

The stress connection in cancer: the adrenergic fuelling of breast tumors

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Cancer progression involves complex interactions between tumor cells and the surrounding microenvironment. Chronic psychosocial stress and sympathetic nervous system activation lead to abnormal catecholamine release, impacting tumor cells directly and indirectly and fuelling cancer-promoting effects. However, the same adrenergic Receptor (AR) that mediate these effects could also convey exercise-related beneficial changes. Epidemiological studies show conflicting associations between stress, AR inhibitors, and breast cancer (BC) metastatic progression. Adrenergic sympathetic stress triggers sustained inflammatory and hypoxic-related signaling pathways, alters function and distribution of immune cell populations, and remodels blood vessels, leading to immunosuppression and premetastatic site formation. Activated AR initiate feedback loops with tyrosine kinase receptors and chemokine receptors, affecting stem-related transcription factors, pro-inflammatory mediators, angiogenic factors, and energy metabolism regulators, promoting tumor growth and invasion. Understanding molecular mechanisms of agonistic and antagonistic AR ligands and crosstalk with other signaling pathways is crucial for developing effective therapies targeting adrenergic-driven BC progression.

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Introduction

Cancer progression is a highly complex process in which multiple and sequential changes in tumor cells occur within a reactive tumor microenvironment, establishing interactions between tumor cells and stromal cells that influence each other and how the tumor evolves [1]. The alteration of signaling pathways governing proliferation, survival, angiogenesis, invasive migration, metastasis, metabolism, or the immune response are key events in cancer initiation and progression. Such alterations can be initiated or reinforced by intrinsic or environmental-induced dysregulation of hormones, growth factors, or neurotransmitters that act on cell receptors, which in turn can show alterations in their normal levels and functionality. In this regard, the adrenergic signaling has been implicated in almost all phases of tumorigenesis, in addition to affecting virtually all tumor traits [2,3].

Compelling evidence indicates that sympathetic overdrive can impact directly on tumoral cells, and indirectly through the tumor microenvironment, to foster cancer-promoting effects on breast cancer (BC) [4]. It has been described that chronic psychosocial stress stimulates the hypothalamic–pituitary adrenal axis and the sympathetic nervous system (SNS), resulting in an abnormal release of catecholamines (CA) that aggravates tumor progression [5,6]. Also, preclinical models of malignancy demonstrate that stress-related adrenergic overstimulation in general promotes progression of different types of tumors [2–4]. Besides, epidemiologic studies provide evidence that psychological and social stress can affect the metastatic progression of BC [7], also revealing correlations between long-term survival and reduced cancer progression with the prescription of β -adrenergic antagonists or β -blockers (BB) [8]. However, the promising use of nonselective β -adrenergic receptor (AR) receptor antagonists to counteract the adverse effects of CA in BC could be questioned due to preclinical studies showing that certain BB, capable of constitutively blocking receptor activity, may actually promote tumor growth. In contrast, it appears that some BB have the ability to act as activators of underappreciated nonconventional adrenergic signaling pathways, which could have antitumoral potential.

Furthermore, in this review, we emphasize the epidemiological evidence and fundamental scientific knowledge that

reveal paradoxical and not-so-straightforward effects of adrenergic stimulation on BC progression. We will explore the question of when and where modulation of adrenoceptor activity may be beneficial in tumor progression, based on the increasing evidence of ‘tumor-in-house’ production of CA and the role of circulating and neural CA in preconditioning the microenvironment in distant organs for metastasis.

Additionally, we will provide an overview of recent studies proving the influence of adrenergic signaling and sympathetic stress in BC feedforward loops involving other receptor families. We will specifically emphasize tumor traits directly related to tumor progression, such as invasion and metastasis, or vascular remodeling, and the underlying molecular mechanisms.

Misregulation of the adrenergic system in breast cancer

BC, the most prevalent cancer among women worldwide [9], is a heterogeneous disease due to multiple molecular signatures, genetic, and genomic variations. These entities are grouped in different subtypes: estrogen-receptor (ER) and progesterone-receptor (PR)-positive luminal, ERBB2+ (or human epidermal growth factor receptor 2 [HER2+]), basal-like (also referred as triple-negative BC [TNBC] due to the absence of ER, PR, and HER2) and claudin-low for simplicity [10]. In all these types of BC, there is some alteration of the adrenergic system, which includes CA, mainly epinephrine (EPI) and norepinephrine (NE), and their receptors [2,3]. Both EPI and NE are directly secreted into the bloodstream by the adrenal medulla (circa 80% EPI:20% NE), along with NE released locally by sympathetic nerves in most tissues and organs. Their cognate adrenergic Receptor (AR) are grouped in three distinct subfamilies of G-protein-coupled receptor (GPCR): α 1, α 2, and β -AR, further divided into subtypes. Of these receptors, α 1A, α 1B, and α 1D are generally coupled to a G_q -protein subunit; α 2A, α 2B, and α 2C are coupled to G_i , down-regulating the activity of adenylyl cyclase; and β 1, β 2, and β 3 interact with G_s , inducing the production of cyclic adenosine monophosphate (cAMP) [11].

Circulating CA are increased in BC patients, correlating with worse disease progression [12]. Similar findings are reported in chronic stress mouse models of BC [13–17]. β -adrenoceptors (mainly β 2AR) are more closely related to metastasis and resistance processes [2,3] and β -AR density increases from low levels in poor metastatic luminal cell lines to very high levels in metastatic TNBC cells [18–20]. Some mechanisms underlying this increase are beginning to be identified. For instance, early inactivation of the transcriptional repressor HIC1 (hypermethylated in cancer 1) leads to Adrenoceptor beta 2 (β 2AR) (ADRB2) upregulation and increased β 2AR protein levels in BC cells [21], while

complex feedforward signaling loops can increase the levels of β 2AR (see below).

Interestingly, there are no differences of ADRB2 (β 2AR) gene expression when cell lines of the luminal, HER2-enriched, or basal-like types are each classified according to metastatic versus nonmetastatic status [12]. This might suggest that β 2AR upregulation is more related to the basal-type breast tumor profile than to the metastatic signature. On the other hand, Adrenoceptor Alpha 2C (α 2c-AR) was found to be highly upregulated in all metastatic cell lines and clinically associated with high-grade tumors in both luminal and basal-like BC patients [22]. Conversely, high levels of Adrenoceptor Alpha 2A (α 2a-AR) denote a better prognosis in patients with luminal BC [22], but Adrenoceptor Alpha 2A polymorphisms are associated with severity [23]. This points out the need to broaden the still-limited knowledge on α AR roles in BC [3].

Remarkably, a recent The Cancer Genome Atlas database analysis showed decreased mRNAs for all adrenoceptors in breast tumors compared with normal tissue [12]. This contrasts with the data at both mRNA and protein levels in most experimentally used BC cell lines when compared with nonmalignant cells [24,25]. The downregulation of ADRB2 mRNA could reflect counterbalancing mechanisms that sense the adrenergic overdrive in patients, a mechanism that may become ineffective in the long term. Meanwhile, alterations in the tumor may favor nontranscriptional processes to increase β 2AR protein levels despite overstimulation.

Some preclinical studies have shown that reducing β -adrenergic signaling is ineffective or might even potentiate cancer growth (see sections below). Indeed, both neutral and beneficial effects of receptor BB have been reported in BC cell lines, animal models, and patients [3], and references therein). Most clinical data on the effects of BB on BC outcomes rely on retrospective studies (Table 1). In these studies, patients were treated with BB due to their hypertensive condition and other diseases. This group tended to be older, less premenopausal, and with slightly different BC features than the untreated patients with whom they were compared [26–29]. The benefits of BB seem to be more sustained in triple breast-negative cancer (TNBC) patients with less-advanced tumors. Moreover, in a recent epidemiological survey, combined therapy with BB and genotoxic anthracyclines was more effective against TNBC progression. This therapy showed that it blunted tumor SNS innervation in animal models [30]. However, protective roles of BB are less evident in hormone-dependent BC patients and even detrimental in HER2-positive patients (Table 1). Furthermore, though retrospective and prospective studies have indicated that selective BB were less effective than nonselective ones [31], high-scale analysis has supported both for and against the use of beta-blockers in

Table 1

The effect of BB in the outcomes of BC patients in clinical studies.

Author (DOI)	Year	Type of study and defined BC subtype	Total number of patients/ BB treated	BB types (number of patients)	Effect of BB on BC outcomes
Powe et al. DOI: 10.18632/oncotarget.101009	2010	Retrospective Overall BC types	374/43	Grouped [atenolol (43), propranolol (7), bisoprolol (7), timolol (4)]	↓ Metastasis formation and tumor recurrence ↓ Risk of cancer-associated mortality
Melhem-Bertrand et al. DOI: 10.1200/JCO.2010.33.4441	2011	Retrospective Overall BC types	1413/102	Grouped [metoprolol (43), atenolol (38), others (n.d.) (21)]	↑ Relapse-free survival in TBNC patients but not in ER+(positive) patients
Barron et al. DOI: 10.1200/JCO.2010.33.5422	2011	Retrospective Stage-I-IV invasive BC	5333/595	Selective [atenolol (525)] Nonselective [propranolol (70)]	↓ T4 tumor, node-positive (N2/N3), or metastatic disease. ↓ BC-specific mortality with nonselective BB. No differences in selective BB users versus nonusers
Shah et al DOI: 10.1111/j.13652125.2011.03980.x	2011	Retrospective Overall BC types	984/194	Grouped [atenolol (n.d.), propranolol (n.d.), others (n.d.)]	Unchanged overall survival in BB users versus nonusers, nor in selective- versus nonselective BB users
Ganz et al. DOI: 10.1007/s10549-011-1505-3	2011	Retrospective Early-stage invasive BC	1779/204	Grouped [atenolol (153), propranolol (28), metoprolol (16)]	Unchanged BC recurrence, cancer-specific death, or overall survival in BB users versus nonusers
Sendur et al. DOI: 10.1016/j.breast.2011.09.015	2012	Retrospective Overall BC types	544/88	Metoprolol (88)	No differences in overall survival and disease-free survival in BB and nonusers
Botteri et al DOI: 10.1007/s10549-013-2654-3	2013	Retrospective Early-stage TBNC, postmenopausal patients	800/74	Grouped [atenolol (27), nebivolol (13), carvedilol (11), bisoprolol (11), metoprolol (8), sotalol (3), betaxolol (1)] Selective [n.d.(10)] Nonselective [n.d.(5)] Grouped [n.d.(91)]	↓ BC recurrence IBC-specific death and overall mortality in BB users
Parada-Huertas et al. DOI: APJCP.2016.17.6.2953	2016	Retrospective Overall BC types	96/15	Selective [n.d.(10)]	↓ Metastasis formation with BB (clearer with nonselective)
Choy et al DOI: 10.3892/or.2016.4710	2016	Retrospective Stage-II primary BC	683/91	Nonselective [n.d.(91)]	↓ BC recurrence and metastasis in stage-II patients with perioperative BB
Cardwell et al. DOI: 10.1186/s13058-016-0782-5	2016	Retrospective Multinational- compiled European cohort	188 503/4746	Propranolol (4746)	No reduced cancer-specific or all-cause mortality with BB either before or after BC diagnosis
Montoya et al. DOI: 10.18632/oncotarget.14119	2017	Retrospective Stage-I patients Prospective Stage I (Her2-negative, ER-positive patient)	404/55 1	Selective [atenolol (1), bisoprolol (12), metoprolol (29)] Nonselective [carvedilol (9), propranolol (1), timolol (1)] Nonselective propranolol	↓ Proliferative index with nonselective BB. No effect of selective BB ↓ Proliferative index after 25 days of treatment
Spera et al. DOI:10.1093/annonc/mdx264	2017	Retrospective HER2-(negative) late-stage BC	1144/153	Grouped [bisoprolol (59), metoprolol (48), atenolol (28), propranolol (13)]	↑ Progression- free survival in overall BB users (higher effect in TBNC patients, no effect in ER-/PR-(positive) patients)
Montoya et al. (re)	2019	Prospective Stage-IIIA patient	1	Nonselective propranolol	↓ Proliferative index, apoptotic index after 25 days of treatment
Santala et al DOI: 10.1158/1055-9965.EPI-20-0711	2020	Retrospective Overall BC types	19 420/8162	Selective [metoprolol (n.d.), nebivolol (n.d.), atenolol (n.d.), acebutolol (n.d.), betaxolol (n.d.), bisoprolol (n.d.), celiprolol (n.d.)] Nonselective [pindolol (n.d.), propranolol (n.d.), timolol (n.d.), labetalol (n.d.), carvedilol (n.d.)]	No association of either BB group with risk of BC death in overall patients. Similar risk in ER-/PR-positive patients. ↓ in TBNC patients, and ↑ in HER2+ BC

Table 1 (continued)

Author (DOI)	Year	Type of study and defined BC subtype	Total number of patients/ BB treated	BB types (number of patients)	Effect of BB on BC outcomes
Modi et al. DOI: 10.3389/fonc.2020.01130	2020	Retrospective Advanced HER2+ BC	2777/266	Grouped [metoprolol (57), atenolol (67), bisoprolol (68), others (20)] Nonselective [propranolol (21), carvedilol (23), others (7)] Grouped [n.d.]	↓ Overall survival in grouped BB users versus nonusers. Analysis with BB subgroups not performed
Lorona et al DOI: 10.1007/s10552-021-01485-3	2021	Luminal, TBNC, and HER2+	4557/n.d.		No protective effect of BB versus reference group (no antihypertensive medication) in recurrence, BC-specific mortality, and all-cause mortality in any BC type
Lofling et al. DOI: 10.1038/s41416-022-01891-7	2022	Retrospective Overall BC types	30 060/4400	Selective [n.d. (3884)] Nonselective [n.d. (577)]	↑ BC-specific survival only in TNBC patients with BB, either selective or nonselective
Hsieh et al DOI:10.1177/20420986231181338	2023	Retrospective HER2-(positive) advanced BC plus trastuzumab	221/94	Selective [bisoprolol (43)] Nonselective [propranolol (46), carvedilol (5)]	Similar progression-free survival and overall survival between selective and nonselective BB users, and lower compared with nonusers
Yang et al. DOI: 10.1016/j.clbc.2023.05.014	2023	Retrospective Meta-analysis of 43 articles covering randomized controlled trials/cohort studies/case-control studies	---	---	↓ Overall survival ↑ Recurrence in luminal BC ↑ Progression-free survival in HER2+ BC ↑ Only selective BB increases BC risk, while nonselective BB decreased it

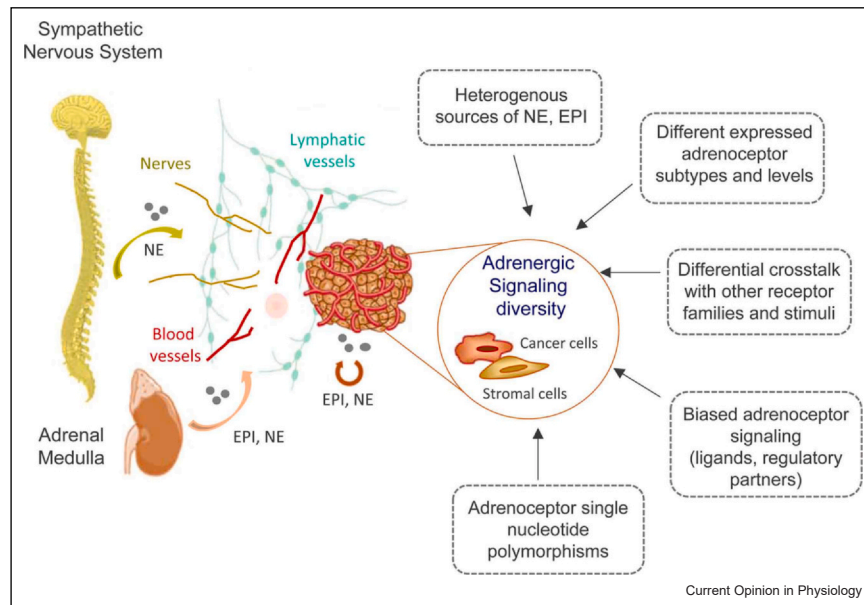
Abbreviations: n.d., not detailed.

overall BC patients. These analyses include beta-blockers as a single homogeneous pharmacologic group or at most two different subgroups according to receptor selectivity (non-selective blockers exhibiting similar affinities for β_1 -/ β_2 -ARs and β_1 -selective BB with a higher affinity for β_1 than for β_2 AR) (Table 1). It is clear now that this classification is an oversimplification that can blur the real clinical impact of these drugs (see below). For instance, nonselective BB carvedilol, which also is an α -AR receptor inhibitor, was more effective than propranolol, which targets only β -AR [31], spotlighting the less-established role of α_1 AR in BC.

As mentioned, also the epidemiological evidence on adrenergic impact in tumor progression and prognosis is controversial. β_1 AR overexpression may predict a better prognosis in some studies, but worse in others ([32] and references therein). The association of lower β_2 AR mRNA levels with worse prognosis has been described in estrogen-positive [22] and in HER2-positive [33] BC patients, while others based on protein data have reported the opposite in ER-negative [34] and ER-positive [35] patients. Furthermore, the association of BC risk with adrenoceptor single-nucleotide polymorphisms (SNP) is ambiguous ([23] and references therein). Of note, the most relevant SNPs in ADRB2 gene at position 16 (rs1042713) encoding Arg16Gly A > G (G being the minor allele) and at position 27 (rs1042714) for Gln27Glu C > G (G being the minor allele) may affect the efficacy of selective β_2 -blockers [36], thus further entangling clinical associations with these compounds.

Taken together, these findings point out the need to address the different pharmacology of BB as well as the complexity of adrenoceptor signaling in different BC subtypes to provide a unifying view (Figure 1). For instance, diverse altered patterns of adrenoceptors and CA are a source of signaling heterogeneity among breast tumor types [12]. The levels of EPI and NE, both in the tumor and in the bloodstream of patients, are highly variable, as the range of CA concentrations used in vitro, hinders the interpretation of the different studies. Most reports on BC cell line stimulation with natural CA (EPI and/or NE)(exhaustively collected in [3,4]), show an increase in some tumoral traits (proliferation and/or migration or invasion), with a predominant involvement of β_2 AR receptors followed by α_2 AR. However, non-selective β -agonists similarly promoted invasion-related features but not proliferation in these cell lines (mainly MCF7 and MDA-MB231 cells), pointing out α_2 AR role in proliferation and β AR in motility/invasion of BC cells. Of note, while Gi-coupled α_2 AR invariably increases BC cell proliferation [37], β AR stimulation with isoproterenol does not, even using the same cellular model [24,25,37,38], suggesting differences in agonist-induced β_2 AR signalosomes, in regulatory patterns, or in crosstalk with other receptor systems, that awaits to be elucidated.

Figure 1



Complexity in adrenergic stimulation of tumor breast tissue. Adrenergic stimulation can alter the function and activity of breast epithelial cells, and other cells present in the tumor microenvironment (stromal cells), toward a phenotype that is not solely protumoral, depending on the profile of activated adrenoceptors and the source (adrenal, neural, and tumoral) and nature of the stimuli (concentrations and ratio of distinct CA or estrogen-derived catechol metabolites), which may differ between different types of BC according to their molecular signatures. Furthermore, regulatory feedback loops between adrenoceptors and other receptor families may mutually reshape downstream signaling. Moreover, adrenoceptor coupling to particular signaling pathways may be biased by dosage of regulatory GRK and β -arrestin proteins and influenced by receptor SNP, leading to different cellular responses (for detailed information, see the text).

In this regard, adrenoceptors exhibit distinct affinities for CA. For example, while the affinities for EPI are similar, the β_1 AR has a tenfold higher affinity for NE than the β_2 AR [11,39]. This difference determines a different profile of activation and signaling pathways in each type of BC, based on the receptor repertoire and stimuli. Furthermore, depending on the type and concentration of the ligand, the β_2 -AR can display a phenomenon known as agonist-biased agonism. This process allows for the switching of coupling from the cAMP-stimulatory Gs protein to an inhibitory Gi protein, initiating a new signaling pathway [40]. This switch is not induced by NE but rather by high concentrations of EPI or chemical β -agonists, such as isoproterenol [39,41]. This phenomenon is favored in conditions of high CA stress, as it requires concurrent receptor phosphorylation by G-protein-coupled receptor kinases (GRKs) and protein kinase A (PKA) for sufficient Gi-coupling [40]. Interestingly, the β_2 AR-Gly16 variant has been described as a loss-of-function polymorphism concerning coupling-switch [42]. Cellular protein levels of GRKs also affect the signaling capacity of adrenoceptors by prompting their internalization and desensitization in combination with β -arrestins. This, in turn, can propagate G-protein-independent signaling events [11,43]. Notably, the β_2 AR/GRK/ β -arrestin module contributes to DNA damage accumulation by reducing p53 levels

[44], which may underlie the promoting effects of chronic stress in cancer. Altered patterns of GRKs have been identified in various types of tumors [43]. In breast tumors, the expression levels of GRK3 and GRK5 are lower compared with normal breast tissue, while those of GRK2 are higher [45]. Either downmodulation of GRK3 or upregulation of GRK2 enhances mammary tumor formation [45,46]. It would be of interest to investigate how such concurrent and opposite alterations in GRK2 and GRK3 may cooperate in promoting aberrant adrenoceptor signaling in BC, although the function of these kinases in tumorigenesis may also involve non-GPCR targets [43].

As mentioned, BB are functionally heterogeneous and cannot consider mere antagonists of the CA actions for the receptors they target [47]. Like other GPCR ligands, individual BB might simultaneously act in antagonistic and agonistic manners on different receptor signaling branches. Indeed, many BB behave as partial agonists or inverse agonists in diverse functional assays (Table 2). Inverse agonism (IA) involves the stabilization of nonactive conformations in the absence of ligand agonists, leading to reduced basal receptor activity. In turn, partial agonist BB impede CA's actions and display intrinsic sympathomimetic activity (ISA), stimulating some agonist responses on

Table 2

Classification of BB most commonly used and mechanisms of action.

BB	β 1AR-selective or nonselective	Rank of relative affinities for β -AR subtypes	Activity effects (β -AR subtypes)
Atenolol	Selective	β 1AR > β 2AR > β 3AR	IA (β 2AR, β 1AR), PA (β 2AR, β 3AR), and ANT (β 1AR)
Acebutolol	Selective	β 1AR > β 2AR > > β 3AR	PA (β 1AR, β 2AR)
Betaxolol	Selective	β 1AR > > β 2AR > > β 3AR	IA (β 2AR)
Bisoprolol	Selective	β 1AR > > β 2AR ~ β 3AR	IA (β 2AR, β 1AR), ANT (β 1AR, β 3AR)
Carvedilol	Nonselective	β 1AR ~ β 2AR > > β 3AR	IA (β 2AR, β 1AR), PA (β 2AR, β 1AR), and ANT (β 2AR, β 3AR)
Celiprolol	Selective	β 1AR > β 2AR (β 3AR, n.d.)	PA (β 2AR)
Labetalol	Nonselective	β 2AR > β 1AR > β 3AR	PA (β 2AR, β 1AR), ANT (β 1AR)
Nadolol	Nonselective	β 2AR > β 1AR > β 3AR	IA (β 2AR)
Nebivolol	Selective	β 1AR > > β 2AR > β 3AR	PA (β 1AR), ANT (β 1AR, β 2AR, and β 3AR)
Metoprolol	Selective	β 1AR > β 2AR ~ β 3AR	IA (β 2AR, β 1AR), ANT (β 1AR, β 3AR)
Propranolol	Nonselective	β 1AR ~ β 2AR > > β 3AR	IA (β 2AR, β 1AR), PA (β 2AR, β 1AR), ANT (β 2AR, β 3AR)
Pindolol	Nonselective	β 1AR ~ β 2AR > β 3AR	IA (β 2AR, β 1AR), PA (β 2AR, β 1AR, and β 3AR)
Sotalol	Nonselective	β 2AR > β 1AR ~ β 3AR	IA (β 2AR)
Timolol	Nonselective	β 2AR > β 1AR > > β 3AR	IA (β 2AR), PA (β 2AR)

Abbreviations: ANT, antagonism; n.d., not determined. Affinities according to [47,48] and classification of selectivity according to [52]. ~ denotes Kd values in the same order of magnitude; > denotes differences of one order of magnitude; > > denotes differences of two or more orders of magnitude.

their own [47]. Compared with physiological full agonists, the nonselective BB pindolol has remarkable ISA on β 1AR and β 3AR but not β 2AR, while nebivolol virtually has no partial agonism (PA) on any of them [48]. Also, at low μ M concentrations, propranolol elicits β 2AR-mediated agonistic-like effects on the cellular cytoskeleton in breast cells [49], and fails to inhibit proliferation in several BC cells [50].

Furthermore, biased agonism also applies to BB, which can have opposite efficacies toward different receptor signaling pathways. Again, this is the case for propranolol, which stimulates the extracellular signal-regulated kinase (ERK)1/2 pathway in addition to inhibiting the canonical cAMP response [51]. Carvedilol and nebivolol also show biased agonism, leading to ERK-1/2 activation and epidermal growth factor receptor transactivation by G-protein-independent and β -arrestin-dependent mechanisms [47,52]. Given this complexity, it is challenging to relate the clinical effects of BB to responsible molecular pathways (G-protein switching, β -arrestin recruitment, or others), but this is key for developing new pharmacological tools in the right direction.

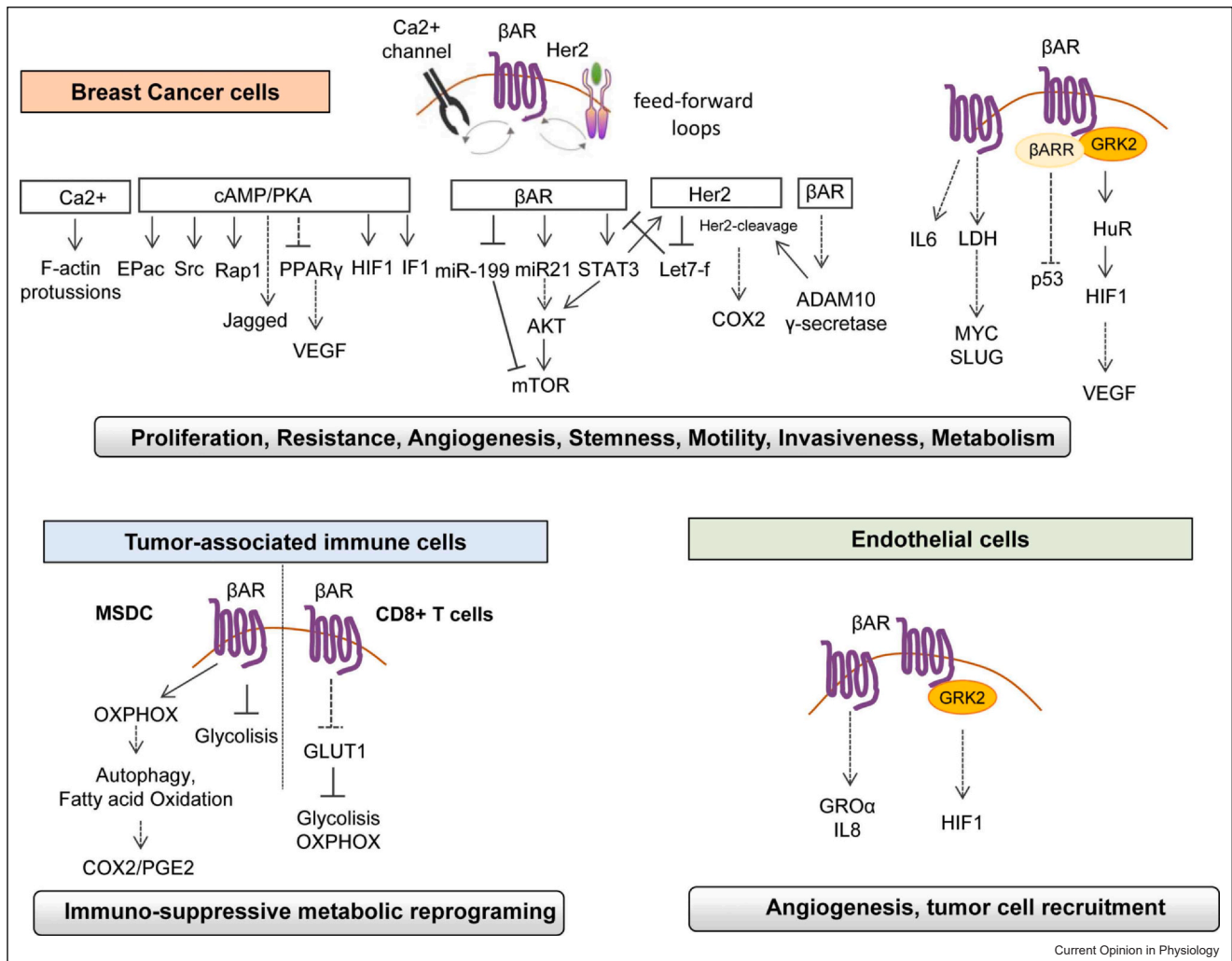
Stressing out the mammary gland, where do catecholamines come from?

CA in cancer originate from several sources, although controversy exists regarding which is the most relevant in stress-related BC progression (Figure 1). Psychosocial stress stimulates the adrenal release of NE and EPI into circulation, along with other stress hormones (e.g. cortisol). Additionally, stress enhances NA release from sympathetic nerve endings that innervate mammary tissue and its vasculature. Circulating EPI appears to be dispensable for stress-related cancer progression, as

reported in human xenografts and immune-intact murine models after denervation of the adrenal medulla. This strategy eliminates basal and stress-induced plasma levels of EPI but not NE [16]. This suggests that peripheral innervation could be the critical source. As nicely revised in [5], tumoral cells can coopt nerves to increase local release of NE. Indeed, in the MMTV-PyMT mice, a model mimicking human hormone-positive BC, the density of sympathetic nerve fibers increases in early stages of the tumor [53].

The idea that cancer cells can also directly contribute to the tumor CA pool could explain the effective activation of β 2AR in both cancer and stromal cells. Human BC cells possess the molecular machinery for synthesizing CA and reuptaking NE released from nerves [12]. The synthesis and conversion of NE to EPI increase in breast tumor cells, particularly in HER2-enriched and luminal-B tumors [12]. Interestingly, a feedforward loop that elevates the EPI/NE ratio through activated β -adrenoceptors has been described [24]. This loop could enable adrenal-independent stimulation of β 2AR by EPI (and NE at high concentrations) in the tumor, enhancing the activation of other adrenoceptors. α 2AR can also be activated by catecholestrogens, metabolites generated by the hydroxylation of estrogens that have reduced hormonal potency. However, both procarcinogenic and noncarcinogenic activities have been ascribed to them [54]. The proliferative effects of catecholestrogens appear to be fully or partially mediated by α 2AR in MDA-MB231 and MCF7 cells, respectively [55], while depending on β ARs in endothelial cells [56]. The crosstalk between adrenergic and estrogen signaling at the adrenoceptor level is an interesting avenue to investigate in BC progression.

Figure 2



Adrenergic signaling pathways in BC and relevant stromal cells. Adrenergic stimulation of βAR receptors, primarily β2AR, in BC cells amplifies several cancer hallmarks that contribute to heightened tumor aggressiveness. The activated β2AR initiates intricate feedback loops involving Ca²⁺ channels and the Her2 receptor tyrosine kinase. These loops not only intensify each other's signaling, but also initiate novel regulatory events aimed at modifying the activity of stem-related transcription factors (MYC, SLUG), pro-inflammatory mediators (COX2, IL-6), pro-angiogenic factors (VEGF, HIF1), and regulators of energy metabolism (IF1). Additionally, adrenergic stimulation reprograms the cellular behavior of immune cells (effector T cells, myeloid-derived suppressor Myeloid-derived suppressor cell (MSDC) cells) and vascular cells to be permissive and provides support for tumor progression (for more details, see the text).

Adrenergic stimulation: too little or too much for tumor progression?

Although β-AR activation mediates stress-enhanced metastasis in most preclinical models, recent results have raised questions about the catecholaminergic influence in cancer. Intriguingly, human TBNC tumor xenografts regress after treatment with pirbuterol, a β2-agonist inhibiting the Raf-1/Mitogen-activated protein kinase kinase-1 (Mek-1)/Erk1/2 pathway via PKA [57]. Furthermore, in MMT-PyMT mice, a model for the spontaneous progression of hormone-positive metastatic tumors, stress reduces the primary tumor burden in a βAR-mediated manner [17]. However, other studies

have reported a higher frequency of metastasis in this model using a less-mild stress protocol [58]. Notably, CA at physiological doses or as a result of short-term stress related to exercise may reduce human BC xenografts [38]. Indeed, the benefits of exercise for cancer patients are increasingly evident, showing reduced BC-specific mortality and lower all-cause deaths in different studies [59–61]. Behind these exercise benefits could be the impact on estrogen levels and insulin resistance or the reduction of tumor-induced infiltration of myeloid immuno-suppressive cells, leading to improved immune capacity [62]. There may be other mechanisms involved in linking physical activity to a reduction in BC. In this

regard, it is captivating that exercise led to a lowering of adrenal GRK2 and reduced SNS overactivity in a mouse model of cardiac disease [63]. Exercise was also associated with a significant reduction in lymphocyte GRK2 protein levels [64], although other studies have reported an increase [65]. Given the immunomodulatory role of GRK2 in several immune cell types [66], its exercise-related changes could be relevant for BC progression.

Similarly, BB in preclinical animal models also have counterintuitive effects. Unexpectedly, the BB nadolol increases lung metastasis in nonstressed MMT-PyMT mice [17], thereby posing when and wherein the adrenergic input should be attenuated. Unlike most antitumoral BB, nadolol mainly exhibits IA activity without showing ISA or other signaling abilities (biased agonism). This suggests that the basal tone of BAR activity plays some protective role [67]. Biased agonists can block ligand-induced classical β -AR signaling ($G\alpha_s$ /cAMP/PKA) while promoting signaling through alternative pathways, including the GRK/ β -arrestin/mitogen-activated protein kinase (MAPK) pathway. Hence, some β -ligands (either β -agonists or BB), but not others, could bias signaling toward a tumor-suppressive pathway. This may be relevant since frequently associated comorbidities such as obesity, metabolic syndrome, and diabetes in cardiovascular patients receiving these drugs are well-known risk factors for BC [7].

Putting pressure on cell-autonomous mechanisms for invasiveness and metastasis

The relevance of β -ARs expressed on tumor cells, particularly the β 2AR subtype, in psychosocial stress-induced tumor growth and lymph node metastasis, was elegantly demonstrated in animal models of human ovarian and BC [14]. This was later corroborated in *in vitro* invasion assays and stress-induced metastasis *in vivo* with β 2AR-manipulated BC cells [68]. Since then, an ever-expanding array of signaling pathways is activated through the direct stimulation of β AR in these cells, promoting their survival, motility, and metastatic potential (Figure 2). Based on cellular models, β 2AR-induced cAMP production is parallel to the metastatic potential of BC cells [18,68,69], and a positive feedforward cAMP/ Ca^{2+} loop was unveiled in highly metastatic cells [20]. This loop relies on $G\beta\gamma$ - and $G\alpha_s$ /cAMP/PKA/exchange protein activated by cAMP (EPAC)-dependent pathways, and both Ca^{2+} and PKA/EPAC signaling branches may impact tumor cell invasion through different effectors. Direct PKA-mediated activation of the nonreceptor tyrosine kinase c-Src occurs in ovarian cancer cells [70], as well as the hyperactivation of PKA/c-Src axis in mammary-transformed cells [71]. Moreover, β 2AR stimulation enhances BC cell motility through PKA-dependent activation of Ras-related protein Rap1B, a key regulator of integrin inside-out signaling

[72], and through an unknown mechanism that upregulates the adhesion-related Ly6/PLAUR domain-containing protein-3 protein [69]. Similar to other aggressive cancer cells, the MDA-MB231 BC line exhibits phenotypic plasticity and can move as individual spindle-shaped mesenchymal-like cells, displaying invadopodia and pericellular proteolysis, or as rounded ameboid-like cells. Stimulation of β 2AR fosters BC cell invasiveness through cAMP-Src-dependent remodeling of focal adhesions into invadopodia [19]. β 2AR-induced Ca^{2+} signaling promotes decreased cell deformability in MDA-MB231 cells, increased cortical F-actin projections, and activation of nonmuscle myosin II [73]. This likely leads to higher intracellular stiffening, which could trigger blebbing motility, a preferred locomotion for the most aggressive cancer cells [74]. The question of how the β 2AR/PKA/ Ca^{2+} axis could influence BC cells' plasticity, allowing them to adapt to microenvironmental conditions for invasion, is an interesting issue that warrants further investigation.

CA also directly influence cellular energy metabolism through the regulation of aerobic glycolysis or mitochondrial oxidative phosphorylation (OXPHOS), both processes involved in the progression of metastatic disease [75]. Metabolic rewiring by chronic adrenergic stress involves activation of lactate dehydrogenase, promoting the Warburg effect. This, in turn, allows the transactivation of master regulator of cell cycle entry (MYC) and the transcription factor Snail family of zinc-finger transcription factor-2 (SLUG) to promote stem-like properties in BC cells [13]. While the β AR/PKA axis increases Adenosine triphosphate (ATP) production through inactivation of ATPase-inhibitory factor IF1, an endogenous inhibitor of mitochondrial H^+ -ATP synthase, the BB nevigolol upregulates IF1 in cancer and endothelial cells, delaying tumor growth *in vivo* ([76] and references therein).

Adrenoceptor crosstalk with other GPCR and receptor families also fosters tumor progression. For instance, β 2AR activation downmodulates the chemokine receptor CXCR4 in MDA-MB231 cells [77], whereas the ligand CXCL12 is upregulated in stromal cells [78], guiding the homing of CXCR4-positive cells to metastatic sites. However, CXCL12 is also highly expressed within the primary tumor, so it is feasible that NE released from tumor nerves might downmodulate CXCR4 in cancer cells to facilitate their egression.

Another relevant crosstalk is the positive-feedback loop between β 2AR and tyrosine kinase receptor HER2. This loop involves β 2AR/STAT3-dependent transactivation of the HER2 promoter [79] and HER2-mediated suppression of the let-7f microRNA, which basally represses β 2AR [80]. The HER2/ β 2AR/let-7f circuit could be self-sufficient in HER2-positive breast tumors, whereas in

other types of BC, chronic stress could prompt it. Moreover, a complex proteolytic processing of HER2 triggered by β 2AR activation has been described that increases metastatic potential [81]. These mechanisms add to adrenergic regulation of miR-21 and miR-199a/b-3p and stimulation of the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway, leading to resistances to therapy in HER2-positive tumors [82].

Adrenergic remodeling of the tumor microenvironment

Adrenergic signaling can alter the tumor microenvironment at various levels, both systemically and locally, by engaging autocrine and paracrine signaling pathways in different cell types (Figure 2). Tumor growth critically depends on the ability to evade immune surveillance [83]. This ability can be modulated by stress, as there is multilevel adrenergic-mediated regulation of immune cell function, homeostasis, and immune cell distribution [84]. Acute physiological release of CA causes a rapid, reversible, and selective mobilization of lymphocyte subsets that positively contribute to stimulating effector T-cell and natural killer (NK) function, leading to immune fitness [85]. In this context, CA-induced β AR activation strengthens the humoral response of T cells by stimulating the survival of CD4⁺ Th2 subset and the secretion of cytokines from Th1 subset cells [86] and Th17 cells [87].

In contrast, chronic activation of the SNS is known to cause β AR desensitization on most leukocyte subtypes, including T cells, monocytes, and NK cells, which is linked to inflammation and reduced immune surveillance [88]. Recently, immunosuppression by CA overdrive has been linked to reduced lymph node blood flow and inhibition of CD4⁺ and CD8⁺ T-cell tissue infiltration, impairing the *in vivo* immune response to melanoma tumor cells [89]. Furthermore, chronic adrenergic stimulation might inhibit the function of NK cells [90]. These effector cells represent the main defense against various types of tumors and their metastatic spread [91]. Interestingly, an increase in tumor-infiltrating NK cells was reported in colorectal cancer patients who were perioperatively treated with propranolol, leading to lower recurrence rates [92].

Some additional mechanisms behind chronic stress-related metastasis involve the accumulation of myeloid-derived suppressor cells (MDSCs) in the tumor via activation of β -adrenergic signaling and IL-6/STAT3 pathway [93], or blockade of metabolic reprogramming in CD8-positive T cells during activation [94] and in MDSCs through increased fatty acid oxidation [95].

Another inflection point in tumor progression is the angiogenic switch and protumoral remodeling of vascular stroma.

This process can be promoted by direct adrenergic stimulation of endothelial cells, as well as other stromal cell types that can influence endothelial cells in a paracrine manner (fibroblasts, peripheral nerve cells, and immune-resident cells). These stromal cells, similar to adrenergic-stimulated tumor cells, influence angiogenesis through the secretion of hormones, cytokines, and growth factors [96]. *In vitro* adrenergic stimulation [18] and psychosocial stress *in vivo* leading to protumoral angiogenesis [14] increase production of the vascular endothelial growth factor (VEGF) through the β 2AR-Gs-cAMP-PKA pathway activated in malignant MDA-MB231 cells. Furthermore, stress-activated β 2AR promotes VEGF/FGF2-mediated angiogenesis via down-regulation of the transcription factor PPAR γ in MDA-MB231-derived tumors, although the exact mechanism behind this is unclear [97]. Instead, the connection between the transcription factor hypoxia-inducible factor-1 (HIF1), the most relevant regulator of VEGF expression under hypoxia [96], and sympathetic and behavioral stress, is more robust and involves β AR-Gs-PKA-dependent mechanisms in metastatic BC cells [98,99]. However, in less-metastatic cells, VEGF production requires high concentrations of isoproterenol [18] or GRK2 overexpression [100], conditions that could favor biased β 2AR signaling from Gs to Gi-coupling, suggesting additional pathways for adrenergic control of VEGF. In this regard, we have reported a novel mechanism by which β -AR regulates HIF1 α protein through GRK2-mediated phosphorylation of the mRNA-binding protein human antigen R (HuR, also termed ELAVL1) [100]. Stress-induced GRK2/HuR/HIF1 α axis could facilitate the survival of malignant cells even before the expanding tumor mass becomes hypoxic, which could improve tumor cell adaptation to hypoxic conditions, particularly in estrogen-positive breast tumors [100]. Interestingly, GRK2 is also required for adrenergic stimulation of HIF1 in endothelial cells [101], although whether the GRK2/HuR axis is involved remains unknown. CA on microvascular cells also induce pro-inflammatory/pro-angiogenic chemokines that paracrinely promote integrin-mediated recruitment of breast tumor cells expressing CXCR1/CXCR2 surface receptors [102], thus highlighting the bidirectional interplay between cancer and endothelial cells.

Other paracrine angiogenic mechanisms of BC cells require physical interaction with endothelial cells or interplay with nonvascular stromal cells. For instance, adrenergic-stimulated BC cells upregulate the Notch ligand Jagged through a PKA-mTOR pathway, leading to angiogenic sprouting upon Notch activation in endothelial cells [103]. On the other hand, in tumor-associated macrophages, chronic stress promotes the pro-inflammatory cyclooxygenase-2 (COX2)-prostaglandin E2 (PGE2) pathway, associated with progressive tumor growth and metastasis. This leads to PGE2-dependent stimulation of MDA-MB231 cells for VEGF-C production [15]. Overexpression of COX2 is also driven by β 2AR activation in BC cells themselves [36,81], and its

clinical relevance is evidenced in BC patients undergoing surgery-related stress [104].

Moreover, the idea that chronic stress may predefine sites for cancer cell homing through the adrenergic remodeling of vascular beds in distant organs is appealing, and recent evidence supports it. Upregulation of VEGF by β -adrenergic stimulation of osteoblasts leads to increased vascular density, facilitating bone metastasis of MDA-MB231 cells [105]. In the lung, metastatic preconditioning by chronic stress involves stromal upregulation of CCL2, a potent chemotactic signal for myeloid cells produced by microvascular cells, fibroblasts, and alveolar epithelial cells [58]. CCL2 changes concur with the upregulation of its cognate receptor CCR2 in monocyte/macrophages, leading to increased macrophage recruitment and inflammation. CCL2 also increases lung vessel density, facilitating macrophage extravasation, inflammation, and further angiogenesis, in a feedforward loop that primes tumor cell seeding [58].

Conclusions and perspectives

Adrenergic dysregulation in BC involves alterations in the expression of adrenoceptors, CA, and other associated regulatory molecules. Different BC subtypes exhibit distinct adrenergic profiles, further complicating the understanding of the role of adrenergic signaling in tumor progression since the BC receptor subtype may dictate the response to chronic stress.

Compelling evidence supports the role of β ARs and α ARs in the pathogenesis of cancer, as their activation initiates canonical signaling pathways, but also alternative routes enabled by dysregulated GRKs, unconventional ligands, or concurrent challenges. Indeed, adrenergic hyperactivation in patients coincides with the dysregulation of other signaling systems in cancer patients, such as estrogens, cortisol, and other glucocorticoids, inflammatory factors, and so on, whose crosstalk is not well-characterized and might influence the formation of specific adrenergic signalosomes. All these pathways allow metabolic reprogramming of tumor and nontumor cells to acquire new functionalities, remodeling of vascular stroma, and changes in resident immune populations. This leads to increased morphological and behavioral plasticity to cope with different environments. In the absence of AR signaling on tumor cells, there are no cancer-promoting effects caused by stress. However, CA have a direct impact on multiple cell populations in the tumor microenvironment, conditionally promoting tumorigenesis by affecting the vasculature and the immune populations both in the primary tumor and in distant organs, thus facilitating metastasis.

This complexity underscores the need for immune-competent animal models to better figure out the true influence of stress on cancer. This influence cannot be fully perceived in certain murine-hosted human breast tumors. For the *in vivo* implantation of human BC cell lines and patient-derived tumor tissue (patient-derived xenograft model), modified mouse models are required that include humanized mice or, more commonly, immunodeficient mice. Among the immunocompromised mice strains, the increasingly popular Nonobese diabetic scid gamma mouse model shows defects in innate immunity, including deficits in NK cell activity and in macrophage function. In contrast, the traditional nude or athymic model has an intact innate immunity [106]. Therefore, considering the role of NK cells in controlling tumor cell metastasis and the impact of adrenergic stress on these cells, it is important to move toward more immunocompetent models.

Overall, the clinical benefits of inhibiting ARs, mainly with BB, cannot be anticipated by default based on most pre-clinical and basic research studies. Indeed, clinical studies and epidemiological evidence present conflicting results regarding the association between adrenergic signaling and BC prognosis and progression. Additionally, the effects of BB are not consistent as their pharmacological profiles range from inverse agonists and antagonists to partial agonists. BB used clinically as receptor antagonists can have sympathomimetic activity and behave as activators of unappreciated signaling pathways, leading to misleading associations with BC outcomes. Multiple signaling pathways and ligand bias can explain differences in the effectiveness of BB, hence, their role in BC treatment requires further investigation.

Therefore, robust prospective clinical trials focusing on particular BC subtypes and combination therapies, without prior cardiovascular comorbidities, are an unmet need to determine the intrinsic impact of individual beta-blockers on BC outcomes. Furthermore, other complementary ways of modulating adrenoceptors, or alternative strategies, should join the arsenal of therapies that combat the chronic stress-promoting effects in BC. In this regard, exercise is a holistic strategy that should be clinically implemented. Patients receiving chemotherapy under an exercise regimen underwent overall improvement in stress-related symptoms (fatigue, depression, anxiety, and insomnia) but also in survival, as the immune-enhancing ability of exercise interventions contributes to these benefits. The beneficial impact of exercise is not limited by a window of opportunity, as it is effective before, during, or after diagnosis, besides being safe [107]. Other nonpharmacological stress reduction strategies include mindfulness and psychological counseling, which beyond emotionally improving the quality of life, have an impact on molecular cancer biomarkers [4].

On the other hand, recent studies showed that several CA biosynthesis (Phenylethanolamine N-methyltransferase, tyrosine hydroxylase), degradation (monoamine oxidase A–B), and transportation (monoamine transporter NET) enzymes are locally altered in BC cells [12]. This opens the possibility to develop nonpermeable blood–brain barrier modulators targeting these molecules to reduce CA overstimulation in BC tissue. Furthermore, based on benefits of some BB with cross-selectivity to α 1- and α 2AR and on their association with BC [4], α -blockers could be evaluated within the pharmacological toolkit aimed at reducing BC progression.

Finally, the same adrenoceptors that mediate cancer-promoting effects of CA in conditions of chronic stress could also convey beneficial effects related to exercise and acute stress. There is a need to identify the differential pathways engaged by these receptors in different situations and to understand whether they are related to different doses and combinations of CA or to crosstalk with other signaling elements. This understanding could lead to the development of innovative therapeutic strategies to improve patient outcomes.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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- This article demonstrates the impact of chronic stress via EPI- β 2AR on BC stem cell growth, a previously underexplored issue. Elevated blood EPI levels are linked to increased lactate dehydrogenase levels and poorer prognosis in both human BC patients and a chronic stress breast tumor mouse model. This effect is mediated by the activation of the LDHA/USP28/ MYC/SLUG signaling axis and cellular stemness. Notably, the administration of vitamin C suppresses lactate dehydrogenase production.
- The authors uncover the interplay between stress-induced neural signaling and inflammation, which affects lymphatic architecture. They characterize nicely the remodeling effects of noradrenaline in skin draining-collecting lymphatic vessels and *in vivo* lymph flow. Chronic restraint stress in xenografts of human breast tumors in nude mice or in mammary tumours from Mouse Mammary Tumor Virus Polyoma Middle T Antigen (MMTV-PyMT) transgenic mice remodels lymphatic vessels through β AR-stimulated release of inflammatory molecules by tumour-associated macrophages. This prompts breast tumor cells to produce VEGFC. Lymphogenous dissemination of tumor cells may be more relevant in patients with higher psychosocial stress.

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