Seminars in Cancer Biology 23P (2013) 533–542

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

β-Adrenergic system, a backstage manipulator regulating tumour progression and drug target in cancer therapy

Jing Tang[a], Zhijie Li[b,*], Lan Lu[b], Chi Hin Cho[b]

[a] Department of Anaesthesia, Nan Fang Hospital, Southern Medical University, Guangzhou, PR China
[b] School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China

ARTICLE INFO

Article history:
Received 2 July 2013
Accepted 27 August 2013

Keywords:
Stress hormones
Tumour progression
Nicotine
β-Adrenoceptors
β-Adrenergic system
β-Blockers
Angiogenesis

ABSTRACT

β-Adrenoceptors are broadly distributed in various tissues of the body. Stress hormones regulate a panel of important physiological functions and disease states including cancer. Nicotine and its derivatives could stimulate the release of stress hormones from cancer cells, leading to the promotion of cancer development. β-Blockers have been widely used to control hypertension for decades. Recently, these agents could have significant implications in cancer therapy through blockade of adrenoceptors in tumour tissues. In this review, we summarize recent advancements about the influence of stress hormones, nicotine and β-adrenoceptors on cancer cell proliferation, apoptosis, invasion and metastasis, and also tumour vasculature normalization. Relevant signal pathways and potential value of β-blockers in the treatment of cancer are also discussed in this review.

1. Introduction

Hanahan and Weinberg revisited and updated the hallmarks of cancer in 2011 based on the conceptual progress of cancer in the last decade [1]. Two emerging hallmarks combined with previous six biological capabilities are widely accepted and acknowledged. They constitute the current eight hallmarks of cancer development and progression. These include: (1) stimulation of continuous proliferative signalling, (2) evasion of growth suppressors, (3) resistance to cell death, (4) potential of limitless replication, (5) induction of angiogenesis, (6) activation of invasion and metastasis, (7) deregulation of cellular energetics and (8) insensitivity of immune destruction [1,2]. A variety of stimulations and signals associated with tumour development are involved in one step or multiple steps of the eight hallmarks or other unapprehend processes to some extent. Tumorigenesis is a multistep and complicated process which is controlled by a cross-connected biological network. Tumour mass is not an independent entity only consisting of proliferative cancer cells. It recruits multiple distinct types of normal cells to form tumour-associated stroma, and further develops vasculature, lymphatic and nervous systems to build up its own microenvironment [1,3]. Neoangiogenesis, lymphangiogenesis and neoneurogenesis are being considered to occur in concert and synergistically orchestrate the development, progression and responsiveness to the prevention and therapy of tumours [4,5]. Experimental and clinical evidences also show that some cancers are innervated by nerve fibres and form neuro-neoplastic synapses which directly secret neurotransmitters to act on the cancer cells [6,7]. Cancer cells not only express receptors of neurotransmitters but also are able to synthesize several different neurotransmitters [3,8]. Some of them could act locally in an autocrine and paracrine manners or systemically circulate and be back to tumour cells to conduct relevant regulation on these cells.

β-Adrenergic system consists of catecholamines and their respective receptors including α- and β-adrenergic receptors which are widely expressed in most of the mammalian tissues. Adrenaline and noradrenaline are classic neurotransmitters mediating fight-to-flight stress responses via sympatho-adrenomedullary system [9,10]. Noradrenaline is released

Abbreviations: FAK, focal adhesion kinase; PKA, protein kinase A; BAD, BCL2-associated death protein; VEGF, vascular endothelial growth factor; PlGF, placenta-derived growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor β; HIF-1α, hypoxia-inducible factor-1; IL-6, interleukin-6; MMP, matrix metalloproteinase; TAM, tumor associated macrophages; GROα, growth-regulated oncogene alpha; nAChR, nicotinic acetylcholine receptors; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; GABA, γ-aminobutyric acid; PVC, perivascular cell; EC, endothelial cells; HRG, histidine-rich glycoprotein; DR, dopamine receptor; AC, adenylyl cyclase; cAMP, cyclic AMP; EPAC, exchange protein activated by adenylyl cyclase; MAPK, mitogen-activated protein kinase; CREB, cAMP response element binding protein; p70S6K, p70S6 kinase; PI3K, phosphoinositide 3-kinase; NF-κB, nuclear factor-κB; AP1, activator protein 1; STAT3, signal transducer and activator of transcription-3.

* Corresponding author at: School of Biomedical Sciences, The Chinese University of Hong Kong, Shatin, NT, Hong Kong, China. Tel.: +852 2609 6886; fax: +852 2607 5139.
E-mail address: xiaoheilzj@126.com (Z. Li).

1044-579X
http://dx.doi.org/10.1016/j.semcancer.2013.08.009

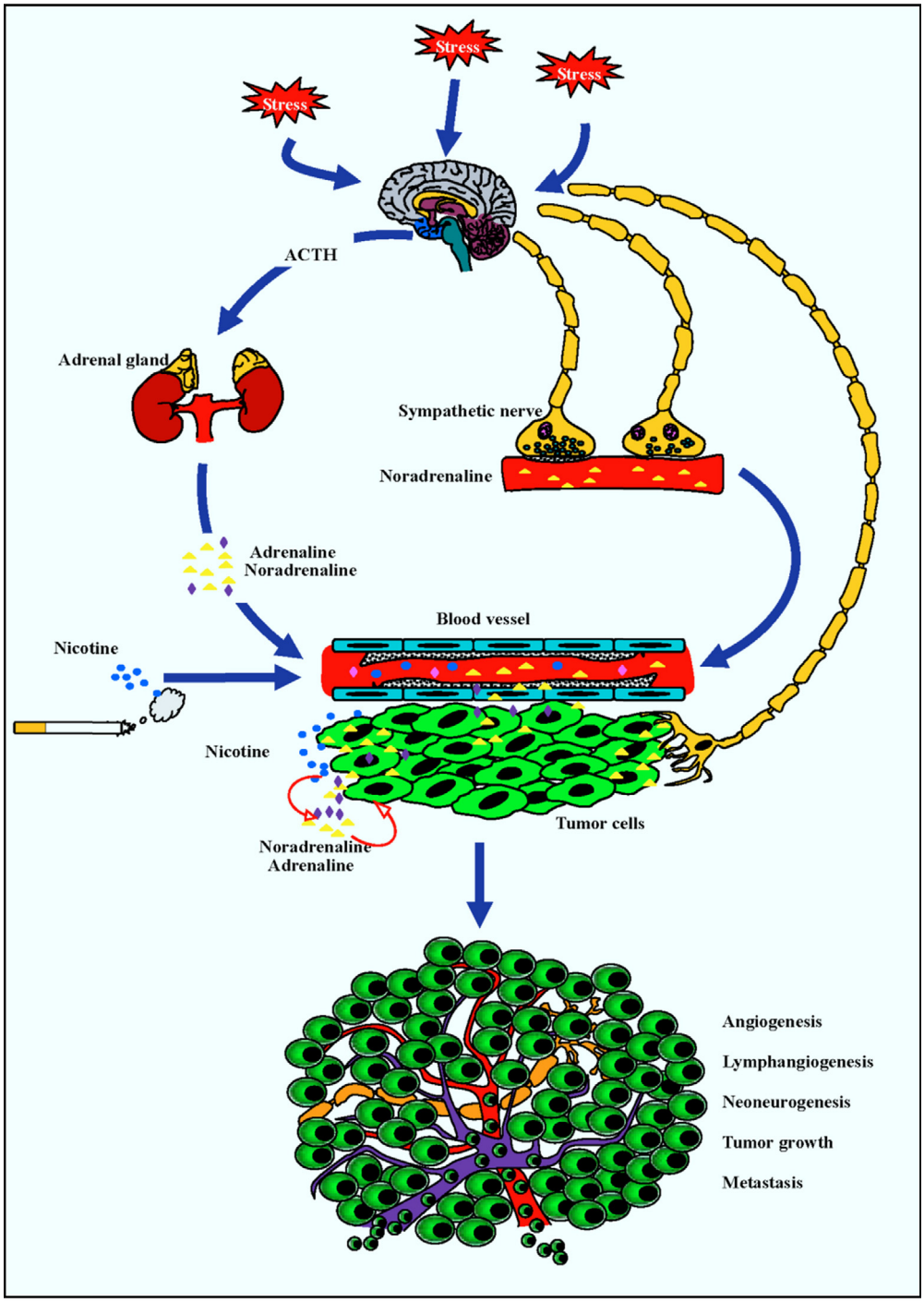

Fig. 1. Stress hormones in cancer development and progression. A variety of physical and lifestyle stress induce the elevation of stress hormones in the body which are mainly released from adrenal gland and sympathetic nervous system. Adrenal gland receives the regulation of adrenocorticotrophic hormone (ACTH) resulting from the activation of pituitary in the hypothalamic–pituitary–adrenal axis after stress stimulation. On the other hand, nicotine from cigarette smoking is able to stimulate tumour cells to directly synthesize and release stress hormones to form an autocrine loop. Additionally, tumour cells might be innervated by nerve fibres which could also release relevant neurotransmitters. Finally, stress hormones originated from different systems contribute to tumour development and progression such as angiogenesis, lymphangiogenesis, neurogenesis, tumour growth and metastasis.

primarily from the sympathetic nerves and adrenaline is secreted mainly by the adrenal medulla. Their release and secretion are triggered by stimulation of the nicotinic/acetylcholine system in the central and peripheral sympathetic nervous systems and in the adrenal medulla (Fig. 1). Recent studies further disclose that some cancer cells contain all the enzymes for the adrenaline synthesis and are capable to secrete adrenaline after stimulation, for example by nicotine [11–13]. Adrenaline and noradrenaline could bind to β-adrenoceptors with different affinities. Adrenaline preferentially binds to β_2-adrenoceptors whereas noradrenaline shows higher affinity to β_1-receptors [14]. Recently, a growing number of studies suggest that biobehavioural factors especially various stress-related persistent stimulations might accelerate cancer progression, which is mainly contributed by β-adrenergic system activation (Fig. 1) [15–17]. In this review, we will focus on the influences of β-adrenergic system on several crucial steps

in cancer development and progression, and further discuss the potential applications of β-blockers in cancer treatment.

2. β-Adrenergic system modulates biological behaviour of tumours

The roles of β-adrenergic system in cancer development and progression almost involve in every hallmarks of cancer development described above. The influences of β-adrenergic system on energy metabolism and immune system have been shown to regulate cancer metastasis [8,18–20]. But here we focus on the discussion on the common tumorigenic pathways during tumour progression. They have been extensively investigated between the relationship of β-adrenergic system and tumorigenic processes such as cellular proliferation and apoptosis and also the vascular events including angiogenesis and vasculature normalization which are important in cancer cell invasion and metastasis during cancer development. Table 1 summarizes the common cancer types, their functional roles, and possible signal molecules and receptor subtypes which are associated with the activation of β-adrenergic system.

2.1. Promotion of cell proliferation and evasion of apoptosis

It has been demonstrated that high level of stress stimulation could contribute to disease progression, including various kinds of cancer. The stress derived from social isolation was found to elevate the tumour noradrenaline level in ovarian cancer patients, and its level was correlated with tumour grades and stages [21]. A growing body of investigations have suggested that stress hormones adrenaline and/or noradrenaline exhibit a tumour-promoting function in a variety of tumour types including but not limited to the cancers of pancreas [22], breast [23], ovary [24,25], colorectum [26], oesophagus [27], lung [28,29], prostate [30], nasopharynx [31], melanoma [32], leukaemia [33,34], even hemangioendotheliom and angiosarcoma [35]. Among these tumours, pancreatic, breast, ovarian and colorectal cancers have been extensively investigated about the effects of β-adrenoceptor system in preclinical and clinical settings. The study from Thaker and colleagues [24] revealed that chronic stress could elevate the tumour noradrenaline level in an orthotopic ovarian cancer in a mouse model and obviously increased tumour burden and aggressiveness of tumour growth. Propranolol, a non-selective β-adrenoceptor antagonist, completely abolished the effects of chronic stress on tumour growth. In contrast terbutaline, a β_2-adrenoceptor agonist produced a similar increase in tumour weight just like under chronic stress. Further study through various experiments by inhibition/elimination of β-adrenoceptors demonstrated that it was the β_2-adrenoceptor on the ovarian tumour cells mainly mediating the signal transduction and tumour development initiated by chronic stress. But Sood et al. [36] uncovered a different tumorigenic mechanism in the regulation of adrenergic system in ovarian tumour growth. In this regard it was thought to inhibit anoikis, a form of programmed cell death (apoptosis) when cells are separated from ECM and proximal cells. They showed that human ovarian cancer cells displayed a lower level of anoikis when cells were stimulated

Table 1
The common cancers reported to be affected by β-adrenergic system.

Tumour types	β-Adrenoceptor subtype	Effects on tumours	Blockers	References
Pancreas	β_1 and β_2	Proliferation Migration Invasion	Propranolol ICI118, 551, Metoprolol, Celecoxib, GABA	[58,60,113]
Breast	β_1 and β_2	Anti-apoptosis(β_2)[a] Migration Adhesion Metastasis	Propranolol	[30,59,62,63]
Ovary	β_2	Anti-apoptosis Tumour growth Angiogenesis Migration invasion	Propranolol	[24,25,36,57,61,99,100]
Colorectum	β_1 and β_2	Cell proliferation Tumour growth Migration(β_2)[a] Metastasis	Atenolol, ICI118,551	[26,38,56,77,114]
Oesophagus	β_1 and β_2	Cell proliferation	Atenolol, ICI118,551	
Stomach	β_1 and β_2	Cell proliferation	Propranolol ICI118,551, Atenolol,	[78,115]
Lung	β_1 and β_2	Cell proliferation Tumour growth	Propranolol GABA	[29,70,116]
Prostate	β_2	Anti-apoptosis Migration Metastasis	ICI118,551 Propranolol	[30,37,59,64]
Nasopharynx	β_1 and β_2	Angiogenesis Invasion	Propranolol	[31]
Melanoma	β_1 and β_2	Angiogenesis Invasion	Propranolol	[31,32]
Leukaemia	β_1 and β_2	Tumour growth Metastasis	Propranolol	[33]
Hemangioma	β_1 and β_2, predominantly β_2	Cell proliferation	ICI118,551, Metoprolol	[117]
Hemangioendotheliom	β_1 and β_2	Cell proliferation	Propranolol	[35]
Angiosarcoma	β_1 and β_2	Cell proliferation	Propranolol	[35]

[a] Relevant functions were mainly mediated by β_2-adrenoceptors reported according to reference papers. Metoprolol, a β_1-selective antagonist; Celecoxib, a selective cyclooxygenase-2 inhibitor; GABA, an inhibitory neurotransmitter γ-aminobutyric acid.

by either adrenaline or noradrenaline. In a mouse model in which animals were exposed to chronic stress, hormones related to stress inhibited anoikis in cancer cells. This action could promote tumour growth through activation of focal adhesion kinase (FAK). Another study in prostate and breast cancer cells also demonstrated that adrenaline stimulation reduced the sensitivity of cancer cells to apoptosis through β_2-adrenoceptors/protein kinase A (PKA)/inactivation of proapoptotic protein BCL2-associated death promoter (BAD)[30]. A recent investigation in preclinical model further confirmed that stress hormone like adrenaline promoted prostate carcinogenesis through inhibition of apoptosis and tumour involution mediated by an adrenaline/β2-adrenoceptor/PKA/BAD antiapoptotic signalling pathway [37]. Our laboratory also observed that both adrenaline and noradrenaline could induce proliferation of colorectal cancer cells through β-adrenoceptors, preferentially the β_2 receptors [26,38]. In contrast, there are reports showing a different action of β-adrenoceptor activation on breast cancer cells. In these studies β-adrenoceptor agonists could decrease cell proliferation in vitro and reduce tumour growth in vivo [39,40]. The reasons of this paradoxical nature of observations remain unknown. It might involve possible antagonistic action of some β-adrenoceptor agonists, different molecular signals and single nucleotide polymorphisms of β-adrenoceptor in the same cancer cells [39,41].

2.2. Induction of angiogenesis

It is well-known that angiogenesis is essential for tumour growth and metastasis. Physiologically, the fine equilibrium between pro- and anti-angiogenic factors governs the complex process and angiogenic switch is off in normal tissues [42]. Cancer is the pathological condition that can tilt the balance towards more stimulatory angiogenic factors to drive the uncontrolled angiogenesis with distinct immature vascular structures from normal blood vessels [42,43]. Common pro-angiogenic factors include vascular endothelial growth factors (VEGFs), placenta-derived growth factor (PlGF), platelet-derived growth factor (PDGF), transforming growth factor β(TGF-β), hypoxia-inducible factor-1 (HIF-1α), angiopoietin-2, insulin-like growth factor, and several chemokines [44]. Among these factors, VEGF is the most studied and best validated as pro-angiogenic molecule in tumour angiogenesis. Solid evidence derived from several cancer models has proven that adrenaline and noradrenline could upregulate the expression of VEGF and induce tumour angiogenesis and aggressive growth [24,25,31,45,46]. Besides VEGF, several reports from different groups [24,31,32,46,47] also identified that other angiogenic factors such as interleukin 6 (IL-6), IL-8, matrix metalloproteinase (MMP)-2 and MMP-9 could be elevated by the stimulation of adrenaline and noradrenaline in a diversity of cancer cells via β-adrenergic receptor signalling. These findings implicate that an amplification cascade might exist among these factors that synergistically strengthen angiogenesis and aggressive development of tumours. But administration of β-adrenoceptor antagonist, propranolol could completely abrogate the secretion of these factors and their mediated functions, implying that β-blockers have potential therapeutic value for the management of relevant cancers. Furthermore, Lutgendorf et al. [48] illuminated that noradrenaline not only induced the increase of MMP-9 and VEGF in ovarian cancer cells but also stimulated the secretion of MMP-9 in macrophages isolated from ovarian cancer specimens. It has been shown that tumour associated macrophages (TAM) and MMP9 released by TAM play an essential role in angiogenesis through presenting VEGF access to relevant receptors on endothelial cells and degrading extracellular matrix to release other pro-angiogenic factors [49,50]. Additionally, a recent study by Park et al. [51] unravelled that noradrenaline induced VEGF expression in several cancer cell lines from prostate, breast and liver via a HIF-1α-dependent manner. Further investigation disclosed that a β-blocker propranolol could completely abolish VEGF production and reduce HIF-1α expression initiated by noradrenaline in cancer cells [51].

2.3. Enhancement of invasion and metastasis

Tumour metastasis as a main cause of cancer-related death is a multistep in cellular/biological process involving the invasion-metastasis cascade. A sequence of molecular events are used to delineate the process including cancer cell local invasion, intravasation, transportation, inoculation, extravasation, micrometastasis formation and colonization (metastatic macroscopic tumour formation) [1,52,53]. Activation of β-adrenergic system seems to involve in each step of the cancer invasion-metastasis cascade. Preclinical investigations have indicated that administration of β-blockers in perioperative and postoperative periods can improve immune status and inhibit cancer metastasis in several cancer models [54–56]. Substantial evidence has demonstrated that stress hormones adrenaline and noradrenaline can induce the release of MMP-2, MMP-7 and MMP-9 in a couple of cancer cell lines and models which are highly associated with metastasis through degradation of extracellular matrix to facilitate cancer cell invasion and migration [24,31,57]. But β-blockers, especially β_2-antagonists, can suppress the secretion of MMPs and reverse the effects related to MMPs such as invasion and migration [58–61]. Strell and colleagues [62] further found that noradrenaline promoted the adhesion of breast cancer cell MDA-MB-231 to human pulmonary microvascular endothelial cells (HMVEC) through the release of growth-regulated oncogene alpha (GROα) and β1-integrin pathway. The process analogizes the extravasation of cancer cells into secondary metastatic loci. Accordingly, β-blockers could abrogate the effects initiated by noradrenaline. Sloan et al. [63] illustrated in an orthotopic mouse model of breast cancer in which stress stimulation or pharmacological activation of β-adrenergic system by isoproterenol induced a 30-fold increase in metastasis to distant organs, which might be mediated by the infiltration of macrophages into primary tumour parenchyma. Stress-induced macrophages can produce the expression of many pro-metastatic genes and exhibit the intendancy towards M2-like differentiation related to aggressive tumour development. Consistently, β-blocker propranolol and macrophage suppressor GW2580 can significantly repress the stress-induced metastasis. A similar result has also been reported in a human prostate cancer cell mouse model [64]. As a result of these investigations, it is suggested that stimulation by stress hormones might switch on metastasis signals during the carcinogenesis of different types of cancer and β-blockers hold great promise to inhibit the initiation and development of metastasis in solid tumours.

2.4. The transactivation of β-adrenoceptors by nicotine and its derivatives

It is known that the synthesis and release of catecholamines are regulated by nicotinic acetylcholine receptors (nAChR) distributed in adrenal medulla and sympathetic nervous endings [3,65]. Cigarette smoking is thought to be a risk factor associated with different types of cancer. Nicotine as a well-documented component in tobacco is believed to be responsible for various cardiovascular diseases and also to promote the relevant tumour progression through binding to nAChR in the nervous system or non-neuronal mammalian cells. A large number of publications have documented that nicotine is capable of inducing proliferation and invasion of various cancer cells in vitro and tumour growth and metastasis *in vivo* [65–68]. Another important component

derived from nicotine is nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) which has been proved to exhibit a stronger potential as a carcinogen in induction and promotion of various tumour development through the binding with higher affinity to AChR than the natural ligand acetylcholine [13,28]. Due to the close connection among nicotine/NNK, nAChR and catecholamines, there should be no surprise that nicotine or NNK can stimulate the secretion of adrenaline and noradrenaline in cancer cells, which can further enhance the nicotine-driven tumour development through aforementioned functions of stress hormones in cancer cells [69–72]. Our laboratory has been focusing on studying the interaction between cigarette smoking and gastrointestinal tract cancers for a number of years. It was found that nicotine, NNK or cigarette extract could not only induce cell proliferation in vitro in a variety of human cancer cells from the upper to the lower gastrointestinal tract, but also promote tumour growth and angiogenesis in vivo through nAChR activation. Nicotine nAChR antagonist could block the effect of nicotine and the down-stream signal transduction [73–76]. Subsequently, we also found that the stimulatory action of NNK on colon cancer cell proliferation could be inhibited by β-blockers [38], and nicotine could induce the synthesis and release of adrenaline in colon cancer cells and β-blockers could reverse nicotine-induced cell proliferation [11]. Similar finding was reported in mice [12]. Interestingly it was found that cigarette smoking together with stress synergistically enhanced colon tumour growth in the same type of animals [77]. Both stress hormone and cigarette smoke active components produced similar stimulatory action on oesophageal and gastric cancer cells via the β-adrenoceptors [27,78,79].

Recently, several reports from the group of Al-Wade and colleagues [13,28,80] unravelled that nicotine or NNK could reduce the production of inhibitory neurotransmitter γ-aminobutyric acid (GABA) when they stimulated the synthesis and release of adrenaline and noradrenaline in the cancers of pancreas and lung. In fact GABA administration could reduce the responses from nicotine stimulation and also inhibit the development of tumours in mice [81]. Likewise, GABA treatment directly reverses the effects of stress on non-small cell lung cancer [29]. All these findings suggest that besides β-blockers, GABA is also a promising agent to be developed to intervene cancers causally related to stress and cigarette smoking.

3. β-Adrenoceptors and β-blockers, possible roles in tumour blood vessel normalization

As previously mentioned, stress hormones could induce angiogenesis in tumours through the release of pro-angiogenic factors. It has been well-documented and accepted that the structure of tumour blood vessels is distinguished from those from normal tissues [82,83]. Tumour vasculature is often dilated, tortuous, leaky and uneven in diameter. These blood vessels also exhibit an heterogeneous distribution in a tumour mass, in which hypervascular and hypovascular areas could be visualized [84]. Additionally, the perivascular cells (PVCs) consisting of pericytes and vascular smooth muscle cells are often absent or detached from endothelial cells (ECs). The PVCs-ECs dissociation is thought to be promoted by numerous pro-angiogenic factors released in the development of tumours [84]. These immature angiogenesis in tumour tissues finally leads to a hostile tumour microenvironment characterized by hypoxia, patchy hypoperfusion, low pH and a high interstitial fluid pressure [85,86]. The abnormality of tumour blood vessels can aggravate the vessel disorganization by hypoxia stimulation, impede the transport and distribution of anti-cancer drugs and oxygen, inhibit the function of immune system, and produce a resistant capacity of cancer cells against various therapies such as radiation, chemotherapy and immune modulation [85,87]. In the past decade, various strategies had been devised to normalize tumour blood vessels. These have been pursued to improve or remodel vessel structure and function. Both preclinical and clinical experimental data have shown that normalized tumour vessels can improve the efficacy of immunotherapy, increase drug delivery and absorption of anti-cancer drugs, and decrease and delay intravastion and metastasis [87,88]. Both genetic alteration and pharmacological intervention can induce the normalization of tumour blood vessels. For example, overexpression of histidine-rich glycoprotein (HRG) in mice [89] resulted in normalization of tumour vessels with increased PVC coverage and blood perfusion, and reduced hypoxia. Meanwhile, HRG-induced normalization decreased tumour growth and metastasis and enhanced the efficacy of chemotherapy; even regulate the polarization of tumour-associated macrophage phenotype. Another typical example is the anti-VEGF antibody therapy. Anti-VEGF antibody bevacizumab when combined with systemic chemotherapy significantly improved progression-free survival and overall survival when compared with chemotherapy alone [87]. Mechanistic study reveals that suitable dose of anti-VEGF antibody can remodel tumour blood vessels, restore oxygenation, reduce hypoxia, leading to enhanced efficacy of chemotherapies [88]. Ample evidence also suggested that some anti-angiogenesis agents could pharmacologically induce vascular normalization in a transient manner and in a special time window [87].

Thaker et al. [24] reported that chronic stress could induce tumour growth and promote angiogenesis in a mouse model bearing ovarian cancer. Further analysis unveiled that stress obviously increased mean vessel density but β-blocker propranolol reversed the effect. Histological finding showed that tumours in stress animals consisted of more tortuous vasculature than the control accompanied with a 24% reduction of pericyte coverage, which is a typical characteristic of immature and abnormal tumour vessels. But in this study, the author did not mention whether administration of β-blocker propranolol could normalize the tumour vasculature. A recent report from the same group [90] demonstrated that dopamine (DA), an inhibitory neurotransmitter which has been proven to be able to antagonize the effect of stress hormones on cancer development, could abrogate the tumour vasculature and ovarian cancer growth driven by chronic stress. Further studies found that administration of DA resulted in a decrease of microvessel density through dopamine receptor 2 (DR2), and stabilization of tumour blood vessels characterized by increased pericyte recruitment to EC through DR1. Moreover, DA-induced normalization enhanced the absorption of cisplatin in mice. But β-blocker as an antagonists on stress hormones were not assessed in this study. Another similar investigation on prostate and colon cancers [91] also suggested that exogenous administration of DA could normalize the structure of tumour blood vessels in both cancer models through acting on the DR2 expressed on pericytes and endothelial cells. Consequently, normalization of tumour vasculature improved the concentration and efficacy of 5-fluorouracil. It is well-established that DA or GABA as an inhibitory neurotransmitter antagonizes the function of stress hormones. These studies would be prone us to believe that β-blockers like other inhibitory neurotransmitters such as GABA and DA discussed above could also normalize blood vessels in cancers. Further investigation is needed to clarify the roles of β-adrenergic system in the normalization of tumour blood vessels and its implications in the treatment of solid tumours in the near future.

4. β-Adrenoceptor signal transduction related to cancer development and progression

Physiologically, activation of β-adrenoceptor system is involved in a couple of signal transduction pathways dependent on ligand, adrenoceptor conformation, tissue environments and functions

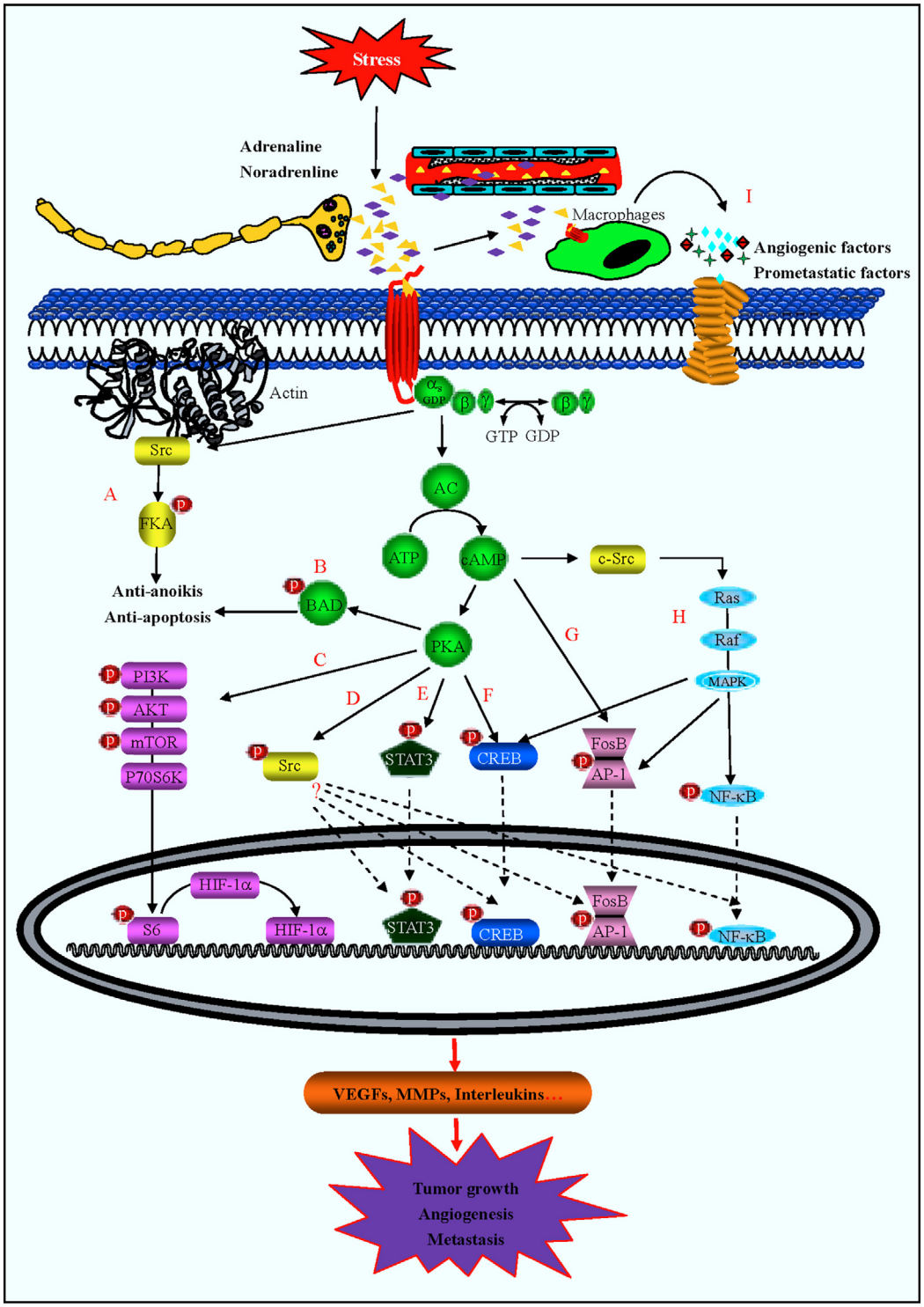

Fig. 2. Possible signal pathways of β-adrenergic system in cancer. β-Adrenoceptors stimulated by stress hormones activate AC via Gαs protein released from Gβγ proteins, resulting in the increase of second messenger cAMP. The cAMP activates PKA protein which can mediate multiple signal pathways via phosphorylation of various downstream signal proteins. PKA-CREB pathway is a well-defined pathway which results in synthesis of several angiogenic factors through the transcription regulation mediated by phosphorylated CREB binding to CRE (F). But direct G protein/Src (related to actin)/FAK phosphorylation pathway mediates the anoikis inhibition and anti-apoptosis (A). The protection of cancer cells from apoptosis could also be regulated by the phosphorylation of cAMP/PKA-dependent BAD (B). The stress hormones induce the activation of AMP/PKA/PI3K/AKT/mTOR/p70S6K/HIF1α, leading to VEGF synthesis via HIF1α-mediated transcription regulation (C). PKA-dependent Src phosphorylation might promote the metastasis via various downstream effectors (D). SATA3 activation induced by stress stimulation is able to regulate the synthesis of MMPs which are highly associated with tumour metastasis (E). FosB stimulated by stress/cAMP signal might constitute a complex with AP-1 to increase IL-8, which could drive tumour growth and metastasis (G). MAPK pathway activated by stress factors can stimulate various transcription factors such as CREB, AP-1 and NF-κB to induce the secretion of VEGFs and MMPs (H). In addition, macrophages stimulated by stress hormones can produce a list of angiogenic and prometastatic factors which influence tumour progression (I). Collectively, various signal pathways induced by stress hormones finally accelerate tumour growth, angiogenesis, as well as metastasis dissemination via a large number of tumour-related factors.

[92]. Due to widespread distribution in the body and important roles in cardiovascular and central nervous systems, related signal pathways have been systematically investigated and reported, which makes β-adrenoceptors become valuable drug targets to design agonists and antagonists to regulate alternative signal pathways with intervention against clinical diseases [93–96]. Classically, β-adrenoceptors as G protein-coupled receptors in response to stress hormones activate the adenylyl cyclase (AC) through Gsα and elevate the second messenger cyclic AMP (cAMP) which activates PKA (Fig. 2). Subsequent signal pathways are normally divided into PKA-dependent and independent signal transduction. PKA is able to phosphorylate numerous proteins to realize relevant function regulations. For PKA-independent pathway, a representative instance is the exchange protein activated by adenylyl cyclase (EPAC) mediated signal transduction in which AC after adrenoceptor activation directly activates EPAC resulting in stimulation of mitogen-activated protein kinase (MAPK) signal pathways [96,97]. However, substantial evidence disclosed that β-adrenoceptors could also initiate and activate some signal pathways independent of the G proteins [92]. A well-characterized example is β-arrestin-mediated activation of MAPK pathways via triggered β_2-adrenoceptors in which stimulation of β_2-adrenoceptors directly recruits relevant signal protein such as c-Src and the receptor via β-arrestin but not the G proteins [92,95,98]. Here we will describe several β-adrenoceptor signal pathways related to cancer development and progression. Fig. 2 presents the common β-adrenoceptor signal pathways in cancer development. As we discussed above, stimulation of β-adrenoceptors by stress hormones promotes the release of several pro-angiogenic factors, such as VEGF, MT1-MMP, MMP-2, MMP-9, IL-6, leading to tumour growth and angiogenesis. The process is mostly mediated by AC-cAMP-PKA pathway. PKA enables transcription factor cAMP response element binding protein (CREB) to be phosphorylated, which promotes the binding of CREB to the cAMP response element (CRB) and induces the transcription of genes encoding these factors [14,24,28,59]. Furthermore, Park and colleagues [51] unveiled another mechanism of VEGF-induced expression dependent on HIF1α protein after adrenoceptor activation by noradrenaline, which is involved in the process of the cAMP/PKA/phosphoinositide 3-kinase (PI3K)/Akt/mTOR/p70S6 kinase (p70S6K)/HIF1α/VEGF signal transduction. Additionally, PKA-independent pathways were reported to involve the activation of transcription factors nuclear factor κB (NFκB) and activator protein 1(AP1) besides CREB, all of which could regulate the transcription of VEGF, MMPs and interleukins. Zhang et al. [60] found that β-adrenoceptor antagonists ICI118,551 and propranolol could stimulate the c-Src-mediated Ras/Raf/MAPK pathway to regulate the activity of transcription factors CREB, AP1 and NF-κB in pancreatic cancer cells.

In stress hormone-mediated protection of cancer cell from apoptosis, Sood and colleagues [36] elucidated that stimulation of β_2-adrenoceptors could lower the level of anoiks through direct activation of actin- related Src and subsequent phosphorylation of focal adhesion kinase $(FAK)^{Y397}$ in ovarian cancer cells. High level of $pFAK^{Y397}$ was found in ovarian cancer patients with behavioural stress states related to adrenergic activity. But Sastry et al. [30] reported that a major anti-apoptotic mechanism is the PKA-dependent BAD phosphorylation at site S112 after activation of β_2-adrenoceptors by adrenaline in prostate and breast cancer cells. Thus, cancer types might be one of important determinants in selection of signal pathways in the context of activation of β-adrenergic system. On the other hand, the metastasis initiated by β-adrenergic system is driven by a distinct set of signal pathways in different cancer cells. A recent study by Armaiz-Pena group [99] illuminated that β-adrenoceptor activation might switch on the metastasis process in ovarian cancer via Src phosphorylation at site Y419 following after at site S17 phosphorylation which is required to expose site Y419. But the noradrenaline-induced Src activation is cAMP/PKA dependent. Additionally, signal transducer and activator of transcription-3 (STAT3), FosB-induced IL-8 signal pathways possibly also drove the growth, invasion and metastasis in ovarian cancer in the cAMP and/or PKA dependent manners [61,100]. Sloan et al. [63] demonstrated that macrophage infiltration into primary breast cancer parenchyma might trigger a metastatic switch via activation of β-adrenergic system since invasive macrophage activated by stress hormones produced various pro-metastatic factors, resulting in secondary metastasis in distant tissues.

Signal network implicates that there are complicated connections and cross talks among signal molecules. Although activation of β-adrenergic system could trigger multiple signal pathways in different cancer cells, we cannot rule out the synergic effects among these signal pathways. It is evident that direct blocking the β-adrenoceptors has a great potential to be able to intervene cancer related signal pathways, resulting in alleviation of cancer progression.

5. β-Blockers, a new opportunity for conventional drugs

We have discussed that stress hormones are highly associated with tumour growth, invasion, and metastasis via activation of β-adrenoceptors in preclinical and clinical settings. Meanwhile, β-blockers could abrogate partly or completely the pathological impact of stress hormones on tumour progression in preclinical settings. β-Blockers are clinically well characterized and have been safely administered as therapeutics for cardiovascular diseases, especially hypertension for decades. As reported in this review, β-blockers should have additional potential to be exploited clinically to alleviate the deleterious progression of cancers influenced by β-adrenergic system. If that is the case, application of β-blockers in cancer therapy could be novel and safe. It is also cost-effective as adjuvant chemotherapeutic agents for cancer treatment. Interestingly, a couple of retrospective studies strongly supported the beneficial actions of β-blockers in relevant cancer treatment. First, an earlier retrospective analysis carried out by Perron et al. in a large case-control study of prostate patients showed that of the different classes of antihypertensives, only β-blockers were correlated to a reduction in prostate cancer risk [101]. Another cohort study involved 839 patients with cardiovascular disease followed up for 10 years suggested that β-blocker users had a significant decrease in cancer incidence compared with those never used [102]. But another two studies in relatively larger population did not support that β-blockers had a significant association with lower risk of prostate cancer [103] or increase cancer risk [104]. These conflicting results would make β-blockers more complex in the role of tumour prevention and occurrence. Recently, several new investigations disclosed that β-blockers might have the ability to repress cancer progression in established cancers, especially breast cancer and melanoma. A more than 10-year retrospective study from Powe et al. [105] reported that breast cancer patients receiving β-blockers for hypertension exhibited an obvious reduction in metastasis development, tumour recurrence and cancer-specific mortality. Another two population-based studies by Barron et al. and Melhem-Bertrandt et al. achieved similar and consistent conclusions in breast cancer patients. Barron et al. [106] reported that β_1/β_2 non-selective blocker propranolol significantly reduced the primary tumour development, nodal/metastatic occurrence and breast cancer-specific mortality but not for β1-blocker atenolol. The finding also suggests that β_2-adrenergic pathway is a predominant mediator for the therapeutic action of propranolol. Melhem-Bertrandt et al. [107] found that β-blockers significantly improved the relapse-free survival in all patients with breast

cancer and in patients with triple-negative breast cancer (oestrogen receptor-negative/progesterone receptor-negative/human epidermal growth factor-negative). But in this study, the conclusion was based on the patients using β1-blocker, which is in contrast with the conclusion of Barron et al. who found no significant benefits for β1-blockers in breast cancer patients. In fact, selective β1-blockers often indicate off-target function through the affinity to other β-adrenoceptors [107]. Thus, more broad β-blockers or more exact adrenoceptor identification are needed in future investigations. For melanoma, two reports from different groups indicated that β-blocker intake might reduce the risk of progression in patients with thick melanoma [108] and increase survival time of patients with melanoma [109]. But a contradicting finding by Shah et al. [110] pointed out that β-blocker treatment had no evident beneficial effect on overall survival of patients with common human tumours such as cancers in the lung, breast and colon, and even produced poorer survival in patients with prostate and pancreatic cancers. Although controversial conclusions are present for the application of β-blockers in cancer treatment, it is noticeable that all of the aforementioned investigations are population-based retrospective studies which limited the interpretation of the results to some extent. It is time to design clinical trials to test β-blockers in adjuvant treatment of relevant cancers, especially breast cancer. Some important issues need to be considered for future studies including but not limited to blocker selectivity, dose titration and local concentration in tumour mass, β-adrenoceptor expression, tumour types and stages, and interaction of β-blockers and tumour microenvironment [111,112]. Based on preclinical translational data and retrospective analysis, we predict that β-blockers hold considerable promise to treat patients with some cancers in the future as a class of well-defined conventional drug used for cardiovascular diseases in the past decades.

6. Summary and perspectives

Numerous evidences from preclinical and epidemiological studies have implicated that stress hormones or behavioural changes are highly associated with tumour formation and progression. Patients diagnosed with cancer often endure different degree of stress complicated with high of stress hormones. Likewise nicotine/NNK from cigarette smoke can also stimulate the secretion of stress hormones in cancer patients. All these could stimulate the adrenergic system. It is known that over activation of β-adrenergic system could accelerate cancer development through multiple-step process. An increasing body of information from preclinical investigations and clinical retrospective analysis have shown that β-blockers as a class of drug broadly used for hypertension regulation have great potential to be used to treat cancer patients impacted by psychological stress. However there is no exact conclusion that can be drawn so far from retrospective clinical studies. It is time to launch a well-designed and meticulous clinical trial to affirm the exact role and clinical application of β-blockers in the treatment of cancer patients. On the other hand, it is worthwhile to explore the mechanistic action of β-blockers in the normalization of tumour blood vessels. Indeed it is an emerging and promising therapeutic strategy that vessel remodelling agents in combination with chemotherapeutic drugs are being exploited to treat patients with solid tumours. Meanwhile, inhibitory neurotransmitters such as GABA and dopamine should also play a significant role in the future in cancer therapy since they can antagonize the carcinogenic action of β-adrenergic system which could be activated during the progression of cancer development. Collectively, β-adrenoceptors are valuable drug targets to control the deleterious effects of β-adrenergic system in tumour development together with psychological stress in cancer patients.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References

[1] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.
[2] Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57–70.
[3] Li ZJ, Cho CH. Neurotransmitters, more than meets the eye – neurotransmitters and their perspectives in cancer development and therapy. Eur J Pharmacol 2011;667:17–22.
[4] Entschladen F, Palm D, Lang K, Lt Drell T, Zaenker KS. Neoneurogenesis: tumors may initiate their own innervation by the release of neurotrophic factors in analogy to lymphangiogenesis and neoangiogenesis. Med Hypotheses 2006;67:33–5.
[5] Schuller HM. Neurotransmission and cancer: implications for prevention and therapy. Anticancer Drugs 2008;19:655–71.
[6] Voss MJ, Entschladen F. Tumor interactions with soluble factors and the nervous system. Cell Commun Signal 2010;8:21.
[7] Palm D, Entschladen F. Neoneurogenesis and the neuro-neoplastic synapse. Prog Exp Tumor Res 2007;39:91–8.
[8] Li S, Sun Y, Gao D. Role of the nervous system in cancer metastasis. Oncol Lett 2013;5:1101–11.
[9] Tilan J, Kitlinska J. Sympathetic neurotransmitters and tumor angiogenesis-link between stress and cancer progression. J Oncol 2010;2010:539706.
[10] Thaker PH, Sood AK. Neuroendocrine influences on cancer biology. Semin Cancer Biol 2008;18:164–70.
[11] Wong HP, Yu L, Lam EK, Tai EK, Wu WK, Cho CH. Nicotine promotes cell proliferation via alpha7-nicotinic acetylcholine receptor and catecholamine-synthesizing enzymes-mediated pathway in human colon adenocarcinoma HT-29 cells. Toxicol Appl Pharmacol 2007;221:261–7.
[12] Wong HP, Yu L, Lam EK, Tai EK, Wu WK, Cho CH. Nicotine promotes colon tumor growth and angiogenesis through beta-adrenergic activation. Toxicol Sci 2007;97:279–87.
[13] Al-Wadei HA, Schuller HM. Nicotinic receptor-associated modulation of stimulatory and inhibitory neurotransmitters in NNK-induced adenocarcinoma of the lungs and pancreas. J Pathol 2009;218:437–45.
[14] Schuller HM, Al-Wadei HA. Neurotransmitter receptors as central regulators of pancreatic cancer. Future Oncol 2010;6:221–8.
[15] Antoni MH, Lutgendorf SK, Cole SW, Dhabhar FS, Sephton SE, McDonald PG, et al. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. Nat Rev Cancer 2006;6:240–8.
[16] Costanzo ES, Sood AK, Lutgendorf SK. Biobehavioral influences on cancer progression. Immunol Allergy Clin North Am 2011;31:109–32.
[17] Lutgendorf SK, Sood AK, Antoni MH. Host factors and cancer progression: biobehavioral signaling pathways and interventions. J Clin Oncol 2010;28:4094–9.
[18] Lang K, Bastian P. Neurotransmitter effects on tumor cells and leukocytes. Prog Exp Tumor Res 2007;39:99–121.
[19] Shi M, Liu D, Yang Z, Guo N. Central and peripheral nervous systems: master controllers in cancer metastasis. Cancer Metastasis Rev 2013 [E-pub ahead of print].
[20] Engler H, Bailey MT, Engler A, Sheridan JF. Effects of repeated social stress on leukocyte distribution in bone marrow, peripheral blood and spleen. J Neuroimmunol 2004;148:106–15.
[21] Lutgendorf SK, DeGeest K, Dahmoush L, Farley D, Penedo F, Bender D, et al. Social isolation is associated with elevated tumor norepinephrine in ovarian carcinoma patients. Brain Behav Immun 2011;25:250–5.
[22] Schuller HM, Al-Wadei HA, Ullah MF, Plummer 3rd HK. Regulation of pancreatic cancer by neuropsychological stress responses: a novel target for intervention. Carcinogenesis 2012;33:191–6.
[23] Hermes GL, Delgado B, Tretiakova M, Cavigelli SA, Krausz T, Conzen SD, et al. Social isolation dysregulates endocrine and behavioral stress while increasing malignant burden of spontaneous mammary tumors. Proc Natl Acad Sci USA 2009;106:22393–8.
[24] Thaker PH, Han LY, Kamat AA, Arevalo JM, Takahashi R, Lu C, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. Nat Med 2006;12:939–44.
[25] Lee JW, Shahzad MM, Lin YG, Armaiz-Pena G, Mangala LS, Han HD, et al. Surgical stress promotes tumor growth in ovarian carcinoma. Clin Cancer Res 2009;15:2695–702.
[26] Wong HP, Ho JW, Koo MW, Yu L, Wu WK, Lam EK, et al. Effects of adrenaline in human colon adenocarcinoma HT-29 cells. Life Sci 2011;88:1108–12.
[27] Liu X, Wu WK, Yu L, Sung JJ, Srivastava G, Zhang ST, et al. Epinephrine stimulates esophageal squamous-cell carcinoma cell proliferation via beta-adrenoceptor-dependent transactivation of extracellular signal-regulated kinase/cyclooxygenase-2 pathway. J Cell Biochem 2008;105:53–60.
[28] Al-Wadei HA, Ullah MF, Al-Wadei MH. Intercepting neoplastic progression in lung malignancies via the beta adrenergic (beta-AR) pathway: implications for anti-cancer drug targets. Pharmacol Res 2012;66:33–40.
[29] Al-Wadei HA, Plummer 3rd HK, Ullah MF, Unger B, Brody JR, Schuller HM. Social stress promotes and gamma-aminobutyric acid inhibits tumor growth

in mouse models of non-small cell lung cancer. Cancer Prev Res (Phila) 2012;5:189–96.
[30] Sastry KS, Karpova Y, Prokopovich S, Smith AJ, Essau B, Gersappe A, et al. Epinephrine protects cancer cells from apoptosis via activation of cAMP-dependent protein kinase and BAD phosphorylation. J Biol Chem 2007;282:14094–100.
[31] Yang EV, Sood AK, Chen M, Li Y, Eubank TD, Marsh CB, et al. Norepinephrine up-regulates the expression of vascular endothelial growth factor, matrix metalloproteinase (MMP)-2, and MMP-9 in nasopharyngeal carcinoma tumor cells. Cancer Res 2006;66:10357–64.
[32] Moretti S, Massi D, Farini V, Baroni G, Parri M, Innocenti S, et al. beta-adrenoceptors are upregulated in human melanoma and their activation releases pro-tumorigenic cytokines and metalloproteases in melanoma cell lines. Lab Invest 2013;93:279–90.
[33] Lamkin DM, Sloan EK, Patel AJ, Chiang BS, Pimentel MA, Ma JC, et al. Chronic stress enhances progression of acute lymphoblastic leukemia via beta-adrenergic signaling. Brain Behav Immun 2012;26:635–41.
[34] Inbar S, Neeman E, Avraham R, Benish M, Rosenne E, Ben-Eliyahu S. Do stress responses promote leukemia progression? An animal study suggesting a role for epinephrine and prostaglandin-E2 through reduced NK activity. PLoS ONE 2011;6:e19246.
[35] Stiles JM, Amaya C, Rains S, Diaz D, Pham R, Battiste J, et al. Targeting of beta adrenergic receptors results in therapeutic efficacy against models of hemangioendothelioma and angiosarcoma. PLoS ONE 2013;8:e60021.
[36] Sood AK, Armaiz-Pena GN, Halder J, Nick AM, Stone RL, Hu W, et al. Adrenergic modulation of focal adhesion kinase protects human ovarian cancer cells from anoikis. J Clin Invest 2010;120:1515–23.
[37] Hassan S, Karpova Y, Baiz D, Yancey D, Pullikuth A, Flores A, et al. Behavioral stress accelerates prostate cancer development in mice. J Clin Invest 2013;123:874–86.
[38] Wu WK, Wong HP, Luo SW, Chan K, Huang FY, Hui MK, et al. 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone from cigarette smoke stimulates colon cancer growth via beta-adrenoceptors. Cancer Res 2005;65:5272–7.
[39] Perez Pinero C, Bruzzone A, Sarappa MG, Castillo LF, Luthy IA. Involvement of alpha2- and beta2-adrenoceptors on breast cancer cell proliferation and tumour growth regulation. Br J Pharmacol 2012;166:721–36.
[40] Carie AE, Sebti SM. 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 2007;26:3777–88.
[41] Luthy IA, Bruzzone A, Pinero CP, Castillo LF, Chiesa IJ, Vazquez SM, et al. Adrenoceptors: non conventional target for breast cancer. Curr Med Chem 2009;16:1850–62.
[42] Weis SM, Cheresh DA. Tumor angiogenesis: molecular pathways and therapeutic targets. Nat Med 2011;17:1359–70.
[43] Sarkar C, Chakroborty D, Basu S. Neurotransmitters as regulators of tumor angiogenesis and immunity: the role of catecholamines. J Neuroimmune Pharmacol 2013;8:7–14.
[44] Sakurai T, Kudo M. Signaling pathways governing tumor angiogenesis. Oncology 2011;81(Suppl. 1):24–9.
[45] Vilardi BM, Bravo-Calderon DM, Bernabe DG, Oliveira SH, Oliveira DTVEGF-C. expression in oral cancer by neurotransmitter-induced activation of beta-adrenergic receptors. Tumour Biol 2013;34:139–43.
[46] Yang EV, Kim SJ, Donovan EL, Chen M, Gross AC, Webster Marketon JI, et al. Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression. Brain Behav Immun 2009;23:267–75.
[47] Madden KS, Szpunar MJ, Brown EB. 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 Res Treat 2011;130:747–58.
[48] Lutgendorf SK, Lamkin DM, Jennings NB, Arevalo JM, Penedo F, DeGeest K, et al. Biobehavioral influences on matrix metalloproteinase expression in ovarian carcinoma. Clin Cancer Res 2008;14:6839–46.
[49] Rogers TL, Holen I. Tumour macrophages as potential targets of bisphosphonates. J Transl Med 2011;9:177.
[50] Coffelt SB, Hughes R, Lewis CE. Tumor-associated macrophages: effectors of angiogenesis and tumor progression. Biochim Biophys Acta 2009;1796:11–8.
[51] Park SY, Kang JH, Jeong KJ, Lee J, Han JW, Choi WS, et al. Norepinephrine induces VEGF expression and angiogenesis by a hypoxia-inducible factor-1alpha protein-dependent mechanism. Int J Cancer 2011;128:2306–16.
[52] Spano D, Heck C, De Antonellis P, Christofori G, Zollo M. Molecular networks that regulate cancer metastasis. Semin Cancer Biol 2012;22:234–49.
[53] Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. Cell 2011;147:275–92.
[54] Benish M, Bartal I, Goldfarb Y, Levi B, Avraham R, Raz A, et al. Perioperative use of beta-blockers and COX-2 inhibitors may improve immune competence and reduce the risk of tumor metastasis. Ann Surg Oncol 2008;15:2042–52.
[55] Goldfarb Y, Sorski L, Benish M, Levi B, Melamed R, Ben-Eliyahu S. Improving postoperative immune status and resistance to cancer metastasis: a combined perioperative approach of immunostimulation and prevention of excessive surgical stress responses. Ann Surg 2011;253:798–810.
[56] Wu W, Murata J, Hayashi K, Yamaura T, Mitani N, Saiki I. Social isolation stress impairs the resistance of mice to experimental liver metastasis of murine colon 26-L5 carcinoma cells. Biol Pharm Bull 2001;24:772–6.
[57] Sood AK, Bhatty R, Kamat AA, Landen CN, Han L, Thaker PH, et al. Stress hormone-mediated invasion of ovarian cancer cells. Clin Cancer Res 2006;12:369–75.
[58] Guo K, Ma Q, Wang L, Hu H, Li J, Zhang D, et al. Norepinephrine-induced invasion by pancreatic cancer cells is inhibited by propranolol. Oncol Rep 2009;22:825–30.
[59] Lang K, Lt Drell T, Lindecke A, Niggemann B, Kaltschmidt C, Zaenker KS, et al. Induction of a metastatogenic tumor cell type by neurotransmitters and its pharmacological inhibition by established drugs. Int J Cancer 2004;112:231–8.
[60] Zhang D, Ma QY, Hu HT. Zhang M. beta2-adrenergic antagonists suppress pancreatic cancer cell invasion by inhibiting CREB, NFkappaB and AP-1. Cancer Biol Ther 2010;10:19–29.
[61] Landen Jr CN, Lin YG, Armaiz Pena GN, Das PD, Arevalo JM, Kamat AA, et al. Neuroendocrine modulation of signal transducer and activator of transcription-3 in ovarian cancer. Cancer Res 2007;67:10389–96.
[62] Strell C, Niggemann B, Voss MJ, Powe DG, Zanker KS, Entschladen F. Norepinephrine promotes the beta1-integrin-mediated adhesion of MDA-MB-231 cells to vascular endothelium by the induction of a GROalpha release. Mol Cancer Res 2012;10:197–207.
[63] Sloan EK, Priceman SJ, Cox BF, Yu S, Pimentel MA, Tangkanangnukul V, et al. The sympathetic nervous system induces a metastatic switch in primary breast cancer. Cancer Res 2010;70:7042–52.
[64] Palm D, Lang K, Niggemann B, Lt Drell T, Masur K, Zaenker KS, et al. The norepinephrine-driven metastasis development of PC-3 human prostate cancer cells in BALB/c nude mice is inhibited by beta-blockers. Int J Cancer 2006;118:2744–9.
[65] Schuller HM. Neurotransmitter receptor-mediated signaling pathways as modulators of carcinogenesis. Prog Exp Tumor Res 2007;39:45–63.
[66] Dasgupta P, Rizwani W, Pillai S, Kinkade R, Kovacs M, Rastogi S, et al. Nicotine induces cell proliferation, invasion and epithelial-mesenchymal transition in a variety of human cancer cell lines. Int J Cancer 2009;124:36–45.
[67] Chen CS, Lee CH, Hsieh CD, Ho CT, Pan MH, Huang CS, et al. Nicotine-induced human breast cancer cell proliferation attenuated by garcinol through down-regulation of the nicotinic receptor and cyclin D3 proteins. Breast Cancer Res Treat 2011;125:73–87.
[68] Chen RJ, Ho YS, Guo HR, Wang YJ. Rapid activation of Stat3 and ERK1/2 by nicotine modulates cell proliferation in human bladder cancer cells. Toxicol Sci 2008;104:283–93.
[69] Weddle DL, Tithoff P, Williams M, Schuller HM. Beta-adrenergic growth regulation of human cancer cell lines derived from pancreatic ductal carcinomas. Carcinogenesis 2001;22:473–9.
[70] Schuller HM, Tithof PK, Williams M, Plummer 3rd H. The tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone is a beta-adrenergic agonist and stimulates DNA synthesis in lung adenocarcinoma via beta-adrenergic receptor-mediated release of arachidonic acid. Cancer Res 1999;59:4510–5.
[71] Jull BA, Plummer 3rd HK, Schuller HM. Nicotinic receptor-mediated activation by the tobacco-specific nitrosamine NNK of a Raf-1/MAP kinase pathway, resulting in phosphorylation of c-myc in human small cell lung carcinoma cells and pulmonary neuroendocrine cells. J Cancer Res Clin Oncol 2001;127:707–17.
[72] Al-Wadei MH, Al-Wadei HA, Schuller HM. Pancreatic cancer cells and normal pancreatic duct epithelial cells express an autocrine catecholamine loop that is activated by nicotinic acetylcholine receptors alpha3, alpha5, and alpha7. Mol Cancer Res 2012;10:239–49.
[73] Ye YN, Liu ES, Shin VY, Wu WK, Cho CH. The modulating role of nuclear factor-kappaB in the action of alpha7-nicotinic acetylcholine receptor and cross-talk between 5-lipoxygenase and cyclooxygenase-2 in colon cancer growth induced by 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone. J Pharmacol Exp Ther 2004;311:123–30.
[74] Liu ES, Shin VY, Ye YN, Luo JC, Wu WK, Cho CH. Cyclooxygenase-2 in cancer cells and macrophages induces colon cancer cell growth by cigarette smoke extract. Eur J Pharmacol 2005;518:47–55.
[75] Ye YN, Wu WK, Shin VY, Bruce IC, Wong BC, Cho CH. Dual inhibition of 5-LOX and COX-2 suppresses colon cancer formation promoted by cigarette smoke. Carcinogenesis 2005;26:827–34.
[76] Shin VY, Wu WK, Ye YN, So WH, Koo MW, Liu ES, et al. Nicotine promotes gastric tumor growth and neovascularization by activating extracellular signal-regulated kinase and cyclooxygenase-2. Carcinogenesis 2004;25:2487–95.
[77] Wong HP, Li ZJ, Shin VY, Tai EK, Wu WK, Yu L, et al. Effects of cigarette smoking and restraint stress on human colon tumor growth in mice. Digestion 2009;80:209–14.
[78] Shin VY, Jin HC, Ng EK, Yu J, Leung WK, Cho CH, et al. Nicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone induce cyclooxygenase-2 activity in human gastric cancer cells: Involvement of nicotinic acetylcholine receptor (nAChR) and beta-adrenergic receptor signaling pathways. Toxicol Appl Pharmacol 2008;233:254–61.
[79] Li P, Wu WK, Wong HP, Zhang ST, Yu L, Cho CH. Chloroform extract of cigarette smoke induces proliferation of human esophageal squamous-cell carcinoma cells: modulation by beta-adrenoceptors. Drug Chem Toxicol 2009;32:175–81.
[80] Al-Wadei HA, Al-Wadei MH, Schuller HM. Cooperative regulation of non-small cell lung carcinoma by nicotinic and beta-adrenergic receptors: a novel target for intervention. PLoS ONE 2012;7:e29915.

[81] Al-Wadei HA, Plummer 3rd HK, Schuller HM. Nicotine stimulates pancreatic cancer xenografts by systemic increase in stress neurotransmitters and suppression of the inhibitory neurotransmitter gamma-aminobutyric acid. Carcinogenesis 2009;30:506–11.
[82] Ruoslahti E, Bhatia SN, Sailor MJ. Targeting of drugs and nanoparticles to tumors. J Cell Biol 2010;188:759–68.
[83] Li ZJ, Wu WK, Ng SS, Yu L, Li HT, Wong CC, et al. A novel peptide specifically targeting the vasculature of orthotopic colorectal cancer for imaging detection and drug delivery. J Control Release 2010;148:292–302.
[84] Goel S, Wong AH, Jain RK. Vascular normalization as a therapeutic strategy for malignant and nonmalignant disease. Cold Spring Harb Perspect Med 2012;2:a006486.
[85] Carmeliet P, Jain RK. Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases. Nat Rev Drug Discov 2011;10:417–27.
[86] Huang Y, Goel S, Duda DG, Fukumura D, Jain RK. Vascular normalization as an emerging strategy to enhance cancer immunotherapy. Cancer Res 2013;73:2943–8.
[87] Goel S, Duda DG, Xu L, Munn LL, Boucher Y, Fukumura D, et al. Normalization of the vasculature for treatment of cancer and other diseases. Physiol Rev 2011;91:1071–121.
[88] Jain RK. Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers. J Clin Oncol 2013;31:2205–18.
[89] Rolny C, Mazzone M, Tugues S, Laoui D, Johansson I, Coulon C, et al. HRG inhibits tumor growth and metastasis by inducing macrophage polarization and vessel normalization through downregulation of PlGF. Cancer Cell 2011;19:31–44.
[90] Moreno-Smith M, Lee SJ, Lu C, Nagaraja AS, He G, Rupaimoole R, et al. Biologic effects of dopamine on tumor vasculature in ovarian carcinoma. Neoplasia 2013;15:502–10.
[91] Chakroborty D, Sarkar C, Yu H, Wang J, Liu Z, Dasgupta PS, et al. Dopamine stabilizes tumor blood vessels by up-regulating angiopoietin 1 expression in pericytes and Kruppel-like factor-2 expression in tumor endothelial cells. Proc Natl Acad Sci USA 2011;108:20730–5.
[92] Audet M, Bouvier M. Insights into signaling from the beta2-adrenergic receptor structure. Nat Chem Biol 2008;4:397–403.
[93] Evans BA, Sato M, Sarwar M, Hutchinson DS, Summers RJ. Ligand-directed signalling at beta-adrenoceptors. Br J Pharmacol 2010;159:1022–38.
[94] Hara MR, Kovacs JJ, Whalen EJ, Rajagopal S, Strachan RT, Grant W, et al. A stress response pathway regulates DNA damage through beta2-adrenoreceptors and beta-arrestin-1. Nature 2011;477:349–53.
[95] Luttrell LM, Ferguson SS, Daaka Y, Miller WE, Maudsley S, Della Rocca GJ, et al. Beta-arrestin-dependent formation of beta2 adrenergic receptor-Src protein kinase complexes. Science 1999;283:655–61.
[96] de Rooij J, Zwartkruis FJ, Verheijen MH, Cool RH, Nijman SM, Wittinghofer A, et al. Epac is a Rap1 guanine-nucleotide-exchange factor directly activated by cyclic AMP. Nature 1998;396:474–7.
[97] Breckler M, Berthouze M, Laurent AC, Crozatier B, Morel E, Lezoualc'h F. Rap-linked cAMP signaling Epac proteins: compartmentation, functioning and disease implications. Cell Signal 2011;23:1257–66.
[98] Drake MT, Violin JD, Whalen EJ, Wisler JW, Shenoy SK. Lefkowitz RJ. beta-arrestin-biased agonism at the beta2-adrenergic receptor. J Biol Chem 2008;283:5669–76.
[99] Armaiz-Pena GN, Allen JK, Cruz A, Stone RL, Nick AM, Lin YG, et al. Src activation by beta-adrenoreceptors is a key switch for tumour metastasis. Nat Commun 2013;4:1403.
[100] Shahzad MM, Arevalo JM, Armaiz-Pena GN, Lu C, Stone RL, Moreno-Smith M, et al. Stress effects on FosB- and interleukin-8 (IL8)-driven ovarian cancer growth and metastasis. J Biol Chem 2010;285:35462–70.
[101] Perron L, Bairati I, Harel F, Meyer F. Antihypertensive drug use and the risk of prostate cancer (Canada). Cancer Causes Control 2004;15:535–41.
[102] Algazi M, Plu-Bureau G, Flahault A, Dondon MG, Le MG. Could treatments with beta-blockers be associated with a reduction in cancer risk? Rev Epidemiol Sante Publique 2004;52:53–65.
[103] Rodriguez C, Jacobs EJ, Deka A, Patel AV, Bain EB, Thun MJ, et al. Use of blood-pressure-lowering medication and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. Cancer Causes Control 2009;20:671–9.
[104] Bangalore S, Kumar S, Kjeldsen SE, Makani H, Grossman E, Wetterslev J, et al. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials. Lancet Oncol 2011;12:65–82.
[105] Powe DG, Voss MJ, Zanker KS, Habashy HO, Green AR, Ellis IO, et al. Beta-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. Oncotarget 2010;1:628–38.
[106] Barron TI, Connolly RM, Sharp L, Bennett K, Visvanathan K. Beta blockers and breast cancer mortality: a population-based study. J Clin Oncol 2011;29:2635–44.
[107] Melhem-Bertrandt A, Chavez-Macgregor M, Lei X, Brown EN, Lee RT, Meric-Bernstam F, et al. Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. J Clin Oncol 2011;29:2645–52.
[108] De Giorgi V, Grazzini M, Gandini S, Benemei S, Lotti T, Marchionni N, et al. Treatment with beta-blockers and reduced disease progression in patients with thick melanoma. Arch Intern Med 2011;171:779–81.
[109] Lemeshow S, Sorensen HT, Phillips G, Yang EV, Antonsen S, Riis AH, et al. beta-Blockers and survival among Danish patients with malignant melanoma: a population-based cohort study. Cancer Epidemiol Biomarkers Prev 2011;20:2273–9.
[110] Shah SM, Carey IM, Owen CG, Harris T, Dewilde S, Cook DG. Does beta-adrenoceptor blocker therapy improve cancer survival? Findings from a population-based retrospective cohort study. Br J Clin Pharmacol 2011;72:157–61.
[111] Powe DG, Entschladen F. Targeted therapies: using beta-blockers to inhibit breast cancer progression. Nat Rev Clin Oncol 2011;8:511–2.
[112] Ganz PA, Cole SW. Expanding our therapeutic options: beta blockers for breast cancer. J Clin Oncol 2011;29:2612–6.
[113] Al-Wadei HA, Al-Wadei MH, Ullah MF, Schuller HM. Celecoxib and GABA cooperatively prevent the progression of pancreatic cancer in vitro and in xenograft models of stress-free and stress-exposed mice. PLoS ONE 2012;7:e43376.
[114] Masur K, Niggemann B, Zanker KS, Entschladen F. Norepinephrine-induced migration of SW 480 colon carcinoma cells is inhibited by beta-blockers. Cancer Res 2001;61:2866–9.
[115] Shin VY, Wu WK, Chu KM, Koo MW, Wong HP, Lam EK, et al. Functional role of beta-adrenergic receptors in the mitogenic action of nicotine on gastric cancer cells. Toxicol Sci 2007;96:21–9.
[116] Park PG, Merryman J, Orloff M, Schuller HM. Beta-adrenergic mitogenic signal transduction in peripheral lung adenocarcinoma: implications for individuals with preexisting chronic lung disease. Cancer Res 1995;55:3504–8.
[117] Ji Y, Chen S, Li K, Xiao X, Zheng S, Xu T. The role of beta-adrenergic receptor signaling in the proliferation of hemangioma-derived endothelial cells. Cell Div 2013;8:1.