Abstract
Cross-sectional observational studies reveal that cancer is more prevalent in depressed persons. Psychosocial stressors such as depression, anxiety, stressful life events, poverty, and lack of social support may favor carcinogenesis. Cancer acquired under these circumstances has a poor prognosis. Conversely, when cancer has developed in the presence of these factors, effective management or treatment of these psychosocial stressors may bring about increased survival time of the affected persons. The purpose of this narrative literature review is to examine the role that maladaptive stress responses play in cancer initiation and progression. Relevant databases, hand searches and authoritative texts were critically analysed and the findings were integrated.

Stress is influenced by genetic, environmental, pharmacological, and infectious factors in addition to the chronicity of depression, social isolation, and poor stress-coping capacity. Chronic psychosocial stress-induced maladaptive activation of the neuroendocrine system may dysregulate immunoinflammatory responses, alter oncogene expression, promote tumor-related angiogenesis, and accelerate growth of cancer with stimulation of neuroendocrine activity, which may favor cancer progression. The evidence that associates psychosocial stressors to cancer progression is stronger than the evidence which links the same psychosocial stressors to cancer incidence.

Keywords: Cancer, HPA-axis, Catecholamines, Psychological stress, Immunoinflammatory responses

Introduction
The hypothalamic corticotrophin-releasing hormone (CRH), arginine vasopressin (AVP), pituitary proopiomelanocortin (POMC)-derived peptides, adrenocorticotropic hormone (ACTH), α-melanocyte stimulating hormone, β-endorphin, and adrenal cortex-derived glucocorticoids (cortisol) constitute the hypothalamic-pituitary-adrenal (HPA) axis. Hypothalamic-pituitary-adrenal neuropeptides, together with catecholamines (noradrenalin and adrenalin), which are released by the
sympathetic nervous system (SNS) regulate responses to acute and chronic stressors.\textsuperscript{1-5}

Stress is a state in which homeostasis is perceived to be, or actually is, disrupted or threatened. The stress response is the reaction that aims to maintain or restore homeostasis.\textsuperscript{5} Stress responses to various chronic psychosocial stressors are complex adaptive processes that comprise stress perception in the brain followed by activation of and interactions between the neural, endocrine, and immune systems. This process is modulated by various factors that include genetic susceptibility, environmental modifiers, age, and gender, which result in an integrated stress response (Figure 1).\textsuperscript{6} The neuroendocrine system influences the activity of the immune system; and reciprocally, the immune system modulates the function of the neuroendocrine system through cytokines and other bioactive agents secreted by immunocytes.\textsuperscript{1,6,7}

Cross-sectional observational studies reveal that cancer is more prevalent in depressed persons, and that psychosocial stressors such as depression, anxiety, stressful life events, poverty, and lack of social support may favor carcinogenesis. Cancer acquired under these circumstances has a poor prognosis.\textsuperscript{1,4,8-10} Conversely, when cancer has developed in the presence of these factors, effective management or treatment of these psychosocial stressors may bring about increased survival time of the affected persons.\textsuperscript{11} The evidence that associates psychosocial stressors to cancer incidence is less strong than evidence, which links the same psychosocial stressors to cancer progression.\textsuperscript{11}

There is evidence that severely immunosuppressed persons are at a higher risk of certain types of cancer compared to immunocompetent persons, and a positive association exists between the presence of numerous lymphocytes in the tumor microenvironment and increased survival.\textsuperscript{12} Thus, chronic psychosocial stress-induced maladaptive activation of the HPA axis and the SNS dysregulate immunoinflammatory responses and enable cancer cells to evade immune surveillance. The proinflammatory cytokines that arise from this immunoinflammatory dysregulation can directly accentuate cancer growth and further stimulate central neuroendocrine activity.\textsuperscript{13-15}

In this short review, we discuss the mechanisms by which chronic psychosocial stress may play a role in cancer progression and possibly carcinogenesis.

**Neuroendocrine control of stress responses**

Biological mediators that play roles in stress responses are produced in various tissues and have both local and remote regulatory functions. Some hormones such as growth hormones and ACTH, which are centrally produced, can act as both central neuropeptides and peripherally as cytokines within the immune system. Cytokines produced by immunocytes in the periphery, under certain circumstances, can reach significant circulating levels and then act as hormones, triggering various biological responses such as

![Figure 1. Stress response to psychological/emotional stressors. Adapted from Chikanza and Grossman.\textsuperscript{6}](image)
Stress and Cancer

neuroendocrine and metabolic reactions. Therefore, it is not practical to group all these biological mediators into classical hormones, growth factors, neurotransmitters, and cytokines.\textsuperscript{16}

Hormones should be regarded as biological mediators that regulate distant tissues and have constant significant functional levels in the blood; neuropeptides as regulatory biological agents produced by the hypothalamus and the anterior pituitary gland; and cytokines as tissue mediators of non-neural origin and those produced by the cells of the immune system (Figure 2).\textsuperscript{16}

Reciprocal stimulatory interactions between the CRH and AVP neurons that originate from the hypothalamus and the noradrenergic sympathetic neurons that originate from the locus coeruleus in the brainstem bring about an integrated stress reaction (Figure 2).\textsuperscript{17} Corticotrophin-releasing hormone and its receptors are found throughout the central nervous system where they mediate a wide range of neural activities that include activation of the HPA axis, noradrenergic neurons in the brainstem, and transcription of the POMC gene in the anterior pituitary with the biosynthesis of POMC-derived neuropeptides (aMSH, opioids, ACTH). These mediators modulate mood, cognition, behavior, and pain experience. Some neurons secrete both CRH and AVP, and it appears that the CRH:AVP ratio is determined by the type, magnitude, and duration of the stressor.\textsuperscript{17} In addition to CRH and AVP, noradrenergic pathways can also induce biosynthesis of POMC-derived opioids. Descending opioidergic pathways inhibit nociceptive neural circuits at the level of the dorsal horn of the spinal cord.\textsuperscript{5,18}

Neuropeptide Y is found in noradrenergic neural pathways or in dedicated neuropeptide Y-containing neurons\textsuperscript{5,17} and, like noradrenalin, it upregulates CRH production in the hypothalamus and acts synergistically with CRH to induce production and release of ACTH.\textsuperscript{18} Serotonin stimulates the HPA axis, probably through upregulation of hypothalamic release of CRH, but the role that serotonin plays during stress

Figure 2. Cognitive/emotional stress as it relates to the neuroendocrine loop determining the stress response. Adapted from Chikanza and Grossman 1996 and Torpy and Chrousos.\textsuperscript{6,17}
response is not clear. Additionally, the serotonin neuronal pathways may interact with substance Y neuronal pathways at the level of the spinal cord to modulate pain perception.

The neuroendocrine-immune loop

There is reciprocity between the neuroendocrine and immune systems. The HPA axis regulates the activity of the immune system during physiological and stress conditions (Figure 2). The physiological concentration of cortisol regulates the traffic of lymphocytes to the peripheral blood, production of inflammatory mediators and proinflammatory cytokines, T cell responses, and function of biomembranes. However, raised levels of cortisol suppress traffic of leukocytes to the peripheral blood, production of inflammatory mediators and proinflammatory cytokines, T cell responses, and alter the functions of the endothelial cell barrier of mast cells and monocytes.

Corticotrophin-releasing hormone indirectly downregulates the function of the immune system through its central stimulation of sympathetic neural pathways. The consequent increased levels of catecholamines downregulate immune functions. In addition, POMC-derived peptides, ACTH, opioids, and αMSH produced centrally may exert an anti-immunoinflammatory effect by modulating the function of mononuclear cells in the peripheral blood and production of proinflammatory cytokines. By contrast, substance P and calcitonin gene-related peptide have proinflammatory properties. Corticotrophin-releasing hormone, ACTH, αMSH, opioids, and substance P are among the neuropeptides that can be produced in the periphery by various cells such as keratinocytes, melanocytes, and immunoinflammatory cells. They function locally as cytokines that modulate immunoinflammatory responses.

Cancer and cancer immunity

Cancer is a potentially fatal disease that is the outcome of a complex process of cytogenetic and epigenetic alterations which dysregulate cell cycle progression, apoptosis, DNA repair, and cell differentiation. Cancer cells are characterized by uncontrolled cell proliferation and prolonged survival. They have the capacity to evade the immune system, invade tissues, and metastasize. Most cancers develop in genetically predisposed subjects with repeated exposures to exogenous carcinogens.

Not all cancer cells are immunogenic to a degree sufficient to activate effective immune responses. The existence of cancer is the evidence of insufficient activation or failure of the immune system, which otherwise might control the initiation and progression of the cancer. However, when the immune system does detect the malignant cells, both NK cells and T lymphocytes are the predominant immune effector cells that respond to the challenge. Any antigens specific to the cancer cells are either presented by the cancer cells on their surfaces in the context of MHC class I molecules, or are recognized and processed by antigen presenting cells (i.e., dendritic cells and macrophages). They are later
expressed on their cell surfaces in the context of MHC class II molecules. In the regional lymph nodes, the antigen presenting cells present the cancer-specific antigens to CD4+ T lymphocytes. Following a complex process, the CD4+ T lymphocytes trigger the generation and activation of antigen-specific CD8+ cytotoxic T lymphocytes. After clonal expansion, these cytotoxic CD8+ T cells recognize cancer-specific antigens in the context of MHC class I molecules and cause cytolysis of cancer cells through the effector molecules, perforin and granzyme B.22

In contrast to the response of T lymphocytes to cancer cells, the anti-cancer cell activity of NK cells is not antigen-specific and does not require prior sensitization. NK cells have both regulatory and cytotoxic activities. They recognize stress-related proteins, proteoglycans, and danger molecules abnormally expressed on certain types of cancer cells. Upon activation by these ligands, NK cells can cause death of cancer cells by lysis through the release of cytotoxic granules, activation of death-receptor pathways, and release of cytokines such as interferon gamma. Some cancer cells have impaired expressions of MHC class 1 molecules on their surfaces. As a result, NK cells recognize these cancers cells as ‘non-self’, causing their cytolysis. The death of cancer cells induced by NK cells results in the release of cancer cell antigens which, in turn, are processed by antigen presenting cells and presented to the T lymphocytes, promoting humoral and cell mediated adaptive anti-tumor immune responses.23,24

Cancer in relation to chronic psychosocial stress with reference to catecholamines and neuropeptides of the HPA axis

Upon stimulation by chronic psychosocial stressors, interactions occur between a multitude of cognitive, emotional, neurosensory, and peripheral somatic signals, which generate an integrated stress response characterized by adaptive physical and behavioral reactions.5 Changes in immune responses are part of these adaptive physical responses.25

It appears that both subjective (i.e., worry) and objective (i.e., being a forced refugee) adverse psychological experiences may lead to chronic stress-related changes in the immune responses, which in turn may act as co-factors in the initiation, and later in the influencing of the clinical course of certain health disorders.5,25 To complicate matters, it is not uncommon for persons exposed to stressful experiences to begin to smoke, drink, and take medications which may directly moderate immune responses.25

Maladaptive neuroendocrine responses to chronic psychosocial stress include upregulation of the activities of the SNS and the HPA axis. While the role that neuropeptides of the HPA axis play in carcinogenesis is not clear, it appears that increased levels of catecholamines (i.e., adrenalin and noradrenalin) have the capacity to promote carcinogenesis and metastasis of certain types of cancer.1

Chronic psychosocial stressors (i.e., social isolation, major stressful life events, chronic illness, cognitive demands) can alter physiological immune activity and bring about psychological symptoms such as depression, anxiety, and feelings of hopelessness or hostility. Cognitive appraisal, emotional control, and personality traits such as neuroticism, conscientiousness, and mental resilience are some factors which have the capacity to modulate physical and psychological responses to chronic psychosocial stressors.26

The nature of the stress response to chronic psychosocial stressors is influenced by developmental, epigenetic, and genetic factors, the type of the stressor and its duration, severity, and ability to be controlled.5,25,27,28 The considerable personal variations in response to similar or identical psychosocial stressors is also related to the cognitive appraisal of the stressor,29 which occurs in the prefrontal cortex. Through neural connections from the prefrontal cortex to the limbic system (amygdala and hippocampus), cognitive/executive mechanisms influence the experience and expression of emotions (Figure 3).30-32 Cognitively-controlled emotions generated in the limbic system, in turn, influence the release of stress effectors of the SNS and of the HPA.
Thus, specific psychosocial stressors may generate physiological and behavioral responses that differ between persons because of differences in cognitive appraisal and executive mechanisms (Figure 3). Catecholamines stimulate β-adrenergic receptors of immunoinflammatory cells that activate the transcription factor nuclear factor-kB (NF-kB) and activator protein 1 (AP-1), which upregulate cellular expression of certain proinflammatory genes. This results in the production of proinflammatory cytokines that drive inflammatory reactions. In the context of cancer, the proinflammatory cytokines may induce cell proliferation and promote cell survival through activation of oncogenes and inhibition of tumor-suppressor genes. This may result in cellular genetic instability with an increased risk of cancerous transformation. Furthermore, the proinflammatory cytokines can promote both angiogenesis and an inflammatory tumor microenvironment which support tumor progression.

Adequate vascularization is essential to tumor growth, invasiveness, and metastasis. Vascular endothelial growth factor (VEGF), interleukin (IL)-6 and IL-8 are angiogenic factors secreted by cancer cells and by tumor associated macrophages. Elevated levels of chronic stress-associated catecholamines can exaggerate the production of these angiogenic factors in the tumor microenvironment, thus promoting tumor angiogenesis. In the context of cancer progression, catecholamines in the tumor microenvironment stimulate the production of the matrix metalloproteinases (MMP)-2 and MMP-9, which can also mediate angiogenesis and degrade components of the extracellular matrix such as collagen, elastin, fibronectin, and basement membranes, which promote invasion and spread of cancer cells.

Psychosocial chronic stress-induced elevated levels of catecholamines and cortisol can impair immune reactions by shifting the balance between Th1-mediated and Th2-mediated immune responses that favor a Th2 immunoinflammatory response, and by suppressing the proliferation of lymphocytes and the production of selective T cell-derived cytokines. They can dysregulate the functions of macrophages, dendritic, natural killer, and endothelial cells. This immune impairment favors cancer cell immune evasion, leading to increased growth of certain tumors.

Animal studies show that chronic psychosocial stress, through activation of β-adrenergic receptor pathways, can activate microglia and CNS macrophages with consequent upregulation of inflammatory mediators in the CNS. This may induce anxiety and alterations to immune reactions with an increased risk of cancer. In subjects with cancer, tumor-derived inflammatory cytokines, inflammation induced by stress of the pain, concern about the treatment, possible recurrence, and death, in addition to inflammation induced by cancer treatment itself (surgery, chemotherapy, and radiotherapy) can impact the brain by altering the metabolism of certain neurotransmitters such as serotonin, dopamine, and noradrenalin. It can directly modulate the function of brain areas engaged in cognitive processes and behavior. Thus, inflammatory cytokine-induced changes in the brain may play a role in the development of mood disorders, anxiety, and depression, with further promotion of inflammation to favor cancer growth.

Conclusion

The stress response is driven by neuropeptides of the HPA axis and of the SNS. The major central effectors are CRH, POMC-derived neuropeptides, and noradrenalin. The major peripheral effectors are cortisol and catecholamines. There are bidirectional complex regulatory interactions between the neuroendocrine system and the immune system, in which proinflammatory cytokines produced by the immune system stimulate the HPA axis and the SNS. Conversely, the neuroendocrine system regulates the immune system.

Conflict of Interest

None declared.
References


29. Denson TF, Spanovic M, Miller N. Cognitive appraisals


