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REVIEW ARTICLE

Neuroendocrine-Immune Mechanisms of Behavioral Comorbidities in Patients With Cancer

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ABSTRACT

Patients with cancer experience a host of behavioral alterations that include depression, fatigue, sleep disturbances, and cognitive dysfunction. These behavioral comorbidities are apparent throughout the process of diagnosis and treatment for cancer and can persist well into the survivorship period. There is a rich literature describing potential consequences of behavioral comorbidities in patients with cancer including impaired quality of life, reduced treatment adherence, and increased disease-related morbidity and mortality. Medical complications of cancer and its treatment such as anemia, thyroid dysfunction, and the neurotoxicity of cancer chemotherapeutic agents account in part for these behavioral changes. Nevertheless, recent advances in the neurosciences and immunology/oncology have revealed novel insights into additional pathophysiologic mechanisms that may significantly contribute to the development of cancer-related behavioral changes. Special attention has been focused on immunologic processes, specifically activation of innate immune inflammatory responses and their regulation by neuroendocrine pathways, which, in turn, influence CNS functions including neurotransmitter metabolism, neuropeptide function, sleep-wake cycles, regional brain activity, and, ultimately, behavior. Further understanding of these immunologic influences on the brain provides a novel conceptual framework for integrating the wide spectrum of behavioral alterations that occur in cancer patients and may reveal a more focused array of translational targets for therapeutic interventions and future research. Such developments warrant complementary advances in identification of cancer patients at risk as well as those currently suffering, including an increased emphasis on the status of behavior as a "sixth vital sign" to be assessed in all cancer patients throughout their disease encounter.

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INTRODUCTION

Receiving a diagnosis of cancer and managing the subsequent psychological and physiological assaults presents a formidable challenge. Although tremendous advancements have been made in the development of more effective and less traumatic cancer therapies, patients continue to struggle with myriad behavioral complications including depression, fatigue, sleep disturbances, and cognitive dysfunction. Mounting research has begun to shed increasing light on these behavioral comorbidities, not only in terms of their prevalence and consequences, but also, most importantly, in terms of potential common underlying mechanisms and related translational implications.[1] Such increasing knowledge will provide a better understanding of treatment strategies and ultimately guidelines for clinical management. Moreover, this knowledge will serve as the basis for implementing more standardized assessments of behavior in the routine care of cancer patients and instantiate behavior as the "sixth vital sign."

In this review, we describe new research at the interface of immunology/oncology and neurobiology/neuroendocrinology as it relates to the major behavioral challenges faced by cancer patients. More specifically, we present data indicating that increased inflammatory responses, in part related to impaired regulation by the neuroendocrine system, interact with pathophysiologic pathways known to be involved in the regulation of behavior, and thus may mediate the development of behavioral symptoms in cancer patients (Fig 1). Of note, this increasing appreciation of the role of inflammation in behavioral pathology is complementary to an increasing awareness of inflammation as a common mechanism in multiple diseases including cardiovascular disease, diabetes, and cancer.[2] Moreover, this novel conceptual framework may ultimately serve to integrate the spectrum of behavioral comorbidities experienced by cancer patients and provide

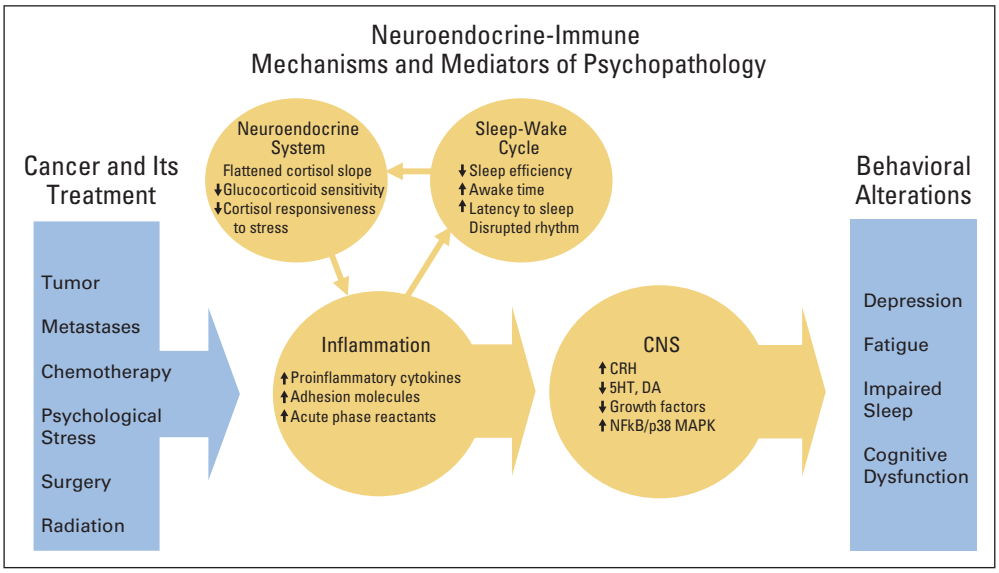

Fig 1. Various aspects of being diagnosed with and treated for cancer activate inflammation through tissue damage/destruction and/or psychological stress. Cytokines of the innate immune response, along with lifestyle changes, pain, and other consequences of cancer and its treatment alter the sleep-wake cycle, which in turn contributes to disruption of the neuroendocrine system, in particular, the hypothalamic-pituitary-adrenal (HPA) axis. Given the role of the HPA axis and glucocorticoids in regulating inflammatory responses, altered HPA axis function may disrupt glucocorticoid-mediated negative regulation of inflammation. Unrestrained inflammation and the associated increased release of proinflammatory cytokines, in turn, interacts with CNS pathways that regulate behavior, leading to pathophysiologic changes that underlie depression, fatigue, impaired sleep, and cognitive dysfunction. MAPK, mitogen-activated protein kinase; CRH, corticotropin-releasing hormone; NFκB, nuclear factor κB.

an organizing principle for determining which patients are at greatest risk under what treatment conditions. We also explore relevant translational implications of this research as well as directions for future study.

INFLAMMATION AND BEHAVIOR

Increasing data indicate that activation of innate immune responses (inflammation) may contribute to the development of behavioral alterations in both medically ill and medically healthy individuals. Studies in laboratory animals and humans provide compelling evidence that administration of innate immune cytokines can induce a syndrome of "sickness behavior" that has many overlapping features with the behavioral comorbidities commonly experienced by cancer patients, including depression, fatigue, impaired sleep, and cognitive dysfunction.[3,4] These behavioral effects of cytokines seem to be secondary to the capacity of peripheral cytokine signals to access the brain and activate inflammatory responses within the brain, which then interact with pathophysiologic pathways known to be involved in behavioral disorders.[5-8] Indeed, cytokine-induced behavioral changes have been associated with alterations in the metabolism of relevant neurotransmitters such as serotonin, norepinephrine, and dopamine, all of which play a major role in the regulation of multiple behaviors and are the primary targets for currently available psychopharmacologic treatments of depression and anxiety as well as fatigue.[9,10] For example, innate immune cytokines, including interferon (IFN)-alpha and interleukin (IL)-6, have been shown to deplete the amino acid tryptophan, the primary precursor of serotonin, via induction of the enzyme indolamine 2,3 dioxygenase (IDO).[11,12] In addition, through activation of p38 mitogen-activated protein kinase (MAPK) signaling pathways, tumor necrosis factor (TNF)-alpha and IL-1 have been found to increase the function and expression of the synaptic reuptake pumps for serotonin and norepinephrine.[13,14] Taken together, these data suggest that innate immune cytokines can lead to a "double hit" on the synaptic availability of relevant neurotransmitters, influencing both their synthesis and reuptake, and thereby potentially contributing to the development of behavioral changes.[9]

Innate immune cytokines also have been found to increase mRNA and protein of the neuropeptide corticotropin-releasing hormone (CRH).[15,16] CRH is a key regulator of the hypothalamic-pituitary-adrenal (HPA) axis and has been found to be increased in the CSF of patients with a number of behavioral disorders including major depression.[17] In addition, administration of CRH to laboratory animals has been found to lead to alterations in behavior including depressive and anxiety-like behaviors, impaired sleep, anorexia, and reduced activity.[17] Increased HPA axis responses to IFN-α, which are believed to be secondary to sensitized CRH pathways, have been associated with the development of major depression in patients with malignant melanoma during IFN-α therapy.[18,19]

Another mechanism by which innate immune cytokines may contribute to alterations in behavior is through their effects on regional brain activity. These effects have been investigated in the context of administration of IFN-α for cancer and infectious diseases. For example, administration of IFN-α has been associated with increased regional blood flow in the dorsal part of the anterior cingulate cortex (dACC) as revealed by functional magnetic resonance imaging during a task of visuospatial attention.[20] The dACC is believed to play an important role in detecting physical and social threat, and subsequently recruiting attention and coping resources to minimize danger.[21] Of note, increased dACC activity has been demonstrated in individuals at risk for mood and anxiety disorders, including those with high-trait anxiety, neuroticism, and obsessive-compulsive disorder.[20] Studies using [^{18}F]fluorodeoxyglucose (FDG) and positron emission tomography (PET) have shown that IFN-α administration also results in significant changes in prefrontal cortex and basal ganglia activity, which have been correlated with the development of depression and fatigue, respectively.[22,23] IFN-α–induced alterations in neurocognitive functions relevant to the basal ganglia (ie, psychomotor slowing) also have been associated with the development of depressive symptoms in cancer patients.[24]

In addition to effects on the function of brain regions that subserve various cognitive processes and behavior, administration of innate immune cytokines to laboratory animals has been shown to disrupt long-term potentiation in the hippocampus and thereby disrupt memory consolidation.[25,26] Moreover, the release of IL-6 from activated macrophages has been shown to mediate the inhibitory effects of cranial x-ray irradiation on the growth and development of neuronal progenitor cells in the hippocampus.[27]

Finally, ongoing research has revealed an emerging relationship between innate immune cytokines and disrupted sleep-wake cycles (Fig 1). Sleep loss induces cellular and genomic markers of inflammation[28] and leads to increases in circulating levels of innate immune cytokines and markers of systemic inflammation such as C-reactive protein (CRP).[29,30] Conversely, elevations of innate immune cytokines such as IL-6, before sleep onset correlate with prolonged sleep latency,[31-33] and IL-6 administration decreases delta wave sleep.[34]

PSYCHOLOGICAL STRESS AND INFLAMMATION

Given the well-known role of psychological stress in the development of a wide variety of behavioral disorders,[35] it is intriguing to note that stress can activate inflammatory cytokines and their signaling pathways (eg, nuclear factor κ B [NFκB]) both in the periphery and in the brain.[36-39] In addition, data in rats indicate that stress can activate microglia in the brain and increase their sensitivity to immunologic stimuli (ie, lipopolysaccharide [LPS]).[38] Of note, stress-induced IL-1 in the brain has been shown to significantly reduce the expression of brain-derived neurotrophic factor (BDNF), which is believed to play a pivotal role in neuronal growth and development, learning, synaptic plasticity, and, ultimately, behavioral disorders.[40,41]

The effects of stress on brain inflammatory pathways are believed to be mediated by activation of the sympathetic nervous system and the release of catecholamines which bind to alpha and beta adrenergic receptors on relevant cells.[36,39] Interestingly, recent data suggest that the parasympathetic nervous system via the release of acetylcholine and subsequent activation of the alpha 7 subunit of the nicotinic acetylcholine receptor can inhibit inflammatory signaling pathways (eg, NFκB),[42] suggesting that sympathetic and parasympathetic pathways have an opposing influence on inflammatory responses during stress.

NEUROENDOCRINE REGULATION OF INFLAMMATORY RESPONSES

The neuroendocrine system, specifically the HPA axis and glucocorticoids, plays a primary role in the negative regulation of inflammatory responses. Indeed, glucocorticoids, such as cortisol, are the most potent anti-inflammatory hormones in the body.[43] These effects are largely mediated by protein-protein interactions between the glucocorticoid receptor and relevant inflammatory signaling molecules including NFκB.[44] Thus, disruption of glucocorticoid signaling either through altered release of glucocorticoid hormones (including changes in the circadian cortisol rhythm) or disruption of glucocorticoid receptor function may contribute to increased inflammatory responses. Of relevance to the potential role of cytokines in this process, cytokine signaling pathways including p38 MAPK have been shown to disrupt glucocorticoid receptor signaling,[45,46] and thereby may contribute to reduced sensitivity of immune cells to the anti-inflammatory effects of glucocorticoids. Disruption of glucocorticoid receptor function may also contribute to altered HPA axis function, including flattening of diurnal cortisol production and the inability to shut down cortisol production (nonsuppression) after administration of the synthetic glucocorticoid dexamethasone (as manifested by an abnormal dexamethasone suppression test [DST]). Of note, abnormal DST responses have been associated with increased production of IL-1 by peripheral-blood mononuclear cells (PBMCs) in healthy patients with major depression.[47] Intense and/or chronic stress has also been associated with alterations in HPA axis function including decreased cortisol production, flattening of the cortisol diurnal rhythm, and reduced glucocorticoid receptor function, as manifested by altered responses to dexamethasone.[48] Taken together, these data suggest that both cytokines and stress can conspire to alter HPA axis and glucocorticoid receptor function, leading to a reduced ability of endogenous glucocorticoids to restrain inflammatory responses.

EVIDENCE FOR THE ROLE OF INFLAMMATION AND ITS ALTERED REGULATION BY THE NEUROENDOCRINE SYSTEM IN BEHAVIORAL COMORBIDITIES IN PATIENTS WITH CANCER

There are a number of factors that increase the likelihood that cancer patients will exhibit activation of inflammatory pathways (Fig 1). Surgery, chemotherapy, and radiation are all associated with significant tissue damage and destruction, which in turn is related to activation of innate immune responses. In addition, chemotherapeutic agents and gamma-irradiation are capable of directly inducing NFκB and its downstream proinflammatory gene products.[2] Moreover, receiving a diagnosis of cancer and battling with chronic uncertainties regarding treatment, recurrence, and mortality is one of the greatest stressors imaginable. Given the impact of stress on inflammatory responses, the confluence of the physical and psychological challenges inherent in having and being treated for cancer place the cancer patient at high risk for the development of inflammation-induced behavioral alterations. The most common of these behavioral changes will be reviewed in the following sections in the context of evidence that inflammation and its regulation by the neuroendocrine system may be involved.

Depression

Of all the behavioral comorbidities that plague cancer patients, major depression, a syndrome characterized by depressed mood and/or anhedonia and accompanied by alterations in appetite, sleep, activity levels, and cognitive function, has been one of the most studied and best characterized. Major depression in patients with cancer occurs at a high rate, with a median point prevalence (15% to 29%) that is approximately three to five times greater than the general population.[49,50] Aside from a profound impact on quality of life, major depression in patients with cancer is associated with increased health care utilization, poor treatment adherence, and, in some cases, increased rates of cancer recurrence and mortality.[49-52]

Relevant to the role of the immune system in depression in cancer patients, increased plasma concentrations of IL-6, have been found in two separate studies in cancer patients diagnosed with major depression (Table 1).[53,54] Nevertheless, results have been inconsistent,

Table 1. Biomarkers of Inflammation in Cancer Patients With Behavioral Comorbidities

Investigator	Cancer Type	Patient Sample	Immune Parameter	Behavioral Comorbidity	Results
Greenberg et al 1993[63]	Prostate	15 male patients receiving local radiation	IL-1 (serum)	Fatigue	IL-1 levels were increased in parallel with fatigue
Morant et al 1993[75]	Mixed	31 male and female patients with advanced cancer and 30 healthy controls	CRP, TNF, IL-1, IL-2R (serum)	Asthenia	No statistically significant correlation was found between asthenia and immune parameters
Knobel et al 2000[72]	Lymphoma	33 male and female patients 4-10 years post-BMT	IL-6, TNF-α, sTNFR p55 and p75 (serum)	Fatigue	No statistically significant correlation was found between fatigue and immune parameters
Musselman et al 2001[53]	Mixed	21 male and female patients with pancreatic, breast, and esophageal cancer	IL-6 (plasma)	Major depression	IL-6 was significantly elevated in cancer patients with depression compared with nondepressed patients
Geinitz et al 2001[66]	Breast	41 female patients with breast-conserving surgery and RT	IL-1β, IL-6, TNF-α (serum)	Fatigue	No correlation was found between fatigue and immune parameters
Bower et al 2002[70]	Breast	40 female breast cancer survivors	IL-1β, IL-1ra, sTNFR p75, neopterin (serum)	Fatigue	IL-1ra, TNFR-p75, and neopterin were significantly higher in fatigued patients. IL-1β was not detectable in the majority of patients
Bower et al 2003[152]	Breast	39 female breast cancer survivors	Peripheral blood lymphocyte phenotypic markers, IL-1ra (serum)	Fatigue	CD3+, CD4+, and CD56+ numbers were significantly higher in fatigued patients, and CD3+ numbers correlated with IL-1ra
Wratten et al 2004[64]	Breast	52 female patients receiving local radiation	IL-6, TNF-α, sICAM-1, TGF-β, PDGF, FGF, CRP (serum)	Fatigue	Fatigue correlated with IL-6, sICAM-1, and CRP at baseline, and with IL-6 at week 5 of RT; no correlation was found between fatigue and immune parameters after controlling for BMI
Dimeo et al 2004[73]	Lymphoma, AML, CML ALL, CLL	71 male and female patients without chemotherapy, radiation, or immunotherapy within 3 months	IL-1-α, IL-1ra, IL-6, neopterin (serum)	Fatigue	No correlation was found between fatigue and immune parameters
Ahlberg et al, 2004[67]	Uterine	15 female patients receiving local radiation	IL-1, IL-6, TNF-α (blood, not otherwise specified)	Fatigue	No changes in cytokines were found during RT; no correlations were found between change in fatigue and change in IL-1 and TNF; change in fatigue negatively correlated with change in IL-6; IL-1 and TNF were not detectable in the majority of patients
Gelinas et al, 2004[153]	Breast	103 female breast cancer survivors	IL-1β (serum)	Fatigue	No correlation was found between fatigue and IL-1β. IL-1 concentrations were extremely high (mean = 1,152 pg/mL)
Pusztai et al, 2004[68]	Breast	90 female patients receiving chemotherapy	IL-1β, IL-6, TNF-α, IL-8, IL-10, IL-12 (plasma)	Fatigue, depressive symptoms	Baseline cytokine levels were not detectable in the majority of patients; increases in IL-6, IL-8, and IL-10 were observed in patients receiving paclitaxel chemotherapy; no correlation was found between changes in cytokines and changes in fatigue or depression
Brown et al, 2005[76]	Lung cancer	38 patients with advanced cancer	CRP (blood, not otherwise specified)	Fatigue	Fatigue was positively correlated with CRP
Costanzo et al, 2005[62]	Ovarian	61 female patients with advanced cancer before surgery	IL-6 (plasma and ascites)	Fatigue, depressive symptoms	Fatigue was positively correlated with plasma IL-6; no correlation was found between depression and IL-6
Shafqat et al, 2005[69]	Mixed	174 male and female patients treated within the last 6 months	TNF-α (blood, not otherwise specified)	Fatigue	No correlation was found between fatigue and TNF

(continued on following page)

Table 1. Biomarkers of Inflammation in Cancer Patients With Behavioral Comorbidities (continued)

Investigator	Cancer Type	Patient Sample	Immune Parameter	Behavioral Comorbidity	Results
Rich et al 2005[80]	Colorectal	80 male and female patients with metastatic disease	TNF-α, IL-6, TGF-α (serum)	WHO performance, fatigue	IL-6 and TGF-α were increased in patients with WHO performance status > 1; TGF-α correlated with fatigue; dampened cortisol rhythm was associated with increased TNF-α, IL-6, and TGF-α
Meyers et al 2005[61]	Leukemia	54 male and female patients with ALS/MDS	TNF-α, IL-1, IL1ra, IL-6, IL-8 (serum)	Neuropsychological performance, fatigue	Higher IL-6 was associated with poorer executive function; higher IL-8 was associated with better memory performance; IL-6, IL-1ra, and TNF-α were correlated with fatigue
Mills et al 2005[65]	Breast	29 women with stage I-IIIA disease before and during anthracycline-based chemotherapy	IL-6, sICAM, VEGF (plasma)	Fatigue, quality of life	sICAM and VEGF were related to increased fatigue and poorer quality of life
Collado-Hidalgo et al 2006[71]	Breast	50 female breast cancer survivors	Peripheral blood lymphocyte phenotypic markers; IL-6, sIL-6R, IL-1ra, TNFR-p75 (plasma); LPS-stimulated intracellular expression of IL-6 and TNF-α	Fatigue	Plasma IL-1ra and sIL-6R and LPS-stimulated IL-6 and TNF-α were elevated in patients with fatigue along with decreased monocyte cell-surface IL-6R and decreased activated T lymphocytes and myeloid dendritic cells
Jehn et al 2006[54]	Metastatic cancer	114 male and female patients with metastatic (stage 4) disease	IL-6 (plasma)	Major depression	Plasma IL-6 was significantly elevated in depressed patients
Bower et al[79]	Breast	25 female breast cancer survivors	Peripheral blood lymphocyte phenotypic markers; LPS-stimulated production of IL-1β, IL-6, TNF-α after stress	Fatigue	LPS-stimulated IL-1β and IL-6 were increased in fatigued patients versus nonfatigued patients after stress

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; BMI, body mass index; BMT, bone marrow transplant; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia; CRP, C-reactive protein; FGF, fibroblast growth factor; IL, interleukin; IL-1ra, interleukin-1 receptor antagonist; IL-2R, interleukin 2 receptor; LPS, lipopolysaccharide; MDS, myelodysplastic syndrome; PDGF, platelet-derived growth factor; RT, radiation therapy; sICAM, soluble intracellular adhesion molecule; sIL-6R, soluble interleukin 6 receptor; TGF, transforming growth factor; TNF, tumor necrosis factor; TNFR, TNF receptor; VEGF, vascular endothelial growth factor.

especially in studies looking at correlations between inflammatory biomarkers and depressive symptoms (as measured by standardized depression rating scales). Of note, however, there is a surprising paucity of studies on depressed cancer patients compared with the rich literature examining patients with other medical illnesses, including cardiovascular disease, as well as healthy depressed individuals, where a large number of studies have revealed a clear relationship between inflammatory markers and both a diagnosis of major depression and depressive symptom severity.[7]

Cancer patients with major depression also have been shown to exhibit neuroendocrine changes that might predispose to activation of inflammatory responses including two studies demonstrating reduced sensitivity to glucocorticoids as manifested by DST nonsuppression[53,55] (Table 2) and one study showing a flattening of the diurnal cortisol curve.[54] To our knowledge, no study to date has linked HPA axis and/or glucocorticoid receptor function and increased inflammatory markers in depressed cancer patients.

Fatigue

Fatigue is one of the most common and distressing adverse effects of cancer treatment.[56] Prevalence estimates of fatigue during treatment range from 25% to 99% depending on the sample and method of assessment.[56,57] Although fatigue typically declines after cancer treatment, there is growing evidence that fatigue may persist for months or years in a significant subpopulation of patients.[58,59] Indeed, a recent study found that 34% of disease-free breast cancer survivors reported significant fatigue 5 to 10 years after diagnosis,[60] similar to estimates obtained in a heterogeneous sample of 5-year cancer survivors.[59]

A number of studies have shown an association between inflammatory markers and fatigue in cancer patients before treatment onset[61,62] and during treatment with radiation[63,64] and chemotherapy,[65] although negative findings have been reported (Table 1).[66-69] There is also evidence that inflammatory processes play a role in post-treatment fatigue. For example, breast cancer survivors with persistent fatigue were found to exhibit significant elevations in several markers of immune activation [ie, IL-1 receptor antagonist (IL-1ra), soluble TNF receptor p75, neopterin] compared with nonfatigued survivors.[70] These findings were recently replicated in a larger cohort of breast cancer patients, with fatigued survivors again showing elevations in circulating IL-1ra and soluble IL-6 receptor, as well as increased production of innate immune cytokines by monocytes after in

Table 2. Neuroendocrine Alterations in Cancer Patients With Behavioral Comorbidities

Investigator	Cancer Type	Patient Sample	Neuroendocrine Parameter	Behavioral Comorbidity	Results
Evans et al 1986[55]	Mixed	47 females with cervical, endometrial, and vaginal cancer of varying stages	DST	Major depression	21% of patients were DST nonsuppressors; 40% of patients with major depression were DST nonsuppressors
Sephton et al 2000[87]	Breast	104 women with metastatic disease	Diurnal salivary cortisol rhythm	Sleep	Flattened cortisol slope was associated with increased nocturnal awakenings and decreased survival
Musselman et al 2001[53]	Mixed	21 male and female patients with pancreatic, breast, and esophageal cancer	DST	Major depression	Postdexamethasone plasma cortisol concentrations correlated with depression, but not with IL-6
Capuron et al 2003[18]	Melanoma	20 male and female participants, stage III-IV	ACTH and cortisol response to IFN-α	Major depression	Exaggerated ACTH and cortisol responses to the first injection of IFN-α were associated with the development of depression during IFN-α therapy
Bower et al 2005[77]	Breast	29 female breast cancer survivors	Salivary cortisol samples collected upon awakening and at 1200, 1700, and 2200 hours on 2 consecutive days	Fatigue	Flattened cortisol slope was found in patients with fatigue
Bower et al 2005[78] and 2007[79]	Breast	27 female breast cancer survivors	Salivary cortisol samples collected at 15-minute intervals throughout a stressful public speaking and mental arithmetic task	Fatigue	Salivary cortisol responses to stress were blunted in fatigued patients versus controls; blunted cortisol responses in fatigued patients were associated with increased LPS-stimulated IL-6 production
Rich et al 2005[80]	Colorectal	80 male and female patients with metastatic disease	Serum cortisol obtained at 800 and 1600 hours	WHO performance, fatigue	Flattened cortisol rhythm was associated with increased TNF-α, IL-6, and TGF-α
Jehn et al 2006[54]	Metastatic Cancer	114 male and female patients with metastatic (Stage 4) disease	Diurnal cortisol secretion	Major depression	Decreased variance in diurnal cortisol secretion (ie, flattened cortisol rhythm) was found in depressed patients compared with controls.

Abbreviations: DST, dexamethasone suppression test; IL, interleukin; ACTH, adrenocorticotropic hormone; IFN, interferon; LPS, lipopolysaccharide; TNF, tumor necrosis factor; TGF, transforming growth factor.

vitro stimulation with LPS.[71] Two studies conducted with patients with hematologic malignancies who had completed treatment found no association between fatigue and inflammatory markers.[72,73] However, in both of these reports, there was considerable variability in diagnosis, disease stage, length of time since treatment, and duration of fatigue symptomatology. Moreover, a recent meta-analysis of the available literature has supported a relationship between inflammatory biomarkers and fatigue in cancer survivors.[74] Among patients with advanced cancer (active disease), there is mixed evidence for an association between fatigue and inflammatory measures.[75,76]

Evidence suggests that enhanced cytokine production in fatigued cancer survivors may stem in part from altered HPA axis function including altered diurnal cortisol secretion and a decreased cortisol response to stress (Table 2). For example, lower levels of morning serum cortisol,[70] flattened diurnal cortisol slopes,[77] and a blunted cortisol response to acute psychosocial stress[78] have been found in breast cancer survivors with persistent fatigue. Interestingly in a recent study of fatigued breast cancer patients, increased stress-induced inflammatory responses (as manifested by increased IL-6 responses to LPS stimulation of whole blood) were associated with decreased stress-induced salivary cortisol responses.[79] Increased inflammatory cytokines have also been associated with dampened cortisol rhythm in patients with metastatic colorectal cancer.[80] Taken together, these data suggest that alterations in cortisol secretion over the circadian cycle and in response to stress may play a role in exaggerated inflammatory responses which in turn may be associated with behavioral changes including fatigue.

Sleep Disturbance

Over 50% of cancer patients report problems with sleep, with polysomnographic data confirming reduced sleep efficiency, prolonged latency to fall asleep, and increased awake time during the night.[81,82] Even before treatment, patients with cancer have reported significant sleep impairment,[83] and among cancer survivors, sleep problems persist well beyond treatment. Indeed, nearly 20% of breast cancer survivors report greater than 6 months of chronic insomnia.[81,84] Sleep disturbances come at a considerable price. For example, insomnia is a powerful predictor of cancer-related fatigue,[58,85,86] and disturbances in sleep-wake activity as well as circadian rhythms have been found to predict increases in mortality in patients with metastatic disease.[87,88]

Interestingly, despite data indicating a relationship between innate immune cytokines such as IL-6 and sleep, the relationship between inflammatory markers and sleep in cancer patients has not been examined. Given the relationship between fatigue and

inflammatory markers, it seems likely that similar relationships may exist with sleep. Clearly, studies are needed in this area.

An important potential mechanism whereby sleep disturbances may contribute to increased inflammation is through desynchronization of circadian rhythms, including the release of cortisol (Fig 1).[89] Twenty-four–hour circadian cortisol secretion is regulated in the hypothalamus in conjunction with the circadian pacemaker located within the suprachiasmatic nucleus. Forced changes in circadian sleep-wake patterns as well as the induction of sleep debt (as occurs in the context of chronic sleep impairment) have been associated with flattening of cortisol rhythms, especially as manifested by increased cortisol secretory activity in the evening, a normally quiescent period of cortisol release.[90,91] In addition, sleep restriction has been associated with reduced adrenocorticotropic hormone responses to stress in rats.[92] Although not adequately studied, there is at least one report in cancer patients that disruption of circadian cycles as manifested by frequent nocturnal awakenings was associated with flattening of circadian cortisol rhythms,[88] which, in turn, has been associated reduced long-term survival.[87] Disruption of circadian rhythms may be initiated during cancer treatment as a result of a vicious cycle of fatigue and daytime inactivity (with resultant impairment in night-time sleep) and/or the impact of immune activation secondary to cancer treatment and/or psychological stress on sleep-wake cycles. Further studies examining sleep-wake cycles, activation of inflammatory responses, and circadian cortisol rhythms are clearly warranted to further clarify these relationships and identify points of therapeutic intervention.

Cognitive Function

Cognitive dysfunction during cancer treatment significantly influences quality of life and social/occupational function, and represents a major concern in patient management.[93] Complaints of cognitive impairment, including alterations in memory, concentration, executive function, and psychomotor skills, are frequent in patients with cancer. Aside from cancers that directly affect the CNS, cancers originating in peripheral tissues have also been associated with the occurrence of neuropsychological changes. These cognitive changes are often secondary to cancer treatments, including most notably chemotherapy and radiation. Approximately 25% to 33% of patients undergoing systemic chemotherapy exhibit impaired performance on tests of cognitive functions.[94-97] Cognitive dysfunction related to chemotherapy seems to be dose dependent; with high doses being associated with greater impairment.[96,98] Although cognitive dysfunction during chemotherapy generally resolves after treatment, several studies have reported residual long-term effects.[99-101] Data indicate that chemotherapy is also associated with significant changes in brain white matter as well as alterations in regional brain activity that correlate with cognitive dysfunction.[102-104] For example, a [^{18}F]FDG PET study on patients treated with chemotherapy for breast cancer demonstrated significant increases in glucose metabolic activity in the inferior frontal gyrus that correlated with cognitive performance on a short-term memory task, possibly indicating a compensatory response to decreased baseline metabolic activity in this and other brain regions.[104] When directed at the brain, not surprisingly, radiation therapy is often accompanied by neurologic complications that may be severe and persist years after treatment.[105] Interestingly, however, moderate/transient cognitive alterations have been reported after radiation of sites other than the brain. For example, a study conducted in 48 women undergoing postoperative radiation therapy after breast-conserving surgery indicated significant increases in the cognitive fatigue subscale of the Fatigue Assessment Questionnaire 4 and 5 weeks after initiation of radiation therapy compared with baseline.[66]

Although candidate mechanisms of cognitive dysfunction in cancer patients clearly involve a complex interplay of genes, hormones, and the immune system,[106] findings suggest that inflammatory factors may play an important role.[25] For example, a significant negative correlation has been found between plasma IL-6 and executive function in patients with acute myelogenous leukemia or myelodysplastic syndrome (Table 1).[61] Probably the most striking example of the effects of cytokines on cognition in cancer patients is the neuropsychological sequelae of cytokine-based immunotherapies such as IFN-α and IL-2. A study conducted in patients treated with high-dose IFN-α for malignant melanoma indicated that complaints of moderate to severe cognitive symptoms are frequent, especially loss of concentration (30% of patients), psychomotor retardation (40%), memory disturbances (15%), and word-finding problems (15%).[107] Cognitive dysfunction in patients undergoing cytokine therapy largely depends on the parameters of treatment (dose, duration, and route of administration) and the cytokine administered.[108] Thus, whereas IFN-α therapy is generally associated with reduced psychomotor speed and concentration difficulties, IL-2 therapy is more frequently associated with alterations in working memory and executive function.[24] Cognitive alterations secondary to high-dose cytokine therapy treatment typically reverse after treatment; however, residual cognitive impairment has been reported.[109,110]

TRANSLATIONAL IMPLICATIONS

Identification of Behavioral Risk

On the basis of the proposed conceptual framework (Fig 1), individuals with high levels of perceived stress (as a function of the cancer diagnosis or other life circumstances) who are undergoing treatments associated with activation of inflammatory responses (eg, surgery, chemotherapy, radiation therapy) may be most at risk for developing behavioral change. In addition, increased risk may be associated with significant disruption of sleep-wake cycles. The relative risk for the development of behavioral comorbidities is also likely influenced by genetic factors. Functional polymorphisms in the *IL-6* gene and the serotonin transporter gene may be especially relevant, given the association of IL-6 with several behavioral pathologies in cancer patients and the demonstrated role of serotonin transporter polymorphisms in the relationship between stress and behavior alterations.[111,112] Future studies identifying psychological and genetic profiles of risk for behavioral change during cancer and its treatment are clearly warranted. Finally, as part of ongoing research into the role of inflammation in behavioral comorbidities and the identification of risk, consideration should be given to the development of standardized assessments of inflammatory biomarkers in cancer patients. On the basis of studies to date, alterations in IL-6 (as assessed by high-sensitivity [hs] enzyme-linked immunoabsorbent assay) and the downstream, liver-derived, acute phase reactant, CRP (as measured by hs assay techniques), seem to be the most reliable regarding both behavioral pathology and medical illness.[7,113-117] Indeed, as shown in Table 1, a number of studies in cancer patients have revealed associations between IL-6 and CRP and depression, fatigue, and cognitive

dysfunction. Furthermore, hsCRP can be run in certified commercial/hospital laboratories, thereby reducing variability across research sites. Moreover, in the case of hsCRP, cutoff values have been established that have both predictive validity and categorization of risk in relation to disease outcome in cardiovascular disorders.[115] Given the fluctuating status of cancer patients during treatment, it is also suggested that longitudinal assessments of both behavior and relevant inflammatory biomarkers be obtained to increase the likelihood of identifying relevant associations between these variables that might otherwise be confounded by the vicissitudes of the cancer treatment experience. Examination of inflammatory biomarkers in cancer survivors versus healthy age- and sex-matched controls is yet another strategy to reduce the impact of treatment on the relationship between inflammation and behavioral change.

Therapeutic Ramifications

Given the prevailing knowledge regarding the potential integrated mechanisms involved in behavioral comorbidities in cancer patients, there are multiple opportunities for translational studies targeting pathways that contribute to the wide range of symptoms (Table 3).

PSYCHOTHERAPEUTIC/BEHAVIORAL INTERVENTIONS

Cognitive-behavioral, supportive, or insight-oriented psychotherapies that reduce stress and restore regular circadian cycles may be especially relevant, given the potential role of stress-induced inflammation and altered regulation of inflammatory responses by the neuroendocrine system. Relevant cognitive-behavioral strategies include relaxation training, enhancement of coping skills, graded exercise, and establishment of appropriate sleep-wake habits and social rhythms (eg, standardized bed and wake-up times, avoidance of daytime napping, and correction of maladaptive beliefs about sleep).[118-129] Such interventions may limit the impact of stress on the immune response and may have direct effects on neuroendocrine-immune interactions. Indeed, psychological interventions such as cognitive-behavioral stress management and mindfulness-based stress reduction have been shown to alleviate psychological distress in breast cancer patients, while increasing lymphocyte proliferative responses and normalizing diurnal cortisol secretion.[124-129] There is also evidence that aerobic exercise can lead to reductions in inflammatory markers in cancer survivors,[130] and the possibility that changes in inflammation may mediate the beneficial effects of exercise (and possibly other behavioral therapies) on cancer-related behavioral comorbidities is an important avenue for future research.[131] Interestingly in this regard, a recent cognitive-behavioral therapy program focusing on coping, sleep, physical activity, and social support was found to lead to significant improvement in fatigue in 54% of cancer survivors compared with 4% of patients assigned to a control condition.[118] Regarding the impact of altered sleep-wake cycles on neuroendocrine and immune function in cancer patients, Irwin et al found that multiple types of behavioral treatments (eg, cognitive behavioral therapies, relaxation, behavioral only) induced robust improvements in subjective measures of sleep quality, sleep onset, and sleep maintenance in adults with primary insomnia,[132] extending the findings of prior studies.[133-135] However, much less is known about the efficacy of these approaches for insomnia in cancer patients.[84] Indeed, only one controlled study has examined the efficacy of a behavioral intervention for insomnia in cancer patients,[136] with other studies limited by lack of a control group and/or small sample sizes.[137,138] Moreover, no study has included assessments of the impact of these interventions on cortisol rhythms, inflammatory mediators, or behavioral changes.

Table 3. Neuroendocrine-Immune Interactions and the Development of Behavioral Comorbidities in Cancer Patients: Translational Targets

Affected Area	Treatment
Immune system	Cytokine antagonists (eg, TNF-α, IL-1, IL-6)
	Cytokine signaling pathway antagonists (eg, NFκB inhibitors, p38 MAPK inhibitors)
	Anti-inflammatory medications (eg, COX-2 inhibitors, PGE_2 inhibitors)
	Exercise
Neuroendocrine system	CRH antagonists
	Glucocorticoid receptor facilitators (eg, phosphodiesterase type IV inhibitors)
Sleep-wake cycle	Chronotherapy (eg, melatonin, light therapy, or sleep regulation)
	Behavioral therapy (cognitive behavioral therapy, graded exercise, improved sleep hygiene)
CNS	5HT, NE, DA reuptake inhibitors (eg, antidepressants)
	DA agonists
	Neuroprotective agents (eg, growth factors)
Stress	Cognitive-behavioral therapy (eg, stress management, coping skills, graded exercise)
	Relaxation training
	Supportive psychotherapy
	Anti-anxiety medication (eg, benzodiazepines)

Abbreviations: 5HT, serotonin; COX, cyclooxygenase; DA, dopamine; IL, interleukin; MAPK, mitogen-activated protein kinase; NE, norepinephrine; NFκB, nuclear factor κ B; PG-prostaglandin; TNF, tumor necrosis factor.

BIOLOGIC INTERVENTIONS

Although further studies are required to characterize the relationship between inflammatory markers and behavior in cancer patients; cytokine antagonists, anti-inflammatory agents, and drugs that disrupt cytokine signaling pathways (eg, NFκB and p38 MAPK) are logical treatment considerations that target the most upstream elements in the cytokine-to-CNS-to-behavior cascade. Of note, given the role of NFκB and p38 pathways in cancer development and progression, exciting opportunities exist for behavioral scientists to work with oncologists to examine the full spectrum of activity of relevant antagonists of inflammatory pathways. For example, several recent trials have demonstrated that TNF-α blockade with etanercept is safe in patients with advanced cancer,[139,140] and it was suggested in at least one study that tolerability of chemotherapy (including reduced fatigue) was improved.[141]

Moving into the CNS, inflammation-induced alterations in neurotransmitter systems may be best addressed by pharmacologic agents that target specific monoamine systems for specific symptom domains (eg, serotonin-active drugs for mood/anxiety symptoms, dopamine-active drugs for fatigue and psychomotor slowing). For example, in at least two double-blind placebo-controlled trials in cancer patients undergoing treatment, paroxetine (a serotonin reuptake inhibitor)

was found to reduce depression while having limited effect on fatigue.[107,142] On the other hand, preliminary evidence suggests that dopaminergic agents such as the psychostimulant, methylphenidate, may treat fatigue and improve neuropsychological functioning in patients undergoing cancer treatments[143] and patients with tumor-related organic brain dysfunction.[144,145]

CRH, which as noted previously herein is stimulated by innate inflammatory cytokines, is another rational CNS target, and although CRH antagonists are not currently available, there is preliminary indication that these agents may have efficacy in treating depression in otherwise healthy individuals.[146] Drugs that enhance glucocorticoid-mediated negative feedback on CRH pathways, through facilitation of glucocorticoid receptor function, may control CRH overexpression. Such drugs (including phosphodiesterase type IV inhibitors), may have the advantage of additionally inhibiting inflammatory pathways.[147] Novel treatments supporting neuronal integrity/plasticity (neuroprotective agents) including drugs that stimulate the activity or signaling of relevant growth factors (eg, BDNF) may be especially important for future development.[148,149]

Regarding sleep and neuroendocrine rhythms, therapies that combine chronobiotics (eg, melatonin-receptor agonists, light therapy, or sleep regulation) might synchronize the circadian rhythms of cancer patients to their environment, in the same manner that these strategies are used to treat transient rhythm disturbances caused by jet lag or shift work. Such treatment may help restore neuroendocrine rhythmicity, reduce inflammation, and potentially improve therapeutic efficacy of cancer treatments.[150,151]

SUMMARY

The research described herein provides a conceptual framework designed to integrate a host of behavioral comorbidities that may share common pathophysiologic features that lend themselves to identification of risk and targeted interventions with broad therapeutic relevance. Further studies examining neuroendocrine-immune interactions as they relate to altered sleep-wake cycles and behavioral comorbidities in patients with a wide variety of cancers will likely lead to novel insights into the contribution of cancer and its treatment to behavioral changes and, possibly, the contributions of behavioral comorbidities to cancer development, progression and recurrence. Finally, given the increasing understanding of the pathophysiology and treatment of behavioral comorbidities in cancer patients, it is especially important that standardized behavioral assessments become part of the routine care of cancer patients. As such, instantiating behavior as the sixth vital sign will go a long way in emphasizing the need for further research and the importance of both recognizing and treating the behavioral consequences of cancer and its treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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