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17Beta-hydroxysteroid dehydrogenase enzymes and breast cancer☆

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ABSTRACT

Sex steroids play an important role in the development and differentiation in several tissues. Biologically active hormones that are locally converted in endocrine organs in the tissue where they exert their effects without release into extracellular space is a field of endocrinology that has been called intracrinology. In pre-menopausal women the ovary is the main source of estrogens, but in post-menopausal women the estrogen production as main site of synthesis moves to peripheral tissues and almost all of the sex steroids are synthesised from precursors of adrenal origin. In breast cancer 60–80% of the tumors express high levels of oestrogen receptor (ER) α which gives estrogen a proliferative effect. Breast tumors tend to have a higher intratumoral estrogen concentration than normal breast tissue and plasma, and in situ synthesis and the metabolism of estrogens is believed to be of great importance for the development and progression of the disease. The activity of estrogen metabolizing enzymes in breast are mainly aromatase, estrone sulfatases and 17HSD enzymes. 17HSD1 and 17HSD2 are the family members known to be of main importance in breast cancer. High expression of 17HSD1 has been associated to poor prognosis in breast cancer and late relapse among patients with ER-positive tumors. One of the mechanisms behind high 17HSD1 expression is gene amplification. Low or absent expression of 17HSD2 is associated to decreased survival in ER-positive breast cancer. 17HSD14 is one of the latest discovered 17HSD enzymes, transfection of 17HSD14 in human breast cancer cells significantly decreased the levels of estradiol in the culture medium. Low expression of 17HSD14 mRNA expression in breast cancer was correlated to decreased survival.

The understanding of intratumoral synthesis of sex steroids in breast cancer is crucial to understand the disease both in pre- and post-menopausal women. Further studies are desirable to state the direct role of these enzymes in breast cancer and which patients that may benefit from new therapeutic strategies targeting 17HSD enzymes. The new inhibitors targeting 17HSD1 have shown promising results in pre-clinical studies to have clinical potential in the future.

1. Background

Sex steroids play an important role in the development and differentiation in several tissues such as bone, brain, breast, testis, prostate, endometrium and colon. Local androgen and estrogen synthesis at their site of action from inactive precursors in both women and men are important in the regulation of growth and function in peripheral tissues. Biologically active hormones that are locally converted in endocrine organs in the tissue where they exert their effects without release into extracellular space is a field of endocrinology that has been called intracrinology [1]. In endocrine systems only small amounts of secreted hormones exert its effect. Since the hormones act at the same place as they are produced in intracrine systems low concentrations may exert maximum effect. In pre-menopausal women the ovary is the main source of estrogen, but in post-menopausal women the estrogen production as main site of synthesis moves to peripheral tissues and almost all of the sex steroids are synthesised from precursors of adrenal origin. Estrogens support hormone-dependent tumors but have also a role to exert beneficial effects as protective against cardiovascular disease, osteoporosis and loss of cognitive function. The synthesis from dehydroepiandrosterone (DHEA) of the most potent local androgen, dihydrotestosterone (DHT) and the most potent natural estrogen, estradiol involves several enzymes such as 3β-hydroxysteroid dehydrogenases (3βHSD), 17β-hydroxysteroid dehydrogenases (17HSD), and aromatase [2]. These enzymes provide the cells with necessary mechanisms to control the level of intracellular active estrogens and androgens and many of these enzymes are tissue or/and cell specific. In post-menopausal women, local aromatisation of andostendion and testosterone is one of the major sources to estrone and estradiol. The rate of estradiol is not only dependent on the immediate syn-

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thesis but also on the level of the products that may serve as a depot. Most of the estrone formed by aromatase is converted to estrone sulfate by estrone sulfotransferase. Estrone sulfate may act as a reservoir of estrone formation through estrone sulfatase [3]. Even if aromatase and estrone sulfatase can increase the level of estrone in locally in peripheral tissues, 17HSDs activity is crucial to regulate the balance between estrone and estradiol.

2. 17HSD enzymes

The enzyme activity of the first discovered 17HSD enzymes was described early in both prokaryotic and eukaryotic species. Genes that encodes 17HSD enzymes developed individually at the same time as the steroid receptors about 540 million years ago [4]. This implicates that 17HSD enzymes had an important role early in evolution. Today there are 15 discovered 17HSD enzymes in mammals. All of these belong to the short-chain dehydrogenase/reduktas family (SDR) except 17HSD5 that is an aldo-keto-reduktase (AKR). SDR enzymes are a large protein family expressed in all different kind of life forms and act as multimeres with NADP as co-factor, AKR enzymes act as monomeres with NADPH as co-factor. There is a large variability of substrates preferred by SDR enzymes including steroids, retinoids, fatty acids and prostaglandins. Even though 17HSD enzymes sometimes are called iso-enzymes it should be avoided since they are coded by non-homologous genes, localized in different parts of the cell, prefer different substrates as well as co-factors. 17HSD enzymes in the SDR family share amino acids in the part of the proteins that are responsible for the protein folding. Outside these conserved regions the sequence similarity is as low as 20%. The 17HSD family has been difficult to study because of the low level of conserved amino acids together with the high substrate specificity.

In 1958 [5] an enzyme was discovered that regulates the balance of estrone against estradiol in human placenta. However, the first 17HSD enzyme was not cloned and characterized until 1996 [6]. The feature in common for all 17HSD enzymes is the possibility to catalyze oxidation or reduce the carbon at position 17 in steroids. The enzymes have different preferences for substrates such as estrone, estradiol, testosterone, andostendione, and dihydrotestosterone, are expressed in different parts of the cell, and in diverse tissues. This shows that the enzymes have separate physiological functions.

The nomenclature of 17HSD enzymes are numbered in the same order as they were described. The structure of five out of the 13 human 17HSD enzymes are characterized, this simplifies the understanding of the whole enzyme family.

2.1. 17HSD enzymes and breast cancer

In breast cancer 60–80% of the tumors express high levels of oestrogen receptor (ER) α which gives estrogen a proliferative effect. Breast tumors tend to have a higher intratumoral estrogen concentration than normal breast tissue and plasma, and in situ synthesis and the metabolism of estrogens is believed to be of great importance for the development and progression of breast cancer [7,8]. Miller et al. [9] and Perel et al. [10] both show that breast neoplasms can produce estradiol in vitro, and there are results that shows that in situ synthesis of estrogens predominates over plasma uptake in the breast after menopause [8]. The activity of oestrogen metabolizing enzymes in breast are mainly aromatase, estrone sulfatases and 17HSD enzymes. 17HSD1 and 17HSD2 are the family members known to be of main importance in breast tissue [11].

2.2. 17HSD1

17HSD1 predominantly catalyzes reduction of estrone to estradiol using NAD(H) or NADP(H) as co-factor. The expression is low in normal breast epithelium but increases in a large proportion of breast tumors. Highly variable amounts of 17HSD1 have been detected in benign and malign breast tissue. In some studies 17HSD1 was detected in all tumors analysed [12,13], but others detected expression in only 20% [14]. In invasive breast tumors 17HSD1 protein expression was detected in approximately 60% [15,16]. Differences in detection level may be due to different methodologies and different tumor material. High expression of 17HSD1 has been associated to poor prognosis in breast cancer [17] and late relapse among patients with ER-positive tumors [18]. One of the mechanisms behind high 17HSD1 expression is gene amplification. The gene encoding 17HSD1 is located at 17q11-21, a region that frequently shows genetic rearrangements in breast cancer. The first study investigating *HSD17B1* copy number found that 15% of the investigated cases exhibited *HSD17B1* amplification. The patients with ER-positive tumors that received tamoxifen and had *HSD17B1* amplification showed decreased breast cancer survival [19]. This is generally a group with good prognosis, and the result indicates that tamoxifen does not completely block the action of estrogen in some patients and that inhibition of 17HSD1 activity could be considered to suppress estrogen dependent proliferation of tumor cells. In another study *HSD17B1* amplification was compared to 17HSD1 mRNA expression, and a significant correlation between gene copy number and expression was found [20]. The development of 17HSD1 inhibitors is at present in focus for many research groups with promising results in pre-clinical studies. These inhibitors could be a new line of endocrine therapy.

Despite the importance of 17HSD1 in breast cancer, few epidemiologic studies concerning *HSD17B1* and breast cancer have been conducted [21–25]. The largest study was reported by Feigelson et al. [25] that investigated 5370 breast cancer cases and 7480 matched normal controls. They did not find any evidence of association between common *HSD17B1* haplotypes and overall risk of breast cancer.

2.3. 17HSD2

17HSD2 catalyzes oxidation from estradiol to estrone testosterone into androstendione with NAD as co-factor, is expressed in normal epithelium of the breast and protects the epithelial cells to balance the amount of estrone against estradiol [26]. Low or absent expression of 17HSD2 is associated to decreased survival in ER-positive breast cancer [14,16–18]. The studies that report expression of 17HSD2 in breast tumors examined materials at different stages at the tumor progression [14,16,17]. Gunnarsson et al. [18] suggests that a ratio between 17HSD2 and 17HSD1 should be determined instead of investigating the enzymes individually. They found that patients with ER-positive breast tumors with a high 17HSD1/17HSD2 ratio showed a significant better prognosis than patients with low ratio. In vitro studies on breast cancer cell lines have shown that 17HSD1 is dominant to 17HSD2, and that the conversion of estrone/estradiol is dependent on 17HSD1 levels [27]. Few studies have investigated the mechanism behind low 17HSD2 expression in cancer. The gene encoding 17HSD2 (*HSD17B2*) is located at chromosome 16q24.1, consists of five exons and give rise to a 42.8-kDa protein [28]. Loss of 16q24 is a frequent event in breast cancer [29–31]. This indicates that this region could harbour genes involved in tumor development [30]. Decreased expression of 17HSD2 in breast cancer may be a result of mutations in the gene. Jansson et al. [32] investigated sporadic-, hereditary breast cancer and breast cancer derived cell lines with different features and found that *HSD17B2* was not a target for inactivating

mutations in breast cancer and cannot clarify why some tumors show low 17HSD2 expression. Another study searching for *HSD17B2* mutations in a French-Canadian population with hereditary breast cancer did neither detect any mutations [33]. Possible mechanisms that may lead to decreased 17HSD2 expression can be incorrect activation/repression of transcription factors that binds to the promoter of *HSD17B2* or promoter hyper methylation. Several polymorphisms have been detected in *HSD17B2*. Even though some of them may affect the stability of the protein and be located at the steroid binding site carriers have not been identified to have an increased risk for breast cancer [23,33]. However, studies based on larger populations are desired.

2.4. 17HSD5

17HSD5 is the only 17HSD that belongs not to the SDR but to the AKR family. The enzyme catalyzes NADPH dependent reduction of androstendione to testosterone and is expressed in the mammary gland. Few studies have investigated the importance of 17HSD5 in breast cancer. Oduwole et al. [14] found that patients with high expression of the enzyme in the tumor had a worse prognosis compared to the group with low or no expression. Jansson et al. [34] found that high 17HSD5 expression was related to significantly higher risk of late relapse in patients with ER-positive tumors. None of these results were verified in multivariate analysis. The importance of 17HSD5 in breast cancer needs to be further clarified.

2.5. 17HSD12

17HSD12 was originally thought to be involved only in fatty acid elongation, but results from Luu-The et al. [35] suggests that 17HSD12 may be as important as 17HSD1 in the reduction of estrone to estradiol. They found that 17HSD12 protein was expressed in higher amounts in the tumors of breast cancer patients than normal breast epithelium. However, 17HSD12 was highly expressed in many lipid metabolizing tissues but at low levels in steroidogenic tissues. We examined 17HSD12 mRNA expression in 131 in the tumors of breast cancer patients, but did not find any relations that indicated that 17HSD12 has an important role in breast cancer. Further, Day et al. [36] found that although 17HSD12 was highly expressed in breast cancer cell lines the enzyme did not efficiently catalyzed estradiol formation.

2.6. 17HSD14

17HSD14 is one of the latest discovered 17HSD enzymes, also known as DHRS10 or retSDR3. 17HSD14 is a NAD dependent estradiol dehydrogenase that is involved in the balance of estrone and estradiol, but may also catalyze oxidation of androgens and fatty acids. Structure determination of the human enzyme revealed that the active site was able to accommodate steroid substrates [37,38]. Transfection of 17HSD14 in human breast cancer cells significantly decreased the levels of estradiol in the culture medium from two cell lines [34]. Even though the decreases of estradiol concentration were small in the experiments, it may be of importance in the long-term and in intracrine systems. Low expression of 17HSD14 mRNA expression in breast cancer was correlated to decreased survival [34]. Further studies are necessary to investigate how 17HSD14 is involved in the biosynthesis of hormones.

2.7. The regulation of 17HSD enzymes

The regulation of 17HSD enzymes is still not clear. There are some studies that indicate that cytokines influence the expression levels [39,40]. Progesterone indirectly stimulates the expression of 17HSD2, which catalyzes the conversion of biologically potent estradiol to weakly estrogenic estrone in the endometrial epithelium by factors secreted from endometrial stromal cells. Transcription factors SP1 and SP3 interact with specific motifs in the 17HSD2 promoter to upregulate enzyme expression in human endometrial epithelial cell lines. Conditioned medium from progestin-treated stromal cells increases levels of SP1 and SP3 in endometrial epithelial cells and induces 17HSD2 mRNA expression [41,42]. In endometriosis a stromal cell defect blocks formation of progesterone-dependent production of factors leading to 17HSD2 deficiency and defective conversion of estradiol to estrone in epithelium [43].

However, it is still unclear how and if the 17HSD family is regulated by progesterone in other hormone sensitive tissues. In several cell types progesterone receptor is not expressed in stromal cells, only epithelial cells. It also remains to identify which one of the two progesterone receptors that is of importance.

3. Conclusions

The understanding of intratumoral synthesis of sex steroids in breast cancer is crucial to understand the disease both in pre- and post-menopausal women. It has been clarified that 17HSD enzymes are associated to poor prognosis, increase cell proliferation and increase in local and distant recurrences. Further studies are desirable to state the direct role of these enzymes in breast cancer and which patients that may benefit from new therapeutic strategies targeting 17HSD enzymes. The new inhibitors targeting 17HSD1 have shown promising results in pre-clinical studies to have clinical potential in the future.

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