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Adrenoceptors and Breast Cancer: Review Article

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Dedicated to Mrs. Minka Klavins and Prof. Janis V. Klavins
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1. Introduction

The incidence of breast cancer has increased greatly in Israel over the past decade. It is estimated that in Israel in 2009 approximately 4800 new patients will suffer from breast cancer. Despite recent advances in the diagnosis and treatment of breast cancer, this disease continues to be a major cause of death. One of the biggest challenges in breast cancer treatment is bone metastasis. Breast cancer cells are capable of migrating to the bone marrow and utilizing the marrow microenvironment to remain quiescent. The preprotachykinin-1 (PPT-1) gene encodes for the tachykinin peptides, which interact with neurokinin (NK) receptors. Studies have correlated this interaction with breast cancer cells integration into the bone marrow and breast cancer progression ⁽¹⁾.

Environmental and psychological stresses have been shown to be associated with an increased incidence of cancer in man and animals. Stress-induced neuron chemical hormonal and immunological changes have been shown to influence tumor development. Stress may promote mammary carcinogenesis by affecting the neuroendocrine system and *I* or immune function. Neuroendocrine affects may involve changes in adrenocortical steroids or opioid peptides which may exert their effects by altering immune functions ⁽²⁾.

One of the risk factors for breast cancer is the increased amount of adipose tissue after menopause which elevates estradiol production.

The adrenergic system plays a role in regulating energy balance through thermogenesis and lipid mobilization from brown or white adipose tissues ⁽³⁾.

The human fat cells are equipped with adrenergic receptors (adreno receptors) β_1 , β_2 (ADRB1/2) and β_3 (ADRB3) ⁽⁴⁾.

2. Physiology

The degree of affinity for adrenaline (epinephrine) is $\beta_2 > \beta_1 > \beta_3$ and the noradrenaline (norepinephrine) it is $\beta_1 \geq \beta_2 > \beta_3$ ⁽⁵⁾.

Norepinephrine, epinephrine and dopamine are members of biogenic amines. They share a common precursor - tyrosine. It is converted to L-dopa by tyrosine hydroxylase and L-dopa is converted to dopamine by dopa decarboxylase. In the nerve terminal dopamine is converted to norepinephrine.

If phenylethanol - N - methyl transferase (PNMT) is present norepinephrine is methylated to epinephrine. Adrenergic neurons secrete norepinephrine because they contain dopamine β hydroxylase.

Adreno receptors may be activated by norepinephrine, which is released from adrenergic neurons, or by epinephrine, which is secreted into the circulation by the adrenal medulla. Among the sympathetic adrenoreceptors, receptor type is related to function ⁽⁶⁾.

In addition to their role as neurotransmitters and stress hormones, catecholamines play a trophic role in the control of cell replication and differentiation in target cells that express adrenergic receptors. In some cell lines, β -adrenergic stimulation elicits a small, promotional effect on cell replication, whereas in others, stimulation of these receptors and the consequent rise in intracellular cAMP levels inhibits mitosis. β -adrenoreceptors on cancer cells, thus, recapitulate both the promotional and inhibitory roles of these receptors in cell replication seen in the development of normal cells.

2.1 Location and mechanism of autonomic action

Adrenoreceptor type	Target organ	Mechanism of action
$\alpha 1$	Vascular smooth muscle, skin, renal and splanchnic gastrointestinal tract, bladder sphincter, iris, radial muscle, sphincters	IP ₃ , increase of intracellular [Ca ²⁺]
$\alpha 2$	Gastrointestinal tract wall, presynaptic adrenergic neurons	Inhibition of adenylyl cyclase, decrease cAMP
$\beta 1$	Heart, salivary gland, adipose tissue, kidney	stimulation of adenylyl cyclase, increase cAMP
$\beta 2$	Vascular smooth muscle of skeletal muscle, GI wall, GI bladder wall, bronchioles	stimulation of adenylyl cyclase, increase cAMP

The β -adrenergic agonist isoproterenol, stimulates mammary epithelial cell division in vitro, as well as the development of end bud structures in the mammary gland of ovariectomized mice from which arise the mammary carcinoma induced by administration of dimethylbenz (α) anthracene (DMBA). Specific β -adrenergic receptors of the $\beta 2$ subtype are present in epithelial cell membranes from lactating mammary gland tissue.

The hormonal modulations of receptors which affect uterine contractility correlates with the onset of psychological responses of the uterus such as contraction and relaxation. In analogy with the uterus the regulation of the physiological status of the mammary gland is achieved by modification of endocrine, autonomic and mechanical factors during adolescence, the menstrual cycle, pregnancy parturition and lactation. The mammary gland, as other paired endocrine glands (adrenals, ovaries and testes), receives sympathetic innervations.

High levels of β -adrenergic receptors are measured as palpable mammary tumors, reaching a maximal concentration well before the actual increase in tumor mass. The hormone

sensitivity of the tumoral β -adrenergic receptor is further confirmed by the high receptor concentration measured in progressing mammary tumors.

Stress effects may involve ACTH, glucocorticoids, catecholamines, prolactin, opioids and immunosuppression, all factors crucially involved in tumor growth.

Catecholestrogens, their receptors, together with their catabolizing enzyme, catecholomethyltransferase (COMT), are locally formed in both normal and neoplastic mammary tissues. COMT levels are significantly increased in the cytosol of malignant tumor cells than in the cytosol of benign tumor or normal cells (7).

2.2 Adrenoceptors and cancer

Recent studies in human cancer cell lines in animal models have shown that the growth of adenocarcinomas of the lungs, pancreas and colon are under β -adrenergic control (8-12).

The expression of β -adrenergic receptors has been correlated with the over-expression of the arachidonic acid-metabolizing enzymes cyclooxygenase-2 (COX-2) and lipoxygenases (LOX) in adenocarcinomas of lungs, colon, prostate and pancreas. Inhibitors of these enzymes have been identified as cancer preventive agents in animal models.

2.3 Adrenoceptors and breast cancer

Many of breast adenocarcinomas over express COX-2 and / or LOX (13).

This may say that a subset of breast cancers may also be under β adrenergic control.

Studies have demonstrated that three estrogen-responsive and three non-estrogen responsive human cell lines derived from breast adenocarcinoma show a reduction in DNA synthesis in response to beta-blockers or inhibitors of the arachidonic acid- metabolizing enzymes COX-2 and 5-LOX.

Another study analysis by reverse transcription polymerase chain reaction (RT-PCR) revealed expression of β_2 -adrenergic receptors in all six breast cancer cell lines tested (MDA-MB-361, ZR-75-1, MCF-7, MDA-MB-453, MDA-MB-468, MDA-MB-4355).

β_1 receptors were not found in two estrogen non-responsive cell lines (MDA-MB4355, MDA-MB-453 (14).

It was found that the second messenger cAMP may be a growth promoter for mouse, rat and human mammary epithelioma (15, 16).

The effects of cAMP observed in malignant cells are involved in redifferentiation amounting to renormalization of number of properties including morphology, adhesive properties, lectin agglutination, cell movement and biochemical functions (17).

A correlation between β adreno receptor (β -AR) stimulation and estrogen and progesterone receptor functions was found in human breast cancer (18).

β_2 -adrenergic stimulation induced cell proliferation in hormone-dependent human breast cancer cell line (C6-5), but without involving the female steroid hormone receptor system (18).

In C6-5 cells, the presence of functional β -AR's could be reasonable related to cell proliferation when exposed to different concentrations of clenbuterol, a β_2 -AR agonist showed increased cell proliferation without involving significantly lower than that induced by oestradiol β adreno receptor-mediated inhibition of DNA synthesis was not shared by another cancer cell line, C6 rat glioma, that expresses a different β -receptor subtype a lower levels whereas found that MDA-MB-231 cells express β_2 -receptors exclusively, C6 cell express primarily the β_1 subtype (19).

In mammary tissue there are data that support a role of catecholamines in the control of many cellular activities. Initial experiments indicate epinephrine sensitive adenylate cyclase

activities in 7, 12 - dimethylbenz (α) anthracene - induced mammary carcinoma. Two groups have demonstrated the presence of β -adrenergic receptors (β -AR) from mammary glands of lactating rats. β -adrenergic compounds stimulated the enzyme leading to the generation of cAMP and its activation was completely abolished by the β -AR blocking drug propranolol.

β -adrenergic - related increases in cAMP formation undoubtedly influence lactose production by the acinar secretory end pieces. The initial response to β -AR is usually an increase in adenylate cyclase activity resulting in an increased cellular cAMP concentration. Among the epithelial, endocrine, and secretory cancer cell lines that express adrenoreceptors, MDA-MB-231 human breast cancer cells exhibit comparatively high concentrations. It is thus of critical interest that stimulation of these receptors leads to immediate inhibition of DNA synthesis and, with prolonged exposure, reductions in the total number of cancer cells: inhibition of DNA synthesis is a reliable predictor of chemotherapeutic responses in breast cancer cells.

In prostate or breast cancer cells stimulated by EGF or androgen or estradiol, small peptides (6-10 amino acids) derived from ER or AR sequences involved in the receptor interaction with Src, prevent AR/ER/Src association, Src/Erk pathway stimulation, cyclin D1 expression and DNA synthesis. The peptide action is restricted to cells expressing the steroid receptors and to signals mediated by these receptors. Remarkably, the peptides do not modify. Although there has been no systematic screening of breast cancer cell lines for β -adrenergic expression these receptors have identified in both estrogen-dependent type and estrogen-independent type, including C6-5, BF 20, T47-D, VHB-1 and MCF-7. Regardless of the ancillary mechanisms involved in β -receptor – mediated inhibition of mitosis in MDA-MB-231 breast cancer cells, the fact that inhibition does not disappear with receptor down regulation and desensitization raises the possibility for therapeutic strategies employing receptor agonists, alone or in combination with glucocorticoids and phosphodiesterase inhibitors (20).

Screening of human cancers for the presence of β -adrenoreceptors or other cAMP –linked neurotransmitter receptors may establish new treatment strategies.

β -adrenergic receptors (β -AR's) were identified in CG-5 breast cancer cells using a radiometric assay. The total β -AR concentration was measured using the highly potent β -adrenergic antagonist CGP 12 177, and the densities of β -AR subtypes were discriminated in the presence of highly selective unlabelled ligands (CGP 207 12A and ICI 118551).

The second messenger cAMP was found to be a growth promoter for mouse, rat and human mammary epithelioma and its levels are elevated in several breast carcinomas.

The effects of cAMP observed in malignant cells are often involved in redifferentiation, amounting to apparent renormalization of a number of properties including morphology, adhesive properties, lectin agglutination, cell movement and biochemical functions. A correlation between β -AR stimulation and estrogen and progesterone receptor functions was found in human breast cancer.

It was observed that β_2 -adrenergic stimulation induced cell proliferation in a hormone-dependent human breast cancer cell line (CG-5), but without involving the female steroid hormone receptor system.

CG-5 cells (mammary breast cell cancer cell line) contain measurable concentrations of specific β AR's coupled to adenylate cyclase. The characteristics of these β -AR's, identified by binding and competition assays, are those of β_1 -AR and β_2 -AR subtypes. β_2 -AR concentration is significantly higher than β_1 -AR concentration in CG-5 cell membranes.

Negligible concentrations of β -AR's were found in MCF-7 breast cancer cells from which CG-5 cells are derived. In C6-5 cells the presence of functional β -AR's could be reasonably related to cell proliferation when exposed to different concentrations of clenbuterol, a β_2 -AR agonist, showed increased cell proliferation without involving steroid hormone receptors.

Although the enhancement of CG-5 cell growth was significantly lower than that induced by estradiol the presence of functional β -AR's (with the prevalence of the β_2 -AR subtype) in tumor cell line suggests that β -adrenergic stimulation and resulting cAMP production may be responsible for CG-5 cell proliferation.

Medroxyprogesterone acetate (MPA) is one of the most widely used compounds in the endocrine therapy of advanced breast cancer in women. The mechanisms underlying the antitumor activity of MPA are poorly understood. This steroid presents a high affinity for progesterone (PgR) as well as for androgen (AR) and glucocorticoid receptors (GR) in human mammary tumors.

The most easily explained effects of MPA are related to its glucocorticoid-like action.

Suppression of adrenal function by MPA is believed to be caused both by an inhibitory action at the pituitary level and by direct inhibition of steroidogenesis.

In addition to ER and PgR, which are the most widely used markers of differentiated endocrine functions in breast cancer; AR and GR (Glucocorticoid receptors) are present in a substantial number of mammary tumors and established cell lines. The ZR-75-1 human breast cancer cell line is an unusually appropriate system to study the direct effect of MPA on cell growth. ZR-75-1 cells contain functional receptors for estrogens, androgens, progestins and glucocorticoids. Progestins inhibit ZR-75-1 cell proliferation exclusively in presence of estrogens and in absence of insulin.

MPA further decreased the growth of ZR-75-1 cells co-incubated with maximally inhibitory concentrations of either 5 α -dihydrotestosterone ((DHT) or dexamethasone (DEX) although at about 300-fold higher MPA concentrations with DHT-treated than with DEX-treated ZR-75-1 cells, thus demonstrating a highly predominant androgenic effect. The main action of MPA on ZR-75-1 human breast cancer cell growth is due to its androgen receptor-mediated inhibitory action.

The majority of breast cancer are adenocarcinomas and many of them over express cyclooxygenase - 2 (COX-2) ⁽⁹⁾ and/or lipoxygenases (LOX). This raises the possibility that comparable to findings in adenocarcinomas of the lungs, pancreas, colon and prostate, and a subset of breast cancer may also be under beta adrenergic control. Studies have demonstrated that three estrogen-responsive and three non-estrogen responsive human cell lines derived from breast adenocarcinomas demonstrated a significant reduction in DNA synthesis in response to beta-blockers or inhibitors of the arachidonic acid metabolizing enzymes COX-2 ⁽⁹⁾ and LOX-5.

Analysis by reverse transcription polymerase chain reaction (RT-PCR) revealed expression of β_2 -adrenergic receptors in all six breast cancer cell tested (MDA-MB- 361, ZR-75-1, MCF-7, MDA-MB -453, MDA-MB-468, MDA-MB-435S) whereas β_1 receptors were not found in two estrogen non-responsive cell lines (MDA-MB-435S, MDA-MB-453).

Expression of mRNA that encodes a G-protein coupled inward by rectifying potassium channel 1 (GIRK1) ⁽⁷⁾ has been shown in 40% breast cancer samples. This expression of GIRK1 was associated with a more aggressive clinical behavior. Previous studies indicated that the beta-adrenergic agonist isoproterenol stimulates growth. GIRK currents have been shown to be increased in cells stimulated with the beta-adrenergic agonist isoproterenol in rat atrial myocytes transferred with β_1 or β_2 receptors. Two polymorphisms in the β_2 or β_3

adrenergic receptors were found to be correlated with decreased risk for breast cancer, suggesting an important role of this receptor family in the genesis of breast cancer.

In C6-5 cells ^(16, 19) the presence of functional β -AR's could be reasonable related to cell proliferation when exposed to different concentration of clenbuterol, a β_2 -AR agonist showed increased cell proliferation without involving significantly lower than that induced by estradiol β adreno receptor-mediated inhibition of DNA synthesis was not shared by another cancer cell line, C6 rat glioma, that expresses a different β -receptor subtype a lower levels whereas ⁽²⁰⁾ found that MOA-MB-23 1 cells express β_2 -receptors exclusively, C6 cell express primarily the β_1 subtype.

There is increasing evidence that describes a histamine role in normal and cancer cell proliferation. To better understand the importance of histamine in breast cancer development, the expression of histamine H3 (H3R) and H4 (H4R) receptors and their association with proliferating cell nuclear antigen (PCNA), histidine decarboxylase (HDC) and histamine content were explored in mammary biopsies. Additionally, we investigated whether H3R and H4R were implicated in the biological responses triggered by histamine in MDA-MB-231⁽²⁰⁾ breast cancer cells.

Centrally assess estrogen receptor (ER) and progesterone receptor (PgR) levels by immunohistochemistry and investigate their predictive value for benefit of chemo-endocrine compared with endocrine adjuvant therapy alone in two randomized clinical trials for node-negative breast cancer.

Low levels of ER and PgR are predictive of the benefit of adding chemotherapy to endocrine therapy. Low PgR may add further predictions among pre-and perimenopausal but not postmenopausal patient whose tumors express ER.

The majority of all breast cancers are hormone responsive, traditionally defined by the expression of oestrogen receptor (ER) alpha and/or progesterone receptors. In contrast to ERalpha, the clinical significance of the relatively recently identified ERbeta is still unclear.

ERalpha and ERbeta seem to be differentially associated to clinicopathological parameters, and this would support the fact that they might have different functions in vivo.

In prostate or breast cancer cells stimulated by EGF or androgen or estradiol, small peptides (6-10 amino acids) derived from ER or AR sequences involved in the receptor interaction with Src, prevent AR/ER/Src association, Src/Erk pathway stimulation, cyclin D1 expression and DNA synthesis. The peptide action is restricted to cells expressing the steroid receptors and to signals mediated by these receptors. Remarkably, the peptides do not modify!

Epidermal growth factor (EGF), transforming growth factor-alpha (TGFalpha), amphiregulin (AREG), betacellulin (BTC), heparin-binding EGF-like growth factor (HB-EGF), epiregulin (EREG) and neuregulins1-4 (NRG1-4) were quantified in 363 tumors by real-time reverse transcription-polymerase chain reaction using TaqMan probes.

Paget's disease (PD) of the breast as well as the vulva is a rare condition, therefore anti-hormonal therapy is not indicated. The high frequency of Her-2/neu and COX-2 overexpression, however, suggests that these molecules could be therapeutically relevant in patients with PD.

Epidemiological evidence indicates that the association between body weight and breast cancer risk may differ across menopausal status as well as the estrogen receptor (ER) and progesterone receptor (PR) tumor status.

The relation between body weight and breast cancer risk is critically dependent on the tumor's ER/PR status and the woman's menopausal status. Body weight control is the effective strategy for preventing ER+PR+ tumors after menopause.

ErbB3 transactivation can make tumor cells resistance to ErbB1/ErbB2 targeting drugs. This urges for a reliable method to determine cell surface ErbB3 levels, but their hands iodinated NRG1 beta is unstable and tends to underestimate the number of ErbB3 receptors in a radio-receptor assay.

Furthermore, they show by differential competition with unlabeled NRG/YYDLL and betacellulin that the number of ErbB3 and ErbB4 receptors can be quantified separately on cultured human breast cancer cells.

Esterogen receptor (ER) antagonists have been widely used for breast cancer treatment, but the efficacy and drug resistance remain to be clinical concerns. The purpose of this study was to determine whether the extracts of coptis, an anti-inflammatory herb, improve the anticancer efficacy of ER antagonists. Their results showed that the combined treatment of ER antagonists and the crude extract of coptis or its purified compound berberine conferred synergetic growth inhibitory effect on MCF-7 cells (ER+), but not on MDA-MB-231 cells (R-). Similar results were observed in the combined treatment of fulvestrant, a specific aromatase antagonist. Analysis of the expression of breast cancer related genes indicated the EGFR, HER2, bcl-2, and COX-2 were significantly downregulated, while IFN-beta and p21 were remarkably upregulated by berberine.

The negative association between the oestrogen receptor (ER) and the human epidermal growth factor 2 (HER-2) in breast cancer travels in both directions. ER+ tumors are less likely HER-2+ and HER-2+ are less likely ER+. Studies the age-related immunohistochemical (IHC) expression of ER, HER-2 in 2,227 tumors using age as a continuous variable ⁽²¹⁾.

Estrogen receptors (ERs) are overexpressed in human breast cancers (BCs) and associated with differentiated tumors and with a more favorable prognosis ⁽²²⁻³⁴⁾.

Paradoxically, ERs mediate the mitogenic action of estrogens in human BC cells and the efficacy of antiestrogens in adjuvant therapy of primary tumors. The exact mechanism underlying the ER protection against cancer progression to metastasis remains to be investigated. They show that ERs decrease invasiveness of BC cells. Detailed studies revealed that the unliganded and the E2-activated ERs decrease cancer cell invasion in vitro through two distinct mechanisms. In the presence of ligand, ERalpha inhibits invasion through a mechanism requiring the functional ERalpha domains involved in the transcriptional activation of target genes.

Hormone receptors play important roles in breast cancer. The expression of hormone receptors in breast cancer was investigated to evaluate the importance of hormone receptors in the clinicopathology of breast cancer.

Androgen receptor (AR), estrogen receptor (ER) and progesterone receptor (PR) expression characteristics were evaluated using immunohistochemistry stain, comparing patient age, tumor size and axillary lymph node status for 23 pure mucinous and 105 non-mucinous infiltrating ductal carcinomas in the human female breast.

Findings revealed that mucinous carcinoma samples from the breast show distinct clinicopathologic and hormone receptor expression features compared to non-mucinous carcinoma.

There is increasing evidence that describes a histamine role in normal and cancer cell proliferations. To better understand the importance of histamine in breast cancer development, the expression of histamine H3 (H3R) and H4 (H4R) receptors and their association with proliferating cell nuclear antigen (PCNA), histidine decarboxylase (HDC) and histamine content were explored in mammary biopsies. Additionally, we investigated whether H3R and H4R were implicated in the biological MDA-MB-231 breast cancer cells.

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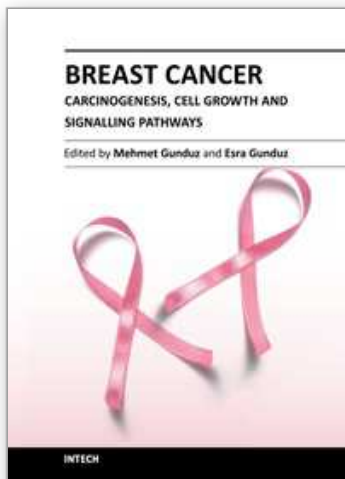
3. Summary

In normal and malignant mammary tissues there are data supporting a role for catecholeamines in the control of many cellular activities. The presence of functional β -AR's in human mammary cell lines has been described. All six breast cell lines express either GIRK2 or GIRK4 indicating that functional GIRK potassium channels are possible in these cancer cell lines. The direct control of cell proliferation shown in vitro could eventually open new avenues for adjuvant therapies in the treatment of breast diseases.

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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various aspects of breast cancer carcinogenesis from clinics to its hormone-based as well as genetic-based etiologies for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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