Regulation of Cancer Progression by β-Endorphin Neuron
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Abstract
It is becoming increasingly clear that stressful life events can affect cancer growth and metastasis by modulating nervous, endocrine, and immune systems. The purpose of this review is to briefly describe the process by which stress may potentiate carcinogenesis and how reducing body stress may prevent cancer growth and progression. The opioid peptide β-endorphin plays a critical role in bringing the stress axis to a state of homeostasis. We have recently shown that enhancement of endogenous levels of β-endorphin in the hypothalamus via β-endorphin neuron transplantation suppresses stress response, promotes immune function, and reduces the incidence of cancer in rat models of prostate and breast cancers. The cancer-preventive effect of β-endorphin is mediated through the suppression of sympathetic neuronal function, which results in increased peripheral natural killer cell and macrophage activities, elevated levels of anti-inflammatory cytokines, and reduced levels of inflammatory cytokines. β-endorphin inhibition of tumor progression also involves alteration in the tumor microenvironment, possibly because of suppression of catecholamine and inflammatory cytokine production, which are known to alter DNA repair, cell-matrix attachments, angiogenic process, and epithelial–mesenchymal transition. Thus, β-endorphin cell therapy may offer some therapeutic value in cancer prevention. Cancer Res; 72(4): 836–40. ©2012 AACR.

Introduction
Emerging evidence suggests that chronic neurobehavioral stress can promote growth and progression of various cancers. Psychologic factors may alter immune and endocrine functions, and it has long been hypothesized that, through this pathway, stress may affect tumor growth and spread. On the other hand, it has long been known that relieving the stress of cancer often leads to faster recovery and general well-being in patients who are undergoing chemotherapy or radiotherapy (1). Recent work with animal models suggests that the body’s neuroendocrine response (release of hormones in circulation) following psychosocial or physical stress can significantly affect many aspects of the body’s immune systems (2) and can also, directly or via immune surveillance, alter important processes of cells that help to protect against the formation of cancer, such as DNA repair and the regulation of cell growth (3–5). Therefore, controlling the body’s stress response may be beneficial to immunity against cancer. Hence, in this review, we first briefly describe the process of how stress may affect immunity and cancer growth and then summarize the data obtained in animal studies showing how reduction of the stress response by β-endorphin cell transplantation may prevent cancer growth and progression.

Neuroendocrine Response to Stress
Environmental and psychosocial stimuli initiate a cascade of physiologic changes in the central nervous system (CNS) and periphery, which subsequently trigger the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal axis (HPA: reviewed in ref. 6). Stressful experiences activate components of the limbic system, including the hypothalamus, the hippocampus, and the amygdala, which modulate the activity of hypothalamic and brain-stem structures that control the HPA and ANS activities. The hypothalamus secretes corticotrophin-releasing hormone (CRH) and arginine vasopressin from the paraventricular nucleus of the hypothalamus, both of which activate the pituitary to release hormones of the proopiomelanocortin peptides, such as adrenocorticotropic hormone (ACTH), which stimulate the secretion of glucocorticoids from the adrenal cortex into the peripheral circulation. Stress response also involves secretion of adrenaline (epinephrine) from the chromaffin cells of the adrenal medulla. In addition to the activation of the HPA axis, stressful stimuli activate the sympathetic nervous system (SNS), what is often termed the “fight or flight” response. Like other parts of the nervous system, the SNS operates through a series of interconnected neurons, many of which have direct connections with the neurons of the paraventricular nucleus, which run through the brain stem and the preganglionic neurons and terminate in the ganglia near the spinal column. From these ganglia, postganglionic fibers run to the effector organs, including spleen and many other lymphoid tissues. The main neurotransmitter of the preganglionic sympathetic fibers is acetylcholine, a chemical messenger that binds and activates nicotinic acetylcholine receptors on postganglionic neurons. The principal neurotransmitter released by the postganglionic neurons is...
noradrenaline (norepinephrine). The other division of the ANS is the parasympathetic nervous system, which is responsible for stimulation of "rest and digest" activities that occur when the body is at rest and normally functioning, in opposition to the sympathetic nervous system. The main neurotransmitter of the parasympathetic fibers is acetylcholine. Acetylcholine acts on 2 types of receptors, the nicotinic cholinergic (at postganglionic neurons) and muscarinic (at the target organ).

The so-called "fight or flight" response can also be seen as an energy redirection program, and the "rest and digest" activities can be seen as an energy storage program (7). During these body responses, hormones and neurotransmitters that provide energy-rich fuels to stores and those that provide energy-rich substrates are being released. Additionally, altered production and secretion of various proinflammatory cytokines, such as TNF-α, interleukins-1β (IL-1β) and -6 (IL-6), and circulating activated immune cells, are being imposed. Many of these conditions contribute to the metabolic syndromes that often co-occur with cancer.

Neuroendocrine–Neuroimmune Pathways of Cancer

Recently, the results of various studies on animals and humans point to the fact that the body's psychophysiologic reactions during stress are associated with a greater likelihood of incidence or relapse of cancer (5, 8). At cellular and molecular levels, psychologic stress-associated increase in production of epinephrine, norepinephrine, and cortisol cause an upregulation of DNA damage sensors Chk1 and Chk2 and the protooncogene CDC25A, which is involved in cell-cycle delay following DNA damage, resulting in increased cell transformation and/or tumorigenicity (9). The findings of transgenic, knockout, and in vitro models suggest that a dysregulated stress response downregulates tumor suppressor genes, such as PTEN, or DNA repair genes, such as BRCA1 (10). Animal studies have shown that activation of the SNS (which happens during various stresses) increased lung tumor metastases, whereas pretreatment of animals with -adrenergic antagonists (to block the activity of SNS activation) and indomethacin (to block in vitro

β-Endorphin, an endogenous opioid polypeptide primarily produced by the hypothalamus and the pituitary gland, is known to have the ability to inhibit stress hormone production and produce analgesia and a feeling of well-being (19). β-endorphin is a cleavage product of pro-opiomelanocortin, which is also the precursor hormone for ACTH and -melanocyte-stimulating hormone (α-MSH). In the hypothalamus, the primary products of pro-opiomelanocortin are β-endorphin and α-MSH, whereas in the pituitary, pro-opiomelanocortin produces 2 other products (β-endorphin, α-MSH, and ACTH). β-endorphin neuronal cell bodies are primarily localized in the arcuate nuclei of the hypothalamus, and its terminals are distributed throughout the CNS, including the paraventricular nucleus of the hypothalamus (20). In the paraventricular nucleus, these neurons innervate CRH neurons and inhibit CRH release (21), whereas a opioid receptor antagonist increases it (22). During stress, secretion of CRH and catecholamine stimulates secretion of hypothalamic β-endorphin and other pro-opiomelanocortin-derived peptides, which in turn inhibit the activity of the HPA axis (23). β-Endorphin is known to bind to δ- and μ-opioid receptors to modulate the neurotransmission in neurons of the ANS via neuronal circuitry within the paraventricular nucleus. β-Endorphin peptides, produced from the pituitary pro-opiomelanocortin that circulates in the periphery, are primarily regulated by CRH and
arginine vasopressin and may have less control over the ANS function.

In the CNS, the opioid peptide \( \beta \)-endorphin is reported to have rewarding and reinforcing properties and to be involved in stress response. Additionally, a low level of central \( \beta \)-endorphin is connected with the process of stress-related psychiatric disorders, depression, and posttraumatic stress disorder (24, 25). Abnormalities in \( \beta \)-endorphin neuronal function are correlated with a higher incidence of cancers and infections in patients with schizophrenia, depression, fetal alcohol
syndrome, and obesity (reviewed in ref. 26). Despite this evidence, the role of the neuronal β-endorphin in these diseases is not well studied, because long-term peripheral administrations of this opioid-like peptide, or its agonist analogue, induce tolerance and dependence in animals and make it difficult to study its action on chronic disease, like cancer, in animals. Furthermore, peripheral β-endorphin may not act like central β-endorphin, and therefore, data from β-endorphin knockout or transgenic mice on the neuroendocrine–immune axis are often difficult to interpret. We have recently circumvented this problem by using β-endorphin cell transplantation, in which pure β-endorphin neurons are differentiated from neuronal stem cells in vitro and then transplanted in the paraventricular nucleus at a site where endogenous β-endorphin neurons make synaptic contact with both CRH and neuronal populations connected with the ANS (27). With this approach, it was feasible to increase the influence of this opioid on 3 important components of body stress regulation: the HPA axis, sympathetic neurons, and parasympathetic neurons. As they do in vivo, in vitro–differentiated β-endorphin cells, when transplanted into the paraventricular nucleus of the hypothalamus of stress hyperresponsive and immune-deficient fetal alcohol–exposed rats, reduced plasma levels of corticosterone and improved NK-cell cytolytic function in these rats (23). β-endorphin transplantation also suppressed plasma corticosterone and increased NK cell activity in control rats.

We have previously shown that the neural stem cell–derived β-endorphin neurons, when injected into the paraventricular nucleus, remained viable at the site of transplantation for a long period and suppressed carcinogen-induced prostate cancer development in rats (27). Additionally, we showed that supplementation of β-endorphin neurons through transplants prevented carcinogen-induced mammary tumorigenesis and tumor metastasis (26). Importantly, when the β-endorphin transplants were given at the early stage of tumor development, many tumors were destroyed, possibly because of increased innate immune activity, and the surviving tumors lost their ability to progress to high-grade cancer owing to β-endorphin cells’ suppressive effects on epithelial–mesenchymal transition regulators. Another remarkable effect of the β-endorphin transplantation was that it promoted the activation of the innate immune (NK cells and macrophages) activity, following tumor cell invasion, to such an extent that tumor cell migration to another site was completely halted. NK cells and macrophages are critical components of the innate immune system and play a vital role in host defense against tumor cells (28, 29). Hence, the increased level of innate immunity may have caused unfavorable conditions for cancer cell survival. In the β-endorphin cell–treated animals, the lower inflammatory milieu that was achieved by the higher level of anti-inflammatory cytokines and the lower level of inflammatory cytokines may have also been involved in inhibiting cancer growth and transformation. Several studies have identified the involvement and roles of inflammatory cytokines in breast malignancy (30). The cancer-preventive and inflammatory cytokine suppression effects of the β-endorphin neuronal transplant could be reversed by treatment with a β-receptor agonist or by a nicotine acetylcholine receptor antagonist. This finding suggests that the suppression of sympathetic neuronal function and the stimulation of parasympathetic neuronal activity are the processes that β-endorphin neurons engage to activate peripheral immunity and anti-inflammatory cytokines to control tumor growth and progression (Fig. 1).

Concluding Remarks

Neurobehavioral stress has been shown to promote tumor growth and progression, possibly by altering the production of hormones, catecholamine, and inflammatory cytokines. Although the cellular mechanisms of stress-activated chemicals on tumor growth and progression are not apparent, it has been found that these chemicals decrease immune surveillance and alter the tumor microenvironment, including cell-matrix attachments, cell migration, invasive potential, and angiogenic mechanisms. Reduction of body stress via β-endorphin neural transplants in the brain decreases cancer growth and progression in animal models of breast and prostate cancers, possibly by altering ANS functioning, leading to activation of innate immunity and reduction in systemic levels of inflammatory and anti-inflammatory cytokine ratios. Thus, it is apparent that stress prevention by β-endorphin cell therapy might be beneficial in controlling breast, prostate, and possibly other cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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