International Journal of Ecophysiology Vol. 05, No. 01, 2023 |42-53

Internasional Journal of Ecophysiology

A systematic review and meta analysis of estrogen receptor beta as a predictive factor in breast cancer patients

Armansyah Maulana Harahap[1,2], Kurnia Agustini[2], and Sri Ningsih[2]

[1][Doktoral Farmasi, Departemen Farmakologi dan Toksikologi, Fakultas Farmasi,Universitas Indonesia]
[2][Pusat Riset Bahan Baku Obat dan Obat Tradisional,Badan Riset InovasiNasional BRIN]
E-mail author :armansyah.maulanahr@gmail.com; kurn005@brin.go.id; srin002@gmail.com

Abstract. It is unclear how estrogen receptor beta (ER) affects prognosis in breast cancer that is in the early stages. To determine the predictive value of ER in patients with early-stage breast cancer, we conducted a systematic review and meta-analysis. We looked for studies that evaluated the ER status in breast cancer patients article between 2010 and 2018 by searching Medline, Embase, and the Web of Science. 1700 participants from 18 studies total who met our inclusion and exclusion criteria were included. *A Technical Expert Panel (TEP) of 3 medical specialist and expertise of disorder the abnormally cell cycle and cancer performed the review using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) model. The TEP planned a research on PubMed selecting "cancer" and "Breast Cancer" as MeSH (Medical Subject Headings) term adding to PubMed Search Builder the terms "Estrogen" and "Estrogen receptor". TEP is considered for eligibility articles published within the last 13 years, including original research, in particular in vitro studies, and animal and clinical studies in English. Results: Of the 90 identified studies, TEP included 15 studies, 8 Systematical Review, and 4 clinical studies and 3 Review report. Our scoping review describes and summarizes the important* develop highly selective anti-ERβ antibodies that are applied to large well characterized human breast cancer samples to validate their diagnostic potential and to explore ERβ-selective agonists in animal models of breast cancer to validate their therapeutic potential

Keyword: [*Cancer, Breast, Breast cancer*, *ERβ*, *Estrogen receptor*]

Received [14 December 2022] | Revised [15 January 2023] | Accepted [25 February 2023]

1 Introduction

It has been demonstrated that the estrogen receptor (ER) is a strong predictor of breast cancer patients' responsiveness to endocrine therapy. The standard-of-care pathological evaluation used to direct adjuvant endocrine therapy following surgery is immunohistochemical (IHC) testing of ER status. In ER+ patients, anti-estrogen methods are advised. The role of estrogen in the normal development of the mammary gland, breast carcinogenesis, and tumor progression has been reevaluated as a result of the

*Corresponding author at: [Doktoral Farmasi, Departemen Farmakologi dan Toksikologi, Fakultas Farmasi,Universitas Indonesia]

E-mail address: [armansyah.maulanahr@gmail.com]

 e-ISSN: 2656-0674
DOI: 10.32734/ijoep.v5i1.12382
Journal Homepage: http://ijoep.usu.ac.id

identification of a second ER, ER. Although ER has been studied for more than 15 years, its clinical significance is still unknown. The relevance of ER in predicting long-term clinical outcomes (such as disease-free survival) in breast cancer patients was initially reported by Mann et al. [1], and this finding was later supported by further investigations [2-4].

Contradictory data, however, imply that ER status is not related to survival [5, 6]. The current systematic review and meta-analysis set out to look into the relationship between breast cancer patients' long-term clinical outcomes, such as disease-free survival and overall survival, and their ER status (positive vs. negative).

2. Material and Methods

This scoping review was carried out following PRISMA-ScR (Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scope Overview). The first step is creation of a technical expert panel (TEP) consisting of 3 specialist and expertise with expertise in the field of cancer. All TEP components are confident with scoping review methodology. As a search strategy, TEP planned research on PubMed (Public MedLine, run by .) National Center for Biotechnology Information, NCBI, of the Bethesda National Library of Medicine, Bethesda, MD, USA), chose the term “Breast cancer” as MeSH (Medical Subject Headings); follower terms added to run PubMed Search Builder: "Cancer", "Estrogen receptor" ("Cell cycle"; “abnormal” and and “Hormone”. According to the purpose of the review, TEP defines the characteristics of sources of evidence, considering the feasibility of every study published in the scientific literature in the last 13 years (last update in June 2018), including original articles, review in particular in vitro, in silico and animal studies and clinical studies in English and Indonesian

3. Results and Discussion

From the 90 identified studies, 60 articles were screened for eligibility after removing duplicates and 30 articles irrelevant to the purpose of the scoping review. This, 15 were excluded for different reasons because based on the study there was still not much discussion about the relationship of exercise with uric acid and specific transporters. Of these, only 15 studies were included (Figure 1). We divided our results in preclinical and clinical studies (Table 1).

Table 1. Features ofinduced studies

Author, Year	Article	Parameters marker oncologi
Chang et al, 2017	Oncology Letters	Correlated to small tumor size, node negativity and low histological grad
Madeira *et al* , 2013	Research Article	Correlated to ERa expression. Inversely correlated to HER2 expression

Oueslati *et al*, 2017	Oncology Letters	Inversely correlated to HER2 expression
Mirza *et al*., 2012	Clinical study	No correlation to clinicopathological parameters
Guo et al., 2014	Clinical study	Correlated to smaller size and lower grade in infiltrating apocrine carcinoma
Yan et al., 2011	Clnical study	Correlated to ERa expression. Inversely correlated to HER2 expression. The absence of ERβ1 was associated with larger tumors, node positivity and higher histological grade
Austin *et al.,* 2018	Clinical study	Nuclear ERβ2 correlated to ERa expression and inversely correlated to metastasis and vascular invasio
Wisinski *et al*., 2016	Clinical study	Correlated to ERa expression and low histological grade
Shanle *et al*., 2015	Clinical study	No correlation to clinicopathological parameters
Guo *et al*., 2015	Research Article	Correlated to increased OS only at high percentage cutoff (65% positive nuclei
Hamilion *et al*., 2015	Research Article	Correlated to response to preoperative systemic therapy
Wang *et al*., 2015	Clinical study	Expression not correlated to response to preoperative systemic therapy
Wu *et al*., 2011	Research Article	Correlated to increased DFS and OS. Predicted response to endocrine therapy. Cytoplasmic localization correlated to decreased OS
Pons *et al*., 2015	Research Article	Correlated to increased DFS in node negative LA and to decreased DFS in node positive LB
Wu *et al*., 2011	Clinical study	Correlated to increased DFS and OS in postmenopausal women but not in premenopausal women and to increased DFS and OS in TNB

Roles of ERβ inBreast cancer Theraphy according article review

Questions with respect to the relationship between the part of ERβ and the treatment of breast cancer have provoked considers around ERβ and drugs. TAM could be a standard select ive estrogen receptor modulator (SERM) that can be utilized as an adjuvant treatment for breast cancer repeat in patients whose essential tumors are ERα positive. The part of ERβ in TAM treatment has been examined [7]. In TAM-treated cells, ERβ overexpression driven to an inwrinkle in autophagy, which diminished cell reasonability [8]. ERβ moreover expanded TAM-induced cell passing and actuated the expression of the proapoptotic quality BIK in cooperation with TAM [9]. TAM locked in mitochondrial Erβ as an enemy, expanding responsive oxygen species (ROS) concentrations from the mitochondria that were required for cytotoxicity [10]. By enlisting ERβ, cJun, cFos, authoritative protein (CBP), and RNA polymerase II to and expelling NCoR from the atomic respiratory figure 1 (NRF-1) promoter, TAM expanded NRF-1 expression.

In spite of this, TAM-induced NRF-1 translation was likely intervened by ERβ [64]. Also, ERβ upgraded the affectability of breast cancer cells to TAM [11]. Erβ re-expression was thought to sensitize MCF-7/TAM R cells to the development inhibitory and proapoptotic impacts of TAM, subsequently demonstrating that ERβ re-expression was dir- ectly connected to reestablishing TAM affectability [12].Numerous medicate medicines have been appeared to be medi- ated by ERβ and its isoforms [13]. ERβ can upgrade the antiproliferative impacts of raloxifene [14, 15] and the affectability to anti-androgens in TNBC [16]. After treating MCF-7 cells with cisplatin, the overexpression of ERβ contributed to the lower rates of apoptosis, autophagy and ROS generation, driving to expanded cell survival. The inverse comes about were found by quieting Erβ in T47D cells [17].

Instruments of ERβ smothering breast cancer movement

Over the a long time, analysts have found numerous mechanisms of ERβ in restraining tumor movement, particularly in breast cancer. ERβ signaling is known to be complex and multifaceted and not fair a component of a straight signaling pathway. By and large, the instruments related with ERβ in vivo and in vitro models show that Erβ may act as a tumor silencer. The structures of the two ERs are compared in (Figure 1) include ERβ

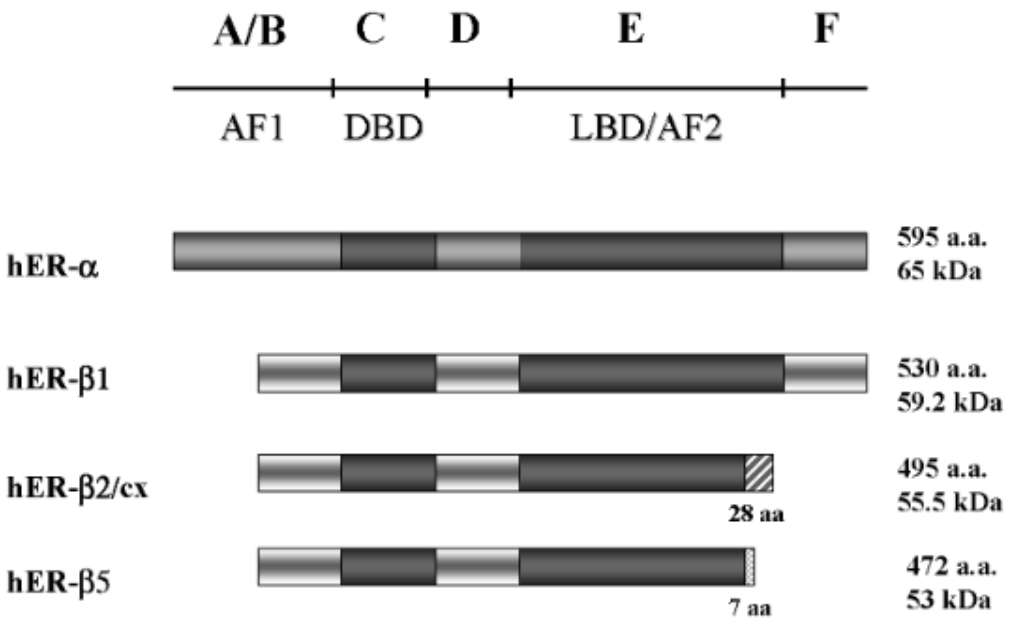

Figure 1. Comparison of the basic organization of human Time, human ERβ1, human ERβ2 and human ERβ5 proteins[43]

Mechanism of Estrogen receptors activation (Erα/Erβ)

Estrogens can act through diverse instruments and pathways to cause their organic impacts. There's a normal atomic receptor superfamily component to tweak the expression of a few qualities. Estrogen actuates ER by ligand authoritative to the receptor, but this solidarity can happen in to shapes. The primary can occur when E2-ER complex has shaped within the cytoplasm and after that is transported to

the core through cytoskeleton controlled components [18]. The moment form has the same last item, but happens by a coordinate E2 official to the ER within the core, with this union permitting for possible ER separation of the chaperon proteins and the rebuilding of the ER to the dormant state. After this separation, ER can frame either heterodimers or homodimers and tie straightforwardly to estrogen reaction component (ERE) through the DNA-binding space as well as by affiliation with distinctive quality control co activators[19].

Another instrument incorporates the inclusion of the SP1 protein within the arrangement of the bridge between the actuated estrogen receptor dimer and ERE. This component shapes an backhanded activation/inhibition of E2 directed qualities and a few creators have found contrasts dependant on the ERα and ERβ union to ERE[20]. Another activity of ERs, in a non-genomic prepare, includes the interaction of actuated ERs with auxiliary flag-bearer proteins (SM) with quick, concomitant impacts in numerous tissues, in spite of the fact that this prepare is still not well caught on[21]. Moreover, ERs have a ligand-independent enactment component, including kinases that phosphorylate and enact ERs and this instrument might clarify the hormone free development of a few tumors. Other components have an imperative part within the enactment components of ERs and serve as corregulators (or cofactors) selected by the ERs to actuate (coactivator) or to quell (corepressor) the transcriptional movement of ERs. These corregulators can adjust the partiality of the ERs to EREs and can be within the shape of acetylases/deacetylases, kinases/phosphatases and methylases/demethylases[22,23,24]. It must be emphasized, in any case, that the pool of corregulators can vary concurring to the sort of tissue, and it is the reality that has been proposed as an clarification for the differential tissue impacts of estrogen and particular estrogen receptor modulator (SERMS)[25]. In addition, not as it were do corregulators vary according to tissue, the conveyance of ERα and ERβ has too been detailed to differ. Within the tissues when both ERα and ERβ coexist, their impacts appear to check each other. In this way, within the uterus, mammary organs and the resistant frameworks, ERα advances cell expansion whereas ERβ has proapoptotic and cell separation capacities (Figure 2)

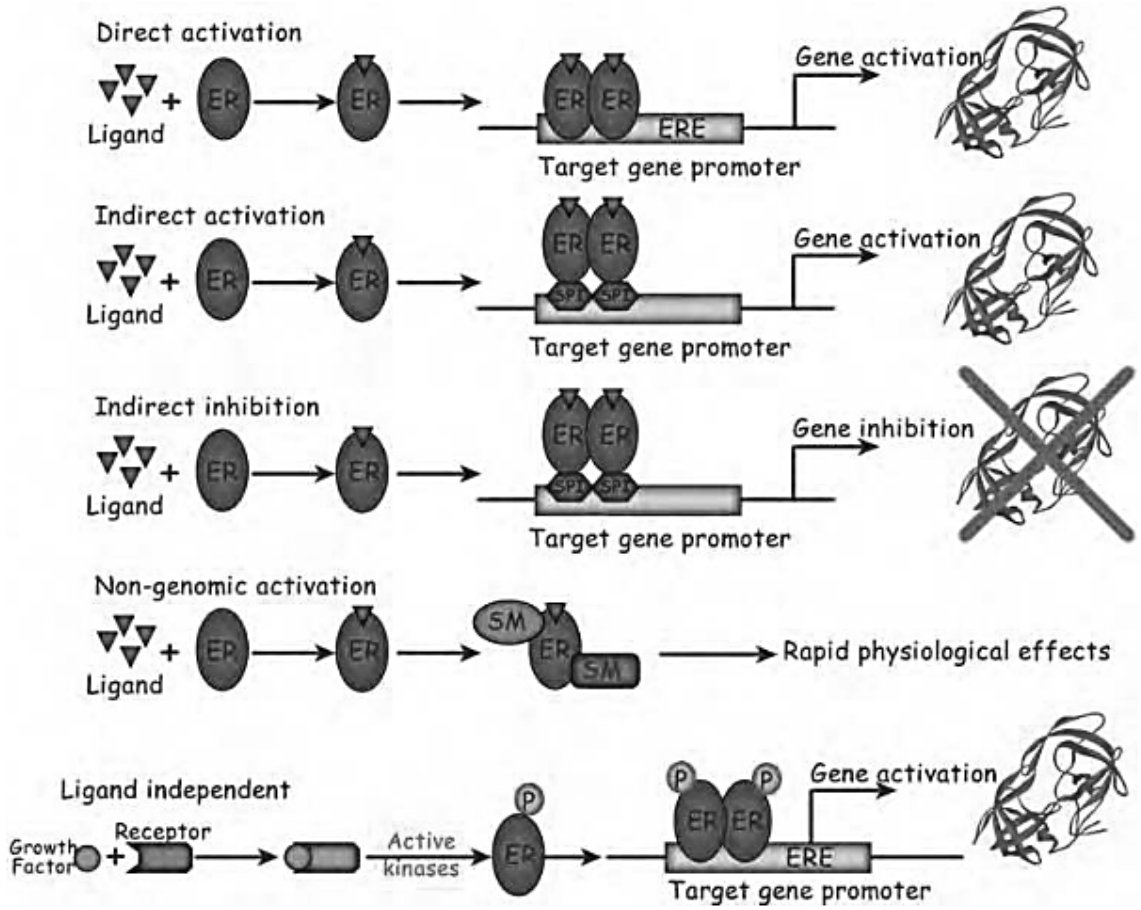

Figure 2. ER Mechanism and activation [41]

The interaction of ERα and ERβ in breast cancer

A few analysts accept that the changes in ERα and ERβ expression within the ordinary breast back a coordinate relationship between the atomic expression of ERs and the proliferative nature of the breast [28]. The relative levels of ERβ and ERα in breast cancer are related to the exercises of numerous signaling pathways mindful for cell multiplication and endocrine treatment reaction [26,27]. A ponder appears that beneath the condition of coexpression of ERα and ERβ, HER2 expression is as often as possible found to be negative, while the Ki-67 record is upregulated, demonstrating an affiliation between this extraordinary combination of biomarkers and breast cancer forcefulness[29]. Moreover, lifted ERβ can influence ERα expression at the transcriptional level through downregulation of basal ERα promoter action. This down control of ERα happens through ERβ-Sp1 protein- protein intuitive inside the ERα promoter locale and enrollment of a corepressor complex containing the atomic receptor corepressor NCoR, hypoacetylation of histone H4 and relocation of RNA-polymerase II [30].

The utilize of an ERβ-specific agonist essentially diminishes the expression and utilitarian movement of Erα in MCF-7 breast cancer cells, went with by diminished translation of a downstream effector, breast cancer related quality 2 (BCA2) [23].Extra prove appears that tumors with a moo

ERα/ERβ proportion have expanded oxidative harm, antioxidant chemical protein levels and uncoupling protein (UCP) and sirtuin 3 (SIRT3) protein levels. Glutathione peroxidase, complex V, complex III, complex II, complex IV, protein kinase B (AKT), stress-activated protein family- ase (SAPK), and ERα are emphatically related with the ERα/ERβ proportion, whereas carbonyl bunches, catalase, CuZn-superoxide dismutase, UCP5, SIRT3, and ERβ are nega- tively connected with the ERα/ERβ proportion [31]. It is rea- sonable to recommend that the awkwardness of two estrogen receptors may lead to the event of breast cancer [32].

Molecular Pathway of ERβ-induced apoptosis in tumor cells

ERβ actuates apoptosis by directing expression of the anti-apoptotic IAP proteins

*T*he anti-apoptotic proteins inhibitors of apoptosis proteins (IAP) are a lesson of useful proteins that tie and hinder caspases to avoid cell passing. A blend of the anticancer drugs mistletoe and triterpene restrains IAP expression in osteosarcoma cells and synergistically actuates apoptosis. Diminished expression of the IAP family protein X-linked inhibitor of apoptosis (X-IAP) restrains multiplication and actuates apoptosis in osteosarcoma cells[33,34,35]. Microarray examination appeared that ERβ controls expression of the IAP family protein SURVIVIN in human breast cancer cells. Additionally, ERβ controls expression of the IAP family protein cIAP2 in epithelial colorectal cancer cells(Figure 3).

ERβ actuates apoptosis by directing the NF-kB/BCL-2 pathway

NF-kB could be a pro-inflammatory calculate that's included in a assortment of cellular forms counting multiplication, separation, apoptosis, and inflammation. It has been detailed that estrogen receptors are related with NF-kB signaling pathways in tumor cells. In bladder cancer cells, ERβ levels are contrarily connected with atomic p65 levels[40]. NF-kB straightforwardly directs translation of the anti-apoptotic figure BCL-2; hence, the NF-jB/BCL-2 pathway is thought to play an imperative part in tumorigenesis and apoptosis[36,37,38]. Immunohistochemical investigation appeared that the event of endometriosis related tumors related with tall BCL-2 expression and diminished expression of estrogen receptors. In hormone safe breast cancer cells, ERβ agonists decrease BCL-2 expression and enact autophagy (Figure 3).

ERβ regulates expression of proapoptotic factor BAX

Protein that promotes apoptosis As a pro-apoptotic factor, BAX, a member of the BCL-2 gene family, joins forces with BCL-2 to create a heterodimer. Cytochrome C is released by BAX after it opens the mitochondrial voltage-dependent anion channel, which causes cells to start the apoptotic process[39]. High levels of ERβ2 and BAX expression were positively linked with patient survival in non-small cell lung cancer clinical studies. Additionally, artificially introducing ERβ into prostate cancer cells can increase the expression of BAX and cause death in those cells (Figure 3).

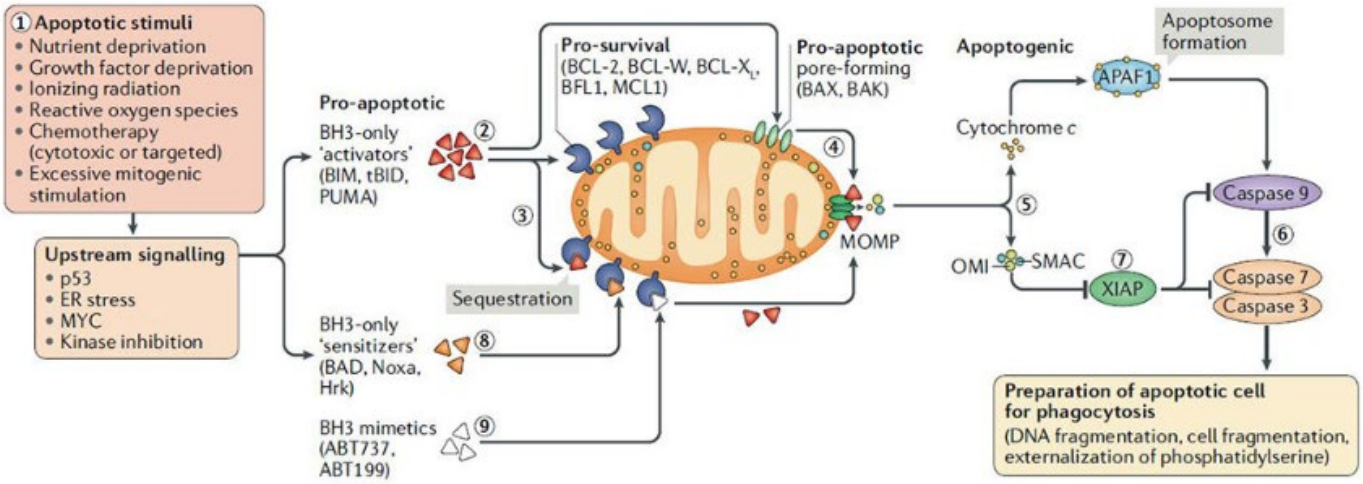

Figure 3. Apoptosis Pathway and ERβ (Molecular Pathway of ERβ-induced apoptosis in tumor cells) [42]

To start apoptosis, cellular stretch or harm signals [1] unleash pro-apoptotic proteins (BH3-only 'activators' of apoptosis) through their upregulation (BIM or Panther) or cleavage (Offered cleaved to make truncated tBID) [2], which can either be bound and sequestered by pro-survival proteins such as BCL-2, BCL-XL or MCL1 [3] or, when these pro-survival proteins are immersed or truant, can actuate BAX and/or BAK [4]. Enacted BAX or BAK oligomerize and frame pores to cause mitochondrial outer membrane permeabilization (MOMP), coming about within the discharge of apoptogenic particles counting SMAC, OMI and cytochrome c from the mitochondrial intermembrane space. Cytochrome c ties APAF1 within the cytosol to make the apoptosome (5), which serves as a stage for the enactment of caspase 9, which at that point goes on to actuate the effector caspases 3 and 7 (6) to destroy the cell and plan it for phagocytosis. Caspase actuation can be blocked by XIAP (7), which in turn is hindered by the discharged SMAC and OMI proteins from mitochondria (7). Upstream harm or push flagging can moreover actuate BH3-only 'sensitizer' proteins that don't productively enact BAX and BAK but hinder the action of pro-survival BCL-2 family proteins to discharge any sequestered BH3-only activators, which trigger MOMP (8). BH3 mimetics are a novel lesson of specialists that are able to sensitize cells to apoptosis by blocking the action of pro-survival BCL-2 family proteins (9).

4. Conclusion

Our scoping review describes and summarizes the important develop highly selective anti-ERβ antibodies that are applied to large well characterized human breast cancer samples to validate their diagnostic potential and to explore ERβ-selective agonists in animal models of breast cancer to validate their therapeutic potential

Reference

[1] Bialesova L, Xu L, Gustafsson J-Å, Haldosen L-A, Zhao C, Dahlman- Wright K, Estrogen receptor β2 induces proliferation and invasiveness of triple negative breast cancer cells: association with regulation of PHD3 and HIF-1α. Oncotarget, 8:76622. doi: 10.18632/oncotarget.20635, 2017.

[2] Dey P, Velazquez-Villegas LA, Faria M, Turner A, Jonsson P, Webb P, et al, Estrogen receptor β2 induces hypoxia signature of gene expression by stabilizing HIF-1α in prostate cancer. PLoS One, 10:e0128239. doi: 10.1371/journal.pone.0128239 17, 2015.

[3] M, Karami S, Granados-Principal S, Dey P, Verma A, Choi DS, et al, The ERβ4 variant induces transformation of the normal breast mammary epithelial cell line MCF-10A; the ERβ variants ERβ2 and ERβ5 increase aggressiveness of TNBC by regulation of hypoxic signaling. Oncotarget, 9:12201. doi: 10.18632/oncotarget.24134, 2018.

[4] Moore JT, McKee DD, Slentz-Kesler K, Moore LB, Jones SA, Horne EL, et al, Cloning and characterization of human estrogen receptor β isoforms. Biochem Biophys Res Commun, 247:75–8. doi: 10.1006/bbrc.1998.8738 19, 1998.

[5] Hall JM, McDonnell DP. The estrogen receptor β-isoform (ERβ) of the human estrogen receptor modulates ERα transcriptional activity and is a key regulator of the cellular response to estrogens and antiestrogens. Endocrinology, 140:5566–78. doi: 10.1210/endo.140.12.7179, 1999.

[7] Reese JM, Suman VJ, Subramaniam M, Wu X, Negron V, Gingery A, et al., ERβ1: characterization, prognosis, and evaluation of treatment strategies in ERα-positive and-negative breast cancer. BMC Cancer, 14:749. doi: 10.1186/1471-2407-14-749, 2014.

[8] Paruthiyil S, Parmar H, Kerekatte V, Cunha GR, Firestone GL, Leitman DC., Estrogen receptor beta inhibits human breast cancer cell proliferation and tumor formation by causing a G2 cell cycle arrest. Cancer Res, 64:423–8. doi: 10.1158/0008-5472.CAN-03-2446 55, 2004.

[9] Ma L, Liu Y, Geng C, Qi X, Jiang J, Estrogen receptor beta inhibits estradiol- induced proliferation and migration of MCF-7 cells through regulation of mitofusin 2. *Int J Oncol*, 42:1993–2000. doi: 10.3892/ijo.2013.1903, 2013.

[10] Pinton G, Zonca S, Manente AG, Cavaletto M, Borroni E, Daga A, et al, SIRT1 at the crossroads of AKT1 and ERβ in malignant pleural mesothelioma cells. Oncotarget, 7:14366–79. doi: 10.18632/oncotarget.7321, 2016.

[11] Manente AG, Pinton G, Zonca S, Cilli M, Rinaldi M, Daga A, et al, Intracellular lactate-mediated induction of estrogen receptor beta (ERβ) in biphasic malignant pleural mesothelioma cells. Oncotarget, 6:25121– 34. doi: 10.18632/oncotarget.4486, 2015.

[12] Cotrim CZ, Fabris V, Doria ML, Lindberg K, Gustafsson JA, Amado F, et al, Estrogen receptor beta growth-inhibitory effects are repressed through activation of MAPK and PI3K signalling in mammary epithelial and breast cancer cells. Oncogen, 32:2390–402. doi: 10.1038/onc.2012.261, 2013.

[13] Hartz AM, Madole EK, Miller DS, Bauer B, Estrogen receptor beta signaling through phosphatase and tensin homolog/phosphoinositide 3- kinase/Akt/glycogen synthase kinase 3 down-regulates blood-brain barrier breast cancer resistance protein. *J Pharmacol Exp Ther*, 334:467–76. doi: 10.1124/jpet.110.168930, 2010.

[14] Stoica GE, Franke TF, Moroni M, Mueller S, Morgan E, Iann MC, et al, Effect of estradiol on estrogen receptor-α gene expression and activity can be modulated by the ERβB2/PI 3-K/Akt pathway. Oncogene, 22:7998. doi: 10.1038/sj.onc.1206769, 2003.

[15]Campbell RA, Bhat-Nakshatri P, Patel NM, Constantinidou D, Ali S, Nakshatri H, Phosphatidylinositol 3-Kinase/AKT-mediated activation of estrogen receptor α A new model for anti-estrogen resistance. *J Biol Chem*, 276:9817–24. doi: 10.1074/jbc.M010840200, 2001.

[16] Monsivais D, Dyson MT, Yin P, Navarro A, Coon JST, Pavone ME, et al, Estrogen receptor β regulates endometriotic cell survival through serum and glucocorticoid-regulated kinase activation. Fertil Steril, 105:1266–73. doi: 10.1016/j.fertnstert.2016.01.01, 2016.

[17] Chang J, Liu J, Li H, Li J, Mu Y, Feng B, Expression of ERβ gene in breast carcinoma and the relevance in neoadjuvant therapy. Oncol Lett, ;13(3): 1641–6, 2017.

[18] Madeira M, Mattar A, Logullo AF, Soares FA, Gebrim LH, Estrogen receptor alpha/beta ratio and estrogen receptor beta as predictors of endocrine therapy responsiveness-a randomized neoadjuvant trial comparison between anastrozole and tamoxifen for the treatment of postmenopausal breast cancer. BMC Cancer, 18(13):425, 2013.

[19] Oueslati M, Bittaieb I, Sassi N, Jemaa AB, Gamoudi A, Rahal K, Oueslati R, ERα and ERβ co-expression: an indicator of aggressive tumors and hormonal sensitivity. *Oncol Lett.* 2017;14(2):1675–82, 2017.

[20] Mirza S, Sharma G, Parshad R, Srivastava A, Gupta SD, Ralhan R, Clinical significance of promoter hypermethylation of ERβ and RARbeta2 in tumor and serum DNA in Indian breast cancer patients. Ann Surg Oncol, 19(9):3107–15, 2012.

[21] Guo L, Zhang Y, Zhang W, Yilamu D, Correlation between estrogen receptor beta expression and the curative effect of endocrine therapy in breast cancer patients. Exp Ther Med, 7(6):1568–72, 2014.

[22] Guo L, Zhang YU, Yilamu D, Liu S, Guo C, ERβ overexpression results in endocrine therapy resistance and poor prognosis in postmenopausal ERα-positive breast cancer patients. Oncol Lett, 11(2):1531–6, 2016.

[23] Yan M, Rayoo M, Takano EA, Fox SB, Nuclear and cytoplasmic expressions of ERβ1 and ERβ2 are predictive of response to therapy and alters prognosis in familial breast cancers. Breast Cancer Res Treat, 126(2): 395–405, 2011.

[24] Austin D, Hamilton N, Elshimali Y, Pietras R, Wu Y, Vadgama J, Estrogen receptor-beta is a potential target for triple negative breast cancer treatment. Oncotarget, 9(74):33912–30, 2018.

[25] Wisinski KB, Xu W, Tevaarwerk AJ, Saha S, Kim K, Traynor A, Dietrich L, Hegeman R, Patel D, Blank J, et al, Targeting estrogen receptor beta in a phase 2 study of high-dose estradiol in metastatic triple-negative breast cancer: a Wisconsin oncology network study. *Clin Breast Cancer*, (4): 256–61, 2016.

[27] Shanle EK, Onitilo AA, Huang W, Kim K, Zang C, Engel JM, Xu W, Wisinski KB Prognostic significance of full-length estrogen receptor beta expression in stage I-III triple negative breast cancer, *Am J Transl Res*, 7(7):1246–59, 2015.

[29] Guo L, Zhu Q, Aisimutuola M, Yilamu D, Liu S, Jakulin A, Expression and prognostic value of estrogen receptor beta in patients with triple-negative and triple-positive breast cancer. *Exp Ther Med,* 9(6):2147–50, 2015.

[30] Hamilton N, Marquez-Garban D, Mah V, Fernando G, Elshimali Y, Garban H, Elashoff D, Vadgama J, Goodglick L, Pietras R. Biologic roles of estrogen receptor-beta and insulin-like growth factor-2 in triple-negative breast cancer, *Journal Biomed Res* Int, e925703, 2015.

[31] Wang J, Zhang C, Chen K, Tang H, Tang J, Song C, Xie X, ERβ1 inversely correlates with PTEN/PI3K/AKT pathway and predicts a favorable prognosis in triple-negative breast cancer. *Breast Cancer Res Trea*t, 152(2):255–69, 2015.

[32] Pons DG, Torrens-Mas M, Nadal-Serrano M, Sastre-Serra J, Roca P, Oliver J, The presence of estrogen receptor beta modulates the response of breast cancer cells to therapeutic agents. *Int J Biochem Cell Biol*, 66:85–9, 2015.

[33] Wu X, Subramaniam M, Grygo SB, Sun Z, Negron V, Lingle WL, Goetz MP, Ingle JN, Spelsberg TC, Hawse JR, Estrogen receptor-beta sensitizes breast cancer cells to the anti-estrogenic actions of endoxifen. Breast Cancer Res, 13(2):R27, 2011.

[34] Razandi M, Pedram A, Jordan VC, Fuqua S, Levin ER, Tamoxifen regulates cell fate through mitochondrial estrogen receptor beta in breast cancer, Oncogene, 32(27):3274–85, 2013.

[35] Ivanova MM, Luken KH, Zimmer AS, Lenzo FL, Smith RJ, Arteel MW, Kollenberg TJ, Mattingly KA, Klinge CM, Tamoxifen increases nuclear respiratory factor 1 transcription by activating estrogen receptor beta and AP-1 recruitment to adjacent promoter binding sites. *FASEB* J, 25(4): 1402–16, 2011.

[37]Lindberg K, Helguero LA, Omoto Y, Gustafsson JA, Haldosen LA, Estrogen receptor beta represses Akt signaling in breast cancer cells via downregulation of HER2/HER3 and upregulation of PTEN: implications for tamoxifen sensitivity, *Breast Cancer Res,* 13(2):R43, 2011.

[38] Treeck O, Lattrich C, Springwald A, Ortmann O, Estrogen receptor betaexerts growth-*inhibitory* effects on human mammary epithelial cells, *Journal Breast Cancer Res Treat*, 120(3):557–65, 2010.

[39] Zhou Y and Liu X, The role estrogen beta in breast cancer, *Article Review*. Biomarker research, 8:39, 2020.

[41] Roca P., Oliver J., Serra JS and Serrano MN. The Importance ERα/ERβ Ratio in Breast cancer: Mitochondrial Function and Oxidative Stress. Carcinogenesis, Cell, Growth and Signalling pathways. *Universities de les illes Balareas*. 2007. Chapter 10, 2010.

[42] Singh R, Letai A and Srosiek K, Regulation of apoptosis in health and desease: the balancing act of BCL-2 family proteins. *Author Manuscript*, 20(3): 175-193, 2019.

[43] Leigh Murphy, Tracy Cherlet, Anthony Lewis, Yasmin Banu & Peter Watson, New insights into estrogen receptor function in human breast cancer, *Annals of Medicine*, 35:8, 614-631, DOI: 10.1080/07853890310014579, 2003.