Stroma-mediated expression of estrogen and its role in cancer

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1. ABSTRACT

Several hormones are well known for their role in tumorigenesis. Among them estrogen is the best characterized hormone. In particular, stromal tissue-produced estrogen plays a key role in breast tumor development and progression, highlighting the importance of communications between stromal tissue and tumor cells in the tumor microenvironment. In this review, we update our current understanding of stroma-mediated expression of hormones (estrogen) and their role in tumorigenesis, focusing on how aromatase produced in stromal tissue affects tumor cell growth. We also briefly touch on hormone therapy involving selective estrogen receptor modulators and aromatase inhibitors.

2. INTRODUCTION

Hormones are the chemical messengers that are involved in signaling from one cell to another through binding to a specific receptor. Once a hormone binds to its receptor, it activates a signal transduction cascade that eventually leads to cell type-specific responses including cellular growth, functions and metabolism. For example, estrogen helps in normal developmental growth of various tissues such as mammary and ovary in females, and testis in male (1).

Hormones work both in endocrine and exocrine fashion, i.e. they are either secreted directly into the blood or through special ducts. They are needed in extremely low amounts for normal physiological functions, thus the rate of
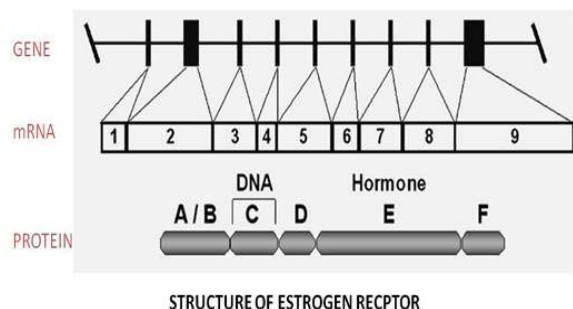
Figure 1. Structure of estrogen receptor.

hormone biosynthesis and secretion is often tightly regulated by a *negative feedback control* mechanism involving factors which influence the metabolism and excretion of hormones.

Several hormones like Growth hormone (GH), Prolactin (PRL), Leutinizing hormone (LH), Estrogen and Progesterone have been implicated in different types of cancers. Among them, estrogen has been studied most profoundly and it is a key modulator in initiation and progression of tumorigenesis. Estrogen is involved in numerous physiological processes including the development and maintenance of female sex organs, the reproductive cycle and various other functions (2). It does so by binding to estrogen receptors (ER alpha and ER beta), specific nuclear receptor proteins. ER alpha is the predominant receptor in female reproductive tract as well as in mammary gland. Hence, in most of the breast and endometrial tumors this receptor is overexpressed both in epithelial and stromal cells (3, 4). Similarly, overproduction of estrogen can also lead to uncontrolled cell growth and proliferation, which can be caused by upregulation of steroid biogenesis enzymes like dehydrogenase and aromatase.

Stroma refers to the connective, non-functional supportive framework of a biological cell, tissue, or organ. The stroma and epithelial cells intercommunicate with each other with the help of growth factors for the normal development of organs. Stromal growth factors (e.g., EGF, TGF, IGF-1 and IGF-2) can modulate epithelial cell proliferation. In contrast, epithelial growth factors can modulate stromal cells proliferations (5). In addition, stroma serves as pool of growth factors which influence the growth of various tissues. Various studies have already implicated the impact of stromal factors in neoplastic development and progression. One of such enzymes is aromatase. Aromatase is mainly expressed in stroma of adipose, ovary and breast tissues in females and prostate in males; and it helps in local production of estrogens from androgens, thus increasing the risk for cancer. This review focuses on hormones that are produced by stromal tissues, in particular estrogen, that profoundly impact tumorigenesis and metastasis.

3. ESTROGEN IN NORMAL TISSUE DEVELOPMENT

Estrogen is a steroidal endocrine hormone secreted from the ovaries and regulates a wide range of physiological functions from the regulation of menstrual cycle and reproduction to the modulation of cholesterol metabolism and bone density (2, 6). This may explain why postmenopausal women are more likely to suffer estrogen-related disorders, such as osteoporosis, chronic heart disease, hot flashes and night sweats.

Biologically estrogen signals are regulated after its binding to its receptor i.e. ER alpha and ER beta, encoded by different genes, and thus activate multiple downstream target genes (7). These two estrogen receptors share several common structural features like an N-terminal (NTD) or A/B domain, the DNA-binding (C) domain, a hinge (D) region, ligand-binding (E) domain and a unique C-terminal F domain of unknown function. The difference between them is in its N –terminal region, sharing only about 20% amino acid identity, and in hormone binding domain (Figure 1). This disparity in N terminal region is the root cause of regulation of different genes by these two receptors on the basis of recognition motif (8). Estrogen-mediated effect through its receptors has been extensively studied, which may involve several distinct *mechanisms* such as 1) binding to estrogen receptors, which dimerize (both homo and hetrodimers), translocate to the nucleus and then bind to *ERE* (estrogen response elements), functioning as a transcription factor with the help of different activators as SRC-1, AIB-1 and P300/CBP (9) and 2) direct binding of estrogen receptor on DNA with the help of AP-1, SP-1 AND NF-kappa B without any ERE (10).

3.1. Breast

The proliferative activity of breast is profoundly influenced by both estrogen and progesterone especially in leutal phase of menstrual cycle (11). Estrogen is known to mediate its effect through its receptors by upregulating stimulatory growth factors like TGF alpha, IGF 2 and EGF and also by downregulating inhibitory factors like TGF beta. In the breast, the epithelium and stroma communicate with each other through the factors mentioned above. The role of this communication has been well studied in breast cancers (12). For instance, platelet-derived growth factor (PDGF) is restricted to benign and malignant breast epithelial cells, while the receptors for PDGF reside only on stromal cells. Thus stromal cells amplify the signals by directly enhancing expression of PDGF, which further stimulates breast epithelial cells (13).

The concept of hormonal influence on breast cancer was first put forward by Cooper in 1836 and then recognized as estrogen dependent by Beatson in 1896 (14). By then role of estrogen and its specific receptors were well established in development of breast cancer. This is generally caused by the additive effect between two events, i.e., production of local estrogen by aromatase and overexpression of receptors, mainly ER alpha, especially in postmenopausal women (15, 16). Approximately 2/3 of all

breast cancer patients are ER alpha positive and these patients, in general, respond well to anti-hormonal therapy.

3.2. Prostate

Androgens are required for normal growth and development of human prostate (17). Testosterone is the main androgen produced mostly by testes (~95%) and then is further metabolized to its more active form dihydrosterone (DHT) by 5-alpha reductase (18). Mode of actions of these steroidal androgens is primarily through androgen receptors.

Although prostate is referred to be an androgen target, it is also targeted by estrogen both by direct and indirect mechanisms. Estrogen is generally considered a female sex hormone. However, in males, it is also an important steroid hormone required for normal growth of prostate, which can be explained by the fact that these tissues express both ER beta and ER alpha in both epithelial and stromal cells (19). It is produced by adipose tissue, testicles and adrenal gland. It can regulate its functions by various indirect mechanisms such as 1) activating several target genes involved in growth of prostate tissues (20, 21) and 2) activation of hypothalamus-pituitary-gonadal axis, causing a decrease in LH and subsequent androgen deprivation (22). It has been shown that estrogen is produced locally in prostate with the help of aromatase through androgens. Several research groups have demonstrated the role of estrogen signaling in prostate using several knockout models. Although ER alpha knockout mice exhibit no difference in normal development of prostate gland, ER beta knockout mice show basal epithelial cell hyperplasia and reduced apoptosis, signifying the anti-proliferative role of ER beta in prostate (23-25).

Prostate cancer is the leading cause of cancer death among men after lung cancer in United States (26). Diagnosis has been improved by markers such as PSA but the primary cause for this deadly disease is still not clear. Numerous lines of evidence suggest the involvement of hormones such as testosterone and estrogen, including 1) E_2:T (Testosterone) levels are higher in cancer patients (27); 2) Elevated levels of E_2:T ratio in African American correlate with higher incidence of cancer in them (28); 3) T in combination with E_2 induces prostate hyperplasia in dogs and also prostate cancer in humans and mice (29); and 4) Incidence of prostate cancer is higher in older people due to high E_2:T ratio, in addition to the fact that AR is often overexpressed in both primary and metastatic prostate cancers (30, 31). Finally, *Fromont et al* observed differential expression of genes related to androgen and estrogen metabolism in hereditary and sporadic prostate cancer (32). They found disparity in levels of AR and ER receptors, implying that a precise pattern of hormone receptors is connected with predisposition to prostate cancer.

3.3. Endometrium

Endometrium is known to proliferate under well organized control of both estrogen and progesterone in a time-dependent manner. It is well studied that endometrium mitotic activity is high when estrogen is high but ceases in the presence of progesterone. Excessive exposure of estrogen is also identified as a cause for endometrial cancers, one of the most common female reproductive cancers (33). Yet it is also true that these estrogen dependent cancers occur mainly at post menopausal period due to local exposure (*in situ*) of estrogen to the endometrium tissue (34).

Hormonal replacement therapy (HRT) has been widely used to relieve the symptoms after menopause like osteoporosis, cardiac diseases and local effects such as dry vagina, and itching. Estrogen is the prime hormone taken to avoid or prevent post menopausal women from above symptoms but this also increases the risk of endometrial cancers. However, the role of estrogen alone or in combination of progestin is still controversial. Two immense studies clearly demonstrated that HRT reduces the risk of endometrial cancer compared to women who have never taken the hormone therapy (35, 36). Actually several studies suggest the protective role of progestin like MPA (Medroxyprogesterone). As a matter of fact this protective effect is observed to be more effective in patients having PR (progesterone receptors), thus indicating that this cause is due to binding of progestin to its receptor (37). PR is present in two isoforms. Reduced expression of either one or both has been observed in most of endometrial cancers. It has also been reported that PR negative patients have shorter disease-free survival, indicating the protective action of progestin in normal endometrium through PR (38). In addition, progestin exerts potent anti-estrogenic effect by inducing 17-HSD (17 beta-hydroxysteroid dehydrogenase) to suppress tumor progression (39, 40). Progestin can induce apoptosis and modulates TGF beta (41). These results suggest an important role of PR in prognosis and recurrence of this cancer.

In addition to the classical pathway mediated by estrogen in cell proliferation, several studies suggest that there is a strong interaction between cancer and stromal cells that markedly affects the proliferation of cancer. For example, breast cancer cell proliferation is mediated by local production of estrogen or other growth factors. Among the stromal cells, fibroblasts comprise the majority of cells, specifically tumor associated fibroblasts (TAFs) which produce aromatase, a key enzyme in estrogen biosynthesis locally. This local production of estrogen generally takes over in post menopausal women, thus increasing the risk for breast cancers. Tumor-stromal interactions, i.e. estrogen production through aromatase, are also affected by various factors as PGE2, COX-2, IL-6/11 and TNF-alpha, which will be discussed in detail in next section. For example, insulin signaling might be involved in aromatase expression in endometrial glands and stroma (42).

4. IMBALANCE IN ESTROGEN SIGNALING AND CANCER

Estrogen as discussed above is an important endocrine factor required both in males and females. However, it is no longer only an endocrine molecule,
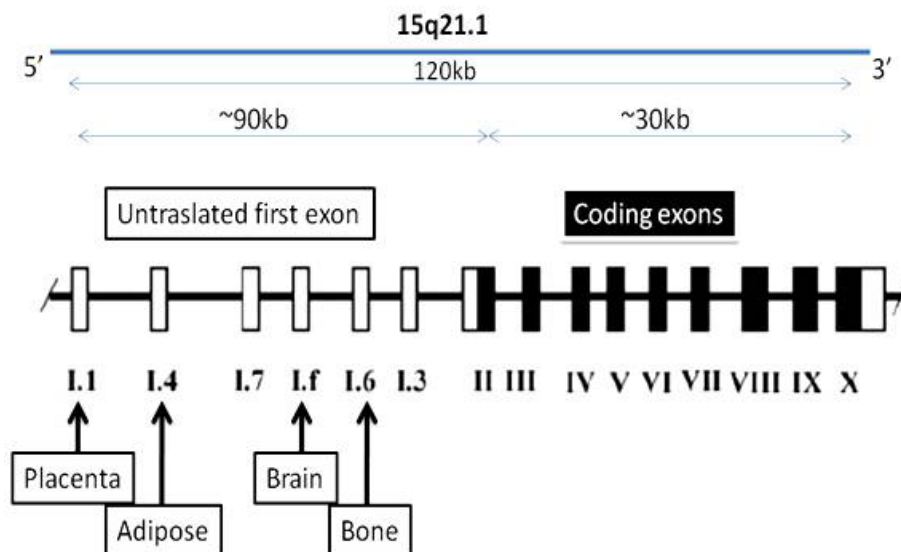
Figure 2. Aromatase gene and its different transcripts.

particularly in postmenopausal women; instead it is produced in a number of mesenchymal cells of various tissues such as bone, breast, adipose, brain and ovary. Therefore, it acts locally in both paracrine and autocrine fashions. There are many enzymes which regulate this local production of estrogen but aromatase is the main factor, which belongs to the cytochrome P450 superfamily of enzymes. In short, aromatase makes use of C19 androgen precursors as a substrate in extragonadal tissues and converts these into active estrogen.

4.1. The aromatase gene and its regulation

Aromatase is a protein found in endoplasmic reticulum of cells and is a member of a big family of enzymes i.e. the cytochrome P450 superfamily containing over 480 members in 74 families (43). This protein is encoded from chromosome 15q21.1 containing a 30 kb coding region with a long regulatory sequence of about 90Kb (44).

The regulation of aromatase is very complex and its expression is derived under strict control of tissue specific promoter (45, 46). Upstream of exon 2, there are various first exons that are spliced into the 5' untranslated region of the transcripts. For instance, placental tissue uses promoter P1.1 which is farthest upstream (approx. 90 kb) of exon 2 compared to bone tissue which is just 2 kb upstream (47). Various tissues have different promoter regions regulated by different transcription factors as seen in Figure 2. Despite different splicing variants involved, the coding region or protein expressed is always the same in every tissue.

4.2. Aromatase structure and function

Aromatase shares a number of features similar to other cytochrome P450 family members as there is a heme binding region at carboxy terminus containing a conserved

cysteine residue that provides additional fifth coordinating ligand for iron.

The heme protein is able to bind to the C 19 androgenic steroids and thus converts it into phenolic ring of estrogen with the help of other enzymes. Aromatase utilizes 3 moles of oxygen and 3 moles of NADPH for every mole of steroid substrate metabolized. These oxygen molecules are utilized to oxidize the C19 angular methyl group to formic acid in the final step, which occurs concomitantly with aromatization of the A ring to give the phenolic A ring characteristic of estrogens (48). The reducing equivalents for above reaction are supplied from NADPH via, a flavoprotein, NADPH-cytochrome P450 Reductase (Figure 3). The unique property of this protein is the presence of thiolate ion instead of nitrogenous base.

4.3. Expression of aromatase in normal and cancer tissues

The aromatase is expressed in different tissues mainly stromal region (Table 1) under control of different tissue-specific promoters. Apart from the tissues mentioned, aromatase levels are also detected in human fetal liver cells but not in adult (49). The transcript 1.4 from the same promoter has also been predominantly found in skin and intestine (50, 51).

Normal endometrium has almost undetectable level of aromatase but has been detected in situations like breast tumors under the influence of PGE2 via promoter II (52). It is also found in vascular smooth muscles of aorta and also both vascular and endothelial smooth muscles of vena cava in humans.

A number of tumor types like of endometrium, hepatic, prostate and breast have been characterized by elevated estrogen production due to profound activity of aromatase. Interestingly, aromatase has been detected not
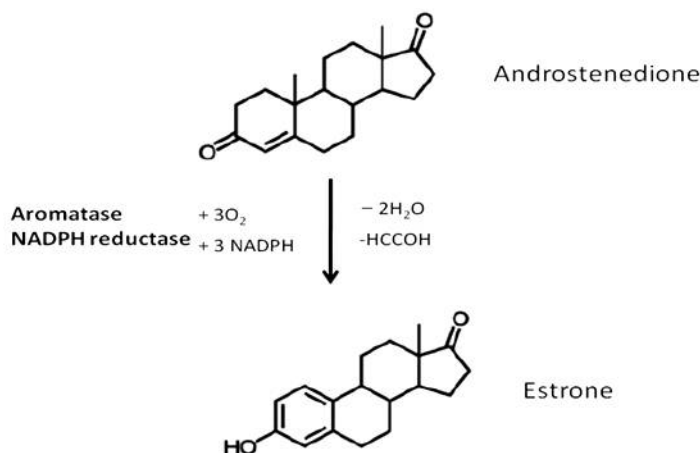
Figure 3. Conversion of androgen to estrogen by aromatase.

only in stromal cell component of normal breast but also in epithelial cells in vitro (53, 54). In fact, expression of aromatase is found highest in or around breast tumor sites. This increased expression in different tissues is essentially due to the switch in the promoter being used with the promoter II in the tissue. As a consequence, the controlled estrogen synthesis is taken over by cAMP mediated pathways especially via PGE2 (52). Prostaglandin E2 is produced by malignant epithelial cells as well as macrophages recruited to tumor sites. This local production of PGE2 is by cycloxygenase enzymes, in particular COX-2 (Figure 4). The role of PGE2 and its upstream biosynthesis enzyme COX-2 in this pathway may be explained by the fact that cycloxygenase inhibitors are beneficial along with the chemotherapy. Several studies also support the finding that there is a positive correlation between CYP19 and COX-2 (55) or between COX-2 and aromatase expression in invasive ductal carcinoma (IDC) and carcinoma *in situ (CIS)* (56). For example, among 47 patients analyzed by immunohistochemistry, COX-2 expression in IDC is correlated with aromatase expression in IDC ($p<0.001$), CIS ($p<0.001$), normal epithelium ($p=0.024$), and stroma tumor ($p<0.001$), highlighting the importance of these two enzymes in the progression of breast cancer (56). A recent study also showed that selective COX-2 inhibitors are able to decrease aromatase expression significantly, raising the possibility of using these inhibitors therapeutically against breast tumor (57).

A study by *Zhou et al* demonstrates the involvement of the orphan nuclear receptor, liver receptor homologue-1 (LRH-1) downstream to PGE2, in regulating aromatase expression in breast adipose tissue (58). Specifically, LRH-1 is markedly expressed in adipose tissue adjacent to breast carcinoma and the levels of LRH-1 are strongly correlated with that of aromatase in this tissue, in addition to induction of the LRH-1 mRNA level in these cells, suggesting one of the mechanisms of PGE2-mediated aromatase expression (58).

Finally, vitamin D, dexamethasone and mifepristone stimulate aromatase expression in gliomas cells using different promoters as in breast cancer cells (59), suggesting the importance of different promoter transcripts in specific tissues. Interestingly, the identification of factors that increase aromatase expression in glial cells but not in peripheral tissues may raise the possibility for the development of new strategies to selectively increase the levels of the neuroprotective steroid estradiol in the nervous system. Similarly, one can also speculate the protective effect of vitamin D in brain by enhancing aromatase expression.

4.4. Aromatase knockouts (ArKO)

The knockout model of CYP19 by fisher *et al* in 1998 clearly demonstrated the importance of aromatase in estrogen biosynthesis. Knockout of the CYP19 gene abolishes the estrogen production and its related function. Many defects in both male and female mice were observed particularly in the reproductive tract. Male mice were less compromised comparatively but severe deficiency in spermatogenesis and sexual behavior was observed. Although the majority of male mice at the age of 1 year had normal testicular morphology, except that few had dysmorphic semniferous tubules, overall aromatase knockdown showed disrupted spermatogenesis (60). All animals also showed leydig cell hypertrophy and hyperplasia (61). Moreover, adult ArKO males (ranging in age from 10 weeks through to 1 year) were shown to take longer to initiate mounting behavior and these mice had significantly fewer mounts than WT littermates (62), or did not mount at all. Prostates of ArKO mice were significantly enlarged compared with those of WT control animals, as measured by wet weight and volume (63).

As anticipated, estrogen deficit, as a result of aromatase knockout, has profound effects upon the reproductive system of ArKO females. In knockout mice, the uteri were underdeveloped, weighing half as much as WT. There were hypotrophies in uteri of all the mice with undeveloped ovaries. Many antral follicles are cystic and hemorrhagic at the later stage. Also all secondary and antral follicles are lost in 1-year-old ovaries, and hemorrhagic cysts are seen in most of the tissue (64). However

Table1. Differential expression and regulatory factors of aromatase in diverse tissues

Tissue	Promoter	Region from tss (kb)	Produced by cells	Regulatory factors	Inducers	Repressors
Placenta	I.1	-93	Placental cells	Retinoid	C/EBP-beta, RXR	Mash-2
Breast	I.3, II[1]	+1	Stromal fibroblasts	PGE2, COX-2	c-AMP	-
Adipose	I.4	-69	stromal mesenchymal cells or preadipocytes	Cytokines, TNF- alpha	STAT-3,GRE,SP-1	PPARgamma
Brain	I.f	-29	preoptic nucleus, the sexually dimorphic nucleus, the bed nucleus of the striata terminalis, and the medial amygdala	alpha 1-adrenergic agonist	c-AMP	-
Bone	I.6	-1	Osteoblasts, chondrocytes	class I cytokines, IL-1, TNF-alpha and TGF-beta		-
ovary	II	+1	granulosa cells	gonadotropin FSH	cAMP, SF-1,CREB	-

[1] (II in breast cancer)

Table 2. Different classes of aromatase inhibitors

Aromatase inhibitors	Examples	Effectiveness	Comments
Steroidal			
Competitive	1-methyl-ADD,7 alpha-APTA	Effective	-
Mechanism based	Formestane, Exemestane	Highly effective	High first pass metabolism.
Non-steroidal			
First/second generation	Aminoglutathemide	Highly effective	Lethargy/ataxia
Third generation	Anastrazole, letrozole	Highly effective	Increase in LH/FSH
Flavonoids	Chrysin, biochaninA	Less effective	-

restoration of estrogen and normalization of gonadotropin levels leads to the normal ovarian functions.

5. PREVENTIVE AND CURATIVE MEASURE AGAINST ESTROGEN IMBALANCE

5.1. Against receptors-SERMs

Selective estrogen receptor modulators (SERMs) are the class of drugs medicated to relieve menopausal symptoms due to deficiency of estrogen. They were introduced to overcome hormone replacement therapy (HRT) as HRT possessed high risk in developing cancer. SERMs are basically made against estrogen receptors (65) and are actually very specific in both its agonist and antagonist actions in different tissues. This tissue specificity is shown to be related with different co-activators and co-repressors (66) but actually confers broad usage of this class of drugs as both agonists and antagonist. For example, it can help prevent the deficiency symptoms like osteoporosis and cardiac stroke and also shown to be effective in treatment against breast cancer (67). There are several molecules which have been studied but three well known which are approved and clinically relevant are tamoxifen, raloxifene and toremifene.

5.1.1. Tamoxifen

Tamoxifen is an antagonist in the breast and is well studied as endocrine therapy for postmenopausal women with ER-positive breast cancer. Data from different breast cancer trials have shown that 5 years of therapy with tamoxifen suppresses the recurrence of breast cancer and reduces the incidence of contra-lateral second primary breast tumors by 50% (68). Evidence also suggests that tamoxifen preserves bone density in postmenopausal patients (69). Although tamoxifen is proven very effective clinically against breast cancer, several studies suggest that longer exposure leads to high rate of endometrial cancer. In addition, in animal models, it has been found that tamoxifen is a potent hepatocarcinogen in rats (70, 71) and it induces DNA adducts in the liver of rats treated with the drug (72, 73).

5.1.2. Raloxifene

Raloxifene is a benzothiophene SERM that is approved for treatment and prevention of osteoporosis. Like tamoxifen, raloxifene also acts as an estrogen antagonist in breast and inhibits estrogen-induced breast tissue proliferation (74) as well as prevents the growth of chemically induced mammary tumors in animal studies (75, 76). The advantage of raloxifene over tamoxifen is that there are no DNA adducts of its metabolites due to its non-steroidal nature.

5.1.3. Toremifene

Toremifene, a triphenylethylene derivative, is an anti-estrogen SERM with similar properties to tamoxifen's (77) but unlike tamoxifen, toremifene does not seem to increase the risk of endometrial cancer. Based on work done so far, the Food and Drug Administration (FDA) has restricted the use of toremifene in post-menopausal women with metastatic breast cancer. Despite the evidence of its chemopreventive action, several studies in the past two decades clearly show the resistance to SERMs in various breast cancer patients (78). This resistance is attributed to two main factors: 1) many breast cancers are ER negative; and 2) those ER positive tumors do not respond to SERM due to activation of different intrinsic signaling, such as altered expression of co-regulators like SMRT (79), N-CoR (co-repressors) or SUG-1 (co-activators) (80, 81).

5.2. Aromatase inhibitors

To suppress estrogen-mediated tumor cell proliferation, two main approaches have been developed: 1) interference between receptor and agonist i.e. estrogen receptor modulators; and 2) depleting levels of estrogen. Being a main regulator in biosynthesis of estrogen, aromatase is the key target enzyme to inhibit the stimulatory effects of estrogen. This has been studied for the past 3 decades and summarized in various research articles as effective therapy in various breast cancers (Table 2).

*T: TESTOSTERONE; E2: ESTROGEN
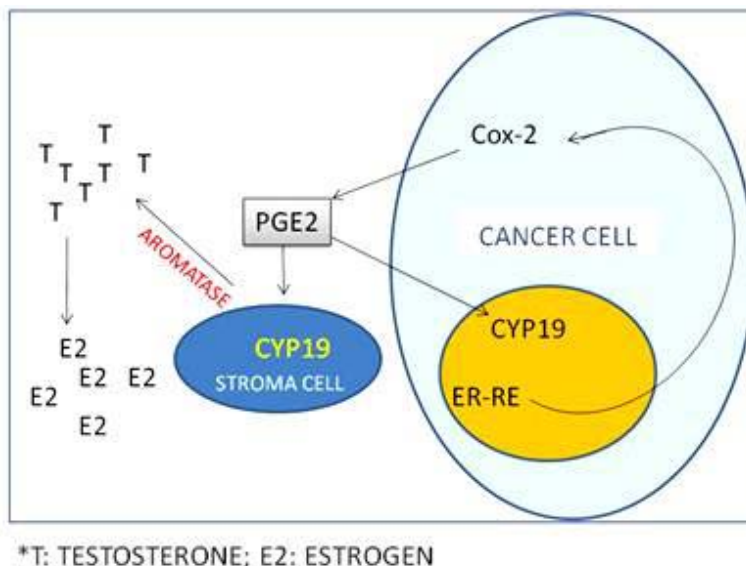
Figure 4. Indirect Interactions between COX-2 and aromatase.

5.2.1. First- and second-generation aromatase inhibitors
5.2.1.1. Aminoglutathemide:

It is the first such inhibitor used and reported in several clinical trials having good efficacy in synergism with other hormone based therapies (82, 83). However it was withdrawn from the breast cancer trials due to its side effects of lethargy, ataxia and skin rashes.

5.2.1.2. 4-Hydroxyandrostenedione

Also called formestane, is the first aromatase inhibitor which was approved in Europe clinically for general use. The drug was found very effective and well tolerated in postmenopausal breast cancer patients with minor side effects of pain and local inflammation. Since it was used as a second inhibitor in patients, it is referred to as second class inhibitor.

5.2.2. Third-generation aromatase inhibitors
5.2.2.1. Anastrazole

This potent nonsteroidal inhibitor was found very effective in decreasing estrogen biosynthesis at a dose of 1mg/day (127). This drug was found more effective than tamoxifen in two randomized, double blind studies as first line therapy in postmenopausal women with breast cancer (84, 85). Anastrazole was also shown to inhibit aromatization up to 97% along with suppression of plasma estrone and estradiol level by 85%, when given recommended dose of 1mg once a day in metastatic breast cancer patients (86).

5.2.2.2. Letrozole

Letrozole is also a potent nonsteroidal aromatase inhibitor that causes approximately 99% inhibition of estrogen synthesis in patients at a dose of 2.5 mg/day. It shows either partial response or stabilization of disease in about 40% of postmenopausal women with advanced breast cancer (87). It is well tolerated with no effect on other endocrine factors. A randomized, double-blind study in advanced breast cancer accounted letrozole more effective than tamoxifen in terms of response rate, clinical benefit, time to progression, and time to treatment failure (88, 89). However, it lacks bone protective effects of tamoxifen.

5.2.2.3. Exemestane

It is a potent steroidal aromatase inhibitor of human placental aromatase which is found well tolerated with long lasting suppression in both plasma and urinary estrogen levels (90). It was shown to inhibit in vivo aromatase up to 98% (91).

6. GENES INVOLVED IN HORMONAL IMBALANCE CANCER

Mutations in genes as well as their altered regulation are the well known cause for various cancers. Genes involved in biosynthesis of hormones, with their role in cancer, have been well studied. Several genes have been shown either with mutations in one of their codon leading to increase in activity or with overexpression. Some of the genes are summarized in Table 3.

For example, *CYP 17* gene codes for an enzyme which mediates both steroid 17 alpha-hydroxylase and 17-20 lyase activities and is very important in steroid biosynthesis pathways. A single base polymorphism in 5'UTR region leads to deregulated androgen biosynthesis (92). Studies also suggest a relation between risk of breast cancer and this polymorphism (93). Similarly a dinucleotide polymorphic repeat in 3'UTR of SRD5A2, i.e. a higher number of repeats has been shown to be a strong candidate conferring risk for prostate cancer (94). AR, androgen receptor, is an important receptor involved in normal physiological function of prostate and is also well studied. Androgen receptor activity has been shown to be negatively correlated with the number of CAG repeats within exon 1 and shown to have a high risk of prostate cancer (95).

Table 3. Genes deregulated in hormonal cancer.

Tissue	Hormones involved	Gene involved
Breast	Estrogen, progesterone	CYP17, CYP19, HSD17B1, ER, PR
Prostate	Dihydrotesterone	CYP17, HSD17B3, AR, SRD5A2
Ovary	FSH, progesterone	FSH, FSHR, PR
Endometrium	Estrogen	CYP17, HSD17B1, ER
Thyroid	TSH, Estrogen	TSH, CYP17, HSD17B1
Testis	Estrogen	CYP17, HSD17B1
Pancreas	Growth hormone	GH

7. SUMMARY

Hormone-responsive tumors constitute for 35-40% of all diagnosed tumors. Several factors have been implicated in cancers, including gene mutation or deregulation, over production of hormones as well as interference with their clearance and overexpression of receptors. Stromal tissue plays a very important role in communicating with epithelium. It provides several biosynthesis enzymes including aromatase, dehydrogenase, and reductase vital for hormones (estrogen) production. Overexpression of aromatase leads to an increase in local production of estrogen which may enhance the risk of tumors in various tissues especially in breast and endometrium. Several treatment approaches such as SERMs and aromatase inhibitors have been shown useful in treating these tumors. These compounds work basically by blocking signaling or by preventing the synthesis of estrogen in the body. Among different compounds, several trials show the effectiveness of aromatase inhibitors over other hormone based therapy with little or no side effects. Especially, the potent and orally active, third generation aromatase inhibitors, like anastrozole, letrozole and exemestane, were shown effective over tamoxifen in several clinical studies and are finding their places in treatment of different breast cancers. In future these inhibitors along with tamoxifen may be useful in eliminating hormone responsive tumors of different tissues.

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