Journal of Steroid Biochemistry & Molecular Biology 114 (2009) 68–71

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Intracrinology of sex steroids in ductal carcinoma *in situ* (DCIS) of human breast: Comparison to invasive ductal carcinoma (IDC) and non-neoplastic breast☆

Yasuhiro Miki[a], Takashi Suzuki[b], Hironobu Sasano[a,*]

[a] *Department of Pathology, Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi-ken 980-8575, Japan*
[b] *Department of Pathology & Histotechnology, Tohoku University Graduate School of Medicine, Sendai, Japan*

ARTICLE INFO

Article history:
Received 28 November 2008
Accepted 31 December 2008

Keywords:
Intracrinology
Estrogen
Androgen
Breast carcinoma
DCIS

ABSTRACT

Sex steroids, including those through intratumoral production in an intracrine manner, play important roles in the development of invasive ductal carcinoma (IDC) of human breast, but biological and/or clinical significance of intratumoral production and metabolism of sex steroids, have remained largely unknown in the ductal carcinoma *in situ* (DCIS), an important precursor lesion of IDC. We recently examined tissue concentration of estradiol and 5α-dihydrotestosterone using liquid chromatography/electrospray tandem mass spectrometry in non-neoplastic breast, DCIS, and IDC tissues. Results of our study suggest that intratumoral concentrations of both estradiol and 5α-dihydrotestosterone are increased in DCIS, which is considered due to intratumoral production of these sex steroids. Therefore, both estradiol and 5α-dehydrotestosterone are considered to play important roles in the development of DCIS as well as IDC through an intracrine manner. Intratumoral metabolism and synthesis of estrogens and androgens as a result of the interactions of various enzymes are therefore also considered to play important roles in hormone dependent DCIS. Aromatase, which is one of the estrogen synthesis enzymes, plays an important role in intratumoral production of estrogen but other enzymes also play pivotal roles in intratumoral estrogen and androgen productions in human breast carcinoma. Therefore, in this review, we also focused on the importance of key intracrine enzymes such as 17β-hydroxysteroid dehydrogenases, steroid sulfatase, estrogen sulfotransferase, 5α-reductases in both IDC and DCIS.

1. Introduction

Invasive ductal carcinoma (IDC) of the breast is a group of malignant epithelial tumors characterized by invasion into adjacent tissues and a tendency to metastasize to distant sites including lymph nodes [1]. Ductal carcinoma *in situ* (DCIS) is defined as a neoplastic intraductal lesion characterized by increased epithelial proliferation, associated with subtle to marked cellular atypia and an inherent but not necessarily obligated tendency for progression to invasive breast cancer [1]. DCIS is also defined as a proliferation of atypical epithelial or ductal cells which was not associated with invasion beyond the basement membrane and is also distinguished from IDC by limitation of the lesion to existing ducts and lobules of the breast tissues [2]. DCIS is also currently considered a precursor lesion, with a relative risk of 8–11 for the development of invasive breast cancer [1]. DCIS is histopathologically classified into its five most common architectural or histological subtypes (papillary, micropapillary, cribriform, solid, and comedo) [3]. The first four are often grouped together as noncomedo DCIS and have been compared with the comedo lesions in both clinical and biological features. Comedo type DCIS has been well known to have higher nuclear grade, large tumor size, aggressive biological marker expression, and a higher risk of the subsequent stromal invasion [4]. Both nuclear grade and comedo-type necrosis are considered to reflect the biologically aggressive potential of the lesion and are currently emphasized in most of the classifications of DCIS [3]. The progression from proliferative disease without atypia (PDWA) to atypical hyperplasia (ADH), from ADH to DCIS, and from DCIS to IDC has been proposed by a number of investigators to be a possible model or cascade for the development of human breast invasive ductal carcinoma, although there have been controversies in this theory [5]. In the early stages of this proposed or putative cascade of breast cancer development, estrogens, especially estradiol, have been considered as one of the most important factors in driving the progression [6].

Sex steroid hormones such as estrogens and androgens are well known to play important roles in IDC cell proliferation and invasion in the estrogen receptor positive cases. In particular, locally produced bioactive androgens and/or estrogens exert their action in the cells where synthesis occurs without release in the extracellular space including circulation. This phenomenon is different from the classical concept of endocrinology such as autocrine, paracrine, and endocrine. This mechanism has been therefore

☆ Lecture presented at the '18th International Symposium of the Journal of Steroid Biochemistry and Molecular Biology', 18–21 September 2008, Seefeld, Tyrol, Austria.

* Corresponding author. Tel.: +81 22 717 8050; fax: +81 22 717 8051.
E-mail address: hsasano@patholo2.med.tohoku.ac.jp (H. Sasano).

0960-0760/$ – see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.jsbmb.2008.12.021

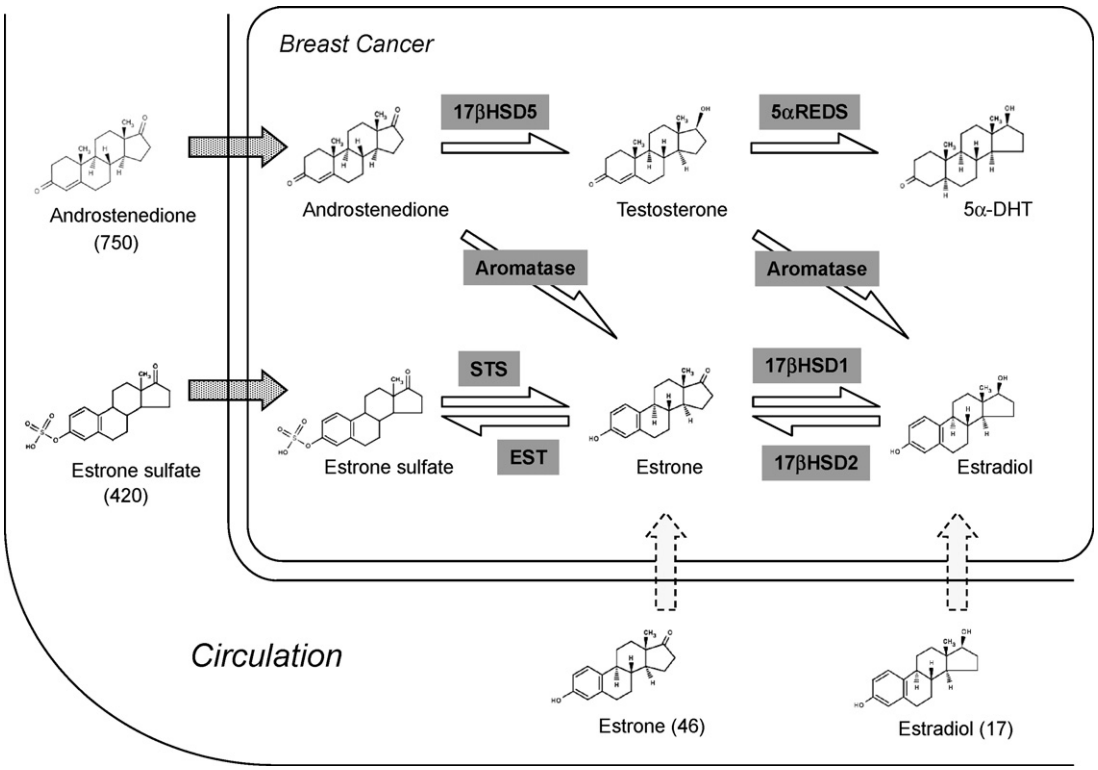

Fig. 1. Summary of intracrinology of estrogens and androgens in human breast carcinoma tissues. Androstenedione and estrone sulfate are the abundant androgen and estrogen in postmenopausal peripheral blood (androstenedione, 750 pg/ml; estrone sulfate, 420 pg/ml; estrone, 46 pg/ml; estradiol, 17 pg/ml) [48]. 17βHSD1, 17β-hydroxysteroid dehydrogenase type 1; 17βHSD2, 17β-hydroxysteroid dehydrogenase type 1; 17βHSD5, 17β-hydroxysteroid dehydrogenase type 5; STS, steroid sulfatase; EST, estrogen sulfotransferase; 5αREDS, 5α-reductases.

termed "intracrine" [7]. Aromatase is a key enzyme in the estrogen biosynthesis involved in aromatization of C19 steroids such as androstenedione and testosterone into estrogens, estrone and estradiol, respectively [7] (Fig. 1). Aromatase inhibitors are currently used in postmenopausal breast carcinoma patients as an estrogen deprivation therapy. Therefore, intratumoral aromatase of breast carcinoma including IDC and DCIS has been well studied and extensively reviewed by a numerous investigators [7–9]. In this review, we focused on the importance of other estrogen synthesis/metabolic pathways via 17β-hydroxysteroid dehydrogenase (17β-HSD) type 1/2 or steroid sulfatase (STS)/estrogen sulfotransferase (EST) and androgen synthesis pathways via 17β-HSD type 5 and 5α-reductases in DCIS with comparison to IDC.

2. DCIS versus IDC: estrogen and androgen receptors

2.1. Estrogen receptors

Many studies examined ERα status using immunohistochemistry in IDC and DCIS. ERα has been reported to be expressed in 65–81% of IDC cases [10–15] and 50–81% of DCIS cases [4,15–17], respectively. Several criteria have been employed in order to define "ER positive" breast carcinoma cases. However, it is also true that ER status in breast carcinoma is relatively abundant at the well-differentiated carcinoma, gradually decreasing to low levels at the poor-differentiated carcinoma. Esslimani-Sahla et al. [18] reported the expression of ERβ and its C-terminal splicing variant ERβcx using immunohistochemistry in IDC and adjacent normal mammary glands and DCIS. In their report, total ERβ expression was high in normal epithelial cells, decreased in DCIS, and increased from DCIS to IDC. ERβcx expression was reported to be low in normal epithelial cells, increased in DCIS, and continued to increase in IDC in both ERβ-positive and ERα-negative cases [18]. ERβ may have been therefore proposed as a tumor suppressor, but the biological roles of ERβ including its splicing variants have remained largely unclear.

2.2. Androgen receptor

In contrast to estrogen, androgens have been demonstrated to predominantly exert anti-proliferative effects via AR in IDC cells, although some divergent findings have been reported. AR immunoreactivity has been reported in IDC tumors [19–23]. AR-negative breast carcinoma patients were reported to be associated with shorter overall survival than AR-positive breast carcinoma patients [23,24]. However, little has been known on the status of AR in DCIS. Conde et al. [25] reported that the cytoplasmic immunoreactivity of AR was detected in 29% of DCIS and 38% of IDC, respectively. Hanley et al. [26] reported that AR positive rates are significantly higher in high- (93%) and non-high grade (89%) DCIS and non-high grade IDC (89%) than in high-grade IDC (55%). Androgen sensitivity has been well known to be subject to individual variations caused by AR gene polymorphism in women as well as men [27,28]. The long AR-CGA repeat has been related to an increase in subsequent breast cancer development risk [29]. Kasami et al. [30] examined the maximum number of CAG repeats in either allele of each patient in DCIS, IDC, and fibroadenoma and demonstrated that microsatellite repeat lengths in DCIS were longer than in fibroadenoma or IDC [30].

3. DCIS versus IDC: intracrinology

3.1. 17β-HSD type 1 and type 2

17β-HSD type 1 catalyzes the conversion of inactive estrogen, estrone, to biologically active estrogen, estradiol [31], while 17β-

HSD type 2 catalyzes the conversion of estradiol to estrone [31] (Figure). 17β-HSD type 1 and type 2 regulate the tissue level of estradiol and modulate estrogenic actions in estrogen target tissues. Both 17β-HSD type 1 and type 2 immunoreactivity was focally detected in the epithelium of normal mammary glands [32]. Suzuki et al. [31] reported no 17β-HSD type 2 immunoreactivity in 111 breast carcinoma tissues examined. In IDC cases, 17β-HSD type 1 immunoreactivity was detected in 47–61% of cases [31,33,34]. Suzuki et al. [31] reported using 111 cases of IDC that 17β-HSD type 1 immunoreactivity was significantly correlated with ER and progesterone receptor (PR), and inversely associated with histological grade and Ki-67. Ariga et al. [32] also reported that 17β-HSD type 1 immunoreactivity was detected in 54% of 22 PDWA cases, 31% of 26 ADH cases, and 63% of 40 DCIS cases, respectively. In addition, Ki-67 or MIB-1 LI in DCIS was significantly higher than in PDWA and ADH. Therefore, an increased concentration of estradiol, possibly produced *in situ* by 17β-HSD type 1, is considered to be involved in the cascade of events leading to the development of human breast carcinoma [6].

3.2. STS and EST

A major circulating form of plasma estrogen is estrone sulfate, a biologically inactive form of estrogen. Estrone sulfate has a relatively long half-life in the peripheral blood [35], where serum levels of estrone sulfate are known to be 10-fold higher than those of unconjugated estrone or estradiol [36]. Estrone sulfate is transformed into a biologically active form, estrone, by STS [37,38] (Fig. 1). Estrone is sulfated into estrone sulfate by cytosolic enzymes, phenol sulfotransferase and EST [37,38] (Figure). STS immunoreactivity was detected in carcinoma cells in 59–88% of IDC cases [37,39,40]. STS immunoreactivity was correlated with tumor size, and was significantly associated with an increased risk of recurrence [37]. Recently, we reported that STS immunoreactivity was also detected in 54% of 83 DCIS cases and mRNA level of STS was significantly higher in DCIS than non-neoplastic breast [41]. No statistically significant correlation was detected between STS mRNA levels of DCIS and IDC. In IDC, EST immunoreactivity was inversely correlated with tumor size or lymph node status, and was significantly associated with a decreased risk of recurrence or improved prognosis [41]. In DCIS, Hudelist et al. [42] demonstrated that EST immunoreactivity was detected in 79% of DCIS cases and the levels of EST were significantly higher in high-grade DCIS than non-high-grade cases. EST but not STS immunoreactivity was also detected in epithelial cells of morphologically normal glands [37,38]. The results of these studies above all demonstrated that EST was high in normal epithelial cells and decreased from DCIS to IDC.

3.3. 17β-HSD type 5 and 5α-reductases

17β-HSD type 5 (or AKR1C3) is a member of the aldo–keto reductase superfamily comprising several multifunctional enzymes that differ in both their tissue specific expression profiles and their substrate specializations [43]. It is the enzyme responsible for the reduction of androstenedione to testosterone in theca ovarian cells and adrenals, the main sources of testosterone in women [44] (Figure). 17β-HSD type 5 immunoreactivity was detected in normal mammary gland and 53% cases of 60 IDC patients [45]. With these 60 cases of IDC, immunoreactivity of 17β-HSD type 5 was significantly associated with that of 5α-reductase type 1 and type 2 [45], but was not significantly associated with other clinicopathological factors including tumor size, lymph node status and histological grade. In 83 cases of DCIS, 17β-HSD type 5 immunoreactivity was detected in 71% of the cases examined [41].

5α-Reductase is the enzyme that catalyzes the conversion of testosterone to 5α-dehydrotestosterone (5α-DHT) [45] (Figure). There are two 5α-reductase isoenzymes, 5α-reductase type 1 and type 2, located on separate chromosomes. The 5α-reductase type 2 occurs predominantly in the male reproductive tissues including seminal vesicles, epididymis, and prostate, whereas the 5α-reductase type 1 was detected in nonreproductive tissues such as the liver and skin. 5α-reductase type 1 has an alkaline pH optimum (pH 7.0–8.5), whereas isozyme type 2 has an acidic pH optimum (pH 5.0) [46]. These different enzyme kinetics may have some important implications for pathological states. In 60 cases of IDC, 5α-reductases immunoreactivity was detected in 58% of the cases for type 1, and 15.0% cases for type 2, respectively [45]. Immunoreactivity for 5α-reductase type 1 and type 2 was also focally detected in morphologically normal glandular epithelia adjacent to the carcinoma [45]. There was a strong positive correlation reported between 5α-reductase type 1 immunoreactivity and AR [45]. In 83 cases of DCIS, 5α-reductases immunoreactivity was detected in 63% cases for type 1, and 16% cases for type 2, respectively [41]. In both IDC and DCIS cases, a statistically significant inverse correlation was detected between 5α-reductase type 1 immunoreactivity and Ki-67 status of the carcinoma tissue [41]. In 115 IDC cases, carcinoma positive for both AR and 5α-reductase type 1 immunoreactivities (46%) demonstrated significant associations with a decreased risk of recurrence and improved prognosis for overall survival, and the AR/5α-reductase type 1 status was subsequently demonstrated as an independent prognostic factor [45]. In 73 DCIS cases, 5α-reductase type 1 immunoreactivity was associated with an increased risk of recurrence, although the association did not reach statistical significance [41]. Results of these reports all suggest that 5α-reductase type 1 and 5α-DHT may play different roles between IDC and DCIS.

3.4. Intratumoral estrogen and androgen concentrations

Very recently, we examined the intratumoral concentrations of both estradiol and 5α-DHT in non-neoplastic breast tissue ($n = 8$), DCIS ($n = 12$), and IDC ($n = 12$) by liquid chromatography/electrospray tandem mass spectrometry [41]. The intratumoral concentration of estradiol in DCIS was 3.3-fold higher than in normal breast tissues, and 4.0-fold lower than in IDC. The intratumoral concentration of 5α-DHT in DCIS was significantly higher than in both normal breast (3.2-fold) and IDC (2.0-fold). The concentrations of intratumoral estradiol and 5α-DHT in DCIS were 2.2-fold (estradiol) and 1.3-fold (5α-DHT) higher in premenopausal patients than in postmenopausal patients, but no significant associations were detected. We also examined mRNA expression of sex steroid hormone producing enzymes using quantitative RT-PCR in these breast specimens described above [41]. mRNA levels of aromatase, 17β-HSD type 1, STS, 17β-HSD type 5, and 5-reductase type 1 were significantly higher in DCIS than non-neoplastic breast tissue[41]. mRNA levels of sex steroid hormone producing enzymes except for aromatase were not significantly changed between DCIS and IDC. In this study, 5-reductase type 1 immunoreactivity was significantly associated with Ki-67 LI in 83 DCIS cases and it was also associated with an increased risk of recurrence in the 78 DCIS cases [41]. In addition, we examined intratumoral 5α-DHT concentration in 38 IDC cases [47]. In the AR-positive breast carcinoma (76%), intratumoral DHT concentration was negatively correlated with tumor size or Ki-67 LI. These discrepancies regarding the role of 5α-DHT between IDC and DCIS may be due to the different AR gene expression such as polymorphism described above.

References

[1] F.A. Tavassoli, P. Devilee (Eds.), World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Breast and Female Genital Tract, IARC Press, Lyon, 2003.

[2] J.C. Boughey, R.J. Gonzalez, E. Bonner, H.M. Kuerer, Current treatment and clinical trial developments for ductal carcinoma in situ of the breast, Oncologist 12 (2007) 1276–1287.
[3] K.A. Skinner, M.J. Silverstein, The management of ductal carcinoma in situ of the breast, Endocr. Relat. Cancer 8 (2001) 33–45.
[4] T. Moriya, H. Hirakawa, T. Suzuki, H. Sasano, N. Ohuchi, Ductal carcinoma in situ and related lesions of the breast: recent advances in pathology practice, Breast Cancer 11 (2004) 325–333.
[5] S.J. London, J.L. Connolly, S.J. Schnitt, G.A. Colditz, A prospective study of benign breast disease and the risk of breast cancer, JAMA 267 (1992) 941–944.
[6] H. Sasano, T. Suzuki, T. Nakata, T. Moriya, New development in intracrinology of breast carcinoma, Breast Cancer 13 (2006) 129–136.
[7] H. Sasano, N. Harada, Intratumoral aromatase in human breast, endometrial, and ovarian malignancies, Endocr. Rev. 19 (1998) 593–607.
[8] R.W. Brueggemeier, J.C. Hackett, E.S. Diaz-Cruz, Aromatase inhibitors in the treatment of breast cancer, Endocr. Rev. 26 (2005) 331–345.
[9] C. Osborne, D. Tripathy, Aromatase inhibitors: rationale and use in breast cancer, Annu. Rev. Med. 56 (2005) 103–116.
[10] G.P. Skliris, A.T. Parkes, J.L. Limer, S.E. Burdall, P.J. Carder, V. Speirs, Evaluation of seven oestrogen receptor beta antibodies for immunohistochemistry, western blotting, and flow cytometry in human breast tissue, J. Pathol. 197 (2002) 155–162.
[11] R.C. Coombes, E. Hall, L.J. Gibson, R. Paridaens, J. Jassem, T. Delozier, S.E. Jones, I. Alvarez, G. Bertelli, O. Ortmann, A.S. Coates, E. Bajetta, D. Dodwell, R.E. Coleman, L.J. Fallowfield, E. Mickiewicz, J. Andersen, P.E. Lønning, G. Cocconi, A. Stewart, N. Stuart, C.F. Snowdon, M. Carpentieri, G. Massimini, J.M. Bliss, C. van de Velde, Intergroup Exemestane Study. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer, N. Engl. J. Med. 350 (2004) 1081–1092.
[12] J. Thomas, A. Hanby, S. Pinder, I. Ellis, J. Macartney, K. Clements, G. Lawrence, H. Bishop, Sloane Project Steering Group. Implications of inconsistent measurement of ER status in non-invasive breast cancer: a study of 1,684 cases from the Sloane Project, Breast J. 14 (2008) 33–38.
[13] M. Nadji, C. Gomez-Fernandez, P. Ganjei-Azar, A.R. Morales, Immunohistochemistry of estrogen and progesterone receptors reconsidered: experience with 5,993 breast cancers, Am. J. Clin. Pathol. 123 (2005) 21–27.
[14] J.M. Harvey, G.M. Clark, C.K. Osborne, D.C. Allred, Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer, J. Clin. Oncol. 17 (1999) 1474–1481.
[15] L. Wiechmann, H.M. Kuerer, The molecular journey from ductal carcinoma in situ to invasive breast cancer, Cancer 112 (2008) 2130–2142.
[16] D.C. Allred, J. Bryant, S. Land, S. Paik, E. Fisher, T. Julian, R. Margolese, R. Smith, T. Mamounas, C.K. Osborne, B. Fisher, N. Wolmark, Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: findings from NSABP Protocol B-24, Breast Cancer Res. Treat. 76 (2002) S36.
[17] P. Meijnen, J.L. Peterse, N. Antonini, E.J. Rutgers, M.J. van de Vijver, Immunohistochemical categorisation of ductal carcinoma in situ of the breast, Br. J. Cancer 15 (2008) 137–142.
[18] M. Esslimani-Sahla, A. Kramar, J. Simony-Lafontaine, M. Warner, J.A. Gustafsson, H. Rochefort, Increased estrogen receptor betacx expression during mammary carcinogenesis, Clin. Cancer Res. 11 (2005) 3170–3174.
[19] V. Kuenen-Boumeester, T.H. Van der Kwast, W.L. van Putten, C. Claassen, B. van Ooijen, S.C. Henzen-Logmans, Immunohistochemical determination of androgen receptors in relation to oestrogen and progesterone receptors in female breast cancer, Int. J. Cancer 52 (1992) 581–584.
[20] J.J. Isola, Immunohistochemical demonstration of androgen receptor in breast cancer and its relationship to other prognostic factors, J. Pathol. 170 (1993) 31–35.
[21] S.N. Agoff, P.E. Swanson, H. Linden, S.E. Hawes, T.J. Lawton, Androgen receptor expression in estrogen receptor-negative breast cancer. Immunohistochemical, clinical, and prognostic associations, Am. J. Clin. Pathol. 120 (2003) 725–731.
[22] F. Moinfar, M. Okcu, O. Tsybrovskyy, P. Regitnig, S.F. Lax, W. Weybora, M. Ratschek, F.A. Tavassoli, H. Denk, Androgen receptors frequently are expressed in breast carcinomas: potential relevance to new therapeutic strategies, Cancer 98 (2003) 703–711.
[23] L.O. Gonzalez, M.D. Corte, J. Vazquez, S. Junquera, R. Sanchez, A.C. Alvarez, J.C. Rodriguez, M.L. Lamelas, F.J. Vizoso, Androgen receptor expression in breast cancer: relationship with clinicopathological characteristics of the tumors, prognosis, and expression of metalloproteases and their inhibitors, BMC Cancer 28 (2008) 149.
[24] R.M. Bryan, R.J. Mercer, R.C. Bennett, G.C. Rennie, T.H. Lie, F.J. Morgan, Androgen receptors in breast cancer, Cancer 54 (1984) 2436–2440.
[25] I. Conde, J.M. Alfaro, B. Fraile, A. Ruíz, R. Paniagua, M.I. Arenas, DAX-1 expression in human breast cancer: comparison with estrogen receptors ER-alpha ER-beta and androgen receptor status, Breast cancer Res. 6 (2004), R140–148.
[26] K. Hanley, J. Wang, P. Bourne, Q. Yang, A.C. Gao, G. Lyman, P. Tang, Lack of expression of androgen receptor may play a critical role in transformation from in situ to invasive basal subtype of high-grade ductal carcinoma of the breast, Hum. Pathol. 39 (2008) 386–392.
[27] A. Vottero, C.A. Stratalis, L. Ghizzoni, C.A. Longui, M. Karl, G.P. Chrousos, Androgen receptor-mediated hypersensitivity to androgen in women with non-hyperandrogenic hirsutism: skewing of X-chromosome inactivation, J. Clin. Endocrinol. Metab. 84 (1999) 1091–1095.
[28] I.S. Brum, P.M. Spritzer, F. Paris, M.A. Maturana, F. Audran, C. Sultan, Association between androgen receptor gene CAG repeat polymorphism and plasma testosterone levels in postmenopausal women, J. Soc. Gynecol. Invest. 12 (2005) 135–141.
[29] B. Nicolás Díaz-Chico, F. Germán Rodríguez, A. González, R. Ramírez, C. Bilbao, A. Cabrera de León, A. Aguirre Jaime, R. Chirino, D. Navarro, J.C. Díaz-Chico, Androgens and androgen receptors in breast cancer, J. Steroid Biochem. Mol. Biol. 105 (2007) 1–15.
[30] M. Kasami, H. Gobbi, W.D. Dupont, J.F. Simpson, D.L. Page, C.L. Vnencak-Jones, Androgen receptor CAG repeat lengths in ductal carcinoma in situ of breast, longest in apocrine variety, Breast 9 (2000) 23–27.
[31] T. Suzuki, T. Moriya, N. Ariga, C. Kaneko, M. Kanazawa, H. Sasano, 17β-hydroxysteroid dehydrogenase type 1 and type 2 in human breast carcinoma: a correlation to clinicopathological parameters, Br. J. Cancer 82 (2000) 518–523.
[32] N. Ariga, T. Moriya, T. Suzuki, M. Kimura, N. Ohuchi, S. Satomi, H. Sasano, 17β-Hydroxysteroid dehydrogenase type 1 and type 2 in ductal carcinoma in situ and intraductal proliferative lesions of the human breast, Anticancer Res. 20 (2000) 1101–1108.
[33] H. Sasano, A.R. Frost, R. Saitoh, N. Harada, M. Poutanen, R. Vihko, S.E. Bulun, S.G. Silverberg, H. Nagura, Aromatase and 17β-hydroxysteroid dehydrogenase type 1 in human breast carcinoma, J. Clin. Endocrinol. Metab. 81 (1996) 4042–4046.
[34] M. Poutanen, V. Isomaa, V.P. Lehto, R. Vihko, Immunological analysis of 17 beta-hydroxysteroid dehydrogenase in benign and malignant human breast tissue, Int. J. Cancer 50 (1992) 386–390.
[35] H.J. Ruder, L. Loriaux, M.B. Lipsett, Estrone sulfate: production rate and metabolism in man, J. Clin. Invest. 51 (1972) 1020–1033.
[36] E. Samojlik, R.J. Santen, T.J. Worgul, Plasma estrone sulfate: assessment of reduced estrogen production during treatment of metastatic breast carcinoma, Steroids 39 (1982) 497–507.
[37] T. Suzuki, T. Nakata, Y. Miki, C. Kaneko, T. Moriya, T. Ishida, S. Akinaga, H. Hirakawa, M. Kimura, H. Sasano, Estrogen sulfotransferase and steroid sulfatase in human breast carcinoma, Cancer Res. 63 (2003) 2762–2770.
[38] Y. Miki, T. Nakata, T. Suzuki, A.D. Darnel, T. Moriya, C. Kaneko, K. Hidaka, Y. Shiotsu, H. Kusaka, H. Sasano, Systemic distribution of steroid sulfatase and estrogen sulfotransferase in human adult and fetal tissues, J. Clin. Endocrinol. Metab. 87 (2002) 5760–5768.
[39] T. Saeki, S. Takashima, H. Sasaki, N. Hanai, D.S. Salomon, Localization of estrone sulfatase in human breast carcinomas, Breast Cancer 6 (1999) 331–337.
[40] Y. Yamamoto, J. Yamashita, M. Toi, M. Muta, S. Nagai, N. Hanai, A. Furuya, Y. Osawa, S. Saji, M. Ogawa, Immunohistochemical analysis of estrone sulfatase and aromatase in human breast cancer tissues, Oncol. Rep. 10 (2003) 791–796.
[41] R. Shibuya, T. Suzuki, Y. Miki, K. Yoshida, T. Moriya, K. Ono, J. Akahira, T. Ishida, H. Hirakawa, D.B. Evans, H. Sasano, Intratumoral concentration of sex steroids and expression of sex steroid-producing enzymes in ductal carcinoma in situ of human breast, Endocr. Relat. Cancer 15 (2008) 113–124.
[42] G. Hudelist, P. Wülfing, C. Kersting, H. Burger, B. Mattsson, C.K. Zerwenka, E. Kubista, D. Gschwantler-Kaulich, A. Fink-Retter, C.F. Singer, Expression of aromatase and estrogen sulfotransferase in preinvasive and invasive breast cancer, J. Cancer Res. Clin. Oncol. 134 (2008) 67–73.
[43] T.M. Penning, S. Steckelbroeck, D.R. Bauman, M.W. Miller, Y. Jin, D.M. Peehl, K.M. Fung, H.K. Lin, Aldo–keto reductase (AKR) 1C3: role in prostate disease and the development of specific inhibitors, Mol. Cell. Endocrinol. 248 (2006) 182–191.
[44] V. Luu-The, I. Dufort, G. Pelletier, F. Labrie, Type 5 17beta-hydroxysteroid dehydrogenase: its role in the formation of androgens in women, Mol. Cell. Endocrinol. 171 (2001) 77–82.
[45] T. Suzuki, A.D. Darnel, J.-I. Akahira, N. Ariga, S. Ogawa, C. Kaneko, J. Takeyama, T. Moriya, H. Sasano, 5α-reductases in human breast carcinoma: possible modulator of in situ androgenic actions, J. Clin. Endocrinol. Metab. 86 (2001) 2250–2257.
[46] D.W. Russell, J.D. Wilson, Steroid 5 alpha-reductase: two genes/two enzymes, Annu. Rev. Biochem. 63 (1994) 25–61.
[47] T. Suzuki, Y. Miki, T. Moriya, J. Akahira, T. Ishida, H. Hirakawa, Y. Yamaguchi, S. Hayashi, H. Sasano, 5α-reductase type 1 and aromatase in breast carcinoma as regulators of in situ androgen production, Int. J. Cancer 120 (2007) 285–291.
[48] S.J. Santner, P.D. Feil, R.J. Santen, In situ estrogen production via the estrone sulfatase pathway in breast tumors: relative importance versus the aromatase pathway, J. Clin. Endocrinol. Metab. 59 (1984) 29–33.