_2O_2 (30 μM) for 3 hr to quantify ROS levels (A), CK2 activity (B) and protein expression (C). Data represent the mean ± SE of two to three independent experiments with three to five samples per experiment. $^*P < 0.001$ versus control group. $^\#P < 0.001$ versus H_2O_2-treated group.

RESULTS

Estrogen increases ROS production and CK2α expression

We first assessed the effect of estrogen on ROS production and CK2α expression using estrogen receptor (ER)-positive MCF-7 and T47D and ER-negative MDA-MB-231 breast cancer cells. ROS production was increased about 1.7-fold in ER^+ MCF-7 and T47D cells upon estrogen stimulation, but such increase was not observed in ER-negative MDA-MB-231 cells (Fig. 1A). The presence of NAC, a commonly used ROS scavenger, blocked the estrogen-induced ROS production (Fig. 1B). CK2α activity was increased in a dose-dependent manner in MCF-7 cells upon estrogen stimulation (Fig. 1C). We also investigated the effect of estrogen on CK2α protein expression by Western blot analysis, which revealed that estrogen increased CK2α protein expression in MCF-7 cells in dose-dependent manners (Fig. 1D). Both estrogen-induced CK2α activity and protein expression were blocked by NAC (Fig. 1C and D). We analyzed the direct role of ROS in CK2α activity and protein expression. The addition of H_2O_2 to MCF-7 cells resulted in increases in ROS production (Fig. 2A), CK2α activity (Fig. 2B) and protein expression (Fig. 2C), which were blocked by NAC. These data indicate that estrogen upregulates CK2α activity and protein expression via ROS production in ER^+ breast cancer cells.

Comparison of ROS production, p38 phosphorylation, and CK2α activity and protein expression: MCF-7 versus MCF-7 HER2 cells

MCF-7 vec and MCF-7 $HER2^+$ cells were stimulated either estrogen alone or estrogen combined with EGF. When the cells were exposed to estrogen alone, ROS production (Fig. 3A), p38 phosphorylation (Fig. 3B), CK2α activity (Fig. 3C), and protein expression (Fig. 3D) were increased similarly in both cell lines. When the cells were stimulated with EGF alone, ROS production (Fig. 3A), p38 phosphorylation (Fig. 3B), CK2α activity (Fig. 3C), and protein expression (Fig. 3D) were only increased in MCF-7 $HER2^+$ cells. When the cells were treated with estrogen + EGF, more higher increases in ROS production (Fig. 3A), p38 phosphorylation (Fig. 3B), CK2α activity (Fig. 3C) and protein expression (Fig. 3D) were observed in MCF-7 $HER2^+$ cells compared to MCF-7 vec cells. All the increases of ROS production and CK2α activity, and protein expression induced by exposure to estrogen combined with EGF in MCF-7 $HER2^+$ cells were blocked by pre-treatment with NAC (Fig. 3A-D). These data indicate that the presence of HER2 in breast cells contributes to higher levels of ROS production

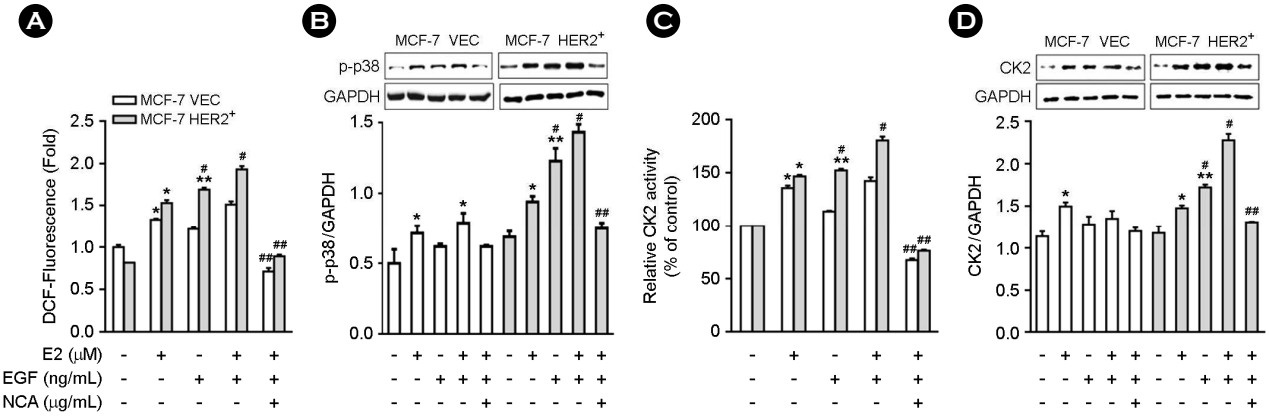

Fig. 3. EGF increases ROS production, CK2 activity and protein expression in MCF-7 HER2$^+$ cells. MCF-7 vec or MCF-7 HER2$^+$ cells (4×10^3/well for A; 1×10^6/well for B and C) were pretreated with NAC (30 μg/mL) for 30 min followed by estrogen (0.5 μM) or EGF (50 ng/mL) for the measurement of ROS (A), p38 phosphorylation (B), CK2 activity (C) and protein expression (D). Data represent the mean ± SE of two to three independent experiments with three to five samples each. $^*P < 0.01$ versus control group. $^{**}P < 0.001$ versus control group. $^{\#}P < 0.01$ versus EGF-treated MCF-7 vec group. $^{\#\#}P < 0.001$ versus estrogen + EGF-treated group.

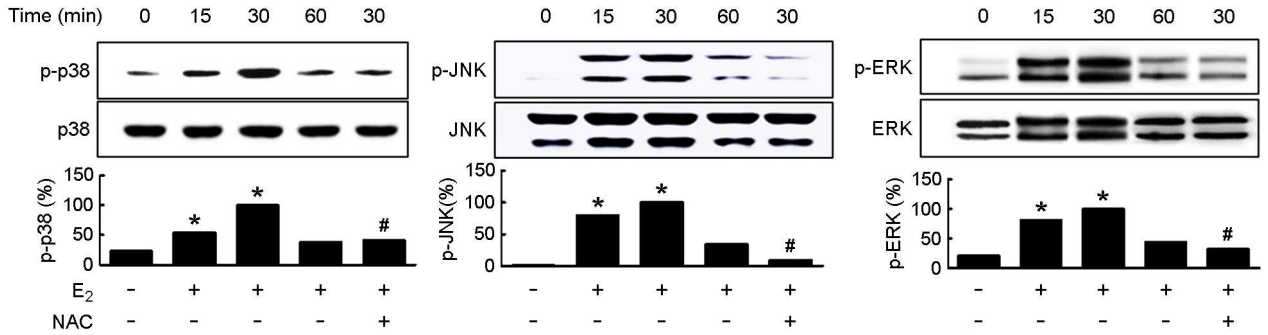

Fig. 4. Estrogen induces MAPK phosphorylation in MCF-7 cells. Cells (1×10^6) were treated with estrogen (0.5 μM) for the time indicated to measure the phosphorylation of p38, JNK, and ERK. To see the effect of NAC, cells were pretreated with NAC (30 μg/mL) for 30 min, and were cultured for another 30 min with estrogen. Data represent the mean ± SE of three independent experiments with three samples each. $^*P < 0.005$ versus control group. $^{\#}P < 0.001$ versus estrogen-treated group.

and CK2α activity and expression.

ROS-dependent p38 mediates CK2α activation

We next investigated the roles of p38, JNK, and ERK MAPK in estrogen-induced CK2α activation. Estrogen induced phosphorylation of the three MAPK in MCF-7 cells, all of which were blocked by NAC (Fig. 4). Pre-treatment of cells with the p38 inhibitor, SB202190, blocked estrogen-induced increases in CK2α activity (Fig. 5A) and protein expression (Fig. 5B). JNK inhibitor or ERK inhibitor failed to inhibit estrogen-induced CK2α expression (data not shown), suggesting that JNK and ERK do not involved importantly in this context. Further, SB202190 inhibited H_2O_2-induced CK2α activation (Fig. 5C) and protein expression (Fig. 5D), suggesting that p38 mediated CK2α activity and protein expression.

DISCUSSION

The mechanism of CK2α overexpression in breast cancers is poorly understood. In this study, we showed that estrogen induced CK2α activation and protein expression via ROS/p38 signaling. It is well known that estrogen increases ROS production via several mechanisms including estrogen me-

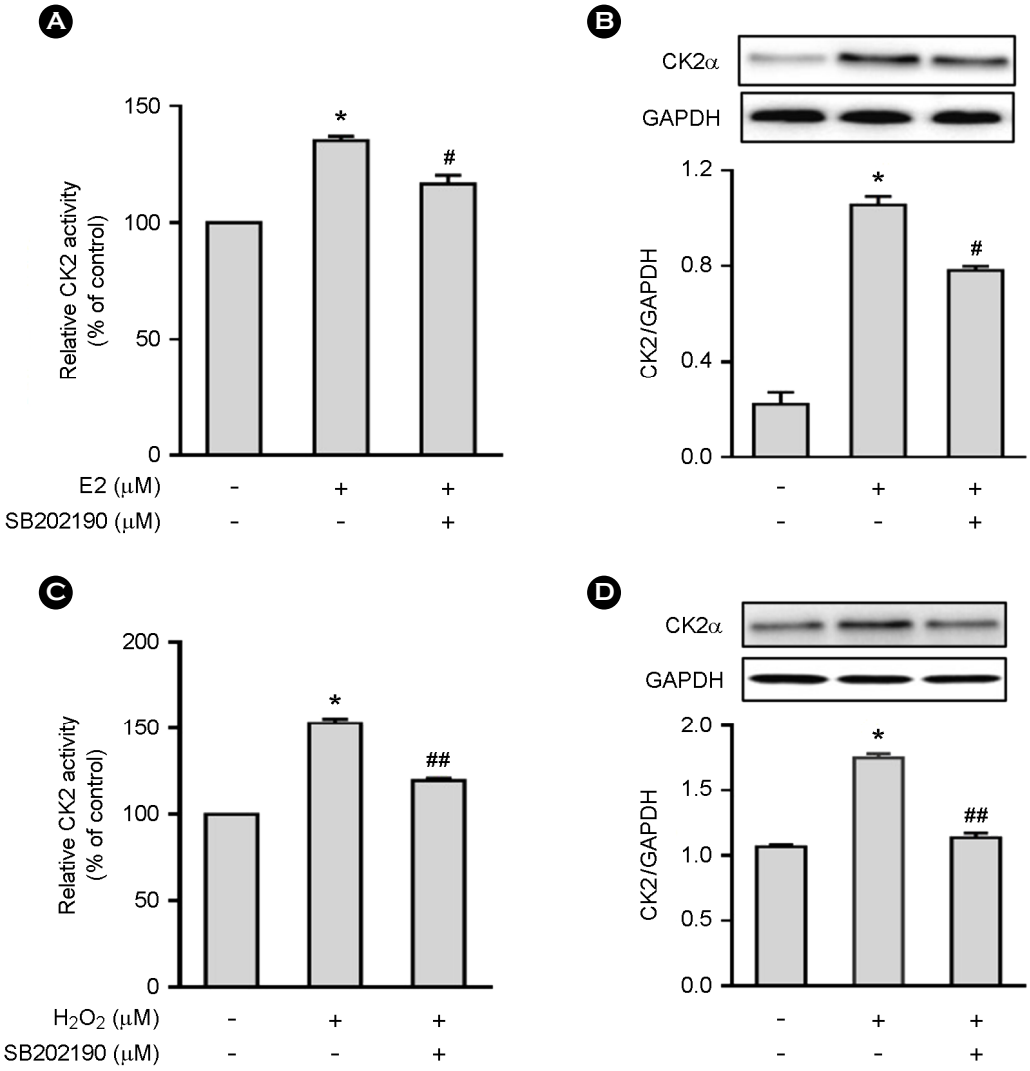

Fig. 5. The p38 mediates estrogen-induced CK2 activation in MCF-7 cells. Cells (1×10^6) were pretreated with SB202190 (20 μM) for 30 min followed by estrogen (0.5 μM, A and B) or H_2O_2 (30 μM, C and D) for the measurement of CK2 activity (A, C) and protein expression (B, D). Data represent the mean ± SE of two to three independent experiments with three to five samples each. $^{*}P < 0.01$ versus control group. $^{\#}P < 0.01$ versus estrogen-treated group. $^{\#\#}P < 0.01$ versus H_2O_2-treated group.

tabolism and generation of genotoxic estrogen metabolites such as catechol estrogen and estrogen-semi-quinones (Roy et al., 2007; Okoh et al., 2011). We found that estrogen produced ROS in ER^+ MCF-7 and T47D cells, but not in ER^- MDA-MB-231 cells. ROS can be generated intracellularly by a variety of enzymes (i.e., NADPH oxidase, xanthine oxidase, lipoxygenase) and through the mitochondrial respiratory chain (Sauer et al., 2001). Mitochondria however, are the largest source of ROS in epithelial cells. Studies have shown that mitochondria is the major source of intracellular ROS in response to estrogen (Felty et al., 2005).

The ROS generated by estrogen induced CK2α activation and protein expression via CK2α activation and protein expression, which were blocked by NAC. The ROS (H_2O_2) also directly increased the CK2α activity and protein expression.

The members of the epidermal growth factor receptor (EGFR)/ErbB family: EGFR (also known as ErbB1 and HER1), HER2 (also known as HER2/neu and ErbB2), ErbB3 (also known as HER3), and ErbB4 (also known as

HER4) are the most notable cancer molecular targets identified to date (Mendelsohn and Baselga, 2003). Overexpression of HER2, which is a transmembrane receptor tyrosine kinase (Groenen et al., 1994; Lemke, 1996) is seen in 30% of breast cancer patients and is associated with poor survival, increased metastasis, and resistance to chemotherapy (Slamon et al., 1987; Toikkanen et al., 1992). As a result, HER2 is the most well established therapeutic target in breast cancer. EGFR overexpression is observed in all subtypes of breast cancer, EGFR is more frequently overexpressed in triple-negative breast cancer (TNBC) and inflammatory breast cancer, which are especially aggressive (Rakha et al., 2007; Burness et al., 2010).

In addition to estrogen, we observed that EGF increased ROS levels and CK2 activation as well in MCF-7 HER 2 cells. Treatment of the cells with the combinations of estrogen and EGF led to enhanced ROS and CK2α activation compared with stimulation with either estrogen or EGF alone. What is the mechanism of up-regulation of ROS/ CK2α in MCF-7 HER 2 cells? NADPH oxidase was specifically involved in the generation of ROS by growth factors, such as transforming growth factor-β1 (Ohba et al., 1994; Thannickal and Fanburg, 1995), insulin (Mahadev et al., 2001), PDGF- and EGF (Sundaresan et al., 1995; Bae et al., 1997). Additionally, we previously reported that exogenous stimuli such as platelet activating factor, LPS, TNF-α, and interleukin-1 triggering ROS generation were found to enhance CK2α activity (Kim et al., 2014). Therefore, up-regulation of CK2α in MCF-7 HER 2 cells is probably attributed to EGF-dependent generation of higher levels of ROS, which may explain the aggressive features of HER2-positive breast carcinomas and their rapid proliferation compared with other types of breast cancer (Me´nard et al., 2003).

The p38 MAPK signaling pathway mediates the inflammatory response via proteins, such as proinflammatory cytokines, chemokines, degradative enzymes, growth factors, and adhesion molecules (Zhang et al., 2007). P38 is an oxidative stress-sensitive kinase. During the ROS-mediated p38 activation, a few protein kinases, such as apoptosis signal-regulated kinase 1, an upstream MAPK kinase kinases (Saitoh et al., 1998; Fujino et al., 2007), cGMP-dependent protein kinase (Li et al., 2006; Hofmann et al., 2006), protein kinase A (Brennan et al., 2006), and protein kinase C (Giorgi et al., 2010) that are directly regulated by ROS, are known to phosphorylate and activate p38 MAPK. We have previously reported that p38 is involved in ROS-mediated CK2α modulation (Kim et al., 2014). Consistent with these findings, we demonstrated that p38 phosphorylation occurred in response to estrogen, which was abrogated by pre-treatment with NAC, indicating that ROS generated by estrogen induced p38 phosphorylation. Indeed, the p38 inhibitor, SB202190, was shown to inhibit CK2α activation and protein expression (Fig. 5), indicating that p38 kinase catalyzed ROS-mediated CK2α activation and protein expression. Therefore, apparently ROS/p38 is a key common upstream pathway underlying the enhanced CK2α activity, suggesting that the ROS/ p38 leading to CK2α activation mediated estrogen signaling.

Classification of breast cancer has been historically based on both analysis of tumor morphology and histological detection of three marker proteins: the ER, the progesterone receptor (PR), and the HER2 or ErbB2. Tumors which express none of these three markers are collectively referred to as triple-negative breast cancer (TNBC; ER^-, PR^-, $HER2^-$). More recent gene expression analyses showed that breast cancer is a more heterogeneous disease than previously assumed. The current classification includes five major transcriptional subtypes: basal-like, HER2-enriched, luminal A, luminal B, and normal breast-like (Perou et al., 2000; Sorlie et al., 2003). Recently, the aberrant expression of CK2α and its subtypes in breast cancers has been reported (Giusiano et al., 2011). Therefore, it is of interest to investigate the linkage between oxidative stress and p38/CK2α expression in various types of breast cancer in the future.

In summary, we demonstrated that ROS/p38 acts as a key inducer of CK2α activation in response to estrogen or growth factor (EGF) stimulation, i.e., estrogen or EGF → ROS↑→ p38 MAPK↑ → CK2α activation↑. Therefore, this study adds an important element to our understanding of the mechanisms underlying CK2α activation in breast cancers.

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CONFLICT OF INTEREST

No conflicts of interest are involved in this manuscript.

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