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Endocrine disruptors and the tumor microenvironment: A new paradigm in breast cancer biology

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ABSTRACT

Breast cancer is one of the most frequently diagnosed malignancies in women and is characterized by predominantly estrogen dependent growth. Endocrine disruptors (EDCs) have estrogenic properties which have been shown to increase breast cancer risk. While the direct effects of EDCs on breast cancer cell biology and tumor progression have been well studied, the roles for EDCs on tumor microenvironment composition, signaling and structure are incompletely defined. Estrogen targeting of tumor stromal cells can drive paracrine signaling to breast cancer cells regulating tumorigenesis and progression. Additionally, estrogen and estrogen receptor signaling has been shown to alter breast architecture and extracellular matrix component synthesis. Unsurprisingly, EDCs have been shown to induce structural changes in the mammary gland as well as increased collagen fibers in the tissue stroma. Previous work demonstrates that human mesenchymal stem cells (hMSC) are essential components of the tumor microenvironment and are direct targets of both estrogens and EDCs. Furthermore, estrogen–stem cell cross talk has been implicated in breast cancer progression and results in increased tumor cell proliferation, angiogenesis and invasion. This review aims to dissect the possible relationship and mechanisms between EDCs, the tumor microenvironment, and breast cancer progression.

1. Introduction

Endocrine disrupting chemicals (EDCs) are exogenous chemicals which can interfere with hormone signaling and action. The number of identified endocrine disruptors is increasing over time, and the uncertainty of the potential detrimental effects of these identified and unidentified compounds is a growing concern (Zoeller et al., 2012). Many compounds have been implicated as endocrine disruptors, and their presence in products used daily by humans, poses a serious health risk. EDCs, including Bisphenol A (BPA), dichlorodiphenyltrichloroethane (DDT), glycophosphate, and phthalates, can be found in plastics, pesticides, herbicides, and cleaning products respectively (Frye et al., 2012). These chemicals can be inhaled or ingested, and are often dispersed into soil, dust, and water reserves, adversely affecting endocrine system function in wildlife and humans alike (Zoeller et al., 2012; McLachlan, 2016).

EDCs are known to mimic, disrupt or antagonize endocrine pathways through their interactions with hormone receptors including estrogen receptor (ER) (Shanle and Xu, 2011). Often, these compounds can activate or antagonize estrogen hormone action through ligand dependent activation, modulation of estrogen biosynthesis via altered aromatase activity, and indirect activation of other transcription factors (Li et al., 2013; Inoshita et al., 2003; Fan et al., 2007). While the effects of EDCs are not limited to the ligand dependent activity of ERs, most EDCs from natural or synthetic sources have structures similar steroid hormones including estrogen (E2) or androgen, and more commonly interfere with the actions of steroid hormones through binding of their respective hormone receptors (McLachlan, 2001; Tilghman et al., 2010). Consequently, ligand dependent endocrine disruption of estrogen signaling is the most well studied mechanism.

E2 regulated cell function occurs through multiple pathways,

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affecting specific, tissue-dependent, responses. E2 is able to regulate transcription of target genes directly through the genomic pathway or indirectly through the extra-nuclear pathway. In the genomic pathway, E2 binds the estrogen receptor (ER) and induces conformational changes which facilitate dimerization and DNA binding capability. These ligand receptor complexes bind estrogen response elements (EREs) in the promoter regions of DNA along with recruited cofactor molecules and transcription factors to regulate target gene expression. Non-genomic rapid estrogen signaling occurs within seconds or minutes of addition of E2, and is mediated by estrogen receptors localized to the cell surface membrane (Bjornstrom and Sjoberg, 2005). The membrane E2-ER complex can interact with multiple growth factor receptors, including IGF-1 and EGF receptors, activate protein kinase cascades which phosphorylate transcription factors, and alter gene expression patterns independent of ER direct binding to the DNA (Marino et al., 2006; Bratton et al., 2009; Frigo et al., 2004).

Low fluctuating doses of endogenous hormones are present in the human body, and small additions or subtractions of hormone activation, as is seen in exposure to low levels of environmental estrogens and endocrine disruptors, can have a significant effect on physiological function (Vandenberg et al., 2012).

2. EDC action in breast development and carcinogenesis

Increased exposure to estrogen is associated with an increased risk of developing breast cancer (Travis and Key, 2003). Breast development is carefully regulated by small fluctuations in levels of endogenous hormones (Javed and Lteif, 2013). These minor fluctuations in hormone production govern critical processes in mammary gland during development, puberty and pregnancy (Gulledge et al., 2001). Breast tissue is particularly sensitive to carcinogenic effects during morphogenesis and remodeling (Paulose et al., 2015). Exposure to low levels of endocrine disruptors prenatally can disrupt the delicate balance of hormone action at these stages, resulting in changes to the mammary epithelium, advanced maturation of the mammary fat pad, and increased ductal growth and branching. These defects in mammary gland development have been shown to lead to increased risk of breast carcinoma in adulthood (Palmer et al., 2006; Thompson and Janerich, 1990). Significantly lower doses of EDCs in utero are sufficient to alter breast morphogenesis and increase the fetus's risk for developing cancer than those needed to produce the same effect after exposure in adulthood (Markey et al., 2001, 2005).

The adverse effects of prenatal EDC exposure are perhaps best exemplified by the reports of increased breast cancer risk in daughters of women prescribed DES during pregnancy. DES was prescribed to pregnant women to prevent miscarriage from the 1940s until its ban in the 1970s (Titus-Ernstoff et al., 2010). The DES daughters had a higher incidence of numerous malignancies when compared to their age matched counterparts, and showed a significant increase in risk for breast cancer development after 40 years of age (Palmer et al., 2006; Fenton et al., 2002; Vandenberg et al., 2009; Troisi et al., 2007). Similarly, multiple studies demonstrate that fetal exposure to low doses of BPA, increases cell proliferation and estrogen sensitivity, decreases apoptosis and alters the architecture of the mammary gland, causing an increase in ductal density and predisposing the mammary gland to carcinogenesis (Gao et al., 2015).

Similarly, rodents exposed to low doses of BPA during gestation show dysregulated mammary gland morphogenesis in utero and increased sensitivity to estrogens and progesterone in adulthood. It is postulated that the observed significant increases in precancerous lesions and breast carcinoma in adulthood is a result of this hypersensitivity (Pike et al., 1993; Wang et al., 2014).

Atrazine is a commonly used herbicide which has been shown to feminize numerous species of animals and induce estrogen like effects in exposed individuals (Fan et al., 2007). Atrazine acts as an endocrine disruptor through upregulation of aromatase, an enzyme which controls the conversion of androgens to estrogens (Vasanth et al., 2015). Furthermore, it has been shown that women whose well water contains traces of atrazine have an increased breast cancer incidence, likely due to the increase in estrogen levels (Kettles et al., 1997).

3. EDCs promote breast cancer progression and metastasis

In addition to the increased risk of carcinogenesis, endocrine disruptors are involved in enhancing the progression and metastasis of established breast tumors, which remains the single largest cause of breast cancer mortality. Chronic exposure to BPA induces tumor proliferation, EMT, and metastasis in multiple breast cancer cell lines (Zhang et al., 2016; Jenkins et al., 2011). Furthermore, when needle aspirates of non-malignant breast epithelial cells taken from individuals diagnosed with breast cancer were treated with BPA they expressed a gene signature that was indicative of high histological grade tumors (Dairkee et al., 2008). This suggests that BPA effects on the tumor microenvironment may contribute to tumor progression. Given this data, it is unsurprising that patients exposed to BPA present with increased tumor aggressiveness.

Additional studies have shown the estrogenic compounds Benzophenone-1 (BP1) and nonylphenol (NP), commonly found in plastics, increase proliferation of MCF-7 breast cancer cells through regulation of cell cycle genes and cathepsin D (In et al., 2015). This effect was abrogated by treatment with ICI 182,780, an estrogen receptor downregulator, implicating the necessity of estrogen receptor activity in BP1 and NP mediated breast cancer progression. Furthermore, NP specifically has been shown to induce estrogen responsive gene transcription (Amaro et al., 2014).

Octylphenol (OP) and Triclosan (TCS) are two compounds which have more recently been identified as having endocrine disrupting potential. TCS is an antimicrobial agent commonly found in products used daily, such as soaps and toothpaste, which has been detected in human breast milk and demonstrated to amplify ER responses (Gee et al., 2008). OP is an alkyl phenol which has accumulated in air, soil, and water due to its use in pesticides and plastics. In addition to its estrogenic effects, OP has been shown to increase aromatase activity (Mills et al., 2014). Similarly to BP1 and NP, these compounds have also been shown to alter the expression of cell cycle regulators and significantly increase MCF-7 proliferation and tumor growth in *in vitro* and *in vivo* breast cancer settings respectively. Inhibition of the effects of these compounds on breast cancer progression by ICI 182,780, implicates ER signaling in the oncogenic activity of these EDCs (Lee et al., 2014).

4. EDCs induce obesity and adipogenesis in breast tissue

Evidence shows that obese women have an increased risk of breast cancer, in part due to the active role of adipose tissue in tumor initiation and growth (Calle and Kaaks, 2004; Wei et al., 2015; Tan et al., 2011; Strong et al., 2015). Postmenopausal obese women have a significantly greater chance of developing breast cancer compared to their lean counterparts, though this effect is not seen in premenopausal women (Reeves et al., 2007; Xia et al., 2014). However, when looking at subtype specific incidences of breast cancer, premenopausal obese women are 42% more likely to develop triple negative breast cancer, which has limited treatment options and high mortality rates (Pierobon and Frankenfeld, 2013). Breast tissue in women is primarily comprised of subcutaneous white adipose tissue. This adipose tissue is the site of generation of