Received: 20 December 2021 | Accepted: 12 February 2022

DOI: 10.1002/jcp.30707

REVIEW ARTICLE

Journal of Cellular Physiology WILEY

Contribution of adrenergic mechanisms for the stress-induced breast cancer carcinogenesis

Dany Silva | Clara Quintas | Jorge Gonçalves | Paula Fresco

Laboratory of Pharmacology, Department of Drug Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal

Correspondence

Jorge Gonçalves, Laboratory of Pharmacology, Department of Drug Sciences, Faculty of Pharmacy, University of Porto, Rua Jorge de Viterbo Ferreira 228, 4050-313 Porto, Portugal.
Email: jgoncalves@ff.up.pt

Funding information

Fundação para a Ciência e Tecnologia (FCT), Grant/Award Number: 2020.08563.BD; InfoSaúde, Associação Nacional das Farmácias (ANF)

Abstract

Breast cancer is the most common and deadliest type of cancer in women. Stress exposure has been associated with carcinogenesis and the stress released neurotransmitters, noradrenaline and adrenaline, and their cognate receptors, can participate in the carcinogenesis process, either by regulating tumor microenvironment or by promoting systemic changes.

This work intends to provide an overview of the research done in this area and try to unravel the role of adrenergic ligands in the context of breast carcinogenesis.

In the initiation phase, adrenergic signaling may favor neoplastic transformation of breast epithelial cells whereas, during cancer progression, may favor the metastatic potential of breast cancer cells. Additionally, adrenergic signaling can alter the function and activity of other cells present in the tumor microenvironment towards a protumor phenotype, namely macrophages, fibroblasts, and by altering adipocyte's function. Adrenergic signaling also promotes angiogenesis and lymphangiogenesis and, systemically, may induce the formation of preneoplastic niches, cancer-associated cachexia and alterations in the immune system which contribute for the loss of quality of life of breast cancer patients and their capacity to fight cancer. Most studies points to a major contribution of β_2-adrenoceptor activated pathways on these effects. The current knowledge of the mechanistic pathways activated by β_2-adrenoceptors in physiology and pathophysiology, the availability of selective drugs approved for clinical use and a deeper knowledge of the basic cellular and molecular pathways by which adrenergic stimulation may influence cancer initiation and progression, opens the possibility to use new therapeutic alternatives to improve efficacy of breast cancer treatments.

KEYWORDS

adrenoceptors, breast cancer, stress, systemic effects, tumor microenvironment

Abbreviations: AKT, protein kinase B; AR, adrenergic receptor; BAD, bcl-2 agonist of cell death; CCL2, chemokine (C-C motif) ligand 2; CCR2, C-C chemokine receptor type 2; COX-2, cyclooxygenase-2; CREB, cAMP response element-binding protein; CSS, cancer specific survival; DFS, disease-free survival; DMFS, distant metastasis-free survival; EMT, epithelial-mesenchymal transition; EPAC, exchange protein activated by cAMP; ER, estrogen receptor; ERK, extracellular signal-regulated kinase 1/2; FADD, Fas-associated protein with death domain; FGF2, basic fibroblast growth factor; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; HER4, human epidermal growth factor receptor 4; HR, hazard ratio; IL-6, interleukin-6; IL-8, interleukin-8; LDHA, lactate dehydrogenase-A; LR, low risk; LYPD3, ly6/PLAUR Domain-Containing Protein 3; Mdr1, multi-drug resistance 1; MDSCs, myeloid-derived suppressor cells; MMP2, matrix metalloproteinase-2; mTOR, mechanistic target of rapamycin; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer; P38/MAPK, p38 mitogen-activated protein kinase; PD-1, programmed cell death 1; PD-L1, programmed cell death 1 ligand 1; PGE2, prostaglandin E2; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PPARγ, peroxisome proliferator-activated receptor γ; PR, progesterone receptor; RANKL, receptor activator of nuclear factor kappa-B ligand; ROS, reactive oxygen species; SNS, sympathetic nervous system; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor beta; USP28, ubiquitin specific peptidase 28; VEGF, vascular endothelial growth factor.

1 | INTRODUCTION

Cancer initiation, progression and metastasis are processes closely related to the tumor microenvironment. Close interactions between cancer cells and a variety of resident and infiltrating noncancer cells, secreted factors and extracellular matrix proteins occur. Besides the interactions occurring at the tumor microenvironment, interactions at systemic level (or organism level) also occur where cancer cells interact with several host systems (e.g., the host immune system or the host cells present in the premetastatic niches) (Mravec et al., 2020; Mulcrone et al., 2017; Qin et al., 2015).

Breast cancer is the most common and deadliest type of cancer, representing approximately 25% of new cancer cases and 16% of death-associated with cancer (Sung et al., 2021). Although major improvements have been accomplished in breast cancer, these statistics still show that breast cancer remains a major health concern and demands continuous research on new ways to improve its treatment.

For a long time, stress, especially when experienced chronically was believed to cause several pathological responses including cardiovascular diseases, mental illness, immune system dysregulation and gastrointestinal disorders (Agorastos & Chrousos, 2021; Mariotti, 2015; Yaribeygi et al., 2017). More recently, chronic exposure to stress has also been suggested to affect cancer initiation and progression. The first link between stress and breast cancer was published at the end of the 19th century, when a putative link between psychological factors and breast cancer was described (Snow, 1893). Since then, observations from epidemiological, preclinical or clinical studies have revealed associations between stressful events and increased incidence of breast cancer and of a more aggressive cancer progression, especially regarding the metastatic phase (Adamekova et al., 2003; Andersen et al., 2008; Boyd et al., 2010; Chang et al., 2016; Chida et al., 2008; P. Du et al., 2020; Kruk et al., 2019; Qin et al., 2015; J. Zhou et al., 2020).

The activation of the sympathetic nervous system (SNS) is one of two main pathways activated under stress conditions, the other being the activation of the hypothalamic–pituitary–adrenal axis. SNS activation has been pointed to have a major role in the effects observed under chronic stress conditions (Bucsek et al., 2017; Campbell et al., 2012; Chang et al., 2016; Cui et al., 2019; P. Du et al., 2020; Kamiya et al., 2019; Lamkin et al., 2015; Le & Nowell, Kim-Fuchs, et al., 2016; Parkin & Neale, 1976; Sloan et al., 2010; J. Zhou et al., 2020). SNS activation results in elevated local and systemic levels of noradrenaline and adrenaline, which trigger what is traditionally known as adrenergic stimulation (Kvetnansky et al., 2013). More importantly, several studies have been showing that these messengers can exert important stimulatory effects in processes related to cancer initiation and progression, as in chronic stress models.

The reported effects of adrenergic stimulation on breast cancer are vast. They involve direct effects on the tumor microenvironmental and indirect effects, through the regulation of other cells at systemic level (Ben-Eliyahu et al., 2000; Campbell et al., 2012; Le et al., 2016; Mulcrone et al., 2017; Qin et al., 2015). At the tumor microenvironmental level, adrenergic stimulation was described to be involved in the regulation of the neoplastic transformation of breast epithelial cells, contributing to cancer initiation (Parkin & Neale, 1976) and further promoting cancer progression by the induction of almost all hallmarks of cancer including proliferation, migration and invasion, angiogenesis, resistance to cell death, evasion to growth suppressors and cell immune destruction and altered cellular energetics (Bucsek et al., 2017; Cui et al., 2019; Kim et al., 2016; Le et al., 2016; Liu et al., 2016; Pon et al., 2016; Qin et al., 2015; Sastry et al., 2007; J. Zhou et al., 2020). At the systemic level, adrenergic stimulation was described to affect critical aspects of breast cancer progression, such as the regulation of the metastatic process, the systemic immune system or the metabolic alterations related to cancer-associated cachexia (Ben-Eliyahu et al., 2000; Chen et al., 2018; Wu, Sun, et al., 2019) (Figure 1).

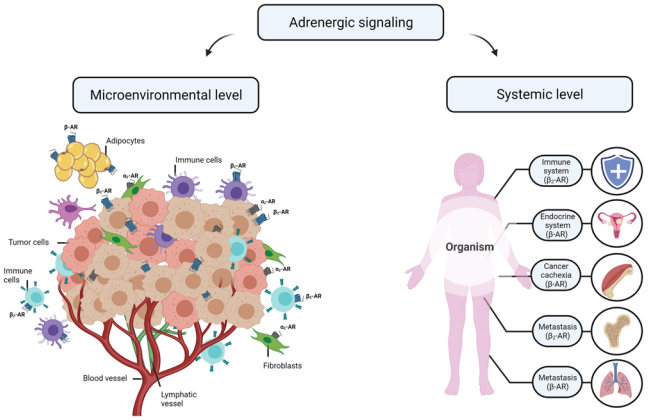

FIGURE 1 Adrenergic influence on breast cancer initiation and progression involves a regulation at microenvironmental and at systemic level. At the microenvironmental level, which includes breast cancer cells and surrounding cells—stromal cells (immune cells, fibroblasts, endothelial cells, adipocytes), activation of adrenergic receptors regulate almost all hallmarks of cancer and alter the function and activity of most cells present at this level towards a protumor phenotype. At the systemic level, adrenergic stimulation can induce several changes on sites/cells far from the tumor itself and help in the promotion of breast cancer progression. These changes may include alterations in the immune and endocrine systems, in the processes related to cancer-associated cachexia or in the modulation of pathways involved in metastasis. Adrenergic receptors subtypes reported to be involved in the interactions described are shown in the figure

In the present review, we aim to present the available evidence concerning the effects that chronic stress and adrenergic stimulation exert in breast cancer, taking into account the capacity of the adrenergic system to modulate breast cancer at both tumor microenvironmental and systemic levels. Whenever appropriate, the transduction mechanisms activated by adrenoceptors will also be discussed. A brief discussion on the potential therapeutic approaches will be also discussed according to the current knowledge regarding the adrenergic effects in breast cancer.

2 | THE ADRENERGIC SYSTEM IN THE CLASSICAL STRESS PATHWAY

The stress response implicates a complex pattern of interactions involving the communication of the central nervous system with the peripheral nervous system and the tissues/organs that it innervates (Thaker et al., 2007) which includes several glands and tissues, such as the ovarian gland (Ojeda & Lara, 1989), pancreas (Faber et al., 2020), adipose tissue (Zhu et al., 2019), thyroid (Nilsson & Karlberg, 1983), adrenal gland (Lowrance et al., 2016), which release several hormones, including estrogens (Roney & Simmons, 2015; Toufexis et al., 2014; Uchida & Kagitani, 2015), progesterone (Ojeda & Lara, 1989), insulin (Faber et al., 2020), thyroid hormones (Becker et al., 1983; Melander et al., 1977; Nilsson & Karlberg, 1983) or cortisol (Lowrance et al., 2016) that may also contribute for the overall response to stress.

The SNS response regulates the function of virtually all organs through the localized release of neuronal catecholamines (mainly noradrenaline) from sympathetic nerve terminals or through a hormonal mechanism exerted by catecholamines (mainly adrenaline) released from the adrenal gland (Kvetnansky et al., 2009; Kvetnansky et al., 2013). Noradrenaline and adrenaline exert their effects acting on α_1 (α_{1A}, α_{1B}, α_{1D}), α_2 (α_{2A}, α_{2B}, α_{2C}) or β (β_1, β_2, β_3) adrenoceptors (Table 1). Although noradrenaline and adrenaline are the endogenous ligands, they present different affinities for all adrenoceptor subtypes. Noradrenaline is more potent than adrenaline in activating α_{1A}, α_{1D}, β_1, and β_3, whereas the opposite occurs in the α_2 subtypes and in the β_2 subtype.

Adrenoceptors signal by activating G proteins (Alexander et al., 2019; Altosaar et al., 2019), although some crosstalk may also occur with other transduction mechanisms (Q. Song et al., 2018; Tilley, 2011). The α_1-adrenoceptor normally interacts with the Gq protein stimulating phospholipase C and calcium channel stimulation while the α_2-adrenoceptor interacts with Gi protein inhibiting adenylyl cyclase (Alexander et al., 2019; Altosaar et al., 2019). The β-adrenoceptors (β_1; β_2; β_3) signal primarily through Gs proteins to promote adenylyl cyclase stimulation (Alexander et al., 2019; Altosaar et al., 2019).

Adrenoceptors have a wide distribution and mediate effects trigger the typical SNS "fight-or-flight" response: mobilization of energy by increasing glycogenolysis and lipolysis, increased heart rate and increased blood pressure, pupil dilation and increased sweating (Alexander et al., 2019; Altosaar et al., 2019; Rabasa & Dickson, 2016; Tank & Lee Wong, 2015). The adrenergic system has also been shown to have other physiological roles under "non-threat" conditions (e.g. physical exercise or sleep disturbances). Adrenoceptors also influence circadian rhythms, modulation of the immune system, control blood pressure, among others (Cole et al., 2015; Goldstein, 2010; Mendez-Ferrer et al., 2008; Scheiermann et al., 2013). In addition to the well-established contribution of the adrenergic system to cardiovascular pathologies, the adrenergic system also seems to be involved in neoplastic transformation and in cancer progression and dissemination (Bucsek et al., 2017; Campbell et al., 2012; Chang et al., 2016; Cui et al., 2019; P. Du et al., 2020; Kamiya et al., 2019; Lamkin et al., 2015; Le et al., 2016; Parkin & Neale, 1976; Sloan et al., 2010; J. Zhou et al., 2020). A deeper knowledge of the role of the adrenergic system in cancer may open the possibility to use in cancer the rich therapeutic adrenergic armamentarium developed for the treatment of several autonomic nervous system diseases.

3 | THE ADRENERGIC SYSTEM IN THE BREAST TUMOR MICROENVIRONMENT

The presence of adrenergic sympathetic nerve fibers has been confirmed in human normal breast tissue and in breast tumors (Eriksson et al., 1996; Kamiya et al., 2019). In human breast tissue, a sparse number of tyrosine hydroxylase-positive nerve fibers (assumed to be indicative of the presence of adrenergic nerves) has been described, with these fibers being mostly present around blood vessels, in connection with lactiferous ducts and alveoli, and in the smooth muscle areas (Eriksson et al., 1996). Studies using rodents have confirmed the presence of noradrenaline in the mammary gland, further showing that the levels of noradrenaline may be affected by the manipulation of the sympathetic nerve fibers around the mammary gland and confirming the capacity of sympathetic nerve fibers in the mammary gland to release noradrenaline and contribute to the pool of noradrenaline in breast tissues (Donoso et al., 1992). Noradrenaline released from sympathetic nerve fibers seems to be substantial since it was found in human milk (Chiba et al., 2019).

In breast tumors, the presence of tyrosine hydroxylase-positive immunoreactivity was demonstrated, both in tumor and in nontumor stromal areas (Kamiya et al., 2019; Szpunar et al., 2016). Their density varies widely between studies (D. Li et al., 2021; Szpunar et al., 2016) what suggests that catecholamine synthesis within the tumor may be a dynamic process and vary according to the progression stage of breast cancer, being higher in early tumor growth (Szpunar et al., 2016). This pattern was demonstrated by Mercedes and colleagues (Szpunar et al., 2016), who showed that in MMTV-PyMT mice, a model that closely mimics clinical breast cancer stages, the sympathetic nerve fibers innervation was higher in early premalignant masses comparatively to that observed in later-stage adenocarcinomas. The density of tyrosine hydroxylase-positive cells may influence cancer pathology since a higher density was seen in patients who suffer from recurrence of breast cancer than those without recurrence (Kamiya et al., 2019).

Circulating catecholamines (mainly adrenaline) have also been shown to influence the breast tumor microenvironment with potential impact in breast carcinogenesis. In animal models, plasma adrenaline was correlated with alterations in the mammary gland functions and in the context of breast cancer, it was associated with changes in gene expression profiles in breast tissue (Cui et al., 2019). In addition to the adrenergic modulation exerted by neuronal and plasma catecholamines, the breast tissue may also be exposed to catecholamines produced in the breast microenvironment by non-neuroendocrine cells. It has been shown that breast cells may also

TABLE 1 Adrenoceptor subtypes, selective ligands and transduction pathways activated by the adrenergic system

AR type	AR subtype	Preferential endogenous ligand	Agonists	Antagonists	Primary transduction pathways	Other transduction pathways (with relevance in cancer)
α_1	α_{1A}		Phenylephrine	Prazosin	G_q/G_{11} family	Activation of PKC and of the MAPK pathway
	α_{1B}		Methoxamine	Doxazosin	G_q/G_{11} family	Activation of PKC and of the MAPK pathway
	α_{1D}		Cirazoline		G_q/G_{11} family	Activation of PKC and of the MAPK pathway
α_2	α_{2A}	Adrenaline	Brimonidine	Rauwolscine	G_i/G_o family	Activation of MAPK/ERK and FADD pathways
	α_{2B}	Adrenaline	Talipexole	Yohimbine	G_i/G_o family	Activation of MAPK/ERK pathway
	α_{2C}	Adrenaline			G_i/G_o family	Activation of MAPK/ERK pathway
β	β_1	Noradrenaline	Isoprenaline	Propranolol (β_1/β_2)	G_s family	Activation of Ras/Raf/MAPK and CREB pathways
	β_2	Adrenaline			G_s family	Activation of β-arrestin2/NF-κB signalling /Activation of cAMP/EPAC/Rap1 pathway
	β_3			Tertalolol (β_3)	G_s family	Activation of PI3K/mTOR-p70(S6K) signalling Activation of endothelial nitric oxide synthase

Note: Data from: Alexander et al. (2019).

Abbreviations: AR, adrenergic receptor; CREB, cAMP response element-binding protein; EPAC, exchange protein activated by cAMP; ERK, extracellular signal-regulated kinase 1/2; FADD, Fas-associated protein with death domain; MAPK, mitogen-activated protein kinase; mTOR-p70(S6K), mammalian target of rapamycin (mTOR)/p70 ribosomal S6 kinase; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C.

produce noradrenaline and acquisition of a tumorigenic phenotype may increase the capacity of breast cells to go further in the catecholamine biosynthetic pathway, increasing the capacity to transform noradrenaline in adrenaline, as recently reported by our research group (Amaro et al., 2020). These locally produced catecholamines may potentiate the adrenergic capacity to promote carcinogenesis creating an adrenergic influence of the tumor autonomous from catecholamines produced elsewhere.

The adrenergic system may influence different cell types that compose the breast cancer microenvironment (breast cells, fibroblasts, adipocytes, immune cells, vascular blood and lymphatic vessels), with impact on how these contribute to the "tumor homeostasis" (Geneste et al., 2020; Kamiya et al., 2019; Mohammadpour et al., 2019; Place et al., 2011; J. Zhou et al., 2020). Such wide influence makes the adrenoceptor-mediated effects within the tumor microenvironment an important contribution for the initiation and progression of breast cancer, by promoting the creation of a cancer niche and by enhancing the traditional hallmarks of cancer: (i) increase in cell proliferation, (ii) activation of invasion and metastasis pathways, (iii) induction of neovascularization, (iv) altered local immune response with a decrease avoidance of immune cell destruction and (v) resistance to cell death induced by breast cancer chemotherapy or targeted therapies (Cui et al., 2019; Kamiya et al., 2019; Liu et al., 2016; Shi et al., 2011; J. Zhou et al., 2020).

In the following subsections, the potential contribution of the adrenergic system to the neoplastic transformation of breast epithelial cells (initiation) and to the cancer progression according to the traditional hallmarks of cancer, as well as possible molecular mechanisms activated by catecholamines, will be discussed in more detail. Table 2 summarizes the studies carried out in vitro and in vivo describing these adrenergic effects on a diverse panel of breast cancer models.

3.1 | Contribution of adrenergic stimulation to cancer initiation

The adrenergic system has been reported to have a role in the control of mammary epithelial end bud development and branching that occurs during pubertal development and/or pregnancy (Gargiulo et al., 2017; Silberstein et al., 1984). Isoprenaline, a nonselective β-adrenoceptor agonist was shown to stimulate end bud formation in ovariectomized mice (Silberstein et al., 1984) and to increase ductal development and maturation, through the regulation of genes involved in mammary gland branching (Gargiulo et al., 2017). Actually, a dynamic influence of the adrenergic system on the mammary gland is suggested by changes in the expression of adrenoceptors (mainly β-adrenoceptors) according to the reproductive phase of the mammary gland, and consequently with the hormonal environment (Marchetti & Labrie, 1990). Like adrenergic stimulation, stress exposure has been shown to influence the mammary gland development affecting ductal development of the mammary gland and lactogenesis, namely by promoting alterations in terminal end buds development and in mammary gland branching (Boyd et al., 2010; Chiba et al., 2019; Dewey, 2001; Dozier et al., 2012; Hasen et al., 2010). One of the earliest and more studied breast alterations described to be affected by stress was the change in the lactation phase, namely altering the milk composition and suppression of lactation (Chiba et al., 2019; Dewey, 2001; Dozier et al., 2012; Salama et al., 2020). The similarities between the effects of adrenergic stimulation and the effect of stress provide the ground to assume that most of the alterations caused by stress on breast have a major contribution from the adrenergic system. Therefore, data from stress studies should take into account adrenergic induced effects. In fact, several studies have shown that adrenergic stimulation may suppress synthesis and secretion of milk proteins, as described for stress exposure (Bisset et al., 1967; "Catecholamine antagonism to oxytocin-induced milk-ejection," 1971; Chiba et al., 2019; Clapp et al., 1985; S. L. Song et al., 1988). Furthermore, in models of chemically induced breast cancer, it was shown that exposure to stress or to adrenergic agonists can accelerate the onset of cancer (Adamekova et al., 2003; Boyd et al., 2010; Parkin & Neale, 1976), whereas propranolol, a nonselective β-adrenoceptor antagonist, can delay its appearance (Tibensky et al., 2021). The results from epidemiological studies may also be taken as an indicator for such connection between stress/adrenergic stimulation and cancer incidence since a correlation between stress exposure and breast cancer incidence has been reported (Chiriac et al., 2018; Kruk et al., 2019; P. Li et al., 2016; Lillberg et al., 2003).

Several mechanisms may be proposed to explain the stress-derived adrenergic contribution for the onset of breast cancer (Figure 2a). One of the putative ways for the adrenoceptor-mediated contribution to tumor initiation may be by driving alterations in the cell cycle progression of breast epithelial cells. In vitro, isoprenaline, a β-adrenoceptor receptor agonist has been shown to stimulate mammary epithelial cell division (Stampfer, 1982; Yang et al., 1980) and in vivo, to increase DNA synthesis in rat mammary gland tissues (Parkin & Neale, 1976) and to promote end bud development (Silberstein et al., 1984). Breast tumorigenesis may also be induced by accumulation of damaged DNA by mammary epithelial cells (Alhmoud et al., 2020), a mechanism that may also be triggered by adrenergic stimulation as described in nontumorigenic human breast cells (Figure 2a) (Yamazaki et al., 2014).

The presence of cells with mesenchymal phenotype is crucial for the induction of tumorigenesis (Greaves, 2010). However, the precursor mesenchymal cells may derive from cells of a differentiated phenotype (mainly epithelial) that go through an epithelial to mesenchymal transition (EMT) to a mesenchymal phenotype (De Craene & Berx, 2013). An aberrant activation of EMT was shown to play a role in the genesis of various tumors, namely gastric (Peng et al., 2014; L. Zhao et al., 2013) and breast cancer (Liang et al., 2013). Both in vitro and in vivo assays have shown that stress or adrenergic stimulation may induce EMT (P. Du et al., 2020). In breast cancer models, the stress-induced adrenaline release was shown to cause activation of the EMT master regulator Slug (Cui et al., 2019), whereas pharmacological blockade or knockdown of β_2-adrenoceptors (using small interfering RNA) inhibited the tumor

TABLE 2 Effects of activation of adrenoceptors on a diverse panel of breast cancer models

Reference	Model	AR	Effect	Drug
(Shi et al., 2011)	MCF-7 (in vitro)	β	Increased proliferation, VEGF, IL-8	Isoprenaline
(Cakir et al., 2002)	MDA-MB-453 *(in vitro)*	β	Increased proliferation	Isoprenaline
(Dethlefsen et al., 2017)	MCF-7 MDA-MB-231 (in vitro and in vivo)	–	Decreased cell proliferation	EpinephrineNorepinephrine
(Bruzzone et al., 2014)	MCF-10A (in vitro)	β_2	Increased adhesion Decreased proliferation	Epinephrine Norepinephrine Isoprenaline Salbutamol Clenbuterol
(Carie & Sebti, 2007)	MDA-MB-231 (in vitro and in vivo)	β_2	Decreased anchorage-dependent and-independent growth Induction of apoptosis	Pirbuterol Isoprenaline
(Perez Pinero et al., 2012)	MDA-MB-231, IBH-6, IBH-4 (in vitro and in vivo) MDA-MB-231, IBH-6, IBH-4 (in vitro)	β_2 α_2	Decreased proliferation Increased proliferation	*Isoprenaline Salbutamol* Adrenaline
(Choy et al., 2016)	MDA-MB-231 (in vitro) MDA-MB-231Br (in vitro)	– β_2	No effect on proliferation and migration Increased proliferation and migration	Terbutaline sulfate
(Gruet et al., 2020)	MDA-MB-468, MDA-MB-231, BT-59, MCF-7 (in vitro)	β_2	Increased adhesion, migration and invasion	Norepinephrine
(Gargiulo et al., 2014)	MCF-10A, HBL-100, MCF-7, MDA-MB-231 (in vitro) MCF-7, MDA-MB-231 (in vitro)	β_2 α_2	Decreased proliferation and migration Increased adhesion Increased migration and adhesion	Isoprenaline Adrenaline Dexmedetomidine
(Vazquez et al., 2006)	MCF-10A, HBL-100, IBH-6, IBH-7, MCF-7, MDA-MB-231 (in vitro)	α_2	Increased cell proliferation	Clonidine
(Amaro et al., 2020)	MCF-7 (in vitro) MCF-10A (in vitro)	β β_2	Decreased cell proliferation Increased cell proliferation	Isoprenaline
(Slotkin et al., 2000)	MDA-MB-231 (in vitro)	β	Decreased cell proliferation	Isoprenaline

TABLE 2 (Continued)

Reference	Model	AR	Effect	Drug
(Ouyang et al., 2019)	MCF-7 MDA-MB-231 (in vitro and in vivo)	β	Increased cell proliferation, migration, and invasion	Epinephrine
(Campbell et al., 2012)	MDA-MB-231 4T1-592 (in vitro and in vivo)	β	Decreased cell proliferation No effect on cell migration	Isoprenaline
(Wilson et al., 2015)	MDA-MB-231 (in vitro)	β_2	Decreased cell-cell adhesion Increased cell migration	Isoprenaline
(Gillis et al., 2021)	MDA-MB-231^{HM} 4T1.2 (in vitro)	β	Increased invasion Increased MMP2 expression	Isoprenaline
(Pon et al., 2016)	MDA-MB-231^{HM} (in vitro)	β_2	Increased invasion	Formoterol
(Kim et al., 2016)	MDA-MB-231 (in vitro)	β_2	Reduced deformability Increased invasion No effect on cell proliferation	Isoprenaline
(Liu et al., 2016)	MCF-7 overexpressing HER2 BT474 MDA-453 cells (in vivo and in vitro)	β_2	Promotion of trastuzumab resistance No effect on cell proliferation	Isoprenaline Epinephrine
(Chang et al., 2016)	MDA-MB-231^{HM} MCF-7 overexpressing β_2-AR (in vitro)	β_2	Increased MMP2 expression Increased cell invasion No effect on cell proliferation	Isoprenaline Formoterol
(Madden et al., 2011)	MCF-7 MB-361 MB-23 MB-231BR (in vitro)	β_2	No effect, decreased or increased expression of VEGF (dependent on the cell model used) Increased IL-6 expression No effect on cell proliferation	Terbutaline Norepinephrine Isoprenaline
(Sastry et al., 2007)	MDA-MB231 (in vitro)	–	Antiapoptotic effect	Epinephrine
(Chen et al., 2014)	MDA-MB-453 MCF-7 MDA-MB-231 4T1 (in vitro and in vivo)	β_2	Increased VEGF and Jagged1 expression Increased angiogenesis	Norepinephrine Isoprenaline Epinephrine Salmeterol
(P. Du et al., 2020)	4T1 (in vitro)	–	Increased cell migration Increased EMT markers	Norepinephrine

(Continues)

TABLE 2 (Continued)

Reference	Model	AR	Effect	Drug
(J. Zhou et al., 2020)	4T1 (in vitro)	β_2	Increased cell proliferation Increased VEGF and FGF2 expression	Norepinephrine
(Le et al., 2016)	MDA-MB-231 (in vivo)	β	Increased metastasis Increased tumor-associated lymphatic vessel density Increased VEGF-C	Isoprenaline
(Su et al., 2005)	MCF-7 (in vivo)	α_2	Chemoresistance to paclitaxel	Epinephrine UK14,304
(Reeder et al., 2015)	MDA-MB-231 HCC1187 MCF-7 (in vivo)	–	Increased DNA damage Cell cycle arrest Chemoresistance	Norepinephrine

Abbreviations: AR, adrenergic receptor; EMT, epithelial-mesenchymal transition; FGF2, basic fibroblast growth factor; IL-8, interleukin-8; IL-6, interleukin-6; MMP2, matrix metalloproteinase 2; VEGF, vascular endothelial growth factor.

growth and the adrenaline-induced breast cancer stem-like traits (Cui et al., 2019). Moreover, this effect does not seem to be limited to breast cancer. In gastric cancer models, β-adrenoceptor activation was shown to increase expression of mesenchymal markers and, conversely, to decrease the expression of epithelial markers (Lu et al., 2015).

The mechanism involved in the adrenergic stimulation of cancer initiation is not known. It may involve a downregulation of miR-337-3p (P. Du et al., 2020), which inhibits activation of the transcription factor signal transducer and activator of transcription 3 (STAT3) (L. Du et al., 2012). This would explain the adrenergic-induced activation of STAT3 (P. Du et al., 2020; Shi et al., 2011) and the consequent loss of epithelial phenotype: downregulation of E-cadherin expression and upregulation of EMT markers such as vimentin (P. Du et al., 2020). It may also involve activation of the transforming growth factor beta as shown to occur in pancreatic cancer cells (Pu et al., 2017). The possibility that cAMP pathways, such as protein kinase A (PKA) and exchange protein activated by cAMP (EPAC), may also be involved must be further explored since activation of β-adrenoceptors increases intracellular cAMP (Silberstein et al., 1984) and most of the evidence links the cAMP pathways to EMT inhibition (Pattabiraman et al., 2016).

3.2 | Adrenergic contribution to breast cancer progression

Cell proliferation is a critical feature for cancer progression and one of the hallmarks of cancer (Hanahan & Weinberg, 2011). It was shown that chronic stress increases cancer cell proliferation and breast tumor growth (Bucsek et al., 2017; Cui et al., 2019; Gillis et al., 2021; Lamkin et al., 2015; Ouyang et al., 2019; J. Zhou et al., 2020). Mechanistically, some studies have proposed pathways by which stress-related adrenergic stimulation may function as a driver of breast cancer progression (see Figure 2b) (Cui et al., 2019; Ouyang et al., 2019). An increase in cell proliferation has been ascribed mainly to β_2-adrenoceptors activation (Choy et al., 2016; Ouyang et al., 2019; Shi et al., 2011) although a participation of α_2-adrenoceptors may also occur (Bruzzone et al., 2011; Vazquez et al., 2006). β_2-adrenoceptors-mediated cell proliferation were shown activate p38 mitogen-activated protein kinase (P38/MAPK) pathway (Ouyang et al., 2019) and of the protooncogene human epidermal growth factor receptor 2 (HER2) receptor (Shi et al., 2011) (Figure 2b). β_2-adrenergic was also shown to activate the lactate dehydrogenase (LDHA)/ubiquitin specific peptidase 28 (USP28)/MYC/SLUG signaling axis, to promote tumor growth as demonstrated by Cui et al. (2019). This effect was dependent on the induction of a metabolic rewiring in breast cancer cells, increasing the production of lactate contributing to the stabilization and transcription of genes involved in the development of breast cancer stem-like traits, leading to tumor growth (Cui et al., 2019). Additionally, adrenoceptors may contribute to breast cancer cell survival by modulating autophagy, as observed in other types of cancer cells (Suzuki et al., 2020; Zhi et al., 2019).

The β-adrenergic influence on breast cancer cell proliferation may also be indirect, through the release of autacoids from non-cancerous cells present in the mammary tumor microenvironment (Qin et al., 2015).

The influence of β_2-adrenoceptors in cell proliferation may depends on the cancer cell phenotype since under some experimental conditions, a decrease, instead of an increase, in cell proliferation was reported (Carie & Sebti, 2007; Gargiulo et al., 2014). While these observations may be seen as contradictory influences of the

β_2-adrenoceptors on carcinogenesis, they may also indicate that, according to the tumor stage or the type of cell used in the studies, β_2-adrenoceptors may modulate cell metabolism to trigger other cancer hallmarks beyond cell proliferation. Such possibilities deserved to be further investigated.

3.3 | Adrenergic contribution to the increase of the metastatic potential of breast cancer

Chronic stress and stress-related adrenergic stimulation are considered major drivers for breast cancer metastasis (Chang et al., 2016; Cui et al., 2019; P. Du et al., 2020; Gillis et al., 2021; Kamiya et al., 2019; Lamkin et al., 2015). Some of the mechanisms proposed for the adrenergic-induced breast cancer metastasis are shown in Figure 2b. Adrenergic stimulation may increase metastasis, by activating pathways involved in cell migration, invasion and trafficking (Cui et al., 2019; P. Du et al., 2020; Gruet et al., 2020; Kim et al., 2016; Pon et al., 2016).

The mechanisms involved in the formation of metastasis may be identical to those involved in cancer initiation since to be able to spread, tumor cells must abandon the contact with adjacent cells within the primary tumor and, therefore, had to assume a more mesenchymal phenotype, which is compatible with the predominant

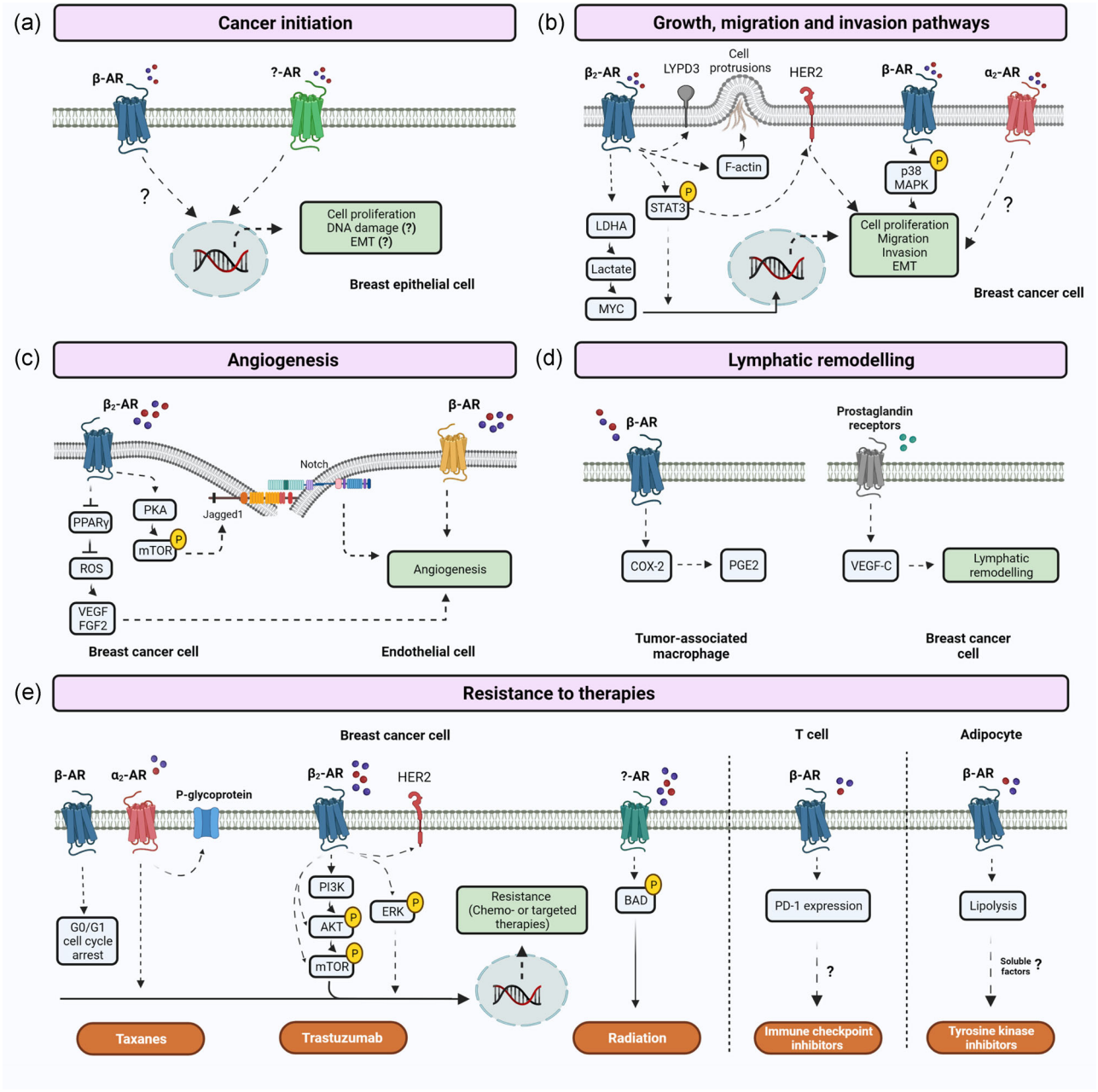

FIGURE 2 (See caption on next page)

phenotype found in the circulating tumor cells (Yu et al., 2013). The putative contributions of adrenergic-induced EMT presented above for cancer initiation may have been applicable in the transformation of cells of the primary tumor into circulating tumor cells with the contribution of the adrenergic stimulation. However, the formation of metastasis may be less dependent on stress-induced adrenergic stimulation than the primary cancer initiation since breast cancer cells may acquire the capacity to synthetize catecholamines themselves (Amaro et al., 2020), and therefore, the adrenergic contribution for the spreading of the primary tumor niche may be more adrenergically autonomous.

Although pathways activated by α_2-adrenergic receptors were shown to be involved in breast cancer metastasis (Gargiulo et al., 2014), most of the evidence point to the involvement of β-adrenoceptors in the increase of the metastatic potential of breast tumor cells (Chang et al., 2016; Cui et al., 2019; Kamiya et al., 2019; Kim et al., 2016). Activation of β_2-adrenoceptors promoted cell migration and invasion in several breast cancer cell lines by upregulating expression of the metastasis-associated molecule Ly6/PLAUR Domain-Containing Protein 3 (LYPD3) (Gruet et al., 2020). Furthermore, knockdown β_2-adrenergic receptors is capable of blunt the stress-enhanced metastatic burden, the number of mesenchymal-like cells, and diminished cell invasion and expression of metalloproteinase 2 caused by β-adrenoceptor agonists (Chang et al., 2016). In addition, the β_2-adrenoceptor-mediated stimulation of metastasis formation may also involve a decrease in cell deformability by remodeling the actin cytoskeleton (this decrease is in opposition to the oversimplified view in the literature that cancer cells become more deformable as they become more invasive), with an increase in F-actin-rich protrusions and an increase in cell invasion (Kim et al., 2016) through activation of a β_2-adrenoceptor dependent cAMP/Ca^{2+} positive feed forward loop (Pon et al., 2016). Another mechanism by which of β_2-adrenoceptors may promote metastasis is the referred LDHA/USP28/MYC/SLUG signaling axis, which was shown to promote metastasis in mouse metastatic models and to increase cell migration and invasion in breast cancer cell lines (Cui et al., 2019).

During metastasis, breast cancer cells exhibit a highly specific tropism for certain organs, namely lungs, bones, liver, and brain (Harbeck et al., 2019). The formation of premetastatic niches comprises the formation of a local microenvironment that favors the survival and outgrowth of tumor cells before their arrival at metastatic sites, playing an important role in selecting preferential sites for colonization (Cox et al., 2012). Lungs and bones, account for 40%–70% of all breast cancer metastasis, respectively (Harbeck et al., 2019) and have been reported as targets of the adrenergic system to promote the creation of local microenvironment conditions in these organs more favorable to colonization by breast cancer cells (Campbell et al., 2012; Chen et al., 2018; Clement-Demange et al., 2018; Mulcrone et al., 2017). The conditions for colonization and the mechanisms involved for their creation, may be different from tissue to tissue. In lung, β-adrenoceptors activation leads to an upregulation of chemokine (C-C motif) ligand 2 (CCL2) in pulmonary stromal cells and of its receptors (C-C chemokine receptor type 2; CCR2) in monocytes/macrophages, leading to the recruitment and infiltration of macrophages into the premetastatic niche in the lung, and consequent metastatic colonization by breast cancer cells (Chen et al., 2018). In bone, several pathways were reported to be involved. Campbell et al. (2012) showed that activation of β_2-adrenoceptors in bone marrow osteoblasts promoted bone metastasis by upregulating the expression of receptor activator of nuclear factor kappa-B ligand, which increases the promigratory activity of breast cancer cells and contributes to bone colonization. Mulcrone et al. (2017) showed that activation of β_2-adrenergic promotes skeletal colonization by

FIGURE 2 Adrenergic signaling pathways in breast cancer hallmarks. (a) A putative role of adrenergic stimulation in the neoplastic transformation of breast epithelial cells is described, although the exact mechanisms deserve further investigation. (b–e) The adrenergic system have been reported to significantly contribute to breast cancer progression by enhancing the traditional hallmarks of cancer in breast cancer cells. (b) β-Adrenergic receptor activation can contribute to breast cancer growth through the activation of different signaling pathways including the MAPK and HER2 signaling pathways and the LDHA/USP28/MYC/SLUG signaling axis. Migration and invasion potential of breast cancer cells can be increased upon β-adrenergic receptors activation, and these can be mediated by either phosphorylation of STAT3, increased expression of LYPD3 or by the LDHA/USP28//MYC/SLUG pathway (shown to induce an EMT-like phenotype on breast cancer cells). Moreover, F-actin was also shown to be regulated by β-adrenergic receptors, allowing the formation of protrusions of the plasma membrane. Increased growth, migration and invasion can be also mediated by α_2-adrenergic receptors, although no downstream signaling pathways were described to date. (c) Increased tumor angiogenesis can be mediated by β-adrenergic receptors activation through two main mechanisms: secretion of VEGF/FGF2 by breast cancer cells and/or an increased expression of Jagged1, which activates the Notch signaling pathway in endothelial cells to drive angiogenesis. (d) Lymphatic vessels remodeling (density, dilation and lymph flow) can be induced upon β-adrenergic receptor activation, involving the participation of COX-2, PGE2, and VEGF-C. (e) Resistance to therapies can be mediated through both α_2- and β-adrenergic receptors activation. On breast cancer cells, adrenergic-mediated ERK phosphorylation, PI3K/AKT/mTOR activation or BAD phosphorylation were shown to confer resistance to taxanes, trastuzumab and radiation, respectively. Activation of β-adrenergic receptors on T cells and adipocytes also confer breast cancer resistance to immune checkpoint and tyrosine kinase inhibitors. Dashed arrows represent indirect pathways; AR, adrenergic receptor; AKT, protein kinase B; BAD, bcl-2 agonist of cell death; COX-2, cyclooxygenase-2; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase 1/2; FGF2, basic fibroblast growth factor; HER2, human epidermal growth factor receptor 2; LDHA, lactate dehydrogenase A; LYPD3, ly6/PLAUR domain-containing protein 3; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PGE2, prostaglandin E2; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; USP28, ubiquitin specific peptidase 28; VEGF, vascular endothelial growth factor

increasing vascular density of osteoblasts and vascular endothelial growth factor (VEGF)-A expression. Moreover, in osteoblasts, β_2-adrenoceptor activation triggered the release of interleukin-1β, favoring adhesion between breast cancer cells and bone marrow-derived endothelial cells, which may help the engraftment of circulating breast cancer cells (Clement-Demange et al., 2018).

3.4 | Adrenergic stimulation induces phenotypic alterations of noncancer cells present in the tumor

Cancer-associated fibroblasts and adipocytes are important players of the breast tumor microenvironment. These cells are known for their role in sustaining tumor growth and in promoting alterations of extracellular matrix components (Houthuijzen & Jonkers, 2018; Wu, Li, et al., 2019; C. Zhao et al., 2020).

In breast cancer, adrenergic stimulation of cancer-associated fibroblasts causes an increase in fibroblast proliferation and tumor growth, an effect ascribed to α_2-adrenoceptors (Bruzzone et al., 2011). Adrenergic stimulation may also be involved in the regulation of extracellular matrix composition namely in collagen deposition (Nagaraja et al., 2017). Using breast, ovarian and colon cancer models, it has been proposed that this may be due to a β_2-mediated inhibin β A production by tumor cells, driving to the appearance a cancer-associated fibroblast phenotype and collagen deposition (Nagaraja et al., 2017). Importantly, increased collagen expression and deposition may allow engaging of integrins on tumor cells, increased stemness and facilitation of cancer invasion, resulting in progression and poor prognosis in breast cancer patients (H. Zhang et al., 2018).

In parallel, adrenergic stimulation in breast cancer-associated adipocytes changed their secretome, leading to an increase in cancer cell proliferation (Avril et al., 2019) and activation of drug resistance pathways (e.g., resistance to tyrosine kinases inhibitors) (Geneste et al., 2020).

3.5 | Adrenergic modulation of the immune response

Both primary and secondary lymphoid organs are known to be strongly innervated by SNS fibers whose influence is key in the adrenergic regulation of the immune system (Nance & Sanders, 2007). In addition to this neuronal adrenergic influence, blood born adrenaline and noradrenaline were also reported to inhibit the immune system activity (Ben-Eliyahu et al., 2000), altering immune cell redistribution and function in several compartments including the spleen, lymph nodes and blood (Andersen et al., 1998; Ben-Eliyahu et al., 2000; Mohammadpour et al., 2019; Shaashua et al., 2017; Shakhar & Ben-Eliyahu, 1998; L. Zhou et al., 2016). The adrenergic modulation of the immune response to breast cancer can even be more oriented than previously expected, having in mind the recent finding that cancer cells may produce locally adrenaline, making the adrenergic contribution for the immunosuppressive tumor microenvironment even more efficient and less dependent from SNS stimulation and from plasma catecholamines (Amaro et al., 2020).

The adrenergic system may alter the immune system in different ways. These alterations can include (i) an increase in the frequency and activation state of immunosuppressive regulatory T cells (L. Zhou et al., 2016), (ii) an increase in frequency and activity of monocytic and granulocytic myeloid-derived suppressor cells (MDSCs) (Mohammadpour et al., 2019), (iii) a decrease in antitumor natural killer (NK) cells activation state (Andersen et al., 1998; Ben-Eliyahu et al., 2000; Shaashua et al., 2017; Shakhar & Ben-Eliyahu, 1998), (iv) an increase in immature dendritic cells populations (Kokolus et al., 2014) and (v) an overall decrease in T cell responses (Andersen et al., 1998).

The β_2-adrenoceptors seem to be the main receptors involved in the adrenergic-regulation of immune cells. In macrophages, activation of β-adrenoceptors was shown to promote recruitment of macrophages into tumor parenchyma, leading them to a M2 like polarization state (tumor-associated macrophages) and to promote the expression of several protumorigenic genes that lead to tumor progression (Qin et al., 2015; Sloan et al., 2010). MDSCs, a population of hematopoietic cells known to be associated with immune suppression and cancer progression were also shown to be increased in breast tumor microenvironment and their immunosuppressive function increased after β-adrenoceptor activation (Mohammadpour et al., 2019). The adrenergic modulation of $CD4^+$ and $CD8^+$ tumor infiltrating lymphocytes may involve a downregulation of interferon-gamma and a β-adrenoceptor-mediated modulation of check-point inhibitors such as programmed cell death 1 (PD-1) (Bucsek et al., 2017; Kamiya et al., 2019). In breast cancer tissue, programmed cell death 1 ligand 1 (PD-L1) may also be regulated by adrenergic stimulation: sympathetic denervation diminished tumor levels of noradrenaline and decreased PD-L1 expression; $PD\text{-}L1^+$ human tumor breast tissues are in close proximity to tumor sympathetic nerve fibers and its expression levels correlated with relapse rates in breast cancer patients (Kamiya et al., 2019).

Being noradrenaline and adrenaline major mediators of chronic stress, the systemic immunosuppression they cause under stress conditions may favor breast cancer progression, affecting not only the quality of life of patients but also survival (Hiam-Galvez et al., 2021; Wang et al., 2020). Breast cancer patients with higher perception of stress revealed lower NK cell lysis, diminished response of NK to stimuli, decreased proliferative response of peripheral blood lymphocytes (Andersen et al., 1998) and overall poor immune responses (Von Ah et al., 2007). A randomized controlled trial using mindfulness-based stress reduction therapy after treatment completion, revealed increased immune recovery with a higher T cells activation state and an increased Th1/Th2 ratio in breast cancer patients/survivors (Lengacher et al., 2013). Taken together, these observations and data from animal models (Mohammadpour et al., 2019; Shakhar & Ben-Eliyahu, 1998) strongly support the view that the adrenergic system decreases the systemic immune response and that inhibiting this pathway may be particularly helpful in the

enhancement of protective-immune responses, critical for the achievement of an antitumor response, but also to protect cancer patients from opportunistic infections.

The adrenergic-induced alterations of the inflammatory status in the context of cancer may have an additional consequence on cancer prognosis by its impact on cancer-associated cachexia. Although the cause of cancer cachexia is believed to be multifactorial, several cytokines and inflammatory mediators have been shown to intervene in the process of cancer-associated cachexia, including tumor necrosis factor-α, interleukin-1 and interleukin-6 (IL-6), and C-reactive protein (Fearon et al., 2012; Roxburgh & McMillan, 2014; Tavares et al., 2021). The adrenergic system is also involved in the regulation of cancer-associated cachexia since its severity in patients with several solid cancers can be ameliorated by the use of β-adrenoceptor antagonists (Argiles et al., 2019; Dev et al., 2014; Hyltander et al., 2000; Petruzzelli et al., 2014). In preclinical models of breast cancer, propranolol significantly decreased cachectic wasting in adipocytes and muscle cells by preventing fat lipolysis and muscle atrophy, in vitro, an effect seemingly mediated by upregulation of the peroxisome proliferator-activated receptor γ (PPARγ) (Wu, Sun, et al., 2019).

In breast cancer, adrenergic stimulation regulated plasmatic levels of IL-6 and C-reactive protein, both linked to cancer-associated cachexia. Shaashua et al. (2017) reported that perioperative cyclooxygenase-2 (COX-2) and β-adrenergic receptor blockade significantly abrogated increases in serum IL-6 and C-reactive protein levels. This study is also in agreement with the work carried out by Mohammadpour et al. (2019) who showed that β_2-adrenergic receptors knockout mice have significantly less IL-6.

Although further studies are needed, the putative adrenergic regulation of cancer-associated cachexia may open the possibility for the development of new therapeutic approaches to target cancer cachexia and help to improve the quality of life of breast cancer patients survivors where cachexia is most often associated with advanced stage of the disease (Biswas & Acharyya, 2020; Consul et al., 2016).

3.6 | Adrenergic contribution to breast cancer angiogenesis

The adrenergic stimulation has been shown to be a driver of tumor angiogenesis. Activation of β-adrenoceptors present in breast cancer cells promotes the expression of several angiogenic mediators, including VEGF (J. Zhou et al., 2020), fibroblast growth factor 2 (FGF2) and Jagged1 (Notch ligand) (J. Zhou et al., 2020). β-adrenergic receptors were also shown to control the expression of IL-6 (Madden et al., 2011), which is also involved in the angiogenesis process (-Figure 2c) (Masjedi et al., 2018). Most studies point to the possibility that the β-adrenoceptors involved have a pharmacology compatible with the β_2 subtype (Chen et al., 2014; J. Zhou et al., 2020). A proposal that β_1-adrenoceptors can also be involved in the adrenergic regulation of angiogenesis is based on the inhibition of angiogenesis by nebivolol (Nuevo-Tapioles et al. 2020). Although nebivolol is clinically used as a selective β_1-adrenoceptor antagonist, the concentrations/doses used in vitro or in vivo were already in the concentration range that blocks also β_2-adrenoceptors (Altosaar et al., 2019). Therefore, the claim for the involvement of β_1-adrenoceptors should be taken carefully.

The effects of β-adrenergic receptors on VEGF/FGF2 expression was shown to be dependent on the inactivation of PPARγ (J. Zhou et al., 2020). Angiogenesis may also be induced by a crosstalk between breast cancer cells and endothelial cells, through an activation of a β_2-PKA-mechanistic target of rapamycin (mTOR) pathway, resulting in upregulation of Jagged1 ligand in breast cancer cells and the activation of the respective Notch signaling pathway in adjacent endothelial cells, driving angiogenesis (J. Zhou et al., 2020). β-Adrenergic receptors activation may also increase the expression of IL-6 (Madden et al., 2011) also known to have proangiogenic effects (Masjedi et al., 2018) and to promote Notch-Jagged signaling (Bocci et al., 2019).

3.7 | Adrenergic contribution to the remodeling of the lymphatic vasculature

The lymphatic system is under the influence of the SNS and stimulation of the SNS cause marked alterations of the lymphatic system (Allen et al., 1983; Felten & Felten, 1988; Le & Sloan, 2016; McGeown et al., 1987; McHale & Thornbury, 1990). Adrenergic stimulation was shown to increase the density of lymph vessels and to promote lymph flow (Le & Nowell, Kim-Fuchs, et al., 2016). In the context of cancer, these effects may favor metastatic dissemination of cancer cells. Under chronic stress, the adrenergic stimulation was shown to cause alterations in lymphatic architecture, increase in lymphatic flow and to promote lymph node metastasis (Le & Nowell, Kim-Fuchs, et al., 2016), a mechanism requiring the release of prostaglandins (namely, PGE2) by tumor-associated macrophages and VEGF-C secretion by breast cancer cells (Figure 2d). These effects were blocked by the β-adrenoceptor antagonist propranolol (Le et al., 2016) confirming a major role of β-adrenoceptors in promoting cancer hallmarks also at the lymphatic system.

4 | ADRENOCEPTOR EXPRESSION AND BREAST CANCER PROGNOSIS

Expression of several adrenergic receptors from the α_1, α_2 and/or β subtypes was observed in a number of preclinical models of breast cancer and in human tissues of breast cancers (Amaro et al., 2020; Y. Du et al., 2014; Gruet et al., 2020; Perez Pinero et al., 2012; Powe et al., 2011; Vazquez et al., 2006). Most of the evidence presented for the adrenergic influence on breast cancer has shown to be mediated by β_2-adrenoceptors as described above. Analysis of the adrenoceptor expression showed that the expression can be linked to a specific breast cancer subtype (Table 3) and may be correlated with the prognosis of breast cancer disease (Caparica et al., 2020; Y. Du

TABLE 3 Association between each adrenoceptor subtype studied and breast cancer subtyping and prognosis

Study	AR subtype	Effect	HR (all cohort)
(Rivero et al., 2019) (mRNA)	α_{2A}	High expression in hormone receptor positive tumors; presented diminished tumor size, grade and not compromised lymph nodes	DMFS: 0.54,
		Absence of metastasis	(95% CI: 0.45–0.65,
		Significantly higher expression in Luminal A tumors	$p < 0.001$)
		Associated with increased distant metastasis-free survival in luminal A and B tumors	
	α_{2C}	High expression was found to be associated with increased tumor size and metastatic relapse	DMFS: 1.45,
		Associated with decreased distant metastasis-free survival in luminal B tumors and with basal-like tumors	(95% CI: 1.16–1.81, $p = 0.001$)
	β_2	High expression was found in smaller, low grade, ER^+ tumors	DMFS: 0.77,
		Absence of metastasis	(95% CI: 0.64–0.93, $p = 0.006$)
(Caparica et al., 2020) (Protein)	β_2	High expression was found to be associated with improved DFS in $HER2^+$ breast cancer	DFS: 0.52, (95% CI: 0.32–0.84, $p = 0.0068$)
(Kurozumi et al., 2019) (Protein)	β_2	High expression was found to be associated with significantly lower cancer specific survival in ER^- breast cancer	CSS: 2.53
		No association was found in ER^+ breast cancer	(95% CI: 1.15–5.58, $p = 0.021$)
(Liu et al., 2015) (Protein)	β_2	High expression was associated with significantly lower DFS in $HER2^+$ breast cancer	DFS: - (95% CI: 1.15–5.58, $p = 0.021$)
(Y. Du et al., 2014) (Protein)	α_{2A}	High expression was inversely associated with HER2 expression	DFS: -
		Not associated with disease free survival	($p = 0.955$)
	β_2	Not associated with disease free survival in the all cohort	DFS: -
		Stratification by breast cancer subtypes, revealed that high expression of β_2-AR was associated with better disease free survival in hormone receptor positive breast cancer	$p = 0.031$)
(Powe et al., 2011) (Protein)	α_{1B}	High expression was found in large high grade, $HER2^+$ or basal-like cancers	**LR**
		Associated with poor cancer specific survival	CSS: 7.628 ($p = 0.022$)
	α_{2C}	High expression was found in high grade $HER3^+/HER4^+$ cancers and PR^- cancers	**LR**
		Expression occurs in high grade basal-like cancers	CSS: 0.962
		Not associated with poor cancer specific survival	$p = 0.0618$)
	β_2	High expression was found in luminal (ER^+) breast cancer; tumors of small-size and of low grade	**LR**
		Associated with poor cancer specific survival, only after 60 months of tamoxifen therapy (probably due to endocrine therapy withdrawn)	CSS: 8.051 ($p = 0.005$)

Abbreviations: AR, adrenergic receptor; CSS,cancer specific survival; DFS, disease-free survival; DMFS, distant metastasis-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; HER4, human epidermal growth factor receptor 4; HR, hazard ratio; LR, Low risk; PR, progesterone receptor.

et al., 2014; Kurozumi et al., 2019; Liu et al., 2015; Powe et al., 2011; Rivero et al., 2019). In breast cancer patients, expression of the α_{1B}-adrenergic receptor has been associated with large, high grade HER2$^+$/basal-like cancers with poor cancer specific survival (Powe et al., 2011); the α_{2C}-adrenergic receptor has been more associated with high grade tumors, namely basal-like tumors (Powe et al., 2011; Rivero et al., 2019); an higher expression of the α_{2A}-adrenergic receptor has been associated with luminal tumors with distant metastasis-free survival (Y. Du et al., 2014; Rivero et al., 2019), while an higher expression of the β_2-adrenergic receptor subtype seems to be associated with smaller, low grade, ER$^+$ tumors with better clinical prognosis, although some conflicting results were reported for this specific adrenergic receptor subtype (see Table 3) (Caparica et al., 2020; Y. Du et al., 2014; Kurozumi et al., 2019; Liu et al., 2015; Powe et al., 2011; Rivero et al., 2019).

5 | ADRENERGIC CONTRIBUTION TO BREAST CANCER RESISTANCE TO THERAPIES

The adrenergic system may also contribute to the resistance of breast cancer therapies (Liu et al., 2016; Su et al., 2005). Relevant signaling pathways to which adrenoceptors are coupled are shown in Figure 2e. Adrenoceptor-mediated reduction in the response to cancer treatments have been described to taxanes (Reeder et al., 2015; Su et al., 2005), drugs commonly used as a first-line agent in the treatment of breast cancer (Harbeck et al., 2019) and to trastuzumab (Liu et al., 2016), which is used to treat HER2$^+$ breast cancers (Harbeck et al., 2019). The adrenoceptor-mediated resistance to taxanes may be mediated by the transcription of a multi-drug resistance (mdr1) gene, which enhances the pump function of P-glycoprotein (Su et al., 2005). Other mechanisms may also be involved since noradrenaline was also shown to arrest breast cancer cells in the G0/G1 phase protecting them from the effects induced by paclitaxel, which targets cells in the S phase to induce apoptosis (Reeder et al., 2015). A mechanism of the adrenoceptor-mediated inhibition of the response of breast cancer to trastuzumab was uncovered by Liu et al. (2016). These authors showed that expression of β_2-adrenoceptors was negatively correlated with trastuzumab effectivity in breast cancer patients, likely by promoting a sustained activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mTOR pathway. Moreover, propranolol blocked the PI3K/Akt/mTOR pathway and made the resistant cells more sensitive to trastuzumab (Liu et al., 2016). This pharmacological interaction may be clinically relevant since it was shown that patients with HER2$^+$ breast cancer receiving both propranolol and trastuzumab present a significant improvement in the progression-free survival and overall survival (Liu et al., 2016).

Adrenoceptors may also contribute to the resistance to tyrosine kinases inhibitors (Geneste et al., 2020), to immune checkpoint inhibitors (Bucsek et al., 2017) and to radiation (Sastry et al., 2007). The adrenergic-induced resistance to tyrosine kinases inhibitors (Geneste et al., 2020) and to immune checkpoint inhibitors (Bucsek et al., 2017) have been reported to be indirect, through the modulation of other cells present in the breast tumor, namely adipocytes and immune cells, respectively. Resistance to tyrosine kinases inhibitors was ascribed to changes in adrenoceptor mediated adipocytes lipolysis (Geneste et al., 2020) whereas the modulation of PD-1 expression in immune cells (CD8$^+$ tumor infiltrating lymphocytes) has been proposed as the mechanism responsible for the resistance of immune checkpoint inhibitors (Bucsek et al., 2017). The protective effect of catecholamines towards apoptosis induced by radiation (resistance to radiation) was observed by Sastry et al. (2007). Using a breast cancer cell line, these authors found that adrenaline treatment significantly increases BAD (Bcl-2 agonist of cell death) phosphorylation and reduces apoptosis induced by radiation (Sastry et al., 2007).

6 | TARGETING ADRENERGIC SIGNALING IN BREAST CANCER

The complex and broad adrenergic influence on cancer makes the adrenergic signaling a promising target to improve the standard breast cancer therapies and to overcome resistance by the use of well-known adrenergic drugs. The use of β-adrenoceptor antagonists (β-blockers) to target β-adrenergic mediated pathways have shown the most promising results (Haldar et al., 2018; Hiller et al., 2020; Shaashua et al., 2017; L. Zhou et al., 2016) even in breast cancer patients (Gillis et al., 2021; Melhem-Bertrandt et al., 2011; Powe et al., 2010). Phase II controlled clinical trials also suggested that β-adrenoceptor antagonists have a possible beneficial effect on reducing the metastatic potential of primary breast tumors (Haldar et al., 2018; Hiller et al., 2020; Shaashua et al., 2017; L. Zhou et al., 2016). In addition to the long-term use of β-adrenoceptor antagonists investigated above, the use β-adrenoceptor antagonists during the perioperative period to prevent the adrenergic-induced immunosuppression and to decrease the expression of genes involved in metastasis has also been proposed (Haldar et al., 2018; Hiller et al., 2020; Shaashua et al., 2017; L. Zhou et al., 2016). Furthermore, the knowledge of the role of adrenergic stimulation in mediating responses to stress also gives a scientific ground to explain the efficacy of nonpharmacological approaches such as psychosocial-mind-body therapies to group support of cancer patients (Spiegel & Bloom, 1983; Spiegel et al., 1981), cognitive behavioral therapy (Eichler et al., 2015; Sun et al., 2019), positive psychotherapy (Dowlatabadi et al., 2016), mindfulness meditation (Carlson et al., 2007), and other therapies (Gosain et al., 2020) in improving not only breast cancer patients´ quality of life (Carlson et al., 2007; Eichler et al., 2015) but also some cancer biomarkers and immune response (Lengacher et al., 2013; P. Zhang et al., 2019). Whether there is room for the use of adrenergic blockers to prevent tumorigenesis and, thus, for their use to prevent cancer, particularly under high stress/high risk situations, remains an open question.

7 | FUTURE PERSPECTIVES

The available evidence about the influence of the adrenergic system, which has a very rich pharmacology and drugs available, opens exciting perspectives about the possibilities to use adrenergic drugs in oncology. However, a long way with many obstacles has to be traveled in the future before the use of adrenergic drugs may become a serious option within breast cancer treatments. The barriers to overcome are related to the insufficient knowledge linking adrenoceptor activation and tumorigenesis. It is not trivial to establish a connection between activation of GPCRs, like adrenoceptors, and the genetic alterations/mutations often believed to be the cause of cancer. However, the increasing relevance that is being given to the metabolic changes in the origin of cancer may create a more appropriate model to understand the connections between adrenoceptors and carcinogenesis including the relevance of adrenoceptors in the metabolic control. Therefore, as the knowledge of carcinogenesis will evolve, better the adrenergic effects in carcinogenesis will be understood. And, *vice versa*, the established knowledge concerning adrenoceptor-mediated effects on metabolism and on the reactions of the organism to adverse conditions (stress exposure) can also be a tool to better understand carcinogenesis and the "tumor homeostasis".

The pharmacology of the adrenergic system is vast, with many drugs approved for clinical use for other clinical indications. The possibility to use drugs with a well-known safety profiles and low prices in breast cancer treatment may turn into a strong argument for the future widespread use of these drugs in cancer. However, this is not so straightforward. The clinical validation of these drugs for new oncological indications still requires investments in the production of clinical evidence, which may not be sustainable for drugs with generics, marketed by several companies and from pharmacological families with several similar drugs, and in a legal framework without the ability to protect and to compensate for new therapeutic claims for known drugs (Drug Repurposing). Therefore, a more widespread use of adrenergic drugs in cancer will be closely related to the success of finding new business models capable to reward the innovation of repurposed drugs by pharmaceutical companies or a more proactive intervention of drug regulatory agencies in promoting clinical studies to obtain clinical evidence for repurposed drugs, in case they respond to unmet therapeutic needs or they present increased sustainability for the health systems.

8 | CONCLUSION

The role of stress-derived catecholamines (noradrenaline and adrenaline) as an important regulator of cancer initiation and progression is being uncovered. This knowledge opens the possibility of not only expanding the knowledge of the basic cellular and molecular biology by which adrenergic stimulation may influence cancer initiation and progression but also understand the pathways that may, potentially, be targeted to improve the efficacy of breast cancer treatments and to offer new therapeutic approaches to breast cancer patients.

Although further research is still needed to fully understand and evaluate the potential of targeting the adrenergic system in breast cancer, there is sufficient evidence to highlight the possibility that it may be particularly useful to reduce several steps of the carcinogenic process, from the tumorigenic effects associated with stress-derived catecholamines to the drastic metabolic imbalances observed in late-stage cancers described in this review.

ACKNOWLEDGMENTS

This research has received funding from the project InfoSaúde, funded by the ANF (Associação Nacional das Farmácias) in the form of scientific patronage. Dany Silva has a PhD grant scholarship (Grant No.: 2020.08563.BD) financed by FCT (Fundação para a Ciência e Tecnologia) through ESF (European Social Fund) and national funds. Figures were created with BioRender.com.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data is not available.

ORCID

Dany Silva http://orcid.org/0000-0002-6800-9621
Clara Quintas http://orcid.org/0000-0002-2087-1773
Jorge Gonçalves http://orcid.org/0000-0002-3045-2150
Paula Fresco http://orcid.org/0000-0001-6705-7798

REFERENCES

Adamekova, E., Markova, M., Kubatka, P., Bojkova, B., Ahlers, I., & Ahlersova, E. (2003). NMU-induced mammary in female rats is influenced by repeated psychoemotional stress. *Neoplasma*, *50*(6), 428–432.

Agorastos, A., & Chrousos, G. P. (2021). The neuroendocrinology of stress: The stress-related continuum of chronic disease development. *Molecular Psychiatry*. Published online July 21, 2021. https://doi.org/10.1038/s41380-021-01224-9

Alexander, S. P. H., Christopoulos, A., Davenport, A. P., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., Sharman, J. L., Southan, C., & Davies, J. A., CGTP Collaborators. (2019). The concise guide to PHARMACOLOGY 2019/20: G protein-coupled receptors. *British Journal of Pharmacology*, *176*, S21–S141.

Alhmoud, J. F., Woolley, J. F., Al Moustafa, A. E., & Malki, M. I. (2020). DNA Damage/Repair Management in Cancers. *Cancers (Basel)*, *12*(4), 1050. https://doi.org/10.3390/cancers12041050

Allen, J. M., McHale, N. G., & Rooney, B. M. (1983). Effect of norepinephrine on contractility of isolated mesenteric lymphatics. *American Journal of Physiology*, *244*(4), H479–H486. https://doi.org/10.1152/ajpheart.1983.244.4.H479

Altosaar, K. B. P., Bond, R. A., Bylund, D. B., Cotecchia, S., Devost, D., Doze, V. A., Eikenburg, D. C., Gora, S., Goupil, E., Graham, R. M., Hébert, T., Hieble, J. P., Hills, R., Kan, S., Machkalyan, G., Michel, M. C., Minneman, K. P., Parra, S., Perez, D., … Zylbergold, P. (2019). Adrenoceptors (version 2019.4) in the

IUPHAR/BPS Guide to Pharmacology Database. *IUPHAR/BPS Guide to Pharmacology CITE*, *2019*. https://doi.org/10.2218/gtopdb/F4/2019.4

Amaro, F., Silva, D., Reguengo, H., Oliveira, J. C., Quintas, C., Vale, N., Gonçalves, J., & Fresco, P. (2020). beta-Adrenoceptor Activation in Breast MCF-10A Cells Induces a Pattern of Catecholamine Production Similar to that of Tumorigenic MCF-7 Cells. *International Journal of Molecular Sciences*, *21*(21), 7968. https://doi.org/10.3390/ijms21217968

Andersen, B. L., Farrar, W. B., Golden-Kreutz, D., Kutz, L. A., MacCallum, R., Courtney, M. E., & Glaser, R. (1998). Stress and immune responses after surgical treatment for regional breast cancer. *Journal of the National Cancer Institute*, *90*(1), 30–36. https://doi.org/10.1093/jnci/90.1.30

Andersen, B. L., Yang, H. C., Farrar, W. B., Golden-Kreutz, D. M., Emery, C. F., Thornton, L. M., Young, D. C., & Carson, W. E3rd (2008). Psychologic intervention improves survival for breast cancer patients: A randomized clinical trial. *Cancer*, *113*(12), 3450–3458. https://doi.org/10.1002/cncr.23969

Argiles, J. M., Lopez-Soriano, F. J., Stemmler, B., & Busquets, S. (2019). Therapeutic strategies against cancer cachexia. *European Journal of Translational Myology*, *29*(1), 7960. https://doi.org/10.4081/ejtm.2019.7960

Avril, P., Vidal, L., Barille-Nion, S., Le Nail, L. R., Redini, F., Layrolle, P., Pinault, M., Chevalier, S., Perrot, P., & Trichet, V. (2019). Epinephrine infiltration of adipose tissue impacts MCF7 breast cancer cells and total lipid content. *International Journal of Molecular Sciences*, *20*(22): 5626. https://doi.org/10.3390/ijms20225626

Becker, R. A., Vaughan, G. M., Goodwin, C. W. Jr., Ziegler, M. G., Zitzka, C. A., Mason, A. D. Jr., Pruitt, B. A. Jr. (1983). Interactions of thyroid hormones and catecholamines in severely burned patients. *Reviews of Infectious Diseases*, *5*(Suppl 5), S908-S913. https://doi.org/10.1093/clinids/5.supplement_5.s908

Ben-Eliyahu, S., Shakhar, G., Page, G. G., Stefanski, V., & Shakhar, K. (2000). Suppression of NK cell activity and of resistance to metastasis by stress: A role for adrenal catecholamines and beta-adrenoceptors. *Neuroimmunomodulation*, *8*(3), 154–164. https://doi.org/10.1159/000054276

Bisset, G. W., Clark, B. J., & Lewis, G. P. (1967). The mechanism of the inhibitory action of adrenaline on the mammary gland. *British Journal of Pharmacology and Chemotherapy*, *31*(3), 550–559. https://doi.org/10.1111/j.1476-5381.1967.tb00419.x

Biswas, A. K., & Acharyya, S. (2020). Understanding cachexia in the context of metastatic progression. *Nature Reviews Cancer*, *20*(5), 274–284. https://doi.org/10.1038/s41568-020-0251-4

Bocci, F., Gearhart-Serna, L., Boareto, M., Ribeiro, M., Ben-Jacob, E., Devi, G. R., Levine, H., Onuchic, J. N., & Jolly, M. K. (2019). Toward understanding cancer stem cell heterogeneity in the tumor microenvironment. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(1), 148–157. https://doi.org/10.1073/pnas.1815345116

Boyd, A. L., Salleh, A., Humber, B., Yee, J., Tomes, L., & Kerr, L. R. (2010). Neonatal experiences differentially influence mammary gland morphology, estrogen receptor {alpha} protein levels, and carcinogenesis in BALB/c mice. *Cancer Prevention Research (Phila)*, *3*(11), 1398–1408. https://doi.org/10.1158/1940-6207.CAPR-10-0111

Bruzzone, A., Pinero, C. P., Rojas, P., Romanato, M., Gass, H., Lanari, C., & Luthy, I. A. (2011). alpha(2)-Adrenoceptors enhance cell proliferation and mammary tumor growth acting through both the stroma and the tumor cells. *Current Cancer Drug Targets*, *11*(6), 763–774. https://doi.org/10.2174/156800911796191051

Bruzzone, A., Sauliere, A., Finana, F., Senard, J. M., Luthy, I., & Gales, C. (2014). Dosage-dependent regulation of cell proliferation and adhesion through dual beta2-adrenergic receptor/cAMP signals. *FASEB Journal*, *28*(3), 1342–1354. https://doi.org/10.1096/fj.13-239285

Bucsek, M. J., Qiao, G., MacDonald, C. R., Giridharan, T., Evans, L., Niedzwecki, B., Liu, H., Kokolus, K. M., Eng, J. W., Messmer, M. N., Attwood, K., Abrams, S. I., Hylander, B. L., & Repasky, E. A. (2017). beta-adrenergic signaling in mice housed at standard temperatures suppresses an effector phenotype in CD8(+) T cells and undermines checkpoint inhibitor therapy. *Cancer Research*, *77*(20), 5639–5651. https://doi.org/10.1158/0008-5472.CAN-17-0546

Cakir, Y., Plummer, H. K3rd, Tithof, P. K., & Schuller, H. M. (2002). Beta-adrenergic and arachidonic acid-mediated growth regulation of human breast cancer cell lines. *International Journal of Oncology*, *21*(1), 153–157.

Campbell, J. P., Karolak, M. R., Ma, Y., Perrien, D. S., Masood-Campbell, S. K., Penner, N. L., Munoz, S. A., Zijlstra, A., Yang, X., Sterling, J. A., & Elefteriou, F. (2012). Stimulation of host bone marrow stromal cells by sympathetic nerves promotes breast cancer bone metastasis in mice. *PLoS Biology*, *10*(7), e1001363. https://doi.org/10.1371/journal.pbio.1001363

Caparica, R., Richard, F., Brandao, M., Awada, A., Sotiriou, C., & de Azambuja, E. (2020). Prognostic and predictive impact of beta-2 adrenergic receptor expression in HER2-positive breast cancer. *Clinical Breast Cancer*, *20*(3), 262–273 e267. https://doi.org/10.1016/j.clbc.2020.01.007

Carie, A. E., & Sebti, S. M. (2007). A chemical biology approach identifies a beta-2 adrenergic receptor agonist that causes human tumor regression by blocking the Raf-1/Mek-1/Erk1/2 pathway. *Oncogene*, *26*(26), 3777–3788. https://doi.org/10.1038/sj.onc.1210172

Carlson, L. E., Speca, M., Faris, P., & Patel, K. D. (2007). One year pre-post intervention follow-up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients. *Brain, Behavior, and Immunity*, *21*(8), 1038–1049. https://doi.org/10.1016/j.bbi.2007.04.002

Catecholamine antagonism to oxytocin-induced milk-ejection. (1971). Acta Endocrinol Suppl (Copenh), *155*, 1–236.

Chang, A., Le, C. P., Walker, A. K., Creed, S. J., Pon, C. K., Albold, S., Carroll, D., Halls, M. L., Lane, J. R., Riedel, B., Ferrari, D., & Sloan, E. K. (2016). beta2-Adrenoceptors on tumor cells play a critical role in stress-enhanced metastasis in a mouse model of breast cancer. *Brain, Behavior, and Immunity*, *57*, 106–115. https://doi.org/10.1016/j.bbi.2016.06.011

Chen, H., Liu, D., Guo, L., Cheng, X., Guo, N., & Shi, M. (2018). Chronic psychological stress promotes lung metastatic colonization of circulating breast cancer cells by decorating a pre-metastatic niche through activating beta-adrenergic signaling. *Journal of Pathology*, *244*(1), 49–60. https://doi.org/10.1002/path.4988

Chen, H., Liu, D., Yang, Z., Sun, L., Deng, Q., Yang, S., & Guo, N. (2014). Adrenergic signaling promotes angiogenesis through endothelial cell-tumor cell crosstalk. *Endocrine-related Cancer*, *21*(5), 783–795. https://doi.org/10.1530/ERC-14-0236

Chiba, T., Maeda, T., Fujita, Y., Takeda, R., Kikuchi, A., & Kudo, K. (2019). Stress-induced suppression of milk protein is involved in a noradrenergic mechanism in the mammary gland. *Endocrinology*, *160*(9), 2074–2084. https://doi.org/10.1210/en.2019-00300

Chida, Y., Hamer, M., Wardle, J., & Steptoe, A. (2008). Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nature Clinical Practice Oncology*, *5*(8), 466–475. https://doi.org/10.1038/ncponc1134

Chiriac, V. F., Baban, A., & Dumitrascu, D. L. (2018). Psychological stress and breast cancer incidence: A systematic review. *Clujul Medical*, *91*(1), 18–26. https://doi.org/10.15386/cjmed-924

Choy, C., Raytis, J. L., Smith, D. D., Duenas, M., Neman, J., Jandial, R., & Lew, M. W. (2016). Inhibition of beta2-adrenergic receptor reduces

triple-negative breast cancer brain metastases: The potential benefit of perioperative beta-blockade. *Oncology Reports*, *35*(6), 3135–3142. https://doi.org/10.3892/or.2016.4710

Clapp, C., Martinez-Escalera, G., Morales, M. T., Shyr, S. W., Grosvenor, C. E., & Mena, F. (1985). Release of catecholamines follows suckling or electrical stimulation of mammary nerve in lactating rats. *Endocrinology*, *117*(6), 2498–2504. https://doi.org/10.1210/endo-117-6-2498

Clement-Demange, L., Mulcrone, P. L., Tabarestani, T. Q., Sterling, J. A., & Elefteriou, F. (2018). beta2ARs stimulation in osteoblasts promotes breast cancer cell adhesion to bone marrow endothelial cells in an IL-1beta and selectin-dependent manner. *Journal of Bone Oncology*, *13*, 1–10. https://doi.org/10.1016/j.jbo.2018.09.002

Cole, S. W., Nagaraja, A. S., Lutgendorf, S. K., Green, P. A., & Sood, A. K. (2015). Sympathetic nervous system regulation of the tumour microenvironment. *Nature Reviews Cancer*, *15*(9), 563–572. https://doi.org/10.1038/nrc3978

Consul, N., Guo, X., Coker, C., Lopez-Pintado, S., Hibshoosh, H., Zhao, B., & Acharyya, S. (2016). Monitoring metastasis and cachexia in a patient with breast cancer: A case study. *Clinical Medicine Insights Oncology*, *10*, 83–94. https://doi.org/10.4137/CMO.S40479

Cox, T. R., Gartland, A., & Erler, J. T. (2012). The pre-metastatic niche: Is metastasis random? *BoneKEy Reports*, *1*, 80. https://doi.org/10.1038/bonekey.2012.80

De Craene, B., & Berx, G. (2013). Regulatory networks defining EMT during cancer initiation and progression. *Nature Reviews Cancer*, *13*(2), 97–110. https://doi.org/10.1038/nrc3447

Cui, B., Luo, Y., Tian, P., Peng, F., Lu, J., Yang, Y., & Liu, Q. (2019). Stress-induced epinephrine enhances lactate dehydrogenase A and promotes breast cancer stem-like cells. *Journal of Clinical Investigation*, *129*(3), 1030–1046. https://doi.org/10.1172/JCI121685

Dethlefsen, C., Hansen, L. S., Lillelund, C., Andersen, C., Gehl, J., Christensen, J. F., & Hojman, P. (2017). Exercise-induced catecholamines activate the hippo tumor suppressor pathway to reduce risks of breast cancer development. *Cancer Research*, *77*(18), 4894–4904. https://doi.org/10.1158/0008-5472.CAN-16-3125

Dev, R., Fabbro, E., & Bruera, E. J. C. i. (2014). Outcomes of novel trials for cancer cachexia. *4*, 247-257.

Dewey, K. G. (2001). Maternal and fetal stress are associated with impaired lactogenesis in humans. *Journal of Nutrition*, *131*(11), 3012S–3015S. https://doi.org/10.1093/jn/131.11.3012S

Donoso, E. A., Sapag-Hagar, M., & Lara, H. E. (1992). Neurochemical evidence for the presence of sympathetic nerve terminals in the rat mammary gland: Changes during the lactogenic cycle. *Molecular and Cellular Neuroscience*, *3*(1), 23–28. https://doi.org/10.1016/1044-7431(92)90004-I

Dowlatabadi, M. M., Ahmadi, S. M., Sorbi, M. H., Beiki, O., Razavi, T. K., & Bidaki, R. (2016). The effectiveness of group positive psychotherapy on depression and happiness in breast cancer patients: A randomized controlled trial. *Electronic Physician*, *8*(3), 2175–2180. https://doi.org/10.19082/2175

Dozier, A. M., Nelson, A., & Brownell, E. (2012). The relationship between life stress and breastfeeding outcomes among low-income mothers. *Advances in Preventive Medicine*, *2012*, 902487. https://doi.org/10.1155/2012/902487

Du, L., Subauste, M. C., DeSevo, C., Zhao, Z., Baker, M., Borkowski, R., & Pertsemlidis, A. (2012). miR-337-3p and its targets STAT3 and RAP1A modulate taxane sensitivity in non-small cell lung cancers. *PLoS One*, *7*(6), e39167. https://doi.org/10.1371/journal.pone.0039167

Du, P., Zeng, H., Xiao, Y., Zhao, Y., Zheng, B., Deng, Y., & Ma, X. (2020). Chronic stress promotes EMT-mediated metastasis through activation of STAT3 signaling pathway by miR-337-3p in breast cancer. *Cell Death & Disease*, *11*(9), 761. https://doi.org/10.1038/s41419-020-02981-1

Du, Y., Zhou, L., Wang, Y., Yan, T., Jiang, Y., Shao, Z., & Lu, J. (2014). Association of alpha2a and beta2 adrenoceptor expression with clinical outcome in breast cancer. *Current Medical Research and Opinion*, *30*(7), 1337–1344. https://doi.org/10.1185/03007995.2014.890928

Eichler, C., Pia, M., Sibylle, M., Sauerwald, A., Friedrich, W., & Warm, M. (2015). Cognitive behavioral therapy in breast cancer patients—A feasibility study of an 8 week intervention for tumor associated fatigue treatment. *Asian Pacific journal of cancer prevention: APJCP*, *16*(3), 1063–1067. https://doi.org/10.7314/apjcp.2015.16.3.1063

Eriksson, M., Lindh, B., Uvnas-Moberg, K., & Hokfelt, T. (1996). Distribution and origin of peptide-containing nerve fibres in the rat and human mammary gland. *Neuroscience*, *70*(1), 227–245. https://doi.org/10.1016/0306-4522(95)00291-p

Faber, C. L., Deem, J. D., Campos, C. A., Taborsky, G. J. Jr., Morton, G. J. (2020). CNS control of the endocrine pancreas. *Diabetologia*, *63*(10), 2086-2094. https://doi.org/10.1007/s00125-020-05204-6

Fearon, K. C., Glass, D. J., & Guttridge, D. C. (2012). Cancer cachexia: Mediators, signaling, and metabolic pathways. *Cell Metabolism*, *16*(2), 153–166. https://doi.org/10.1016/j.cmet.2012.06.011

Felten, D. L., & Felten, S. Y. (1988). Sympathetic noradrenergic innervation of immune organs. *Brain, Behavior, and Immunity*, *2*(4), 293–300. https://doi.org/10.1016/0889-1591(88)90031-1

Gargiulo, L., Copsel, S., Rivero, E. M., Gales, C., Senard, J. M., Luthy, I. A., & Bruzzone, A. (2014). Differential beta(2)-adrenergic receptor expression defines the phenotype of non-tumorigenic and malignant human breast cell lines. *Oncotarget*, *5*(20), 10058–10069. https://doi.org/10.18632/oncotarget.2460

Gargiulo, L., May, M., Rivero, E. M., Copsel, S., Lamb, C., Lydon, J., & Bruzzone, A. (2017). A novel effect of beta-adrenergic receptor on mammary branching morphogenesis and its possible implications in breast cancer. *Journal of Mammary Gland Biology and Neoplasia*, *22*(1), 43–57. https://doi.org/10.1007/s10911-017-9371-1

Geneste, A., Duong, M. N., Molina, L., Conilh, L., Beaumel, S., Cleret, A., & Dumontet, C. (2020). Adipocyte-conditioned medium induces resistance of breast cancer cells to lapatinib. *BMC Pharmacology & Toxicology*, *21*(1), 61. https://doi.org/10.1186/s40360-020-00436-z

Gillis, R. D., Botteri, E., Chang, A., Ziegler, A. I., Chung, N. C., Pon, C. K., & Sloan, E. K. (2021). Carvedilol blocks neural regulation of breast cancer progression in vivo and is associated with reduced breast cancer mortality in patients. *European Journal of Cancer*, *147*, 106–116. https://doi.org/10.1016/j.ejca.2021.01.029

Goldstein, D. (2010). Adrenaline and Noradrenaline. In *Encyclopedia of Life Sciences (ELS): www.els.net*. John Wiley & Sons, Ltd.

Gosain, R., Gage-Bouchard, E., Ambrosone, C., Repasky, E., & Gandhi, S. (2020). Stress reduction strategies in breast cancer: Review of pharmacologic and non-pharmacologic based strategies. *Seminars in Immunopathology*, *42*(6), 719–734. https://doi.org/10.1007/s00281-020-00815-y

Greaves, M. (2010). Cancer stem cells: Back to Darwin? *Seminars in Cancer Biolog*, *20*(2), 65–70. https://doi.org/10.1016/j.semcancer.2010.03.002

Gruet, M., Cotton, D., Coveney, C., Boocock, D. J., Wagner, S., Komorowski, L., & Powe, D. G. (2020). Beta2-adrenergic signalling promotes cell migration by upregulating expression of the metastasis-associated molecule LYPD3. *Biology (Basel)*, *9*(2):39. https://doi.org/10.3390/biology9020039

Haldar, R., Shaashua, L., Lavon, H., Lyons, Y. A., Zmora, O., Sharon, E., & Ben-Eliyahu, S. (2018). Perioperative inhibition of beta-adrenergic and COX2 signaling in a clinical trial in breast cancer patients improves tumor Ki-67 expression, serum cytokine levels, and PBMCs transcriptome. *Brain, Behavior, and Immunity*, *73*, 294–309. https://doi.org/10.1016/j.bbi.2018.05.014

Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. *Cell*, *144*(5), 646–674. https://doi.org/10.1016/j.cell.2011.02.013

Harbeck, N., Penault-Llorca, F., Cortes, J., Gnant, M., Houssami, N., Poortmans, P., Ruddy, K., Tsang, J., & Cardoso, F. (2019). Breast cancer. *Nature Reviews Disease Primers*, *5*(1), 66. https://doi.org/10.1038/s41572-019-0111-2

Hasen, N. S., O'Leary, K. A., Auger, A. P., & Schuler, L. A. (2010). Social isolation reduces mammary development, tumor incidence, and expression of epigenetic regulators in wild-type and p53-heterozygotic mice. *Cancer Prevention Research (Phila)*, *3*(5), 620–629. https://doi.org/10.1158/1940-6207.CAPR-09-0225

Hiam-Galvez, K. J., Allen, B. M., & Spitzer, M. H. (2021). Systemic immunity in cancer. *Nature Reviews Cancer*, *21*, 345–359. https://doi.org/10.1038/s41568-021-00347-z

Hiller, J. G., Cole, S. W., Crone, E. M., Byrne, D. J., Shackleford, D. M., Pang, J. B., & Sloan, E. K. (2020). Preoperative beta-blockade with propranolol reduces biomarkers of metastasis in breast cancer: A phase II randomized trial. *Clinical Cancer Research*, *26*(8), 1803–1811. https://doi.org/10.1158/1078-0432.CCR-19-2641

Houthuijzen, J. M., & Jonkers, J. (2018). Cancer-associated fibroblasts as key regulators of the breast cancer tumor microenvironment. *Cancer and Metastasis Reviews*, *37*(4), 577–597. https://doi.org/10.1007/s10555-018-9768-3

Hyltander, A., Daneryd, P., Sandstrom, R., Korner, U., & Lundholm, K. (2000). Beta-adrenoceptor activity and resting energy metabolism in weight losing cancer patients. *European Journal of Cancer*, *36*(3), 330–334. https://doi.org/10.1016/s0959-8049(99)00273-7

Kamiya, A., Hayama, Y., Kato, S., Shimomura, A., Shimomura, T., Irie, K., Kaneko, R., Yanagawa, Y., Kobayashi, K., & Ochiya, T. (2019). Genetic manipulation of autonomic nerve fiber innervation and activity and its effect on breast cancer progression. *Nature Neuroscience*, *22*(8), 1289–1305. https://doi.org/10.1038/s41593-019-0430-3

Kim, T. H., Gill, N. K., Nyberg, K. D., Nguyen, A. V., Hohlbauch, S. V., Geisse, N. A., & Rowat, A. C. (2016). Cancer cells become less deformable and more invasive with activation of beta-adrenergic signaling. *Journal of Cell Science*, *129*(24), 4563–4575. https://doi.org/10.1242/jcs.194803

Kokolus, K. M., Spangler, H. M., Povinelli, B. J., Farren, M. R., Lee, K. P., & Repasky, E. A. (2014). Stressful presentations: Mild cold stress in laboratory mice influences phenotype of dendritic cells in naive and tumor-bearing mice. *Frontiers in Immunology*, *5*, 23. https://doi.org/10.3389/fimmu.2014.00023

Kruk, J., Aboul-Enein, B. H., Bernstein, J., & Gronostaj, M. (2019). Psychological stress and cellular aging in cancer: A meta-analysis. *Oxidative Medicine and Cellular Longevity*, *2019*, 1270397. https://doi.org/10.1155/2019/1270397

Kurozumi, S., Kaira, K., Matsumoto, H., Hirakata, T., Yokobori, T., Inoue, K., & Shirabe, K. (2019). beta2-Adrenergic receptor expression is associated with biomarkers of tumor immunity and predicts poor prognosis in estrogen receptor-negative breast cancer. *Breast Cancer Research and Treatment*, *177*(3), 603–610. https://doi.org/10.1007/s10549-019-05341-6

Kvetnansky, R., Lu, X., & Ziegler, M. G. (2013). Stress-triggered changes in peripheral catecholaminergic systems. *Advances in Pharmacology*, *68*, 359–397. https://doi.org/10.1016/B978-0-12-411512-5.00017-8

Kvetnansky, R., Sabban, E. L., & Palkovits, M. (2009). Catecholaminergic systems in stress: Structural and molecular genetic approaches. *Physiological Reviews*, *89*(2), 535–606. https://doi.org/10.1152/physrev.00042.2006

Lamkin, D. M., Sung, H. Y., Yang, G. S., David, J. M., Ma, J. C., Cole, S. W., & Sloan, E. K. (2015). alpha2-Adrenergic blockade mimics the enhancing effect of chronic stress on breast cancer progression. *Psychoneuroendocrinology*, *51*, 262–270. https://doi.org/10.1016/j.psyneuen.2014.10.004

Le, C. P., Nowell, C. J., Kim-Fuchs, C., Botteri, E., Hiller, J. G., Ismail, H., & Sloan, E. K. (2016). Chronic stress in mice remodels lymph vasculature to promote tumour cell dissemination. *Nature Communications*, *7*, 10634. https://doi.org/10.1038/ncomms10634

Le, C. P., & Sloan, E. K. (2016). Stress-driven lymphatic dissemination: An unanticipated consequence of communication between the sympathetic nervous system and lymphatic vasculature. *Molecular & Cellular Oncology*, *3*(4), e1177674. https://doi.org/10.1080/23723556.2016.1177674

Lengacher, C. A., Kip, K. E., Post-White, J., Fitzgerald, S., Newton, C., Barta, M., & Klein, T. W. (2013). Lymphocyte recovery after breast cancer treatment and mindfulness-based stress reduction (MBSR) therapy. *Biological Research for Nursing*, *15*(1), 37–47. https://doi.org/10.1177/1099800411419245

Li, D., Hu, L. N., La, T., Wei, L. Y., Zhang, X. J., Zhang, Z. H., & Gao, J. N. (2021). High nerve density in breast cancer is associated with poor patient outcome. Research Square.

Li, P., Huang, J., Wu, H., Fu, C., Li, Y., & Qiu, J. (2016). Impact of lifestyle and psychological stress on the development of early onset breast cancer. *Medicine (Baltimore)*, *95*(50), e5529. https://doi.org/10.1097/MD.0000000000005529

Liang, Q., Li, L., Zhang, J., Lei, Y., Wang, L., Liu, D. X., & Lu, J. (2013). CDK5 is essential for TGF-beta1-induced epithelial-mesenchymal transition and breast cancer progression. *Scientific Reports*, *3*, 2932. https://doi.org/10.1038/srep02932

Lillberg, K., Verkasalo, P. K., Kaprio, J., Teppo, L., Helenius, H., & Koskenvuo, M. (2003). Stressful life events and risk of breast cancer in 10,808 women: A cohort study. *American Journal of Epidemiology*, *157*(5), 415–423. https://doi.org/10.1093/aje/kwg002

Liu, D., Deng, Q., Sun, L., Wang, T., Yang, Z., Chen, H., & Shi, M. (2015). A Her2-let-7-beta2-AR circuit affects prognosis in patients with Her2-positive breast cancer. *BMC Cancer*, *15*, 832. https://doi.org/10.1186/s12885-015-1869-6

Liu, D., Yang, Z., Wang, T., Yang, Z., Chen, H., Hu, Y., & Guo, N. (2016). beta2-AR signaling controls trastuzumab resistance-dependent pathway. *Oncogene*, *35*(1), 47–58. https://doi.org/10.1038/onc.2015.58

Lowrance, S. A., Ionadi, A., McKay, E., Douglas, X., & Johnson, J. D. (2016). Sympathetic nervous system contributes to enhanced corticosterone levels following chronic stress. *Psychoneuroendocrinology*, *68*, 163–170. https://doi.org/10.1016/j.psyneuen.2016.02.027

Lu, Y. J., Geng, Z. J., Sun, X. Y., Li, Y. H., Fu, X. B., Zhao, X. Y., & Wei, B. (2015). Isoprenaline induces epithelial-mesenchymal transition in gastric cancer cells. *Molecular and Cellular Biochemistry*, *408*(1–2), 1–13. https://doi.org/10.1007/s11010-015-2477-0

Madden, K. S., Szpunar, M. J., & Brown, E. B. (2011). beta-Adrenergic receptors (beta-AR) regulate VEGF and IL-6 production by divergent pathways in high beta-AR-expressing breast cancer cell lines. *Breast Cancer Research and Treatment*, *130*(3), 747–758. https://doi.org/10.1007/s10549-011-1348-y

Marchetti, B., & Labrie, F. (1990). Hormonal regulation of beta-adrenergic receptors in the rat mammary gland during the estrous cycle and lactation: Role of sex steroids and prolactin. *Endocrinology*, *126*(1), 575–581. https://doi.org/10.1210/endo-126-1-575

Mariotti, A. (2015). The effects of chronic stress on health: New insights into the molecular mechanisms of brain-body communication. *Future Science OA*, *1*(3), FSO23. https://doi.org/10.4155/fso.15.21

Masjedi, A., Hashemi, V., Hojjat-Farsangi, M., Ghalamfarsa, G., Azizi, G., Yousefi, M., & Jadidi-Niaragh, F. (2018). The significant role of interleukin-6 and its signaling pathway in the immunopathogenesis and treatment of breast cancer. *Biomedicine and Pharmacotherapy*, *108*, 1415–1424. https://doi.org/10.1016/j.biopha.2018.09.177

McGeown, J. G., McHale, N. G., & Thornbury, K. D. (1987). The effect of electrical stimulation of the sympathetic chain on peripheral lymph flow in the anaesthetized sheep. *Journal of Physiology*, *393*, 123–133. https://doi.org/10.1113/jphysiol.1987.sp016814

McHale, N. G., & Thornbury, K. D. (1990). Sympathetic stimulation causes increased output of lymphocytes from the popliteal node in anaesthetized sheep. *Experimental Physiology*, *75*(6), 847–850. https://doi.org/10.1113/expphysiol.1990.sp003467

Melander, A., Westgren, U., Ericson, L. E., & Sundler, F. (1977). Influence of the sympathetic nervous system on the secretion and metabolism of thyroid hormone. *Endocrinology*, *101*(4), 1228–1237. https://doi.org/10.1210/endo-101-4-1228

Melhem-Bertrandt, A., Chavez-Macgregor, M., Lei, X., Brown, E. N., Lee, R. T., Meric-Bernstam, F., Sood, A. K., Conzen, S. D., Hortobagyi, G. N., & Gonzalez-Angulo, A. M. (2011). Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. *Journal of Clinical Oncology*, *29*(19), 2645–2652. https://doi.org/10.1200/JCO.2010.33.4441

Mendez-Ferrer, S., Lucas, D., Battista, M., & Frenette, P. S. (2008). Haematopoietic stem cell release is regulated by circadian oscillations. *Nature*, *452*(7186), 442–447. https://doi.org/10.1038/nature06685

Mohammadpour, H., MacDonald, C. R., Qiao, G., Chen, M., Dong, B., Hylander, B. L., Mccarthy, P. L., Abrams, S. I., & Repasky, E. A. (2019). beta2 adrenergic receptor-mediated signaling regulates the immunosuppressive potential of myeloid-derived suppressor cells. *Journal of Clinical Investigation*, *129*(12), 5537–5552. https://doi.org/10.1172/JCI129502

Mravec, B., Horvathova, L., & Hunakova, L. (2020). Neurobiology of cancer: The role of beta-adrenergic receptor signaling in various tumor environments. *International Journal of Molecular Sciences*, *21*(21):7958. https://doi.org/10.3390/ijms21217958

Mulcrone, P. L., Campbell, J. P., Clément-Demange, L., Anbinder, A. L., Merkel, A. R., Brekken, R. A., Sterling, J. A., & Elefteriou, F. (2017). Skeletal colonization by breast cancer cells is stimulated by an osteoblast and beta2AR-dependent neo-angiogenic switch. *Journal of Bone and Mineral Research*, *32*(7), 1442–1454. https://doi.org/10.1002/jbmr.3133

Nagaraja, A. S., Dood, R. L., Armaiz-Pena, G., Kang, Y., Wu, S. Y., Allen, J. K., & Sood, A. K. (2017). Adrenergic-mediated increases in INHBA drive CAF phenotype and collagens. *JCI Insight*, *2*(16), e93076. https://doi.org/10.1172/jci.insight.93076

Nance, D. M., & Sanders, V. M. (2007). Autonomic innervation and regulation of the immune system (1987-2007). *Brain, Behavior, and Immunity*, *21*(6), 736–745. https://doi.org/10.1016/j.bbi.2007.03.008

Nilsson, O. R., & Karlberg, B. E. (1983). Thyroid hormones and the adrenergic nervous system. *Acta Medica Scandinavica Supplementum*, *672*, 27–32. https://doi.org/10.1111/j.0954-6820.1983.tb01610.x

Nuevo-Tapioles, C., Santacatterina, F., Stamatakis, K., Nunez de Arenas, C., Gomez de Cedron, M., Formentini, L., & Cuezva, J. M. (2020). Coordinate beta-adrenergic inhibition of mitochondrial activity and angiogenesis arrest tumor growth. *Nat Commun*, *11*(1), 3606. https://doi.org/10.1038/s41467-020-17384-1

Ojeda, S. R., & Lara, H. E. (1989). *Role of the Sympathetic Nervous System in the Regulation of Ovarian Function*. Berlin, Heidelberg.

Ouyang, X., Zhu, Z., Yang, C., Wang, L., Ding, G., & Jiang, F. (2019). Epinephrine increases malignancy of breast cancer through p38 MAPK signaling pathway in depressive disorders. *International Journal Of Clinical And Experimental Pathology*, *12*(6), 1932–1946.

Parkin, R., & Neale, S. (1976). The effect of isoprenaline on induction of tumours by methyl nitrosourea in the salivary and mammary glands of female wistar rats. *British Journal of Cancer*, *34*(4), 437–443. https://doi.org/10.1038/bjc.1976.189

Pattabiraman, D. R., Bierie, B., Kober, K. I., Thiru, P., Krall, J. A., Zill, C., Reinhardt, F., Tam, W. L., & Weinberg, R. A. (2016). Activation of PKA leads to mesenchymal-to-epithelial transition and loss of tumor-initiating ability. *Science*, *351*(6277), aad3680. https://doi.org/10.1126/science.aad3680

Peng, Z., Wang, C. X., Fang, E. H., Wang, G. B., & Tong, Q. (2014). Role of epithelial-mesenchymal transition in gastric cancer initiation and progression. *World Journal of Gastroenterology*, *20*(18), 5403–5410. https://doi.org/10.3748/wjg.v20.i18.5403

Perez Pinero, C., Bruzzone, A., Sarappa, M. G., Castillo, L. F., & Luthy, I. A. (2012). Involvement of alpha2- and beta2-adrenoceptors on breast cancer cell proliferation and tumour growth regulation. *British Journal of Pharmacology*, *166*(2), 721–736. https://doi.org/10.1111/j.1476-5381.2011.01791.x

Petruzzelli, M., Schweiger, M., Schreiber, R., Campos-Olivas, R., Tsoli, M., Allen, J., Swarbrick, M., Rose-John, S., Rincon, M., Robertson, G., Zechner, R., & Wagner, E. F. (2014). A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. *Cell Metabolism*, *20*(3), 433–447. https://doi.org/10.1016/j.cmet.2014.06.011

Place, A. E., Jin Huh, S., & Polyak, K. (2011). The microenvironment in breast cancer progression: Biology and implications for treatment. *Breast Cancer Research*, *13*(6), 227. https://doi.org/10.1186/bcr2912

Pon, C. K., Lane, J. R., Sloan, E. K., & Halls, M. L. (2016). The beta2-adrenoceptor activates a positive cAMP-calcium feedforward loop to drive breast cancer cell invasion. *FASEB Journal*, *30*(3), 1144–1154. https://doi.org/10.1096/fj.15-277798

Powe, D. G., Voss, M. J., Habashy, H. O., Zanker, K. S., Green, A. R., Ellis, I. O., & Entschladen, F. (2011). Alpha- and beta-adrenergic receptor (AR) protein expression is associated with poor clinical outcome in breast cancer: An immunohistochemical study. *Breast Cancer Research and Treatment*, *130*(2), 457–463. https://doi.org/10.1007/s10549-011-1371-z

Powe, D. G., Voss, M. J., Zanker, K. S., Habashy, H. O., Green, A. R., Ellis, I. O., & Entschladen, F. (2010). Beta-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. *Oncotarget*, *1*(7), 628–638. https://doi.org/10.18632/oncotarget.101009

Pu, J., Zhang, X., Luo, H., Xu, L., Lu, X., & Lu, J. (2017). Adrenaline promotes epithelial-to-mesenchymal transition via HuR-TGFbeta regulatory axis in pancreatic cancer cells and the implication in cancer prognosis. *Biochemical and Biophysical Research Communications*, *493*(3), 1273–1279. https://doi.org/10.1016/j.bbrc.2017.09.146

Qin, J. F., Jin, F. J., Li, N., Guan, H. T., Lan, L., Ni, H., & Wang, Y. (2015). Adrenergic receptor beta2 activation by stress promotes breast cancer progression through macrophages M2 polarization in tumor microenvironment. *BMB Reports*, *48*(5), 295–300. https://doi.org/10.5483/bmbrep.2015.48.5.008

Rabasa, C., & Dickson, S. L. (2016). Impact of stress on metabolism and energy balance. *Current Opinion in Behavioral Sciences*, *9*, 71–77. https://doi.org/10.1016/j.cobeha.2016.01.011

Reeder, A., Attar, M., Nazario, L., Bathula, C., Zhang, A., Hochbaum, D., Roy, E., Cooper, K. L., Oesterreich, S., Davidson, N. E., Neumann, C. A., & Flint, M. S. (2015). Stress hormones reduce the efficacy of paclitaxel in triple negative breast cancer through induction of DNA damage. *British Journal of Cancer*, *112*(9), 1461–1470. https://doi.org/10.1038/bjc.2015.133

Rivero, E. M., Martinez, L. M., Bruque, C. D., Gargiulo, L., Bruzzone, A., & Luthy, I. A. (2019). Prognostic significance of alpha- and beta2-adrenoceptor gene expression in breast cancer patients. *British Journal of Clinical Pharmacology*, *85*(9), 2143–2154. https://doi.org/10.1111/bcp.14030

Roney, J. R., & Simmons, Z. L. (2015). Elevated psychological stress predicts reduced estradiol concentrations in young women. *Adaptive Human Behavior and Physiology*, *1*(1), 30–40. https://doi.org/10.1007/s40750-014-0004-2

Roxburgh, C. S., & McMillan, D. C. (2014). Cancer and systemic inflammation: Treat the tumour and treat the host. *British Journal of Cancer*, *110*(6), 1409–1412. https://doi.org/10.1038/bjc.2014.90

Salama, A. A. K., Contreras-Jodar, A., Love, S., Mehaba, N., Such, X., & Caja, G. (2020). Milk yield, milk composition, and milk metabolomics of dairy goats intramammary-challenged with lipopolysaccharide under heat stress conditions. *Scientific Reports*, *10*(1), 5055. https://doi.org/10.1038/s41598-020-61900-8

Sastry, K. S., Karpova, Y., Prokopovich, S., Smith, A. J., Essau, B., Gersappe, A., Carson, J. P., Weber, M. J., Register, T. C., Chen, Y. Q., Penn, R. B., & Kulik, G. (2007). Epinephrine protects cancer cells from apoptosis via activation of cAMP-dependent protein kinase and BAD phosphorylation. *Journal of Biological Chemistry*, *282*(19), 14094–14100. https://doi.org/10.1074/jbc.M611370200

Scheiermann, C., Kunisaki, Y., & Frenette, P. S. (2013). Circadian control of the immune system. *Nature Reviews Immunology*, *13*(3), 190–198. https://doi.org/10.1038/nri3386

Shaashua, L., Shabat-Simon, M., Haldar, R., Matzner, P., Zmora, O., Shabtai, M., Sharon, E., Allweis, T., Barshack, I., Hayman, L., Arevalo, J., Ma, J., Horowitz, M., Cole, S., & Ben-Eliyahu, S. (2017). Perioperative COX-2 and beta-adrenergic blockade improves metastatic biomarkers in breast cancer patients in a phase-II randomized trial. *Clinical Cancer Research*, *23*(16), 4651–4661. https://doi.org/10.1158/1078-0432.CCR-17-0152

Shakhar, G., & Ben-Eliyahu, S. (1998). In vivo beta-adrenergic stimulation suppresses natural killer activity and compromises resistance to tumor metastasis in rats. *Journal of Immunology*, *160*(7), 3251–3258.

Shi, M., Liu, D., Duan, H., Qian, L., Wang, L., Niu, L., Zhang, H., Yong, Z., Gong, Z., Song, L., Yu, M., Hu, M., Xia, Q., Shen, B., & Guo, N. (2011). The beta2-adrenergic receptor and Her2 comprise a positive feedback loop in human breast cancer cells. *Breast Cancer Research and Treatment*, *125*(2), 351–362. https://doi.org/10.1007/s10549-010-0822-2

Silberstein, G. B., Strickland, P., Trumpbour, V., Coleman, S., & Daniel, C. W. (1984). In vivo, cAMP stimulates growth and morphogenesis of mouse mammary ducts. *Proceedings of the National Academy of Sciences of the United States of America*, *81*(15), 4950–4954. https://doi.org/10.1073/pnas.81.15.4950

Sloan, E. K., Priceman, S. J., Cox, B. F., Yu, S., Pimentel, M. A., Tangkanangnukul, V., Arevalo, J. M., Morizono, K., Karanikolas, B. D., Wu, L., Sood, A. K., & Cole, S. W. (2010). The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Research*, *70*(18), 7042–7052. https://doi.org/10.1158/0008-5472.CAN-10-0522

Slotkin, T. A., Zhang, J., Dancel, R., Garcia, S. J., Willis, C., & Seidler, F. J. (2000). Beta-adrenoceptor signaling and its control of cell replication in MDA-MB-231 human breast cancer cells. *Breast Cancer Research and Treatment*, *60*(2), 153–166. https://doi.org/10.1023/a:1006338232150

Snow, H. (1893). *A Treatise, Practical and Theoretic on Cancers and the Cancer-process*. J. & A.

Song, Q., Ji, Q., & Li, Q. (2018). The role and mechanism of betaarrestins in cancer invasion and metastasis (Review). *International Journal of Molecular Medicine*, *41*(2), 631–639. https://doi.org/10.3892/ijmm.2017.3288

Song, S. L., Crowley, W. R., & Grosvenor, C. E. (1988). Evidence for involvement of an adrenal catecholamine in the beta-adrenergic inhibition of oxytocin release in lactating rats. *Brain Research*, *457*(2), 303–309. https://doi.org/10.1016/0006-8993(88)90700-7

Spiegel, D., & Bloom, J. R. (1983). Group therapy and hypnosis reduce metastatic breast carcinoma pain. *Psychosomatic Medicine*, *45*(4), 333–339. https://doi.org/10.1097/00006842-198308000-00007

Spiegel, D., Bloom, J. R., & Yalom, I. (1981). Group support for patients with metastatic cancer. A randomized outcome study. *Archives of General Psychiatry*, *38*(5), 527–533. https://doi.org/10.1001/archpsyc.1980.01780300039004

Stampfer, M. R. (1982). Cholera toxin stimulation of human mammary epithelial cells in culture. *In Vitro*, *18*(6), 531–537. https://doi.org/10.1007/BF02810076

Su, F., Ouyang, N., Zhu, P., Ouyang, N., Jia, W., Gong, C., Ma, X., Xu, H., & Song, E. (2005). Psychological stress induces chemoresistance in breast cancer by upregulating mdr1. *Biochemical and Biophysical Research Communications*, *329*(3), 888–897. https://doi.org/10.1016/j.bbrc.2005.02.056

Sun, H., Huang, H., Ji, S., Chen, X., Xu, Y., Zhu, F., & Wu, J. (2019). The efficacy of cognitive behavioral therapy to treat depression and anxiety and improve quality of life among early-stage breast cancer patients. *Integrative Cancer Therapies*, *18*, 1534735419829573. https://doi.org/10.1177/1534735419829573

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209–249. https://doi.org/10.3322/caac.21660

Suzuki, S., Yamamoto, M., Sanomachi, T., Togashi, K., Sugai, A., Seino, S., Okada, M., Yoshioka, T., & Kitanaka, C. (2020). Doxazosin, a classic alpha 1-adrenoceptor antagonist, overcomes osimertinib resistance in cancer cells vi a the upregulation of autophagy as drug repurposing. *Biomedicines*, *8*(8), 273. https://doi.org/10.3390/biomedicines8080273

Szpunar, M. J., Belcher, E. K., Dawes, R. P., & Madden, K. S. (2016). Sympathetic innervation, norepinephrine content, and norepinephrine turnover in orthotopic and spontaneous models of breast cancer. *Brain, Behavior, and Immunity*, *53*, 223–233. https://doi.org/10.1016/j.bbi.2015.12.014

Tank, A. W., & Lee Wong, D. (2015). Peripheral and central effects of circulating catecholamines. *Compr Physiol*, *5*(1), 1–15. https://doi.org/10.1002/cphy.c140007

Tavares, P., Gonçalves, D. M., Santos, L. L., & Ferreira, R. (2021). Revisiting the clinical usefulness of C-reactive protein in the set of cancer cachexia. *Porto Biomedical Journal*, *6*(1), e123. https://doi.org/10.1097/j.pbj.0000000000000123

Thaker, P. H., Lutgendorf, S. K., & Sood, A. K. (2007). The neuroendocrine impact of chronic stress on cancer. *Cell Cycle*, *6*(4), 430–433. https://doi.org/10.4161/cc.6.4.3829

Tibensky, M., Cernackova, A., Horvathova, L., Macejova, D., Tillinger, A., & Mravec, B. (2021). Chronic propranolol treatment moderately attenuated development of N-methyl-N-nitrosourea-induced mammary carcinoma in female rats. *Anti-Cancer Drugs*, *32*, 1011–1018. https://doi.org/10.1097/CAD.0000000000001113

Tilley, D. G. (2011). G protein-dependent and G protein-independent signaling pathways and their impact on cardiac function. *Circulation Research*, *109*(2), 217–230. https://doi.org/10.1161/CIRCRESAHA.110.231225

Toufexis, D., Rivarola, M. A., Lara, H., & Viau, V. (2014). Stress and the reproductive axis. *Journal of Neuroendocrinology*, *26*(9), 573–586. https://doi.org/10.1111/jne.12179

Uchida, S., & Kagitani, F. (2015). Autonomic nervous regulation of ovarian function by noxious somatic afferent stimulation. *The Journal Of Physiological Sciences: JPS*, *65*(1), 1–9. https://doi.org/10.1007/s12576-014-0324-9

Vazquez, S. M., Mladovan, A. G., Perez, C., Bruzzone, A., Baldi, A., & Luthy, I. A. (2006). Human breast cell lines exhibit functional alpha2-

adrenoceptors. *Cancer Chemotherapy and Pharmacology*, *58*(1), 50–61. https://doi.org/10.1007/s00280-005-0130-4

Von Ah, D., Kang, D. H., & Carpenter, J. S. (2007). Stress, optimism, and social support: Impact on immune responses in breast cancer. *Research in Nursing and Health*, *30*(1), 72–83. https://doi.org/10.1002/nur.20164

Wang, L., Simons, D. L., Lu, X., Tu, T. Y., Avalos, C., Chang, A. Y., Dirbas, F. M., Yim, J. H., Waisman, J., & Lee, P. P. (2020). Breast cancer induces systemic immune changes on cytokine signaling in peripheral blood monocytes and lymphocytes. *EBioMedicine*, *52*, 102631. https://doi.org/10.1016/j.ebiom.2020.102631

Wilson, J. M., Lorimer, E., Tyburski, M. D., & Williams, C. L. (2015). beta-Adrenergic receptors suppress Rap1B prenylation and promote the metastatic phenotype in breast cancer cells. *Cancer Biology & Therapy*, *16*(9), 1364–1374. https://doi.org/10.1080/15384047.2015.1070988

Wu, Q., Li, B., Li, Z., Li, J., Sun, S., & Sun, S. (2019). Cancer-associated adipocytes: Key players in breast cancer progression. *Journal of Hematology & Oncology*, *12*(1), 95. https://doi.org/10.1186/s13045-019-0778-6

Wu, Q., Sun, S., Li, Z., Yang, Q., Li, B., Zhu, S., Wang, L., Wu, J., Yuan, J., Wang, C., Li, J., & Sun, S. (2019). Breast cancer-released exosomes trigger cancer-associated cachexia to promote tumor progression. *Adipocyte*, *8*(1), 31–45. https://doi.org/10.1080/21623945.2018.1551688

Yamazaki, S., Sakakibara, H., Takemura, H., Yasuda, M., & Shimoi, K. (2014). Quercetin-3-O-glucronide inhibits noradrenaline binding to alpha2-adrenergic receptor, thus suppressing DNA damage induced by treatment with 4-hydroxyestradiol and noradrenaline in MCF-10A cells. *Journal of Steroid Biochemistry and Molecular Biology*, *143*, 122–129. https://doi.org/10.1016/j.jsbmb.2014.02.014

Yang, J., Guzman, R., Richards, J., Imagawa, W., McCormick, K., & Nandi, S. (1980). Growth factor- and cyclic nucleotide-induced proliferation of normal and malignant mammary epithelial cells in primary culture. *Endocrinology*, *107*(1), 35–41. https://doi.org/10.1210/endo-107-1-35

Yaribeygi, H., Panahi, Y., Sahraei, H., Johnston, T. P., & Sahebkar, A. (2017). The impact of stress on body function: A review. *EXCLI Journal*, *16*, 1057–1072. https://doi.org/10.17179/excli2017-480

Yu, M., Bardia, A., Wittner, B. S., Stott, S. L., Smas, M. E., Ting, D. T., Isakoff, S. J., Ciciliano, J. C., Wells, M. N., Shah, A. M., Concannon, K. F., Donaldson, M. C., Sequist, L. V., Brachtel, E., Sgroi, D., Baselga, J., Ramaswamy, S., Toner, M., Haber, D. A., & Maheswaran, S. (2013). Circulating breast tumor cells exhibit dynamic changes in epithelial and mesenchymal composition. *Science*, *339*(6119), 580–584. https://doi.org/10.1126/science.1228522

Zhang, H., Fredericks, T., Xiong, G., Qi, Y., Rychahou, P. G., Li, J. D., Pihlajaniemi, T., Xu, W., & Xu, R. (2018). Membrane associated collagen XIII promotes cancer metastasis and enhances anoikis resistance. *Breast Cancer Research*, *20*(1), 116. https://doi.org/10.1186/s13058-018-1030-y

Zhang, P., Mo, L., Li, X., & Wang, Q. (2019). Psychological intervention and its immune effect in cancer patients: A meta-analysis. *Medicine (Baltimore)*, *98*(38), e17228. https://doi.org/10.1097/MD.0000000000017228

Zhao, C., Wu, M., Zeng, N., Xiong, M., Hu, W., Lv, W., Yi, Y., Zhang, Q., & Wu, Y. (2020). Cancer-associated adipocytes: Emerging supporters in breast cancer. *Journal of Experimental & Clinical Cancer Research*, *39*(1), 156. https://doi.org/10.1186/s13046-020-01666-z

Zhao, L., Li, W., Zang, W., Liu, Z., Xu, X., Yu, H., Yang, Q., & Jia, J. (2013). JMJD2B promotes epithelial-mesenchymal transition by cooperating with beta-catenin and enhances gastric cancer metastasis. *Clinical Cancer Research*, *19*(23), 6419–6429. https://doi.org/10.1158/1078-0432.CCR-13-0254

Zhi, X., Li, B., Li, Z., Zhang, J., Yu, J., Zhang, L., & Xu, Z. (2019). Adrenergic modulation of AMPKdependent autophagy by chronic stress enhances cell proliferation and survival in gastric cancer. *International Journal of Oncology*, *54*(5), 1625–1638. https://doi.org/10.3892/ijo.2019.4753

Zhou, J., Liu, Z., Zhang, L., Hu, X., Wang, Z., Ni, H., Wang, Y., & Qin, J. (2020). Activation of beta2-adrenergic receptor promotes growth and angiogenesis in breast cancer by down-regulating PPARgamma. *Cancer Research and Treatment: Official Journal of Korean Cancer Association*, *52*(3), 830–847. https://doi.org/10.4143/crt.2019.510

Zhou, L., Li, Y., Li, X., Chen, G., Liang, H., Wu, Y., Tong, J., & Ouyang, W. (2016). Propranolol attenuates surgical stress-induced elevation of the regulatory T cell response in patients undergoing radical mastectomy. *Journal of Immunology*, *196*(8), 3460–3469. https://doi.org/10.4049/jimmunol.1501677

Zhu, Q., Glazier, B. J., Hinkel, B. C., Cao, J., Liu, L., Liang, C., & Shi, H. (2019). Neuroendocrine regulation of energy metabolism involving different types of adipose tissues. *International Journal of Molecular Sciences*, *20*(11), 2707. https://doi.org/10.3390/ijms20112707

How to cite this article: Silva, D., Quintas, C., Gonçalves, J., & Fresco, P. (2022). Contribution of adrenergic mechanisms for the stress-induced breast cancer carcinogenesis. *Journal of Cellular Physiology*, 1–21. https://doi.org/10.1002/jcp.30707