Endocrine Diseases:

special reference to Endometrial Cancer and Breast Cancer

for PG Sem II

by

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Unbalanced sex hormone signalling can induce endometrial cancer

Endometrial cancer is one of the most common cancers of the female genital tract. Endometrial carcinoma can be divided into two subtypes.

Type I endometrial cancer

comprising approximately 85% of the total endometrial carcinoma burden among western societies, resembles normal endometrial hyperplasia in morphology and is associated with increased or unopposed estrogen signalling.

often shows mutations in the *PTEN* and in DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*). Also, oncogenic mutations in K-ras and/ or β-catenin are recognized major alterations in uterine cancer.

Type II endometrial cancer

occurs predominantly in older post-menopausal women, is not correlated to increased estrogen exposure, and is generally associated with a poorer prognosis. Type II endometrial cancers often show mutations in P53 and ERBB2.

In western, industrialized countries, two large groups of women are at increased risk of developing endometrial cancer:

(i) women with significant overweight and

(ii) those receiving tamoxifen for breast cancer treatment.

Tamoxifen is a selective estrogen receptor modulator (SERM) acting as an anti estrogen in mammary tissue, but showing estrogenic activity in the endometrium.

REMARK: Currently, it is estimated that up to 40% of all endometrial cancers could be related to obesity. Since the prevalence of obesity is increasing, the incidence of obesity-related endometrial cancer is also on the rise.

The relationship between sex hormone and Wnt / β-catenin signaling in the endometrium

Central in Wnt signaling is the destruction complex, a multi-protein complex consisting of the scaffold proteins AXIN1 and AXIN2 (conductin), β-catenin (CTNNB1), the tumor suppressor APC (adenomatosis polyposis coli) and the Ser-Thr kinases CK1 (casein kinase I) and GSK3β (glycogen synthase kinase 3 beta). In the absence of Wnt ligands, formation of the destruction complex triggers Thr/Ser-phosphorylation of β-catenin by CK1 and GSK3β, and its subsequent ubiquitination and proteasomal degradation. Upon Wnt signaling, the formation of the destruction complex is inhibited thus leading to cytoplasmic accumulation of β-catenin and its nuclear translocation.

Estradiol regulation of Wnt/β-catenin signaling

The putative mechanisms underlying estrogen mediated Wnt/β-catenin activation in the uterus are at present poorly understood.

A direct effect of ERα as a transcription factor on the expression of Wnt ligands, modulators and targets has been described by many authors: the ligands Wnt4, Wnt5A and Wnt7A have been shown to be induced by estradiol

[Katayama S, Ashizawa K, Fukuhara T, Hiroyasu M, Tsuzuki Y, Tatemoto H, et al. Differential expression patterns of Wnt and beta-catenin/TCF target genes in the uterus of immature female rats exposed to 17alpha-ethynyl estradiol. Toxicol Sci. 2006; 91: 419-30].

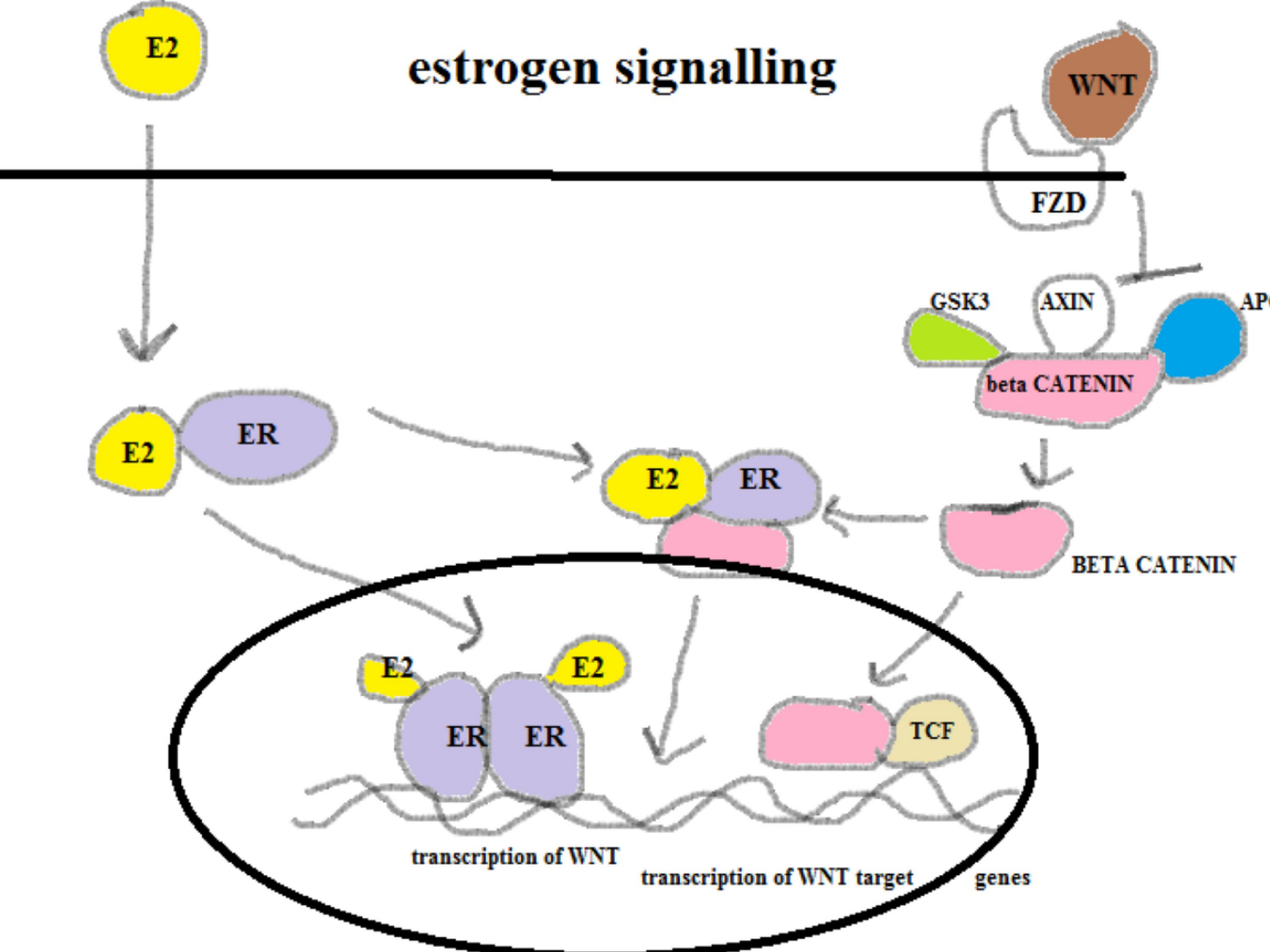
Wnt-target gene *WISP2* (Wnt-1 induced signaling pathway protein 2) was shown to be upregulated through direct interaction of activated ERα with its promoter region in human breast cancer cells

[Fritah A, Redeuilh G, Sabbah M. Molecular cloning and characterization of the human WISP-2/CCN5 gene promoter reveal its upregulation by oestrogens. J Endocrinol. 2006; 191: 613-24].

ERα (estrogen receptor), however, can also function as a transcriptional modulator without directly binding to DNA sequences in the promoter region of the affected genes.

Furthermore, ERα has also been observed to associate with important growth factor pathways such as the PI3K pathway thus indirectly cross-talking with Wnt signaling

[Cardona-Gomez P, Perez M, Avila J, Garcia-Segura LM, Wandosell F. Mol Cell Neurosci. 2004; 25: 363-73].


E2
estrogen signalling
WNT
FZD
GSK3
AXIN
beta CATENIN
E2
ER
E2
ER
BETA CATENIN
E2
E2
ER
ER
TCF
transcription of WNT
transcription of WNT target
genes

Conclusion

Enhanced or unopposed estrogen signaling is the most important risk factor for endometrial hyperplasia and
endometrial cancer. In view of the observations according to which

i. Wnt/β-catenin signaling plays a central role in endometrial homeostasis,

ii. it possibly represents one of the downstream effectors of estrogen signaling, and

iii. its constitutive activation is likely to underlie **malignant transformation** in the uterus, it is important to assess whether Wnt can trigger endometrial hyperplasia and cancer in the absence of enhanced estrogen signaling.

Breast cancer: role of estrogen

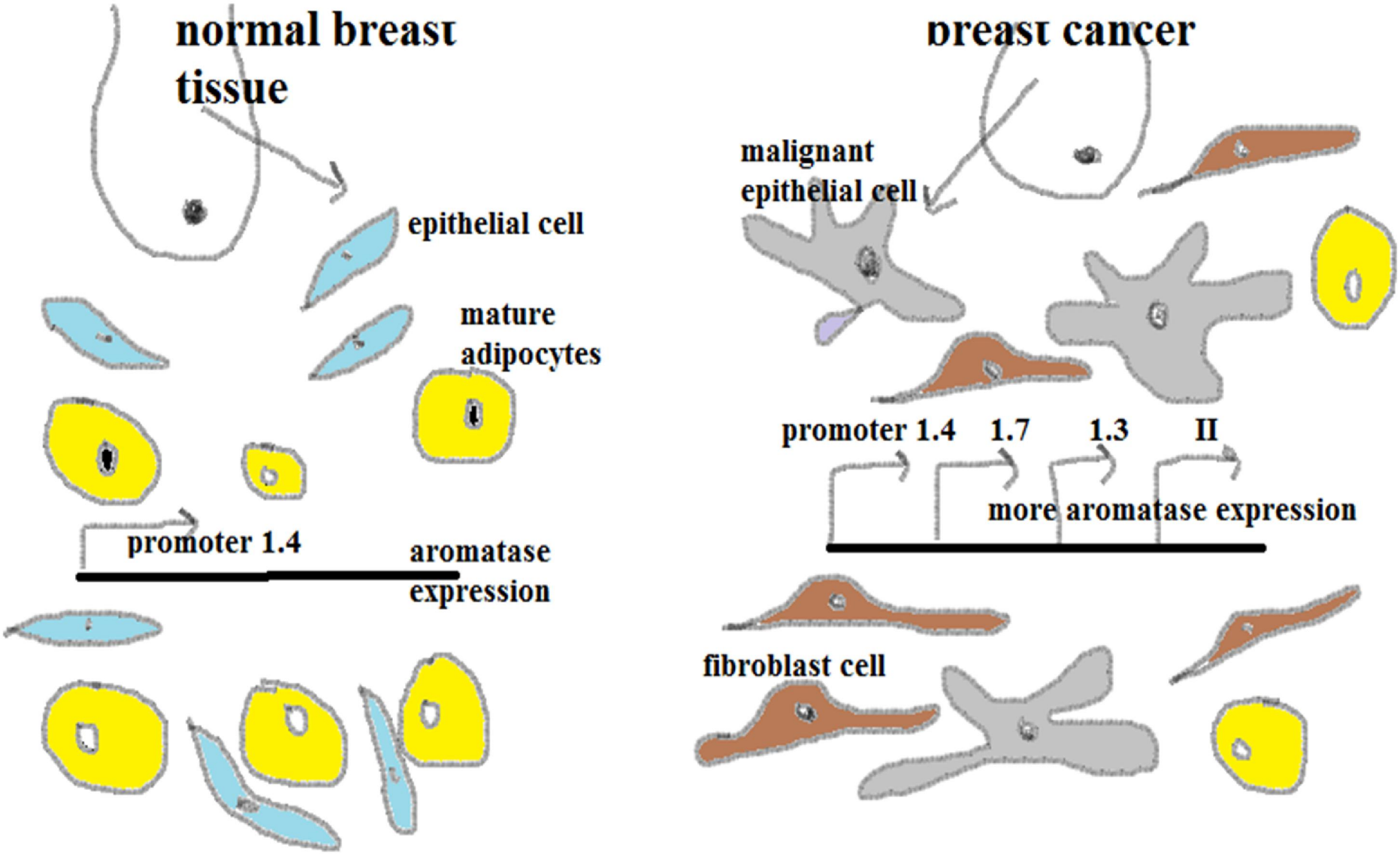
A single gene encodes the key enzyme for estrogen biosynthesis termed aromatase, inhibition of which effectively eliminates estrogen production. Aromatase inhibitors successfully treat breast cancer and endometriosis, whereas their roles in endometrial cancer, uterine fibroids, and aromatase excess syndrome are less clear. Ovary, testis, adipose tissue, skin, hypothalamus, and placenta express aromatase normally, whereas breast cancer overexpress aromatase and produce local estrogen that exerts tumerogenic effects.

Pathology Related to Aromatase Over expression

Breast cancer is highly responsive to estrogen for growth, as evidenced by high concentrations of estrogen receptors in these tissues (Bulun et al., 1997).

The levels of total aromatase mRNA levels in breast cancer tissue are strikingly higher than normal breast tissue. The normal breast adipose tissue maintains low levels of aromatase expression primarily via promoter I.4. Promoters I.3 and II are used only minimally in normal breast adipose tissue. Promoter II and I.3 activities in the breast cancer are strikingly increased. Additionally, the endothelial-type promoter I.7 is also up-regulated in breast cancer. Thus, it seems that the prototype estrogen dependent malignancy breast cancer takes advantage of four promoters (II, I.3, I.7, and I.4) for aromatase expression. The sum of aromatase mRNA species arising from these four promoters markedly increase total aromatase mRNA levels in breast cancer compared with the normal breast.

Aromatase Over expression



Aromatase Inhibitors in the Treatment of Breast Cancer

Today, aromatase inhibitors are the most effective endocrine treatment of estrogen-responsive breast cancer (Santen, 2002). Six recent head-to-head randomized clinical trials published since 2000 demonstrated the superiority of aromatase inhibitors to tamoxifen in the treatment of breast cancer (Bonneterre et al., 2000; Mouridsen et al., 2001; Baum et al., 2002, 2003; Goss et al., 2003; Milla-Santos et al., 2003; Paridaens et al., 2003; Buzdar et al., 2004).

Long-term side effect profiles of these agents will determine whether aromatase inhibitors will replace tamoxifen or other selective estrogen receptor modulators in the long run. There are two intriguing implications of these results.

First, it is pharmacologically more efficacious to block estrogen formation rather than its action at least by currently approved estrogen antagonists or selective estrogen receptor modulators.

Second, the local effect of aromatase inhibitors at the target tissue level to block local estrogen formation possibly represents the most critical mechanism for the superior therapeutic potential of aromatase inhibitors.

Aminoglutethimide was the first aromatase inhibitor tested for this purpose

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