Cancer Chemother Pharmacol (2005) 56 (Suppl 1): s21–s26
DOI 10.1007/s00280-005-0107-3

Shigehira Saji · Makiko Hirose · Masakazu Toi

Clinical significance of estrogen receptor β in breast cancer

Published online: 5 November 2005

Abstract Ever since the estrogen receptor (ER) β was discovered in 1996, we have been trying to determine its value as a prognostic and/or predictive factor in breast cancer and its potential as a novel target for pharmacological intervention. Recent progress in cellular experiments has shown that ERβ works as counter partner of ERα through inhibition of the transactivating function of ERα by heterodimerization, distinct regulation on several specific promoters by ERα or ERβ, and ERβ-specific regulated genes which are probably related to its anti-proliferative properties. Accumulated data from protein studies in breast cancer tissues indicate that positive expression of ERβ appears to correlate with a favorable prognosis. Although the number of studies is small, a positive response to tamoxifen treatment is observed in both ERα- and ERβ-positive populations. The significance of ERβ2/cx, a splicing variant of ERβ, remains controversial and needs to be analyzed in further studies. We postulate that a combined evaluation of ERβcx with progesterone receptor may help the stratification of ERα-positive breast cancer. Epidemiological studies of hormone replacement therapy and isoflavone (genistein) consumption indicate the possible contribution of ERβ-specific signaling in breast cancer prevention. A selective estrogen receptor modulator, which works as an antagonist of ERα and an agonist of ERβ, may be a promising chemo-preventive treatment.

This work was presented at the 20th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "New Concepts of Treatment Strategies for Hormone-Related Cancer", 11–12 March 2005, Nagoya, Japan.

S. Saji (✉) · M. Hirose · M. Toi
Department of Surgery and Breast Oncology,
Department of Clinical Trials and Research,
Tokyo Metropolitan Komagome Hospital,
3-18-22 Honkomagome, Bunkyo-ku, 113-8677 Tokyo, Japan
E-mail: shige@cick.jp
Tel.: +81-3-38232101
Fax: +81-3-38241552

Keywords Estrogen receptor · Breast cancer · Selective estrogen receptor modulator (SERM) · Endocrine therapy

Character and expression of estrogen receptor β in breast tissues

Ever since the discovery of a protein that specifically binds to tritium-labeled estradiol in the uterus during the 1960s [13] and the cloning of the cDNA sequence coding that protein in 1986 [10, 11], it was believed that the action of estrogen signaling is regulated via a single type of estrogen receptor (ER). In 1996, a second estrogen receptor, named ERβ, was cloned from a male rat organ prostate [14], and this has raised concerns about the unexpected functions of estrogen in the broader area of biology.

ERβ belongs to the nuclear receptor superfamily, members of which share a common structural architecture. It is composed of three independent, but interacting, functional domains (Fig. 1). The N-terminal domain encodes a ligand-independent activation function (AF-1), a region of the receptor involved in protein–protein interactions and constitutive transcriptional activation of target-gene expression [reviewed in 22]. Comparison of the AF-1 domains of the two ERs revealed that, in ERα, this domain is relatively active on an estrogen response element (ERE), but the activity of the AF-1 domain of ERβ is weak [6]. The DNA binding domain (DBD) possesses a two zinc-finger structure, which plays an important role in receptor dimerization and in binding of receptors to specific DNA sequences. The DBDs of ERα and ERβ are highly homologous [7]. Thus ERα and ERβ are expected to bind to EREs with similar affinity and specificity. The E/F portion of the ER is called the ligand-binding domain (LBD), and mediates ligand binding, receptor dimerization, and transactivation of target gene upon ligand binding (AF-2). The LBD of ERβ is 60% homologous with the LBD of ERα. It is therefore not surprising that estradiol binds

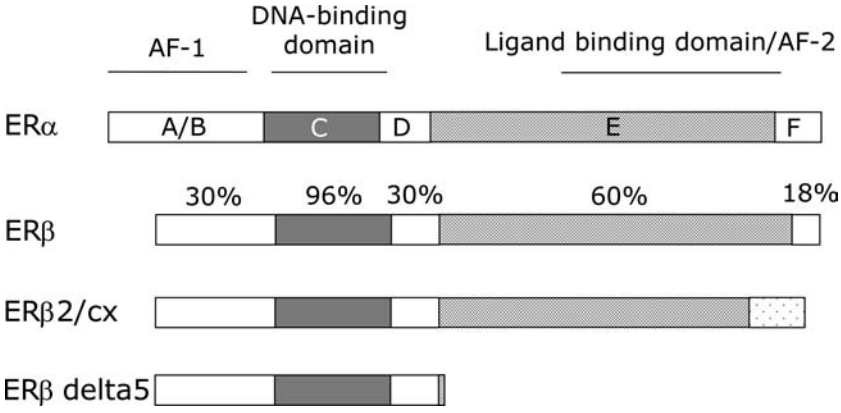

Fig. 1 Schematic representation of estrogen receptor (*ER*) structures. Percentages indicate the homology of ERβ amino acid sequences to ERα

to ERα and ERβ with almost similar affinities (Kd = 0.05 nM for ERα; Kd = 0.09 nM for ERβ). However, the phytoestrogen genistein has at least a tenfold higher affinity for ERβ [15].

Several types of splicing variants of ERβ have been reported to date [reviewed in 22, 29, 37]. Among them, ERβ2/cx is an important target in breast cancer biology (Fig. 1). ERβcx is identical to wild-type ERβ (530 a.a. form) in exons 1–7, but exon 8 is replaced by 26 unique amino acid residues [18, 23]. Due to the difference in the last exon, ERβcx lacks the amino acid residues important for ligand binding and those that constitute the core of the AF-2 domain. Therefore, ERβcx does not bind estradiol and lacks the ability to activate transcription of an estrogen-sensitive reporter gene [23]. Moreover, ERβcx prefers to heterodimerize with ERα rather than with ERβ, inhibiting ERα DNA binding. Functionally, the heterodimerization of ERβcx with ERα has a dominant negative effect on the ligand-dependent transactivation function of ERα [23].

Although expression of ERβ in the mammary gland and breast cancer tissues was controversial until specific antibodies for ERβ became available, recent studies with certain antibodies reported almost similar results [37]. In the mature mammary gland, ERβ is more broadly expressed in epithelial cells and stromal cells including fibroblast and endothelial cells, whereas ERα is spontaneously observed in epithelial cells [36]. In breast cancer archives, ERβ positivity was reported to be approximately 50–70% by immunohistochemistry [37]. Data from sucrose gradient profiling also indicated that the protein concentration of ERβ in breast cancer tissues appeared to be comparable with that of ERα; i.e., range of ERα protein was 13–3,700 fmol/mg, and that of ERβ was 20–475 fmol/mg protein [29].

The function of ERβ in breast cancer

It is generally thought that the function of ERβ is to counter that of ERα (Fig. 2). Introduction of the ERβ expression vector into representative ERα-positive breast cancer cell lines MCF-7 and T47D led to a reduction in estrogen-stimulated proliferation [26, 39]. When ERα works as a transcriptional activator on ERE, the function of ERα is suppressed by dimerization with ERβ. Lindberg et al. [16] using microarray analysis, observed that compared with wild-type mice, ERα-regulated genes were significantly enhanced in ERβ knockout mice. The other mechanism of ERs is found on the AP-1 response element; ERα exerts positive transcriptional activation for a downstream target, whereas ERβ shows null or reduced activity for transcription from this promoter [28]. Microarray analysis has demonstrated the presence of estrogen-regulated genes that are only enhanced by ERα or ERβ. Stossi et al. [38] established U2OS osteosarcoma cells, which stably express ERα or ERβ. In their study, 52 genes were identified as common estrogen-regulated genes by ERα and ERβ. However, beside these genes, 24 were enhanced only by ERα and 9 were induced only by ERβ. Among the nine genes induced by ERβ, the functions of six were unknown. It would be interesting to define the ERβ-specific regulated genes, because we speculate that these genes might be related to anti-proliferative or pro-apoptotic properties.

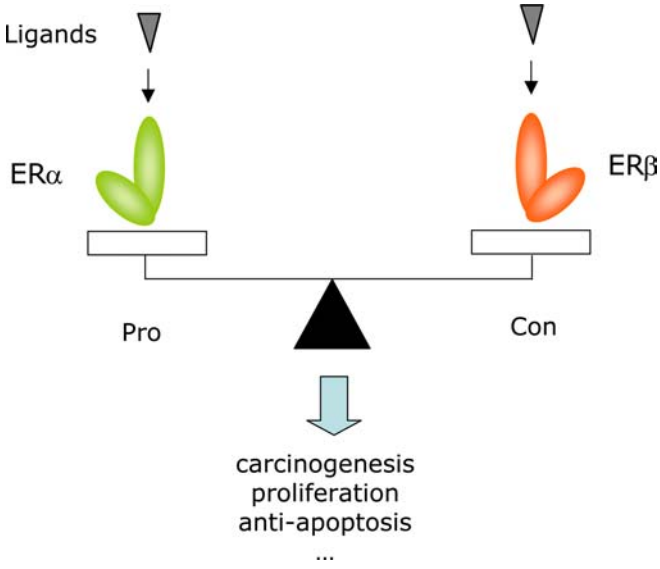

Fig. 2 Schematic representation of the function of estrogen receptor (ER)α and β

Table 1 Summary of estrogen receptor (ER)α and ERβ expression pattern in primary breast cancer evaluated by immunohistochemical staining

Author (Reference)	*n*	α+ β+ (%)	α+ β− (%)	α− β+ (%)	α− β− (%)
Skliris et al. [34]	319	62	13	18	8
Fuqua et al. [9]	234	62	14	15	9
Mann et al. [17]	47	53	11	17	19
Saji (2005, unpublished data)	108	45	15	12	28

Table 2 Summary of recent studies evaluating the possibility of estrogen receptor (ER)β expression as a prognostic indicator (*IHC* immunohistochemical analysis, *TAM* tamoxifen)

Author (Reference)	*n*	Sample	Adjuvant treatment	Prognosis in ERβ+
Myers et al. [20]	150	Protein (IHC)	Not specified	Favorable
Fuqua et al. [9]	242	Protein (IHC)	Not specified	No correlation
Omoto et al. [25]	57	Protein (IHC)	Not specified	Favorable
Omoto et al. [24]	88	Protein (IHC)	Not specified	Favorable
Hopp et al. [12]	305	Protein (Western)	TAM	Favorable
O'Neill et al. [27]	167	Protein (IHC)	TAM	No correlation
Nakopoulou et al. [21]	181	Protein (IHC)	TAM	Favorable
Mann et al. [17]	118	Protein (IHC)	TAM	Favorable
Mann et al. [17]	47	Protein (IHC)	Without TAM	No correlation

When ERβcx was expressed in ERα-positive breast cancer MCF-7 cells, the ERα/ERβcx complex did not bind to ERE, although the ERα/ERβ did [26]. This may indicate that although both ERβ and ERβcx inhibit ERα function by heterodimerization, the site of this action is not the same. It is interesting to speculate that ERβcx preferably inhibits DNA-unbound ERα, which works through other transcriptional factors such as jus and fos, or membrane-related ERα.

Expression of ERβ and its role as a prognostic and predictive factor

While there is strong expression of ERβ in normal mammary gland, its expression appears to be reduced during carcinogenesis [31, 33, 34]. For instance, Shaaban et al. [33] carried out an immunohistochemical analysis of 283 samples of breast tissue. They found that the median proportion of cells expressing ERβ was 94.3% in normal breast lobules, 76.7% in ductal hyperplasia, 70.0% in ductal carcinoma in situ and 60.0% in invasive cancer.

Table 1 summarizes the reported population of ERα and/or ERβ-positive tumors in human breast cancer specimens [9, 17, 34]. Although it is not fair to compare these results directly due to the difference in patient populations tested and in the antibodies used, it is noteworthy that about 50% of breast cancer patients express both ERα and ERβ.

To date, many investigators have tried to define the significance of ERβ expression as a prognostic indicator because, in general, ERα-positive patients have a favorable prognosis compared to those who do not express ERα. Table 2 summarizes recent publications evaluating ERβ protein expression and its correlation to prognosis [9, 12, 17, 20, 21, 24, 25, 27]. There is no paper showing a correlation with poor prognosis in ERβ-positive patients. It would not be surprising to find a favorable prognosis in ERβ-positive patients, considering the biological function of ERβ against ERα.

In terms of predictive factors for treatment, there are studies evaluating ERβ mRNA and immunohistochemical staining (Table 3) [4, 5, 8, 19, 35]. In these reports, relapse rates in adjuvant treatment and response rates of metastatic or primary tumors to antiestrogen treatment were used as markers for defining the predictive value of ERβ. It is interesting to note the discrepancy in mRNA and protein studies. Expression of ERβ mRNA appears to indicate a poor response to treatment [4, 5, 19, 35], whereas positive ERβ protein staining is thought to indicate a favorable response to antiestrogen treatment [8, 19]. Although there is no clear explanation for these differences, we should be careful when extrapolating the results of these studies to microarray or proteomics analysis. Balfe et al. [2] re-

Table 3 Summary of recent studies evaluating the possibility of estrogen receptor (ER)β expression as a predictive factor for endocrine therapy (*IHC* immunohistochemical analysis, *n*−, node negative, *Adj* adjuvant treatment, *TAM* tamoxifen, *TOR* toremifen, *Rec* recurrence)

Author (Reference)	*n*	Sample	Target	Drug setting	Response in ERβ+
Speirs et al. [35]	17	mRNA		Adj, TAM	Poor
Murphy et al. [19]	27	mRNA	ERα+, n−	Adj, TAM	No correlation
Chang et al. [5]	102	mRNA		Rec, TAM	Poor
Cappelletti et al. [4]	47	mRNA	ERα+	Neo-adj, TOR	No correlation
Esslimani-Sahla et al. [8]	50	Protein (IHC)	ERα+	Adj, TAM	Favorable
Murphy et al. [19]	27	Protein (IHC)	ERα+, n−	Adj, TAM	Favorable

Table 4 Summary of studies evaluating the possibility of ERβcx expression as a predictive factor for endocrine therapy (*IHC* immunohistochemical analysis, *Adj* adjuvant treatment, *TAM* tamoxifen, *Meta-LABC* metastatic or local advanced breast cancer)

Author (Reference)	*n*	Sample	Target	Drug setting	Response in ERβcx+
Esslimani-Sahla et al. [8]	50	Protein (IHC)	ERα+	Adj, TAM	No correlation
Saji (2005, unpublished data)	67	Protein (IHC)	ERα+	Adj, TAM	No correlation
Palmieri et al. [30]	23	Protein (Western)		Meta-LABC, TAM	Favorable

ported that ERα mRNA had a positive correlation with its protein expression; however, only 54% of ERβ mRNA-positive cases showed concordance with ERβ protein evaluation. In addition to regulation at a transcription level, it is possible that the ERβ protein is more dominantly regulated by a degradation process.

Prediction of response to endocrine therapy by ERβcx expression is also a challenging subject. Results of our unpublished data and two other papers with a specific antibody for ERβcx developed by Dr. Jan-Åke Gustafsson's group at the Karolinska Institute, Sweden, are summarized in Table 4 [8, 30]. Due to the limitation of sample number and differences in patient settings, the answer remains controversial. We have already reported the data in neo-adjuvant tamoxifen treatment for primary breast cancer [32]. In this study, we were not able to demonstrate the predictive power of ERβcx expression itself. However, evaluation with progesterone receptor (PgR) helped to discriminate poor responders to tamoxifen treatment from others. Our idea is that in ERα-positive tumors, ERβcx-positivity and PgR-negativity indicates the presence of dominant negative-regulation by ERβcx, whereas ERβcx-positivity and PgR-positivity indicate higher activity of ERα in overcoming ERβcx inhibition. Former tumors may not respond to endocrine therapy, but should have sensitivity at a later time. To date, our preliminary data in 67 breast cancer specimens could not prove this idea in the adjuvant setting (Fig. 3), and it needs to be evaluated using a larger number of specimens with uniform background.

Future perspectives

We postulate that selective estrogen receptor modulators (SERMs), which work as complete antagonists for ERα and agonists for ERβ, may be useful in cancer treatment, especially in chemoprevention strategies. Meta-analysis of randomized trials of hormone replacement therapy shows a statistically significant increased risk of breast cancer (HR = 1.27) and decreased risk of colon cancer (0.64) by administering estrogen with or without progesterone [3]. In epidemiological studies, several reports have suggested that isoflavone consumption (especially genistein) may reduce the risk of breast cancer and colon cancer [1, 41]. In the ductal cells of mammary glands, both ERα and ERβ are expressed; however, ERβ is the only receptor expressed in the tubular cells of the colon [40]. When merging these with the fact that genistein has a higher affinity for ERβ, it is not difficult to suppose that agonists for ERβ may work

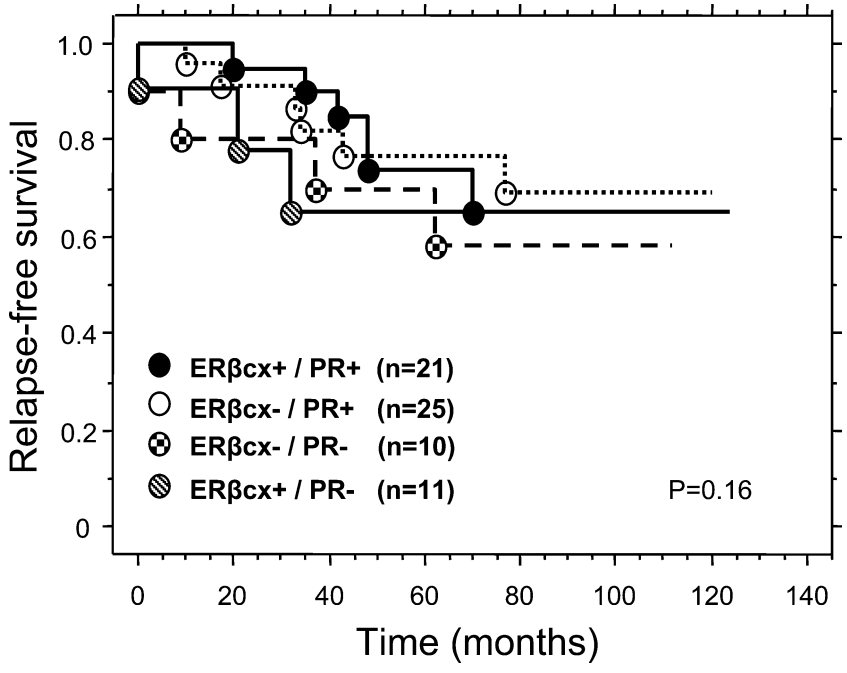

Fig. 3 Kaplan-Maier analysis of relapse-free survival in 67 estrogen receptor (ER)α-positive patients treated with adjuvant tamoxifen treatment. ERβcx+ indicates 2–8 points in Allred scoring. Patients with 5–8 points are considered PR+

preventively for breast cancer and colon cancer. Of course, this is speculation and we need further data before proceeding with this strategy. TAS-108, a SERM showing antagonistic property toward ERα signaling accompanied with a partial agonistic effect for ERβ, is currently undergoing phase II trials for metastatic breast cancer treatment [42]. In order to utilize this characteristic, it will be important to include ERβ expression in tumor tissues and molecular analysis of estrogen signaling in other organs as subjects to be evaluated in clinical trials. Since the clinical application of aromatase inhibitors for breast cancer treatment has spread rapidly, SERMs will need to show benefits in a broader range of estrogen biology throughout the whole body.

References

1. Adlercreutz H (2002) Phyto-oestrogens and cancer. Lancet Oncol 3:364–373
2. Balfe P, McCann A, McGoldrick A, McAllister K, Kennedy M, Dervan P, Kerin MJ (2004) Estrogen receptor alpha and beta profiling in human breast cancer. Eur J Surg Oncol 30:469–474
3. Beral V, Banks E, Reeves G (2002) Evidence from randomised trials on the long-term effects of hormone replacement therapy. Lancet 360:942–944
4. Cappelletti V, Celio L, Bajetta E, Allevi A, Longarini R, Miodini P, Villa R, Fabbri A, Mariani L, Giovanazzi R, Galante E, Greco M, Grazia Daidone M (2004) Prospective evaluation of estrogen receptor-beta in predicting response to neoadjuvant antiestrogen therapy in elderly breast cancer patients. Endocr Relat Cancer 11:761–770
5. Chang HG, Kim SJ, Chung KW, Noh DY, Kwon Y, Lee ES, Kang HS (2005) Tamoxifen-resistant breast cancers show less frequent methylation of the estrogen receptor beta but not the estrogen receptor alpha gene. J Mol Med 83:132–139
6. Cowley SM, Parker MG (1999) A comparison of transcriptional activation by ER alpha and ER beta. J Steroid Biochem Mol Biol 69:165–175
7. Enmark E, Pelto-Huikko M, Grandien K, Lagercrantz S, Lagercrantz J, Fried G, Nordenskjold M, Gustafsson JA (1997) Human estrogen receptor beta-gene structure, chromosomal localization and expression pattern. J Clin Endocrinol Metab 82:4258–4265
8. Esslimani-Sahla M, Simony-Lafontaine J, Kramar A, Lavaill R, Mollevi C, Warner M, Gustafsson JA, Rochefort H (2004) Estrogen receptor beta (ER beta) level but not its ER beta cx variant helps to predict tamoxifen resistance in breast cancer. Clin Cancer Res 10:5769–5776
9. Fuqua SA, Schiff R, Parra I, Moore JT, Mohsin SK, Osborne CK, Clark GM, Allred DC (2003) Estrogen receptor beta protein in human breast cancer: correlation with clinical tumor parameters. Cancer Res 63:2434–2439
10. Green S, Walter P, Kumar V, Krust A, Bornert JM, Argos P, Chambon P (1986) Human oestrogen receptor cDNA: sequence, expression and homology to v-erb-A. Nature 320:134–139
11. Greene GL, Gilna P, Waterfield M, Baker A, Hort Y, Shine J (1986) Sequence and expression of human estrogen receptor complementary DNA. Science 231:1150–1154
12. Hopp TA, Weiss HL, Parra IS, Cui Y, Osborne CK, Fuqua SA (2004) Low levels of estrogen receptor beta protein predict resistance to tamoxifen therapy in breast cancer. Clin Cancer Res 10:7490–7499
13. Jensen EV, Jacobsen HI (1962) Basic guides to the mechanism of estrogen action. Rec Prog Horm Res 18:387–414
14. Kuiper GG, Enmark E, Pelto-Huikko M, Nilsson S, Gustafsson JA (1996) Cloning of a novel receptor expressed in rat prostate and ovary. Proc Natl Acad Sci USA 93:5925–5930
15. Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT, van der Burg B, Gustafsson JA (1998) Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology 139:4252–4263
16. Lindberg MK, Moverare S, Skrtic S, Gao H, Dahlman-Wright K, Gustafsson JA, Ohlsson C (2003) Estrogen receptor (ER)-beta reduces ERalpha-regulated gene transcription, supporting a "ying yang" relationship between ERalpha and ERbeta in mice. Mol Endocrinol 17:203–208
17. Mann S, Laucirica R, Carlson N, Younes PS, Ali N, Younes A, Li Y, Younes M (2001) Estrogen receptor beta expression in invasive breast cancer. Hum Pathol 32:113–118
18. Moore JT, McKee DD, Slentz-Kesler K, Moore LB, Jones SA, Horne EL, Su JL, Kliewer SA, Lehmann JM, Willson TM (1998) Cloning and characterization of human estrogen receptor beta isoforms. Biochem Biophys Res Commun 247:75–78
19. Murphy LC, Leygue E, Niu Y, Snell L, Ho SM, Watson PH (2002) Relationship of coregulator and oestrogen receptor isoform expression to de novo tamoxifen resistance in human breast cancer. Br J Cancer 87:1411–1416
20. Myers E, Fleming FJ, Crotty TB, Kelly G, McDermott EW, O'higgins NJ, Hill AD, Young LS (2004) Inverse relationship between ER-beta and SRC-1 predicts outcome in endocrine-resistant breast cancer. Br J Cancer 91:1687–1693
21. Nakopoulou L, Lazaris AC, Panayotopoulou EG, Giannopoulou I, Givalos N, Markaki S, Keramopoulos A (2004) The favourable prognostic value of oestrogen receptor beta immunohistochemical expression in breast cancer. J Clin Pathol 57:523–528
22. Nilsson S, Makela S, Treuter E, Tujague M, Thomsen J, Andersson G, Enmark E, Pettersson K, Warner M, Gustafsson JA (2001) Mechanisms of estrogen action. Physiol Rev 81:1535–1565
23. Ogawa S, Inoue S, Watanabe T, Orimo A, Hosoi T, Ouchi Y, Muramatsu M (1998) Molecular cloning and characterization of human estrogen receptor betacx: a potential inhibitor of oestrogen action in human. Nucleic Acids Res 26:3505–3512
24. Omoto Y, Inoue S, Ogawa S, Toyama T, Yamashita H, Muramatsu M, Kobayashi S, Iwase H (2001) Clinical value of the wild-type estrogen receptor beta expression in breast cancer. Cancer Lett 163:207–212
25. Omoto Y, Kobayashi S, Inoue S, Ogawa S, Toyama T, Yamashita H, Muramatsu M, Gustafsson JA, Iwase H (2002) Evaluation of oestrogen receptor beta wild-type and variant protein expression, and relationship with clinicopathological factors in breast cancers. Eur J Cancer 38:380–386
26. Omoto Y, Eguchi H, Yamamoto-Yamaguchi Y, Hayashi S (2003) Estrogen receptor (ER) beta1 and ERbetacx/beta2 inhibit ERalpha function differently in breast cancer cell line MCF7. Oncogene 22:5011–5020
27. O'Neill PA, Davies MP, Shaaban AM, Innes H, Torevell A, Sibson DR, Foster CS (2004) Wild-type oestrogen receptor beta (ERbeta1) mRNA and protein expression in tamoxifen-treated post-menopausal breast cancers. Br J Cancer 91:1694–1702
28. Paech K, Webb P, Kuiper GG, Nilsson S, Gustafsson J, Kushner PJ, Scanlan TS (1997) Differential ligand activation of estrogen receptors ERalpha and ERbeta at AP1 sites. Science 277:1508–1510
29. Palmieri C, Cheng GJ, Saji S, Zelada-Hedman M, Warri A, Weihua Z, Van Noorden S, Wahlstrom T, Coombes RC, Warner M, Gustafsson JA (2002) Estrogen receptor beta in breast cancer. Endocr Relat Cancer 9:1–13
30. Palmieri C, Lam EW, Mansi J, MacDonald C, Shousha S, Madden P, Omoto Y, Sunters A, Warner M, Gustafsson JA, Coombes RC (2004) The expression of ER beta cx in human breast cancer and the relationship to endocrine therapy and survival. Clin Cancer Res 10:2421–2428

31. Roger P, Sahla ME, Makela S, Gustafsson JA, Baldet P, Rochefort H (2001) Decreased expression of estrogen receptor beta protein in proliferative preinvasive mammary tumors. Cancer Res 61:2537–2541
32. Saji S, Omoto Y, Shimizu C, Warner M, Hayashi Y, Horiguchi S, Watanabe T, Hayashi S, Gustafsson JA, Toi M (2002) Expression of estrogen receptor (ER) (beta)cx protein in ER(alpha)-positive breast cancer: specific correlation with progesterone receptor. Cancer Res 62:4849–4853
33. Shaaban AM, O'Neill PA, Davies MP, Sibson R, West CR, Smith PH, Foster CS (2003) Declining estrogen receptor-beta expression defines malignant progression of human breast neoplasia. Am J Surg Pathol 27:1502–1512
34. Skliris GP, Munot K, Bell SM, Carder PJ, Lane S, Horgan K, Lansdown MR, Parkes AT, Hanby AM, Markham AF, Speirs V (2003) Reduced expression of oestrogen receptor beta in invasive breast cancer and its re-expression using DNA methyl transferase inhibitors in a cell line model. J Pathol 201:213–220
35. Speirs V, Malone C, Walton DS, Kerin MJ, Atkin SL (1999) Increased expression of estrogen receptor beta mRNA in tamoxifen-resistant breast cancer patients. Cancer Res 59:5421–5424
36. Speirs V, Skliris GP, Burdall SE, Carder PJ (2002) Distinct expression patterns of ER alpha and ER beta in normal human mammary gland. J Clin Pathol 55:371–374
37. Speirs V, Carder PJ, Lane S, Dodwell D, Lansdown MR, Hanby AM (2004) Oestrogen receptor beta: what it means for patients with breast cancer. Lancet Oncol 5:174–181
38. Stossi F, Barnett DH, Frasor J, Komm B, Lyttle CR, Katzenellenbogen BS (2004) Transcriptional profiling of estrogen-regulated gene expression via estrogen receptor (ER) alpha or ERbeta in human osteosarcoma cells: distinct and common target genes for these receptors. Endocrinology 145:3473–3486
39. Strom A, Hartman J, Foster JS, Kietz S, Wimalasena J, Gustafsson JA (2004) Estrogen receptor beta inhibits 17beta-estradiol-stimulated proliferation of the breast cancer cell line T47D. Proc Natl Acad Sci USA 101:1566–1571
40. Taylor AH, Al-Azzawi F (2000) Immunolocalisation of oestrogen receptor beta in human tissues. J Mol Endocrinol 24:145–155
41. Yamamoto S, Sobue T, Kobayashi M, Sasaki S, Tsugane S, Japan Public Health Center-Based Prospective Study on Cancer Cardiovascular Diseases Group (2003) Soy, isoflavones, and breast cancer risk in Japan. J Natl Cancer Inst 95:906–913
42. Yamamoto Y, Shibata J, Yonekura K, Sato K, Hashimoto A, Aoyagi Y, Wierzba K, Yano S, Asao T, Buzdar AU, Terada T (2005) TAS-108, a novel oral steroidal antiestrogenic agent, is a pure antagonist on estrogen receptor alpha and a partial agonist on estrogen receptor beta with low uterotrophic effect. Clin Cancer Res 11:315–322