Inflammatory responses to psychological stress in fatigued breast cancer survivors: Relationship to glucocorticoids

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Abstract

Fatigue is a common problem following cancer treatment and our previous studies suggest that a chronic inflammatory process might contribute to cancer-related fatigue. However, immune responses to challenge have not yet been evaluated among individuals with cancer-related fatigue, and it is not known what mechanisms drive increased levels of inflammatory markers in fatigued cancer survivors. We have previously reported that fatigued breast cancer survivors show a blunted cortisol response to an experimental psychological stressor. In this report, we focus on inflammatory responses to this stressor and their relationship to circulating glucocorticoids and cellular sensitivity to glucocorticoid inhibition. Relative to non-fatigued control survivors, participants experiencing persistent fatigue showed significantly greater increases in LPS-stimulated production of IL-1β and IL-6 following the stressor (Group × Time interaction: p < .05). Fatigued participants did not show any difference in cellular sensitivity to cortisol inhibition of cytokine production, but they did show significantly less salivary cortisol increase in the aftermath of the stressor. Moreover, blunted cortisol responses were associated with significantly increased production of IL-6 in response to LPS stimulation (p < .05). These data provide further evidence of enhanced inflammatory processes in fatigued breast cancer survivors and suggest that these processes may stem in part from decreased glucocorticoid response to stress.

Keywords: Breast cancer; Fatigue; Inflammation; HPA axis; Stress

1. Introduction

Fatigue is a common complaint among cancer patients undergoing treatment (Wagner and Cella, 2004) and approximately 30% will continue to experience fatigue after successful treatment completion, leading to significant impairment in quality of life (Bower et al., 2000; Bower et al., 2006; Cella et al., 2001). Both biological and psychological factors may contribute to cancer-related fatigue, including low hemoglobin (Cella et al., 2004; Holzner et al., 2002; Jacobsen et al., 2004b), depressed mood (Andrykowski et al., 1998; Bower et al., 2000; Jacobsen et al., 2003), and a catastrophizing coping style (Jacobsen et al., 2004a). However, none of these factors fully account for fatigue symptoms in cancer patients and survivors.

Basic research on neuro-immune signaling has shown that proinflammatory cytokines signal the central nervous system, leading to fatigue and other behavioral changes (Dantzer, 2001). Indeed, cancer patients who are treated...
with pharmacological doses of cytokines (i.e., IL-2, IFN-α) frequently report fatigue and other sickness behaviors (Capuron et al., 2000; Valentine et al., 1998), as do healthy individuals treated with low doses of proinflammatory cytokines (Speth-Schwalbe et al., 1998) or endotoxin (Reichenberg et al., 2001). Based on these findings, we have proposed that cancer-related fatigue may be driven, at least in part, by activation of the proinflammatory cytokine network (Bower et al., 2002). In support of this hypothesis, we have shown that breast cancer survivors with persistent fatigue show correlated elevations in circulating inflammatory markers (Bower et al., 2002; Collado-Hidalgo et al., 2006) and CD4+ T lymphocytes (Bower et al., 2003), as well as increased intracellular production of proinflammatory cytokines by monocytes in response to LPS stimulation (Collado-Hidalgo et al., 2006). However, the biological mechanisms driving persistent inflammatory activity in cancer survivors have not yet been determined.

The hypothalamic–pituitary–adrenal (HPA) axis is a potent modulator of the immune system, with suppressive effects on proinflammatory cytokine production and activity (McEwen et al., 1997). Thus, it is possible that alterations in glucocorticoid signaling may set the stage for overactive inflammatory processes in cancer survivors. Raison and Miller (2003) outlined 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. Both dynamics have been observed among individuals with fatigue-related disorders, including chronic fatigue syndrome (Demitrack et al., 1991; Visser et al., 2000), vital exhaustion (Wirtz et al., 2003), and depression (Miller et al., 2005; Pariante and Miller, 2001).

In previous research, we have found that fatigued breast cancer survivors show alterations in HPA axis function, including a flattened diurnal cortisol slope (Bower et al., 2005b) and a blunted cortisol response to experimental stress (Bower et al., 2005a). This pattern of HPA axis dysregulation, particularly the blunted cortisol response, would appear to support the first pathway (i.e., reduced hormone availability) as a mechanism for fatigue-related inflammation. Indeed, there is evidence that reductions in cortisol output following stress may be associated with increases in proinflammatory cytokines (Kunz-Ebrecht et al., 2003; Rohleder et al., 2003b; von Kanel et al., 2006). However, it is unclear whether alterations in cortisol output are associated with an enhanced inflammatory response in fatigued cancer survivors. In addition, glucocorticoid responsiveness at the cellular level has not yet been examined among individuals with cancer-related fatigue.

The current study was designed to examine the inflammatory response to a model psychological stressor in breast cancer survivors with persistent fatigue and the modulation of this response by cortisol. We have previously reported that fatigued survivors show a blunted salivary cortisol response to this stressor relative to non-fatigued controls (Bower et al., 2005a). In this report, we focus on stress-induced changes in proinflammatory cytokine production in response to ex vivo leukocyte stimulation with LPS. LPS-stimulated cytokine production was of interest because it provides a measure of the immune system’s response to antigen stimulation, can be modulated by glucocorticoids, and is responsive to acute stress (Segerstrom and Miller, 2004). We hypothesized that fatigued breast cancer survivors would show greater stress-induced increases in stimulated cytokine production than non-fatigued survivors, consistent with the tonic elevations in proinflammatory processes seen in fatigued patients in our previous research (Bower et al., 2002; Collado-Hidalgo et al., 2006). We tested two competing hypotheses regarding glucocorticoid modulation of the inflammatory response. First, we evaluated whether the blunted cortisol response observed in fatigued survivors in our previous report (Bower et al., 2005a) was associated with alterations in the inflammatory response to stress, which would support the glucocorticoid availability hypothesis of fatigue-related immune dysregulation. Second, we evaluated whether leukocytes from fatigued survivors might show reduced sensitivity to the anti-inflammatory effects of cortisol, which would support the glucocorticoid sensitivity hypothesis. Receptor sensitivity was assessed using an in vitro assay that measures the ability of peripheral immune cells to produce proinflammatory cytokines following LPS stimulation in the presence of various concentrations of cortisol.

2. Methods

2.1. Participants

Twenty-five women (10 fatigued, 15 non-fatigued) were recruited from a previously described cohort of early stage (Stage 0, I, or II) breast cancer survivors (Ganz et al., 1998b; Ganz et al., 1998a). This sample was the focus of a previous report that provides more detailed information about recruitment and sample characteristics (Bower et al., 2005a). Briefly, participants were screened to exclude individuals with cancer recurrence, diagnosis with other cancers, history of immunologic or hormonal disease, current medical illness, and heavy use of alcohol (i.e., more than 2 drinks/day). Fatigue was assessed using the vitality scale of the SF-36 with scores below 50 indicating significant fatigue and scores above 70 indicating absence of significant fatigue-related impairment (Ware, Jr. and Sherbourne, 1992).

2.2. Procedure

Experimental sessions were conducted in the UCLA General Clinical Research Center. Following participant arrival at 3:30 PM, an indwelling catheter was placed in the anteceubital vein of the arm contralateral to the original tumor resection. A baseline blood sample was drawn after a 30-min resting period, and participants subsequently underwent the Trier Social Stress Test (TSST), a 30-min task that involves preparing and delivering a speech and performing mental arithmetic in front of an audience (Kirschbaum et al., 1993). Blood samples were drawn into sodium heparin Vacutainers (Becton–Dickinson, San Jose, CA) immediately after TSST and following a 30-min recovery period. Saliva samples were collected at 15-min intervals throughout the laboratory session for determination of salivary cortisol levels by enzyme immunoassay (Bower et al., 2005a). All procedures were approved by the UCLA Institutional Review Board, and all subjects provided informed consent.
2.3. Leukocyte phenotyping

In peripheral blood samples obtained at baseline, immediately post-stress, and after 30 min of recovery, circulating monocytes and lymphocytes were enumerated by differential blood count, and multi-color flow cytometry assessed the prevalence of CD3-/CD56+16+ natural killer (NK) cells, CD3+/CD4+ T lymphocytes, and CD3+/CD8+ T lymphocytes. Flow cytometry data were acquired on a FACSScan flow cytometer and analyzed using CellQuest software (BD Immunocytometry Systems, San Jose, CA).

2.4. Stimulated cytokine production and glucocorticoid sensitivity

Heparinized whole blood was diluted 1:5 with RPMI-1640 culture media supplemented with HEPES buffer, Penicillin-Streptomycin, and 1-glutamine (complete medium) and stimulated with LPS and four different concentrations of cortisol (all reagents from Sigma–Aldrich, St. Louis, MO). Two hundred microliters of whole blood was added to 800 μl of solution containing complete medium alone or complete medium with LPS (25 μg) and one of four concentrations of cortisol (50 μg) in 5 ml Falcon culture tubes (Becton–Dickinson, San Jose, CA). The final concentrations were 100 pg/ml of LPS and 0, 10–9, 10–7, and 10–5 M cortisol. After incubation in culture tubes for 20 h at 37°C in an atmosphere of 5% CO2, cells were briefly centrifuged and supernatants were stored at −80°C for batch testing. Supernatant cytokine levels were assessed using ELISAs for IL-1β and TNF-α (R&D Systems, Minneapolis, MN) and IL-6 (Bio-source International, Camarillo, CA), according to the manufacturer’s instructions. Samples were diluted 4-, 10-, and 40-fold for TNF-α, IL-1β, and IL-6, respectively. Assay sensitivities were 1 pg/ml for IL-1β, 1.6 pg/ml for TNF-α, and 2 pg/ml for IL-6, with intraassay coefficients of variation less than 8%. All assays were performed in duplicate, and all samples for a given participant were run in parallel to minimize interassay variability. To control for any stress-induced change in monocyte prevalence within assayed blood samples, cytokine concentrations were corrected for the number of monocytes in circulation by dividing cytokine concentrations by number of monocytes at each blood draw (Miller et al., 2005; Rohleder et al., 2001). Cytokine measurements were log transformed prior to analysis to stabilize variance.

Assays of glucocorticoid sensitivity were performed on blood samples collected at baseline and 30-min recovery as in previous studies (Rohleder et al., 2001; Rohleder et al., 2002). Glucocorticoid sensitivity was quantified as the concentration of cortisol required to inhibit basal cytokine production by 50% (IC50). Individual IC50 values were estimated from the dose–response curve regressing % inhibition values against log-transformed cortisol concentrations in a standard four-component sigmoidal function. Regression functions were estimated using SAS PROC NLIN (modified Gauss–Newton estimation with field search for starting parameter estimates, and lower and upper limits fixed to 0 and 100% inhibition). IC50 estimates falling ≥3 orders of magnitude above the cortisol concentrations utilized were considered invalid and treated as missing data.

2.5. Self-report measures

Participants completed questionnaires assessing demographic and treatment-related characteristics, fatigue (SF-36 vitality scale; Ware, Jr. and Sherbourne, 1992), depressed mood (BDI-II; Beck et al., 1996), and health behaviors linked to immune outcomes (Bower et al., 2002; Kiecolt-Glaser and Glaser, 1988). These included number of servings of caffeine and alcohol consumed in the last week.

2.6. Data analysis

Fatigued and non-fatigued participants were compared on demographic and treatment-related characteristics using independent samples t-tests and χ² tests. A two-way ANOVA for mixed measures was used to evaluate changes in immune parameters in response to the TSST, with time as a within-subject repeated factor and fatigue group as a between-subject factor. Degrees of freedom were altered by missing data for two subjects due to failures in the stimulated cytokine assay; the final sample for these analyses includes 8 fatigued survivors and 15 non-fatigued survivors. Preliminary analyses of potential behavioral confounders identified caffeine use as significantly associated with inflammatory responses to stress, and this variable was included as a covariate in subsequent analyses.

3. Results

3.1. Demographic and treatment-related characteristics

As expected given our selection criteria, fatigued participants scored significantly lower than non-fatigued controls on the SF-36 vitality scale (mean score for fatigued = 32.0, mean score for non-fatigued = 81.3; t(10.2) = 8.6, p < .0001). Fatigue scores were highly stable, with a substantial correlation between vitality scores at entry into the parent cohort (conducted 1–5 years post-diagnosis) and at entry into the present study (conducted 6.5–10 years post-diagnosis), (r = 0.83, p < .0001). Other sample characteristics are shown in Table 1. Of note, fatigued women in this report were comparable to fatigued women in the larger parent cohort in terms of age and fatigue scores (Bower et al., 2000).

3.2. Leukocyte responses to stress

The TSST significantly increased circulating leukocyte counts, with both monocytes and lymphocytes showing a significant elevation from baseline to the immediate post-stress assessment, and subsequent return to baseline levels after 30 min of recovery (Table 2; time main effect for
monocytes: \( F(2, 46) = 7.48, p = .002 \), and for lymphocytes: \( F(2, 46) = 46.7, p < .0001 \). Similar changes occurred in the number of circulating NK cells and CD8+ T cells, with an acute increase at post-stress and return to baseline levels at 30 min recovery (time main effect for NK cells: \( F(2, 46) = 80.9, p < .0001 \), and CD8+ cells: \( F(2, 46) = 23.1, p < .0001 \)). There was no main effect of group and no Group × Time interaction for any of these cell subsets, indicating that the TSST induced similar leukocyte mobilization in fatigued and non-fatigued survivors. The sole exception involved CD4+ T cells, which showed a significant main effect of time (\( F(2, 46) = 17.3, p < .0001 \)), as well as a main effect of group (\( F(1, 23) = 5.8, p = .024 \)), and a Group × Time interaction (\( F(2, 46) = 4.0, p = .024 \)). Fatigued survivors had a higher level of CD4+ T cells throughout the experimental session and also showed a greater increase in CD4+ T lymphocytes in response to the TSST.

### 3.3. LPS-stimulated cytokine responses to stress

We next examined changes in LPS-stimulated production of IL-1β, IL-6, and TNF-α from baseline to 30-min recovery. There were no significant group differences in any of the three cytokines at the baseline assessment. There was a significant effect of time for IL-1β (\( F(1, 20) = 10.9, p = .004 \)) and for IL-6 (\( F(1, 20) = 8.1, p = .01 \)), and the time main effect approached statistical significance for TNF-α (\( F(1, 20) = 3.9, p = .06 \)). Significant Group × Time interactions emerged for IL-1β (\( F(1, 20) = 6.1, p = .02 \)) and IL-6 (\( F(1, 20) = 9.3, p = .006 \)), with the Group × Time interaction approaching significance for TNF-α (\( F(1, 20) = 3.0, p = .098 \)), all controlling for caffeine use. Results are displayed graphically in Fig. 1. The Group × Time interactions for IL-1β and IL-6 remained significant in analyses controlling for potential demographic and medical confounds (i.e., age, marital status, cancer treatment, body mass index, and BDI-II scores) with two exceptions: controlling for chemotherapy and BDI-II scores reduced the interaction for IL-1β to non-significance.

Post hoc paired-samples \( t \)-tests were conducted to evaluate changes in stimulated cytokine production from baseline to recovery within each group. The fatigued group showed a significant increase in production of IL-1β (\( t = 2.99, p = .02 \)), a trend towards an increase in production of IL-6 (\( t = 2.19, p = .065 \)), and a non-significant increase in production of TNF-α (\( t = 0.63, p = .55 \)). The non-fatigued group showed a non-significant decrease in production of all three cytokines (all \( ps > .20 \)).

Analyses of ex vivo glucocorticoid inhibition of LPS-stimulated cytokine production showed no evidence that fatigued survivors differed from their non-fatigued counterparts in glucocorticoid sensitivity. There were no significant differences in IC\(_{50}\) values at baseline, and no significant effect of group, time, or Group × Time interactions for IL-1β, IL-6, or TNF-α in response to stress.

### 3.4. Relationship between immune and neuroendocrine changes

As described previously (Bower et al., 2005a), non-fatigued survivors showed a significant increase in salivary cortisol concentrations following the TSST, whereas fatigued survivors showed a negligible cortisol response to the stressor. To assess relationships between cortisol response to stress and altered patterns of cytokine production, we correlated baseline-to-recovery changes in cortisol with changes in stimulated cytokine production. Analyses focused on cortisol changes from baseline to 15-min recovery, as that time point reflects the peak in salivary cortisol response (Bower et al., 2005a). Analyses showed a significant inverse relationship between changes in salivary cortisol level and changes in stimulated IL-6 production (Spearman \( r = -.43, p = .023 \); Fig. 2). There was no significant association between salivary cortisol changes and changes in stimulated production of IL-1β or TNF-α (\( ps > .40 \)).

To compare more directly the relative contributions of glucocorticoid response and glucocorticoid sensitivity to changes in cytokine production, standardized (i.e., \( z \)
transformed) measures of both parameters were included as simultaneous predictors of individual variation in stress-induced change in LPS-stimulated IL-6 production. In this analysis, the standardized regression coefficient for glucocorticoid production significantly exceeded that for glucocorticoid sensitivity (\( b_g = -0.419 \) and 0.187, respectively; difference \( p = .022 \)). Thus, naturally occurring differences in glucocorticoid response to stress are significantly more prognostic of differential cytokine response than are naturally occurring differences in glucocorticoid sensitivity.

Exploratory analyses were conducted to examine the association between stress-induced changes in cytokine production and CD4+ T lymphocytes, given that fatigued survivors showed a greater mobilization of CD4+ T cells in response to stress than non-fatigued controls. Prior to conducting these analyses, the number of CD4+ T cells at each blood draw was divided by the number of monocytes to obtain a similar metric to the stimulated cytokine data and ensure that differences in monocyte counts were not confounding analyses. Results showed a significant positive correlation between changes in CD4+ cells and production of IL-6 (Spearman \( r = 0.65, p = .001 \)), IL-1β (Spearman \( r = 0.61, p = .002 \)) and TNF-α (Spearman \( r = 0.46, p = .029 \)), with increases in CD4+ T cell numbers associated with greater cytokine response to stress.

4. Discussion

One of the primary goals of this study was to evaluate inflammatory responses to a model psychological stressor in breast cancer survivors with persistent fatigue, focusing on changes in LPS-stimulated proinflammatory cytokine production. As predicted, fatigued survivors showed a greater increase in cytokine production than non-fatigued controls following stress exposure. Effects for production of IL-6 were particularly robust and remained significant controlling for potential demographic, medical, and behavioral confounds. It is important to note that the data showed an interaction effect, with a different pattern of cytokine response in the two groups; fatigued survivors showed an increase in cytokine production that was significant for IL-1β in post hoc within group analyses, whereas non-fatigued controls showed a non-significant decrease in production of all three cytokines. There were no significant group differences in cytokine production at any assessment point. Overall, findings are consistent with our hypothesis that elevations in proinflammatory cytokine production may
underlie symptoms of fatigue in breast cancer survivors and extend our previous results by demonstrating a heightened reactivity to acute stress in this group.

The present data also provide clues about potential biological mechanisms for altered inflammatory processes in fatigued cancer survivors. Our previous analyses of this cohort showed a significantly weakened glucocorticoid response to acute stress in fatigued survivors (Bower et al., 2005a). In the present analyses, we show that the magnitude of blunted cortisol response is directly proportional to the magnitude of the stress-induced increase in IL-6 production. These findings are consistent with research conducted in healthy populations showing that high cortisol responders show a decreased plasma (Kunz-Ebrecht et al., 2003; von Kanel et al., 2006) and LPS-stimulated (Rohleder et al., 2003) cytokine response to acute psychosocial stress. Although the mechanistic basis for this relationship cannot be determined from this study, it is possible that reduced ambient cortisol levels in the assayed whole blood samples provide decreased anti-inflammatory signaling through the glucocorticoid receptor during the over-night LPS stimulation assay, permitting enhanced cytokine production as a consequence. One of the functions of cortisol in the context of acute stress is to restrain other components of the stress response, including production of proinflammatory cytokines (Raison and Miller, 2003). Thus, inadequate secretion of cortisol may set the stage for exaggerated inflammatory responses to challenge, and possibly to a chronic inflammatory state in a subgroup of cancer survivors.

In contrast to results for glucocorticoid availability, we found little evidence that alterations in proinflammatory cytokine production were due to impaired glucocorticoid sensitivity. There were no significant group differences in IC50 values at baseline or in response to stress, and changes in cytokine production were more strongly correlated with glucocorticoid response than with cellular sensitivity to glucocorticoid inhibition. The lack of change in glucocorticoid sensitivity at 30 min following stress exposure is generally consistent with previous research on healthy women (Rohleder et al., 2001; Rohleder et al., 2003a), although a recent study found more immediate changes in glucocorticoid sensitivity in both depressed women and healthy controls (Miller et al., 2005). The protocol used in this study differs somewhat from these reports in that we used lower concentrations of LPS and assayed the specific effects of cortisol (the physiologically relevant hormone) rather than dexamethasone (a more potent pharmacologic glucocorticoid). Our protocol was designed to more closely approximate in vivo physiologic conditions, but it is unclear whether these results tap the same specific response dynamics assessed by previous studies employing higher concentrations of LPS and pharmacologic glucocorticoids.

CD14-mediated signaling represents the primary molecular mechanism by which LPS induces proinflammatory cytokine responses, and it is notable that the number and relative prevalence of CD14+ monocytes was not differentially affected in fatigued survivors, and that differential cytokine responses emerged despite statistical control for individual variations in monocyte numbers. As in previous studies, we did find elevated levels of CD4+ T lymphocytes in fatigued survivors (Bower et al., 2003), as well as a greater increase in CD4+ T cells in response to stress. Further, stress-induced elevations in CD4+ cell numbers were associated with increases in proinflammatory cytokine production. CD4+ T lymphocytes do not generally express the CD14 molecule and therefore would not be expected to be primary mediators of differential cytokine production in response to LPS stimulation. However, it is possible that CD4+ T cells participate in “bystander effects” that enhance proinflammatory cytokine responses by monocytes (e.g., by secreting IFN-γ in response to proinflammatory signals initially generated by monocytes, which might then enhance monocyte activation to further drive cytokine production). Definitive answers will require future analyses of isolated leukocyte subsets.

This study provides novel insights into the biological mechanisms that underlie aberrant inflammatory biology in fatigued survivors of breast cancer, but several limitations qualify the interpretation of these results. First, this study focuses on a small, carefully selected group of individuals who reported elevated levels of fatigue at several points years after cancer diagnosis and treatment. Analysis of this highly selected sample rules out several potential counter-explanations for variations in inflammatory biology (e.g., confounded medical conditions, effects of concurrent cancer therapy, recurrent disease, and transient fluctuations in fatigue) but limit the generalizability of study results and may undermine this study’s statistical power to detect weak influences on inflammatory dynamics. Indeed, some of the negligible relationships observed in this study might have emerged as statistically significant in a more strongly powered study (e.g., effects of glucocorticoid resistance). Thus, results should be considered preliminary and require replication in a larger and more representative sample. Second, we focused on one measure of the inflammatory response, extracellular production of proinflammatory cytokines in response to ex vivo stimulation with LPS, which is known to be responsive to acute stress (Segerstrom and Miller, 2004) and to glucocorticoid modulation. A more comprehensive picture of inflammatory biology would include additional measures such as circulating proinflammatory cytokines (e.g., Steptoe et al., 2001) and intracellular cytokine production by monocytes (Collado-Hidalgo et al., 2006). Third, it would be preferable to include additional assessment points to provide a more detailed picture of the dynamic response to stress and to use multiple doses of LPS to ensure that changes in the dose–response curve do not account for study results. Fourth, results do not address the specificity of blunted cortisol responses in fatigued participants. Analyses of glucocorticoid response to other behavioral stimuli and pharmacologic probes (e.g., dexamethasone challenge or exogenous ACTH) would help clarify the physiologic basis for altered neuroendocrine response in cancer-related
fatigue. Longitudinal studies would also be helpful in clarifying whether altered HPA regulation is a stable individual characteristic that pre-dated the impact of cancer, or somehow related to or amplified by the effects of tumor growth or therapy. Finally, future research should examine other potential mediators of altered inflammatory processes in fatigued cancer survivors, including catecholamines, opioids, and other stress hormones.

This is the first study to examine the association between inflammatory responses to stress and cancer-related fatigue, and results suggest that altered activity of anti-inflammatory neuroendocrines may play a critical role in the genesis of aberrant inflammatory response. In particular, the present data suggest that alterations in cortisol availability, rather than receptor sensitivity, play a central role in those dynamics. The study also provides evidence that alterations in the CD4+ T cell compartment may play a role in stress-related inflammatory processes. Although the mechanistic basis for these associations requires further examination, these results identify potential targets for behavioral or pharmacologic interventions to ameliorate aberrant inflammatory biology and remediate fatigue in the growing population of cancer survivors.

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