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Review

Catechol Estrogen 4-Hydroxyestradiol is an Ultimate Carcinogen in Breast Cancer

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Excessive exposure to estrogens is the most important risk factor for the development of hormone-sensitive cancers, especially breast cancer. Estrogen stimulates the expression of genes and proteins involved in cell proliferation by binding to estrogen receptor (ER). Another possible mechanism of ER-independent carcinogenicity of estrogens is based on the hydroxylation of estradiol resulting in the formation of catechol estrogens. Catechol estrogen 4-hydroxyestradiol (4-OHE_2) is further oxidized to catechol estrogen-3,4-quinones, the major carcinogenic metabolites of estrogens. Evidence increasingly supports the critical role of 4-OHE_2 in hormonal carcinogenesis via DNA adduct formation or production of reactive oxygen species, which finally contribute to the transformation of normal mammary epithelial cells and the enhanced growth of breast cancer cells. It is also reported that the level of 4-OHE_2 or its quinones is highly up-regulated in urine or tissues of breast cancer patients. Thus, we highlight the oncogenic roles of 4-OHE_2 in catechol estrogen-induced breast carcinogenesis.

Key Words: Breast cancer, Catechol estrogen-3,4-quinones, DNA adducts, 4-Hydroxyestradiol, Reactive oxygen species

INTRODUCTION

Breast cancer is one of the most frequent disorders among women worldwide. In recent years, early detection has increased the survival rate of patients. However, breast cancer remains one of the most malignant cancers with increased risk of relapse and metastasis. In particular, patients lacking estrogen receptor (ER), progesterone receptors, and hormone epidermal growth factor receptor 2, have limited treatment options (Wahba and El-Hadaad, 2015; Lukong, 2017). Therefore, it is necessary to investigate not only the mechanism of estrogen/ER-induced breast cancer but also other mechanisms. It has been proposed that genotoxicity induced by estrogen metabolites, including 2-hydroxyestradiol (2-OHE_2) and 4-hydroxyestradiol (4-OHE_2), may contribute to breast carcinogenesis (Cavalieri et al., 2006; Fernandez et al., 2006). Interestingly, these metabolites are involved in breast carcinogenesis mainly via DNA adducts or reactive oxygen species (ROS) formation, without essentially binding to ER (Chang, 2011; Wen et al., 2017).

Estradiol (E_2) is biosynthesized by both aromatase and 17β-estradiol dehydrogenase from androstenedione via testosterone or estrone (Zhu and Conney, 1998). This E_2 is metabolized via two major pathways: formation of catechol estrogens and, to a lesser extent, 16α-hydroxylation (Zhu and

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Conney, 1998; Cavalieri et al., 2006). The catechol estrogens including 2-OHE_2 and 4-OHE_2, are further oxidized initially to their semiquinone intermediates and then to quinone metabolites by peroxidases or cytochrome P450 (CYP)s (Zhang et al., 2007). Redox cycling via reduction of quinones to semiquinones, catalyzed by CYP reductase, and subsequent oxidation back to catechol estrogen-3,4-quinones (CE-3,4-Q) by oxygen yields super-anion radicals and hydrogen peroxide (H_2O_2). Because quinones and semiquinones are capable of redox cycling as long as molecular oxygen is available, a minor amount of estradiol may trigger substantial cellular damage (Cavalieri et al., 2000).

Interestingly, numerous studies suggested that 4-OHE_2 is a more potent carcinogen than 2-OHE_2. The 2-OHE_2 has little or no carcinogenic activity compared with 4-OHE_2 (Liehr et al., 1986; Zhu and Conney, 1998; Newbold and Liehr, 2000). Treatment of MCF-10F cells with E_2 or 4-OHE_2 was mutagenic even at the lowest dose used (0.007 and 70 nM), whereas 2-OHE_2-transformed cells manifested these mutations only at the highest dose (3.6 μM) (Fernandez et al., 2006). The extremely weak carcinogen 2-OHE_2 also forms depurinating adducts, but to a much lesser extent (Zahid et al., 2006). Notably, an elevated ratio of 4-OHE_2/2-OHE_2 formation was detected in microsomes prepared from human mammary adenocarcinoma and fibroadenoma (Liehr and Ricci, 1996). 4-OHE_2 or its quinone conjugates were detected in human breast tumor biopsies at significantly higher levels compared with the levels in the normal breast tissues (Rogan et al., 2003). *O*-methylation of 2-OHE_2 is faster than that of 4-OHE_2 and leads to a more rapid clearance, and therefore, lacks carcinogenicity (Zhu and Conney, 1998). Here, this review summarizes the carcinogenic role of 4-OHE_2 through various aspects, especially in human mammary carcinogenesis (Fig. 1). Finally, this review strongly support the hypothesis that 4-OHE_2 is not only a tumor initiator but also an ultimate carcinogen.

4-OHE_2-derived quinones react with DNA

The reactive quinones derived from 4-OHE_2 generated depurinating DNA adducts such as 4-OHE_2-N7-guanine (4-OHE_2-N7-G) and 4-OHE_2-N3-adenine (4-OHE_2-N3-A) (Belous et al., 2007). The mutagenic effects of 4-OHE_2 were reported in BB rat2 embryonic cells exposed to multiple low doses (50~200 nM) (Zhao et al., 2006). In addition, media from 4-OHE_2-treated MCF-10F cells, which are ER-negative immortalized human breast epithelial cells, contained depurinating N7-G and N3-A adducts (Saeed et al., 2007). Mutagenic activity of 4-OHE_2 and CE-3,4-Q have also been reported in the mammary gland of BB rats and ACI rats, respectively (Mailander et al., 2006; Zhao et al., 2006). Intramammary injection of 4-OHE_2 or CE-3,4-Q into female rats, followed by excision of mammary tissue 1 h later, revealed the presence of depurinating adducts 4-OHE_2-N7-G and 4-OHE_2-N3-A (Cavalieri et al., 1997; Li et al., 2004). The intraperitoneal injection of 4-OHE_2 into male Syrian golden hamsters increased the formation of glutathione (GSH) and Cys conjugates of 4-OHE_2 and 4-OHE_2-N7-G adducts (Devanesan et al., 2001; Todorovic et al., 2001). Moreover, the urinary level of 4-OHE_2-derived depurinating DNA adducts was substantially elevated in high-risk women and women diagnosed with breast cancer compared with those of the control subjects (Gaikwad et al., 2008). These adducts generate apurinic sites that may lead to cancer-initiating mutations (Chakravarti et al., 2001). It is also reported that catechol estrogens induce oxidative DNA damage (Hiraku et al., 2001). The interaction of 4-OHE_2 and copper induced DNA modification and damage involving single/double strand breaks, base modification and so on (Khan et al., 2007).

Imbalance of estrogen metabolizing enzymes is involved in 4-OHE_2-induced genotoxicity

Imbalance in estrogen homeostasis leads to substantial formation of 4-OHE_2 or 4-OHE_2-derived DNA adducts (Cavalieri and Rogan, 2006; Cavalieri and Rogan, 2016). CYP1B1, which is abundantly expressed in extrahepatic tissues such as mammary glands, ovary, and uterus, specifically catalyzes the 4-hydroxylation of E_2 and further oxidizes 4-OHE_2 to its semiquinone and quinone conjugates (Zhang et al., 2007). The estrogen 4-hydroxylase, CYP1B1, is also overexpressed in tumors of the breast (Murray et al., 1997; Singh et al., 2005) and promotes breast cancer cell survival (Kwon et al., 2016). In addition, CYP1B1 is genetically polymorphic, and variations in the *CYP1B1* gene are correlated with the risk of breast cancer (Zheng et al., 2000).

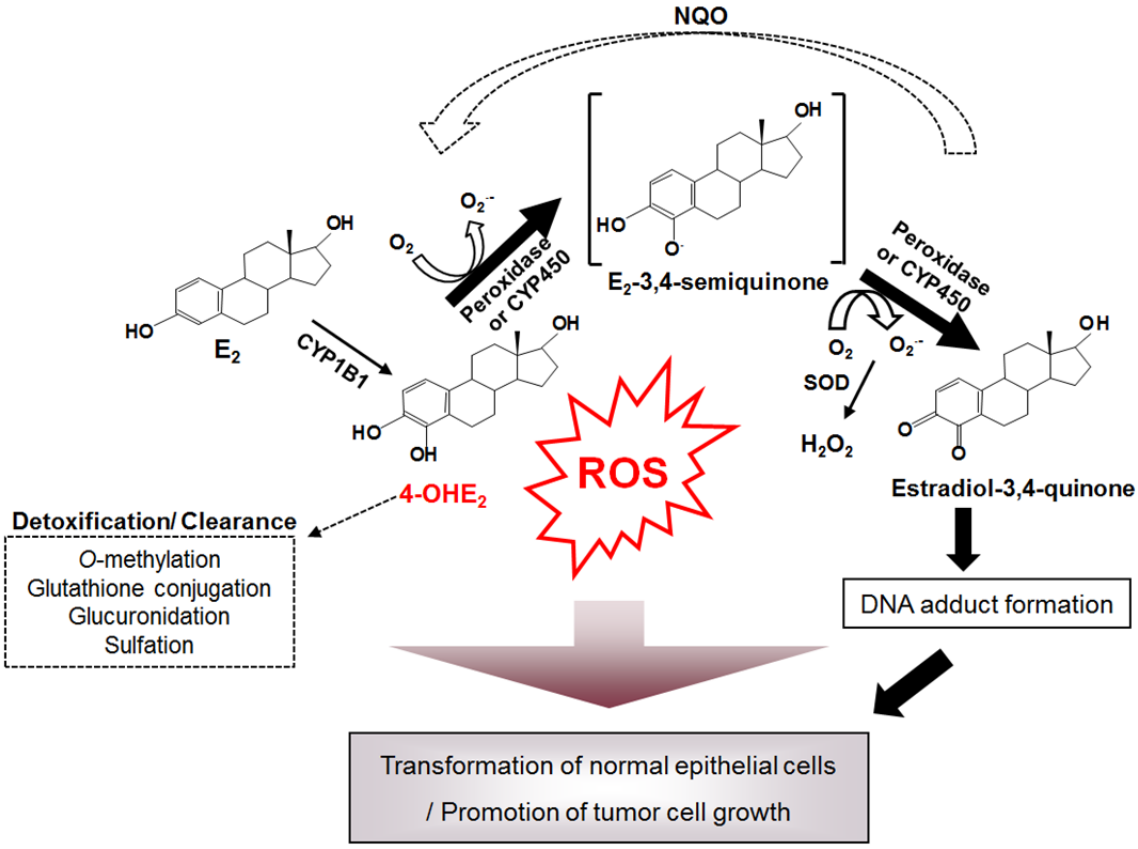

Fig. 1. Role of 4-OHE$_2$ in hormonal carcinogenesis. E_2 is catalyzed by CYP1B1 to form 4-OHE$_2$, which is further oxidized to the genotoxic estradiol-3,4-quinone. During redox cycling of 4-OHE$_2$ and its metabolites, ROS is overproduced. The reactive quinone and ROS contribute to induce the transforamtion of normal epithelial cells and promote the growth of tumor cells. Unbalanced control of estrogen-metabolizing enzymes also trigger to produce 4-OHE$_2$-derived quinones, which can act as an ultimate carcinogen. E_2: estradiol, 4-OHE$_2$: 4-hydroxyestradiol, ROS: reactive oxygen species, NQO: NAD(P)H:quinone oxidoreductase, CYP450: cytochrome P450.

In contrast, the reactivity of catechol estrogen-derived quinones can be prevented via conjugation with GSH. Further, quinone metabolites are reduced to their original catechol estrogen by NAD(P)H:quinone oxidoreductase (NQO) and/or CYP reductase (Roy and Liehr, 1988). If these inactivating processes are insufficient and/or ineffective or the level of CYP450s, especially CYP1B1, is abnormally high, catechol estrogen-derived quinones metabolites may react with DNA to form predominantly depurinating adducts. Additionally, the oxidation of 4-OHE$_2$ by peroxidase or CYPs contributes to ROS overproduction in human mammary epithelial MCF-10A cells. Similary, dicoumarol, the inhibitor of NQO activity, enhanced 4-OHE$_2$-induced ROS production under similar conditions (Park et al., 2009).

Additionally, the catechol estrogens are excreted in the urine and/or feces by metabolic conversion to hormonally inactive or less active metabolites. The conjugative metabolism includes glucuronidation, sulfonation, and *O*-methylation. It has been well documented that the metabolic conjugation of estrogens by conjugating enzymes decreases their hormonal activity and facilitates their excretion (Zhu and Conney, 1998). Especially, the *O*-methylation of catechol estrogens is catalyzed by catechol-*O*-methyltransferase that blocks the further metabolism of catechol estrogen (Yager, 2012). This event has been reported as a critical detoxification pathway for the catechol intermediates (Zhu and Conney, 1998; Raftogianis et al., 2000). Altogether, the unbalanced regulation of estrogen metabolizing enzymes finally results in the formation

of catechol estrogen-derived quinones resulting in carcinogenesis.

4-OHE_2 produces ROS

The catechol estrogen 4-OHE_2 and its semiquinones/quinones also undergo redox cycling, which results in the production of ROS. Excessive ROS induce oxidative DNA damage (Liehr and Roy, 1990; Nutter et al., 1994). Human breast epithelial MCF-10A cells treated with 4-OHE_2 increased intracellular ROS accumulation and 8-oxo-7,8-dihydroxy-2'-deoxyguanosine (8-oxo-dG) formation. Further, extracellular signal-regulated protein kinases and nuclear factor-κB (NF-κB), which are redox-sensitive molecules, were transiently activated by 4-OHE_2 treatment (Chen et al., 2005). It was reported that catechol metabolites of endogenous estrogens generated H_2O_2 and hydroxyl radicals in breast epithelial cells (Fussell et al., 2011). The concomitant synthesis of ROS, overproduced during redox cycling of 4-OHE_2, further activated IκB kinase (IKK)-NF-κB signaling (Park et al., 2009) or phosphoinositide 3-kinase-Akt pathway (Okoh et al., 2013) which may result in neoplastic transformation of human mammary epithelial cells.

4-OHE_2 induces neoplastic transformation of normal epithelial cells

Transformation of normal cells into neoplastic cells results from a series of genetic and epigenetic alterations and is a critical event in induction of carcinogenesis. Multiple lines of evidence suggest that 4-OHE_2 contributes to neoplastic transformation of normal epithelial cells. Treatment of human breast epithelial MCF-10F cells with E_2 or 4-OHE_2 induced neoplastic transformation, even in the presence of anti-estrogen ICI-182,780 (Lareef et al., 2005). The failure of anti-estrogen to abrogate the transformation phenotypes suggests that 4-OHE_2-induced cell transformation is independent of ER binding. When MCF-10F cells were treated with benz(*a*)pyrene, E_2, 2-OHE_2, 4-OHE_2, or 16α-OHE_2, 4-OHE_2 effectively induced larger colonies and numbers at doses of 0.007 nM (Russo et al., 2003). The effect of 4-OHE_2 on neoplastic transformation of human mammary epithelial cells was repeatedly observed. 4-OHE_2 markedly induced anchorage-independent colony formation in MCF-10A cells via activation of IKK-NF-κB signaling pathway (Park et al., 2009).

4-OHE_2 promotes the growth of cancer cells

4-OHE_2 not only induces cell transformation in normal cells but also promotes the growth of cancer cells. Treatment with 4-OHE_2, but not 2-OHE_2, induced renal cancer in Syrian hamster (Liehr et al., 1986). The administration of E_2, 2-OHE_2, and 4-OHE_2 induced endometrial carcinomas in 7%, 12%, and 66%, respectively, of treated CD-1 mice (Newbold and Liehr, 2000). Interestingly, when female ACI rats were treated with E_2, co-treatment with E_2 plus vitamin C or E_2 plus estrogen metabolic inhibitor α-naphthoflavone (ANF), breast tumor incidence was 82%, 29% and 0%, respectively. Since ANF inhibits 4-hydroxylation of E_2 and decreases formation of the highly carcinogenic 4-OHE_2, these results suggest that E_2 metabolism toward 4-OHE_2 pathway is critically involved in estrogen-induced breast carcinogenesis (Mense et al., 2009).

In addition, numerous studies demonstrated that 4-OHE_2 stimulated specific intracellular signaling molecules, which support the oncogenic role of 4-OHE_2. Especially, the effects of estradiol metabolites on cell cycle has been well studied (Lottering et al., 1992; Lewis et al., 2001; Chang, 2011). Among those metabolites, the estrogens E_2, 4-OHE_2 and 16-OHE_1 showed a proliferative effect on MCF-7 human breast cancer cells which was accompanied by a down-regulation of apoptosis (Seeger et al., 2006). Also, the expression of cell cycle-related genes such as cdc2, protein regulator of cytokinesis 1, and proliferating cell nuclear antigen was up-regulated by 4-OHE_2 treatment (Okoh et al., 2013).

Generally, invasion and metastases follow the degradation of extracellular matrix (ECM), which acts as a barrier to cancer cell movement. ECM proteins are degraded by proteases, mainly the matrix metalloproteinases (MMPs) and increase the risk of invasive and metastatic processes. Enzymatic assay and gel zymography demonstrated that 4-OHE_2 led to the conversion of pro MMP-2 and -9 to active MMP-2 and -9, which resulted in dissemination of cancer cells (Paquette et al., 2003; Paquette et al., 2005). Further, 4-OHE_2 and not 2-OHE_2, induced the expression of hypoxia-inducible factor 1 and vascular endothelial growth factor A, which are

critical molecules in angiogenesis or invasion of cancer cells (Gao et al., 2004).

CONCLUSION

Although ER-mediated hormonal carcinogenesis has been largely understood, results from cell/animal/human-based studies suggested that catechol estrogen, especially 4-OHE_2 acts as an ultimate carcinogen independent of ER. The catechol estrogen is further metabolized by CYP-mediated oxidation, *O*-methylation, reaction with glutathione, glucuronidation, and sulfation. Apparently, a specific equilibrium exists in the metabolic pathways of catechol estrogen to maintain hormonal homeostasis. Disturbed equilibrium may trigger carcinogenesis by increasing the levels of catechol estrogen-derived quinones. Further, semiquinones/quinones and hydroxyl radicals generated during the oxidative estrogen metabolism induce either oxidative DNA damage such as formation of 8-oxo-dG or apurinic DNA adducts (Chen et al., 2005; Fussell et al., 2011).

Previously, 4-OHE_2 treatment produced tumors in kidney of Syrian hamsters (Liehr et al., 1986) and uterine of CD-1 mice (Newbold and Liehr, 2000) rather than in mammary gland. In addition, 4-OHE_2 exposure was not sufficient to produce mammary tumors in female ACI rats (Turan et al., 2004). Since 4-OHE_2 is more water soluble and unstable than E_2, Turan and his colleagues suggested that it may be critical for 4-OHE_2 formation in or near mammary tissues to effectively initiate carcinogenesis (Turan et al., 2004). Importantly, the level of 4-OHE_2 is correlated with the pathogenesis of breast cancer. Studies of breast tissue from women with and without breast cancer provide evidence to support the impact of unbalanced estrogen homeostasis on cancer (Castagnetta et al., 2002; Singh et al., 2005). The accumulation of 4-OHE_2 is also correlated with the invasiveness of breast cancer cells (Paquette et al., 2003; Paquette et al., 2005).

4-OHE_2 acts as a tumor initiator when its quinone metabolites react with DNA and also acts as a tumor promoter through ROS overproduction. Additional induction of a number of cellular signaling pathways leads to neoplastic epithelial transformation, cell proliferation, or tumor promotion. Therefore, catechol estrogen 4-OHE_2 or its quinoid metabolites may serve as a biomarker for breast cancer and methods that facilitate the detection of these metabolites more easily and accurately are needed.

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CONFLICT OF INTEREST

The authors have no conflict of interest regarding the publication of this article.

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