OPINION

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 programmes 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 haematopoietic differentiation programmes. In addition to identifying a molecular basis for physiologic stress effects on cancer, these findings have also identified new pharmacological strategies to inhibit cancer progression *in vivo*.

The sympathetic nervous system (SNS) regulates the function of virtually all human organ systems by localized release of catecholamine neurotransmitters from sympathetic nerve terminals and by systemic circulation of catecholamines from the adrenal gland[1–3] (BOX 1). Physiologists have long focused on the effects of acute 'fight-or-flight' spikes in SNS activity in response to stress that transiently enhance bodily strength, mobility, perceptual acuity and tissue defence 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 on gene expression by altering constitutive gene expression profiles in a wide variety of tissues and organ systems[4–11]. These SNS-modulated transcriptional dynamics stem from evolutionarily conserved molecular mobility and defence programmes (MMDPs) that adapt a broad range of cellular functions to detect and respond more effectively to challenging, threatening, or novel environments (for example, mobilizing energy and promoting mobility, strength, perceptual acuity, antimicrobial defences 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 REFS 11,13–16). More recent pharmaco-epidemiological studies have linked β-adrenergic antagonists to reduced progression of incident tumours[14,17], implying that SNS signalling 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.

SNS regulation of gene expression

The SNS regulates systemic physiology by two general signalling pathways: one involving direct innervation of target organs throughout the body by SNS nerve fibres that release the sympathetic neurotransmitter noradrenaline, and a second one involving hormonal regulation of organ systems via vascular distribution of adrenaline released from the adrenal gland[1–3,11] (BOX 1; FIG. 1).

Acute SNS activation. Perceptions of acute threat mediated by the central nervous system (CNS) can activate the sympathetic nerves, which stimulate rapid release of pre-synthesized adrenaline (and smaller amounts of noradrenaline) from chromaffin cells of the adrenal medulla[1–3]. Adrenaline levels in plasma can spike by >tenfold 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; these modifications are mediated by activation of two broad classes of adrenergic receptors, α-adrenergic receptor and β-adrenergic receptor, 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 β1-adrenergic receptors in the heart muscle, redistribute blood from superficial tissues to long muscles by activating vascular α1- and β2-adrenergic receptors, increase respiratory rate and depth by activating bronchial α1- and β2-adrenergic receptors, mobilize energy by activating β2- and β3-adrenergic receptors in adipose tissue and the liver, and mobilize leukocytes (especially natural killer (NK) cells) into circulation by activating β2-adrenergic receptors on leukocytes[1–3].

Activation of sympathetic nerve fibres that directly innervate most of the body's organ systems also has a notable role in acute fight-or-flight stress reactions. This occurs through direct regulation of organ function by micromolar concentrations of noradrenaline that is released from sympathetic nerve terminals, and by circulation of noradrenaline that spills over from sympathetic innervation of smooth muscles surrounding blood vessels (the primary source of noradrenaline in plasma)[1–3] (FIG. 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-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 adrenaline, noradrenaline 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 even in situations that people do not experience consciously such 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 upregulates noradrenaline levels more strongly than hormonal adrenaline levels (for example, in post-traumatic stress disorder[20]), and it is commonly observed in people who are chronically exposed to adverse social environments (for example, 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 fibres in peripheral tissues (neo-innervation), and thereby upregulate basal activity of target tissue adrenergic receptors and downstream MMDPs[5,21].

Low-grade SNS neural activation (and to a lesser extent, adrenal adrenaline 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 upregulation of molecular programmes 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 haematopoietic 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 haematopoiesis) or sites of injury (to facilitate inflammation and localized tissue remodelling)[4,8,11,25,26] (FIG. 1). Within the bone marrow haematopoietic environment, SNS signalling 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 downregulating lymphocyte trafficking to tissues[28], by inhibiting transcription of type I interferons (such as interferon-α and interferon-β) and type II interferon (that is, interferon-γ), and by stimulating transcription of cytokines expressed in type 2 T helper (T_H2) cells and T_H17 cells, all of which act to impair innate antiviral responses and promote humoral immune responses at the expense of cellular immunity[5,12,29–31] (FIG. 2). Adrenergic signalling also acts on innate immune cells such as monocytes, macrophages and NK cells to stimulate transcription of pro-inflammatory cytokines (such as interleukin-1β (*IL1B*), *IL6*, *IL8* and tumour necrosis factor (*TNF*)), chemokines (such as chemokine C-C motif ligand 2 (*CCL2*; also known as *MCP1*), *CCL4* (also known as *MIP1*) and CXC-chemokine ligand 2 (CXCL2; also known as *MIP2*), and prostaglandin synthesis enzymes such as *PTGS2* (also known as *COX2*)[7,12,30,32]. SNS signalling can also modulate wound-healing in epithelial tissues by stimulating molecular programmes underlying epithelial–mesenchymal transition (EMT) (S.C., S.L. and A.S., 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 remodelling 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 favours 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

Box 1 | **Sympathetic nervous system signalling**

The sympathetic nervous system (SNS) regulates gene expression and cellular function in the nervous, endocrine, cardiovascular, gastrointestinal, respiratory, reproductive and immune systems by releasing two catecholamine neuroeffector molecules: noradrenaline, which is released from SNS nerve fibres that traverse the body to directly innervate target tissues and adrenaline, which is released from the adrenal gland and circulates via blood to target tissues. These adrenergic effector molecules regulate cellular function through five types of adrenergic receptors that are differentially expressed across target tissues and couple to distinct G protein-mediated signal transduction pathways:

- α1-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).
- α2-adrenergic receptors are expressed on smooth muscles and platelets, as well as on neurons, where they function as autoreceptors to inhibit noradrenaline release. α2-adrenergic-receptors signal through $G_{\alpha i}$ inhibition of cyclic AMP activity, which in turn downregulates the serine-threonine protein kinase A (PKA), the guanine exchange protein activated by adenylyl cyclase (EPAC), and β-arrestin-mediated activation of MAP kinases (MAPK).
- β1-adrenergic receptors enhance cardiac output, mediate neural signalling and mobilize energy from adipose tissue. They signal through $G_{\alpha s}$-mediated activation of cAMP, which stimulates PKA, EPAC, and MAPK signalling.
- β2-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 tumour cells of epithelial and lymphoid origin. They signal through $G_{\alpha s}$–cAMP stimulation of PKA, EPAC and MAPK.
- β3-adrenergic receptors are predominately expressed in adipose tissue, where they mobilize energy by signalling through $G_{\alpha s}$–cAMP stimulation of PKA, EPAC and MAPK.

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

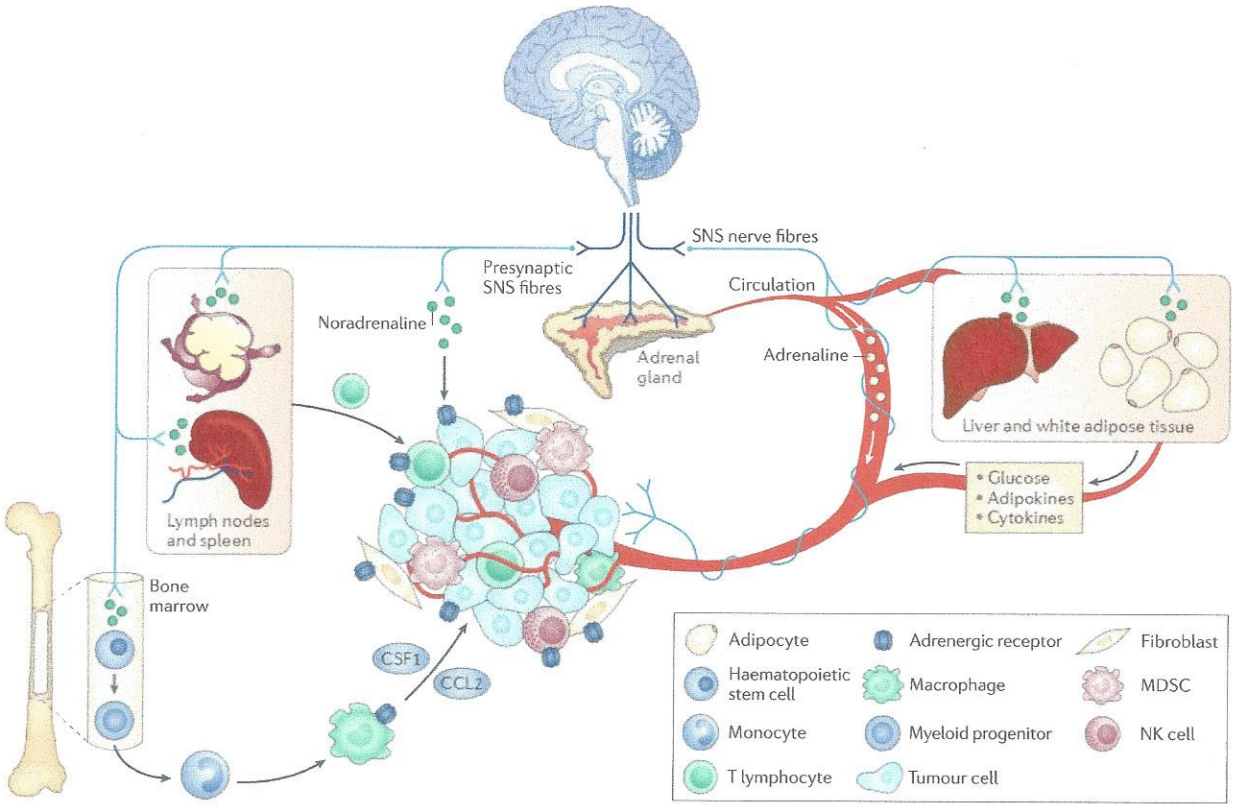

Figure 1 | **Sympathetic nervous system regulation of the tumour microenvironment.** Sympathetic nervous system (SNS) activation can regulate gene expression and cellular function in the tumour microenvironment through various pathways. Direct SNS effects on tumour biology are mediated by catecholamine neuroeffector molecules (adrenaline and noradrenaline) that are released into the tumour microenvironment to engage adrenergic receptors that are expressed on many types of tumour cells and their surrounding stromal elements, such as tumour-associated macrophages and vascular endothelial cells. Adrenaline is released from the adrenal gland and circulates to the tumour microevironment through the vasculature, whereas noradrenaline is released from sympathetic nerve fibres within the tumour microenvironment, which generally associate with the vasculature and can sometimes radiate dendritic fibres into the tumour parenchyma. Indirect effects on tumour biology are mediated by release of catecholamine neuroeffector molecules into distal tissue sites that regulate systemic biological processes that subsequently impinge on tumour biology, such as regulation of immune cell development (for example, myelopoiesis in the bone marrow and spleen, and lymphocyte differentiation in secondary lymphoid organs such as the spleen and lymph nodes) and trafficking (for example, monocyte and macrophage recruitment by chemokines such as C-C motif ligand 2 (CCL2) and growth factors such as colony-stimulation factor 1 (CSF1)), or regulation of systemic metabolic and hormonal regulators of tumour growth (for example, 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 tumours (for example, breast, prostate, ovary, lung and pancreas tumours) as well as haematological malignancies by innervation of lymphoid organs such as the bone marrow, spleen and lymph nodes. MDSC, myeloid-derived suppressor cell; NK cell, natural killer cell.

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 pharmacoepidemiological data that showed reduced disease progression in cancer patients who were incidentally exposed to β-adrenergic antagonists (also known as β-blockers) before diagnosis[39–48]. Experimental analyses in *in vivo* animal models have now shown that behavioural 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 tumour progression have also identified a diverse array of cellular and molecular processes that can mediate SNS effects on tumour progression (FIG. 2). These include DNA repair, oncogene activation, inflammation and immune response, haematopoiesis, angiogenesis, survival and apoptosis.

DNA repair. β-adrenergic signalling 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

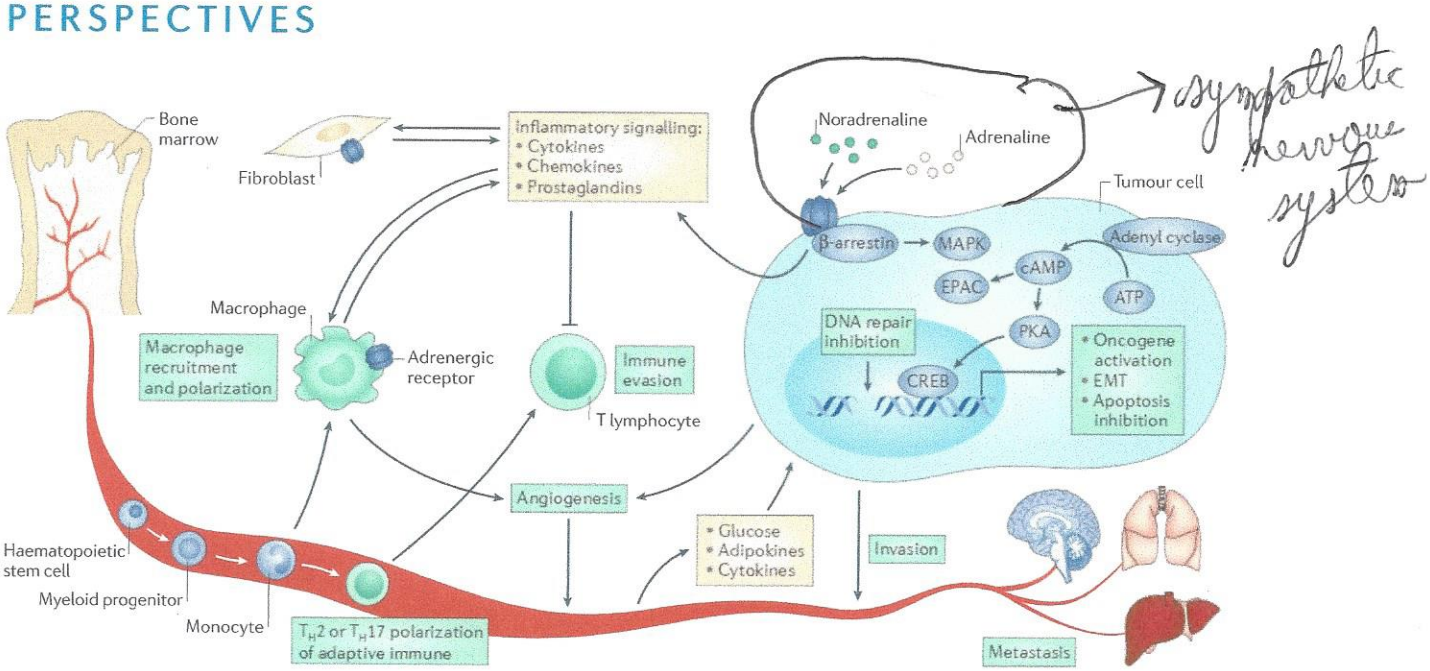

Figure 2 | **Molecular mechanisms for sympathetic nervous system regulation of tumour progression.** Sympathetic nervous system (SNS) signalling through α-adrenergic and β-adrenergic receptor systems can regulate a wide variety of molecular processes involved in tumour progression and metastasis, including DNA damage repair, signalling by cellular and viral oncogenes, expression of pro-inflammatory mediators (such as cytokines, chemokines and prostaglandins) by tumour cells and immune cells, recruitment and pro-metastatic transcriptional programming of macrophages, angiogenesis and lymphangiogenesis, epithelial–mesenchymal transition (EMT), tumour 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 haematopoietic 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 extramedullary 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 affect 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, which regulate cellular and viral gene expression via activation of multiple intracellular signal transduction pathways including cyclic AMP-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 signalling pathways. β-adrenergic-induction of multiple intracellular signalling pathways further amplifies the impact of the multiple parallel extracellular signalling pathways (FIG. 1) to generate a highly pleiotropic network of molecular effects that generally stimulate tumour progression and metastasis. T_H, T helper.

and Rad3-related (ATR)–p21 pathway[62] and β-arrestin-induced activation of the AKT signalling 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 upregulates p53 levels, promotes apoptosis, and sensitizes tumour cells to the effects of the topoisomerase inhibitor SN-38 (REF. 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 signalling can stimulate several oncogenic signalling pathways including SRC[63] and HER2 (which is encoded by *ERBB2*)[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 signalling 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 signalling can also activate a diverse array of oncogenic viruses[13]. As one example, catecholamine induction of β-adrenergic signalling on B lymphocytes triggers PKA-mediated activation of the cellular transcription factor cyclic AMP response element binding protein (CREB), which in turn activates a key viral promoter in the episomal Kaposi's sarcoma-associated human herpesvirus 8 (HHV8) genome[66]. As a result, the viral genome upregulates expression of the viral transcription factor Rta, which serves as a master regulator of HHV8 gene expression and stimulates transcription of a diverse array of viral oncogenes and dissemination of the viral genome[66]. HHV8 contributes to several types of B lymphocyte malignancy in addition to Kaposi 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 signalling 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 signalling 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 signalling can markedly enhance macrophage recruitment into the tumour parenchyma by stimulating tumour cells' production of chemotactic factors such as macrophage colony-stimulating factor 1 (CSF1; also known as M-CSF) and CCL2 (REFS 49,72). β-adrenergic signalling may also enhance the density of 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 (FIG. 1). Within the tumour microenvironment, β-adrenergic signalling also stimulates macrophage expression of gene programmes that promote tumour progression, including transforming growth factor-β (*TGFB*), vascular endothelial growth factor (*VEGF*), *IL6*, 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 MCP1 signalling can abrogate stress effects on metastasis *in vivo*[49,72].

In contrast to its stimulatory effects on inflammation and macrophage biology, SNS signalling can profoundly inhibit the transcription of the type I and type II interferons[49,73,74] that play crucial parts in generating cell-mediated immune responses against cancers and tumour-associated viruses. β-adrenergic signalling 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 lymphocytes[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 signalling can activate a wide range of mesenchymal cell types present in tumour stroma (such as fibroblasts, 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[11,82] (FIG. 2). Emerging data suggest that β-adrenergic activation of SNAIL family of transcription factors may also promote the expression of mesenchymal gene expression programmes in epithelial tumours, promoting EMT (S.C., S.L. and A.S., 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 signalling stimulates the expression of angiogenic growth factors such as VEGF and IL-6 (REFS 34,35,68,87–91), which catalyse the development of vasculature to support tumour growth and metastasis. Studies using pharmacological and genetic inhibitors of angiogenesis have confirmed that that SNS-induced upregulation of angiogenesis mediates stress effects on tumour growth and metastasis *in vivo*[35].

Survival and programmed cell death. β-adrenergic signalling can modulate a wide variety of growth and survival pathways, including inhibition of anoikis (programmed cell death induced by anchorage-dependent cells detaching from the surrounding extracellular matrix) mediated by focal adhesion kinase (FAK; also known as PTK2)[92] and inhibition of apoptotic responses to chemotherapy mediated by the BCL-2-associated agonist of cell death (BAD) and p53 pathways[52–54,93]. β-adrenergic signalling 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 signalling can promote the growth and dissemination of acute lymphocytic leukaemias *in vivo*[58,59], most likely by some of the same molecular pathways through which the SNS regulates physiological haematopoiesis[4,7,11,25–27,95]. Sympathetic innervation of the bone marrow also helps maintain normal stromal cell populations, and it may facilitate immunologic recovery following haematopoietic stem cell transplant[11,96]. However, SNS regulation of the bone marrow haematopoietic 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 leukaemia (AML), for example, β-adrenergic antagonists unexpectedly accelerated disease by disrupting the haematopoietic stem cell niche in ways that favoured leukaemia 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 tumour types. The general pattern of effects (and non-effects) observed in the experimental literature is broadly consistent with the pattern of relationships observed in epidemiological studies of stress and cancer[13,38] and studies of pharmacological β-adrenergic antagonists 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 currently little *in vivo* evidence that SNS activation has a notable 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 signalling altered circulating adipokines produced by white adipose tissue, such as leptin, which subsequently inhibited the growth of leptin-dependent distant tumours[80,81]. Another found a protective effect of β-adrenergic signalling on AML

progression stemming from SNS maintenance of the bone marrow haematopoietic 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 physiological pathways though which the SNS communicates with the tumour microenvironment.

SNS and the tumour microenvironment

The SNS is a network of distinct neural signalling 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 adrenaline or leptin, which are biochemically different from the primary noradrenaline signal released by SNS neurons and can circulate more diffusely throughout the body[81]. Many SNS nerve fibres also release small amounts of other signalling molecules in tandem with noradrenaline, such as the SNS 'co-transmitter' neuropeptide Y[1]. Given the diverse array of physiological mediator pathways that could potentially regulate tumour biology, research has started to map several of the general 'nervous system-side' pathways for SNS regulation of tumour progression.

Hormonal catecholamines. Blood supply and tissue perfusion are essential for tumour growth and progression, and also provide a channel through which SNS catecholamines can access tumour 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 adrenaline or noradrenaline might penetrate into the parenchyma of solid tumours to exert regulatory effects. Blood-based circulation of catecholamines has played a central part in physiological concepts of the fight-or-flight response, but this signalling 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 tumours receive direct innervation from the SNS. The most common pattern involves sympathetic nerve fibres that enter the tumour in association with the vasculature and occasionally radiate fibres into the tumour parenchyma[11,32,77,98]. SNS fibres 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 fibres and may even stimulate development of new neurons (neurogenesis) via the expression of neurotrophic factors such as nerve growth factor (NGF), brain-derived growth factor (BDNF), semaphorins, netrins, and slit molecules[11,98,99] (A.S., unpublished observations). SNS activation may also reciprocally attract tumour cells to neural fibres by upregulating expression of trophic factors and chemokines such as CXCL12 (REFS 11,98–101). Local sympathetic innervation seems to supply much of the catecholamine content within tumour tissues because intratumour noradrenaline levels are generally higher than (and largely uncorrelated with) blood levels of noradrenaline or adrenaline[6,97]. Haematological cancers are also subject to regulation by SNS nerve fibres that innervate the bone marrow haematopoietic 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[4,7,11,25–27,95].

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 signalling 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] (FIG. 1). Activated macrophages can also synthesize catecholamines under some circumstances[102] and may thus provide a local non-neuronal source of adrenergic signalling 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 physiological pathways by which SNS signalling can reach the tumour microenvironment and its pleiotropic effects on tumour biology, pharmacologic antagonism of β-adrenergic signalling might represent a highly leveraged therapeutic opportunity with the potential to favourably affect a wide range of tumour, microenvironmental and systemic mechanisms of cancer progression. Consistent with that concept, several observational epidemiologic studies have documented associations between exposure to β-adrenergic antagonists 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 (probably due to methodological variations considered below). In experimental animal models of human cancer, β-adrenergic 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]. Blockade of β-adrenergic receptors 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-adrenergic antagonists 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-adrenergic antagonists, several practical issues 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 pharmacological agents (for example, non-selective antagonists that block β2 receptors — such as propranolol — are likely to be more effective than the β1-selective agents more commonly used in cardiology)[14,35,40,53,54,107,111]; optimal disease settings (for example, for reasons that are not yet understood mechanistically, some pharmacoepidemiological studies have found that

β-adrenergic antagonists are associated with greater protective effects on breast tumours that were negative for oestrogen receptor (ER), progesterone receptor (PR) and HER2 (triple-negative breast cancer) than those that expressed any of these receptors[41,45]), and optimal intervention timing and duration. For example, experimental models suggest that initiating β-adrenergic antagonists before surgery may reduce SNS-mediated promotion of peri-surgical metastasis[112,113]. The general pattern of preclinical evidence summarized above also implies that blockade of β-adrenergic receptors may have the greatest effect 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 tumour cells has not substantially predicted tumour 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 probably 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 (for example, 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-adrenergic antagonists in cancer owing to a variety of methodological limitations, which include: confounding by indication (for example, the primary historical indication for β-adrenergic antagonists — cardiovascular disease — shares common pathophysiological drivers with cancer progression such as smoking, adiposity and systemic inflammation); confounding with other pharmacological exposures that can affect cancer progression (such as angiotensin-converting enzyme inhibitors); poor ascertainment (for example, archival cardiovascular studies provide poor information on cancer progression and/or mortality, and archival cancer studies provide poor measures of β-adrenergic antagonist exposure); and temporal confounding of trends in cancer survival with trends in β-adrenergic antagonist utilization (particularly for the non-selective β-adrenergic 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-adrenergic antagonists on cancer-related outcomes. The availability of preclinical data and approved, safe, and inexpensive β-adrenergic antagonists with well-understood pharmacology and minimal side-effects provide a favourable risk–benefit profile for initial proof-of-concept biomarker trials in clinical oncology.

> The SNS exerts highly pleiotropic effects on tumour progression and metastasis

Some laboratory studies have implicated β3-adrenergic or α-adrenergic receptors in SNS effects on cancer, but the clinical significance of these effects remains to be determined. β3-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 β3-adrenergic effects in human cancer, and interpretation of preclinical laboratory studies is complicated by the poor specificity of β3-adrenergic pharmacologic agents and the potential for non-selective β-antagonists, such as propranolol, to at least partly modulate β3 receptors. β3-adrenergic receptors also have a key role in SNS regulation of mesenchymal stromal cells in the bone marrow haematopoietic niche[8,11,115,116], suggesting potential applications in haematopoietic cell transplantation and antitumour immunity. Biological effects of α-adrenergic agents in laboratory models of cancer have been complex and inconsistent[117,118]. However, human epidemiological 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 had a major role). Indeed, some α-adrenergic effects may actually be mediated by downstream stimulation of β-adrenergic signalling that results from blockade of α2-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 cancer is structured in major ways by interactions between tumour 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 programmes 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 tumour 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 blockade of β-adrenergic receptors may well have passed once occult tumours become clinically evident. Even so, β-blockade may still have substantial 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].

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, pharmacological 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 presynaptic 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, pharmacological 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 tumour 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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Competing interests statement
The authors declare no competing interests.