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Recent insight on the control of enzymes involved in estrogen formation and transformation in human breast cancer

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Abstract

The great majority of breast cancers are in their early stage hormone-dependent and it is well accepted that estradiol (E_2) plays an important role in the genesis and evolution of this tumor. Human breast cancer tissues contain all the enzymes: estrone sulfatase, 17β-hydroxysteroid dehydrogenase, aromatase involved in the last steps of E_2 bioformation. Sulfotransferases which convert estrogens into the biologically inactive estrogen sulfates are also present in this tissue. Quantitative data show that the 'sulfatase pathway', which transforms estrogen sulfates into the bioactive unconjugated E_2, is 100–500 times higher than the 'aromatase pathway', which converts androgens into estrogens.

The treatment of breast cancer patients with anti-aromatases is largely developed with very positive results. However, the formation of E_2 via the 'sulfatase pathway' is very important in the breast cancer tissue. In recent years it was found that antiestrogens (e.g. tamoxifen, 4-hydroxytamoxifen), various progestins (e.g. promegestone, nomegestrol acetate, medrogestone, dydrogesterone, norelgestromin), tibolone and its metabolites, as well as other steroidal (e.g. sulfamates) and non-steroidal compounds, are potent sulfatase inhibitors. In another series of studies, it was found that E_2 itself has a strong anti-sulfatase action. This paradoxical effect of E_2 adds a new biological response of this hormone and could be related to estrogen replacement therapy in which it was observed to have either no effect or to decrease breast cancer mortality in postmenopausal women. Interesting information is that high expression of steroid sulfatase mRNA predicts a poor prognosis in patients with +ER. These progestins, as well as tibolone, can also block the conversion of estrone to estradiol by the inhibition of the 17β-hydroxysteroid dehydrogenase type I (17β-HSD-1). High expressison of 17β-HSD-1 can be an indicator of adverse prognosis in ER-positive patients.

It was shown that nomegestrol acetate, medrogestone, promegestone or tibolone, could stimulate the sulfotransferase activity for the local production of estrogen sulfates. This is an important point in the physiopathology of this disease, as it is well known that estrogen sulfates are biologically inactive. A possible correlation between this stimulatory effect on sulfotransferase activity and breast cancer cell proliferation is presented. In agreement with all this information, we have proposed the concept of selective estrogen enzyme modulators (SEEM).

In conclusion, the blockage in the formation of estradiol via sulfatase, or the stimulatory effect on sulfotransferase activity in combination with anti-aromatases can open interesting and new possibilities in clinical applications in breast cancer.

Keywords: Breast cancer; Estradiol; Estrogens; 17β-HSD; Progestins; Sulfatase; Sulfotransferase

1. Introduction

Most breast cancers (about 95%), whether in pre- or postmenopausal women, are initially hormone-dependent, where the hormone estradiol plays a crucial role in their development and progression [1–4]. The hormone and estrogen receptor complex can mediate the activation of proto-oncogenes and oncogenes (e.g. c-fos, c-myc), nuclear proteins, as well as other target genes. Consequently, processes that modulate the intracellular concentrations of active estrogens can have the ability to affect the etiology of this disease.

After a period that may last several years, the tumor becomes hormone-independent by a mechanism, which though not yet fully elucidated is under scrutiny. One explanation for the progression towards hormone-independence may be the presence of estrogen receptor mutants [5,6]. In hormone-dependent cells, the interaction of the hormone with the receptor molecule is the basic step for eliciting a hormone re-

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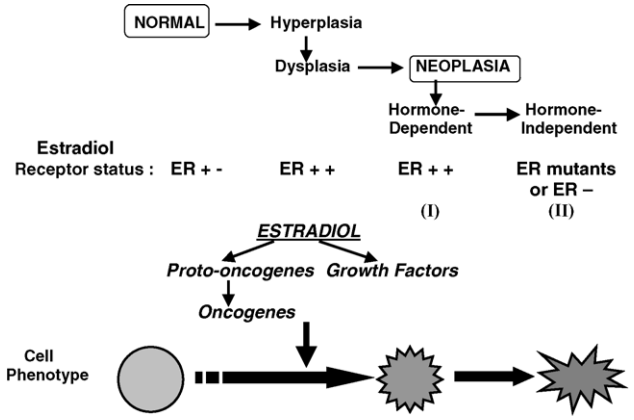

Fig. 1. Evolutive transformation of the breast cell from normal to carcinogen. Prognosis of the disease evolution is very good in the period when the breast cancer is hormone-dependent (I), but very poor when the cancer becomes hormone-independent (II). ER+, Estrogen receptor positive (detectable and functional); ER mutants, estrogen receptor detectable but non-functional; ER−, estrogen receptor negative (not detectable).

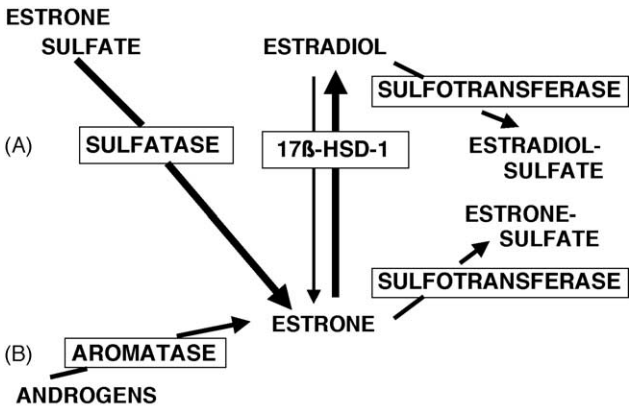

Fig. 2. Enzymatic mechanism involved in the formation and transformation of estrogens in human breast cancer. The sulfatase pathway (A) is quantitatively 100–500 times higher than that of the aromatase pathway (B). 17β-HSD-1 = 17β-hydroxysteroid dehydrogenase type 1.

sponse. As the cancer cell evolves, mutations, deletions and truncations appear in the receptor gene [7–9]; the estrogen receptor (ER) becomes 'non-functional' and, despite the estrogen binding, the cell fails to respond to the hormone. Fig. 1 describes the progression of normal mammary cells towards a hormone-independent carcinoma. A 'non-functional' estrogen receptor might explain why 35–40% of patients with ER-positive tumors fail to respond to antiestrogen therapy [10,11]. The remaining 5% of breast cancers, denoted BRCA-1, are considered hereditary. The gene was localized on Chromosome 17q21 [12,13] but its characterization and use as a marker are still a matter of great controversy (for a review see Ref. [14]).

The majority of breast cancers occur during the postmenopausal period when the ovaries have ceased to be functional. Despite the low levels of circulating estrogens, the tissular concentrations of estrone (E_1), estradiol (E_2) and their sulfates (E_1S, E_2S) are several times higher than those found in the plasma or in the area of the breast considered as normal tissue, suggesting a specific tumoral biosynthesis and accumulation of these hormones [15–19].

Several factors could be implicated in this process, including higher uptake of steroids from plasma and local formation of the potent E_2 by the breast cancer tissue itself. This infomation extends the concept of 'intracrinology' where a hormone can have its biological response in the same organ where it is produced.

In this review is summarized the recent information on the control of the enzymes involved in the formation and transformation of estrogens in breast cancer.

2. Steroid enzymes and breast cancer

There is substantial information that mammary cancer tissue contains all the enzymes responsible for the local biosynthesis of E_2 from circulating precursors. Two principal pathways are implicated in the last steps of E_2 formation in breast cancer tissues: the 'aromatase pathway', which transforms androgens into estrogens [20–22] and the 'sulfatase pathway' which converts E_1S into E_1 by the estrone sulfatase (EC: 3.1.6.2) [23–27]. The final step of steroidogenesis is the conversion of the weak E_1 to the potent biologically active E_2 by the action of a reductive 17β-hydroxysteroid dehydrogenase type 1 activity (17β-HSD-1; EC: 1.1.1.62) [28–30]. Quantitative evaluation indicates that in human breast tumor E_1S 'via sulfatase' is a much more likely precursor for E_2 than is androgens 'via aromatase' [17,31].

It is also well established that steroid sulfotransferases (ST), which convert estrogens into their sulfates, arte also present in breast cancer tissues [32,33]. Fig. 2 gives a general view of estrogen formation and transformation in human breast cancer.

3. Hydroxylated metabolites of estrogens and breast cancer

There is extensive information that the metabolic product of natural or synthetic steroids can have a biological response or more than other compounds. Concerning estrogens, three hydroxylated metabolites in positions C2, C4 and C16 are of biological importance. Fig. 3 gives a general view of this transformation.

It is interesting to note that 2-methoxy estradiol can inhibit the proliferation of breast cancer cells [34,35]. As this anti-proliferative effect can be obtained in negative estrogen receptor estrogen receptor cell lines, it is suggested that the biological response of 2-methoxy estradiol is mediated by another pathway, that of the classical estrogen receptor. This assumption is confirmed by the fact that the binding affinity to ER is only 0.1% compared with estradiol [36]. Zhu and Conney [37] suggest that 2-methoxy estradiol can have an-