Published in final edited form as:
Nat Rev Cancer. 2006 March ; 6(3): 240–248. doi:10.1038/nrc1820.

The influence of bio-behavioural factors on tumour biology: pathways and mechanisms

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Competing interests statement
The authors declare no competing financial interests.

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Abstract

Epidemiological studies indicate that stress, chronic depression and lack of social support might serve as risk factors for cancer development and progression. Recent cellular and molecular studies have identified biological processes that could potentially mediate such effects. This review integrates clinical, cellular and molecular studies to provide a mechanistic understanding of the interface between biological and behavioural influences in cancer, and identifies novel behavioural or pharmacological interventions that might help improve cancer outcomes.

Clinical studies indicate that stress, chronic depression, social support and other psychological factors might influence cancer onset and progression[1–5]. Recent mechanistic studies have identified biological signalling pathways that could contribute to such effects. Environmental and psycho-social processes initiate a cascade of information-processing pathways in the central nervous system (CNS) and periphery, which subsequently trigger fight-or-flight stress responses in the autonomic nervous system (ANS), or defeat/withdrawal responses that are produced by the hypothalamic–pituitary–adrenal axis (HPA)[6]. FIGURE 1 shows the areas of the brain that are thought to be responsible for mediating stress responses and their effects on the adrenal glands and other target tissues. Cognitive and emotional feedback from cortical and limbic areas of the brain modulate the activity of hypothalamic and brain-stem structures that directly control HPA and ANS activity[7].

HPA responses are mediated by hypo-thalamic production of corticotrophin-releasing factor and arginine vasopressin, both of which activate the secretion of pituitary hormones such as adrenocortico-tropic hormone (ACTH), enkephalins and endorphins. ACTH induces downstream release of glucocorticoids such as cortisol from the adrenal cortex. Glucocorticoids control growth, metabolism and immune function, and have a pivotal role in regulating basal function and stress reactivity across a wide variety of organ systems[8]. ANS responses to stress are mediated primarily by activation of the sympathetic nervous system (SNS) and subsequent release of catecholamines (principally noradrenaline and adrenaline) from sympathetic neurons and the adrenal medulla. Levels of catecholamines are increased in individuals who experience acute or chronic stress, and are responsible for ANS effects on cardiac, respiratory, vascular and other organ systems[8]. Examples of stressors associated with alterations in the HPA and/or ANS include marital disruption, bereavement, depression, chronic sleep disruption, severe trauma and post-traumatic stress disorder[9,10].

The activation of these pathways prepares an individual to survive a threat, and the physiological stress responses are therefore generally considered adaptive. However, under chronic stress most physiological systems are negatively affected by prolonged exposure to glucocorticoids and catecholamines[11]. These changes are manifested by deleterious health consequences such as increased risk for cardiac disease, slower wound healing and increased risk from infections[11]. In the past decade, it has become increasingly clear that chronic alterations in neuroendocrine dynamics can also alter multiple physiological processes involved in tumour pathogenesis[12–15].

In this article, we review the clinical and experimental evidence regarding the effects of stress on tumour development, growth and progression. Special emphasis is placed on neuroendocrine influences on the tumour microenvironment, viral oncogenesis and the immune system (FIG. 2). Although the mechanisms and clinical relevance of these pathways are described separately, there are numerous interactions between them, reflecting the complexity of cancer pathogenesis. These pathways might provide additional clues about

factors that regulate the course of disease in cancer patients and might offer new opportunities for therapeutic interventions.

Endocrine stress response and cancer

There is evidence linking stress, concomitant behavioural response patterns and resultant neurohormonal and neurotransmitter changes (all of which are referred to collectively within this paper as bio-behavioural factors) to cancer development and progression. Epidemiological data show that psychological and social characteristics might be associated with differential cancer onset, progression and mortality. For example, a twofold increase in breast cancer risk is evident after disruption of marriage owing to divorce, separation or death of a spouse[5]. Data from 3 eastern and midwestern states in the United States indicate that cancer risk increases after chronic depression that has lasted for at least 6 years[16]. A third study found that the combination of extreme stress and low social support was related to a ninefold increase in breast cancer incidence[4]. However, findings have been inconsistent. In general, stronger relationships have been observed between psycho-social factors and cancer progression than between psychosocial factors and cancer incidence (see REF. 3 for a discussion of the strengths and weaknesses of this literature). Data from patients with existing tumours show that cancer diagnosis and treatment cause substantial distress, and that those who tend toward depressive coping methods, such as hopelessness and helplessness, might experience accelerated disease progression[2]. By contrast, positive factors such as social support and optimism have predicted longer survival[17,18]. Additionally, there are important interactions between behavioural stress factors and health behaviours — including smoking, insomnia, alcohol abuse and obesity — that might have a further impact on cancer risk[19]. Recent experimental studies have begun to elucidate the mechanisms underlying these observations.

Animal models have provided compelling evidence regarding the effects of behavioural stress on tumorigenesis and the biological mechanisms involved (TABLE 1). For example, immobilization stress in rats that were given a carcinogen, diethylnitrosamine, increased both the incidence and rate of tumour growth[20]. Experimental stressors have also been found to increase the pathogenesis of various virally mediated tumours in animal models (see below). Swim stress, surgical stress, social confrontation and hypothermia resulted in increased lung metastasis from injected breast cancer cells[21–24]. Swim stress, laparotomy (opening the abdomen) and social confrontation caused a 2- to 5-fold increase in the number of rat MADB106 breast tumour metastases present in the lung[24,25] and a similar increase in the number of lung metastases counted 3 weeks later[24–26]. β-Adrenergic agonists (which simulate activation of the SNS) such as metaproterenol show dose-dependent increases in lung tumour metastases. Similarly, adrenaline injections promoted mammary tumour metastasis[21–24]. Perhaps most importantly, pre-treatment of animals with β-adrenergic antagonists (to block the activity of SNS activation) and indomethacin (to block inflammation) synergistically blocked the effects of behavioural stress on lung tumour metastasis[27].

Cellular and molecular events that promote cancer growth are also affected by stress. Swim stress in rodents results in induction of chromosomal aberrations and sister chromatid exchanges[28] as well as lower activity of metaphase nucleolar organizer regions in bone marrow cells[29]. These findings indicate that stress might compromise DNA repair mechanisms. Stress can also influence the expression of viral oncogenes and replication of tumorigenic viruses (see below). In an orthotopic murine model of ovarian carcinoma, immobilization stress increased tumour burden and enhanced angiogenesis and tumour production of vascular endothelial growth factor (VEGF)[30], indicating that stress might promote tumour growth by facilitating development of a blood supply. VEGF is a pro-

angiogenic molecule that stimulates endothelial cell migration, proliferation and proteolytic activity[31]. VEGF also interferes with the development of T cells and the functional maturation of dendritic cells[32,33], indicating possible effects on anti-tumour immune responses (see below). In line with these findings, recent clinical studies have shown links between higher levels of social support and lower serum levels of VEGF in patients with ovarian cancer[34]. Furthermore, social support has also been linked to lower levels of interleukin-6 (IL-6), another pro-angiogenic factor, both in peripheral blood and in ascites from patients with ovarian cancer[35].

Understanding the mechanisms responsible for mediating the effects of stress on human tumour tissues is crucial for determining the full impact of stress on tumorigenesis and for devising effective interventions. Experimental evidence indicates that stress hormones have multiple effects on human tumour biology. Hormones that are associated with SNS activation might favour angiogenesis in human tumours. Noradrenaline has been shown to upregulate VEGF in adipose tissue and two ovarian cancer cell lines through the β-adrenergic receptor (βAR)–cyclic AMP (cAMP)–protein kinase A (PKA) pathway[36,37]. This effect was abolished by a β-blocker, propranolol, and was mimicked by isopro-terenol (a synthetic drug that mimics the effects of SNS stimulation), and was therefore thought to be mediated through βARs36,37. Noradrenaline also promotes various steps that are essential to tumour metastasis, including invasion and migration. In *in vitro* experimental models, noradrenaline increased colon cancer cell migration, an effect that was inhibited by β-blockers38. Both adrenaline and noradrenaline promoted *in vitro* invasion of ovarian cancer cells by increasing the expression levels of matrix metalloproteinase 2 (MMP2) and MMP9 [12].

βARs, which mediate most of the effects of catecholamines, have been identified on breast and ovarian cancer cells[12,13]. In both of these studies, β_2AR was the dominant adrenergic receptor present. β ARs are G-protein-coupled receptors whose primary function is the transmission of information from the extracellular environment to the interior of the cell, leading to activation of adenylyl cyclase and accumulation of the second messenger cAMP[39]. In mammary tumours, activation of βARs has been linked to accelerated tumour growth[13–15]. The cAMP-responsive-element-binding (CREB) protein is an important transcription factor that is activated by multiple signal-transduction pathways in response to external stimuli, including stress hormones[40,41]. Several studies have shown a role for the CREB family of proteins in tumour cell proliferation, migration, angiogenesis and inhibition of apoptosis[40–42], as well as the expression of viral oncogenes (see below). An additional cAMP target, EPAC (also known as Rap guanine-nucleotide-exchange factor 3 (RAPGEF3)) is an exchange protein that is directly activated by cAMP. EPAC was recently shown to control a number of cellular processes that were previously attributed to PKA[43]. For example, βAR-mediated activation of cAMP promotes ovarian cancer cell adhesion through the EPAC–RAP1 pathway[44]. Collectively, these studies demonstrate the growing evidence that mediators of SNS activate cellular pathways within tumours that contribute to growth and progression. However, the clinical relevance in human studies of the bio-behavioural stress mechanisms described above remains to be demonstrated.

Glucocorticoids and other mediators

Glucocorticoids regulate a wide variety of cellular processes through glucocorticoid-receptor-mediated activation or repression of target genes. Recent studies have demonstrated that whereas glucocorticoid hormones induce apoptosis in lymphocytes[45], these hormones activate survival genes that protect cancer cells from the effects of chemotherapy in both *in vitro* and *in vivo* experimental models[46,47]. Glucocorticoids can also activate oncogenic viruses and inhibit anti-tumour and antiviral cellular immune responses (see below).

Glucocorticoids such as cortisol might function in a synergistic fashion with catecholamines to facilitate cancer growth. For example, in lung carcinoma cells cortisol increased βAR density and potentiated the isoproterenol-induced increase in cAMP accumulation[48]. So, it is plausible that stressful situations characterized by both increased catecholamine and cortisol concentrations (for example, uncontrollable stress) might have the greatest impact on cancer-related processes.

The expression levels of other hormones affected by stress include prolactin, which increases with stress[49,50], and oxytocin and dopamine, which decrease with stress[51]. Prolactin can promote cell growth and survival in breast tumour and other tumour cells[52]. Oxytocin inhibits the growth of epithelial cell (such as breast and endometrial) tumours and those of neuronal or bone origin, but the hormone has a growth-stimulating effect in trophoblast and endothelium tumours[53]. For example, exogenous oxytocin has a dose-dependent mitogenic effect on human small-cell lung cancer cell lines, which is blocked by an oxytocin receptor antagonist[54]. Dopamine, which is known to inhibit the growth of several types of malignant tumours[55], blocks VEGF-induced angiogenesis both *in vitro* and *in vivo*, primarily by inducing endocytosis of VEGF receptor 2 in endothelial cells[56].

Effect of circadian deregulation on cancer

Evidence indicates that circadian deregulation influences the secretion of some stress-associated hormones, and this might explain the associations between stress and cancer[57,58]. Data from separate lines of investigation show that stress can disrupt circadian glucocorticoid rhythms[57,59] and favour tumour initiation and progression[57,58,60]. Night-time shift work, a condition that is known to disrupt endocrine rhythms, is a risk factor for breast and colorectal cancer[61]. Mice with circadian disruption owing to *Per1* (period 1) or *Per2* gene mutations are prone to tumour development and early death[62,63]. Tumour-bearing animals and cancer patients have disrupted endocrine, metabolic and immunological cycles, with greater disruption in cases where the tumour is advanced or fast-growing[64]. In murine studies, tumour progression and mortality are dramatically accelerated after elimination of circadian rhythms by manipulation of light–dark cycles (imposed ‘jet-lag’) and by the use of bilateral electrolytic lesions to destroy the suprachiasmatic nuclei (SCN), which eliminates circadian rhythms[60]. Two clinical studies have also shown that the status of circadian cycles, such as cortisol or the 24-hour-rest–activity cycle, can predict long-term cancer survival[58,65].

Stress-related disruption of circadian cycles might impair cancer-defence mechanisms through genetic and/or gluco-corticoid and immune pathways. Animal studies show that behavioural factors such as imposed chronic jet-lag can alter *Per1* expression in the SCN[60], and circadian genes, including *Per1*, regulate tumour suppression, cellular response to DNA damage, and apoptosis[63]. Glucocorticoid rhythms that are driven by the SCN[62] are linked to both enumerative and functional immunity[66]. Sleep disruption can increase the release of cortisol as well as increase the expression of pro-inflammatory cytokines (for example, IL-6 and tumour-necrosis factor-α (TNFα)) in cancer patients[67]. Pro-inflammatory cytokines might promote tumorigenesis by inducing DNA damage or inhibiting DNA repair through the generation of reactive oxygen species. Pro-inflammatory cytokines can also lead to the inactivation of tumour-suppressor genes, the promotion of autocrine or paracrine growth and survival of tumour cells, the stimulation of angiogenesis, or the subversion of the immune response (which leads to the activation of B cells rather than T cells in the tumour microenvironment)[68]. Conversely, agents that are capable of re-establishing circadian regulation (for example, melatonin) might have anti-tumour effects. Research on oestrogen-receptor-positive MCF-7 human breast cancer cells has shown that melatonin reversibly inhibits cell proliferation, increases p53 expression, modulates the cell cycle, and reduces

metastatic capacity by increasing the expression of cell-surface adhesion proteins[69,70]. Taken together, these data indicate a potentially important role of circadian regulation in cancer defence and treatment[62].

Influences on viral oncogenesis

The first experimental demonstration that bio-behavioural factors could promote cancer came from animal studies of tumour viruses[71]. Many studies have demonstrated the accelerated growth of virally induced tumours in stressed animals, as well as the more surprising protective effects of handling, fighting and crowding[72,73]. Neuroendocrine function has a central role in these processes because it can modulate viral replication, activate viral oncogenes, increase tumour metabolism and regulate the immune response[74–76]. The evidence for a viral contribution to human cancer has grown[77] (BOX 1), and stress hormones have been found to influence the activity of various human tumour viruses (BOX 2; TABLE 2).

Box 1

Physiological pathways, bio-behavioural processes and oncogenesis

- Environmental and social processes activate interpretive processes in the central nervous system (CNS) that can subsequently trigger fight-or-flight stress responses in the autonomic nervous system (ANS) or defeat/withdrawal responses through the activation of the hypothalamic–pituitary–adrenal axis (HPA)[141].
- Individual differences in perception and evaluation of external events (coping) creates variability in individual ANS and HPA activity levels.
- Over long periods of time, these neuroendocrine dynamics can alter various physiological processes involved in tumorigenesis, including oxidative metabolism, DNA repair, oncogene expression by viruses and somatic cells, and production of growth factors and other regulators of cell growth.
- Once a tumour is initiated, neuroendocrine factors can also regulate the activity of proteases, angiogenic factors, chemokines and adhesion molecules involved in invasion, metastasis and other aspects of tumour progression.
- CNS processes can also shape behavioural processes that govern cancer risk (for example, smoking, transmission of oncogenic viruses or exposure to genotoxic compounds).

Box 2

Viral oncology

- Viral infections contribute to approximately 15% of human cancers worldwide[77]
- Pathogenic mechanisms include expression of viral oncogenes (for example, human T-cell lymphotropic virus Tax, and Epstein–Barr virus nuclear antigens and latent membrane protein 1), inhibition of host-cell tumour-suppressors (for example, human papillomavirus E6, which targets p53 and E7, which targets RB), and genomic damage stemming from immune-mediated cell turnover (for example, hepatitis B and C viruses)[77,142,143].
- All major human tumour viruses are sensitive to the intracellular signalling pathways activated by the hypothalamic–pituitary–adrenal axis and autonomic

nervous system. These mediators can reactivate latent tumour viruses, stimulate oncogene expression and inhibit host-cell antiviral responses.

Epstein–Barr virus (EBV) is reactivated in healthy people who experience prolonged psychological stress[78,79]. In these studies HPA activity increased in parallel with reactivation of EBV[79,80], and gluco-corticoid hormones were subsequently found to increase EBV gene expression *in vitro*[80,81]. High-risk human papilloma viruses (HPVs), which contribute to cervical and rectal carcinomas, also respond to glucocorticoids by activating gene expression[82–84], interacting with cellular proto-oncogenes such as *HRAS*[85], and evading cellular immune responses by downregulating the expression of tumour MHC-I (major histocompatibility complex class I) molecules[86]. Clinical studies have identified stressful life events as a risk factor for increased progression of cervical dysplasia in HPV-positive women[87,88]. Furthermore, glucocorticoid antagonists can inhibit HPV activity *in vitro*[89–91], providing a molecular rationale for clinical interventions that target HPA activity. Although hepatitis B and C viruses come from different viral lineages, glucocorticoids increase gene expression in and replication of both viruses[90,92–94]. These dynamics are so pronounced that glucocorticoids are employed clinically to activate hepatitis B and C viruses for eradication by replication-dependent antiviral drugs[93,95].

Cancer-related viruses are also sensitive to catecholamines and the PKA signalling pathway. Molecular mechanisms are especially well defined for AIDS-associated malignancies. Catecholamines can accelerate human immunodeficiency virus 1 (HIV1) replication by increasing cellular susceptibility to infection[96,97], activating viral gene transcription[96] and suppressing antiviral cytokines[98]. People with heightened ANS activity show an increased viral load in the plasma and an impaired response to antiretroviral therapy[96], placing them at increased risk for AIDS-associated B-cell lymphomas[99]. Catecholamines can also activate the Kaposi sarcoma-associated herpesvirus (KSHV) through PKA induction of the viral transcription factor Rta[100]. Human T-cell lymphotropic viruses 1 and 2 (HTLV1 and HTLV2, respectively) are sensitive to PKA-mediated induction of the oncogenic Tax transcription factor[101]. Hormonal regulation of viral replication represents an important pathway by which bio-behavioural factors might influence malignant processes, but it also indicates novel therapeutic approaches such as β-adrenergic priming of viral genomes for clearance by replication-dependent nucleoside analogue drugs.

In addition to direct effects on viral gene expression, bio-behavioural factors can also indirectly affect tumour viruses by modulating host immune responses (see below). Antiviral vaccines will have an increasing role in the primary prevention of virally mediated cancers, and bio-behavioural influences on vaccine-induced immune responses will become especially relevant[102,103]. Neuroendocrine influences on the immune response might also explain why oncogenic viruses so consistently acquire hormone-responsive replication dynamics. Viruses that coordinate their gene expression with periods of hormone-induced immunosuppression should enjoy a significant survival advantage. Similar selective pressures might also shape the evolution of non-viral malignancies[104] such that genomic alterations are selected based on their ability to evade immune clearance or to synergize with endocrine dynamics to optimize tumour growth and metastasis.

Influences on immune mechanisms

Chronic stress has been shown to suppress different facets of immune function[2] such as antigen presentation, T-cell proliferation, and humoral and cell-mediated immunity, mainly through the release of catecholamine and/or glucocorticoid hormones[105–107]. Relevant neuroendocrine and immune system interactions include direct synapse-like connections between sympathetic nerves and lymphocytes in lymphoid organs[108], neural and endocrine

modulation of lymphocyte trafficking[109], and modulation of leukocyte function through glucocorticoid receptors and other receptors[70]. Tumour incidence and progression based on modulation of the immune response by chronic stress has been demonstrated in many animal models (see above). Recent studies have shown that chronic stress experienced during exposure to non-blistering ultraviolet radiation significantly increases susceptibility to squamous cell carcinoma by suppressing type 1 cytokines and the infiltration of protective T cells. Regulatory or suppressor T-cell numbers within the tumours and in the circulation were also increased[110]. Studies in mice of the immune response to transplanted syngeneic tumours showed that noradrenaline[111] and adrenaline[112,113] directly inhibited the generation of anti-tumour cytotoxic T cells through β-adrenergic signalling mechanisms. Chronic stress has been shown to modulate lymphocyte apoptosis through an increase in FAS (also known as CD95 or APO1) expression. It has been hypothesized that such lymphocyte reduction might result in an increase in the incidence of oncogenic viral infections and DNA damage[114].

Compromised natural killer (NK)-cell function has been shown in both animal and clinical studies of surgical stress[22,115]. High levels of psychological distress have been linked to reduced cellular immunity in patients with breast[116] and ovarian cancer[117]. More specifically, distress measured by self-report was correlated with low NK-cell cyto-toxicity in tumour-infiltrating lymphocytes from human ovarian cancers[117]. Low peripheral NK-cell counts are prognostic for early breast cancer mortality, and reduced NK-cell cytotoxicity is predictive of a poor clinical outcome in patients with breast carcinoma[58]. Positive psycho-social factors such as social support have been associated with increased levels of NK-cell cytotoxicity in patients with breast[118] and ovarian cancer[117]. The relationship of increased NK-cell cytotoxicity with social support was not limited to the periphery; it was also seen in tumour-infiltrating lymphocytes isolated from human ovarian cancers, reflecting possible psycho-social influences on the tumour microenvironment[117]. Patients with breast cancer who reported increased psychological growth through participation in a cognitive behavioural intervention programme demonstrated increased levels of cellular immune function[119]. Preliminary studies have found that the expression of spirituality was related to increased numbers of circulating T cells in patients with breast cancer[120], and that the use of humour as a coping mechanism was associated with increased NK-cell activity in cancer patients[121].

Clinical opportunities and challenges

Our understanding of the biological and clinical significance of psycho-social and bio-behavioural influences on cancer pathogenesis is expanding. As described in this review, factors such as chronic stress, depression and social support have been linked to tumour biology, viral oncogenesis and cell-mediated immunity (FIG. 3). Although the molecular pathways have not been completely delineated, observations to date indicate a need for novel therapeutic paradigms that integrate a bio-behavioural perspective.

It is plausible that successful management of factors such as stress and negative mood might have a salubrious effect on the neuroendocrine regulation of oncogenesis, tumour growth and metastasis, and cancer immunoediting processes. Psycho-social interventions such as relaxation and cognitive behavioural techniques that alter negative mood seem to modulate ANS and HPA hormonal activity[122–124]. Moreover, such interventions can potentially be used in conjunction with conventional therapies to maximize treatment efficacy[125,126]. Stress-management interventions that dampen chronic-stress-related physiological changes might facilitate immune system ‘recovery’ and thereby increase immune surveillance during the active treatment of cancer[119,124]. Group-based psycho-social interventions that combine relaxation with cognitive behavioural techniques, such as cognitive behavioural stress

management (CBSM), have been shown to increase indicators of immune responses against potentially oncogenic viral infections, such as EBV[127]. Such alterations are paralleled by decreased expression levels of cortisol in the serum, a reduced depressive mood, increased social support and enhanced relaxation skills[122].

In HIV-infected individuals, who as a group are at risk for multiple opportunistic cancers, CBSM seems to accelerate reconstitution of naive T-lymphocytes, increase $CD8^+$ cytotoxic T-cell numbers and decrease the viral load of HIV over time[122,128]. These changes are pre-dated by decreases in negative mood and decreases in urinary cortisol and noradrenaline output[122,129]. It is plausible that CBSM might also help decrease the replication and function of other oncogenic viruses such as HPV and improve immune defences against them. Psycho-social interventions in cancer patients have resulted in alterations in neuroendocrine regulation and immunological functions[124,130,131] that are relevant for monitoring neoplastic cell changes. For example, two recent randomized clinical trials have documented increases in lymphocyte proliferation in patients with breast cancer following psycho-social interventions[119,124], and post-intervention changes in NK-cell activity have also been shown in patients with malignant melanoma[131]. Collectively, this work indicates that stress management can modify neuroendocrine deregulation and immunological functions that potentially have implications for tumour progression. This might be particularly important among vulnerable populations such as older adults because ageing is associated with a suppression of the immune response.

Clinical studies of psycho-social interventions with cancer survival as an outcome have been methodologically flawed or have failed to confirm a survival advantage in the treatment group[1,126,132–134]. Similar to most medical interventions for cancer, the effectiveness of psycho-social interventions is likely to vary with the type and stage of cancer, characteristics of the patient (for example, age, gender, education, co-morbid medical conditions, and health behaviours such as tobacco use, alcohol consumption and physical activity) and the type and delivery of the intervention. Nevertheless, epidemiological evidence correlating psychological and social factors (for example, chronic depression, hopelessness, marital disruption and social support) with cancer incidence, progression and survival give credence to examining the biological signalling pathways and mechanisms that underlie these observations.

Pharmacological interventions can potentially be used to ameliorate stress-associated influences on cancer development and progression. As discussed above, β-blockers have been shown to block many of the deleterious effects of stress. In a large case–control study of patients with prostate cancer who were taking anti-hypertensive medication, only β-blockers were associated with a reduction of cancer risk[135]. A cohort study of cardiovascular patients showed that the use of β-blockers, relative to never-using, resulted in a 49% decrease in cancer risk, with a 6% decrease in risk for every year of use[136]. Large population-based case–control studies have not confirmed alterations in risk for invasive breast carcinoma with β-blocker use[137,138]. The use of antidepressant medications might be promising, owing to a concomitant suppression of an inflammatory response that has been associated with certain types of cancer[139]. For example, lithium inhibits prostaglandin E1, and tricyclic antidepressants antagonize thromboxanes[140]. Some monoamine oxidase inhibitors exert a more potent anti-prostaglandin effect than indomethacin[140]. Whether these agents can be used to reduce cancer risk through bio-behavioural-related mechanisms remains to be determined, but these studies indicate that further inquiry is warranted.

Conclusion

Despite significant progress in the past decade, further research is needed to define the mechanisms underlying the complex circuits involving the HPA and ANS axes and their effects on the processes involved in cancer development and progression. The body of data outlined above supports a model in which bio-behavioural factors influence multiple aspects of tumorigenesis through their impact on neuroendocrine function (FIG. 3). These effects include direct promotion of tumour growth by affecting steps in the metastatic cascade and viral oncogenesis. Furthermore, the interplay between behavioural processes and cellular immune factors also supports a favourable physiological environment for tumour establishment and growth. In the context of this 'systems biology' perspective, pharmacological and behavioural interventions that address neuroendocrine dysfunction could have a clinically significant role in avoiding these deleterious effects on tumour growth. Although stress *per se* does not cause cancer, the clinical and experimental data outlined above indicate that factors such as mood, coping mechanisms and social support can significantly influence the underlying cellular and molecular processes that facilitate malignant cell growth. As cancer treatment evolves towards a more patient-specific approach, consideration of the influence of bio-behavioural factors provides a novel perspective for mechanistic studies and new therapeutic targets.

Acknowledgments

The authors gratefully acknowledge the support of several Institutes and Centers of the National Institutes of Health; National Cancer Institute (M.H.A., S.K.L., F.S.D., and A.K.S.), National Center for Complementary and Alternative Medicine (S.K.L.), National Institute of Allergy and Infectious Diseases (S.W.C. and F.S.D.) and National Institute of Mental Health (M.H.A.). The authors also acknowledge support received from the Dana Foundation (F.S.D.), Jonssen Comprehensive Cancer Center (S.W.C.) and Norman Cousins Center at the University of California, Los Angeles (S.W.C.). Preparation of this perspective was facilitated by support from the Division of Cancer Control and Populations Sciences at the National Cancer Institute. We are indebted to Wendy Nelson for her editorial review of the manuscript.

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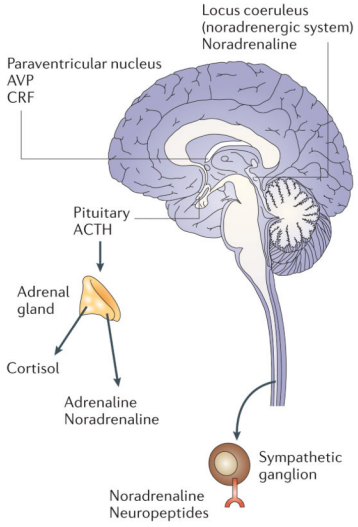

Figure 1. Important components of the central and peripheral stress systems

Stressful experiences activate components of the limbic system, which includes the hypothalamus, the hippocampus, the amygdala, and other nearby areas. In response to neurosensory signals, the hypothalamus secretes corticotrophin-releasing factor (CRF) and arginine vasopressin (AVP), both of which activate the pituitary to produce hormones such as adrenocorticotropic hormone (ACTH). Circulating ACTH stimulates the production of glucocorticoids from the adrenal cortex. The sympathetic nervous system originates from the brainstem, and the pre-ganglionic neurons terminate in the ganglia near the spinal column. From these ganglia, post-ganglionic fibres run to the effector organs. The main neurotransmitter of the pre-ganglionic sympathetic fibres is acetylcholine and the typical neurotransmitter released by the post-ganglionic neurons is noradrenaline. The adrenal medulla contains chromaffin cells, which release mainly adrenaline.

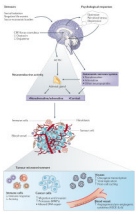

Figure 2. Effects of stress-associated factors on the tumour microenvironment

The responses to stressors involve central nervous system (CNS) perceptions of threat and subsequent activation of the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal (HPA) axis. Catecholamines, glucocorticoids and other stress hormones are subsequently released from the adrenal gland, brain and sympathetic nerve terminals and can modulate the activity of multiple components of the tumour microenvironment. Effects include the promotion of tumour-cell growth, migration and invasive capacity, and stimulation of angiogenesis by inducing production of pro-angiogenic cytokines. Stress hormones can also activate oncogenic viruses and alter several aspects of immune function, including antibody production, cytokine production profiles and cell trafficking (see REF. 6 for a comprehensive review of immune effects). Collectively, these downstream effects create a permissive environment for tumour initiation, growth and progression. CRF, corticotrophin-releasing factor; IL-6, interleukin-6; MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor.

Figure 3. Integrated model of bio-behavioural influences on cancer pathogenesis through neuroendocrine pathways

In this model, bio-behavioural factors such as life stress, psychological processes and health behaviours (blue panel) influence tumour-related processes (green panel) through the neuroendocrine regulation of hormones, including adrenaline, noradrenaline and glucocorticoids (red panel). Central control of peripheral endocrine function also allows social, environmental and behavioural processes to interact with biological risk factors such as genetic background, carcinogens and viral infections to systemically modulate malignant potential (red panel). Direct pathways of influence include effects of catecholamines and glucocorticoids on tumour-cell expression of genes that control cell proliferation, invasion, angiogenesis, metastasis and immune evasion (green panel). Stress-responsive neuroendocrine mediators can also influence malignant potential indirectly through their effects on oncogenic viruses and the cellular immune system (red panel). These pleiotropic hormonal influences induce a mutually reinforcing system of cellular signals that collectively support the initiation and progression of malignant cell growth (green panel). Furthermore, neuroendocrine deregulation can influence the response to conventional therapies such as surgery, chemotherapy and immunotherapy (green panel). In addition to explaining bio-behavioural risk factors for cancer, this model suggests novel targets for pharmacological or behavioural intervention. CTL, cytotoxic T lymphocytes; IL, interleukin; MRD, minimal residual disease; NKC, natural killer cell; TGFβ, transforming growth factor-β; TNFα, tumour-necrosis factor-α; TSH, thyroid-stimulating hormone.

Table 1

Effects of stress and stress-associated hormones on cancer

Experimental manipulation	Animal	Biological effect	Tumour type	Effect on tumour growth	References
Confrontation	Rats	NA	Breast	Increased metastasis of tumour cells to the lung	25
Restraint stress	Rats	Decreased numbers of T cells	Mammary	Increased growth during stress	144
Forced swim	Rats	Decreased natural-killer-cell activity	Leukaemia	Increased mortality	22
Abdominal surgery	Rats	Decreased natural-killer-cell activity	Mammary	Increased metastasis of tumour cells to the lung	22
High versus low dopaminergic reactivity	Rats	Decreased angiogenesis with high dopaminergic reactivity	Mammary	Fewer lung metastasis with increased dopaminergic reactivity	145
Dopamine administration	Mice	Decreased angiogenesis; decreased VEGF– VEGFR2 binding and phosphorylation	Ovarian	Decreased ascites formation	56
Dopamine administration	Mice	Decreased angiogenesis	Gastric	Decreased growth	55
Social isolation	Mice	Decreased macrophage activity	Ehrlich	Increased growth	146
Immobilization stress	Mice	Increased angiogenesis	Ovarian	Increased growth	30
Restraint stress	Mice	Decreased IL-12, IFNγ, CCL27 (also known as CTACK) and numbers of infiltrating T cells; increased numbers of suppressor cells	Skin and squamous cell carcinoma	Increased incidence, number, size and density	110

CTACK, cutaneous T-cell attracting chemokine; IL-12, interleukin-12; IFNγ, interferon-γ; NA, not available; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2.

Table 2

Neuroendocrine influences on tumour viruses

Human tumour virus	Malignancy	Sensitivity*
Human papilloma viruses 16 and 33	Cervical and head/neck cancer	HPA
Hepatitis B virus	Hepatocellular carcinoma	HPA
Hepatitis C virus	Hepatocellular carcinoma	HPA
Epstein–Barr virus	Lymphoma, and nasopharygeal carcinoma	HPA
Human T-cell lymphotropic viruses 1 and 2	Adult T-cell leukaemia/lymphoma	ANS
Kaposi sarcoma-associated herpesvirus	Kaposi sarcoma, and primary effusion lymphoma	ANS

*Presumptive, based on *in vitro* studies. ANS, autonomic nervous system; HPA, hypothalamic–pituitary–adrenal axis. Vaccination is an important primary prevention strategy against viral tumours, and behavioural factors can influence the efficacy of this approach by modulating vaccine-induced immune responses[102,103].