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Invited Review

Cancer-related fatigue: Links with inflammation in cancer patients and survivors

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Abstract

Fatigue is one of the most common and distressing side effects of cancer and its treatment and may persist long after successful treatment completion. Emerging evidence suggests that inflammatory processes may be involved in cancer-related fatigue both during and after treatment. In this review, we consider the evidence for an association between inflammation and fatigue in cancer patients and survivors. Further, we identify potential mechanisms for persistent inflammation, focusing on the HPA axis. Risk factors and treatments for cancer-related fatigue are also discussed.

Keywords: Cancer; Cytokines; Fatigue; Inflammation; HPA axis; Review

1. Introduction

There are a growing number of cancer survivors in the United States, and a concomitant rise in attention to quality of life after cancer diagnosis and treatment. In particular, behavioral side effects of cancer treatment have become a focus of research and clinical attention. The most common and distressing side effect of cancer treatment is fatigue (Lawrence et al., 2004). Fatigue occurs across different types of cancer and cancer treatments and may persist for months or years after successful treatment completion. In addition to its importance for patients' well-being, cancer-related fatigue is of interest as a potential clinical model of sickness behavior that may provide valuable insight into proinflammatory cytokine effects on the brain and behavior. This review will consider the evidence for a link between inflammation and cancer-related fatigue, focusing on research conducted by our group with breast cancer patients and survivors.

2. Prevalence and description of cancer-related fatigue

Prevalence estimates of fatigue during treatment range from 25% to 99%, depending on the patient population and type of assessment. Most studies find that 30% to 60% of patients report moderate or severe fatigue while undergoing treatment with radiation, chemotherapy, hormone therapy, and biological therapies (Lawrence et al., 2004). A substantial minority of these patients continue to experience problems with fatigue long after treatment completion. In a large cohort study, we found that approximately one-third of disease-free breast cancer survivors reported fatigue at 1 to 5 and at 5 to 10 years post-diagnosis; 21% reported problems with fatigue at both assessments (Bower et al., 2000, 2006). Similar estimates have been obtained in other survivor populations (Cella et al., 2001).

Qualitative reports suggest that cancer-related fatigue differs from "normal" fatigue due to lack of sleep or

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overexertion as it is more severe, longer lasting, and is not relieved by adequate sleep or rest (Poulson, 2001). Empirical studies have confirmed that the intensity and duration of fatigue experienced by cancer patients and survivors is significantly greater than healthy controls (Andrykowski et al., 1998; Jacobsen et al., 1999). Fatigue has a detrimental impact on all aspects of quality of life among both cancer patients and survivors. For example, in a nationwide survey of cancer patients over 50% reported that fatigue affected their ability to work, their physical and emotional well-being, their social activity, and their ability to enjoy life in the moment (Curt et al., 2000).

Assessment of cancer-related fatigue is challenging as there is no commonly agreed on definition of this symptom (Jacobsen, 2004). One definition that captures several of the key features of cancer-related fatigue describes fatigue 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). As indicated by this definition, fatigue is thought to be a subjective phenomenon and thus self-report measures are currently the gold standard for fatigue assessment. Numerous instruments are used to assess cancer-related fatigue, including items and subscales from mood and quality of life measures as well as multidimensional scales that were developed and validated specifically for cancer patients. A structured interview has also been developed to ascertain the presence of a clinical syndrome of cancer-related fatigue based on a set of diagnostic criteria, although this is not yet widely used.

3. Etiology of cancer-related fatigue

Fatigue is a non-specific, multidimensional symptom that is likely influenced by multiple factors that coexist and vary in influence depending on individual characteristics of the patient. Fatigue is not linked to a specific type of cancer or cancer therapy, although patients with advanced cancer and those undergoing chemotherapy typically report more severe fatigue. Psychosocial factors are strongly correlated with fatigue, including depression, anxiety, and coping style (Andrykowski et al., 2005; Lawrence et al., 2004). Demographic factors, physical symptoms, and comorbid medical conditions have also been identified as correlates of fatigue (Bower et al., 2000; Lawrence et al., 2004). Although there is much speculation about the role of biological factors in cancer-related fatigue, empirical research has been extremely limited. Indeed, among the biological parameters evaluated to date (i.e., hemoglobin, albumin, thyroid hormone), none fully account for fatigue during or after cancer treatment.

There is growing interest in the role of proinflammatory cytokines and the cytokine network in cancer-related fatigue. Basic research on neural-immune signaling in animal models has shown that peripheral proinflammatory cytokines signal the central nervous system and exert potent effects on behavioral processes, including reduced activity, reduced social and sexual behavior, reduced food and water intake, altered sleep, increased pain sensitivity and reactivity, and cognitive alterations (Dantzer, 2001). Conversely, antagonists or synthesis blockers of cytokines abolish these effects. In humans, less is known about the behavioral effects of cytokines, although there is evidence that acute induction of cytokines in healthy individuals has behavioral effects (Reichenberg et al., 2001; Spath-Schwalbe et al., 1998). There is also evidence of cytokine alterations in behavioral disorders, particularly depression (e.g., Miller et al., 2002).

In the context of cancer, it is well known that treatment with pharmacologic doses of cytokines (i.e., IFN-α, IL-2) leads to fatigue and other sickness behaviors (Valentine et al., 1998). It is possible that cytokines may also contribute to fatigue in patients who are not receiving immunotherapy. Proinflammatory cytokines interleukin 1 beta (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α) may be released in response to the tumor or to cancer treatments and may continue to be expressed long after treatment completion. These findings provide a physiological basis for examination of cytokine-fatigue links in cancer patients and survivors (see Fig. 1).

At the behavioral level, there is ample evidence that cancer-related fatigue is associated with other sickness behaviors. Our initial research on cancer-related fatigue focused on demographic, medical, and behavioral correlates of fatigue in breast cancer survivors. Fatigue was assessed in a large cohort of women ($n = 1957$) who had been diagnosed with early-stage breast cancer between 1 and 5 years earlier and had completed local and/or adjuvant cancer therapy (Bower et al., 2000). In multivariate analyses, the three strongest correlates of fatigue status were depressed mood, pain, and sleep disturbance. These results were replicated in a follow-up study with a subset of this cohort ($n = 763$) who were re-assessed between 5 and 10 years post-diagnosis (Bower et al., 2006). At this time point, depressed mood and pain were again associated with fatigue; moreover, depression at the initial assessment predicted fatigue at the long-term follow-up. These findings are consistent with previous research and led us to more directly examine the role of inflammatory processes in cancer-related fatigue.

4. Fatigue and inflammation during radiation therapy

To test the hypothesis that activation of inflammatory cytokines is associated with fatigue onset during cancer treatment, we recently conducted a study among early stage breast and prostate cancer patients undergoing radiation therapy (Bower et al., 2005). Radiation provides an interesting model in which to examine links between inflammation and fatigue for several reasons. First, radiation is a mainstay of cancer treatment and is known to elicit symptoms of fatigue. Second, exposure to radiation initiates a programmed molecular and cellular response designed to promote tissue repair that includes activation of proinflammatory cytokines (Stone et al., 2003) and there

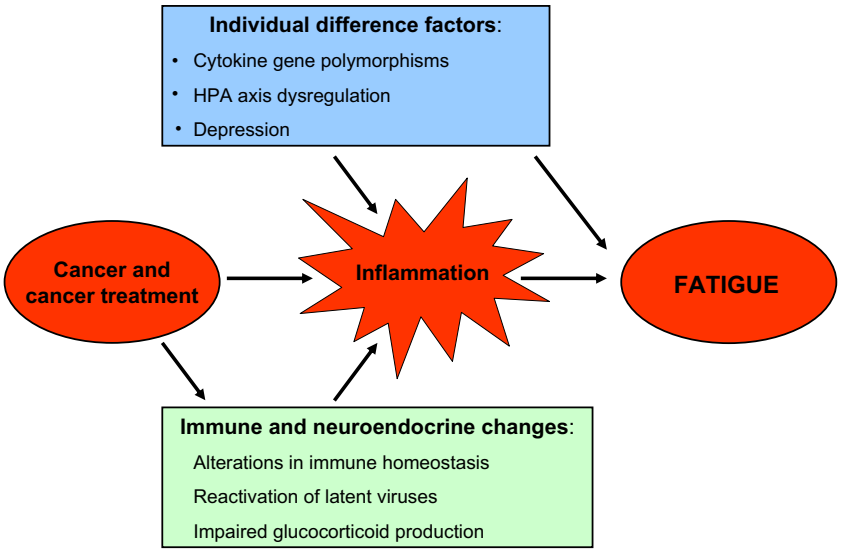

Fig. 1. Potential mechanisms for cancer-related fatigue, focusing on factors identified or implicated by our research. Cancer and its treatment can activate the proinflammatory cytokine network, leading to symptoms of fatigue through cytokine effects on the central nervous system. Chronic inflammation may develop when cancer and cancer treatments induce long-term changes in immune homeostasis, including alterations in immune cell subsets, alterations in expression and signaling of Toll-like receptors, and latent virus reactivation. Cancer-related changes in neuroendocrine function may also contribute to chronic inflammation, particularly impairments in glucocorticoid production that result in ineffective control of inflammatory processes. In addition, individual difference factors may increase the risk for chronic inflammation following cancer diagnosis and treatment. Potential risk factors include single nucleotide polymorphisms in cytokine genes, alterations in HPA axis function, and depressive symptoms. Of note, HPA dysregulation and depression may also have direct effects on fatigue.

is evidence of elevated cytokine levels in patients with breast and prostate cancer undergoing radiation therapy (Petrini et al., 1992). Finally, localized radiation for early stage breast and prostate cancer is associated with less toxicity than chemotherapy, minimizing the potential for confounding effects on fatigue (e.g., nausea, anemia).

The association between proinflammatory cytokines and fatigue during radiation therapy has been examined in a handful of previous reports, with mixed results. An early study conducted with prostate cancer patients documented increases in fatigue and serum levels of IL-1β during radiation therapy (Greenberg et al., 1993), and fatigue was positively correlated with serum levels of IL-6 and other inflammatory markers in a more recent study of breast cancer patients undergoing radiation, although this association appeared to be mediated by body mass index (Wratten et al., 2004). Other studies have shown increases in fatigue but no changes in serum levels of proinflammatory cytokines among women undergoing radiation therapy for breast (Geinitz et al., 2001) or uterine cancer (Ahlberg et al., 2004), and no correlation between fatigue and cytokine levels (Geinitz et al., 2001). These mixed results may be due to constraints of the respective study designs (e.g., small sample sizes, use of non-standard measures to detect cytokine levels; Ahlberg et al., 2004) as well as the focus on cross-sectional associations between cytokine levels and fatigue. This approach may not adequately capture the dynamic changes in these systems that occur over the course of treatment, or individual differences in baseline levels of cytokines or fatigue. To address these concerns, we elected to examine within-subject relationships between fatigue and cytokines at multiple time points during treatment using hierarchical linear models.

This study included 49 patients diagnosed with early stage breast ($n = 28$) or prostate ($n = 21$) cancer who had completed surgery and had not been treated with chemotherapy. Patients were assessed before onset of radiation therapy and at four time points during treatment (at weeks 1, 2, 4, and the final week of treatment, which was typically week 6). Self-reported fatigue and circulating concentrations of IL-1β and IL-6 were measured at each assessment. We tested two possible pathways through which proinflammatory cytokines might influence fatigue. Expression of proinflammatory cytokines during radiation therapy is thought to occur in waves, which should result in periodic peaks in cytokine levels during treatment (Herskind et al., 1998). These peaks may lead to acute increases in fatigue, similar to effects seen in experimental cytokine induction studies. On the other hand, exposure to cytokines over the course of treatment may have more cumulative effects on fatigue. To evaluate this pathway, we constructed a cumulative cytokine index that provided a measure of total cytokine exposure at each assessment. For example, cumulative IL-6 at week 2 was the sum of (baseline IL-6) + (week 1 IL-6) + (week 2 IL-6) levels.

There was a steady increase in fatigue over the course of treatment for both breast and prostate cancer patients, consistent with previous research. Moreover, there was a positive association between cumulative cytokine exposure and fatigue. As cumulative levels of cytokines increased, there was a corresponding increase in the number of days fatigued in both patient groups. At the individual patient

level, this suggests that as patients experienced more frequent or more robust elevations in cytokine concentrations during treatment they reported a greater increase in fatigue symptoms. We found no association between acute changes in cytokine concentrations and changes in fatigue, perhaps because cytokine concentrations were not sufficiently elevated at any individual assessment point to elicit acute increases in fatigue.

Fatigue co-occurred with depressed mood and sleep disturbance among patients undergoing radiation therapy, consistent with research conducted with cancer survivors (Bower et al., 2000). Because depression and sleep disturbance have both been associated with elevations in proinflammatory cytokines, we conducted analyses to determine whether these variables might account for the association between cytokines and fatigue. Neither depressed mood nor sleep disturbance was associated with cumulative cytokine exposure (or transient changes in cytokines), and the association between cytokines and fatigue remained significant after controlling for these variables. Moreover, cumulative cytokine exposure was a significant predictor of fatigue in analyses controlling for other potential confounds, including age, body mass index, and use of alcohol and caffeine.

Overall, results from this study support the hypothesis that exposure to proinflammatory cytokines during radiation therapy is associated with subjective reports of fatigue. Further, the association between proinflammatory cytokines and fatigue was apparent in both breast and prostate cancer patients, suggesting that activation of the proinflammatory cytokine network may be a non-specific mediator of fatigue in different cancer populations. Of course, the observational nature of this study does not allow us to draw conclusions about causality, and it is possible that other factors may mediate or drive this association. The association between cytokines and fatigue was evident only in within-subject analyses that focused on cumulative cytokine exposure, suggesting that it may be necessary to utilize analytic approaches that reflect the dynamic nature of immune responses when evaluating relationships with behavioral variables during treatment.

5. Fatigue and inflammation in cancer survivors

As mentioned above, fatigue continues long after successful treatment completion in approximately one-third of cancer survivors (Bower et al., 2000; Cella et al., 2001). Persistent fatigue typically cannot be explained by underlying medical or psychiatric problems or treatment-related biological changes such as anemia. We have conducted several studies to test the hypothesis that post-treatment fatigue in breast cancer survivors is associated with elevated inflammatory processes. This research has focused on women who were initially diagnosed with early stage breast cancer (Stage 0, I, or II), have completed cancer treatment with the exception of hormonal therapies, and show no evidence of residual or recurrent disease, thus reducing the possibility that disease-related processes might be driving persistent inflammation. Further, participants have no chronic or recurrent medical conditions that involve the immune system or regular use of immunosuppressive medications. We have identified fatigued survivors based on their responses to the vitality subscale of the SF-36; women had to score below 50 on this scale (indicating limitations or disability related to fatigue) on at least two occasions after cancer diagnosis and treatment in order to be classified as fatigued.

In our first report, we recruited 20 breast cancer survivors with persistent post-treatment fatigue and a control group of 20 non-fatigued survivors (Bower et al., 2002). Women in this study had been diagnosed with breast cancer between 3 and 7 years earlier. Consistent with hypotheses, fatigued survivors showed significantly higher levels of soluble inflammatory markers than non-fatigued controls, including elevations in IL-1ra, sTNF-RII, and neopterin. No differences in IL-1β were observed, although levels were undetectable for almost half of the study participants. Fatigued women also reported a number of other sickness behaviors, including depressed mood, decreased activity level, decreased social interest, and cognitive problems (i.e., forgetfulness, distractibility). However, the association between fatigue and inflammatory markers remained significant in analyses controlling for depression and other potential confounds. There were no differences between fatigued and non-fatigued survivors in the type of cancer treatment received or in the length of time since diagnosis and treatment.

We also examined cellular immune status in these patients to determine whether elevations in soluble inflammatory markers might stem from alterations in the cellular immune response (Bower et al., 2003). Indeed, fatigued survivors showed a 31% increase in circulating T lymphocytes relative to non-fatigued controls, particularly CD4+ T lymphocytes (41% increase) and CD56+ effector T lymphocytes (52% increase). These effects remained significant after controlling for potential confounders including age, body mass index, depressed mood, and treatment type. In contrast, no alterations in numbers of circulating B cells, NK cells, granulocytes, and monocytes were observed. Elevations in T cells were correlated with elevations in serum levels of IL-1ra, suggesting that a T cell mediated inflammatory process might be driving fatigue symptomatology via systemic distribution of cytokines.

We recently replicated and extended these findings in a larger cohort of 50 breast cancer survivors, including 32 women with persistent fatigue and 18 non-fatigued controls (Collado-Hidalgo et al., 2006). Consistent with our previous report, fatigued survivors showed elevations in soluble markers of proinflammatory cytokine activity, including IL-1ra and the soluble IL-6 receptor (sIL-6R). Increases in plasma sIL-6R were accompanied by significant reductions in cell surface expression of IL-6R on CD14+ monocytes among fatigued participants. Decreased cell surface expression of IL-6R is thought to reflect cytokine-induced receptor shedding, and in vitro studies confirmed that

exposure to proinflammatory cytokines was associated with loss of IL-6R from the cell surface of PBMCs. Analysis of the cellular immune system revealed decreases in the frequency of circulating monocyte dendritic cells and activated T cells among fatigued survivors, as well as a selective increase in CD4+ T lymphocytes. All of the relationships between fatigue and immune variables remained significant in analyses controlling for potential confounds.

In addition to assessing soluble and cellular markers of inflammation, this study analyzed the functional basis for altered inflammatory response by measuring monocyte production of proinflammatory cytkines following ligation of Toll-like receptor 4 (TLF4) with lipopolysaccharide (LPS). As predicted, fatigued survivors showed significant increases in intracellular production of IL-6 and TNF in monocytes following exposure to LPS relative to non-fatigued controls. Overall, these results confirm our earlier findings and provide the first evidence of a functional alteration in the innate immune response associated with cancer-related fatigue.

To probe another aspect of the innate immune response, we evaluated changes in cytokine production in response to experimental challenge in a separate cohort of survivors. Acute psychological stress is known to induce increases in LPS-stimulated proinflammatory cytokine production (Segerstrom and Miller, 2004). To determine whether this response is altered in patients with cancer-related fatigue, we recruited 10 breast cancer survivors with persistent fatigue and 15 non-fatigued controls (mean = 8.4 years post-diagnosis) (Bower et al., 2007). Study participants underwent the Trier Social Stress Task (TSST), a 30-min task that involves preparing and delivering a speech and performing mental arithmetic in front of an audience. Fatigued survivors showed greater increases in LPS-stimulated production of IL-1β and IL-6 from baseline to 30-min recovery than non-fatigued controls. Effects for TNF were in the same direction but did not reach statistical significance. Fatigued survivors also had higher levels of CD4+ T cells throughout the experimental session and showed a greater increase in CD4+ T lymphocytes in response to the TSST. Exploratory analyses revealed that increases in CD4+ T lymphocytes were correlated with greater cytokine responses to stress, suggesting that CD4+ T cells may participate in bystander effects that enhance proinflammatory cytokine responses by monocytes.

To summarize, we have documented alterations in several inflammatory processes in breast cancer survivors with persistent fatigue, including elevations in soluble markers of inflammation as well as increased cytokine production in response to LPS at rest and in response to experimental challenge. How do these findings compare with other research on inflammation and fatigue in cancer survivors? We identified three studies conducted with cancer patients who had successfully completed treatment and included an evaluation of inflammatory markers. One was conducted with breast cancer survivors who had successfully completed treatment between 3 and 24 months previously (Gelinas and Fillion, 2004). The authors found no association between circulating levels of IL-1β and fatigue, although it should be noted that the levels of IL-1β in this report were extremely high (mean = 1152 pg/ml, range = 9−3, 952 pg/ml), well above levels seen in other groups of cancer patients and healthy individuals. Two other studies examined inflammatory parameters among patients with hematological malignancies who had completed treatment at least 3 months previously (Dimeo et al., 2004; Knobel et al., 2000). Neither study found an association between fatigue and markers of inflammation, including serum levels of IL-1β, IL-1ra, IL-6, neopterin, CRP, and the soluble TNF receptors.

Aside from differences in disease and treatment-related characteristics, one critical feature that distinguishes our research from other studies conducted with cancer survivors is our focus on severe and persistent fatigue. Whereas other studies have recruited individuals without regard for fatigue status, we have specifically focused on survivors who reported significant fatigue on at least two occasions after diagnosis and treatment. This methodology was used to identify women with persistent post-treatment fatigue and to rule out possible confounding effects of fluctuations in fatigue symptoms due to non cancer-related factors.

6. Mechanisms for persistent inflammation and fatigue

Treatment with radiation and chemotherapy may elicit acute increases in proinflammatory cytokines, with subsequent effects on fatigue. However, the physiologic basis for the prolonged inflammatory processes observed in our research with fatigued breast cancer survivors is unclear. Alterations in immune regulatory systems provide one plausible mechanism for chronic inflammatory activity. Our research has focused on the hypothalamic–pituitary–adrenal (HPA) axis, given the well known effects of adrenal cortex-derived steroids on immune cell development, maturation, trafficking, and cytokine production, including production of proinflammatory cytokines (McEwen et al., 1997). There are two potential pathways for impaired control of proinflammatory cytokines by the HPA axis: decreased glucocorticoid production, and decreased response of the glucocorticoid receptor to hormone ligation (Raison and Miller, 2003). In an initial study, we found that fatigued breast cancer survivors had lower levels of morning serum cortisol than non-fatigued controls, supporting decreased production as a potential mechanism for enhanced inflammation (Bower et al., 2002). Because a single measure of cortisol provides little information about this system, we have also examined two dynamic measures of HPA axis activity, diurnal cortisol secretion and cortisol response to challenge, as well as glucocorticoid receptor sensitivity, in relation to cancer-related fatigue.

Cortisol levels typically peak before awakening then decrease over the course of the day, and the steepness of this decline is thought to be an important indicator of

HPA competence. Indeed, diurnal cortisol rhythms are altered in cancer patients with advanced disease and have been shown to predict decreased survival time in women with metastatic breast cancer (Sephton et al., 2000). However, behavioral correlates of diurnal cortisol rhythms have not been well characterized. We examined diurnal cortisol rhythm in 13 breast cancer survivors with persistent fatigue and 16 non-fatigued controls using salivary cortisol measures collected four times a day over two consecutive days (Bower et al., 2005). As in our previous research, all women had completed cancer treatment (mean = 6.6 years post diagnosis) and were currently disease-free. Results showed that fatigued survivors had a significantly flatter cortisol slope than non-fatigued survivors, with a less rapid decline in cortisol levels in the evening hours. The association between fatigue and cortisol slope remained significant in analyses controlling for potential confounds, including depression and body mass index.

In addition to diurnal rhythm, another important index of HPA axis function is responsiveness to external challenge. Activation of the HPA axis and release of cortisol in response to acute stress is critical for mobilization of energy resources and modulation of other stress response systems, including the immune system. We evaluated cortisol responses to an experimental psychological stressor, the Trier Social Stress Task (TSST), in a sample of 11 breast cancer survivors with persistent fatigue and 16 non-fatigued controls (Bower et al., 2005). As described earlier, fatigued women in this study showed increased LPS-stimulated cytokine production following this task relative to non-fatigued survivors (Bower et al., 2007). Salivary cortisol levels were assessed at baseline and at 15 min intervals throughout the experimental session. Although both groups of women reported that the task was similarly challenging, fatigued women showed a significantly blunted cortisol response to the stressor. The difference between groups was quite pronounced; whereas salivary cortisol levels for non-fatigued controls increased by more than 4-fold, fatigued women showed a negligible change in cortisol levels. Moreover, blunted cortisol responses were associated with significantly increased production of IL-6 in response to LPS stimulation.

We also examined glucocorticoid receptor sensitivity in this study using an in vitro assay that measures the ability of peripheral immune cells to produce proinflammatory cytokines in the presence of various concentrations of cortisol (Bower et al., 2007). In contrast to effects for cortisol response, we saw no differences between fatigued and non-fatigued survivors in receptor sensitivity either at baseline or in response to challenge, suggesting that decreased receptor sensitivity may not play a critical role in the elevated inflammatory processes observed in this sample. Indeed, differences in cortisol production were more prognostic of differential cytokine response than differences in receptor sensitivity.

These results provide preliminary evidence of alterations in HPA axis function among breast cancer survivors with persistent fatigue, including subtle dysregulation of the diurnal cortisol rhythm and a more pronounced deficit in cortisol response to challenge. Further, these findings suggest that deficits in cortisol production may play a role in promoting or sustaining inflammatory responses. Of course, because these studies were conducted many years after cancer diagnosis and treatment, the etiology of HPA axis alterations is unclear. In particular, it is unclear whether HPA axis dysregulation pre-dated the cancer diagnosis or was somehow related to effects of the tumor or cancer therapy.

7. Risk factors for inflammation and fatigue

The possibility that individual differences may set the stage for enhanced inflammatory responses to cancer diagnosis and treatment has led us to investigate other potential risk factors for chronic inflammation and associated symptoms of fatigue. One of the primary factors that influence cytokine expression levels is genetic variation or gene polymorphisms. Cytokine gene polymorphisms have been linked to cancer susceptibility and severity (Hefler et al., 2005), and to physiological responses to cancer treatment (Andreassen et al., 2005). To determine whether differences in single nucleotide polymorphisms (SNPs) might contribute to persistent post-treatment fatigue, we recently examined SNPs in the promoter regions of three cytokine genes [IL-1β −511 (T/C), IL-6 −174 (G/C), and IL-6R −183 (G/A)] in fatigued and non-fatigued breast cancer survivors (Collado-Hidalgo et al., under review). These SNPs are thought to influence the binding of transcription factors with downstream effects on cytokine expression. We have previously documented elevations in inflammatory markers and cytokine responses to LPS among fatigued women in this sample (Collado-Hidalgo et al., 2006) and selected SNPs that were relevant to these parameters.

Polymorphisms in each of the cytokine genes assessed were associated with fatigue status. For the IL-1β polymorphism at −511 (C/T), fatigued survivors were more frequently (C/C) than non-fatigued controls, and risk for fatigue declined with the number of T alleles. Fatigued breast cancer survivors also had a higher percentage of homozygous genotypes (G/G) and (C/C) for the IL-6 −174 promoter polymorphism, and a higher percentage of homozygous (A/A) and heterozygous (G/A) genotypes for the IL-6R −183 polymorphism. Each of these genotypes has been associated with increased expression of their respective cytokine (e.g., Brull et al., 2001; Burzotta et al., 2001; Galicia et al., 2004; Di Giovine et al., 1992). We did not find an association between fatigue-related genotypes and circulating cytokine concentrations, possibly due to the small sample size and the relatively low levels of these markers in this otherwise healthy sample; it is possible that differences might have emerged following in vivo immune stimulation, as seen in previous research (e.g., Bennermo et al., 2004). These findings provide preliminary evidence

that gene polymorphisms may increase risk for persistent cancer-related fatigue, presumably through effects on cytokine expression triggered by cancer and its treatment.

8. Conclusions and recommendations for future research

These results provide mounting support for the hypothesis that proinflammatory cytokines contribute to cancer-related fatigue. We have documented elevations in soluble markers of inflammation in two separate cohorts of breast cancer survivors that are suggestive of a chronic inflammatory state (Bower et al., 2002; Collado-Hidalgo et al., 2006). Our recent work extends these findings to the acute treatment setting and suggests that activation of proinflammatory cytokines may also play a role in fatigue onset during radiation therapy among both breast and prostate cancer patients (Bower et al., 2005). These results are consistent with a recent review of the literature on fatigue and inflammatory markers in cancer patients, which found a positive association between cancer-related fatigue and circulating levels of IL-1ra, IL-6, and neopterin (Schubert et al., 2007).

Our research also provides clues about potential cellular and molecular mechanisms for persistent inflammation and fatigue in breast cancer survivors (Fig. 1). Fatigued survivors show alterations in the cellular immune system and in cytokine responses to LPS stimulation that are correlated with alterations in inflammatory markers. These findings suggest that long-term changes in immune cell homeostasis, particularly elevations in CD4+ T lymphocytes, and alterations in expression and signaling of Toll-like receptors may contribute to chronic inflammatory activity in the aftermath of cancer treatment. Pathogenic changes in the HPA axis may also play a role, given evidence of HPA axis dysregulation in fatigued survivors. In particular, insufficient cortisol production may lead to ineffective control of inflammatory processes.

Because we have primarily studied patients after treatment completion, we can only speculate that the changes in immune system functioning observed in cancer survivors were initiated by cancer and its treatment. There is evidence that cancer treatments may have long-term effects on the cellular immune system or may induce reactivation of latent infections, with chronic effects on immune homeostasis (Solomayer et al., 2003). In addition, it is possible that treatment-induced cytokine cascades may continue for months or years after treatment completion (Herskind et al., 1998). Clearly, longitudinal research that evaluates patients before, during, and after treatment is needed to better characterize changes in immune and neuroendocrine status and their association with fatigue. In addition, extension of this research to other cancer populations is critical for determining the generalizability of our results.

Individual difference factors that pre-date cancer may also have effects on immune and behavioral responses to cancer diagnosis and treatment. Our recent work highlights one such risk factor: SNPs in genes that control proinflammatory cytokine expression and activity. Other potential risk factors include HPA axis dysregulation, which may exist prior to cancer diagnosis, as well as depression, which is associated with the onset and persistence of cancer-related fatigue (Andrykowski et al., 2005; Bower et al., 2006). Depression may be associated with neuroendocrine and immune changes that increase risk for fatigue during and after treatment, or may influence fatigue through its effects on cognitive processes (e.g., catastrophizing). However, depression does appear to be distinct from fatigue in cancer patients and survivors, and our research suggests that symptoms of depression do not account for the association between fatigue and inflammatory processes. The identification of additional risk factors, and the mechanisms that underlie their effects, is an important focus for future research.

The neural pathways that mediate proinflammatory cytokine effects on fatigue have not been determined. Capuron and Miller (2004) have hypothesized that in the context of interferon-alpha (IFN-α) treatment, fatigue and other neurovegetative symptoms may be related to alterations in dopamine neurotransmission in the basal ganglia. This can be contrasted with depressed mood, which appears to be linked to alterations in CRH pathways and serotonin metabolism in IFN-α treated patients. Of note, treatment with antidepressants is not effective for cancer-related fatigue but does lead to reductions in depressed mood among cancer patients (Morrow et al., 2003), supporting distinct neural mechanisms for depression and fatigue in this population.

Research on inflammation and cancer-related fatigue helps to elucidate the biological basis for this common and troublesome symptom and may also promote the development of targeted therapies. In particular, use of cytokine antagonists may be a promising direction for intervention efforts. There is preliminary evidence that TNF blockade with etanercept is safe and effective in reducing fatigue among patients with advanced cancer (Monk et al., 2006), but effects among patients with early stage cancer and cancer survivors have not been determined. Behavioral and mind–body interventions also show considerable promise for treating fatigue and other cancer-related symptoms, and there is preliminary evidence for their effects on immune function (Carlson et al., 2003; Fairey et al., 2005). These treatments may be more palatable to cancer patients than pharmacologic therapies and are another important avenue for research efforts.

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