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

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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 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 Figure 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 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-1 β 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 & 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, 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-1 β , TNF, or Scya5. Peak levels for these effects in circulation were observed at 6 hours after TBI and had mostly resolved by 24 hours. In a follow-up study, spontaneous locomotor behavior in the home cage was examined with automated telemetry (Van de Meeren & 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 hours following exposure. Mice exhibited a decrease in locomotion by 6 hours 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 & 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, Puszta 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 2012). 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-1 β , 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 intracellular cytokine production by monocytes 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- κ B 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- κ B/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 & 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 hours 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 hours 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., 2009). 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 & 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 & 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 & 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 & 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 & 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 & 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 Figure 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 (indicated by dashed lines in Figure 1). 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 & 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. In particular, 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 & 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 2005a) 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- κ B observed in fatigued survivors (Bower et al 2011a), consistent with studies linking GR desensitization to increased NF- κ B 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 2011). 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 2009) 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-1 β , 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 etanercept, 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- κ B (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.

References

- Aggarwal BB. Nuclear factor- κ B: The enemy within. *Cancer Cell*. 2004; 6:203–8. [PubMed: 15380510]
- Aggarwal BB, Vijayalekshmi RV, Sung B. Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. *Clin Cancer Res*. 2009; 15(2):425–30. [PubMed: 19147746]
- Ahlberg K, Ekman T, Gaston-Johansson F. Levels of fatigue compared to levels of cytokines and hemoglobin during pelvic radiotherapy: a pilot study. *Biol Res Nurs*. 2004; 5(3):203–10. [PubMed: 14737921]

- Alexander S, Minton O, Andrews P, Stone P. A comparison of the characteristics of disease-free breast cancer survivors with or without cancer-related fatigue syndrome. *European Journal of Cancer*. 2009; 45(3):384–92. [PubMed: 18977131]
- Aley KO, Reichling DB, Levine JD. Vincristine hyperalgesia in the rat: a model of painful vincristine neuropathy in humans. *Neuroscience*. 1996; 73:259–65. [PubMed: 8783247]
- Alfano CM, Imayama I, Neuhouster ML, Kiecolt-Glaser JK, Wilder Smith A, Meeske K, McTiernan A, Bernstein L, Baumgartner KB, Ulrich CM, Ballard-Barbash R. Fatigue, Inflammation, and ω -3 and ω -6 Fatty Acid Intake Among Breast Cancer Survivors. *Journal of Clinical Oncology*. 2012
- Andrykowski MA, Curran SL, Lightner R. Off-treatment fatigue in breast cancer survivors: a controlled comparison. *J Behav Med*. 1998; 21(1):1–18. [PubMed: 9547419]
- Andrykowski MA, Schmidt JE, Salsman JM, Beacham AO, Jacobsen PB. Use of a case definition approach to identify cancer-related fatigue in women undergoing adjuvant therapy for breast cancer. *J Clin Oncol*. 2005; 23(27):6613–22. [PubMed: 16170168]
- Antoni MH, Lutgendorf SK, Blomberg B, Carver CS, Lechner S, Diaz A, Stagl J, Arevalo JM, Cole SW. Cognitive-behavioral stress management reverses anxiety-related leukocyte transcriptional dynamics. *Biol Psychiatry*. 2012; 71(4):366–72. [PubMed: 22088795]
- Aouizerat BE, Dodd M, Lee K, West C, Paul SM, Cooper BA, Wara W, Swift P, Dunn LB, Miaskowski C. Preliminary Evidence of a Genetic Association Between Tumor Necrosis Factor Alpha and the Severity of Sleep Disturbance and Morning Fatigue. *Biological Research for Nursing*. 2009; 11(1):27–41. [PubMed: 19419979]
- Appels A, Bar FW, Bar J, Bruggeman C, de Baets M. Inflammation, depressive symptomatology, and coronary artery disease. *Psychosom Med*. 2000; 62(5):601–5. [PubMed: 11020087]
- Arpin D, Perol D, Blay JY, Falchero L, Claude L, Vuillermoz-Blas S, Martel-Lafay I, Ginestet C, Alberti L, Nosov D, Etienne-Mastroianni B, Cottin V, Perol M, Guerin JC, Cordier JF, Carrie C. Early variations of circulating interleukin-6 and interleukin-10 levels during thoracic radiotherapy are predictive for radiation pneumonitis. *J Clin Oncol*. 2005; 23(34):8748–56. [PubMed: 16314635]
- Borowski T, Kokkinidis L, Merali Z, Anisman H. Lipopolysaccharide, central in vivo biogenic amine variations, and anhedonia. *Neuroreport*. 1998; 9:3797–3802. [PubMed: 9875707]
- Bower JE. Cancer-related fatigue: links with inflammation in cancer patients and survivors. *Brain Behav Immun*. 2007; 21(7):863–71. [PubMed: 17543499]
- Bower JE, Ganz PA, Aziz N. Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. *Psychosom Med*. 2005a; 67(2):277–80. [PubMed: 15784794]
- Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosom Med*. 2002; 64(4):604–11. [PubMed: 12140350]
- Bower JE, Ganz PA, Aziz N, Fahey JL, Cole SW. T-cell homeostasis in breast cancer survivors with persistent fatigue. *J Natl Cancer Inst*. 2003; 95(15):1165–8. [PubMed: 12902446]
- Bower JE, Ganz PA, Aziz N, Olmstead R, Irwin MR, Cole SW. Inflammatory responses to psychological stress in fatigued breast cancer survivors: relationship to glucocorticoids. *Brain Behav Immun*. 2007; 21(3):251–8. [PubMed: 17008048]
- Bower JE, Ganz PA, Desmond KA, Bernaards C, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in long-term breast carcinoma survivors: a longitudinal investigation. *Cancer*. 2006; 106(4):751–8. [PubMed: 16400678]
- Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. *J Clin Oncol*. 2000; 18(4):743–53. [PubMed: 10673515]
- Bower JE, Ganz PA, Dickerson SS, Petersen L, Aziz N, Fahey JL. Diurnal cortisol rhythm and fatigue in breast cancer survivors. *Psychoneuroendocrinology*. 2005b; 30(1):92–100. [PubMed: 15358446]
- Bower JE, Ganz PA, Irwin MR, Arevalo JM, Cole SW. Fatigue and gene expression in human leukocytes: increased NF-kappaB and decreased glucocorticoid signaling in breast cancer survivors with persistent fatigue. *Brain Behav Immun*. 2011a; 25(1):147–50. [PubMed: 20854893]

- Bower JE, Ganz PA, Irwin MR, Kwan L, Breen EC, Cole SW. Inflammation and behavioral symptoms after breast cancer treatment: do fatigue, depression, and sleep disturbance share a common underlying mechanism? *J Clin Oncol*. 2011b; 29(26):3517–22. [PubMed: 21825266]
- Bower JE, Ganz PA, Tao ML, Hu W, Belin TR, Sepah S, Cole S, Aziz N. Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. *Clin Cancer Res*. 2009; 15(17): 5534–40. [PubMed: 19706826]
- Bower JE, Garet D, Sternlieb B, Ganz PA, Irwin MR, Olmstead R, Greendale G. Yoga for persistent fatigue in breast cancer survivors: A randomized controlled trial. *Cancer*. 2011c
- Broeckel JA, Jacobsen PB, Horton J, Balducci L, Lyman GH. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *J Clin Oncol*. 1998; 16(5):1689–96. [PubMed: 9586880]
- Brush J, Lipnick SL, Phillips T, Sitko J, McDonald JT, McBride WH. Molecular mechanisms of late normal tissue injury. *Semin Radiat Oncol*. 2007; 17(2):121–30. [PubMed: 17395042]
- Capuron L, Gumnick JF, Musselman DL, Lawson DH, Reemsnyder A, Nemeroff CB, Miller AH. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology*. 2002; 26:643–52. [PubMed: 11927189]
- Capuron L, Miller AH. Cytokines and psychopathology: lessons learned from interferon-alpha. *Biol Psychiatry*. 2004; 56:819–824. [PubMed: 15576057]
- Capuron L, Pagnoni G, Demetrasvili MF, Lawson DH, Fornwalt FB, Woolwine B, Berns GS, Nemeroff CB, Miller AH. Basal ganglia hypermetabolism and symptoms of fatigue during interferon-alpha therapy. *Neuropsychopharmacology*. 2007; 32:2384–92. [PubMed: 17327884]
- Capuron L, Raison CL, Musselman DL, Lawson DH, Nemeroff CB, Miller AH. Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. *Am J Psychiatry*. 2003; 160(7):1342–5. [PubMed: 12832253]
- Carlo-Stella N, Badulli C, De Silvestri A, Bazzichi L, Martinetti M, Lorusso L, Bombardieri S, Salvaneschi L, Cuccia M. A first study of cytokine genomic polymorphisms in CFS: Positive association of TNF-857 and IFNgamma 874 rare alleles. *Clin Exp Rheumatol*. 2006; 24(2):179–82. [PubMed: 16762155]
- Catley D, Kaell AT, Kirschbaum C, Stone AA. A naturalistic evaluation of cortisol secretion in persons with fibromyalgia and rheumatoid arthritis. *Arthritis Care Res*. 2000; 13(1):51–61. [PubMed: 11094926]
- Cavaletti G, Marzorati L, Bogliun G, Colombo N, Marzola M, Pittelli MR, Tredici G. Cisplatin-induced peripheral neurotoxicity is dependent on total-dose intensity and single-dose intensity. *Cancer*. 1992; 69:203–7. [PubMed: 1309303]
- Cella D, Davis K, Breitbart W, Curt G. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *J Clin Oncol*. 2001; 19(14):3385–91. [PubMed: 11454886]
- Cella D, Peterman A, Passik S, Jacobsen P, Breitbart W. Progress toward guidelines for the management of fatigue. *Oncology (Huntingt)*. 1998; 12(11A):369–77. [PubMed: 10028520]
- Chabner, BA.; Longo, DL., editors. *Cancer chemotherapy and biotherapy: Principles and practices*. Lippincott; Philadelphia: 2006.
- Cleare AJ. The neuroendocrinology of chronic fatigue syndrome. *Endocr Rev*. 2003; 24(2):236–252. [PubMed: 12700181]
- Cliffer KD, Siuciak JA, Carson SR, Radley HE, Park JS, Lewis DR, Zlotchenko E, Nguyen T, Garcia K, Tonra JR, Stambler N, Cedarbaum JM, Bodine SC, Lindsay RM, DiStefano PS. Physiological characterization of Taxol-induced large-fiber sensory neuropathy in the rat. *Ann Neurol*. 1998; 43:46–55. [PubMed: 9450768]
- Cole SW, Hawkey LC, Arevalo JM, Sung CY, Rose RM, Cacioppo JT. Social regulation of gene expression in human leukocytes. *Genome Biol*. 2007; 8(9):R189. [PubMed: 17854483]
- Collado-Hidalgo A, Bower JE, Ganz PA, Cole SW, Irwin MR. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. *Clin Cancer Res*. 2006; 12(9):2759–66. [PubMed: 16675568]

- Collado-Hidalgo A, Bower JE, Ganz PA, Irwin MR, Cole SW. Cytokine gene polymorphisms and fatigue in breast cancer survivors: Early findings. *Brain Behav Immun*. 2008
- Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002; 420:860–7. [PubMed: 12490959]
- Crnic LS, Segall MA. Prostaglandins do not mediate interferon-alpha effects on mouse behavior. *Physiol Behav*. 1992; 51:349–52. [PubMed: 1557446]
- Crofford LJ, Pillemer SR, Kalogeras KT, Cash JM, Michelson D, Kling MA, Sternberg EM, Gold PW, Chrousos GP, Wilder RL. Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. *Arthritis Rheum*. 1994; 37(11):1583–92. [PubMed: 7980669]
- Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. *Proc Natl Acad Sci U S A*. 2007; 104(4):1319–24. [PubMed: 17229839]
- Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008; 9(1):46–56. [PubMed: 18073775]
- DeMichele A, Gray R, Horn M, Chen J, Aplenc R, Vaughan WP, Tallman MS. Host genetic variants in the interleukin-6 promoter predict poor outcome in patients with estrogen receptor-positive, node-positive breast cancer. *Cancer Res*. 2009; 69(10):4184–91. [PubMed: 19435922]
- Donovan KA, Jacobsen PB, Andrykowski MA, Winters EM, Balducci L, Malik U, Kenady D, McGrath P. Course of fatigue in women receiving chemotherapy and/or radiotherapy for early stage breast cancer. *J Pain Symptom Manage*. 2004; 28(4):373–80. [PubMed: 15471655]
- Donovan KA, Small BJ, Andrykowski MA, Munster P, Jacobsen PB. Utility of a cognitive-behavioral model to predict fatigue following breast cancer treatment. *Health Psychol*. 2007; 26(4):464–72. [PubMed: 17605566]
- Drevets WC, Gautier C, Price JC, Kupfer DJ, Kinahan PE, Grace AA, Price JL, Mathis CA. Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol Psychiatry*. 2001; 49:81–96. [PubMed: 11164755]
- Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Arch Gen Psychiatry*. 2007; 64:327–37. [PubMed: 17339521]
- Fagundes CP, Lindgren ME, Shapiro CL, Kiecolt-Glaser JK. Child maltreatment and breast cancer survivors: Social support makes a difference for quality of life, fatigue and cancer stress. *Eur J Cancer*. 2011
- Fagundes CP, Glaser R, Alfano CM, Bennett JM, Povoski SP, Lipari AM, Agnese DM, Yee LD, Carson WE III, Farrar WB, Malarkey WB, Kiecolt-Glaser JK. Fatigue and herpesvirus latency in women newly diagnosed with breast cancer. *Brain Behav Immun*. 2012; 26(3):394–400. [PubMed: 21988771]
- Fairey AS, Courneya KS, Field CJ, Bell GJ, Jones LW, Martin BS, Mackey JR. Effect of exercise training on C-reactive protein in postmenopausal breast cancer survivors: a randomized controlled trial. *Brain Behav Immun*. 2005; 19(5):381–8. [PubMed: 15922556]
- Frenois F, Moreau M, O'Connor J, Lawson M, Micon C, Lestage J, Kelley KW, Dantzer R, Castanon N. Lipopolysaccharide induces delayed FosB/DeltaFosB immunostaining within the mouse extended amygdala, hippocampus and hypothalamus, that parallel the expression of depressive-like behavior. *Psychoneuroendocrinology*. 2007; 32:516–31. [PubMed: 17482371]
- Geinitz H, Zimmermann FB, Stoll P, Thamm R, Kaffenberger W, Ansorg K, Keller M, Busch R, van Beuningen D, Molls M. Fatigue, serum cytokine levels, and blood cell counts during radiotherapy of patients with breast cancer. *Int J Radiat Oncol Biol Phys*. 2001; 51(3):691–8. [PubMed: 11597810]
- Gerstner HB. Acute clinical effects of penetrating nuclear radiation. *J Am Med Assoc*. 1958; 168:381–8. [PubMed: 13575164]
- Gielissen MF, Verhagen S, Witjes F, Bleijenberg G. 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*. 2006; 24(30):4882–7. [PubMed: 17050873]
- Glaser R, Padgett DA, Litsky ML, Baiocchi RA, Yang EV, Chen M, Yeh PE, Klimas NG, Marshall GD, Whiteside T, Herberman R, Kiecolt-Glaser J, Williams MV. Stress-associated changes in the

- steady-state expression of latent Epstein-Barr virus: implications for chronic fatigue syndrome and cancer. *Brain Behav Immun.* 2005; 19(2):91–103. [PubMed: 15664781]
- Godbout JP, Moreau M, Lestage J, Chen J, Sparkman NL, O'Connor J, Castanon N, Kelley KW, Dantzer R, Johnson RW. Aging exacerbates depressive-like behavior in mice in response to activation of the peripheral innate immune system. *Neuropsychopharmacology.* 2008; 33:2341–51. [PubMed: 18075491]
- Gothelf D, Apter A, Reidman J, Brand-Gothelf A, Bloch Y, Gal G, Kikinzon L, Tyano S, Weizman R, Ratzoni G. Olanzapine, risperidone and haloperidol in the treatment of adolescent patients with schizophrenia. *J Neural Transm.* 2003; 110:545–60. [PubMed: 12721815]
- Greenberg DB, Gray JL, Mannix CM, Eisenthal S, Carey M. Treatment-related fatigue and serum interleukin-1 levels in patients during external beam irradiation for prostate cancer. *J Pain Symptom Manage.* 1993; 8(4):196–200. [PubMed: 7963760]
- Groenvold M, Petersen MA, Idler E, Bjorner JB, Fayers PM, Mouridsen HT. Psychological distress and fatigue predicted recurrence and survival in primary breast cancer patients. *Breast Cancer Res Treat.* 2007; 105:209–19. [PubMed: 17203386]
- Haveman J, Geerdink AG, Rodermond HM. TNF, IL-1 and IL-6 in circulating blood after total-body and localized irradiation in rats. *Oncol Rep.* 1998; 5:679–83. [PubMed: 9538175]
- Heim C, Wagner D, Maloney E, Papanicolaou DA, Solomon L, Jones JF, Unger ER, Reeves WC. Early adverse experience and risk for chronic fatigue syndrome: results from a population-based study. *Arch Gen Psychiatry.* 2006; 63(11):1258–66. [PubMed: 17088506]
- Holland JF, Scharlau C, Gailani S, Krant MJ, Olson KB, Horton J, Shnider BI, Lynch JJ, Owens A, Carbone PP, Colsky J, Grob D, Miller SP, Hall TC. Vincristine treatment of advanced cancer: a cooperative study of 392 cases. *Cancer Res.* 1973; 33:1258–64. [PubMed: 4352365]
- Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med.* 2009; 71(2):171–86. [PubMed: 19188531]
- Irwin M. Effects of sleep and sleep loss on immunity and cytokines. *Brain Behav Immun.* 2002; 16(5):503–12. [PubMed: 12401464]
- Jacobsen PB, Donovan KA, Weitzner MA. Distinguishing fatigue and depression in patients with cancer. *Semin Clin Neuropsychiatry.* 2003; 8(4):229–40. [PubMed: 14613050]
- Jim HS, Park JY, Permut-Wey J, Rincon MA, Phillips KM, Small BJ, Jacobsen PB. Genetic Predictors of Fatigue in Prostate Cancer Patients Treated with Androgen Deprivation Therapy: Preliminary Findings. *Brain Behav Immun.* 2012
- Juengling FD, Ebert D, Gut O, Engelbrecht MA, Rasenack J, Nitzsche EU, Bauer J, Lieb K. Prefrontal cortical hypometabolism during low-dose interferon alpha treatment. *Psychopharmacology (Berl).* 2000; 152:383–9. [PubMed: 11140330]
- Kangas M, Bovbjerg DH, Montgomery GH. Cancer-related fatigue: a systematic and meta-analytic review of non-pharmacological therapies for cancer patients. *Psychol Bull.* 2008; 134(5):700–41. [PubMed: 18729569]
- Kent S, Bluth RM, Kelley KW, Dantzer R. Sickness behavior as a new target for drug development. *Trends Pharmacol Sci.* 1992; 13(1):24–8. [PubMed: 1542935]
- Khayyal MT, El-Ghazaly MA, El-Hazek RM, Nada AS. The effects of celecoxib, a COX-2 selective inhibitor, on acute inflammation induced in irradiated rats. *Inflammopharmacology.* 2009; 17:255–66. [PubMed: 19798548]
- Kiecolt-Glaser JK, Christian L, Preston H, Houts CR, Malarkey WB, Emery CF, Glaser R. Stress, inflammation, and yoga practice. *Psychosom Med.* 2010; 72(2):113–21. [PubMed: 20064902]
- Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci U S A.* 2003; 100(15):9090–5. [PubMed: 12840146]
- King GL, Landauer MR. Effects of zacopride and BMY25801 (batanopride) on radiation-induced emesis and locomotor behavior in the ferret. *J Pharmacol Exp Ther.* 1990; 253:1026–33. [PubMed: 2359014]
- Kumai T, Tateishi T, Tanaka M, Watanabe M, Shimizu H, Kobayashi S. Effect of interferon-alpha on tyrosine hydroxylase and catecholamine levels in the brain of rats. *Life Sci.* 2000; 67:663–9. [PubMed: 12659172]

- Kuo CP, Wu CL, Ho HT, Chen CG, Liu SI, Lu YT. Detection of cytomegalovirus reactivation in cancer patients receiving chemotherapy. *Clinical Microbiology and Infection*. 2008; 14(3):221–7. [PubMed: 18070129]
- Lamkin DM, Lutgendorf SK, Lubaroff D, Sood AK, Beltz TG, Johnson AK. Cancer induces inflammation and depressive-like behavior in the mouse: modulation by social housing. *Brain Behav Immun*. 2011; 25:555–64. [PubMed: 21182930]
- Lammers CH, Diaz J, Schwartz JC, Sokoloff P. Selective increase of dopamine D3 receptor gene expression as a common effect of chronic antidepressant treatments. *Mol Psychiatry*. 2000; 5:378–88. [PubMed: 10889548]
- Landmark-Hoyvik H, Reinertsen KV, Loge JH, Fossa SD, Borresen-Dale AL, Dumeaux V. Alterations of gene expression in blood cells associated with chronic fatigue in breast cancer survivors. *Pharmacogenomics J*. 2009; 9(5):333–40. [PubMed: 19546881]
- Laruelle M, Abi-Dargham A, van Dyck CH, Rosenblatt W, Zea-Ponce Y, Zoghbi SS, Baldwin RM, Charney DS, Hoffer PB, Kung HF, et al. SPECT imaging of striatal dopamine release after amphetamine challenge. *J Nucl Med*. 1995; 36:1182–90. [PubMed: 7790942]
- Lawrence DP, Kupelnick B, Miller K, Devine D, Lau J. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. *J Natl Cancer Inst Monogr*. 2004; (32):40–50. [PubMed: 15263040]
- Lebaron-Jacobs L, Wysocki J, Griffiths NM. Differential qualitative and temporal changes in the response of the hypothalamus-pituitary-adrenal axis in rats after localized or total-body irradiation. *Radiat Res*. 2004; 161:712–22. [PubMed: 15161348]
- Levant B, Grigoriadis DE, DeSouza EB. Characterization of [3H]quinpirole binding to D2-like dopamine receptors in rat brain. *J Pharmacol Exp Ther*. 1992; 262:929–35. [PubMed: 1356154]
- Lindner, DJ.; Taylor, KL.; Reu, FJ.; Masci, PA.; Borden, EC. Interferons. In: Chabner, BA.; Longo, DL., editors. *Cancer chemotherapy and biotherapy: Principles and practices*. Lippincott; Philadelphia: 2006.
- Lutgendorf SK, Weinrib AZ, Penedo F, Russell D, DeGeest K, Costanzo ES, Henderson PJ, Sephton SE, Rohleder N, Lucci JA III, Cole S, Sood AK, Lubaroff DM. Interleukin-6, cortisol, and depressive symptoms in ovarian cancer patients. *J Clin Oncol*. 2008; 26(29):4820–7. [PubMed: 18779606]
- Malik NM, Liu YL, Cole N, Sanger GJ, Andrews PL. 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*. 2007; 555:164–73. [PubMed: 17141213]
- Malik NM, Moore GB, Smith G, Liu YL, Sanger GJ, Andrews PL. Behavioural and hypothalamic molecular effects of the anti-cancer agent cisplatin in the rat: A model of chemotherapy-related malaise? *Pharmacol Biochem Behav*. 2006; 83:9–20. [PubMed: 16443263]
- McCauley J, Kern DE, Kolodner K, Dill L, Schroeder AF, DeChant HK, Ryden J, Derogatis LR, Bass EB. Clinical characteristics of women with a history of childhood abuse: unhealed wounds. *JAMA*. 1997; 277(17):1362–8. [PubMed: 9134941]
- McEwen BS, Biron CA, Brunson KW, Bulloch K, Chambers WH, Dhabhar FS, Goldfarb RH, Kitson RP, Miller AH, Spencer RL, Weiss JM. The role of adrenocorticoids as modulators of immune function in health and disease: neural, endocrine and immune interactions. *Brain Res Brain Res Rev*. 1997; 23(1–2):79–133. [PubMed: 9063588]
- Meyer, JS.; Quenzer, LF. *Psychopharmacology: Drugs, The Brain, and Behavior*. Sunderland, MA: Sinauer Associates; 2005.
- Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. *Cancer*. 2005; 104(4):788–93. [PubMed: 15973668]
- Miaskowski C, Dodd M, Lee K, West C, Paul SM, Cooper BA, Wara W, Swift PS, Dunn LB, Aouizerat BE. 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 Symptom Manage*. 2010; 40(4):531–44. [PubMed: 20570482]

- Miller AH. Norman Cousins Lecture. Mechanisms of cytokine-induced behavioral changes: psychoneuroimmunology at the translational interface. *Brain Behav Immun*. 2009; 23:149–58. [PubMed: 18793712]
- Miller AH, Ancoli-Israel S, Bower JE, Capuron L, Irwin MR. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *J Clin Oncol*. 2008a; 26(6):971–82. [PubMed: 18281672]
- Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF, Cole S, Kobor MS. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. *Proc Natl Acad Sci U S A*. 2009; 106(34):14716–21. [PubMed: 19617551]
- Miller GE, Chen E, Sze J, Marin T, Arevalo JM, Doll R, Ma R, Cole SW. A functional genomic fingerprint of chronic stress in humans: blunted glucocorticoid and increased NF-kappaB signaling. *Biol Psychiatry*. 2008b; 64(4):266–72. [PubMed: 18440494]
- Miller GE, Freedland KE, Duntley S, Carney RM. 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*. 2005; 95(3):317–21. [PubMed: 15670537]
- Mills PJ, Parker B, Dimsdale JE, Sadler GR, Ancoli-Israel S. The relationship between fatigue and quality of life and inflammation during anthracycline-based chemotherapy in breast cancer. *Biol Psychol*. 2005; 69(1):85–96. [PubMed: 15740827]
- Mills PJ, Parker B, Jones V, Adler KA, Perez CJ, Johnson S, Cohen-Zion M, Marler M, Sadler GR, Dimsdale JE, Ancoli-Israel S. The effects of standard anthracycline-based chemotherapy on soluble ICAM-1 and vascular endothelial growth factor levels in breast cancer. *Clin Cancer Res*. 2004; 10(15):4998–5003. [PubMed: 15297400]
- Minton O, Richardson A, Sharpe M, Hotopf M, Stone PC. Psychostimulants for the Management of Cancer-Related Fatigue: A Systematic Review and Meta-Analysis. *J Pain Symptom Manage*. 2011; 41(4):761–7. [PubMed: 21251796]
- Mollman JE. Cisplatin neurotoxicity. *N Engl J Med*. 1990; 322(2):126–7. [PubMed: 2152970]
- Monk JP, Phillips G, Waite R, Kuhn J, Schaaf LJ, Otterson GA, Guttridge D, Rhoades C, Shah M, Criswell T, Caligiuri MA, Villalona-Calero MA. Assessment of tumor necrosis factor alpha blockade as an intervention to improve tolerability of dose-intensive chemotherapy in cancer patients. *J Clin Oncol*. 2006; 24(12):1852–9. [PubMed: 16622259]
- Morrow GR, Hickok JT, Roscoe JA, Raubertas RF, Andrews PL, Flynn PJ, Hynes HE, Banerjee TK, Kirshner JJ, King DK. 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*. 2003; 21(24):4635–41. [PubMed: 14673053]
- Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, Greiner K, Nemeroff CB, Miller AH. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med*. 2001; 344:961–6. [PubMed: 11274622]
- Nater UM, Youngblood LS, Jones JF, Unger ER, Miller AH, Reeves WC, Heim C. Alterations in diurnal salivary cortisol rhythm in a population-based sample of cases with chronic fatigue syndrome. *Psychosom Med*. 2008; 70(3):298–305. [PubMed: 18378875]
- Nazmi A, Diez-Roux AV, Jenny NS, Tsai MY, Szklo M, Aiello AE. 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*. 2010; 10:706. [PubMed: 21083905]
- O'Connor JC, Lawson MA, Andre C, Moreau M, Lestage J, Castanon N, Kelley KW, Dantzer R. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. *Mol Psychiatry*. 2009; 14:511–22. [PubMed: 18195714]
- O'Connor MF, Bower JE, Cho HJ, Creswell JD, Dimitrov S, Hamby ME, Hoyt MA, Martin JL, Robles TF, Sloan EK, Thomas KS, Irwin MR. To assess, to control, to exclude: Effects of biobehavioral factors on circulating inflammatory markers. *Brain Behav Immun*. 2009; 23:887–97. [PubMed: 19389469]

- Orre IJ, Murison R, Dahl AA, Ueland T, Aukrust P, Fosså SD. Levels of circulating interleukin-1 receptor antagonist and C-reactive protein in long-term survivors of testicular cancer with chronic cancer-related fatigue. *Brain, Behavior, and Immunity*. 2009; 23(6):868–74.
- Orre IJ, Reinertsen KV, Aukrust P, Dahl AA, Fosså SD, Ueland T, Murison R. Higher levels of fatigue are associated with higher CRP levels in disease-free breast cancer survivors. *Journal of Psychosomatic Research*. 2011; 71(3):136–41. [PubMed: 21843747]
- Pace TW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, Heim CM. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *Am J Psychiatry*. 2006; 163(9):1630–3. [PubMed: 16946190]
- Papp M, Klimek V, Willner P. Parallel changes in dopamine D2 receptor binding in limbic forebrain associated with chronic mild stress-induced anhedonia and its reversal by imipramine. *Psychopharmacology (Berl)*. 1994; 115:441–6. [PubMed: 7871087]
- Poulson MJ. Not just tired. *J Clin Oncol*. 2001; 19(21):4180–1. [PubMed: 11689589]
- Pfeffer LM, Dinarello CA, Herberman RB, Williams BR, Borden EC, Borden R, Walter MR, Nagabhushan TL, Trotta PP, Pestka S. Biological properties of recombinant alpha-interferons: 40th anniversary of the discovery of interferons. *Cancer Res*. 1998; 58:2489–99. [PubMed: 9635566]
- Piraino B, Vollmer-Conna U, Lloyd AR. Genetic associations of fatigue and other symptom domains of the acute sickness response to infection. *Brain, Behavior, and Immunity*. 2012
- Polomano RC, Mannes AJ, Clark US, Bennett GJ. A painful peripheral neuropathy in the rat produced by the chemotherapeutic drug, paclitaxel. *Pain*. 2001; 94:293–304. [PubMed: 11731066]
- Pullen PR, Nagamia SH, Mehta PK, Thompson WR, Benardot D, Hammoud R, Parrott JM, Sola S, Khan BV. Effects of yoga on inflammation and exercise capacity in patients with chronic heart failure. *J Card Fail*. 2008; 14(5):407–13. [PubMed: 18514933]
- Pusztai L, Mendoza TR, Reuben JM, Martinez MM, Willey JS, Lara J, Syed A, Fritsche HA, Bruera E, Booser D, Valero V, Arun B, Ibrahim N, Rivera E, Royce M, Cleeland CS, Hortobagyi GN. Changes in plasma levels of inflammatory cytokines in response to paclitaxel chemotherapy. *Cytokine*. 2004; 25(3):94–102. [PubMed: 14698135]
- Pyter LM, Pineros V, Galang JA, McClintock MK, Prendergast BJ. Peripheral tumors induce depressive-like behaviors and cytokine production and alter hypothalamic-pituitary-adrenal axis regulation. *Proc Natl Acad Sci U S A*. 2009; 106:9069–74. [PubMed: 19451634]
- Ray MA, Trammell RA, Verhulst S, Ran S, Toth LA. Development of a mouse model for assessing fatigue during chemotherapy. *Comp Med*. 2011; 61:119–30. [PubMed: 21535922]
- Raison CL, Miller AH. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *Am J Psychiatry*. 2003; 160(9):1554–65. [PubMed: 12944327]
- Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol*. 2006; 27(1):24–31. [PubMed: 16316783]
- Rausch SM, Clark MM, Patten C, Liu H, Felten S, Li Y, Sloan J, Yang P. Relationship between cytokine gene single nucleotide polymorphisms and symptom burden and quality of life in lung cancer survivors. *Cancer*. 2010; 116(17):4103–13. [PubMed: 20564140]
- Reinertsen KV, Grenaker Alnaes GI, Landmark-Hoyvik H, Loge JH, Wist E, Kristensen VN, Fossa SD, Edvardsen H. Fatigued breast cancer survivors and gene polymorphisms in the inflammatory pathway. *Brain, Behavior, and Immunity*. 2011; 25(7):1376–83.
- Rogers MA, Bradshaw JL, Phillips JG, Chiu E, Vaddadi K, Presnel I, Mileskin C. Parkinsonian motor characteristics in unipolar major depression. *J Clin Exp Neuropsychol*. 2000; 22:232–44. [PubMed: 10779837]
- Rotstein S, Blomgren H, Petrini B, Wasserman J, Baral E. 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*. 1985; 11(5):921–5. [PubMed: 3157666]
- Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC. Clinical toxicities encountered with paclitaxel (Taxol). *Semin Oncol*. 1993; 20:1–15. [PubMed: 8102012]
- Sandler SG, Tobin W, Henderson ES. Vincristine-induced neuropathy. A clinical study of fifty leukemic patients. *Neurology*. 1969; 19:367–74. [PubMed: 5813374]

- Schubert C, Hong S, Natarajan L, Mills PJ, Dimsdale JE. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain Behav Immun*. 2007; 21(4):413–27. [PubMed: 17178209]
- Segall MA, Crnic LS. An animal model for the behavioral effects of interferon. 1990; 104:612–18.
- Seruga B, Zhang H, Bernstein LJ, Tannock IF. Cytokines and their relationship to the symptoms and outcome of cancer. *Nat Rev Cancer*. 2008; 8(11):887–99. [PubMed: 18846100]
- Servaes P, Gielissen MF, Verhagen S, Bleijenberg G. The course of severe fatigue in disease-free breast cancer patients: a longitudinal study. *Psychooncology*. 2006; 16(9):787–95. [PubMed: 17086555]
- Servaes P, Verhagen C, Bleijenberg G. Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. *Eur J Cancer*. 2002; 38(1):27–43. [PubMed: 11750837]
- Shuto H, Kataoka Y, Horikawa T, Fujihara N, Oishi R. Repeated interferon-alpha administration inhibits dopaminergic neural activity in the mouse brain. *Brain Res*. 1997; 747:348–51. [PubMed: 9046014]
- Smith AJ, Humphries SE. Cytokine and cytokine receptor gene polymorphisms and their functionality. *Cytokine Growth Factor Rev*. 2009; 20(1):43–59. [PubMed: 19038572]
- Solomayer EF, Feuerer M, Bai L, Umansky V, Beckhove P, Meyberg GC, Bastert G, Schirmacher V, Diel IJ. Influence of adjuvant hormone therapy and chemotherapy on the immune system analysed in the bone marrow of patients with breast cancer. *Clin Cancer Res*. 2003; 9(1):174–80. [PubMed: 12538466]
- Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. *Brain Behav Immun*. 2007; 21(7):901–12. [PubMed: 17475444]
- Stone HB, Coleman CN, Anscher MS, McBride WH. Effects of radiation on normal tissue: consequences and mechanisms. *The Lancet Oncology*. 2003; 4(9):529–36. [PubMed: 12965273]
- Taylor SE, Lehman BJ, Kiefe CI, Seeman TE. 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*. 2006; 60(8):819–24. [PubMed: 16712805]
- Tredici G, Tredici S, Fabbria D, Minoia C, Cavaletti G. Experimental cisplatin neuropathy in rats and the effect of retinoic acid administration. *J Neurooncol*. 1998; 36:31–40. [PubMed: 9525823]
- Tremblay LK, Naranjo CA, Cardenas L, Herrmann N, Busto UE. Probing brain reward system function in major depressive disorder: altered response to dextroamphetamine. *Arch Gen Psychiatry*. 2002; 59:409–16. [PubMed: 11982444]
- Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, Lalla D, Woolley M, Jahreis A, Zitnik R, Cella D, Krishnan R. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *The Lancet*. 2006; 367(9504):29–35.
- Van der Meeren A, Lebaron-Jacobs L. Behavioural consequences of an 8 Gy total body irradiation in mice: regulation by interleukin-4. *Can J Physiol Pharmacol*. 2001; 79:140–3. [PubMed: 11233562]
- Van der Meeren A, Monti P, Lebaron-Jacobs L, Marquette C, Gourmelon P. Characterization of the acute inflammatory response after irradiation in mice and its regulation by interleukin 4 (IL4). *Radiat Res*. 2001; 155:858–65. [PubMed: 11352769]
- Wang XS, Shi Q, Williams LA, Cleeland CS, Mobley GM, Reuben JM, Lee BN, Giralt SA. Serum interleukin-6 predicts the development of multiple symptoms at nadir of allogeneic hematopoietic stem cell transplantation. *Cancer*. 2008; 113(8):2102–9. [PubMed: 18792065]
- Wang XS, Shi Q, Williams LA, Mao L, Cleeland CS, Komaki RR, Mobley GM, Liao Z. Inflammatory cytokines are associated with the development of symptom burden in patients with NSCLC undergoing concurrent chemoradiation therapy. *Brain Behav Immun*. 2010; 24:968–74. [PubMed: 20353817]
- Wang XS, Williams LA, Krishnan S, Liao Z, Liu P, Mao L, Shi Q, Mobley GM, Woodruff JF, Cleeland CS. Serum sTNF-R1, IL-6, and the development of fatigue in patients with gastrointestinal cancer undergoing chemoradiation therapy. *Brain Behav Immun*. 2012 in press.

- Weinrib AZ, Sephton SE, Degeest K, Penedo F, Bender D, Zimmerman B, Kirschbaum C, Sood AK, Lubaroff DM, Lutgendorf SK. Diurnal cortisol dysregulation, functional disability, and depression in women with ovarian cancer. *Cancer*. 2010; 116(18):4410–9. [PubMed: 20564155]
- Willner P, Hale AS, Argyropoulos S. Dopaminergic mechanism of antidepressant action in depressed patients. *J Affect Disord*. 2005; 86:37–45. [PubMed: 15820269]
- Willner P, Muscat R, Papp M. Chronic mild stress-induced anhedonia: a realistic animal model of depression. *Neurosci Biobehav Rev*. 1992; 16:525–34. [PubMed: 1480349]
- Wratten C, Kilmurray J, Nash S, Seldon M, Hamilton CS, O'Brien PC, Denham JW. Fatigue during breast radiotherapy and its relationship to biological factors. *Int J Radiat Oncol Biol Phys*. 2004; 59(1):160–7. [PubMed: 15093912]
- Young, RW. Mechanisms and treatment of radiation-induced nausea and vomiting. In: Davis, CJ.; Lake-Bakaar, GV.; Grahame-Smith, DG., editors. *Nausea and vomiting: Mechanisms and treatment*. Springer-Verlag; New York: 1986.

Figure 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 the 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.