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Inflammation and cancer-related fatigue: Mechanisms, contributing factors, and treatment implications

Julienne E. Bower [a,b,c,d,*], Donald M. Lamkin [b]

[a] UCLA Department of Psychology, CA, USA
[b] Cousins Center for Psychoneuroimmunology, Semel Institute at UCLA, CA, USA
[c] UCLA Department of Psychiatry and Biobehavioral Sciences, CA, USA
[d] Division of Cancer Prevention and Control Research, Jonsson Comprehensive Cancer Center at UCLA, CA, USA

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ABSTRACT

Fatigue is one of the most common and distressing side effects of cancer and its treatment, and may persist for years after treatment completion in otherwise healthy survivors. Guided by basic research on neuro-immune interactions, a growing body of research has examined the hypothesis that cancer-related fatigue is driven by activation of the pro-inflammatory cytokine network. In this review, we examine the current state of the evidence linking inflammation and cancer-related fatigue, drawing from recent human research and from experimental animal models probing effects of cancer and cancer treatment on inflammation and fatigue. In addition, we consider two key questions that are currently driving research in this area: what are the neural mechanisms of fatigue, and what are the biological and psychological factors that influence the onset and/or persistence of inflammation and fatigue in cancer patients and survivors? Identification of the mechanisms driving cancer-related fatigue and associated risk factors will facilitate the development of targeted interventions for vulnerable patients.

1. Introduction

Fatigue is increasingly recognized as one of the most common and distressing side effects of cancer and its treatment (Lawrence et al., 2004). Prevalence estimates of fatigue during cancer treatment range from 25% to 99% depending on the sample, type of treatment, and method of assessment (Servaes et al., 2002; Lawrence et al., 2004). Energy typically improves in the year after treatment completion, although a significant minority of patients continue to experience fatigue for months or years after successful treatment (Bower et al., 2000; Cella et al., 2001). Studies of long-term cancer survivors suggest that approximately one-quarter to one-third experience persistent fatigue for up to 10 years after cancer diagnosis (Bower et al., 2006; Servaes et al., 2006). Fatigue has a negative impact on work, social relationships, mood, and daily activities and causes significant impairment in overall quality of life (Andrykowski et al., 1998; Bower et al., 2000; Broeckel et al., 1998). Fatigue may also be a predictor of shorter survival in cancer patients (Groenvold et al., 2007).

Qualitative reports suggest that cancer-related fatigue is more severe, more enduring, and more debilitating than "normal" fatigue caused by lack of sleep or overexertion and is not relieved by adequate sleep or rest (Poulson, 2001). In addition, cancer-related fatigue involves mental, physical, and emotional components. One definition that captures several of the key features of cancer-related fatigue describes it as "a subjective state of overwhelming and sustained exhaustion and decreased capacity for physical and mental work that is not relieved by rest" (Cella et al., 1998).

Studies conducted over the past decade have begun to elucidate the biological underpinnings of cancer-related fatigue, with a focus on inflammation. This research is motivated by basic research on neural-immune signaling, which indicates that pro-inflammatory cytokines can signal the central nervous system to generate symptoms of fatigue and other behavioral changes in animals and healthy humans (Dantzer et al., 2008). In the cancer context, inflammation may be induced by common cancer treatments, including radiation and chemotherapy, or by the tumor itself. Previous reviews of this literature have generally supported a link between inflammation and behavioral symptoms in cancer patients, including fatigue (Miller et al., 2008; Schubert et al., 2007; Seruga et al., 2008; Bower, 2007). This is a growing area of research that has seen important advances in methodological rigor (e.g., larger sample sizes, controls for confounders, advanced statistical methods) and examination of underlying mechanisms. In this review we will examine the current state of the evidence linking inflammation and cancer-related fatigue, drawing from recent human research and from experimental animal models probing effects of cancer and cancer treatment on inflammation and fatigue. We will

* Corresponding author at: UCLA Department of Psychology, 1285 Franz Hall, Los Angeles, CA 90095-1563, USA. Tel.: +1 310 825 3004; fax: +1 310 206 5895.
E-mail address: jbower@ucla.edu (J.E. Bower).

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then consider two key questions that are currently driving research in this area. First, what are the neural underpinnings of fatigue, and can they be discriminated from depression? Second, what are the biological and psychological factors that contribute to inflammation and fatigue during and after treatment? We conclude with implications for interventions and recommendations for future research.

2. Human and animal research on inflammation and cancer-related fatigue

We consider human and animal studies that have examined links between inflammation and fatigue at three stages of the cancer continuum: before, during, and after cancer treatment. The basic model guiding this area of research is that tumors and the treatments used to eradicate them can activate the proinflammatory cytokine network, leading to symptoms of fatigue via effects on the central nervous system (see Fig 1). In the pre-treatment period, the tumor itself may be a source for proinflammatory cytokines (Aggarwal, 2004; Coussens and Werb, 2002) while during treatment, cytokines may be produced in response to tissue damage from radiation or chemotherapy (Stone et al., 2003; Aggarwal et al., 2009). In addition to these direct effects, other processes may influence proinflammatory cytokine production and will be discussed in section 4.

2.1. Fatigue prior to cancer treatment

A few studies have investigated links between inflammatory markers and fatigue in cancer patients prior to treatment. In patients with newly diagnosed acute myelogenous leukemia or myelodysplastic syndrome, levels of several inflammatory markers were correlated with symptoms of fatigue (Meyers et al., 2005). In a sample of ovarian cancer patients assessed prior to surgery, those with advanced stage disease had higher levels of IL-6 as well as elevations in vegetative symptoms of depression (including fatigue) relative to those with early stage disease or tumors of low malignant potential (Lutgendorf et al., 2008). Moreover, elevations in plasma and ascites levels of IL-6 were correlated with fatigue and other vegetative depressive symptoms, but not with mood or affective symptoms of depression. On the other hand, a recent study of breast cancer patients assessed prior to surgery did not find elevated levels of CRP in those categorized as "fatigued" (Fagundes et al., 2012). It is possible that small, localized breast tumors may not produce elevations in systemic cytokine concentrations that are sufficient to induce symptoms of fatigue.

In rodents, fatigue has usually been measured by the amount of reduced spontaneous locomotor activity the animal exhibits (Kent et al., 1992). Recently, a mouse model of ovarian cancer was used to investigate the effect of tumor on inflammation and spontaneous locomotor activity (Lamkin et al., 2011). In this model, a syngeneic ovarian carcinoma cell line was injected into the peritoneum of the mice to grow over a period of two months. Congruent with what often happens in ovarian cancer patients, ascites (i.e., a build-up of fluid that forms around the tumor) forms in the peritoneum of the mice in this model and contains high levels of IL-6 and TNF-α. Consequently, levels of IL-6 and TNF-α as well as IL-17 and IL-10 are significantly elevated in systemic circulation as a result of tumor. We found reductions in home cage locomotion in tumor-bearing animals without any significant deficit in motor capacity (i.e., the animals were *able* to engage in spontaneous locomotion). Mediation analysis suggested that tumor-induced IL-6 in the circulation carried part of the effect of tumor on decreased locomotion, supporting a role for tumor-associated cytokines in the development of fatigue.

2.2. Fatigue during cancer treatment

Radiation therapy and chemotherapy are two of the most common types of cancer treatment, and both are associated with increases in fatigue (Donovan et al., 2004) and with elevations in certain inflammatory markers (Arpin et al., 2005; Mills et al., 2004). A handful of studies have examined the association between inflammation and fatigue during radiation therapy to test the

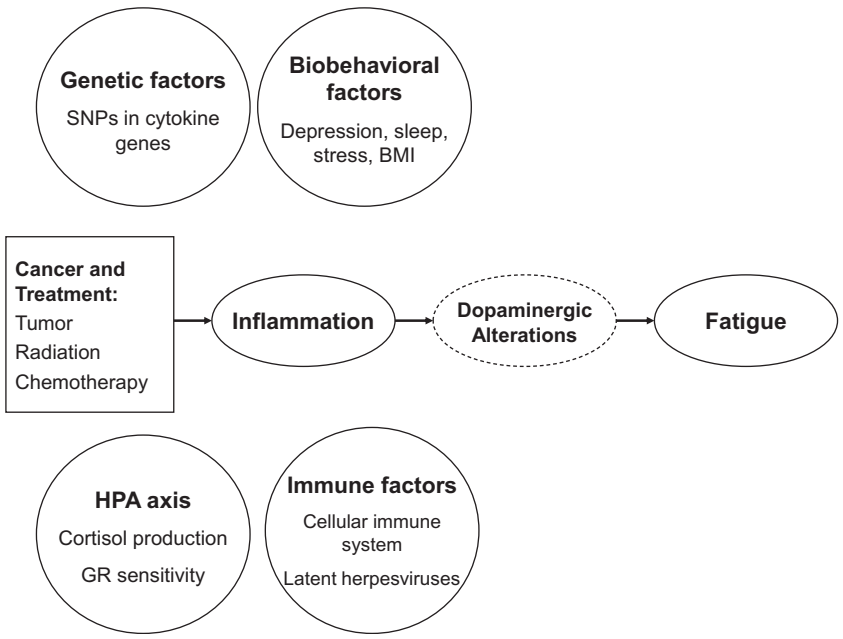

Fig. 1. Conceptual model linking cancer and cancer treatments to inflammation and symptoms of fatigue. These effects may be mediated by alterations in dopaminergic transmission; the dashed line around this mediator indicates that this pathway has not been fully elucidated. Host factors that may influence that onset and persistence of inflammation and fatigue in cancer patients are depicted in circles and include genetic polymorphisms, alterations in the hypothalamic–pituitary-adrenal (HPA) axis, alterations in the cellular immune system, and biobehavioral factors such as history of depression, sleep disturbance, early life stress, and body mass index.

hypothesis that inflammation may contribute to radiation-induced fatigue. Early reports on this topic were conflicting, possibly due to constraints of study designs (including use of non-standard measures to detect cytokine levels) and focus on cross-sectional associations between cytokine levels and fatigue (Greenberg et al., 1993; Wratten et al., 2004; Geinitz et al., 2001; Ahlberg et al., 2004). Our group examined within-subject relationships between inflammatory markers and fatigue before, during and after radiation therapy in patients with early-stage breast and prostate cancer (Bower et al., 2009). Results showed that changes in serum levels of inflammatory markers CRP and IL-1RA were positively associated with increases in fatigue symptoms; patients reported higher levels of fatigue on weeks when these biomarkers were elevated. Effects remained significant in analyses controlling for potential biobehavioral confounders including age, BMI, depression, and sleep disturbance. Of note, we found no evidence that serum concentrations of IL-6 or IL-1β were associated with fatigue in this study. These findings provide initial evidence that activation of the proinflammatory cytokine network may be a general mediator of radiation-induced fatigue, but require replication in larger samples. Further, these findings suggest that downstream markers of proinflammatory cytokine activity may be more reliably associated with cancer-related fatigue; similar results have emerged in our work with cancer survivors.

Investigators have also utilized animal models of ionizing radiation to study its effects on fatigue (e.g., King and Landauer, 1990). Likewise, researchers have used animal models to study the effects of radiotherapy on inflammatory processes, and have shown acute elevations in inflammatory responses following a single session of total body irradiation (TBI) (e.g., Haveman et al., 1998; Khayyal et al., 2009). However, very few researchers have looked at radiation-induced inflammation in conjunction with measures of fatigue. Van der Meeren and colleagues (2001) modeled the effects of radiotherapy in mice and found that TBI caused an increase in plasma levels of IL-6, serum amyloid A, Gro1, and granulocytes but no increase in IL-1β, TNF, or Scya5. Peak levels for these effects in circulation were observed at 6 h after TBI and had mostly resolved by 24 h. In a follow-up study, spontaneous locomotor behavior in the home cage was examined with automated telemetry (Van der Meeren and Lebaron-Jacobs, 2001). In accord with the acute rise in systemic inflammation, locomotion dropped significantly within a few hours of TBI. However, whereas inflammatory markers quickly returned to baseline levels, locomotion continued to decline until Days 13–17 before starting to recover by Day 25. Of note, the slow recovery of normal locomotion roughly parallels that seen with repeated radiation exposure in the clinical setting and may reflect late effects of radiation on irradiated tissues (Brush et al., 2007).

More recently, a study by York and colleagues (2012) examined the effect of TBI on spontaneous locomotion in mice at multiple time points during the first 24 h following exposure. Mice exhibited a decrease in locomotion by 6 h after exposure, but the effect waned afterward. Also at this time point, gene expression for TNF-α was significantly elevated in the whole brain, but not IL-1, IL-1RA, IL-6, or IFN-γ. Examination of cytokine gene expression in whole blood found evidence for IL-1 expression around this time as well, but not for TNF-α, IL-6, or IFN-γ.

Investigation into chemotherapy-associated inflammation and fatigue is complicated by the fact that there are numerous classes of antineoplastic drugs with unique mechanisms of action within and between each class (e.g., antimetabolites, antimicrotubule agents, alkylating agents, platinum agents, cytotoxic antibiotics, DNA topoisomerase I and II inhibitors) (Chabner and Longo, 2006). Nonetheless, clinical investigators have been interested in linkages between inflammation and fatigue during chemotherapy. Several early studies showed links between inflammatory markers and fatigue in cancer patients undergoing various chemotherapy regimens (Mills et al., 2005; Pusztai et al., 2004). More recently, Wang and colleagues intensively examined sickness symptoms and inflammatory markers in patients undergoing combined radiation and chemotherapy therapy for locally advanced colorectal, esophageal, and non-small cell lung cancer (Wang et al., 2010; Wang et al., in press). These investigators documented acute increases in markers of inflammation that were correlated with increases in fatigue and other prominent sickness symptoms. Similar effects were seen in a study of individuals undergoing allogeneic hematopoietic stem cell transplantation (which includes high-dose chemotherapy) for acute myelogenous leukemia and myelodysplastic syndrome (Wang et al., 2008).

Preclinical investigators have developed animal models of chemotherapy-induced fatigue using some of the more wide-spread antineoplastic agents. For example, a study by Wood and colleagues (2006) examined the effect of etoposide, a topoisomerase II inhibitor, on locomotion with voluntary wheel running. Etoposide caused a step-wise reduction in voluntary running that began after the first dose, resulting in an 80% reduction by the study's end. Examination of systemic IL-6 showed that a single administration of the drug induced an 18-fold increase compared to control mice, and levels at the end of the two-week administration schedule were still significantly elevated by more than 10-fold.

Malik and colleagues (2006) found that a single dose of the platinum-based drug, cisplatin, caused rats to exhibit decreased motor activity several hours after injection during their normally active nocturnal phase, and this decrease grew in magnitude until Days 3–4 before beginning to recover by Day 8. Although no differences in gene expression were found for specific proinflammatory cytokines examined, the investigators found that administration of the potent anti-inflammatory glucocorticoid, dexamethasone, inhibited the decrease of spontaneous motor activity in the model in a subsequent study (Malik et al., 2007), suggesting that yet undefined inflammatory mechanisms in the model may be at work.

One potential limitation of an investigation into the effect of cisplatin or other chemotherapeutic drugs on spontaneous locomotor activity is lack of information regarding motor capacity, because such drugs can cause peripheral neuropathy and, thus, contribute to decreased locomotion via this mechanism (Cavaletti et al., 1992; Mollman, 1990; Rowinsky et al., 1993). Recently, Ray and colleagues (2011) tested a model of paclitaxel-induced inflammation and fatigue where they examined motor capacity alongside spontaneous locomotion in mice. Results showed that paclitaxel reduced spontaneous home cage locomotion during the week of dosing and for an additional two weeks without substantially altering motor capacity. However, the investigators found no changes in a panel of 21 cytokines and chemokines in the blood at the conclusion of the week of dosing, including IL-1β, IL-6, and TNF-α, compared to saline-injected animals. Overall, these studies support an association between chemotherapy and fatigue, but provide less insight into how inflammatory mechanisms may underlie these effects.

2.3. Post-treatment fatigue in cancer survivors

Although fatigue typically abates in the year after cancer treatment, approximately 25–30% of cancer survivors report persistent fatigue that may last for 5–10 years post-treatment and beyond (Bower et al., 2006). In our earlier work, we documented consistent alterations in the pro-inflammatory cytokine network among breast cancer survivors with persistent post-treatment fatigue, including elevations in circulating markers of inflammation (Bower et al., 2002; Collado-Hidalgo et al., 2006) and elevated cytokine production after LPS stimulation (Collado-Hidalgo et al., 2006; Bower et al., 2007), controlling for potential demographic and

biobehavioral confounds. We have more recently shown an association between fatigue and elevations in plasma levels of the soluble TNF receptor type II (sTNF-RII), a downstream marker of TNF activity, in breast cancer survivors within one month after treatment; this association was particularly strong among women treated with chemotherapy (Bower et al., 2011b).

These findings have recently been replicated by other groups. For example, Alexander et al. found significant elevations in CRP in breast cancer survivors who met stringent criteria for cancer-related fatigue syndrome ($n = 60$) relative to non-fatigued controls ($n = 104$) (Alexander et al., 2009). Similarly, in sample of 299 disease-free survivors, Orre et al. found a positive association between CRP and fatigue that remained significant after controlling for age, BMI, depressive symptoms, sleep disturbance, medication use, and self-rated health (Orre et al., 2011). In a recent study by Alfano and colleagues, higher CRP was associated with increased odds of being classified as fatigued in a sample of 633 breast cancer survivors controlling for age, race, menopausal status, antidepressant/anxiolytic use, comorbidities, and BMI. (Alfano et al., 2012). This study also found a significant linear association between CRP levels and fatigue, particularly physical and behavioral dimensions of fatigue; however, these associations were attenuated to non-significant after controlling for use of antidepressants/anxiolytics, comorbidities, and BMI. A positive association between inflammatory markers and fatigue has also been documented in long-term survivors of testicular cancer (Orre et al., 2009).

Two recent studies have probed the molecular underpinnings of cancer-related fatigue by conducting genome-wide expression analyses on leukocytes from breast cancer survivors with persistent fatigue compared to non-fatigued survivors. A study conducted by our group focused on transcription of inflammation-related genes, particularly those responsive to the proinflammatory NF-κB transcription control pathway, guided by the hypothesis that peripheral inflammatory signaling may contribute to cancer-related fatigue (Bower et al., 2011a). Results showed that breast cancer survivors experiencing persistent fatigue showed increased expression of genes encoding proinflammatory cytokines and other mediators of immunologic activation. Further, promoter-based bioinformatic analyses indicated increased activity of proinflammatory NF-κB/Rel transcription factors in leukocytes from fatigued breast cancer survivors, which might structure the observed differences in the expression of inflammation-related genes. In contrast, an exploratory study by Landmark-Hoyvik et al. found that fatigued breast cancer survivors showed altered expression of genes involved in plasma or B cell pathways (Landmark-Hoyvik et al., 2009). These differences might be explained by differences in the populations studied, the microarray assay platforms, and the statistical methods used.

3. Convergence of inflammation on neural systems mediating fatigue

3.1. Lessons from research on sickness behavior and depression

To date, there is limited understanding of the neural processes that may mediate effects of peripheral inflammation on behavioral outcomes, including fatigue, in cancer patients. However, insight into these effects can be gleaned from the large array of information that has accrued over the last 25 years on inflammation-induced sickness behavior and major depressive disorder (MDD). For example, careful research into IFN-α treatment has shown that 30–50% of patients on this therapy can develop a full complement of the criteria used to make a diagnosis of MDD (Capuron and Miller, 2004). A landmark double-blind controlled trial in 2001 showed that development of MDD in these patients could be attenuated by administering the SSRI antidepressant, paroxetine, two weeks before beginning IFN-α and continuing the antidepressant for the duration of the 12-week IFN-α therapy (Musselman et al., 2001). Interestingly, however, the antidepressant was not able to attenuate significant increases in two of the symptoms that can constitute MDD: fatigue and loss of appetite (Capuron et al., 2002). Furthermore, when examining the temporal occurrence of symptoms in just the placebo group, researchers found that these more "neurovegetative" symptoms occurred early during treatment while depressive and anxious symptoms occurred later. Both of these results led the investigators to conclude that the effects of cytokine treatment on these two different symptom dimensions are mediated by different neural mechanisms. Similar results emerged from a randomized controlled trial of cancer patients undergoing chemotherapy, which found that paroxetine reduced depressive symptoms but not symptom of fatigue (Morrow et al., 2003).

Investigators using animal models have come to similar conclusions. One study showed that aged mice (80–96 weeks) exhibited normal locomotor activity by 72 h following intraperitoneal injection of the inflammatory endotoxin, LPS, but behavior in a measure known as the Tail Suspension Test (TST), which is considered representative of depression, was still significantly elevated compared to vehicle-injected controls (Godbout et al., 2008). Similar results were found in a report that showed younger mice (10–14 weeks) exhibited normal locomotor activity by 24 h after peripheral LPS injection but still manifested significantly higher levels of depressive-like behavior in the TST compared to vehicle-injected controls (O'Connor et al., 2009a). Based on these findings, it has been suggested that inflammation-induced increases in fatigue-like behavior during general locomotion and depressive-like behavior during the TST are mediated by partially different systems in the brain (Frenois et al., 2007).

3.2. The inflammation-dopamine hypothesis

Given the results of several studies looking at the relationship between inflammatory activity and dopamine alterations in the brain, it has been proposed that dopaminergic mechanisms may constitute the specific system underlying inflammation-induced neurovegetative symptoms like fatigue as well as anhedonic behavior that can follow from inflammation (Capuron and Miller, 2004; Miller, 2009). Indeed, a large and growing body of clinical and experimental research has now demonstrated that anhedonia is associated with functional alterations of dopaminergic neurons emanating from the ventral tegmental area (VTA) and terminating in the limbic system (Dunlop and Nemeroff, 2007). This system of neurons is known as the mesolimbic dopamine pathway and is seen as an essential component of how the perception of pleasure or reward is mediated by the brain. Dopaminergic neurons emanating from an area adjacent to the VTA, known as the nigrostriatal dopamine tract, are critical to how the brain mediates psychomotor function and are damaged in Parkinson's disease (Meyer and Quenzer, 2005). Capuron and colleagues (2007) showed that cancer patients undergoing IFN-α therapy exhibited a significant positive correlation between fatigue and glucose metabolism in both the putamen, which constitutes the terminal end of the nigrostriatal dopamine pathway, and the nucleus accumbens at the terminal end of the mesolimbic dopamine pathway. That study replicated a previous finding of increased glucose metabolism in the putamen following 12 weeks of IFN-α therapy in hepatitis C patients (Juengling et al., 2000).

Some investigators conclude that the nature of the dopaminergic alteration underlying symptoms of fatigue may be an overall reduction in dopaminergic neurotransmission (see review by Miller, 2009). Indeed, research on the effect of repeated IFN-α

administration on dopamine levels in the whole brains of mice suggests that such treatment causes a decrease in dopaminergic tone (Shuto et al., 1997). In contrast, chronic repeated administration in rats was found to *increase* levels of dopamine in specific areas of the brain, including the cerebral cortex, hypothalamus, and medulla oblongata but not the hippocampus or thalamus (Kumai et al., 2000). Also, when looking at synaptic dopamine levels specifically in the mesolimbic system, one study found that LPS-induced peripheral inflammation causes a significant increase in this area (Borowski et al., 1998).

Given what is known about dopaminergic signaling in decreased locomotor behavior, there is reason to believe that "too much" dopaminergic tone may exist specifically in the neural systems underlying fatigue. Dopaminergic neurotransmission is regulated in part by two major types of receptors (Meyer and Quenzer, 2005). Activation of D1-like receptors (i.e., D1 and D5) causes an increase in the rate of cyclic adenosine monophosphate (cAMP) production inside the cell, which results in an increase of dopamine synthesis inside the cell. Activation of D2-like receptors (i.e., D2, D3, D4) causes a decrease in cAMP activity with subsequent decreased production of dopamine. D2-like receptor activation can also increase the opening of potassium ion channels on the cell membrane, thus facilitating a hyperpolarization of the neuron and decreasing its excitability. These inhibitory D2-like receptors reside on both the presynaptic cell as an autoreceptor and on the postsynaptic cell (Dunlop and Nemeroff, 2007), and their role in psychomotor retardation is well-established. For example, quinpirole, a standard D2/D3 agonist used in experimental research since the early 1980s (see review by Levant et al., 1992), causes increased spontaneous locomotion. Conversely, full antagonism of D2 function can result in complete psychomotor retardation in rodents, as exemplified by high doses of the first generation antipsychotic drug and D2 receptor antagonist, haloperidol (Meyer and Quenzer, 2005). In accord with this finding, fatigue can often be the biggest side effect reported by patients taking haloperidol in clinical trials (Gothelf et al., 2003). Thus, it is conceivable that results showing increased activity in the nigrostriatal tract in patients undergoing proinflammatory immunotherapy and a correlation between this activity and fatigue in cancer patients (Capuron et al., 2007; Juengling et al., 2000) could be mediated by decreased function of D2-like receptors in that area of the brain, giving rise to an increase in dopaminergic tone. However, further research is needed to confirm D2-like receptor deficiency as a definite mechanism of inflammation-dopamine alternations in cancer-related fatigue.

4. Biobehavioral factors that influence inflammation and cancer-related fatigue

As described previously, the basic model underlying research on inflammation and cancer-related fatigue suggests that tumors and the treatments used to treat them activate pro-inflammatory cytokines, leading to fatigue. However, there is considerable variability in the extent of the inflammatory response and in the experience of fatigue in cancer populations. This is particularly evident in the post-treatment period, with some patients reporting high and persistent fatigue symptoms and other reporting very low levels of fatigue (Donovan et al., 2007). At this point, our understanding of factors that influence the severity and persistence of inflammation and associated symptoms of fatigue in cancer patients and survivors is extremely limited. Identification of these factors is important for advancing our understanding of this symptom and for improving detection and treatment of vulnerable patients. In this section, we examine biological factors that are known to regulate pro-inflammatory cytokine production and have been associated with fatigue in cancer survivors and/or other populations, including polymorphisms in inflammatory risk genes, alterations in the hypothalamic–pituitary-adrenal (HPA) axis, and alterations in the cellular immune system and reactivation of latent herpesviruses. We also consider psychological and behavioral factors that may contribute to cancer-related fatigue through inflammatory pathways, including depression, sleep disturbance, psychological stress, and physical activity/body mass index (BMI). These factors are illustrated in Fig 1. Of note, some of these factors (e.g., SNPs, early life stress) are present prior to cancer diagnosis and treatment, whereas others (e.g., cellular immune system, HPA axis) may also be influenced by treatment exposures. Also, these factors may influence the onset, the severity, and/or the persistence of cancer-related fatigue.

4.1. Polymorphisms in inflammation-related genes

Genetic factors play an important role in regulating proinflammatory cytokine production. Single nucleotide polymorphisms (SNPs) that influence quantitative gene expression levels have been identified in the promoters of *IL1B* (−511 bases upstream of the transcription start site), *IL6* (−174), and *TNF* (−308), as well as other locations (Smith and Humphries, 2009). There is preliminary evidence that inflammation-related SNPs are associated with cancer-related fatigue during and after treatment. In a sample of 185 patients undergoing radiation therapy for breast, prostate, lung, or brain cancer, polymorphisms in *TNFA* and *IL6* were associated with elevations in fatigue (Aouizerat et al., 2009; Miaskowski et al., 2010). Jim and colleagues also found an association between polymorphisms in *TNFA* and *IL6* and fatigue in a small sample of 53 prostate cancer patients undergoing androgen deprivation therapy (Jim et al., 2012). In a large sample of lung cancer survivors, Rausch and colleagues found that polymorphisms in *IL1B* and *IL1RN* were associated with fatigue (Rausch et al., 2010). Similarly, we found an association between polymorphisms in *IL1B* and *IL6* and fatigue in breast cancer survivors (Collado-Hidalgo et al., 2008), although these findings were not replicated by another group (Reinertsen et al., 2011). Of note, cytokine polymorphisms have been linked to fatigue in other patient populations (Carlo-Stella et al., 2006; Piraino et al., 2012) and to clinical outcomes in cancer patients (DeMichele et al. 2009).

4.2. HPA axis alterations

Alterations in immune regulatory systems provide another plausible mechanism for elevated inflammatory activity and associated symptoms of fatigue in cancer populations. The HPA axis is known to regulate pro-inflammatory cytokine production (McEwen et al., 1997) via alterations in glucocorticoid production and/or decreased sensitivity of the glucocorticoid receptor (GR) to hormone ligation (Raison and Miller, 2003). We have shown deficits in both pathways in breast cancer survivors with persistent fatigue. In particular, fatigued breast cancer survivors show alterations in diurnal cortisol slope, with elevated levels of evening cortisol (Bower et al., 2005b) as well as blunted cortisol responses to psychological stress (Bower et al., 2005) that are correlated with elevations in stimulated cytokine production (Bower et al., 2007). To probe alterations in glucocorticoid receptor sensitivity, we conducted genome-wide transcriptional profiling of leukocytes from an independent sample of fatigued breast cancer survivors. Results showed a marked down-regulation of genes with response elements for the glucocorticoid receptor in fatigued vs. non-fatigued survivors, suggesting a state of functional GR resistance (Bower et al., 2011a). Reduced GR sensitivity may contribute to the tonic upregulation of NF-κB observed in fatigued survivors (Bower et al., 2011a), consistent with studies linking GR desensitization

to increased NF-κB activity in non-cancer populations (Cole et al., 2007; Miller et al., 2009; Miller et al., 2008b). Research in other cancer populations has also supported a link between HPA alterations and fatigue. For example, in a sample of ovarian cancer patients, higher levels of evening cortisol and reduced cortisol variability were associated with fatigue, vegetative depression, and functional disability (Weinrib et al., 2010).

Because these findings come from cross-sectional studies, it is unclear whether alterations in the HPA axis drive, or are driven by, inflammatory processes. In a longitudinal study of patients with malignant melanoma undergoing treatment with interferon-alpha (IFN-α), exaggerated HPA axis responses to the initial IFN-α administration predicted subsequent development of depression (Capuron et al., 2003), suggesting that HPA alterations may set the stage for behavioral disturbances in cancer patients. Further, HPA axis alterations have been observed in chronic fatigue syndrome and other fatigue-related disorders, and may act as a vulnerability factor for the development of these syndromes (Nater et al., 2008; Cleare, 2003; Crofford et al., 1994; Catley et al., 2000). Additional research on the role of HPA axis alterations in cancer-related fatigue (and other cancer-related behavioral disturbances) is required.

4.3. Cellular immune system and latent herpesvirus activation

Cancer treatments can cause pronounced and prolonged alterations in the cellular immune system (Rotstein et al., 1985; Solomayer et al., 2003), which may underlie long-term alterations in inflammatory activity. In our previous research, we have shown alterations in T cell populations and myeloid dendritic cells in breast cancer survivors with persistent fatigue that are correlated with inflammatory processes (Bower et al., 2003; Collado-Hidalgo et al., 2006). Other groups have shown more global changes in the cellular immune system in relation to fatigue, including elevations in leukocyte numbers among fatigued breast cancer survivors (Landmark-Hoyvik et al., 2009; Alexander et al., 2009).

Another potential explanation for elevated inflammatory processes in cancer patients is reactivation of latent herpesviruses (Glaser et al., 2005; Nazmi et al., 2010). A recent study conducted with breast cancer patients prior to treatment found that elevated CMV antibody titers were associated with a greater likelihood of being fatigued, as well as higher levels of CRP (Fagundes et al., 2012). These findings are consistent with earlier studies showing an association between seropositivity to latent herpesviruses and depressive symptoms in cardiac patients (Miller et al., 2005; Appels et al., 2000). Cancer treatments such as chemotherapy promote viral reactivation and associated increases in inflammatory markers (Kuo et al., 2008), which may have long-term implications for immune regulation and recovery as well as behavioral symptoms.

4.4. Psychological and behavioral factors

A number of psychological and behavioral factors are correlated with fatigue in cancer patients and survivors. We focus here on factors that have been linked with inflammatory processes and may influence fatigue through this pathway. Fatigue is strongly correlated with depression in cancer populations (Jacobsen et al., 2003), and history of depression predicted post-treatment fatigue in a longitudinal study of breast cancer survivors (Andrykowski et al., 2005). Given links between depression and inflammation (Howren et al., 2009; Raison et al., 2006), including increased inflammatory response to challenge in depressed individuals (Pace et al., 2006), it is possible that prior or current depression may set the stage for elevated inflammatory processes and associated symptoms of fatigue during cancer diagnosis and treatment. Similarly, sleep disturbance is correlated with cancer-related fatigue (Bower et al., 2000) and with inflammation (Irwin, 2002) and could plausibly contribute to inflammation-related fatigue in cancer populations.

Another psychosocial factor that may increase risk for inflammation and fatigue is psychological stress, including stress in early life. Both acute and chronic stressors are associated with elevations in proinflammatory cytokines (Steptoe et al., 2007; Kiecolt-Glaser et al., 2003), though links between stress and cancer-related fatigue have not been established. Early life stress is also associated with increased inflammation (Taylor et al., 2006; Danese et al., 2007) as well as elevated fatigue symptoms (McCauley et al., 1997) and chronic fatigue syndrome (Heim et al., 2006) in non-cancer populations. There is preliminary evidence that breast cancer survivors who experienced abuse or neglect as children report higher levels of fatigue (as well as elevated distress and reduced quality of life) (Fagundes et al., 2012). Together, these findings suggest a potential role for psychological stress in the etiology of cancer-related fatigue.

Physical inactivity and elevated body mass index (BMI) are both linked with cancer-related fatigue; indeed, in a large longitudinal study of women with early-stage breast cancer, BMI emerged as one of the key predictors of fatigue at 6 months and 42 months post-treatment (Donovan et al., 2007). These factors are also correlated with increased inflammatory markers (O'Connor et al., 2009b) and might influence fatigue through inflammatory pathways.

5. Conclusions, recommendations, and implications for treatment

The evolving literature on cancer-related fatigue increasingly supports the hypothesis that inflammation is associated with fatigue symptoms in cancer populations. The evidence linking inflammation and fatigue in cancer survivors is particularly strong, with consistent findings emerging from large, well-controlled studies of breast cancer survivors. At this point, there are no well-established animal models of cancer-related fatigue, which limits our ability to probe the underlying mechanisms for this symptom. Initial evidence suggests that the tumor itself, radiation, and chemotherapy can elicit increases in inflammation as well as alterations in locomotor activity in animal models, but links between these systems are still under investigation. The development of animal models of cancer-related fatigue is an important avenue for future research.

This review also highlighted several new frontiers in research on cancer-related fatigue. There is growing interest in neural mechanisms underlying inflammation-related fatigue, with a focus on dopaminergic pathways. However, there has been minimal examination of these processes in cancer patients and survivors. This is a promising avenue for future research. Another important research direction is the identification of factors that increase risk for inflammation and fatigue. There are a number of plausible biological and psychological factors that may contribute to cancer-related fatigue through inflammatory pathways. However, longitudinal studies of fatigue are still extremely limited, and to our knowledge none have simultaneously examined biological and psychological risk factors for fatigue and associated mechanisms in a prospective study design. This type of integrated assessment is critical for determining who is at risk for fatigue and why, which will direct the development and implementation of personalized, targeted interventions for prevention and treatment. Although not highlighted here, there is also substantial interest on "symptom clusters" in cancer populations and the potential for common underlying mechanisms.

At the methodological level, we have found stronger links between cancer-related fatigue and downstream markers of

inflammatory activity (e.g., sTNF-RII, IL-1RA, CRP) as compared to noisier instantaneous plasma cytokine levels (e.g., IL-1β, IL-6). These downstream markers may provide a more robust, stable, and sensitive marker of systemic inflammation, facilitating the detection of relationships with fatigue. Thus, we recommend their incorporation in future research, particularly studies with post-treatment survivors.

Another issue of great importance in this field is the development of effective treatments for cancer-related fatigue. If fatigue is driven by activation of pro-inflammatory cytokines, cytokine antagonists may have promise for reducing this symptom in cancer populations. Indeed, clinical trials have documented beneficial effects of cytokine antagonists on fatigue in patients with inflammatory disorders (Tyring et al., 2006), and there is preliminary evidence that these therapies may also decrease fatigue in patients with advanced cancer. In a study of patients with advanced malignancies undergoing weekly docetaxel chemotherapy, those randomized to receive eterancept, a TNF decoy receptor, reported significantly lower levels of fatigue (Monk et al., 2006). Our research group (Bower, Ganz, Irwin, & Cole) conducted a small pilot study to evaluate the acute effects of infliximab, a monoclonal antibody against TNF, in breast cancer survivors with severe, persistent fatigue. The five women enrolled in this trial had completed their cancer treatments at least one year previously, showed no evidence of cancer recurrence, and were determined to be healthy after careful screening. Participants completed daily diaries for two weeks before and after receiving a single dose of infliximab to assess changes in the severity and duration of daily fatigue. All five women reported reductions in daily fatigue, including a mean 1.9 point decrease in "worst" fatigue from pre- to post-treatment (range = 0.3–2.7 point decrease). These very preliminary findings require replication in a larger, double-blind trial, but do offer initial support for a possible role of cytokine antagonists as therapeutic agents for post-treatment fatigue.

Many cancer patients and survivors will not be eligible for or interested in treatment with cytokine antagonists or other pharmacotherapies (e.g., methylphenidate; Minton et al., 2011). Fortunately, psychological and behavioral approaches also show considerable promise for treating cancer-related fatigue. In randomized controlled trials with cancer populations, exercise has been associated with reduced fatigue (Kangas et al., 2008); exercise also leads to reductions in inflammatory markers in cancer patients (Fairey et al., 2005), and may influence fatigue through effects on inflammatory processes. We recently evaluated a specialized yoga intervention for breast cancer survivors with persistent fatigue and found clinically significant improvements in fatigue and vigor in survivors randomized to yoga vs. health education (Bower et al., 2011c). Cognitive-behavioral therapy is also effective in reducing fatigue among cancer survivors with severe, persistent fatigue (Gielissen et al., 2006). Both yoga and cognitive-behavioral therapies are associated with reduced inflammatory activity (Kiecolt-Glaser et al., 2010; Pullen et al., 2008), including decreased activity of the pro-inflammatory transcription factor NF-κB (Antoni et al., 2012), suggesting one pathway for their beneficial effects. Ultimately, identifying the mechanisms underlying cancer-related fatigue and developing targeted interventions to prevent and/or ameliorate this symptom will enhance survivorship and long-term quality of life in the growing population of cancer survivors.

Conflict of Interest

The authors of this manuscript have nothing to declare.

References

Aggarwal, B.B., 2004. Nuclear factor-κB: the enemy within. Cancer Cell 6, 203–208.

Aggarwal, B.B., Vijayalekshmi, R.V., Sung, B., 2009. Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. Clin. Cancer Res. 15 (2), 425–430.

Ahlberg, K., Ekman, T., Gaston-Johansson, F., 2004. Levels of fatigue compared to levels of cytokines and hemoglobin during pelvic radiotherapy: a pilot study. Biol. Res. Nurs. 5 (3), 203–210.

Alexander, S., Minton, O., Andrews, P., Stone, P., 2009. A comparison of the characteristics of disease-free breast cancer survivors with or without cancer-related fatigue syndrome. Eur. J. Cancer 45 (3), 384–392.

Alfano, C.M., Imayama, I., Neuhouser, M.L., Kiecolt-Glaser, J.K., Wilder Smith, A., Meeske, K., McTiernan, A., Bernstein, L., Baumgartner, K.B., Ulrich, C.M., Ballard-Barbash, R., 2012. Fatigue, Inflammation, and -ë-3 and -ë-6 Fatty Acid Intake Among Breast Cancer Survivors. J. Clin. Oncol. 30 (12), 1280–1287.

Andrykowski, M.A., Curran, S.L., Lightner, R., 1998. Off-treatment fatigue in breast cancer survivors: a controlled comparison. J. Behav. Med. 21 (1), 1–18.

Andrykowski, M.A., Schmidt, J.E., Salsman, J.M., Beacham, A.O., Jacobsen, P.B., 2005. Use of a case definition approach to identify cancer-related fatigue in women undergoing adjuvant therapy for breast cancer. J. Clin. Oncol. 23 (27), 6613–6622.

Antoni, M.H., Lutgendorf, S.K., Blomberg, B., Carver, C.S., Lechner, S., Diaz, A., Stagl, J., Arevalo, J.M., Cole, S.W., 2012. Cognitive-behavioral stress management reverses anxiety-related leukocyte transcriptional dynamics. Biol. Psychiatry 71 (4), 366–372.

Aouizerat, B.E., Dodd, M., Lee, K., West, C., Paul, S.M., Cooper, B.A., Wara, W., Swift, P., Dunn, L.B., Miaskowski, C., 2009. Preliminary evidence of a genetic association between tumor necrosis factor alpha and the severity of sleep disturbance and morning fatigue. Biol. Res. Nurs. 11 (1), 27–41.

Appels, A., Bar, F.W., Bar, J., Bruggeman, C., de Baets, M., 2000. Inflammation, depressive symptomtology, and coronary artery disease. Psychosom. Med. 62 (5), 601–605.

Arpin, D., Perol, D., Blay, J.Y., Falchero, L., Claude, L., Vuillermoz-Blas, S., Martel-Lafay, I., Ginestet, C., Alberti, L., Nosov, D., Etienne-Mastroianni, B., Cottin, V., Perol, M., Guerin, J.C., Cordier, J.F., Carrie, C., 2005. Early variations of circulating interleukin-6 and interleukin-10 levels during thoracic radiotherapy are predictive for radiation pneumonitis. J. Clin. Oncol. 23 (34), 8748–8756.

Borowski, T., Kokkinidis, L., Merali, Z., Anisman, H., 1998. Lipopolysaccharide, central in vivo biogenic amine variations, and anhedonia. NeuroReport 9, 3797–3802.

Bower, J.E., 2007. Cancer-related fatigue: links with inflammation in cancer patients and survivors. Brain Behav. Immun. 21 (7), 863–871.

Bower, J.E., Ganz, P.A., Aziz, N., 2005. Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. Psychosom. Med. 67 (2), 277–280.

Bower, J.E., Ganz, P.A., Aziz, N., Fahey, J.L., 2002. Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom. Med. 64 (4), 604–611.

Bower, J.E., Ganz, P.A., Aziz, N., Fahey, J.L., Cole, S.W., 2003. T-cell homeostasis in breast cancer survivors with persistent fatigue. J. Natl. Cancer Inst. 95 (15), 1165–1168.

Bower, J.E., Ganz, P.A., Aziz, N., Olmstead, R., Irwin, M.R., Cole, S.W., 2007. Inflammatory responses to psychological stress in fatigued breast cancer survivors: relationship to glucocorticoids. Brain Behav. Immun. 21 (3), 251–258.

Bower, J.E., Ganz, P.A., Desmond, K.A., Bernaards, C., Rowland, J.H., Meyerowitz, B.E., Belin, T.R., 2006. Fatigue in long-term breast carcinoma survivors: a longitudinal investigation. Cancer 106 (4), 751–758.

Bower, J.E., Ganz, P.A., Desmond, K.A., Rowland, J.H., Meyerowitz, B.E., Belin, T.R., 2000. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. J. Clin. Oncol. 18 (4), 743–753.

Bower, J.E., Ganz, P.A., Dickerson, S.S., Petersen, L., Aziz, N., Fahey, J.L., 2005. Diurnal cortisol rhythm and fatigue in breast cancer survivors. Psychoneuroendocrinology 30 (1), 92–100.

Bower, J.E., Ganz, P.A., Irwin, M.R., Arevalo, J.M., Cole, S.W., 2011a. Fatigue and gene expression in human leukocytes: increased NF-kappaB and decreased glucocorticoid signaling in breast cancer survivors with persistent fatigue. Brain Behav. Immun. 25 (1), 147–150.

Bower, J.E., Ganz, P.A., Irwin, M.R., Kwan, L., Breen, E.C., Cole, S.W., 2011b. Inflammation and behavioral symptoms after breast cancer treatment: do fatigue, depression, and sleep disturbance share a common underlying mechanism? J. Clin. Oncol. 29 (26), 3517–3522.

Bower, J.E., Ganz, P.A., Tao, M.L., Hu, W., Belin, T.R., Sepah, S., Cole, S., Aziz, N., 2009. Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. Clin. Cancer Res. 15 (17), 5534–5540.

Bower, J.E., Garet, D., Sternlieb, B., Ganz, P.A., Irwin, M.R., Olmstead, R,, Greendale, G., 2011c. Yoga for persistent fatigue in breast cancer survivors: A randomized controlled trial. Cancer. [Epub ahead of print]

Broeckel, J.A., Jacobsen, P.B., Horton, J., Balducci, L., Lyman, G.H., 1998. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. J. Clin. Oncol. 16 (5), 1689–1696.

Brush, J., Lipnick, S.L., Phillips, T., Sitko, J., McDonald, J.T., McBride, W.H., 2007. Molecular mechanisms of late normal tissue injury. Semin. Radiat. Oncol. 17 (2), 121–130.

Capuron, L., Gumnick, J.F., Musselman, D.L., Lawson, D.H., Reemsnyder, A., Nemeroff, C.B., Miller, A.H., 2002. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsychopharmacology 26, 643–652.

Capuron, L., Miller, A.H., 2004. Cytokines and psychopathology: lessons learned from interferon-alpha. Biol. Psychiatry 56, 819–824.

Capuron, L., Pagnoni, G., Demetrashvili, M.F., Lawson, D.H., Fornwalt, F.B., Woolwine, B., Berns, G.S., Nemeroff, C.B., Miller, A.H., 2007. Basal ganglia hypermetabolism and symptoms of fatigue during interferon-alpha therapy. Neuropsychopharmacology 32, 2384–2392.

Capuron, L., Raison, C.L., Musselman, D.L., Lawson, D.H., Nemeroff, C.B., Miller, A.H., 2003. Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. Am. J. Psychiatry 160 (7), 1342–1345.

Carlo-Stella, N., Badulli, C., De Silvestri, A., Bazzichi, L., Martinetti, M., Lorusso, L., Bombardieri, S., Salvaneschi, L., Cuccia, M., 2006. A first study of cytokine genomic polymorphisms in CFS: positive association of TNF-857 and IFN gamma 874 rare alleles. Clin. Exp. Rheumatol. 24 (2), 179–182.

Catley, D., Kaell, A.T., Kirschbaum, C., Stone, A.A., 2000. A naturalistic evaluation of cortisol secretion in persons with fibromyalgia and rheumatoid arthritis. Arthritis Care Res. 13 (1), 51–61.

Cavaletti, G., Marzorati, L., Bogliun, G., Colombo, N., Marzola, M., Pittelli, M.R., Tredici, G., 1992. Cisplatin-induced peripheral neurotoxicity is dependent on total-dose intensity and single-dose intensity. Cancer 69, 203–207.

Cella, D., Davis, K., Breitbart, W., Curt, G., 2001. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. J. Clin. Oncol. 19 (14), 3385–3391.

Cella, D., Peterman, A., Passik, S., Jacobsen, P., Breitbart, W., 1998. Progress toward guidelines for the management of fatigue. Oncology (Huntingt) 12 (11A), 369–377.

Chabner, B.A., Longo, D.L. (Eds.), 2006. Cancer chemotherapy and biotherapy: Principles and practices. Lippincott, Philadelphia.

Cleare, A.J., 2003. The neuroendocrinology of chronic fatigue syndrome. Endocr. Rev. 24 (2), 236–252.

Cole, S.W., Hawkley, L.C., Arevalo, J.M., Sung, C.Y., Rose, R.M., Cacioppo, J.T., 2007. Social regulation of gene expression in human leukocytes. Genome Biol. 8 (9), R189.

Collado-Hidalgo, A., Bower, J.E., Ganz, P.A., Cole, S.W., Irwin, M.R., 2006. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. Clin. Cancer Res. 12 (9), 2759–2766.

Collado-Hidalgo, A., Bower, JE., Ganz, PA., Irwin, MR., Cole, S.W., 2008. Cytokine gene polymorphisms and fatigue in breast cancer survivors: Early findings. Brain Behav. Immun. 22 (8), 1197–1200.

Coussens, L.M., Werb, Z., 2002. Inflammation and cancer. Nature 420, 860–867.

Crofford, L.J., Pillemer, S.R., Kalogeras, K.T., Cash, J.M., Michelson, D., Kling, M.A., Sternberg, E.M., Gold, P.W., Chrousos, G.P., Wilder, R.L., 1994. Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. Arthritis Rheum. 37 (11), 1583–1592.

Danese, A., Pariante, C.M., Caspi, A., Taylor, A., Poulton, R., 2007. Childhood maltreatment predicts adult inflammation in a life-course study. Proc. Natl. Acad. Sci. USA 104 (4), 1319–1324.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9 (1), 46–56.

DeMichele, A., Gray, R., Horn, M., Chen, J., Aplenc, R., Vaughan, W.P., Tallman, M.S., 2009. Host genetic variants in the interleukin-6 promoter predict poor outcome in patients with estrogen receptor-positive, node-positive breast cancer. Cancer Res. 69 (10), 4184–4191.

Donovan, K.A., Jacobsen, P.B., Andrykowski, M.A., Winters, E.M., Balducci, L., Malik, U., Kenady, D., McGrath, P., 2004. Course of fatigue in women receiving chemotherapy and/or radiotherapy for early stage breast cancer. J. Pain Symptom. Manage. 28 (4), 373–380.

Donovan, K.A., Small, B.J., Andrykowski, M.A., Munster, P., Jacobsen, P.B., 2007. Utility of a cognitive-behavioral model to predict fatigue following breast cancer treatment. Health Psychol. 26 (4), 464–472.

Dunlop, B.W., Nemeroff, C.B., 2007. The role of dopamine in the pathophysiology of depression. Arch. Gen. Psychiatry 64, 327–337.

Fagundes, C.P., Lindgren, M.E., Shapirom C.L., Kiecolt-Glaserm J.K., 2012. Child maltreatment and breast cancer survivors: Social support makes a difference for quality of life, fatigue and cancer stress. Eur. J. Cancer. 48, 728–736.

Fagundes, C.P., Glaser, R., Alfano, C.M., Bennett, J.M., Povoski, S.P., Lipari, A.M., Agnese, D.M., Yee, L.D., Carson III, W.E., Farrar, W.B., Malarkey, W.B., Kiecolt-Glaser, J.K., 2012. Fatigue and herpesvirus latency in women newly diagnosed with breast cancer. Brain Behav. Immun. 26 (3), 394–400.

Fairey, A.S., Courneya, K.S., Field, C.J., Bell, G.J., Jones, L.W., Martin, B.S., Mackey, J.R., 2005. Effect of exercise training on C-reactive protein in postmenopausal breast cancer survivors: a randomized controlled trial. Brain Behav. Immun. 19 (5), 381–388.

Frenois, F., Moreau, M., O'Connor, J., Lawson, M., Micon, C., Lestage, J., Kelley, K.W., Dantzer, R., Castanon, N., 2007. Lipopolysaccharide induces delayed FosB/DeltaFosB immunostaining within the mouse extended amygdala, hippocampus and hypothalamus, that parallel the expression of depressive-like behavior. Psychoneuroendocrinology 32, 516–531.

Geinitz, H., Zimmermann, F.B., Stoll, P., Thamm, R., Kaffenberger, W., Ansorg, K., Keller, M., Busch, R., van Beuningen, D., Molls, M., 2001. Fatigue, serum cytokine levels, and blood cell counts during radiotherapy of patients with breast cancer. Int. J. Radiat. Oncol. Biol. Phys. 51 (3), 691–698.

Gielissen, M.F., Verhagen, S., Witjes, F., Bleijenberg, G., 2006. Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. J. Clin. Oncol. 24 (30), 4882–4887.

Glaser, R., Padgett, D.A., Litsky, M.L., Baiocchi, R.A., Yang, E.V., Chen, M., Yeh, P.E., Klimas, N.G., Marshall, G.D., Whiteside, T., Herberman, R., Kiecolt-Glaser, J., Williams, M.V., 2005. Stress-associated changes in the steady-state expression of latent Epstein-Barr virus: implications for chronic fatigue syndrome and cancer. Brain Behav. Immun. 19 (2), 91–103.

Godbout, J.P., Moreau, M., Lestage, J., Chen, J., Sparkman, N.L., O' Connor, J., Castanon, N., Kelley, K.W., Dantzer, R., Johnson, R.W., 2008. Aging exacerbates depressive-like behavior in mice in response to activation of the peripheral innate immune system. Neuropsychopharmacology 33, 2341–2351.

Gothelf, D., Apter, A., Reidman, J., Brand-Gothelf, A., Bloch, Y., Gal, G., Kikinzon, L., Tyano, S., Weizman, R., Ratzoni, G., 2003. Olanzapine, risperidone and haloperidol in the treatment of adolescent patients with schizophrenia. J. Neural. Trans. 110, 545–560.

Greenberg, D.B., Gray, J.L., Mannix, C.M., Eisenthal, S., Carey, M., 1993. Treatment-related fatigue and serum interleukin-1 levels in patients during external beam irradiation for prostate cancer. J. Pain Symptom. Manage. 8 (4), 196–200.

Groenvold, M., Petersen, M.A., Idler, E., Bjorner, J.B., Fayers, P.M., Mouridsen, H.T., 2007. Psychological distress and fatigue predicted recurrence and survival in primary breast cancer patients. Breast Cancer Res. Treat. 105, 209–219.

Haveman, J., Geerdink, A.G., Rodermond, H.M., 1998. TNF, IL-1 and IL-6 in circulating blood after total-body and localized irradiation in rats. Oncol. Rep. 5, 679–683.

Heim, C., Wagner, D., Maloney, E., Papanicolaou, D.A., Solomon, L., Jones, J.F., Unger, E.R., Reeves, W.C., 2006. Early adverse experience and risk for chronic fatigue syndrome: results from a population-based study. Arch. Gen. Psychiatry 63 (11), 1258–1266.

Howren, M.B., Lamkin, D.M., Suls, J., 2009. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom. Med. 71 (2), 171–186.

Irwin, M., 2002. Effects of sleep and sleep loss on immunity and cytokines. Brain Behav. Immun. 16 (5), 503–512.

Jacobsen, P.B., Donovan, K.A., Weitzner, M.A., 2003. Distinguishing fatigue and depression in patients with cancer. Semin. Clin. Neuropsychiatry 8 (4), 229–240.

Jim, H.S., Park, J.Y., Permuth-Wey, J., Rincon, M.A., Phillips, K.M., Small, B.J., Jacobsen, P.B., 2012. Genetic Predictors of Fatigue in Prostate Cancer Patients Treated with Androgen Deprivation Therapy: Preliminary Findings. Brain Behav. Immun. [Epub ahead of print]

Juengling, F.D., Ebert, D., Gut, O., Engelbrecht, M.A., Rasenack, J., Nitzsche, E.U., Bauer, J., Lieb, K., 2000. Prefrontal cortical hypometabolism during low-dose interferon alpha treatment. Psychopharmacology 152, 383–389.

Kangas, M., Bovbjerg, D.H., Montgomery, G.H., 2008. Cancer-related fatigue: a systematic and meta-analytic review of non-pharmacological therapies for cancer patients. Psychol. Bull. 134 (5), 700–741.

Kent, S., Bluthe, R.M., Kelley, K.W., Dantzer, R., 1992. Sickness behavior as a new target for drug development. Trends Pharmacol. Sci. 13 (1), 24–28.

Khayyal, M.T., El-Ghazaly, M.A., El-Hazek, R.M., Nada, A.S., 2009. The effects of celecoxib, a COX-2 selective inhibitor, on acute inflammation induced in irradiated rats. Inflammopharmacology 17, 255–266.

Kiecolt-Glaser, J.K., Christian, L., Preston, H., Houts, C.R., Malarkey, W.B., Emery, C.F., Glaser, R., 2010. Stress, inflammation, and yoga practice. Psychosom. Med. 72 (2), 113–121.

Kiecolt-Glaser, J.K., Preacher, K.J., MacCallum, R.C., Atkinson, C., Malarkey, W.B., Glaser, R., 2003. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc. Natl. Acad. Sci. USA 100 (15), 9090–9095.

King, G.L., Landauer, M.R., 1990. Effects of zacopride and BMY25801 (batanopride) on radiation-induced emesis and locomotor behavior in the ferret. J. Pharmacol. Exp. Ther. 253, 1026–1033.

Kumai, T., Tateishi, T., Tanaka, M., Watanabe, M., Shimizu, H., Kobayashi, S., 2000. Effect of interferon-alpha on tyrosine hydroxylase and catecholamine levels in the brain of rats. Life Sci. 67, 663–669.

Kuo, C.P., Wu, C.L., Ho, H.T., Chen, C.G., Liu, S.I., Lu, Y.T., 2008. Detection of cytomegalovirus reactivation in cancer patients receiving chemotherapy. Clin. Microbiol. Infect. 14 (3), 221–227.

Lamkin, D.M., Lutgendorf, S.K., Lubaroff, D., Sood, A.K., Beltz, T.G., Johnson, A.K., 2011. Cancer induces inflammation and depressive-like behavior in the mouse: modulation by social housing. Brain Behav. Immun. 25, 555–564.

Landmark-Hoyvik, H., Reinertsen, K.V., Loge, J.H., Fossa, S.D., Borresen-Dale, A.L., Dumeaux, V., 2009. Alterations of gene expression in blood cells associated with chronic fatigue in breast cancer survivors. Pharmacogenomics J. 9 (5), 333–340.

Lawrence, D.P., Kupelnick, B., Miller, K., Devine, D., Lau, J., 2004. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. J. Natl. Cancer Inst. Monogr. (32), 40–50.

Levant, B., Grigoriadis, D.E., DeSouza, E.B., 1992. Characterization of [3H]quinpirole binding to D2-like dopamine receptors in rat brain. J. Pharmacol. Exp. Ther. 262, 929–935.

Lutgendorf, S.K., Weinrib, A.Z., Penedo, F., Russell, D., DeGeest, K., Costanzo, E.S., Henderson, P.J., Sephton, S.E., Rohleder, N., Lucci III, J.A., Cole, S., Sood, A.K.,

Lubaroff, . Interleukin-6, cortisol, and depressive symptoms in ovarian cancer patients. J. Clin. Oncol. 26 (29), 4820–4827.
Malik, N.M., Liu, Y.L., Cole, N., Sanger, G.J., Andrews, P.L., 2007. Differential effects of dexamethasone, ondansetron and a tachykinin NK1 receptor antagonist (GR205171) on cisplatin-induced changes in behaviour, food intake, pica and gastric function in rats. Eur. J. Pharmacol. 555, 164–173.
Malik, N.M., Moore, G.B., Smith, G., Liu, Y.L., Sanger, G.J., Andrews, P.L., 2006. Behavioural and hypothalamic molecular effects of the anti-cancer agent cisplatin in the rat: a model of chemotherapy-related malaise? Pharmacol. Biochem. Behav. 83, 9–20.
McCauley, J., Kern, D.E., Kolodner, K., Dill, L., Schroeder, A.F., DeChant, H.K., Ryden, J., Derogatis, L.R., Bass, E.B., 1997. Clinical characteristics of women with a history of childhood abuse: unhealed wounds. JAMA 277 (17), 1362–1368.
McEwen, B.S., Biron, C.A., Brunson, K.W., Bulloch, K., Chambers, W.H., Dhabhar, F.S., Goldfarb, R.H., Kitson, R.P., Miller, A.H., Spencer, R.L., Weiss, J.M., 1997. The role of adrenocorticoids as modulators of immune function in health and disease: neural, endocrine and immune interactions. Brain Res. Brain Res. Rev. 23 (1–2), 79–133.
Meyer, J.S., Quenzer, L.F., 2005. Psychopharmacology: Drugs, The Brain, and Behavior. Sinauer Associates, Sunderland, MA.
Meyers, C.A., Albitar, M., Estey, E., 2005. Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. Cancer 104 (4), 788–793.
Miaskowski, C., Dodd, M., Lee, K., West, C., Paul, S.M., Cooper, B.A., Wara, W., Swift, P.S., Dunn, L.B., Aouizerat, B.E., 2010. Preliminary evidence of an association between a functional interleukin-6 polymorphism and fatigue and sleep disturbance in oncology patients and their family caregivers. J. Pain Symp. Manage. 40 (4), 531–544.
Miller, A.H., 2009. Norman Cousins Lecture. Mechanisms of cytokine-induced behavioral changes: psychoneuroimmunology at the translational interface. Brain Behav. Immun. 23, 149–158.
Miller, A.H., Ancoli-Israel, S., Bower, J.E., Capuron, L., Irwin, M.R., 2008a. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. J. Clin. Oncol. 26 (6), 971–982.
Miller, G.E., Chen, E., Fok, A.K., Walker, H., Lim, A., Nicholls, E.F., Cole, S., Kobor, M.S., 2009. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc. Natl. Acad. Sci. USA 106 (34), 14716–14721.
Miller, G.E., Chen, E., Sze, J., Marin, T., Arevalo, J.M., Doll, R., Ma, R., Cole, S.W., 2008b. A functional genomic fingerprint of chronic stress in humans: blunted glucocorticoid and increased NF-kappaB signaling. Biol. Psychiatry 64 (4), 266–272.
Miller, G.E., Freedland, K.E., Duntley, S., Carney, R.M., 2005. Relation of depressive symptoms to C-reactive protein and pathogen burden (cytomegalovirus, herpes simplex virus, Epstein-Barr virus) in patients with earlier acute coronary syndromes. Am. J. Cardiol. 95 (3), 317–321.
Mills, P.J., Parker, B., Dimsdale, J.E., Sadler, G.R., Ancoli-Israel, S., 2005. The relationship between fatigue and quality of life and inflammation during anthracycline-based chemotherapy in breast cancer. Biol. Psychol. 69 (1), 85–96.
Mills, P.J., Parker, B., Jones, V., Adler, K.A., Perez, C.J., Johnson, S., Cohen-Zion, M., Marler, M., Sadler, G.R., Dimsdale, J.E., Ancoli-Israel, S., 2004. The effects of standard anthracycline-based chemotherapy on soluble ICAM-1 and vascular endothelial growth factor levels in breast cancer. Clin. Cancer Res. 10 (15), 4998–5003.
Minton, O., Richardson, A., Sharpe, M., Hotopf, M., Stone, P.C., 2011. Psychostimulants for the management of cancer-related fatigue: a systematic review and meta-analysis. J. Pain Symptom Manage. 41 (4), 761–767.
Mollman, J.E., 1990. Cisplatin neurotoxicity. N. Engl. J. Med. 322 (2), 126–127.
Monk, J.P., Phillips, G., Waite, R., Kuhn, J., Schaaf, L.J., Otterson, G.A., Guttridge, D., Rhoades, C., Shah, M., Criswell, T., Caligiuri, M.A., Villalona-Calero, M.A., 2006. Assessment of tumor necrosis factor alpha blockade as an intervention to improve tolerability of dose-intensive chemotherapy in cancer patients. J. Clin. Oncol. 24 (12), 1852–1859.
Morrow, G.R., Hickok, J.T., Roscoe, J.A., Raubertas, R.F., Andrews, P.L., Flynn, P.J., Hynes, H.E., Banerjee, T.K., Kirshner, J.J., King, D.K., 2003. Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. J. Clin. Oncol. 21 (24), 4635–4641.
Musselman, D.L., Lawson, D.H., Gumnick, J.F., Manatunga, A.K., Penna, S., Goodkin, R.S., Greiner, K., Nemeroff, C.B., Miller, A.H., 2001. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N. Engl. J. Med. 344, 961–966.
Nater, U.M., Youngblood, L.S., Jones, J.F., Unger, E.R., Miller, A.H., Reeves, W.C., Heim, C., 2008. Alterations in diurnal salivary cortisol rhythm in a population-based sample of cases with chronic fatigue syndrome. Psychosom. Med. 70 (3), 298–305.
Nazmi, A., Diez-Roux, A.V., Jenny, N.S., Tsai, M.Y., Szklo, M., Aiello, A.E., 2010. The influence of persistent pathogens on circulating levels of inflammatory markers: a cross-sectional analysis from the Multi-Ethnic Study of Atherosclerosis. BMC. Public Health 10, 706.
O'Connor, J.C., Lawson, M.A., Andre, C., Moreau, M., Lestage, J., Castanon, N., Kelley, K.W., Dantzer, R., 2009a. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. Mol. Psychiatry 14, 511–522.
O'Connor, M.F., Bower, J.E., Cho, H.J., Creswell, J.D., Dimitrov, S., Hamby, M.E., Hoyt, M.A., Martin, J.L., Robles, T.F., Sloan, E.K., Thomas, K.S., Irwin, M.R., 2009b. To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. Brain Behav. Immun. 23, 887–897.
Orre, I.J., Murison, R., Dahl, A.A., Ueland, T., Aukrust, P., Fossσ, S.D., 2009. Levels of circulating interleukin-1 receptor antagonist and C-reactive protein in long-term survivors of testicular cancer with chronic cancer-related fatigue. Brain Behav. Immun. 23 (6), 868–874.
Orre, I.J., Reinertsen, K.V., Aukrust, P., Dahl, A.A., Foss+Ñ, S.D., Ueland, T., Murison, R., 2011. Higher levels of fatigue are associated with higher CRP levels in disease-free breast cancer survivors. J. Psychosom. Res. 71 (3), 136–141.
Pace, T.W., Mletzko, T.C., Alagbe, O., Musselman, D.L., Nemeroff, C.B., Miller, A.H., Heim, C.M., 2006. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am. J. Psychiatry 163 (9), 1630–1633.
Poulson, M.J., 2001. Not just tired. J. Clin. Oncol. 19 (21), 4180–4181.
Piraino, B., Vollmer-Conna, U., Lloyd, AR., 2012. Genetic associations of fatigue and other symptom domains of the acute sickness response to infection. Brain, Behav. Immun. 26 (4), 552–558.
Pullen, P.R., Nagamia, S.H., Mehta, P.K., Thompson, W.R., Benardot, D., Hammoud, R., Parrott, J.M., Sola, S., Khan, B.V., 2008. Effects of yoga on inflammation and exercise capacity in patients with chronic heart failure. J. Card Fail. 14 (5), 407–413.
Pusztai, L., Mendoza, T.R., Reuben, J.M., Martinez, M.M., Willey, J.S., Lara, J., Syed, A., Fritsche, H.A., Bruera, E., Booser, D., Valero, V., Arun, B., Ibrahim, N., Rivera, E., Royce, M., Cleeland, C.S., Hortobagyi, G.N., 2004. Changes in plasma levels of inflammatory cytokines in response to paclitaxel chemotherapy. Cytokine 25 (3), 94–102.
Ray, M.A., Trammell, R.A., Verhulst, S., Ran, S., Toth, L.A., 2011. Development of a mouse model for assessing fatigue during chemotherapy. Comp. Med. 61, 119–130.
Raison, C.L., Miller, A.H., 2003. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. Am. J. Psychiatry 160 (9), 1554–1565.
Raison, C.L., Capuron, L., Miller, A.H., 2006. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 27 (1), 24–31.
Rausch, S.M., Clark, M.M., Patten, C., Liu, H., Felten, S., Li, Y., Sloan, J., Yang, P., 2010. Relationship between cytokine gene single nucleotide polymorphisms and symptom burden and quality of life in lung cancer survivors. Cancer 116 (17), 4103–4113.
Reinertsen, K.V., Grenaker Alnaes, G.I., Landmark-Hoyvik, H., Loge, J.H., Wist, E., Kristensen, V.N., Fossa, S.D., Edvardsen, H., 2011. Fatigued breast cancer survivors and gene polymorphisms in the inflammatory pathway. Brain, Behav. Immun. 25 (7), 1376–1383.
Rotstein, S., Blomgren, H., Petrini, B., Wasserman, J., Baral, E., 1985. Long term effects on the immune system following local radiation therapy for breast cancer I. Cellular composition of the peripheral blood lymphocyte population. Int. J. Radiat. Oncol. Biol. Phys. 11 (5), 921–925.
Rowinsky, E.K., Eisenhauer, E.A., Chaudhry, V., Arbuck, S.G., Donehower, R.C., 1993. Clinical toxicities encountered with paclitaxel (Taxol). Semin. Oncol. 20, 1–15.
Schubert, C., Hong, S., Natarajan, L., Mills, P.J., Dimsdale, J.E., 2007. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. Brain Behav. Immun. 21 (4), 413–427.
Seruga, B., Zhang, H., Bernstein, L.J., Tannock, I.F., 2008. Cytokines and their relationship to the symptoms and outcome of cancer. Nat. Rev. Cancer 8 (11), 887–899.
Servaes, P., Gielissen, M.F., Verhagen, S., Bleijenberg, G., 2006. The course of severe fatigue in disease-free breast cancer patients: a longitudinal study. Psychooncology 16 (9), 787–795.
Servaes, P., Verhagen, C., Bleijenberg, G., 2002. Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. Eur. J. Cancer 38 (1), 27–43.
Shuto, H., Kataoka, Y., Horikawa, T., Fujihara, N., Oishi, R., 1997. Repeated interferon-alpha administration inhibits dopaminergic neural activity in the mouse brain. Brain Res. 747, 348–351.
Smith, A.J., Humphries, S.E., 2009. Cytokine and cytokine receptor gene polymorphisms and their functionality. Cytokine Growth Factor Rev. 20 (1), 43–59.
Solomayer, E.F., Feuerer, M., Bai, L., Umansky, V., Beckhove, P., Meyberg, G.C., Bastert, G., Schirrmacher, V., Diel, I.J., 2003. Influence of adjuvant hormone therapy and chemotherapy on the immune system analysed in the bone marrow of patients with breast cancer. Clin. Cancer Res. 9 (1), 174–180.
Steptoe, A., Hamer, M., Chida, Y., 2007. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain Behav. Immun. 21 (7), 901–912.
Stone, H.B., Coleman, C.N., Anscher, M.S., McBride, W.H., 2003. Effects of radiation on normal tissue: consequences and mechanisms. Lancet Oncol. 4 (9), 529–536.
Taylor, S.E., Lehman, B.J., Kiefe, C.I., Seeman, T.E., 2006. Relationship of early life stress and psychological functioning to adult C-reactive protein in the coronary artery risk development in young adults study. Biol. Psychiatry 60 (8), 819–824.
Tyring, S., Gottlieb, A., Papp, K., Gordon, K., Leonardi, C., Wang, A., Lalla, D., Woolley, M., Jahreis, A., Zitnik, R., Cella, D., Krishnan, R., 2006. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 367 (9504), 29–35.

Van der Meeren, A., Lebaron-Jacobs, L., 2001. Behavioural consequences of an 8 Gy total body irradiation in mice. regulation by interleukin-4. Can. J. Physiol. Pharmacol. 79, 140–143.

Van der Meeren, A., Monti, P., Lebaron-Jacobs, L., Marquette, C., Gourmelon, P., 2001. Characterization of the acute inflammatory response after irradiation in mice and its regulation by interleukin 4 (Il4). Radiat. Res. 155, 858–865.

Wang, X.S., Shi, Q., Williams, L.A., Cleeland, C.S., Mobley, G.M., Reuben, J.M., Lee, B.N., Giralt, S.A., 2008. Serum interleukin-6 predicts the development of multiple symptoms at nadir of allogeneic hematopoietic stem cell transplantation. Cancer 113 (8), 2102–2109.

Wang, X.S., Shi, Q., Williams, L.A., Mao, L., Cleeland, C.S., Komaki, R.R., Mobley, G.M., Liao, Z., 2010. Inflammatory cytokines are associated with the development of symptom burden in patients with NSCLC undergoing concurrent chemoradiation therapy. Brain Behav. Immun. 24, 968–974.

Wang, X.S., Williams, L.A, Krishnan, S,, Liao, Z., Liu, P., Mao, L., Shi, Q., Mobley, G.M., Woodruff.J.F., Cleeland, C.S., In press. Serum sTNF-R1, IL-6, and the development of fatigue in patients with gastrointestinal cancer undergoing chemoradiation therapy. Brain Behav. Immun, in press.

Weinrib, A.Z., Sephton, S.E., Degeest, K., Penedo, F., Bender, D., Zimmerman, B., Kirschbaum, C., Sood, A.K., Lubaroff, D.M., Lutgendorf, S.K., 2010. Diurnal cortisol dysregulation, functional disability, and depression in women with ovarian cancer. Cancer 116 (18), 4410–4419.

Wood, L.J., Nail, L.M., Perrin, N.A., Elsea, C.R., Fischer, A., Druker, B.J., 2006. The cancer chemotherapy drug etoposide (VP-16) induces proinflammatory cytokine production and sickness behavior-like symptoms in a mouse model of cancer chemotherapy-related symptoms. Biol. Res. Nurs. 8, 157–169.

Wratten, C., Kilmurray, J., Nash, S., Seldon, M., Hamilton, C.S., O'Brien, P.C., Denham, J.W., 2004. Fatigue during breast radiotherapy and its relationship to biological factors. Int. J. Radiat. Oncol. Biol. Phys. 59 (1), 160–167.

York, J.M., Blevins, N.A., Meling, D.D., Peterlin, M.B., Gridley, D.S., Cengel, K.A., Freund, G.G., 2012. The biobehavioral and neuroimmune impact of low-dose ionizing radiation. Brain Behav. Immun. 26, 218–227.