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Estrogen, phospholipase A and breast cancer

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TABLE OF CONTENTS

1. ABSTRACT

The development of breast cancer is promoted by diverse factors that impact on intracellular signaling to promote proliferation and cell survival. The role of eicosanoid signaling through prostaglandin release and the up-regulation of cyclooxygenase-2 (COX-2) is established, however, the impact of phospholipase A (PLA) activity and over-expression is less certain. Here we review current literature concerning the role of PLA in breast cancer and describe how eicosanoid signaling may be a facet of estrogen-stimulated breast cancer etiology and progression.

2. INTRODUCTION

Eicosanoid signaling has been implicated in the development and progression of cancers in different tissues including the mammary gland. Over expression of arachidonic acid metabolizing enzymes, principally cyclooxygenase-2 (COX-2) can be detected in many breast cancer tumors and correlates with poor prognosis (1, 2). The merit of chemotherapeutic intervention using COX-2 inhibitors in the treatment of breast cancer was first demonstrated in a series of animal model studies (3-6). Recent epidemiological evidence shows that chronic use of COX-2 inhibitors by patients being treated for arthritis resulted in a significantly reduced risk of breast cancer development (7). Clinical trials are currently evaluating the efficacy of COX-2 inhibitors in combination with other chemotherapeutic strategies for breast cancer treatment, reviewed in (8). The contribution of phospholipase A (PLA) activity to the development of breast cancer is less clear. The published data is often conflicting in its attribution of promotional or inhibitory effects to PLA reaction products on breast cancer progression. Recent data has suggested a link between eicosanoid signaling and estrogen stimulated signaling events in breast cancer cells both at the level PLA and COX activity.

Breast cancer is the most common form of cancer experienced by women and affects 1 in 9 of the global female population over their lifetime. In the year 2000 more than one million people were diagnosed with this disease worldwide. Breast cancer is a significant cause of death amongst women post menopause, however, the mortality rates have declined in recent years, especially in younger patients through early diagnosis and more effective treatment (9). Inherited genetic factors, predominantly mutation of the *BRCA1* and *BRCA2* genes account for 10% of all cases of breast cancer and 25 to 40% of breast cancers among younger women (10). Sporadic incidences account for the vast majority of cases and are associated with diverse risk factors that have a biological or social basis. Factors that correlate with increased lifetime exposure to estrogens are major predisposing factors in breast cancer development that are related to the hormone-dependent proliferation of the cells of the mammary gland. Since Beatson first recognized the link between ovarian function and breast cancer in 1896 (11), considerable epidemiological and clinical evidence has supported the link between cumulative and sustained exposure to estrogens with increased risk of breast cancer development. At least some of the mechanisms by which estrogen promotes breast cancer have been elucidated in recent years. Estrogen stimulates cell proliferation in target tissues including the mammary gland through receptor-dependent up-regulation of proliferative signaling intermediates. The increased rate of cell proliferation increases the frequency of genetic mutations that are accumulated by daughter cells and which may ultimately lead to carcinogenesis. The second mechanism is a direct, receptor-independent genotoxic effect elicited by reactive intermediates generated through aromatase, cytochrome P450-mediated metabolic activation, which increase the rate of genetic mutation. This is supported by the observation that estrogen promotes mammary tumor development in ERα knockout mice (12). A third mechanism is postulated to involve a compromise of the DNA repair system, leading to accumulation of genetic lesions, such as locus deletions in chromosomes 9 and 4 that are essential for tumorigenesis (13).

The correlation between COX-2 activity and progression in estrogen-dependent breast cancer is at least in part attributable to PGE_2-dependent up-regulation of aromatase activity (14). There are other facets of the eicosanoid biosynthetic pathway that potentially impact on breast cancer development and fully elucidating these effects will allow for more refined treatment regimes. The aim of this review is to summarize knowledge about PLA activity in breast cancer and how it may be coupled to the more established effects of estrogen on tumor etiology and progression.

3. MECHANISMS OF ESTROGEN ACTION

The most active estrogenic hormone, 17-beta-estradiol (E_2) is synthesized through testosterone aromatization in the ovary and in other tissues including the mammary gland. Circulatory levels of E_2 decrease by 90% after menopause, however, mammary tissue levels remain constant through peripheral aromatization (15). E_2 plays a central role in the control of important reproductive and homeostatic functions in the body. It is now well recognized that the impact of E_2 on human physiology is much wider than previously thought, encompassing the differentiation of tissues in diverse organ systems. E_2 modulates cell proliferation, apoptosis and inflammation as well as having pronounced effects on brain and cardiovascular functions. Estrogens can modulate pathogenesis of different hormone-dependent diseases (16), and the mitogenic activity of these hormones exerts a critical role in the etiology and progression of different human cancers, including those of the breast (17), uterus (18), prostate (19), colon (20) and lung (21). In particular, the proliferative effects of E_2 on breast tissue and the contribution of E_2 to breast cancer development has been the subject of intense investigation (22-24).

The biological effects of E_2 are mediated by two receptors referred to as ER-alpha and ER-beta, which are both members of the nuclear receptor (NR) super-family (ER-alpha in the sub-group NR3A1 and ER-beta in sub-group NR3A2, respectively). ER-alpha was first identified by Jensen and Jacobson during their studies on the effects of E_2 in the uterus (25) and then cloned in the mid 1980's (26). The second ER, ER-beta, was cloned in 1995 from a prostate cDNA library (27-29). The discovery of ERβ opened new avenues in the understanding of the pleiotropic effects of E_2 both in the female and in the male. ER-alpha and ER-beta have markedly different tissue distributions, and they have different roles in general development and physiology, as shown in knockout mouse models (30). The cellular mechanisms underlying the broader effects of E_2 were, initially, accounted for entirely by the ability of ERs to modulate gene expression (31). E_2 binds to ER-alpha and ER-beta, which shuttle between the nucleus and cytoplasm acting as ligand-dependent transcription factors that modulate the expression of estrogen responsive genes including COX-2 (32). In the "*genomic"* model, after ligand binding, ERs undergo dramatic structural modifications leading to receptor dimerization followed by translocation to the nucleus where they bind to the ERE sequences located in the promoter of E_2-responsive genes. ER-regulated gene transcription can also occur in a manner that does not require direct DNA binding; this is referred to as "*indirect genomic mechanism"* and it occurs through the interaction of ER with specific transcription factors such as stimulating protein 1 (Sp1) and activator protein 1 (AP-1) which in turn direct gene transcription interacting with different promoter elements such as GC-rich and TRE. In MCF-7 breast cancer cells, a significant number of genes responding to E_2 were found by DNA micro-array analysis and some of them have been characterized (33). Among these, tumor-associated genes, oncogenes and tumor promoting genes are generally up-regulated, whereas the genes related to tumor suppression are down-regulated (33, 34). This is consistent with the effects of E_2 in the promotion of tumor cell growth (35, 36).

The *genomic* action of steroid hormones occurs after a time lag of at least 2 hours after E_2 stimulation and explains some of hormone functions in physiological and

pathological situations (37, 38). However, it has been apparent for many years that not all biological effects of steroids are accomplished via direct regulation of gene expression, since E_2 can also induce activation of signal transduction pathways in a time frame (seconds to minutes) that is too rapid to be mediated by protein or RNA biosynthesis and with a mechanism that is not abrogated by transcriptional inhibitors. These E_2 rapid actions received major attention in 1967 when a physiological dose of E_2 was reported to increase the uterine cAMP level in ovariectomized rats within 15 seconds (39), and since then the rapid, *non-genomic* actions of E_2 were intensively studied. The distinction between *genomic* and *non-genomic* mechanisms is not a rigid one. The rapid membrane initiated pathways also modulate gene transcription and the integration between signaling and transcription is a key feature of the estrogen response, providing a fine degree of control in the regulation of the final cellular response (40). Many of the signaling pathways lead to modulation of ion fluxes across membranes and stimulation of kinase and phosphatase cascades, which influence such processes as proliferation in various cell types including the mammary epithelium. Recent studies suggest that E_2 could mediate a rapid increase in intracellular Ca^{2+} concentration through activation of ERK1/2 MAPK, $cPLA_2$-alpha and COX-2, leading to PGE_2 production and activation of downstream proliferative signals (41). The mechanism underlying these effects still needs to be fully elucidated. The involvement of plasma membrane-associated ERs in the rapid, E_2-induced proliferative effect is also unclear. ER-alpha, ER-beta and GPR30 are putative receptors that have recently been linked to E_2-induced rapid signaling pathways. A crosstalk between ERs, GPR30 and the EGFR/HER2 family of growth factors receptors has also been correlated to the development of resistance to hormonal therapy in breast cancer (42).

4. ESTROGEN AND THE EICOSANOID SIGNALING PATHWAY

The Arachidonic Acid (AA)-based eicosanoid signaling pathway plays an important role in normal cellular homeostasis and, under certain circumstances, it can influence human pathologies such as inflammation and cancer. This pathway is also involved in the rapid estrogen responses in the colon (43) and in embryonic membranes (44). The Phospholipase A_2 (PLA_2) super-family is a group of enzymes that catalyze the hydrolysis of membrane phospholipids to release AA and other lipid second messengers. There are three major groups of PLA_2 isoforms: the Ca^{2+}-dependent secretory PLA_2 ($sPLA_2$), the Ca^{2+}-independent intracellular PLA_2 ($iPLA_2$) and the Ca^{2+}-dependent cytosolic PLA_2 ($cPLA_2$) (45). The $cPLA_2$-alpha isoform, in particular, is ubiquitously and constitutively expressed in most cells and its high selectivity on membrane phospholipids containing AA has been the reason for a large number of recent studies on the link between $cPLA_2$-alpha activity and tumorigenesis (46). $cPLA_2$-alpha is cytosolic but translocates to intracellular membranes once activated by Ca^{2+} binding and phosphorylation (47). Free AA produced by $cPLA_2$-alpha activity is a potent cytotoxic compound inducing cell death via the mitochondrial-mediated apoptosis and the SMase-ceramide pathway (46) and is rapidly metabolized by COX, Lipoxygenases and Cytocrome P450 enzymes, leading to a panel of downstream eicosanoid metabolites, such as Prostaglandins, Leukotrienes and Hydroxy-eicosatetraenoic acids, respectively. The COX family enzymes, in particular, catalyze the conversion of AA to Prostaglandin H_2 (PGH_2) (45) which in turn is substrate for Prostaglandin E_2 synthase (PGES) for PGE_2 production (48).

Prostaglandins regulate many physiological processes through G-protein coupled receptor activation (49), leading to production of second messengers that induce proliferation, migration, apoptosis and angiogenesis (50). PGE_2 levels are increased in several cancers and correlate to tumor formation. PGE_2 can stimulate growth-promoting gene expression (namely c-fos and VEGF) (51) and can also modulate COX-2 gene expression in colorectal cancer and epithelial cells (51, 52) leading to a positive feedback over the downstream growth-promoting signaling. PGE_2 can act both in a autocrine and paracrine fashion to increase aromatase expression in breast cancer and normal tissue (53), thus up-regulating E_2 production and subsequent proliferative signaling pathways. The up-regulation of COX-2 expression in malignant breast tissue correlated with an increase in aromatase activity (54). In addition, PLA_2 can also mediate carcinogenesis by releasing lysophospholipids which can induce cell growth via their metabolism to lysophosphatidic acid (LPA) (55).

The inducible over expression of the LPA receptor, LPA_1 in MDA-BO2 breast cancer cells promoted the mitogenic effect of LPA in these cells (56). Murine xenografts of LPA_1 over-expressing cells demonstrated enhanced subcutaneous growth and bone metastasis. The authors noted that the LPA was not endogenously released by the MDA-BO2 cells but rather that these cells stimulated LPA release from platelets. Inhibition of platelet activation attenuated metastasis of these cells and also reduced the progression of osteolytic lesions produced by a heterologous ovarian tumor cell line. The authors concluded that the release of LPA by tumor stimulated platelets enhanced tumor growth and promoted cytokine-dependent bone destruction at metastatic sites. This is consistent with the observation by some workers that PLA_2 is not over expressed in breast cancer cells compared to normal mammary epithelium, but to the contrary is under-expressed in tumor cells (57). Similar observations have been described for PLA_2 under expression in human colonic cancer cells compared to normal colonic epithelium (58, 59). Boyan *et al.* also reported that E_2 treatment of ER(-) and ER(+) breast cancer cell lines did not result in PLA_2 activation (60). However, earlier work had suggested that membrane associated PLA_2 expression was a good indicator for metastatic potential (61) and breast cancer survival (62). AA is a promoter of apoptosis and it has been suggested that the elevated level of COX-2 expression detected in many breast cancers not only serves to increase prostaglandin release but also to reduce cytoplasmic AA concentration. This view is strengthened by the observation that COX-2 becomes associated with the mitochondria of cancer cells as does calcium-independent PLA_2 (63).

Dysregulation of downstream AA metabolizing enzymes such as COX-2, leads to high levels of proliferative eicosanoids, such as PGE_2 (46). COX expression is also increased in different cancers, including colon, pancreatic, prostate, lung, skin, liver and breast cancers (50, 63, 64). Furthermore, COX inhibition decreased cell growth and exacerbated chemotherapeutic-induced apoptosis in breast cancer cells (65). These studies suggest a role of COX inhibitors in decreasing tumor formation *in vivo*, which is supported by the correlation between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and growth reduction in breast cancer (50). NSAIDs have recently been used as chemotherapeutic agents against different types of cancer (66) although they present critical side effects. At present more interest is given to the development of specific COX-2 or PGES inhibitors (67).

5. ESTROGEN RECEPTORS AND PHOSPHOLIPASE A

Signaling processes that are initiated when E_2 binds to ER-alpha promote cell proliferation. Treatment of MCF-7 cells breast cancer cells with E_2 triggers ER-alpha association with Src tyrosine kinase and the regulatory subunit of phosphatidyl inositol 3-kinase (PI3K) leading to DNA synthesis (68). It has also been reported that E_2 can decrease cell growth by promoting apoptosis in several cell types, reviewed in (69). Epidemiological, clinical, and experimental evidence show that E_2 confers protection against prostate and colon cell proliferation and malignant transformation (70-73). ER-beta seems to participate in these E_2-induced blockades of cell proliferation and a progressive decline in ER-beta expression has been reported in breast (74) and prostate cancer (71). Analysis of gene expression in cultured cell lines and knockout mice indicate that E_2-activated ER-beta functions as a tumor suppressor by modulating the proliferative effects of ER-alpha (30, 75, 76). Recent studies suggest that ER-beta could also exert anti-proliferative effects independently of its ER-alpha co-repressing mechanism, by directly activating pro-apoptotic signaling pathways (77-79).

Interruption of the interaction between E_2 and ER-alpha has been a key facet of treating breast cancer for many years and the ER antagonist Tamoxifen has been the primary drug of choice. It has been described that the use of Tamoxifen to treat breast cancer is a risk factor in the development of endometrial cancer in post-menopausal women and this has contributed to the increased emphasis on aromatase inhibition therapy for breast cancer. The molecular basis of this enhanced endometrial cancer risk remains unclear. Levine demonstrated that the treatment of cultured rat liver cells with Tamoxifen caused them to release AA through enhanced PLA_2 activity (80). More studies are necessary to establish whether this effect is tissue–specific or whether the estrogenic effects of Tamoxifen on the endometrium that promote cancer development are linked to the up-regulation of PLA_2 activity. Raloxifene is an ER antagonist that displays fewer estrogenic side effects than Tamoxifen and is less of a risk in promoting endometrial cancer, reviewed in (81). Raloxifene was less potent than Tamoxifen in stimulating AA release from liver cells and also inhibited the release of PGI_2 in response to Tamoxifen (80). The different effects of these specific estrogen receptor modulators (SERMs) in stimulating AA release may contribute to the reduced endometrial cancer risk associated with Raloxifene treatment of breast cancer as compared to Tamoxifen. Further work is needed to investigate this fully, however, it may be the case that the safety of Tamoxifen in breast cancer treatment could be enhanced if this SERM is used in combination with COX-2 inhibition.

The importance of the interaction between ER and epidermal growth factor receptor (EGFR) coupled signaling and transcription regulation in breast cancer development has become evident. The identification of EGFR activation as an important contributory factor has provided novel and effective avenues for breast cancer treatment though EGFR antagonists such as Herceptin. The up-regulation of $cPLA_2$-alpha activity can be coupled to EGFR activation (82) and the induction of COX-2 gene expression in human glioma tumor cells is coupled to EGFR activation that results in activation of the SP1 transcription factor through p38 MAP kinase activation (83). Correlation has also been found in breast cancer between COX-2 activity and EGFR activity (84, 85). The regulation of the eicosanoid signaling pathway may be an important consequence of cross-talk between ER and EGFR coupled processes. ER expression is both a prognostic and a predictive factor in breast cancer, related to growth-rate, metastatic potential and sensitivity to therapeutic agents: estrogen receptor positive tumors (ER+) account for 60-70% of all human breast tumors (86), even though only two-thirds of them are responsive to hormonal therapy due to de novo and acquired resistance. A growing body of evidence suggest that crosstalk between ER and growth factor receptor signaling pathways, especially the EGFR family, is one of the mechanism for resistance to endocrine therapy in breast cancer (42, 87). The EGFR family of tyrosine kinases includes EGFR/HER1, cERBb2/HER2, HER3 and HER4. Growth factors such as epidermal growth factor (EGF), transforming growth factor (TGF)-alpha and amphiregulin bind to the external domain of EGFR and induce heterodimerization with other members of the family, which initiates various kinase signaling cascades inducing proliferation, inhibition of apoptosis, enhanced invasion and cell motility (88). Several studies had linked rapid estrogen signaling to EGFR trans-activation: the group of Filardo reported an involvement of GPR30 through G protein-mediated activation of matrix metalloproteinases (MMPs), release of heparin bound (HB)-EGF and activation of EGFR (89). MMP production by cancer cells and stromal fibroblasts plays an important role in tumor cell invasion. The production of MMP2 by fibroblasts is stimulated by breast carcinoma cells

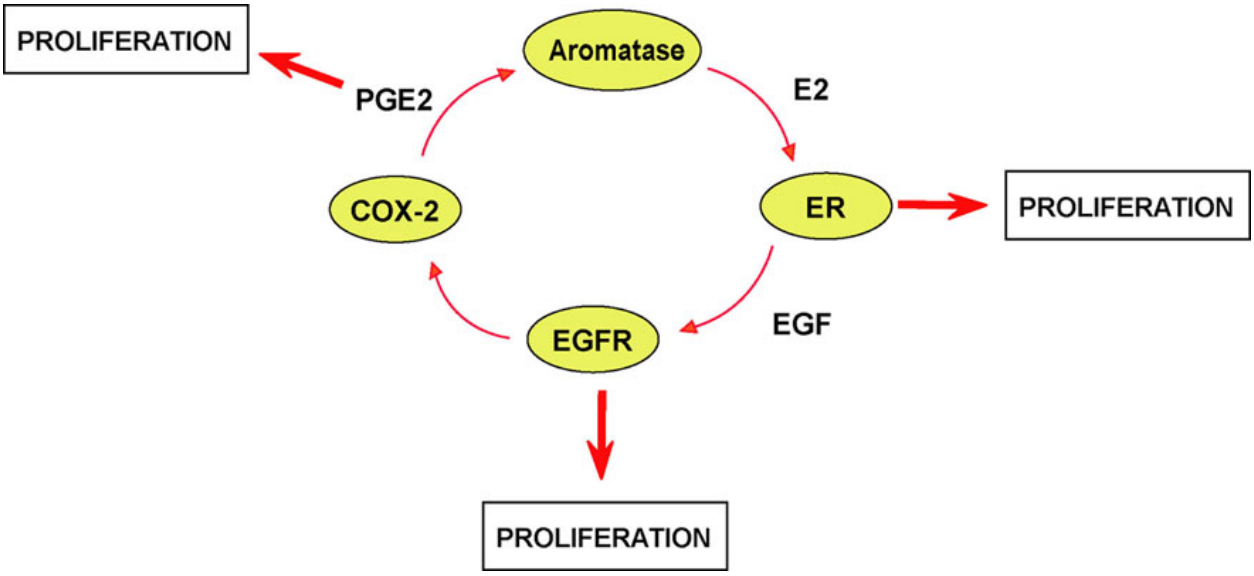

Figure 1. Positive feedback between estrogen and PGE_2. There is the potential for a positive feedback loop between estrogen and PGE_2 release in breast cancer cells leading to uncontrolled proliferation. PGE_2 stimulates aromatase activity in breast tissue to increase localized estrogen production (14). Estrogen promotes proliferative ER-dependent gene expression and also the trans-activation of EGFR (87). EGFR activation promotes proliferative signaling including the up-regulation of COX-2 expression that increase PGE_2 production to complete the cycle (85).

and is sensitive to PLA_2 inhibition (90).

EGFR and HER2 have been implicated in the development of human cancers. Patients whose tumors have an alteration in these receptors are associated with more aggressive disease (91). About 25-30% of human breast cancers have over-expression or amplification of HER2, and its increased expression correlates with poor clinical outcome and with resistance to endocrine therapy (92, 93). HER2 has become an important therapeutic target in breast cancer, leading to the development of targeted therapies such as the HER2 antibody Trastuzumab (94, 95). HER2 has the strongest catalytic activity between the four members of the family and HER2-containing heterodimers have the strongest signaling function (96). HER2 is also least subject to inactivating mechanisms and its recruitment into heterodimeric-signaling complexes leads to prolonged signaling. HER2 induces transformation through different signaling pathways and transcriptional functions (96). EGFR/HER1 is also over-expressed in 50% of breast tumors (97) correlating with resistance to hormonal therapy (92, 98). In these tumors the crosstalk between ER and EGFR/HER2 pathways results in a positive feedback cycle of cell survival stimuli. It is therefore clinically crucial to block this crosstalk by inhibiting both signaling pathways. Studies on nude mice supporting xenografts of human breast cancer cell lines, which over-expressed HER2 demonstrated that a combination of Gefitinib (Irresa), an EGFR inhibitor, and estrogen deprivation is more efficient at inhibiting ER+ breast cancer growth than either therapy alone (99). Furthermore, synergistic interactions were demonstrated between Gefitinib and Trastuzumab in breast cancer cells (100). Over expression of COX-2 by breast cancer cells is often associated with HER-2 expression and the direct regulation of COX-2 gene expression by HER-2 has been reported in breast cancer cells (85). Lanza-Jacoby et al. recently demonstrated a combined effect of EGFR and COX-2 inhibitors in breast cancer cells, suggesting a potential crosstalk between the two signaling pathways (84).

6. SUMMARY

The key roles of estrogen and the up-regulation of COX-2 in promoting breast cancer are established. These two factors are linked together through a positive feed back loop where COX-2 transcription is up regulated by estrogen through EGFR trans-activation and where COX-2 activity stimulates aromatase activity with important consequences for cell proliferation in estrogen-responsive tumor cells (Figure 1). The role of PLA_2 in providing AA, the substrate for COX-2 is apparent, however, over expression of PLA_2 must be coupled to elevated COX-2 expression to counter the cytotoxic effects of free AA. The need to balance PLA_2 activity with COX-2 activity may account for discrepancies in the literature regarding the role of PLA_2 in supporting or suppressing breast cancer progression (Figure 2). The role of PLA_2 in the progression of estrogen–dependent breast cancer still needs to be conclusively established. The role of eicosanoid signaling in endocrine-resistant breast cancer also needs further investigation with a view to supplementing recent developments in pharmacological intervention through HER-2 antagonism.

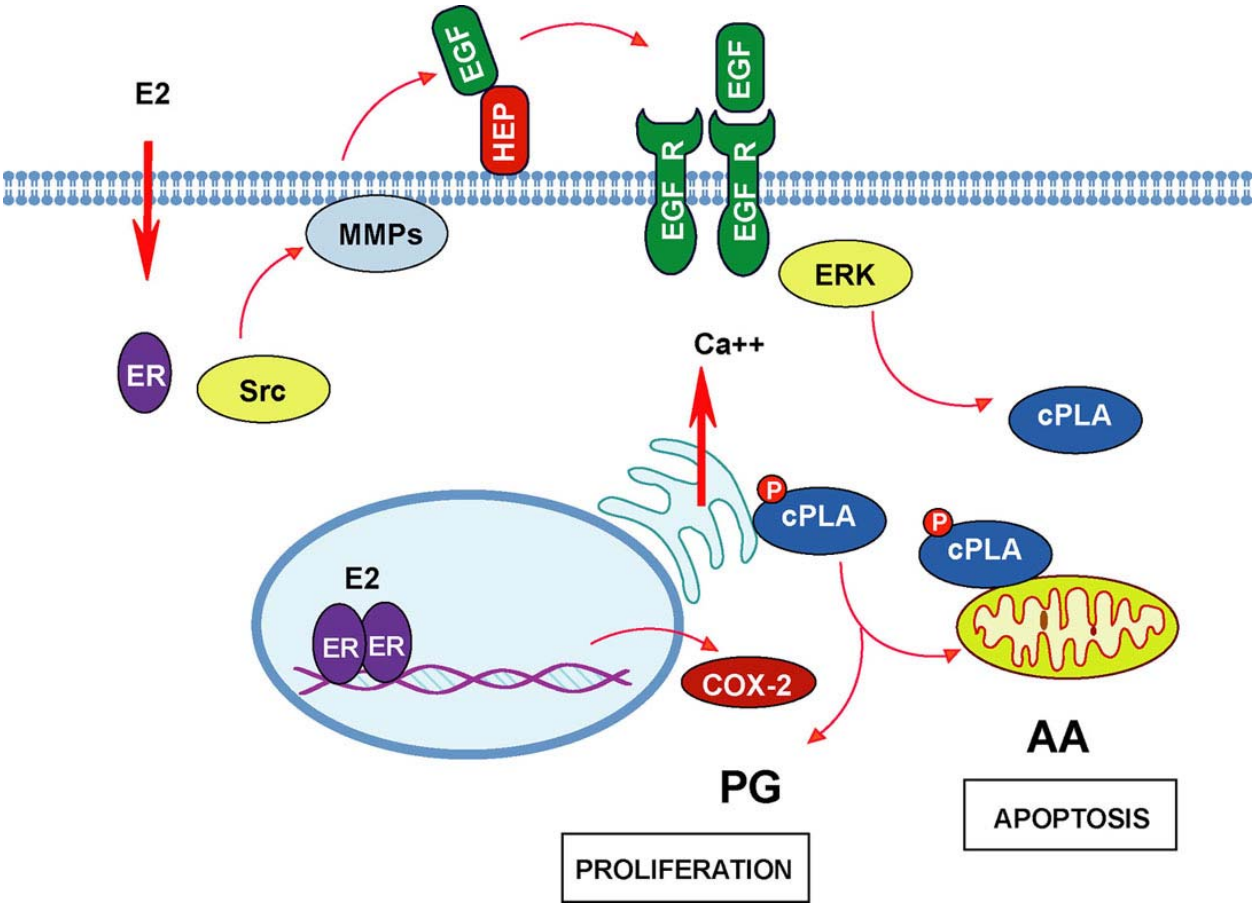

Figure 2. The biologically active estrogen 17-beta-estradiol (E_2) binds to the classical estrogen receptor (ER) to promote its dimerization and translocation to the nucleus where it modulates the expression of estrogen responsive genes. The interaction of E_2 with ER-alpha also activates signaling cascades that promote cell proliferation, such as the activation of c-Src tyrosine kinase (Src). Src activation stimulates a matrix metalloproteinase cascade, which culminates in the liberation of epidermal growth factor (EGF) that is bound to heparin (HEP) on the cell surface. Free EGF ligand binds to EGFR family receptors such as HER2 that activates a p42/p44 extracellular stimulus regulate kinase (ERK) signaling cascade. Cytosolic phospholipase A_2 ($cPLA_2$) is a substrate for ERK and phosphorylation of $cPLA_2$ promotes its association with intracellular membranes such as those of the endoplasmic reticulum and mitochondria. PLA activity releases lysophospholipids and arachidonic acid (AA) from these membranes. Lysophospholipids stimulate proliferative signaling, however AA promotes apoptosis. Cyclooxygenase-2 (COX-2) catalyses the first step in the conversion off AA into biologically active prostaglandins (PG) that promote proliferation. E_2 promotes the transcriptional up-regulation of COX-2, which maintains the intracellular levels of free AA at a low level. Over expression of COX-2 is often detected in malignant breast cancer. The transient activation of $cPLA_2$ has been observed in response to E_2 treatment of MCF-7 breast cancer cells. The transient rise in $[Ca^{2+}]_i$ that follows is prerequisite for the sustained activation of ERK and PKC-alpha that follows treatment of MCF-7 cells with E_2.

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Abbreviations: COX-2: cyclooxygenae-2; c/s/iPLA: calcium-dependent/secretory/intracellular phospholpiase A; ER: estrogen receptor; $PGE_2/H_2/I_2$: prostaglandin $E_2/H_2/I_2$; E_2: 17-beta-estradiol; NR: nuclear receptor; DNA: deoxyribonucleic acid; SP1: stimulating proin 1; AP1: activator protein 1; RNA: ribonucleic acid; cAMP: cyclic adenosine monophosphate; ERK: extra-cellular stimulus regulated kinase; GPR30: G-protein coupled receptor 30; EGFR: epidermal growth factor receptor; AA: arachidonic acid; PGES: prostaglandin E synthase; VEGF: vascular endothelium growth factor; LPA: lysophosphatidic acid; NSAID: non-steroidal anti-inflammatory drug; PI3K: phosphatidyl inositol 3-kinase; SERM: selective estrogen receptor modulator; TGF: transforming growth factor; MMP: matrixmetalloproteinase.

Key Words: Phospholipase A, Breast cancer, Estrogen, EGFR, Cyclooxygenase, Review

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