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Diverse pathways of epithelial mesenchymal transition related with cancer progression and metastasis and potential effects of endocrine disrupting chemicals on epithelial mesenchymal transition process

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ABSTRACT

Endocrine disrupting chemicals (EDCs) are natural or synthetic compounds that interfere with normal functions of natural hormones in the body, leading to a disruption of the endocrine system. Specifically, EDCs have the potential to cause formation of several hormone-dependent cancers, including breast, ovarian, and prostate cancers. Epithelial mesenchymal transition (EMT) process by which epithelial cells lose their cell polarity and cell-cell adhesion and acquire mesenchymal phenotype is closely associated with malignant transformation and the initiation of cancer metastasis. As a key epithelial marker responsible for adherens junction, E-cadherin enables the cells to maintain epithelial phenotypes. EMT event is induced by E-cadherin loss which can be carried out by many transcription factors (TFs), including Snail, Slug, ZEB1, ZEB2, Kruppel-like factor 8 (KLF8), and Twist. N-cadherin, fibronectin, and vimentin are mesenchymal markers needed for cellular migration. The EMT process is regulated by several signaling pathways mediated by transforming growth factor β (TGF-β), Wnt−β-catenin, Notch, Hedgehog, and receptor tyrosine kinases. In the present article, we reviewed the current understanding of cancer progression effects of synthetic chemical EDCs such as bisphenol A (BPA), phthalates, tetrachlorodibenzo-*p*-dioxin (TCDD), and triclosan by focusing their roles in the EMT process. Collectively, the majority of previous studies revealed that BPA, phthalates, TCDD, and triclosan have the potential to induce cancer metastasis through regulating EMT markers and migration via several signaling pathways associated with the EMT program. Therefore, it is considered that the exposure to these EDCs can increase the risk aggravating the disease for the patients suffering cancer and that more regulations about the use of these EDCs are needed.

1. Introduction

The endocrine system refers to the collection of hormone producing glands that regulate reproduction, development, growth, metabolism, and maintenance of homeostasis (Kavlock et al., 1996). Hormones are signaling molecules that are secreted from diverse glands and affect the target cells by binding to specific receptor proteins, resulting in cell type-specific responses.

Endocrine disrupting chemicals (EDCs) are natural or synthetic compounds that interfere with normal functions of natural hormones in the body, leading to a disruption of the endocrine system (Diamanti-Kandarakis et al., 2009, Gore et al., 2015). EDCs are found in environment by industrial, agricultural, food, and consumer products such as detergents, toys, and cosmetics and can be exposed to humans through various routes. Oral intake is the major route of exposure to EDCs through consumption of packaged food or pesticide residue (Yang et al., 2015, Schecter et al., 2004, Cichna-Markl, 2012). Nowadays, EDC exposure sometimes occurs through inhalation of air with EDCs due to increased air pollution or cigarette smoke (Azuma et al., 2016). Even embryos can be exposed to EDCs through their mothers (Diamanti-Kandarakis et al., 2009). A variety of industrial compounds, such as dioxins, bisphenol A (BPA), alkylphenols (APs), and phthalates have been classified into EDCs, and some other compounds including polycyclic aromatic hydrocarbons and phenol derivatives have been found as putative EDCs.

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As EDCs impair the hormone homeostasis by altering the regulation of hormone synthesis, secretion, transport, or specific hormone receptor binding at even low concentrations (Celik et al., 2008, Lopez et al.,2002 , Bjornstrom and Sjoberg, 2005, Shanle and Xu, 2011, Lee et al., 2013), they are also often used as synonym for xenohormones, hormonally active agents (Krimsky, 2001). EDCs have the potential to cause serious abnormalities in body functions, including impaired sexual developmental and reproductive functions and formation of several hormone-dependent cancers, including breast, ovarian, and prostate cancer (Celik et al., 2008, Masuno et al., 2005, Go et al., 2015, Fowler et al., 2008, Lee et al., 2014).

The relevance of EDCs in carcinogenesis of hormone-dependent cancers has been associated with the findings that sex hormones are linked to the pathogenesis of several cancers in the reproductive organs. For instance, circulating levels of estrogens may be strongly associated with the risks of breast, ovarian, endometrial, and cervical cancers which are estrogen-responsive or estrogen receptor (ER)-positive cancers (Missmer et al., 2004, Rodriguez et al., 2001, Grady et al., 1995, Chung et al., 2010). Therefore, EDCs that have estrogenic activity or estrogenicity have been emerging as another risk factor for estrogen-responsive cancers (Cabaravdic, 2006, Keri et al., 2007, Aschengrau et al., 1998, Yang et al., 2009, Liu et al., 2015a). Previous investigations revealed that BPA may increase risk of carcinogenesis in breast, brain, and prostate etc. (Soto and Sonnenschein, 2010, Fernandez and Russo, 2010, Duan et al., 2012, Ho et al., 2006).

Moreover, EDCs can affect not only initiation but metastasis of hormone dependent cancers (In et al., 2015, Chen et al., 2015, Lee and Choi, 2013). Metastasis occurs when cancer cells dissociate from the cell to cell junction in a primary tumor site, enter the bloodstream or lymphatic system, and migrate to a secondary site (Gupta and Massague, 2006, Wen et al., 2011). It is a key process in cancer progression and the major cause of death from cancer (McGuire, 2016). The epithelial mesenchymal transition (EMT) is a critical process by which epithelial cells lose their cell polarity and cell-cell adhesion and acquire mesenchymal phenotype, leading to enhanced migratory capacity of cancer cells for metastasis (Son and Moon, 2010). The EMT process has been considered to be closely associated with malignant transformation and the initiation of cancer metastasis (Thiery et al., 2009, Chaffer and Weinberg, 2011). In addition to EMT, cancer cells can acquire diverse cell invasion modes for efficient metastatic spread according to the context of epithelial de-differentiation, which is characterized by the further loss of epithelial characteristics. For instance, cancer cells that gain a mesenchymal-like mode of invasion as a result of the completion of EMT can secure the amoeboid invasion mode in the process of mesenchymal-amoeboid transition (MAT) (Gandalovicova et al., 2016). Therefore, cells undergoing the amoeboid invasion mode represent the most de-differentiated state by the loss of both cell-cell and cell-extracellular matrix (ECM) contacts (Gandalovicova et al., 2016).

In the present article, we review the current understanding of cancer progression effects of synthetic chemical EDCs such as BPA, phthalates, TCDD, and triclosan by mainly focusing their roles in the EMT process, a fundamental initiation step of cancer metastasis. For better understanding, the descriptions about the EMT process and related molecular markers and signaling pathways are firstly introduced.

2. EMT and EMT inducing signaling pathways

2.1. EMT and EMT markers

Epithelial cells have uniform cell shape, apical-basal polarity, strong cell-cell adhesion junction, and polarization of the actin cytoskeleton. They normally form single-layered tubes or sheets to cover the organs and to compose glands (Debnath and Brugge, 2005, Pitot, 1976). On the other hand, mesenchymal cells lack the polarization and cell-cell interaction and have a spindle-shaped or fibroblast-like morphology and increased moving ability (Kong et al., 2006, Larue and Bellacosa, 2005, Micalizzi and Ford, 2009). Each cellular type expresses the respective proteins; epithelial cells express high levels of E-cadherin which is a crucial epithelial marker and a transmembrane protein responsible for adherens junction, with its cytoplasmic component linked to the actin cytoskeleton by α- and β-catenin (Tian et al., 2011), whereas mesenchymal cells express N-cadherin, fibronectin, and vimentin, which are mesenchymal markers needed for cellular migration (Shirakihara et al., 2007). N-cadherin (neural cadherin), another adhesion molecule, is associated with an increased invasive potential in cancer invasiveness by mediating interactions between cancer and stromal cells (Nakajima et al., 2004, Hazan et al., 2000). Fibronectin is a stromal ECM protein and has a role in epithelial cell transition from cell-cell contacts to mainly cell-ECM interactions during EMT (Park and Schwarzbauer, 2014). Vimentin as a type III intermediate filament protein contributes to EMT of cancer cells by mediating cytoskeletal organization and focal adhesion maturation (Liu et al., 2015b).

The EMT is a biological process during which epithelial cells lose their cell polarity and cell-cell junction as well as acquire migratory and invasive characteristics to become mesenchymal cells (Lamouille et al., 2014). It plays important roles in numerous developmental processes, wound healing, fibrosis, and cancer metastasis (Phua et al., 2013, Kalluri and Weinberg, 2009). Especially, tumor cells need the invasion to other sites for cancer progression and metastasis, which is initiated by the EMT process (Kalluri and Weinberg, 2009): primary cancer cells preferentially lose their cell-cell adhesion and gain mesenchymal properties through E-cadherin repression to be transformed to migratory and invasive cancer cells, which break through the basement membrane, enter the bloodstream through intravasation, exit the bloodstream to form micrometastases at the metastatic sites, and finally undergo mesenchymal epithelial transition (MET), the reverse process of EMT, to form malignant, secondary tumors (Gunasinghe et al., 2012, Benesch et al., 2016).

As E-cadherin is a key epithelial marker that enables the cells to maintain epithelial phenotypes, the EMT event is induced by E-cadherin loss, which can be carried out by many transcription factors (TFs) that can repress E-cadherin expression (Peinado et al., 2007, Yang and Weinberg, 2008): TFs such as Snail 1, Snail 2 (commonly known as Slug), ZEB1, ZEB2, Kruppel-like factor 8 (KLF8), Twist, lymphoid enhancer binding factor-1 (LEF-1), and fork-head box protein C2 (FOXC2) can bind to E-cadherin promoter and repress its transcription directly or indirectly. Snail and ZEB proteins are zinc finger transcriptional repressors that can bind to E-box of an E-cadherin promoter region to repress the expression of E-cadherin and induce the tightly bound epithelial cells to break loose from each other and to become mesenchymal cells (Peinado et al., 2007, Villarejo et al., 2014). Twist is a basic helix-loop-helix transcription factor that can directly or indirectly bind to the E-box elements on the E-cadherin promoter to induce the transcriptional repression of E-cadherin (Yang et al., 2004). As another zinc-finger transcription factor, KLF8 represses the promoter of E-cadherin independent of E boxes through direct binding to the GT box in the promoter (Wang et al., 2007). In contrast to a potent ability to repress E-cadherin expression either directly or indirectly of these EMT-inducing TFs, FOXC2 has been reported to have a key different functional trait: it redirects the E-cadherin from the plasma membrane to the cytoplasm to induce the mesenchymal