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# Sympathetic nervous system regulation of the tumour microenvironment

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## Abstract

The peripheral autonomic nervous system (ANS) is known to regulate gene expression in primary tumours and their surrounding microenvironment. Activation of the sympathetic division of the ANS in particular modulates gene expression programs that promote metastasis of solid tumours by stimulating macrophage infiltration, inflammation, angiogenesis, epithelial-mesenchymal transition, and tumour invasion, and by inhibiting cellular immune responses and programmed cell death. Haematological cancers are modulated by sympathetic nervous system (SNS) regulation of stem cell biology and hematopoietic differentiation programs. In addition to identifying a molecular basis for physiologic stress effects on cancer, these findings have also identified new pharmacologic strategies to inhibit cancer progression *in vivo*.

## Introduction

The sympathetic nervous system (SNS) regulates the function of virtually all human organ systems via localized release of catecholamine neurotransmitters from sympathetic nerve terminals and via systemic circulation of catecholamines from the adrenal gland (Box 1) [1–3]. Physiologists have long focused on the effects of acute ‘fight-or-flight’ stress spikes in SNS activity that transiently enhance bodily strength, mobility, perceptual acuity, and tissue defense at the expense of long-term trophic activities such as digestion, reproduction, growth, and exploration [1–3]. However, long-term variations in basal levels and circadian cycles of SNS activity can also exert more enduring regulatory effects by altering constitutive gene expression profiles in a wide variety of tissues and organ systems [4–11].

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These SNS-modulated transcriptional dynamics stem from evolutionarily conserved molecular mobility and defense programs (MMDPs) that adapt a broad range of cellular functions to detect and respond more effectively to challenging, threatening, or novel environments (e.g., mobilizing energy and promoting mobility, strength, perceptual acuity, antimicrobial defenses, and wound healing) [3,10–12]. In the past decade, it has become apparent that many MMDPs also promote tumour progression and metastasis (reviewed in [11,13–16]). More recent pharmaco-epidemiologic studies have linked β-adrenergic antagonists to reduced progression of incident tumours [14,17], implying that SNS signaling may potentially exert clinically significant effects on tumour biology. This Opinion article surveys some of the key physiological pathways and molecular dynamics involved in SNS regulation of tumour progression, highlights some of the ensuing translational therapeutic opportunities, and outlines critical issues for future research.

**Box 1**

### Sympathetic nervous system signaling

The sympathetic nervous system (SNS) regulates gene expression and cellular function in the nervous, endocrine, cardiovascular, gastrointestinal, respiratory, reproductive, and immune systems by releasing 2 catecholamine neuroeffector molecules:

**Norepinephrine** is released from SNS nerve fibers that traverse the body to directly innervate target tissues.

**Epinephrine** is released from the adrenal gland and circulates via blood to target tissues. These adrenergic effector molecules regulate cellular function via 5 adrenergic receptor types that are differentially expressed across target tissues and couple to distinct G protein-mediated signal transduction pathways:

**$\alpha_1$ adrenergic receptors** are expressed mainly in smooth muscles and signal through $G_{\alpha q}$ induction of phospholipase C to activate calcium flux and protein kinase C (PKC).

**$\alpha_2$ adrenergic receptors** are expressed on smooth muscles and platelets, as well as on neurons where they function as autoreceptors to inhibit norepinephrine release. $\alpha_2$ receptors signal through $G_{\alpha i}$ inhibition of cyclic 3′-5′ adenosine monophosphate (cAMP) activity, which in turn down-regulates the serine-threonine protein kinase A (PKA), the guanine exchange protein activated by adenylyl cyclase (EPAC), and β-arrestin-mediated activation of mitogen-activated protein kinases (MAPK).

**$\beta_1$ adrenergic receptors** enhance cardiac output, mediate neural signaling, and mobilize energy from adipose tissue. They signal through $G_{\alpha s}$-mediated activation of cAMP, which stimulates PKA, EPAC, and MAPK signaling.

**$\beta_2$ adrenergic receptors** are expressed on smooth muscles of the heart and lung, where they mediate vasodilation, on immune cells, where they mediate cell trafficking and effector activities, and on many tumor cells of epithelial and lymphoid origin. They signal through $G_{\alpha s}$/cAMP stimulation of PKA, EPAC and MAPK.

**$\beta_3$ adrenergic receptors** are predominately expressed in adipose tissue, where they mobilize energy by signaling through $G_{\alpha s}$/cAMP stimulation of PKA, EPAC and MAPK.

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Each adrenergic pathway stimulates transcription of distinct molecular mobility and defense programs(MMDPs) in characteristic target cells via post-translational activation of transcription factors such as the cAMP response element-binding protein (CREB).

## SNS regulation of gene expression

The SNS regulates systemic physiology via two general signaling pathways: one involving direct innervation of target organs throughout the body by SNS nerve fibers that release the sympathetic neurotransmitter norepinephrine, and a second one involving hormonal regulation of organ systems via vascular distribution of epinephrine released from the adrenal gland [1–3,11](Box 1 and Figure 1).

### Acute SNS activation

Perceptions of acute threat mediated by the central nervous system (CNS) can activate the splanchnic nerves — which stimulate rapid release of pre-synthesized epinephrine (and smaller amounts of norepinephrine) from chromaffin cells of the adrenal medulla [1–3]. Epinephrine levels in plasma can spike by >10-fold during acute fight-or-flight stress responses, leading to rapid physiological changes in cardiovascular, respiratory, muscular, metabolic, neural, immune, and other functions that typically return to baseline within 20–60 minutes following the abatement of perceived threat [1,2,18]. These rapid physiological alterations generally involve post-translational modifications of protein function that are mediated by activation of two broad classes of adrenergic receptors, α and β, each of which contains multiple receptor subtypes that are differentially distributed across tissue sites and linked to distinct signal transduction pathways to induce distinct molecular effects [1–3] (Box 1). For example, acute fight-or-flight responses increase heart rate and beat strength by activating $\beta_1$-adrenergic receptors in the heart muscle, redistribute blood from superficial tissues to long muscles by activating vascular $\alpha_1$- and $\beta_2$-adrenergic receptors, increase respiratory rate and depth by activating bronchial $\alpha_1$-and $\beta_2$-adrenergic receptors, mobilize energy by activating $\beta_2$- and $\beta_3$-adrenergic receptors in adipose tissue and the liver, and mobilize leukocytes (especially natural killer (NK) cells) into circulation by activating $\beta_2$-adrenergic receptors on leukocytes [1–3].

Activation of sympathetic nerve fibers that directly innervate most of the body's organ systems also has a significant role in acute fight-or-flight stress reactions. This occurs through direct regulation of organ function by μmolar concentrations of norepinephrine released from sympathetic nerve terminals, and by circulation of norepinephrine that spills over from sympathetic innervation of smooth muscles surrounding blood vessels (the primary source of norepinephrine in plasma) [1–3] (Figure 1).

### Circadian and chronic changes in SNS activity

In addition to the acute fight-or-flight dynamics that are mediated via rapid post-translational modification of protein function, variations in chronic SNS activity can also modulate gene expression and cellular structure [8,11]. Many of these effects are mediated by transcriptional activation of MMDPs that evolved to prepare the body to respond to physical demands, cognitive challenges, and wounding injury [1–3,9,10,12]. Unlike other stress-activated neuro-

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endocrine systems such as the hypothalamus-pituitary-adrenal axis, the SNS is easily activated by the mere anticipation of threat [1,18]. For example, first-time parachute jumpers show peak plasma levels of epinephrine, norepinephrine, and target organ cardiovascular responses before they actually commence their first fall (that is, in response to anticipation of the fall, rather than the fall itself) [18]. Anticipatory SNS responses can often occur at thresholds below those consciously experienced as fear, stress, or injury. Moreover, unlike the hypothalamus-pituitary-adrenal axis, SNS stress responses do not decay over time with repeated threat exposure [1,19]. Chronic or repetitive low-grade SNS activation up-regulates norepinephrine levels more strongly than hormonal epinephrine levels (e.g., in post-traumatic stress disorder [20]), and is commonly observed in people who are chronically exposed to adverse social environments (e.g., poverty, isolation, combat, and demanding or uncontrollable jobs) [1]. Experimental studies in animal models have shown that chronic social stress can also increase the growth and branching of sympathetic nerve fibers in peripheral tissues (neo-innervation), and thereby up-regulate basal activity of target tissue adrenergic receptors and downstream MMDPs [5,21].

Low-grade SNS neural activation (and to a lesser extent, adrenal epinephrine responses) also occurs in response to many ‘non-threat’ homeostatic challenges such as temperature change, general bodily movement, sleep disturbance, physical exertion, speaking, and intense concentration or vigilance[1,3,22–24]. These activity-related dynamics induce a substantial circadian rhythm in SNS activity, which peaks during waking hours and reaches a nadir during periods of extended rest or sleep [8,22,23,25]. Like chronic low-grade SNS activation, circadian variations in SNS activity exert many of their effects via adrenergic receptor-mediated modulation of gene transcription in target tissues [8,25].

Chronic and circadian variations in SNS activity have recently been found to play a major part in regulating constitutive gene expression in a wide range of SNS target tissues. Many of the activated MMDPs involve suppression of long-term growth and maintenance processes and up-regulation of molecular programs that facilitate physical mobility (such as cardiac output, respiration, and glucose mobilization), mental acuity (such as CNS perceptual and mnemonic processes), and response to wounding injuries (such as shock and acute phase responses, inflammation, and wound healing) [1,2]. In the immune system, for example, tonic SNS activity mobilizes hematopoietic stem cells out of their bone marrow niches and into circulation, where they subsequently transit to peripheral tissues such as the spleen (to facilitate extramedullary hematopoiesis) or sites of injury (to facilitate inflammation and localized tissue remodeling) [4,8,11,25,26]. Within the bone marrow hematopoietic environment, SNS signaling transcriptionally stimulates the development of monocytes, granulocytes, and other myeloid lineage immune cells at the expense of lymphoid and erythroid lineages, resulting in a pro-inflammatory shift in the overall immunoregulatory set-point of the circulating leukocyte pool [7,27]. SNS innervation of secondary lymphoid tissues — such as the spleen and lymph nodes — also modulates the evolution of peripheral immune responses, for example by down-regulating lymphocyte trafficking to tissues [28], by inhibiting transcription of Type I (α and β) and Type II (γ) interferons, and by stimulating transcription of cytokines expressed in type 2 T helper cells (Th2) and Th17 cells, all of which act to impair innate anti-viral responses and promote humoral immune responses at the expense of cellular immunity [5,12,29–31]. Adrenergic

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signaling also acts on innate immune cells such as monocytes, macrophages, and NK cells to stimulate transcription of pro-inflammatory cytokines (such as interleukin 1 β (*IL1B*), *IL6*, *IL8*, and tumor necrosis factor (*TNF*)), chemokines (such as chemokine (C-C motif) ligand 2 (*CCL2*, also known as MCP-1), *CCL4*, and *CXCL2* (also known as *MIP1* and *MIP2*, respectively)), and prostaglandin synthesis enzymes such as *PTGS2* (also known as *COX2*) [7,12,30,32]. SNS signaling can also modulate wound-healing in epithelial tissues by stimulating molecular programs underlying epithelial-mesenchymal transition (EMT) (S. Cole, S. Lutgendorf, and A. Sood, unpublished observations), fibroblast activation [33,34], and angiogenesis [34–36]. Throughout most of human evolution, SNS-mediated transcriptional activation of MMDPs presumably allowed the body's comparatively slow molecular response systems to adapt to and perhaps even anticipate the changing physiological demands associated with changing environmental conditions such as increased risk of injury and need for mobility in novel or threatening circumstances [37]. SNS activation of MMDPs by anticipated threat may have been particularly adaptive in allowing molecular remodeling processes to initiate in advance of acute injury rather than reacting only after the fact (a key element in allostatic theories of physiology, which argue that natural selection favors physiological systems that anticipatorily adapt to homeostatic challenges rather than responding to them post hoc [37]). Although SNS-mediated MMDP transcriptional activation might have been an evolutionarily adaptive response to threatening environments under ancestral conditions, it has also enabled the very different conditions of modern life to chronically stimulate biological stress responses [2,37] that inadvertently facilitate the development and progression of cancer.

## SNS regulation of cancer biology

Analyses of SNS effects on cancer biology were initially motivated by clinical observations that suggested a potential link between stress and cancer progression [13,15,38], and were more recently spurred by pharmaco-epidemiologic data that showed reduced disease progression in cancer patients who were incidentally exposed to β-adrenergic antagonists (β-blockers) prior to diagnosis [39–48]. Experimental analyses in *in vivo* animal models have now shown that behavioral stress can accelerate the progression of breast, prostate, and ovarian carcinomas [35,49–52], neuroblastomas [53,54], malignant melanomas [55,56], pancreatic carcinoma [24,57], and some haematopoietic cancers such as leukaemia [58,59]. In many of these experimental models, the biological effects of stress could be efficiently blocked by β-adrenergic antagonists and mimicked by pharmacologic β-agonists [14]. Mechanistic analyses of tumor progression have also identified a diverse array of cellular and molecular processes that can mediate SNS effects on tumour progression (Figure 2). These include DNA repair, oncogene activation, inflammation and immune response, haematopoiesis, angiogenesis, survival and apoptosis and haematopoiesis.

### DNA repair

β-adrenergic signaling can inhibit DNA damage repair [60–62] and p53-associated apoptosis [54], raising the possibility that SNS activity might potentially contribute to tumour initiation or chromosomal instability. Several molecular pathways have been implicated in β-adrenergic inhibition of DNA damage repair, including activation of the ataxia-telangiectasia

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and Rad3-related (ATR)/p21 pathway[62] and β-arrestin-induced activation of the AKT signaling pathway, which stimulates the E3 ubiquitin ligase murine double minute 2 (MDM2) to degrade p53 protein and thereby inhibit p53-mediated responses to chromosomal damage [60]. These effects are sufficient to increase the prevalence of spontaneous chromosomal aberrations in tissues such as the thymus and brain, and such effects can be efficiently blocked by the β-adrenergic antagonist propranolol [60,61]. Similar effects are observed in neuroblastoma cells, in which propranolol up-regulates p53 levels, promotesapoptosis, and sensitizes tumour cells to the effects of the topoisomerase inhibitor SN-38 [54]. However, it is not yet clear whether β-adrenergic inhibition of DNA damage repair is sufficient to increase the rate of spontaneous tumour initiation *in vivo*.

## Oncogene activation

β-adrenergic signaling can stimulate several oncogenic signaling pathways including Src [63] and HER2 (encoded by the *ERBB2* gene) [64,65]. In the case of HER2, catecholamine activation of β-adrenergic receptors activates signal transducer and activator of transcription 3 (STAT3), which subsequently activates the *ERBB2* promoter to stimulate gene transcription [64]. In the case of SRC, β-adrenergic signaling stimulates protein kinase A (PKA) to phosphorylate SRC on residue Y419, resulting in SRC-mediated activation of a complex phosphoproteomic network that stimulates tumour growth, migration, and invasion *in vivo* [63]. In addition to these effects on cellular oncogenes, β-adrenergic signaling can also activate a diverse array of oncogenic viruses [13]. As one example, catecholamine induction of β-adrenergic signaling on B lymphoid cells triggers PKA-mediated activation of the cellular transcription factor cyclic 3′-5′ adenosine monophosphate response element binding protein (CREB), which in turn activates a key viral promoter in the episomal Kaposi's Sarcoma-associated Human Herpesvirus 8 (HHV-8) genome [66]. As a result, the viral genome up-regulates expression of the viral transcription factor Rta, which serves as a master regulator of HHV-8 gene expression and stimulates transcription of a diverse array of viral oncogenes and dissemination of the viral genome [66]. HHV-8 contributes to several types of B cell malignancy in addition to Kaposi's Sarcoma of vascular endothelial cells [67], providing a virally mediated pathway by which SNS activation can contribute to human cancer.

## Inflammation and immune response

β-adrenergic signaling also stimulates the transcription of pro-inflammatory cytokines such as IL-6 and IL-8 by tumour cells [32,68–70] by myeloid lineage immune cells in the tumour microenvironment [32,49]. Adrenergic stimulation of inflammatory arachidonic acid metabolism can also promote tumour growth [71]. Several *in vivo* studies have shown that SNS stimulation of inflammatory signaling can enhance tumour progression and metastasis [49,72]. However, no studies have yet determined whether SNS effects on inflammation are sufficient to increase rates of tumour initiation.

Macrophages play a key part in mediating inflammation, modulating the tumour microenvironment, and promoting metastasis. β-adrenergic signaling can markedly enhance macrophage recruitment into the tumour parenchyma by stimulating tumour cells' production of chemotactic factors such as macrophage colony stimulating factor (CSF1, also known as M-CSF) and MCP-1 [49,72]. β-adrenergic signaling may also enhance the density of

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tumour-associated macrophages by stimulating myelopoietic development of precursor monocytes in the bone marrow [7,27] and spleen [26], which can then be recruited into the tumour microenvironment (Figure 1). Within the tumour microenvironment, β-adrenergic signaling also stimulates macrophage expression of gene programs that promote tumour progression, including transforming growth factor β (*TGFB*), vascular endothelial growth factor (*VEGF*), IL-6, matrix metalloproteinase 9 (*MMP9*), and *PTGS2*. β-adrenergic regulation of macrophage biology has a major role in SNS-induced metastasis as pharmacologic inhibition of CSF1 or MCP-1 signaling can abrogate stress effects on metastasis *in vivo* [49,72].

In contrast to its stimulatory effects on inflammation and macrophage biology, SNS signaling can profoundly inhibit the transcription of the Type I and Type II interferons [49,73,74] that play critical parts in generating cell-mediated immune responses against cancers and tumour-associated viruses. β-adrenergic signaling can also suppress the cytotoxic function of T lymphocytes and NK cells [59], and these effects contribute to the increased cancer cell dissemination observed during surgery [56,75,76]. However, several lines of research in severe combined immunodeficiency disease (SCID) and nude mice have found that the SNS can promote tumour metastasis even in the absence of NK and cytotoxic T cells [35,49,52,77]. As such, neural modulation of cellular immune responses may contribute to SNS influences on tumour progression in some contexts, but it is not an essential mediator of stress effects on cancer progression *in vivo*.

## Mesenchymal activation and EMT

Adrenergic signaling can activate a wide range of mesenchymal cell types present in tumour stroma (such asfibroblasts, pericytes, and mesenchymal stem cells) [33,34,36,78,79], as well as adipocytes [80,81] and bone marrow mesenchymal cells that can indirectly regulate cancer biology by altering haematopoiesis of tumour-infiltrating immune cells or modulating the cancer stem cell niche (Figure 2) [11,82]. Emerging data suggest that β-adrenergic activation of SNAIL family of transcription factors may also promote the expression of mesenchymal gene expression programs in epithelial tumors, promoting EMT, (S. Cole, S. Lutgendorf, and A. Sood, unpublished observations), and thereby modulate pro-metastatic processes such as tumour cell motility [51,63,83,84] and matrix metalloproteinase-mediated invasion of basement membrane [63,85–87]. Research is still defining the molecular mediators involved in EMT dynamics and defining their contribution to SNS effects on metastasis *in vivo*.

## Angiogenesis

β-adrenergic signaling stimulates the expression of angiogenic growth factors such as VEGF and IL-6 [34,35,68,87–91], which catalyze the development of vasculature to support tumour growth and metastasis. Studies using pharmacologic and genetic inhibitors of angiogenesis have confirmed that that SNS-induced up-regulation of angiogenesis mediates stress effects on tumour growth and metastasis *in vivo* [35].

## Survival and programmed cell death

β-adrenergic signaling can modulate a wide variety of growth and survival pathways, including inhibition of anoikis (programmed cell death induced by anchorage-dependent

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cells detaching from the surrounding extracellular matrix) mediated by focal adhesion kinase (FAK, also known as *PTK2*) [92], inhibition of apoptotic responses to chemotherapy mediated by the BCL2-associated agonist of cell death (*BAD*) and p53 pathways [52–54,93]. β-adrenergic signaling can also modulate the expression of growth and survival factors —such as VEGF, IL-6, and IL-8 — that are associated with resistance to tyrosine kinase inhibitors [91,94]. Several of these studies have documented consequent impacts on tumour growth and metastasis *in vivo*, showing that inhibition of programmed cell death represents a bona fide mediator of SNS effects on cancer progression.

## Haematopoiesis

β-adrenergic signaling can promote the growth and dissemination of acute lymphocytic leukaemias *in vivo* [58,59], likely via some of the same molecular pathways through which the SNS regulates physiological hematopoiesis [4,7,11,25–27,95]. Sympathetic innervation of the bone marrow also helps maintain normal stromal cell populations, and may facilitate immunologic recovery following haematopoietic stem cell transplant [11,96]. However, SNS regulation of the bone marrow hematopoietic environment is complex and can have unpredictable effects that depend greatly on the specific biological interactions between tumour cell biology and the bone marrow microenvironment [11]. In a model of acute myelogenous leukemia (AML), for example, β-adrenergic antagonists unexpectedly accelerated disease by disrupting the haematopoietic stem cell niche in ways that favoured leukemia stem cell growth [11,82]. AML colonization of the marrow itself produced similar effects by degrading sympathetic innervation and consequently stimulating leukaemia stem cell growth [11,82]. Beyond the context of leukaemia, little is known about potential SNS influences on lymphomas and other haematological malignancies.

In summary, a growing body of experimental research has identified specific cellular and molecular mechanisms through which SNS activation can accelerate the progression of diverse tumor types. The general pattern of effects (and non-effects) observed in the experimental literature is broadly consistent with the pattern of relationships observed in epidemiologic studies of stress and cancer [13,38], and pharmacologic β-blockers and cancer [14,17]: SNS activation exerts its most pronounced effects in the early stages of tumour progression as primary tumours interact with the surrounding microenvironment to initiate dissemination and colonization of distant tissues. There is so far little *in vivo* evidence that SNS activation has a significant role in the earlier stage of tumour initiation or that it can significantly affect the subsequent course of already disseminated metastatic disease. However, the experimental literature provides some occasional exceptions to this general pattern. One line of research has shown a paradoxical protective effect of SNS activation in which β-adrenergic signaling altered white adipose tissue production of circulating adipokines such as leptin, which subsequently inhibited the growth of leptin-dependent distant tumors [80,81]. Another found a protective effect of β-adrenergic signaling on AML progression stemming from SNS maintenance of the bone marrow hematopoietic niche [11,82]. However, the vast majority of the extant experimental literature indicates that SNS activity generally promotes tumour progression through a pleiotropic array of molecular alterations in the primary tumour microenvironment. This opens up basic questions about the

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physiological pathways though which the SNS communicates with the tumor microenvironment.

## SNS signaling to the tumour microenvironment

The SNS is a network of distinct neural signaling pathways that share some degree of common regulation by the CNS, but are also subject to independent regulatory input from the target tissues they innervate and from distinct regions of the brain [81]. For example, the brain structures that regulate gene expression in adipose tissue are different from those that mediate fight-or-flight control of the cardiovascular system or adrenal medulla [81]. SNS innervation of some target tissues — such as the adrenal gland and white adipose tissue — can also stimulate the release of hormones, such as epinephrine or leptin, which are biochemically distinct from the primary norepinephrine signal released by SNS neurons and can circulate more diffusely throughout the body [81]. Many SNS nerve fibers also release small amounts of other signaling molecules in tandem with norepinephrine, such as the SNS "co-transmitter" neuropeptide Y [1]. Given the diverse array of physiologic mediator pathways that could potentially regulate tumour biology, research begun to map several of the general "nervous system-side" pathways for SNS regulation of tumor progression:

### Hormonal catecholamines

Blood supply and tissue perfusion are essential for tumor growth and progression, and also provide a channel through which SNS catecholamines can access tumor tissue [6,97]. However, clinical studies have so far failed to identify any substantial association between catecholamine levels in plasma and differential gene expression in tumours (even when tumour gene expression profiles are clearly associated with psychological risk factors such as depressive symptoms and low social support [6]). It also remains unclear how readily circulating epinephrine or norepinephrine might penetrate into the parenchyma of solid tumours to exert regulatory effects. Blood-based circulation of catecholamines has played a central role in physiologic conceptions of the fight-or-flight response, but this signaling pathway does not so far seem to constitute a major proximal pathway by which the SNS modulates tumour biology.

### Tumour innervation

Although long overlooked by pathologists, many solid tumors receive direct innervation from the SNS. The most common pattern involves sympathetic nerve fibers that enter the tumour in association with the vasculature and occasionally radiate fibers into the tumour parenchyma [11,32,77,98]. SNS fibers may also infiltrate into the outer perimeter of a growing tumour mass from surrounding healthy tissue [77,98], possibly in response to tumour cell expression of neurotrophic factors [11]. Some experimental data suggest that tumours can actively promote the growth and branching of nerve fibers and may even stimulate development of new neurons (neurogenesis) via the expression of neurotrophic factors such as NGF, BDNF, semaphorins, netrins, and slit molecules [11,98,99] (A. Sood, unpublished observations). SNS activation may also reciprocally attract tumour cells to neural fibers by up-regulating expression of trophic factors and chemokines such as CXCL12[11,98–101]. Local sympathetic innervation seems to supply much of the catecholamine content within tumour

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tissues because intra-tumor norepinephrine levels are generally higher than (and largely uncorrelated with) blood levels of norepinephrine or epinephrine [6,97]. Haematological cancers are also subject to regulation by SNS nerve fibers that innervate the bone marrow hematopoietic niche and all other primary and secondary lymphoid organs. Sympathetic innervation of lymphoid tissues and the vasculature regulates cell trafficking and gene expression profiles in both developing progenitor cells and mature leukocytes [4,7,25,26,27 lHanoun, 2015 #2226,95].

### Indirect hormonal and cellular regulation

SNS activation can also modulate tumour biology via indirect pathways in which SNS innervation of distant tissues triggers secondary hormonal or cellular effects that subsequently affect the tumour microenvironment. For example, SNS signaling to white adipose tissue can suppress circulating leptin levels and thereby inhibit the growth of leptin-sensitive tumours [80,81]. SNS innervation of bone marrow can also stimulate the production of monocytes, neutrophils, and other myeloid lineage immune cells [7,26], which may then transit to the tumour microenvironment and promote metastasis [49] (Figure 1). Activated macrophages can also synthesize catecholamines under some circumstances [102] and may thus provide a local non-neuronal source of adrenergic signaling within the tumour microenvironment. SNS innervation may also modulate the bone marrow microenvironment to make it a more receptive niche for metastatic colonization [103] or tumour cell growth and dissemination [11,82].

## Therapeutic implications

Given the multiple physiologic pathways by which SNS signaling can reach the tumour microenvironment and its pleiotropic effects on tumour biology, pharmacologic antagonism of β-adrenergic signaling might represent a highly leveraged therapeutic opportunity with the potential to favorably impact a wide range of tumor, microenvironmental, and systemic mechanisms of cancer progression. Consistent with that concept, several observational epidemiologic studies have documented associations between β-blocker exposure and reduced progression of prostate [47,48,104], breast [39–41,45], lung [44,105], and ovarian cancer [106,107], as well as malignant melanoma [42,43,46]. However, the epidemiological literature is also inconsistent, and some studies fail to find any evidence of a protective effect (likely due to methodological variations considered below). In experimental animal models of human cancer, β-antagonists can inhibit the progression of prostate [51,52], breast [49,50,103], ovarian [35], lung [108,109], pancreatic [24,57], and colon cancer [110], neuroblastomas [53,54], and leukaemia [58,59]. β-blockade can also inhibit systemic SNS influences on cancer progression such as haematopoietic production of pro-metastatic monocytes [7,27,49] and bone marrow receptivity to metastatic colonization [11,103]. β-blockers seem to provide a viable pharmacologic strategy for simultaneously inhibiting many of the pathways through which the SNS can stimulate tumour progression [14].

Despite the availability of safe, approved, and inexpensive β-antagonists, several practical issues will need to be resolved in order to advance the concept of clinically applying β-blockade in cancer therapy. These issues include the selection of optimal pharmacologic agents (for example, non-selective antagonists that block $\beta_2$ receptors — such as propranolol

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— are likely to be more effective than the $\beta_1$-selective agents more commonly used in cardiology)[14,35,40,53,54,107,111]; optimal disease settings (e.g., for reasons that are not yet understood mechanistically, some pharmaco-epidemiologic studies have found that β-antagonists are associated with greater protective effects on triple negative breast tumours than on tumours that express oestrogen receptor (ER), progesterone receptor (PR), or HER2[41,45]), and optimal intervention timing and duration. For example, experimental models suggest that initiating β-antagonists prior to surgery may reduce SNS-mediated promotion of peri-surgical metastasis [112,113]. The general pattern of pre-clinical evidence summarized above also implies that β-blockade may have the greatest impact on early stage tumours in which metastatic capacity is physiologically modifiable, and may have much more limited therapeutic impact in the setting of highly disseminated disease.

Beyond general considerations of disease stage, some molecular analyses suggest that it might also be possible to target individual tumours for adjuvant β-blockade based on SNS-related gene expression profiles [6,16,49]. High expression of adrenergic receptors on tumor cells has not substantially predicted tumor responsiveness to β-antagonists *in vivo* [54,114], perhaps because SNS effects on tumour progression can also be mediated by adrenergic receptors on other cells in the surrounding microenvironment, systemic vasculature, and bone marrow haematopoietic and metastatic target tissues. Given the diversity of molecular pathways through which SNS activity might modulate tumour progression, the precise molecular indicators for adjuvant β-blockade will likely need to be empirically defined. However, there are grounds for expecting that the search for such transcriptomic fingerprints of SNS activity might be successful in both emerging patterns of stress- and SNS-related gene expression in tumours [16] and similar precedents in other cell types (e.g., the conserved transcriptional response to adversity observed in circulating immune cells [10,16]).

These empirical considerations underscore the need for randomized controlled, biomarker-enriched trials to assess initial proof-of-concept evidence that β-blockade can causally influence aspects of tumour biology that are relevant to disease progression. Further observational studies cannot definitively establish a clinical utility for β-blockers in cancer owing to a variety of methodological limitations including: confounding by indication (e.g., the primary historical indication for β-blockers, cardiovascular disease, shares common pathophysiologic drivers with cancer progression such as smoking, adiposity, and systemic inflammation); confounding with other pharmacologic exposures that can affect cancer progression (e.g., angiotensin-converting enzyme inhibitors); poor ascertainment (e.g., archival cardiovascular studies provide poor information on cancer progression and/or mortality, and archival cancer studies provide poor measures of β-blocker exposure); and temporal confounding of trends in cancer survival with trends in β-blocker utilization (particularly for the non-selective β-antagonists which are most likely to be efficacious). Randomized controlled studies will provide the only certain way to overcome these issues and definitively assess effects of β-antagonists on cancer-related outcomes. The availability of pre-clinical data and approved, safe, and inexpensive β-antagonists with well-understood pharmacology and minimal side-effects provide a favorable risk/benefit profile for initial proof-of-concept biomarker trials in clinical oncology.

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Some laboratory studies have implicated $\beta_3$- or α-adrenergic receptors in SNS effects on cancer, but the clinical significance of these effects remains to be determined. $\beta_3$-adrenergic receptors are expressed on several types of cancer and stromal cells, and pharmacologic antagonists have been found to inhibit melanoma growth and vascularization in vivo [34,36]. However, little is known about potential $\beta_3$-adrenergic effects in human cancer, and interpretation of pre-clinical laboratory studies is complicated by the poor specificity of $\beta_3$-adrenergic pharmacologic agents and the potential for non-selective β-antagonists such as propranolol to at least partly modulate $\beta_3$ receptors. $\beta_3$-adrenergic receptors also have a key role in SNS regulation of mesenchymal stromal cells in the bone marrow hematopoietic niche [8,11,115,116], suggesting potential applications in hematopoietic cell transplantation and anti-tumor immunity. Biological effects of α-adrenergic agents in laboratory models of cancer have been complex and inconsistent [117,118]. However, human epidemiologic studies have not generally indicated any notable effect of α-adrenergic antagonists on cancer risk or progression (some evidence suggests they may actually weakly promote some cancers) [119] and β-adrenergic inhibition has generally been sufficient to block physiological stress effects on cancer in in vivo models (which would not happen if α-adrenergic receptors played a major role). Indeed, some 'α-adrenergic effects' may actually be mediated by downstream stimulation of β-adrenergic signaling that results from blockade of $\alpha_2$-adrenergic autoreceptors [118]. As such, the prospects for α-adrenergic agents in clinical cancer management are more ambiguous than those of β-adrenergic antagonists.

## Perspective

Over the past decade it has become evident that malignancy is structured in major ways by interactions between cancer cells and their local tissue microenvironment [120]. We are now beginning to appreciate how the broader physiological macroenvironment of the body can regulate these local tumour microenvironmental dynamics and thereby affect tumour progression and metastasis [13]. SNS regulation of MMDP gene expression programs in tumour cells and their stromal elements represents one of the most clearly defined pathways by which systemic physiology can regulate cancer biology [15,16]. However, a great deal more research will be required to translate these basic observations into effective therapeutic approaches.

Much remains to be discovered about the cellular and molecular pathways through which SNS activation influences cancer biology. We know little about what effect, if any, the SNS might have on tumor initiation, on the development and conditioning of the metastatic niche, or on responses to therapy. It also remains unclear how much therapeutic leverage might be available from pharmacologic inhibition of SNS activity. If the dominant effect of the SNS in cancer occurs early in progression with the initial development of metastatic potential, the window of opportunity for β-blockade may well have passed once occult tumors become clinically evident. Even so, β-blockade may still have significant clinical utility in disease settings in which tumours are detected relatively early in development and metastatic capacity depends highly on upon physiological conditions. This might be particularly relevant in diseases for which current medical therapies show little efficacy (such as triple-negative breast cancer). Moreover, recent studies showing treatment-sensitizing effects of β-blockade imply some potential for value even in late-stage disease [24,52–54,62,91,94,109,121,122].

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Much also remains to be clarified regarding regulation of tumour biology by the parasympathetic division of the autonomic nervous system. Recent studies suggest that parasympathetic innervation may contribute to tumour development and progression in certain tissue environments — such as the stomach and prostate gland [77,123] — via acetylcholine-mediated activation of muscarinic acetylcholine receptors. However, pharmacologic intervention in such effects may be complicated by the fact that parasympathetic activity generally antagonizes the effects of the SNS [1,3] and anti-cholinergic interventions may have the potential to indirectly stimulate SNS-mediated promotion of cancer. Moreover, the nicotinic acetylcholine receptors that mediate many parasympathetic effects on target tissues also serve as pre-synaptic neurotransmitters in the SNS [1,3], so the effects of some anti-cholinergic interventions may act through inhibition of SNS activity rather than (or in parallel with) inhibition of parasympathetic activity [124]. As such, pharmacologic antagonism of cholinergic receptor systems may have more complex and unpredictable effects on tumour progression than the more focal targeting of β-adrenergic receptors. However, the central role of the (surprisingly dispensable) vagus nerve in mediating parasympathetic effects on cancer suggests a novel alternative strategy of surgically denervating selected target organs [77,123,125].

The highly pleiotropic effects of SNS activity on tumour biology suggest that even if nervous system-targeted interventions have moderate effects on any single pathway, their integrated effect across many parallel pathways may nevertheless be clinically significant. In an era of highly targeted therapies for the molecular pathogenesis of tumor cell proliferation, an adjuvant therapeutic strategy such as β-blockade that harnesses multiple microenvironmental pathways could provide a highly synergistic approach for controlling cancer progression.

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## Biographies

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**Paige A. Green** is Chief, Basic Biobehavioral and Psychological Sciences Branch in the Behavioral Research Program, Division of Cancer Control and Population Sciences at the National Cancer Institute (NCI). She serves as Chair for the NCI Network on Biobehavioral Pathways in Cancer, a research consortium that strives to accelerate the discovery, development, and clinical translation of cancer relevant molecular pathways and networks regulated by social, behavioral, and psychological factors through the central nervous system.

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**Anil K. Sood** is Professor and Vice Chairman for Translational Research in the Department of Gynecologic Oncology and has a joint appointment in the Department of Cancer Biology at the University of Texas M.D. Anderson Cancer Center. He is also Co-Director of the Center for RNA Interference (RNAi) and Non-Coding RNA and Director of the Blanton-Davis Ovarian Cancer Research Program. His main research interests include neuroendocrine effects on cancer metastasis, RNAi therapeutics, and development of new strategies for targeting the tumour microenvironment.

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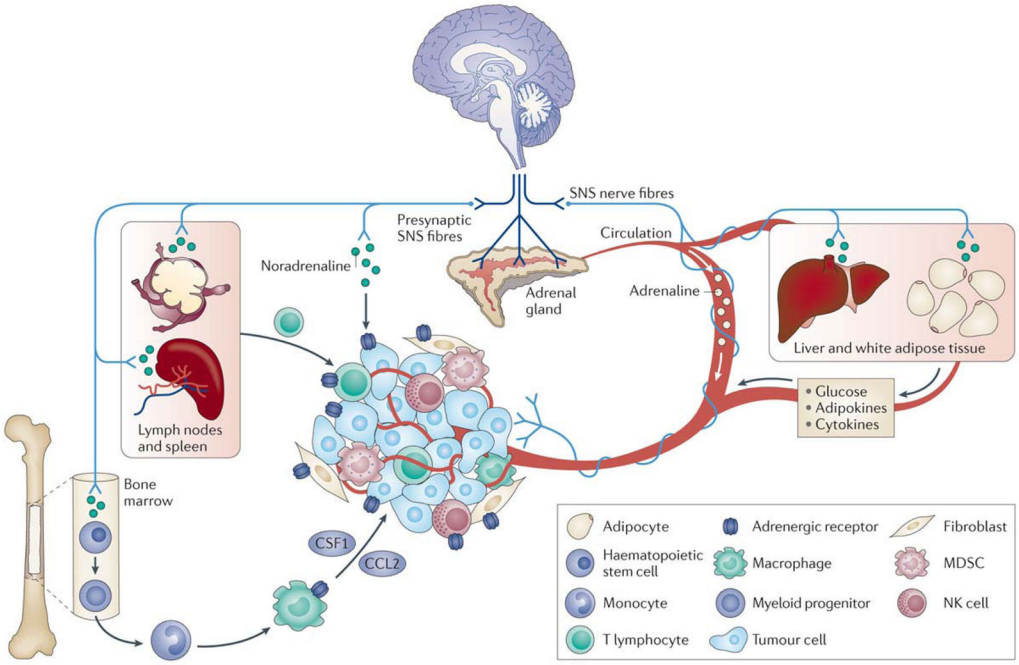


**Figure 1. SNS regulation of the tumour microenvironment**

SNS activation can regulate gene expression and cellular function in the tumour microenvironment through a variety of pathways. Direct SNS effects on tumour biology are mediated by catecholamine neuroeffector molecules (epinephrine and norepinephrine) that are released into the tumor microenvironment to engage adrenergic receptors that are expressed on many types of tumor cells and their surrounding stromal elements such as tumor-associated macrophages and vascular endothelial cells. Epinephrine is released from the adrenal gland and circulates to the tumour microevironment through the vasculature, whereas norepinephrine is released from sympathetic nerve fibers within the tumour microenvironment, which generally associate with the vasculature and can sometimes radiate dendritic fibers into the tumor parenchyma. Indirect effects on tumor biology are mediated by release of catecholamine neuroeffector molecules into distal tissue sites that regulate systemic biological processes which subsequently impinge on tumour biology, such as regulation of immune cell development (e.g., myelopoiesis in the bone marrow and spleen, and lymphocyte differentiation in secondary lymphoid organs such as the spleen and lymph nodes) and trafficking (e.g., monocyte/macrophage recruitment via chemokines such as MCP-1/*CCL2* and growth factors such as M-CSF/*CSF1*), or regulation of systemic metabolic and hormonal regulators of tumour growth (e.g., glucose mobilization from the liver and circulating adipokines from white adipose tissue). These multiple regulatory pathways allow the SNS to exert highly pleiotropic effects on tumour progression and metastasis of many solid epithelial tumors (e.g., breast, prostate, ovary, lung, pancreas) as well as hematologic malignancies via innervation of lymphoid organs such as the bone marrow, spleen, and lymph nodes.

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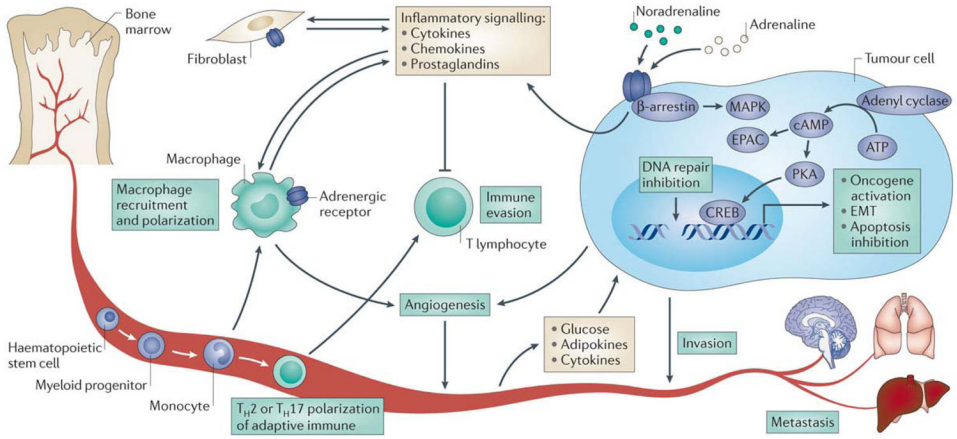


**Figure 2. Molecular mechanisms for SNS regulation of tumor progression**

SNS signaling through α- and β-adrenergic receptor systems can regulate a wide variety of molecular processes involved in tumour progression and metastasis, including DNA damage repair, signaling by cellular and viral oncogenes, expression of pro-inflammatory mediators (cytokines, chemokines, prostaglandins) by tumour cells and immune cells, recruitment and pro-metastatic transcriptional programming of macrophages, angiogenesis and lymphangiogenesis, epithelial-mesenchymal transition, tumor cell motility and invasive capacity, resistance to apoptosis and chemotherapy-mediated cell death, and inhibition of cytokines and cytotoxic function in adaptive immune responses. SNS activation also exerts immunoregulatory effects through innervation of the bone marrow hematopoietic niche to promote stem cell mobilization and development of myeloid lineage immune cells (monocytes and macrophages and myeloid-derived suppressor cells), through innervation of the spleen to influence extra-medullary myelopoiesis of monocytes, macrophages and myeloid-derived suppressor cells, and through innervation of other primary and secondary lymphoid organs to inhibit cellular immune responses and promote humoral immune responses. SNS activation additionally regulates a wide variety of systemic metabolic and hormonal processes that can impact tumour progression, including mobilization of glucose and fatty acids from the liver and adipokines and pro-inflammatory cytokines from white adipose tissue. Many of these molecular effects have been found to be regulated by β-adrenergic receptors (ADRB), which regulate cellular and viral gene expression via activation of multiple intracellular signal transduction pathways including cyclic-3′-5′-adenosine monophosphate (cAMP)-mediated activation of protein kinase A (PKA), which subsequently phosphorylates transcription factors such as cAMP response element-binding protein (CREB); cAMP-mediated activation of the guanine exchange protein activated by adenylyl cyclase (EPAC); and β-arrestin-mediated activation of MAP kinase signaling pathways. β-adrenergic-induction of multiple intracellular signaling pathways further amplifies the impact of the multiple parallel extracellular signaling pathways (Figure 1) to generate a highly pleiotropic network of molecular effects that generally stimulate tumor progression and metastasis.