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Recent advances on the stimulatory effects of metals in breast cancer

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ABSTRACT

Certain environmental chemicals may accumulate in human serum and tissues eliciting estrogenic and/or carcinogenic effects. Therefore, there is heightened interest in determining whether environmental chemicals may increase the risk for endocrine-related tumors like breast cancer. For instance, metals as cadmium, zinc, copper, iron, nickel and aluminum have been shown to mimic estrogen action. Moreover, the exposure to these chemicals has been reported to stimulate diverse malignancies including breast cancer, which is the most common tumor in women worldwide. In this review, we summarize the epidemiologic and experimental evidence regarding the association between the exposure to some trace elements and breast cancer risk. We also address recent insights on the molecular mechanisms involved by metals in breast tumorigenesis.

1. Introduction

Breast cancer is mainly stimulated by endogenous estrogens (Yager and Davidson, 2006), however numerous environmental estrogen-like compounds may also contribute to the progression of this malignancy (Colborn et al., 1993; Giulivo et al., 2016). For instance, certain phytoestrogens activate the classical estrogen receptor (ER) and the G protein estrogen receptor (GPER) (reviewed in Prossnitz and Arterburn, 2015). Likewise, various nonsteroidal chemicals named xenoestrogens trigger diverse transduction pathways as the endogenous estrogens, therefore contributing to the development of breast cancer (Byrne et al., 2013; Fucic et al., 2012; Jobling et al., 1995; Prossnitz and Arterburn, 2015). In this regard, the term "metalloestrogens" has been used to identify small ionic metals and metalloids that are able to activate ERα, mimicking the actions of physiological estrogens and then stimulating breast cancer (Darbre, 2006). Many reports have demonstrated a relation between the exposure to metals and an increased risk of breast cancer (Florea and Büsselberg, 2011), however the matter is still controversial as some metal-derived compounds have displayed beneficial effects in different tumors including breast cancer (Florea and Büsselberg, 2011). The exposure to metals mainly occurs through environmental contamination of food, groundwater, drinking water, air and soil (Augustsson et al., 2015; Chowdhury et al., 2016; Peña-Fernández et al., 2014) as well as by diverse consumer products (Bocca et al., 2014; Iwegbue, 2015). Here, we recapitulate recent findings on the role exerted by certain metals in the progression of breast cancer. In particular, we dissect the molecular mechanisms by which metallic compounds may contribute to important processes toward the development of breast cancer.

2. Breast cancer

Breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer death in women, in particular it accounts for 25% of all tumor cases and 15% of cancer deaths among females worldwide (Spitale et al., 2009; Stewart and Wild, 2015). Breast tumor is characterized by high genetic heterogeneity, disease aggressiveness and clinical features in diverse populations of patients (Simpson et al., 2005). Studies on gene expression profiling for invasive breast carcinoma lead to the classification into 5 following subtypes: luminal A, luminal B, normal breast-like, human epidermal growth factor receptor 2 (HER2) overexpressing

Abbreviations: cAMP, cyclic adenosine monophosphate; EGFR, epidermal growth factor receptor; ER, estrogen receptor; ERK, extracellular signal-regulated kinases; FGF2, fibroblast growth factor 2; GPER, G protein estrogen receptor; HER2, human epidermal growth factor receptor 2; HIF-1α, hypoxia-inducible factor-1α; IL-1α, interleukin-1α; PR, progesterone receptor; VEGF, vascular endothelial growth factor.

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and basal-like (Perou et al., 2000; Sørlie et al., 2001; Sorlie et al., 2003). Each subtype may occur upon exposure to different risk factors, presents distinct histopathological and clinical features, displays peculiar outcome and therapeutic responses (Blows et al., 2010; Desmedt et al., 2009; Iwamoto and Pusztai, 2010; Sotiriou and Pusztai, 2009; Tang et al., 2008; Weigelt et al., 2010). As prognostic factors and biomarkers for breast cancer classification, ER, progesterone receptor (PR), HER2, epidermal growth factor receptor (EGFR), Ki-67 and cytokeratin (CK) have been mainly proposed and used (Dai et al., 2016; Fulford et al., 2006; Parsa et al., 2016; Tang et al., 2008). Standard treatment options for early, localized or operable breast cancer may include surgery, pre-operative systemic therapy, post-operative radiation and/or systemic therapy (Khatcheressian et al., 2006). Much interest has been recently given to ER, PR and HER2 negative breast tumors (triple-negative breast cancer, TNBC), which exhibit a poor outcome respect to other breast cancer subtypes (Sharma, 2016). TNBCs show several potential molecular targets like BRCA1/2 mutations, the androgen receptor and rare genomic alterations (Bianchini et al., 2016). Genomic changes have also been reported in the least frequent but the most severe breast tumor called inflammatory breast cancer (IBC) (Van Laere et al., 2007; Zell et al., 2009). For instance, it has been suggested that the aggressive biological characteristics and weaker prognosis of IBC may depend on over-expression of certain genes like HER2 and downregulation of others as ER and PR (Van Laere et al., 2007; Zell et al., 2009).

3. Risk factors for breast cancer: the role of metals

The identification of women with high breast cancer risk is important toward early treatment options (Visvanathan et al., 2009). Likewise, knowing the molecular mechanisms involved in breast carcinogenesis could contribute to the aforementioned assessment (Adami et al., 1995; Persson, 2000). Increasing age, family history of breast cancer, major inheritance susceptibility, breast density, hormone-based therapies, exposure to ionizing radiation, obesity and alcohol consumption are associated with a major risk of breast tumor (Valle et al., 2015). Besides, an excessive and/or prolonged exposure to estrogens has been well established to play a key role in the development of breast cancer (Ascenzi et al., 2006; Deroo and Korach, 2006; Hankinson et al., 2004; Key et al., 2002). Estrogens regulate important physiological processes in the reproductive, nervous, immune, vascular, muscular, skeletal and endocrine systems (Hall et al., 2001). Estrogen signaling is mainly mediated by ERα and ERβ, which interact with estrogen responsive elements (EREs) located within the promoter regions of target genes (Ascenzi et al., 2006; Sanchez et al., 2002). Activated ERs may regulate gene transcription also through the association with other transcription factors, including AP-1 and Sp-1 (Dahlman-Wright et al., 2006). It has been reported that membrane-bound populations of ERs mediate rapid signaling responses to estrogens as cAMP production, calcium mobilization, ion channel and protein kinase activation that lead to gene modulation (Adlanmerini et al., 2014; Pedram et al., 2014). Additionally, ER action can occur in a ligand-independent manner through the involvement of growth factors transduction signaling (Kato, 2001; Levin, 2002). In recent years, a member of the G protein coupled receptor (GPCR) family named G protein estrogen receptor (GPER/GPR30) has been involved in estrogen signaling in different normal and malignant tissues, including breast cancer (Avino et al., 2016; Bartella et al., 2016; De Francesco et al., 2014; De Marco et al., 2016; Gaudet et al., 2015; Prossnitz and Barton, 2011; Santolla et al., 2015; Vivacqua et al., 2015). In this regard, it has been shown that GPER may trigger a network of transduction pathways as the transactivation of EGFR and the activation of MAPK and PI3K-dependent signaling, which mediate gene transcription and important biological responses like proliferation and migration of breast cancer cells (Lappano et al., 2014; Maggiolini and Picard, 2010; Prossnitz and Maggiolini, 2009). It is worth to mention that both ERα and GPER may cooperate toward breast cancer progression and endocrine resistance by interacting with the EGFR and insulin-like growth factor-I receptor (IGF-IR) transduction pathways (De Marco et al., 2013; Lappano et al., 2013; Pisano et al., 2016; Voudouri et al., 2015).

Numerous studies have suggested that certain environmental factors like phytoestrogens, xenoestrogens and metalloestrogens may exhibit estrogen-like properties, including the ability to influence breast carcinogenesis (Byrne et al., 2013; Hess-Wilson et al., 2006; Sirotkin and Harrath, 2014; Wallace, 2015). For instance, metalloestrogens are small ionic metals and metalloids that trigger ERα-mediated effects (Martin et al., 2003). In this vein, specific amino acids within the hormone-binding domain of ERα have been identified as potential interaction sites with divalent metals and metal anions (Garcia-Morales et al., 1994; Martin et al., 2003). Metalloestrogens fall into the two following subclasses: oxyanions that include arsenite, antimony, nitrite, selenite as well as vanadate and bivalent cations that include cadmium, calcium, cobalt, copper, nickel, chromium, lead, mercury and tin (Byrne et al., 2013). Metals elicit diverse biological functions from being essential to toxic and carcinogenic. Chromium, cobalt, copper, zinc, arsenic, selenium and nickel are essential metals that play an important role in metabolism and respiration, membrane integrity and permeability, cell growth and viability (World Health Organization, 1996). Cadmium, lead, mercury and tin are nonessential metals that exert toxic effects mimicking or blocking the function of essential metals (Waalkes et al., 2000). Cadmium, chromium and nickel are well acknowledged carcinogens, while copper, lead and mercury have been classified as probable carcinogens or co-carcinogens (Byrne et al., 2013; Hayes, 1997; Navarro Silvera and Rohan, 2007). Below are discussed the mechanisms by which certain metals may stimulate breast tumorigenesis, as summarized in Fig. 1.

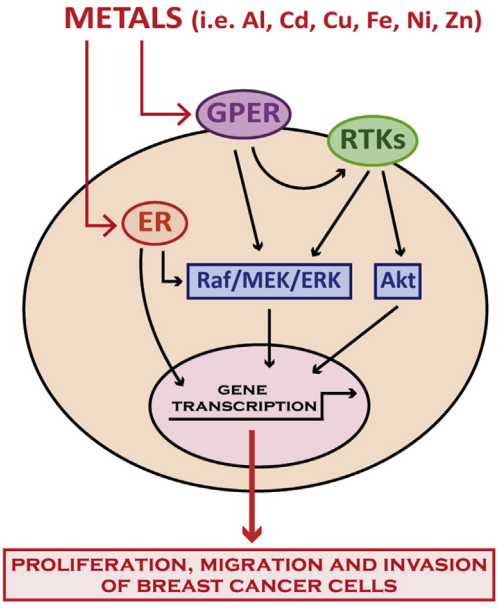

Fig. 1. Schematic representation of estrogen receptor (ER), G protein estrogen receptor (GPER) and tyrosine kinase receptors (RTKs)-mediated signaling of certain metals toward the proliferation, migration and invasion of breast cancer cells.