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Perspective

The Neuroendocrine Impact of Chronic Stress on Cancer

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ABSTRACT

Behavioral processes have long been suspected to influence many health processes including effects on cancer. However, mechanisms underlying these observations are not fully understood. Recent work has demonstrated that chronic behavioral stress results in higher levels of tissue catecholamines, greater tumor burden, and a more invasive pattern of ovarian cancer growth in an orthotopic mouse model. These effects are mediated primarily through the β_2 adrenergic receptor (ADRB2) activation of the tumor cell cyclic AMP (cAMP)-protein kinase A (PKA) signaling pathway. Additionally, tumors in stressed animals have increased vascularization and enhanced expression of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) -2 and -9. In this review, we highlight the importance of the neuroendocrine stress response in tumor biology and discuss mechanisms by which the β-adrenergic receptors on ovarian cancer cells enhance angiogenesis and tumor growth.

INTRODUCTION

Over twenty-five years ago, Engel recognized that biological factors alone cannot account for all changes in physical health and that social and behavioral dimensions must also be considered.[1] In clinical and epidemiological studies, cancer progression, and to a lesser extent, cancer onset have been related to chronic stress, depression, lack of social support and other psychological factors.[2-6] Stress is a complex process encompassing environmental and psychosocial factors and initiates a cascade of information-processing pathways in both the central and peripheral nervous systems. Ultimately, the fight-or-flight stress responses in the autonomic nervous system (ANS) or the defeat/withdrawal responses in the hypothalamic-pituitary-adrenal axis (HPA) are generated and secrete catecholamines and cortisol, respectively (Fig. 1).[7,8] Activation of these pathways in acute stress are necessary for survival and are adaptive processes. In contrast, chronic stress negatively affects most physiological systems due to prolonged exposure to catecholamines and glucocorticoids.[9]

Chronic stress has been shown to decrease cellular immune parameters, such as natural killer (NK) cell cytotoxicity and T-cell responses to mitogen stimulation.[10-12] Effects of biobehavioral factors on the immune system are thought to be mediated in part by the sympathetic nervous system, the HPA axis, and a variety of other hormones and peptides.[13,14] To date, the majority of neuroendocrinological research dealing with stress and accelerated tumor growth has focused on suppressed immune response to malignant tissue.[7] Recently, we and others have considered other biological pathways that may be affected by stress mediators. These observations are the focus of the current review.

NEUROENDOCRINE INFLUENCES ON CANCER

Tumorigenesis is a multistep process, and according to Hanahan and Weinberg, there are six essential acquired alterations in cell physiology that promote malignant growth: (1) self-sufficiency in growth signals, (2) insensitivity to anti-growth signals, (3) evasion of apoptosis, (4) limitless replicative potential, (5) sustained angiogenesis and (6) tissue invasion and metastasis.[15] After a cell acquires tumorigenic potential, then cancer metastasis can occur if another series of sequential interrelated steps including proliferation/angiogenesis, invasion, embolism/circulation, transport, adherence in organs, adherence to vessel wall and extravasation occur.[16] Tumor progression is a result of crosstalk between different cell types within the tumor and its surrounding supporting tissue, tumor stroma and microenvironment.[17] Emerging research is now beginning to explore the role of neuropeptides

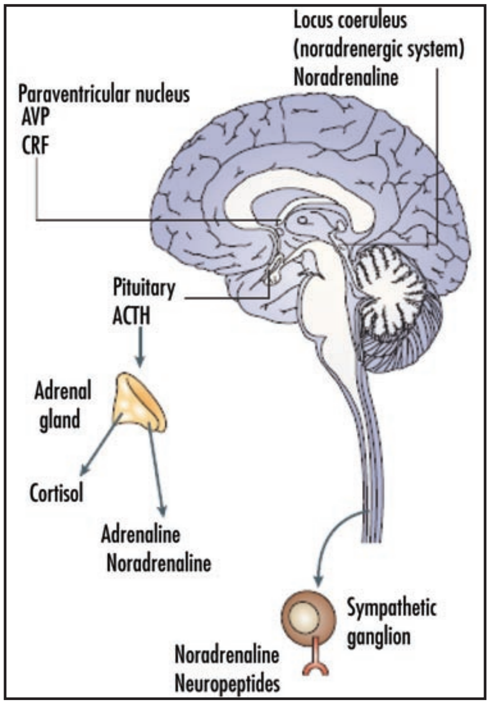

Figure 1. Key components of the central and peripheral stress systems. In response to neurosensory signals, the hypothalamus secretes corticotrophin-releasing factor (CRF) and arginine vasopressin (AVP), which cause the pituitary to secrete adrenocorticotropic hormone (ACTH). Subsequently, ACTH promotes the production of glucocorticoids from the adrenal cortex. The sympathetic nervous system originates in the brain stem, and ultimately through post-ganglionic fibers releases noradrenaline. The adrenal medulla releases mainly adrenaline. Reprinted with permission from *Nature Reviews Cancer* (see ref. 8).

and neurotransmitters, which are increased in certain biobehavioral states on the multistep process of cancer metastasis.

In order to proliferate, tumor cells rely on nutrient and oxygen diffusion. The effects of stress-related hormones on tumor cell proliferation can be either stimulatory or inhibitory depending on the type of hormone and tumor type. For example, in breast carcinoma, activation of β-adrenergic receptors (ADRB) has been associated with accelerated tumor growth.[18-20] In contrast, catecholamines may inhibit tumor cell proliferation that may be mediated by α-adrenergic receptors or the dopamine transporter. Scarparo and colleagues found that melanoma cells treated with the α_1-adrenergic agonist phenylephrine led to a dose-dependent decrease in proliferation, which could be reversed by the α_1-adrenergic antagonist prazosin.[21] Additionally, norepinephrine treatment shifted neuroblastoma cells expressing the dopamine transporter into the G_0/G_1 phase, thereby inhibiting proliferation.[22] Similarly, the role of glucocorticoid hormones on proliferation is dual.[23,24]

The ability of a tumor cell to invade and metastasize to distant tissues is highly dependent on malignant cell adhesion to the extracellular matrix.[25] Enserink and colleagues have shown that the β-agonist isoproterenol promotes ovarian cancer cell spreading and adhesion via integrins through Epac (exchange factor directly activated by cAMP)-Rap1 pathway.[26,27] Additionally, there is growing evidence that stress hormones may affect tumor cell motility and invasion. Norepinephrine has been shown to induce breast and colon cancer migration.[28,29] We have previously demonstrated that physiologic stress concentrations of norepinephrine and epinephrine can enhance the invasive potential of ovarian carcinoma cells via the ADRB-mediated increases in matrix metalloproteinases (MMPs). The β-adrenergic antagonist propranolol and pharmacologic blockade of MMPs abrogated the effects of norepinephrine on the increases in tumor cell invasive potential.[30] This work provided the in vitro evidence that stress hormones can increase the invasive potential of ovarian cancer cells.

Avoidance of apoptosis is a critical component of the metastatic cascade. Thus far, glucocorticoids, which regulate a variety of cellular processes, have been the focus of research elucidating the role of stress hormones on tumor cell survival. Glucocorticoids downregulate proapoptotic elements of the death receptor and mitochondrial apoptosis pathways in cervical and lung cancer cell lines.[31] Wu and colleagues found that breast cancer cell lines pretreated with dexamethasone inhibited chemotherapy-induced apoptosis via transcriptional induction of serum and GC-inducible protein kinase-1 (SGK-1) and mitogen activated protein kinase phosphatase-1 (MKP-1).[32] The antiapoptotic effects of glucocorticoid treatment could be reversed by blockade of SGK-1 and MKP-1.[32] Additionally, glucocorticoids and catecholamines may act synergistically to facilitate cancer growth as evidenced in lung carcinoma cell lines.[33]

Angiogenesis is a key process in the growth of most solid tumors beyond 1–2 mm in diameter, and their metastatic spread involves recruitment of nearby blood vessels to permeate the tumor.[34] In vascular endothelial cells, ischemic neoangiogenesis causes proliferation via overexpression of the ADRB.[35] Vascular endothelial growth factor (VEGF) is a key proangiogenic cytokine that is produced by tumor cells, endothelial cells, and platelets.[36] We have previously reported that higher levels of social support were correlated with lower VEGF levels in serum from presurgical patients with ovarian carcinoma providing a possible mechanism by which poor social support may be associated with disease progression.[37] We have also demonstrated that VEGF production by ovarian cancer cell lines was enhanced by stress hormones such as norepinephrine, epinephrine, and isoproterenol in vitro and blocked by the β-antagonist propranolol.[38] Based on our previous studies, we sought to elucidate whether chronic stress and the associated increase in sympathetic nervous system activity had a causal effect on growth and metastasis of ovarian cancer in vivo.[39]

THE ROLE OF CHRONIC STRESS ON TUMOR GROWTH AND ANGIOGENESIS IN ORTHOTOPIC OVARIAN CARCINOMA

We recently demonstrated that chronic stress (daily restraint) quantitated by elevated organ catecholamine (norepinephrine and cortisol) levels enhanced the pathogenesis of ovarian carcinoma in vivo, as evidenced by increased tumor weight and more invasive pattern of metastasis including parenchymal liver, spleen, and diaphragm involvement. Propranolol, a non-specific β-blocker, completely blocked the effects of immobilization stress on tumor growth, indicating a critical role for β-adrenergic signaling in stress mediated increases in tumor growth. The β-adrenergic receptors are G-protein-coupled receptors that mainly function to transmit extracellular information to the interior of the cell, causing an activation of adenylyl cyclase and an accumulation of the second messenger cAMP to activate the protein kinase A pathway.[40] Ultimately, after catecholamine stimulation, the activation of the tumor cell cAMP-protein kinase A signaling pathway led to increased VEGF gene expression, resulting in increased tumor vascularization and more aggressive growth. A series of experiments using either ADRB-null cell lines, pharmacological β-agonists, or ADRB-silencing with siRNA, demonstrated that ADRB2 on the tumor cells plays a functionally significant role in stress-mediated angiogenesis. The increased angiogenesis occurred in response to increases in catecholamine induced VEGF production by tumor cells. The tumor vasculature in stressed animals contained more tortuous and numerous blood vessels than controls, and was accompanied by a significant decrease in the proportion of blood vessels with pericyte coverage in tumors from stressed animals, which suggests more immature vasculature. Additionally, magnetic resonance imaging and kinetic analysis of the stressed tumors showed substantial anatomical and functional alterations in tumor vasculature.

Both propranolol and VEGF blocker such as the VEGF-R2 inhibitor PTK787 or the monoclonal VEGF-specific antibody bevacizumab completely blocked the stress induced effects on tumor burden and invasiveness. These results demonstrated that behavioral stressors can enhance the pathogenesis of ovarian carcinoma via VEGF-mediated angiogenesis in vivo (Fig. 2), and underscores the importance of the neuroendocrine system in cancer pathogenesis.

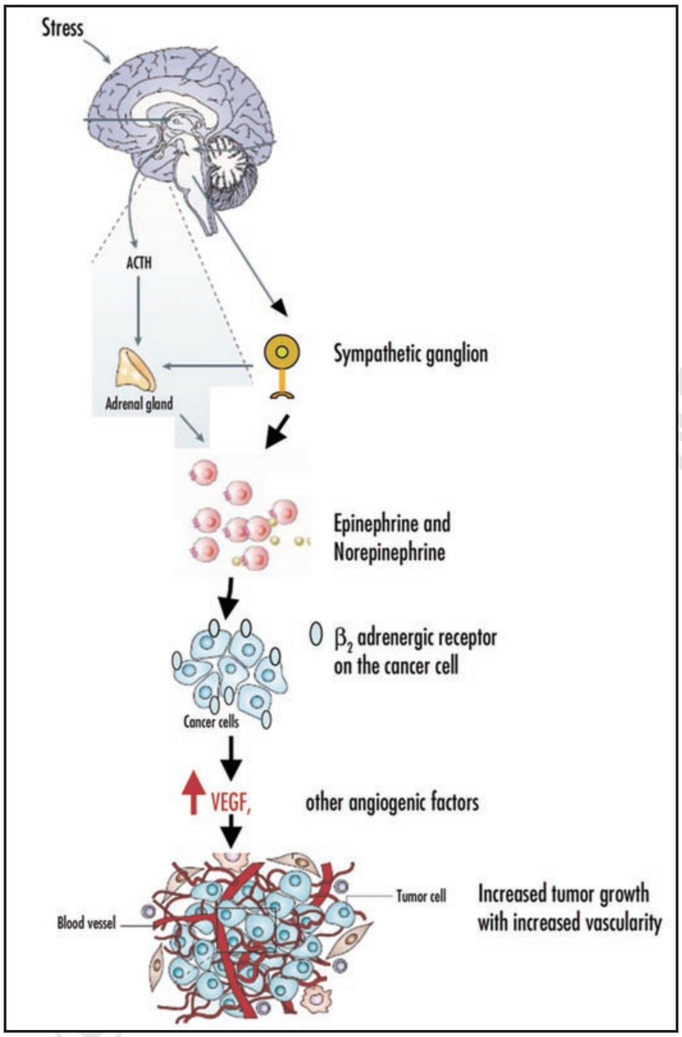

Figure 2. Effects of stress on ovarian cancer growth via VEGF-mediated angiogenesis. Chronic stress leads to the activation of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis, which result in release of catecholamines such as norepinephrine and epinephrine. These catecholamines then activate the β-adrenergic receptors on ovarian cancer cells to secrete VEGF and other angiogenic factors, leading to enhanced tumor growth and increased vascularity. Reprinted and modified with permission from *Nature Reviews Cancer* (see ref. 8).

CLINICAL OPPORTUNITIES AND CHALLENGES

The knowledge of how stress biology affects tumor initiation and pathogenesis is gradually expanding. Biobehavioral factors such as chronic stress, depression, and social support have been linked to tumor biology via their endocrine consequences and cell mediated immunity. Although the molecular pathways have not been fully elucidated, the studies to date indicate possible opportunities for behavioral and pharmacological intervention that target tumor-supporting neuroendocrine dynamics.

Pharmacologic and genetic manipulations identify β-adrenergic signaling as a central mediator of stress effects on cancer growth; therefore, pharmacological interventions such as β-blockers potentially could be used to alleviate the effects of stress on cancer growth and progression. Interestingly, in a large case-control study of prostate cancer patients, Perron and colleagues found that among individuals taking anti-hypertensive medications, only β-blockers were associated with a reduction in cancer risk.[41] A cohort study of cardiovascular patients that used β-blockers had a 49% decrease in cancer risk compared to patients that never used β-blockers. Moreover, there was a 6% decrease in risk for every additional year of β-blocker use.[42] However, other population-based case-control studies of breast carcinoma patients have not confirmed alterations in risk with the use of β-blockers.[43,44] The efficacy of β-blockers in blocking the stress-mediated effects on tumor remains to be examined.

To the extent that behavioral and central nervous system processes modulate the activity of multiple hormones[45-48] and those processes are linked to angiogenic parameters in human clinical studies[37,49] interventions targeting neuroendocrine function at the CNS level might also represent novel strategies for protecting cancer patients from the detrimental effects of stress biology on the progression of malignant disease. Such interventions may include behavioral interventions alone or in combination with pharmacological approaches.[8]

CONCLUSIONS

Although research has shown that stress hormones affect tumor pathogenesis at multiple levels (initiation, tumor growth, and metastasis), our understanding of the underlying mechanisms is in its infancy and needs to be expanded. Based on the importance of the interplay between immunological and behavioral factors providing a favorable microenvironment for tumor initiation and growth, there is a crucial need to integrate a bio-behavioral perspective in therapeutic paradigms of human carcinoma. Interventions targeting neuroendocrine function at the level of the central nervous system could represent a novel strategy for protecting cancer patients from the deleterious effects of stress biology on cancer progression. Theoretically, these pharmacologic and behavioral interventions can be used concomitantly with conventional therapies to maximize efficacy and warrant further study, especially as cancer treatment evolves to encompass more patient-specific therapeutic approaches.

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