Mitochondrial oestrogen receptors and their potential implications in oestrogen carcinogenesis in human breast cancer

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Abstract

Background. Prolonged exposure to oestrogens (17β-estradiol) (E2), xenoestrogens, hormone replacement therapy and contraceptives has been recognized as a key aetiological factor of human breast cancer. The biological and carcinogenic effects of E2 and xenoestrogens are mediated via oestrogen receptors alpha (ERα) and beta (ERβ). Both receptors are localized in the nucleus of E2-targeted cells including human breast cells where they are involved in the regulation of nuclear gene expression. There is increasing evidence indicating that a small fraction of total cellular ERs, particularly ERα, are localized in the membrane of E2-targeted cells where they mediate E2-dependent and/or E2-independent rapid and non-nuclear genomic signal pathways.

Results. The present work will present evidence that: (1) there is mitochondrial localization of ERs in human breast cancer cells; (2) there is a functional role of the mitochondrial ERs in the regulation of mitochondrial genes encoding respiratory chain proteins.

Conclusions. The potential implications of the mitochondrial ER-mediated pathways in oestrogen carcinogenesis, particularly in stimulation of cell proliferation and inhibition of apoptosis, in human breast cancer and the potential nutritional and environmental perspectives of these effects will be addressed.

Key words: Breast cancer, oestrogen receptors, oestrogen carcinogenesis, mitochondria

Introduction

Prolonged exposure to oestrogens, e.g. 17β-estradiol (E2), xenoestrogens, hormone replacement therapy and oral contraceptives, has been recognized as a key aetiological factor of human breast cancer [1,2]. It is generally thought that the physiological and pathological effects of oestrogens, endogenous and/or exogenous, are mediated by oestrogen receptors (ER) α and β, localized predominantly in nuclei, on the expression of nuclear oestrogen responsive genes [3]. The regulatory actions of ERα and ERβ have been extensively studied in nuclear gene transcription [3–5] and more recently in cell membrane signal transduction [6,7]. In this paper, we focus on a newly discovered...
mitochondrial localization of ERα and ERβ in human breast cancer cells and human breast epithelial cells and discuss the potential implications in human breast cancer, nutritional and environmental perspectives.

**Mitochondrial localization of ERα and ERβ**

During the last decade, a number of studies reported detection of a various degrees of immunochemical staining for both ERα and ERβ in the cytoplasm of a variety of cells and tissues [8]. However, it is unknown from these reports whether the receptors reside in the cytoplasm or in cytosolic organelle(s). Monje and colleagues [9,10] were the first reporting the detection of ERα and ERβ in mitochondria of rat ovarian and uterine tissue. A number of recent studies have definitively demonstrated the presence of ERα and ERβ in mitochondria. For instance, Chen et al. [8,11] detected ERα and ERβ in mitochondria of MCF-7 cells. They demonstrated that ERβ is the major ER isoform in mitochondria of MCF-7 cells and that E2 significantly enhanced levels of ERα and ERβ in mitochondria. Using confocal microscopy and immunogold electron microscopy, they observed that ERα and ERβ are localized in the mitochondrial matrix. Pedram et al. [12] confirmed the mitochondrial localization of ERα and ERβ in MCF-7 cells. Recently, Chen et al. [13] observed predominant mitochondrial localization of ERβ in immortal and transformed human breast epithelial cells (HBEC) and a shift of ERβ from mitochondria to nuclei during the progression of transformation and tumourigenesis of HBEC. Several groups of investigators detected ERβ in mitochondria of a number of E2-target cells, including human liver cancer HepG2 cells [14,15]; human osteosarcoma SaOS-2 cells [15], sperm [16], lens epithelial cells [17,18], human cardiomyocytes [19], rat primary neuron, cardiomyocyte [19] and murine hippocampus cells [19,20]. Stirone et al. [21] observed ERα in mitochondria of rat cerebral blood vessels. Interestingly, all of these cells have high demand on mitochondrial energy supply for their proper functions.

**Potential role of mitochondrial ERs in E2-induced expression of mtDNA genes**

The presence of ERα and ERβ in mitochondria suggests that the mitochondrial ERs may play a direct role in E2-regulation of mitochondrial respiratory chain (MRC) structure and functions. Mitochondria contain their own DNA (mtDNA), which codifies a small, but essential number of polypeptides for the oxidative phosphorylation system. The human mitochondrial genome (see Figure 1) is extremely economic showing a compact gene organization. The coding sequences for two ribosomal RNAs (12S and 16S rRNAs), 22 transfer RNAs (tRNAs) and 13 polypeptides are contiguous and without introns. A single major non-coding region, called the D-loop region, contains the main regulatory sequences for transcription and replication initiation. MtDNA is first transcribed to a larger mitochondrial transcript precursor, from which 13 mRNAs, 22 tRNAs and two rRNAs are derived. The mRNAs are translated into 13 proteins within mitochondria [22,23]. The mitochondrial genes are primary sites for the action of glucocorticoid and its receptor [24]. It has been reported that in several types of cells oestrogens enhance the transcript levels of both nuclear-encoded and mitochondrial DNA (mtDNA)-encoded proteins consisting of MRC and that these effects are associated with increased MRC activity and are likely mediated via ERs [21,25,26]. Our recent study [13] indicates that the mitochondrial ERβ is involved in E2-induced synthesis of mitochondrial respiratory chain proteins in HBEC.
In summary, several lines of evidence demonstrate: (1) the mitochondrial localization of ERs, particularly ERβ, in human breast cancer MCF-7 cells and immortal human breast epithelial cells (MCF-10F cells); and (2) the potential involvement of the mitochondrial ERs in E₂-induced transcript levels of mtDNA-encoded genes. Through induction of MRC protein synthesis, E₂/ERs may contribute to the preservation and maintenance of mitochondrial structure and function and thus to the other energy-dependent physiological processes. We propose (see Figure 2) that once inside the cells, binding of E₂ to ERα and/or ERβ enhances their translocation to the nucleus where they stimulate the expression of nuclear genes encoding for MRC proteins and nuclear factors for mtDNA transcription such as mitochondrial transcription factor A (mtTFA) and accessory factors for assembly of

Figure 1. Human mitochondrial genome and genes encoding proteins for mitochondrial respiratory chain (MRC) complexes. (A) Human mitochondrial genome, relative locations of genes encoding MRC proteins, rRNAs and tRNAs are shown. (B) Genes encoding proteins for MRC complexes D-loop: displacement loop; CO I, II and III: cytochrome c oxydase sub-units I, II and III; ND1, ND2, ND3, ND4L, ND4, ND5 and ND6: NADH dehydrogenase sub-units 1, 2, 3, 4L, 4 5 and 6; cyt b: cytochrome b; ATPase 6/8: ATP synthase sub-units 6 and 8.
MRC complexes. These proteins are synthesized in cytosols and imported into mitochondria. On the other hand, binding of E2 to ERβ (or ERα) in cytosol enhances the import of ERβ or ERα into mitochondria where it stimulates mtDNA transcription, leading to increased mtDNA-encoded MRC protein synthesis. Assembly of both nuclear and mtDNA-encoded sub-units into MRC complexes enhances MRC activity [14,16], leading to increased ATP and ROS, which are involved in the control of cell proliferation and apoptosis. However, several important questions pertaining to this novel E2/ER-mediated mitochondrial pathway need to be addressed: (1) are either or both ERα and ERβ directly involved in E2-induced MRC protein synthesis; (2) Do ERs mediate the E2-induced MRC protein synthesis and activity via their interactions with mtTFA and p53 within mitochondria; and (3) Importantly, what are the pathological implications of the over-abundance of E2/ER-mediated mitochondrial effects in breast cancer cells? These questions warrant further investigation.

Potential physiological and pathological implications in human breast cancer

Mitochondria are the ‘power plant’ of the cells. Thus, they are essential to the proper functions of the cells. It is not surprising that abnormal mitochondrial functions are implicated in many diseases including cancers.

Imagine a major city with half its power plants shut down. At best, such conditions would produce a ‘brown out’ with large sections of the city working far below
optimum efficiency. Now, imagine your body with one-half of its energy producing facilities shut down? The brain will be impaired, vision would be dim, muscle would twitch spastically or would be too weak to allow his body to work or write, his heart would be weakened, and he would not able to eat and digest his food. For large number of people, especially children, this is precisely the situation in which they find themselves due to defects in mitochondria, organelles found in every cells of the body which are responsible for body’s energy production. Mitochondrial diseases compromise their live and can be fatal (quoted from Statement of United Mitochondrial Disease Foundation (UMDF)).

Now imagine what will happen when ‘some stimulating molecules’ persistently drive your body’s power plant to produce too much energy power, more than is actually needed? It is quite possible that the enhanced mitochondrial effects driven by these ‘stimulating molecules’ (e.g. oestrogens, phytoestrogens, environmental oestrogens and other stimuli) could have a wide spectrum of physiological and pathological influences on the functions the cells. Thus, E2/ER-mediated stimulation of the syntheses of MRC proteins and energy metabolism/utilization will confer a number of potentially important physiological and pathological implications. Deficiency and over-abundance of these mitochondrial effects could lead to different consequences, depending on the types/ages of tissues and cells where the energy requirement, the availability and amounts of E2 and ERs vary.

These effects may have important implications in E2 carcinogenesis in human breast cells. Human breast cells are exposed to relative high levels of E2 due to the in situ synthesis of E2 by local aromatase activity [27,28]. E2 is aetiologicaly important in the development and progression of human breast cancer. There are several lines of epidemiological evidence suggesting the importance of physical activity and caloric limitations in reducing breast cancer risk. A potential link exists between altered energy balance and increased breast cancer risk, i.e. breast cancer risk is increased in women who have higher energy intake and lower energy expenditure, whereas the breast cancer risk is lower in women who have lower energy intake/higher energy expenditure. This evidence is consistent with the hypothesis that persistent E2/ER-enhanced mitochondrial energy metabolism/utilization contributes to increased breast cancer risk due to over-production of ATP and reactive oxygen species (ROS).

In addition to stimulating MRC protein synthesis and MRC activity, as described above, oestrogens are known to enhance the expression of genes encoded for several key enzymes/proteins involved in energy metabolism pathways, including glucose transport/glycolysis [29,30], tricarboxylic acid (TCA) cycle [21,31,32], fatty acid (FA) β-oxidation [33–35] and ATP-ADP transport shuttle [36]. The persistent stimulation of these pathways leads to abnormal energy production and utilization, causing over-production of ATP and superoxide, reactive oxygen species (ROS).

While ATP is required for the normal function of the cells, over-abundance of ATP may lead to pathological consequences. Cell survival, growth and proliferation required large amounts of ATP supply because a large number of cellular processes are involved in cell proliferation, e.g. cell cycle progression, the biosynthesis pathways, kinase-mediated signal transduction pathways and cross-membrane ion channels/transporters, are all energy-dependent. Over-abundance of ATP may accelerate these biochemical processes. For instance, over-expression of mtDNA-encoded genes for MRC proteins has been observed in rapidly proliferating cells and the cell proliferation rate was associated with enhanced mtDNA-encoded gene expression and MRC activity [37]. Therefore, the E2/ER-mediated
Mitochondrial pathway may contribute to enhanced cell proliferation. Several recent studies suggest that over-production of ATP may be related to tumourigenesis [38–40].

**Mitochondrially-derived ROS as the signal molecules up-regulating the expression of growth-related proteins**

In addition to generating ATP, MRC generates the large majority of ROS as a byproduct. A number of recent studies [41–43] have suggested that the mitochondrially-derived ROS can act as the signal molecules regulating the expression of growth-related proteins. For instance, a number of proteins involved in redox-regulated signalling pathways, including A-Raf, Akt, protein kinase C (PKC), MAPK/ERK kinase (MEK), extracellular recognition kinase (ERK) and transcription factors AP-1, nuclear factor κB (NF-κB) and cAMP response element-binding protein (CREB), are targets of both oestrogen and ROS. Felty and Roy [41,42] have demonstrated that oestrogen-induced mitochondrial ROS stimulate redox sensor kinase A-Raf, Akt or PKC, which, in turn, activate transcription factors NF-κB, CREB or AP-1 via the MEK/ERK pathway. E2-induced mitochondrial ROS leading to the activation of cell cycle genes containing AP-1, NF-κB or CREB response elements are involved in the progression of the cell cycle of the oestrogen-dependent cells. In another study, Felty et al. [44] observed that E2-induced ROS formation from mitochondria enhanced cell motility as shown by the increase in cdc42 and activation of Pyk2 and the increased phosphorylation of signalling proteins c-jun and CREB. E2-induced mitochondrial ROS also activated the binding of three oxidant-sensitive transcription factors: AP-1, CREB and nuclear respiratory factor 1. These findings reveal that E2-induced mitochondrial ROS act as signal transducing messengers.

**Potential oxidative damage and mutations to mtDNA and mitochondrial proteins due to enhanced generation of mitochondrial superoxide**

Persistent E2/ER-mediated mitochondrial effects may cause oxidative damage and mutations to mtDNA and mitochondrial proteins due to enhanced generation of mitochondrially derived superoxide. It has been demonstrated that in rat hepatocytes and human liver cancer HepG2 cells, treatment of cells with E2 or ethinyl estradiol (EE) enhanced mitochondrial production of superoxide by several folds and that these effects are mediated via ERs [45,46]. In normal circumstances, superoxide generated by MRC is detoxified by mitochondrial antioxidant systems including mitochondrally localized manganese superoxide dismutase (Mn-SOD)/catalase/glutathione. Since oestrogens also induce MnSOD expression and activity, the increased superoxide generation by E2 can be detoxified by the increased MnSOD activity. However, if the antioxidant system is defective, e.g MnSOD expression and its activity is defective within mitochondria, superoxide generated by E2/ER-induced MRC activity would be accumulated within mitochondria. On the other hand, oestrogens are known to stimulate the expression of the mitochondrial form of the inducible nitrite oxide synthase, which catalyses the generation of nitrite oxite within mitochondria. Superoxide can combine with nitrite oxite (NO\(^{2-}\)) to form a highly toxic species (OONO\(^{-}\)). The increased levels of superoxide itself and/or the increased formation of this highly toxic species (OONO\(^{-}\)) by oestrogens could lead to severe oxidative damages to mtDNA and to the redox, heme-containing proteins located in the inner membrane (see Figure 3). In fact, a number of mutations of mtDNA in human
breast cancer tissues have been reported [47–50]. Some of the mtDNA mutations may lead to gain functions and altered (enhanced) mtDNA transcription was observed in breast cancer tissues [51].

**Contribution of E2/ER-induced mitochondrial effects to E2-mediated inhibition of apoptosis**

Mitochondria integrate a number of cellular apoptotic signal transduction pathways and amplify the apoptotic response [52]. Several lines of evidence suggest that up- or down-regulation of MRC biogenesis and functions is related to the control of apoptosis. For instance, disruption of mitochondrial electron transport and energy metabolism is recognized as an early event in apoptosis [13]. Inhibiting MRC activity in HL60 cells [53] or specifically knocking out mitochondrial transcription factor A (mtTFA) gene in mouse heart tissue, which results in deficiency in mtDNA gene expression [54], is associated with significantly increased in vivo apoptosis. E2 and ERβ are involved in the regulation of apoptosis. For example, E2 inhibits apoptosis in a number of cells [55,56]. We have observed that the increased mtDNA gene expression by EE was associated with increased levels of glutathione in nuclei and mitochondria and the inhibition by EE of TGFβ-induced apoptosis [45,46,57–61]. Wang et al [62] observed that there were more apoptotic cells in the ventricular zone of mice lacking ERβ. Pedram et al. [12] demonstrated that functional mitochondrial ERβ in MCF-7 cells is involved in inhibition of UV-induced apoptosis via activation of mitochondrial MnSOD activity. Hsiesh et al. [63] observed up-regulation of MRC complex IV by ERβ, which was required for anti-apoptosis via mitochondrial signalling in rat heart. Together, these observations imply that the up- and down-regulation of MCR functions is important in controlling the balance between anti-apoptosis and apoptosis. Persistent E2/ERβ-mediated induction of mtDNA transcription will shift the balance toward apoptotic inhibition. This could be one of the mechanisms of E2 carcinogenesis.

![Figure 3. Proposed models for the mitochondrial generation of ROS and the action of antioxidant enzymes within mitochondria.](image)
MRC as important target of tamoxifen and potential implications in tamoxifen resistance

The tamoxifen (TAM) is an anti-oestrogen targeting ERs. TAM has been widely used to treat ER positive breast cancer. However, a major clinical problem of TAM therapy is the development of TAM-resistance (TAM-R) [64]. To date, no prominent mechanisms leading to TAM-R have been identified [65–69]. However, there is evidence suggesting that MRC is a potentially important target for TAM. For instance, it has been shown that TAM has inhibitory effects on oxidative phosphorylation in isolated rat liver mitochondria [70–73] and that tamoxifen interacts with the flavin mononucleotide site of MRC complex I, leading to mitochondrial failure in isolated liver mitochondria [74]. Several clinical trials demonstrate that tamoxifen reduces the risk of heart disease and osteoporosis. The mechanism by which tamoxifen causes cardioprotection is unclear and Zhao et al. [75] observed that pre-treatment of mice with TAM confer a remarkable protection against TNFα-induced mitochondrial damage. Tamoxifen treatment significantly improved the MRC function and enhanced superoxide-scavenging activity of mitochondria. Since TAM can target to MRC, it is likely that altered mtDNA gene expression and MRC function by E2 and oestrogen receptors could be associated with cell transformation [48] and the acquisition of resistance to anticancer drugs [76–82]. TAM treatment of TAM-sensitive breast cancer cells (early passage) resulted in a decrease in mitochondrial function preceding the apoptosis, whereas TAM-R in late passages of these cells correlated with increased mitochondrial activities [83]. These observations suggest that altered mitochondrial functions may contribute to TAM-R. It has been reported that there was an increased ERβ expression in TAM-R breast cancer cells [84] and that low level of ERβ protein predict TAM-R in breast cancer [85]. Chang et al. [86] observed less frequent methylation of ERβ in TAM resistant breast cancers, associated with increased percentage of cells with positive staining of Ki67, the proliferation marker. The ERβcx isoform [87] may have a role in the processing of TAM-R, particularly in the presence of low levels of progesterone receptor [88,89]. It is likely that the mitochondrial ERβ plays a role in TAM-R. This potential mechanism for TAM-R needs to be investigated further.

Nutritional impact

A number of synthetic oestrogens and plant-derived oestrogens, called phytoestrogens, are selective oestrogen receptor modulators. These compounds can induce tissue-specific, time- and dose-dependent oestrogenic or anti-oestrogenic responses. Therefore, the effects of synthetic and/or phytoestrogens on the incidence of breast cancer depend on both the levels and the timing of exposure to these compounds, particularly during stages of mammary gland development that are extremely sensitive to hormone levels.

As mentioned above, lifetime exposure to endogenous oestrogens, e.g. E2, is an established risk factor for breast cancer. Prolonged exposures to other oestrogenic and anti-oestrogenic chemicals may also modify the risk of breast cancer. Epidemiological studies [90] indicate that Asian women have a lower incidence of breast cancer compared with their counterparts in the West. Differences in dietary consumption of soybean products and animal products between Asian and Western women have been suggested to be one of the contributory factors. Asian women intake more soy products enriched in phytoestrogens whereas Western women eat more pork and beef, containing considerable oestrogenic residues. The phytoestrogens and the oestrogenic chemicals in diets could have significant
effects on mitochondrial energy metabolisms: the mitochondrial respiratory chains could be potentially important targets for the phytoestrogens and the oestrogenic chemicals in diets (see Figure 4). Phytochemicals in soybean products and other plant-derived products (e.g. grapes and red wine), including genistin, genistein, daidzein, bioanin A and resveratrol (RSV), have a various degrees of oestrogenic and/or anti-oestrogenic activities. Several studies suggested that oestrogenic phytochemicals confer effects on mitochondrial structure and functions. For instance, Zhai et al. [91] investigated the effects of phytoestrogen on global myocardial ischemia-reperfusion injury of female rats. Their results indicate that diets containing phytoestrogen extract improve mitochondrial respiratory chain activity and play a cardioprotective role in global myocardial ischemia-reperfusion in female rats. The studies by Zhang and Ramirez [92] also indicate that mitochondrial respiratory chain, particularly mitochondrial F0F1-ATPase/ATP syntheses, is a target for several dietary phytochemicals.

Diminished mitochondrial oxidative phosphorylation and aerobic capacity are associated with reduced longevity. Lagouge et al. [93] tested whether resveratrol (RSV), a

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**Figure 4.** Two potentially important targets in MRC for EDCs: genes encoded by nuclear DNA (nDNA) are indicated by green; genes encoded by mitochondrial DNA (mtDNA) are indicated by blue. The number indicates the number of protein sub-units. The red, bold arrows indicate the potential effects of E2 on the expression of nDNA- and mtDNA-MRC proteins. Potential targets for oestrogenic EDCs are marked by the block symbols. CoQ: cytochrome co-enzyme Q; NRF, nuclear respiratory factor; PGC-1: peroxisome proliferator-activated receptor gamma coactivator-1; The radio indicates the number of mtDNA-encoded sub-units to the number of nDNA-encoded sub-units.
phytoestrogen enriched in grapes and red wine which is known to extend lifespan, impacts mitochondrial function and metabolic homeostasis. These investigators observed that treatment of mice with RSV significantly increased their aerobic capacity, as evidenced by their increased running time and consumption of oxygen in muscle fibres. They further demonstrated that these RSV’s effects were associated with an induction of genes for oxidative phosphorylation and mitochondrial biogenesis and were largely explained by an RSV-mediated decrease in PGC-1alpha acetylation and an increase in PGC-1alpha activity. This mechanism is consistent with RSV being a known activator of the protein deacetylase, SIRT1, and by the lack of effect of RSV in SIRT1\(^{-/-}\) MEFs. Importantly, RSV treatment protected mice against diet-induced-obesity and insulin resistance. These pharmacological effects of RSV combined with the association of three Sirt1 SNPs and energy homeostasis implicates SIRT1 as a key regulator of energy and metabolic homeostasis. Therefore, in addition to their nuclear effects, oestrogenic chemicals in diets could have profound effects on mitochondrial energy metabolism.

**Potentially important target for environmental endocrine disrupter chemicals**

An endocrine disrupter chemical (EDC) is an exogenous substance that alters the function of the endocrine system, provoking adverse health effects. A number of environmental chemicals have oestrogenic or anti-oestrogenic activities. These chemicals, named xenoestrogens, are the most studied EDCs and they follow the similar mechanisms of action to that of \(E_2\). The known EDCs include dioxins/PCBs, DDT/DDE, bisphenol A, phthalates, alkylphenols and metalo-oestrogens in tobacco (a mixed source of EDC-related endocrine disorders). The oestrogenic responses of environmental EDCs, whether weak or strong, will add extra oestrogenic burden to biological systems including animals and human. Because of their widespread distribution, the potential exposure for humans and animals to EDCs is high. Increasing exposure to EDCs is a potentially contributing factor to breast cancer risk. Only a limited number of EDCs have been used to assess the biochemical and molecular changes at the cellular level. To date, the oestrogenic activities of environmental oestrogenic pollutants has been based on the property of these compounds to bind to oestrogen receptors (ERs), either ER\(\alpha\) or ER\(\beta\), and to act subsequently as transcription factors when binding to the oestrogen response element (ERE) in the DNA. New evidence indicates that the definition of oestrogenicity for a chemical should take into account other oestrogen receptors as well as new signalling pathways [94]. These include the activation of additional transcription factors as well as the action of xenoestrogens through oestrogen receptors located outside the nucleus: in the plasma membrane, mitochondria and probably the cytosol [94]. Currently employed laboratory tests measure the effects solely via the classical nuclear-genomic pathways of EDCs. Because \(E_2\), EDCs and ERs could act in nucleus, plasma membrane and mitochondria, there are missing pathways whereby these EDCs operate. One of them is the disturbance by EDCs on \(E_2\)/membrane ER-mediated rapid, non-nuclear genomic pathways. Another important one that could be disturbed by EDCs is \(E_2\)/ER-induced MRC protein synthesis and MRC energy metabolism, which could be more directly related to obesity and breast cancer. As indicated in Figure 4, there are two potentially important targets for EDCs: (i) the \(E_2\)/nuclear ER-mediated nDNA-encoded MRC proteins and other protein factors/transcription factors involved in the regulation of mtDNA transcription, translation and MRC complex assembly, and (ii) the \(E_2\)/mitochondrial ER-mediated mtDNA-encoded MRC proteins. Full investigation of the effects of EDCs on MRC protein...
synthesis could lead us to identify the reliable mitochondrial markers for EDCs and to develop unique, accurate, rapid and cost effective methods for assessing the potential EDC activity during development of breast cancer.

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References

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