Exploring Biologic Correlates of Cancer-Related Fatigue in Men With Prostate Cancer: Cell Damage Pathways and Oxidative Stress

Kristin Dickinson, PhD, RN, OCN^{1,2} , Adam J. Case, PhD³, Kevin Kupzyk, PhD¹, and Leorey Saligan, PhD, RN, CRNP, FAAN²

Abstract

The pathobiology of cancer-related fatigue (CRF) remains elusive, hindering the development of targeted treatments. Radiation therapy (RT), a common treatment for men with prostate cancer, induces cell damage through the generation of free radicals and oxidative stress. We hypothesized that disruption in cellular responses to this surge of nonphysiological oxidative stress might contribute to CRF in men with prostate cancer treated with RT. We evaluated the potential role of three cell damage pathways (apoptosis, autophagy, necrosis) and oxidative stress in CRF in men with prostate cancer receiving RT. Fatigue was measured by the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) questionnaire. Gene expression was measured in whole blood using RT² profilerTM PCR arrays. Data were collected at two time points: either baseline or Day 1 of treatment (T1) and completion of treatment (T2). Participants were grouped into either the fatigued or nonfatigued phenotype at T2 using the recommended FACT-F cut-off score for clinical significance. We observed significant upregulation of seven genes related to three cell damage pathways in the fatigued group from T1 to T2 and no significant changes in the nonfatigued group. We also observed significant downregulation of two genes related to oxidative stress in the fatigued group compared to the nonfatigued group at T2. These collective results provide preliminary evidence that cell damage might be upregulated in the CRF phenotype. Validation of these findings using a larger and more diverse sample is warranted.

Keywords

fatigue, prostate cancer, radiation

Cancer-related fatigue (CRF) is one of the most common symptoms reported by patients with cancer. The treatment of CRF has been substantially hindered by the lack of insights into its etiology, resulting in poor management of this distressing symptom. The pathobiology of CRF is complex and likely attributable to a myriad of events. Self-reported descriptions of CRF, such as reduced energy, exercise intolerance, and weakness, lend support for a potential relationship of CRF to mitochondrial dysfunction. Our previous investigation in men with prostate cancer explored the potential contribution of mitochondrial oxidative phosphorylation enzymes to CRF. Findings from that study revealed a pattern of change that suggests a potential role for mitochondrial involvement in the pathobiology of CRF (Filler et al., 2016). Mitochondria play an essential role in many cellular activities such as energy production, metabolism, production of reactive oxygen species, and regulation of cell damage (Nunnari & Suomalainen, 2012). Radiation therapy (RT), one of the most common prostate cancer treatment options, generates stress-induced increases in free radicals and oxidative stress, resulting in cell damage and tissue toxicity (Mapuskar, et al., 2019).

Adaptive responses to oxidative stress and reactive oxygen species damage occur through the balance of three cell damage pathways: apoptosis, autophagy, and necrosis (Doherty & Baehrecke, 2018). Compensation for mild stress requires the activation of autophagy, which results in the removal of damaged intracellular components through lysosomal degradation. However, more-devastating damage requires more-severe cellular responses, such as apoptosis and necrosis, both of which are forms of cell death. Overt cell death results in inflammation, which can lead to the onset of various pathological

¹ College of Nursing, University of Nebraska Medical Center, Omaha, NE, USA

² Symptom Biology Unit, National Institute of Nursing Research, National Institutes of Health, Bethesda, MD, USA

³ Department of Cellular and Integrative Physiology, College of Medicine, University of Nebraska Medical Center, Omaha, NE, USA

Corresponding Author:

Kristin Dickinson, PhD, RN, OCN, College of Nursing, University of Nebraska Medical Center, 985330 Nebraska Medical Center, Omaha, NE 68198, USA.
 Email: kristin.dickinson@unmc.edu

conditions (Galluzzi et al., 2012; Mammucari & Ruzzuto, 2010), possibly including CRF. We hypothesized that disruption in cellular adaptive responses to oxidative stress might contribute to CRF in men with prostate cancer receiving RT. Therefore, the purpose of this exploratory genomic association study was to evaluate the potential role of three cell damage pathways (apoptosis, autophagy, necrosis) and oxidative stress in CRF among men with prostate cancer receiving RT.

Method

We obtained data for this study from an ongoing descriptive, longitudinal, institutional review board–approved study (NCT00852111) investigating CRF in men with nonmetastatic prostate cancer receiving external beam radiation therapy (EBRT). All participants provided written informed consent. Study visits were conducted at the Radiation Oncology Department of the National Cancer Institute, National Institutes of Health, Bethesda, MD. Men were eligible for inclusion if they (a) had nonmetastatic prostate cancer, (b) were scheduled to receive EBRT, and (c) were ≥ 21 years of age. Men were excluded if they (a) had any inflammatory or infectious condition, (b) had other types of cancer, (c) had a major psychiatric disorder or had abused alcohol or drugs within the past 5 years, (d) were receiving chemotherapy during EBRT, (e) were taking steroids, nonsteroidal anti-inflammatories, or tranquilizers, or (f) were not receiving androgen deprivation therapy (ADT).

Data Collection

Data were collected at two time points: either baseline (before start of treatment) or Day 1 of EBRT (T1) and completion of EBRT (T2). Data were obtained from participant medical records, self-report questionnaires, and blood samples.

Medical-record data. We used data collected from medical records to assess demographic (age, race, ethnicity) and disease-related characteristics (Gleason score, T-stage, radiation dose and fractions).

Fatigue. Scores on the 13-item Functional Assessment of Cancer Therapy–Fatigue (FACT-F) questionnaire were used to assess fatigue in participants. The FACT-F, which has been validated in the oncology population, has good test–retest reliability ($r = .90$) and internal consistency reliability ($\alpha s = .93-.95$) on initial and test–retest administration, suggesting that it is a reliable one-dimensional measure of fatigue (Yellen et al., 1997). In order to capture CRF triggered by EBRT, participants were phenotyped (fatigued versus nonfatigued) at T2 using a FACT-F score of 43. A score < 43 is considered an indicator of clinically significant fatigue (Feng et al., 2016).

Blood samples. Blood samples were collected at each time point via a peripheral blood draw. A 2.5-mL PAXgene Blood RNA Tube (PreAnalytiX) was used to collect peripheral blood for RNA extraction. An 8-mL BD Vacutainer CPT™

Mononuclear Cell Preparation Tube–Sodium Heparin was used to collect peripheral blood for buffy coat and plasma extraction. RNA isolation was performed using the PAXgene Blood RNA Kit according to the manufacturer's protocol (SABiosciences, Qiagen). Polymerase chain reaction (PCR) arrays were carried out using QuantStudio 6K Flex (384 well; Applied Biosystems).

Gene expression for cell damage pathways. RT² polymerase chain reaction (PCR) profiler arrays (SABiosciences, Qiagen) were used to determine the expression profiles of genes involved in cell damage pathways (84 genes per array): RT² Profiler™ PCR Array Human Apoptosis (PAHS-012Z), RT² Profiler™ PCR Array Human Autophagy (PAHS-084Z), and RT² Profiler™ PCR Array Human Necrosis (PAHS-141Z).

Gene expression for oxidative stress. The RT² Profiler™ PCR Array Human Oxidative Stress Plus (SABiosciences, Qiagen) was used to analyze the expression profiles of 84 genes related to oxidative stress.

Proteomic confirmation. Plasma samples were obtained during the processing of a cell-preparation tube (CPT). The plasma layer was extracted in 250- μ L aliquots and stored at -80°C until batch analysis. Plasma samples were sent to the NIH Clinical Laboratory for analysis of lactate dehydrogenase (LDH) concentration.

Statistical Analyses

Descriptive statistics were used to describe demographic and clinical characteristics of the sample at each time point. Paired t-tests were used to describe changes in fatigue scores and LDH concentration between the time points. Independent-samples t-tests were used to assess differences in LDH concentrations and change in concentration between fatigue groups. Statistical analyses were conducted using SPSS, version 25 (IBM Corp.). PCR data were analyzed using software provided through Qiagen's GeneGlobe Data Analysis Center (<https://www.qiagen.com/us/shop/genes-and-pathways/data-analysis-center-overview-page/>). *HPRT1* was used as the housekeeping gene for the normalization of data. Additionally, to control for multiple comparisons, a false discovery rate (FDR) p -value was calculated. Genes with ≥ 2 -fold change in gene expression and FDR $p < .05$ were considered to be significantly up- or downregulated.

Results

Sample Demographics

We included data from 29 men with prostate cancer who had completed the larger ongoing study (NCT00852111; Table 1). Participants were included from the larger study based upon availability and quality of stored biological samples. The average age of the participants was 68.4 (SD 7.0) years, most were White (72.4%), not Hispanic or Latino (96.6%), and had an average body mass index of 29.6 (SD 4.3) kg/m^2 . The average

Table 1. Demographic and Clinical Data for the Sample.

Variable	Fatigue (<i>n</i> = 19)	No Fatigue (<i>n</i> = 10)
Age, years [mean (SD)]	68.3 (7.1)	68.5 (7.1)
Race [count (%)]		
White	14 (73.7)	7 (70.0)
Black or African American	4 (21.1)	3 (30.0)
Asian	1 (5.3)	0
Ethnicity [count (%)]		
Not Hispanic	19 (100)	9 (90)
Hispanic	0	1 (10)
BMI, kg/m ² [mean (SD)]	29.9 (4.7)	29.2 (3.6)
Gleason score [mean (SD)]	7.8 (0.9)	7.9 (1.0)
T-stage [count (%)]		
T1c	9 (47.4)	3 (30.0)
T2a	4 (21.1)	6 (60.0)
T2b	1 (5.3)	0
T2c	1 (5.3)	1 (10.0)
T3a	2 (10.5)	0
T3b	2 (10.5)	0
Radiation fractions [count (%)]		
42	17 (89.5)	7 (70.0)
43	0	1 (10.0)
44	2 (10.5)	2 (20.0)
Radiation dose [count (%)]		
7560 cGy	17 (89.5)	6 (60.0)
7740 cGy	0	1 (10.0)
7900 cGy	0	1 (10.0)
7920 cGy	2 (10.5)	2 (20.0)

Note. BMI = body mass index.

Gleason score was 7.8 (SD 0.9), and most of the tumors were staged either T1c (41.4%) or T2a (34.6%). Most men received an EBRT dose of 7560 cGy (79.3%) in 42 fractions (82.8%). The ADT regimen consisted of the antiandrogen Casodex and the luteinizing hormone-releasing hormone (LHRH) agonist Lupron.

Participants were phenotyped into fatigue groups based upon their T2 FACT-F scores. When comparing between fatigued and nonfatigued groups, we found no significant differences with regards to any of the demographic or health-related variables (Table 1).

Fatigue Scores

At each time point, the fatigued group had significantly lower FACT-F scores (more fatigue) than the nonfatigued group ($p < .01$; Table 2). As expected, the fatigued group had a significant worsening in FACT-F scores ($p < .001$) from baseline or Day 1 of EBRT (T1) to completion of EBRT (T2), whereas the nonfatigued group had no significant change in FACT-F scores from T1 to T2.

Expression of Genes Related to Cell Damage Pathways

We explored differences in the expression of genes related to cell damage pathways between groups at each time point (T1

Table 2. FACT-F Scores [mean (SD)] at T1 and T2 by Study Group.

Fatigue Phenotype	<i>N</i>	Study Time Point		<i>p</i> -value
		T1	T2	
Fatigue	19	42.0 (6.2)	33.4 (6.0)	< .001
No Fatigue	10	48.3 (4.3)	47.9 (3.6)	.64
<i>p</i> -value		.008	< .001	

Note. FACT-F = Functional Assessment of Cancer Therapy-Fatigue questionnaire.

Table 3. Genes Involved in Cell Damage Pathways (Apoptosis, Autophagy, and Necrosis) Whose Expression Changed in Both Groups from T1 to T2, Indicating the Change Was Related to the Effects of Radiation and Not Cancer-Related Fatigue.

Gene	Fatigued Group FΔ	Nonfatigued Group FΔ
Apoptosis (<i>n</i> = 28 samples)		
<i>BCL2</i>	−1.7	−1.8
<i>BIRC3</i>	−1.6	−1.9
<i>CD40LG</i>	−1.6	−1.9
<i>TNFRSF10A</i>	−1.6	−1.6
<i>TNFRSF25</i>	−1.7	−1.8
Autophagy (<i>n</i> = 29 samples)		
<i>BCL2</i>	−1.8	−2.1
Necrosis (<i>n</i> = 28 samples)		
<i>BIRC3</i>	−2.0	−2.0
<i>TNFRSF10A</i>	−1.8	−2.2
<i>TNFRSF25</i>	−1.9	−2.0

Note. All of the genes in this table had a false discovery rate $p < .05$, but they did not all meet the remaining criterion for significant change in expression (fold change ≥ 2). FΔ = fold change.

and T2) and within each group from T1 to T2. We considered differential expression of a particular gene from T1 to T2 ($p < .05$ and fold change ≥ 2) within both groups to be related to the effects of radiation; hence, we eliminated those genes as potential CRF correlates (Table 3).

Apoptosis. There were no significant differences in the expression of genes related to the apoptosis pathway between the fatigued and nonfatigued groups at either time point (T1 or T2) after FDR correction. Within the fatigued group, three genes were differentially expressed from T1 to T2 after FDR correction: *BCL2L1*, *CD70*, and *GADD45A*. Within the nonfatigued group, there were no unique genes that were differentially expressed from T1 to T2 (Table 4).

Autophagy. There were no significant differences in the expression of genes related to the autophagy pathway between the fatigued and nonfatigued groups at either time point (T1 or T2) after FDR correction. Within the fatigued group, four genes were differentially expressed from T1 to T2 after FDR correction: *TGM2*, *SNCA*, *GABARAPL2*, and *BCL2L1*. Within the

Table 4. Significant Changes in Gene Expression From T1 to T2 in the Fatigued Group for Genes Involved in Cell Damage Pathways (Apoptosis, Autophagy, and Necrosis).

Gene	FDR <i>p</i> -value (Fold-change)	Related Pathways
Apoptosis (<i>n</i> = 28 samples)		
<i>BCL2L1</i>	< .001 (3.4)	Anti-apoptotic; negative regulation of apoptosis
<i>CD70</i>	.003 (2.6)	Induction of apoptosis (pro-apoptotic); positive regulation of apoptosis
<i>GADD45A</i>	.004 (2.1)	Induction of apoptosis (pro-apoptotic)
Autophagy (<i>n</i> = 29 samples)		
<i>BCL2L1</i>	.003 (2.9)	Regulation of autophagy: co-regulator of apoptosis and autophagy
<i>GABARAPL2</i>	.002 (2.0)	Autophagy machinery components: vacuole formation and protein transport
<i>SNCA</i>	< .001 (2.7)	Regulation of autophagy: co-regulator of apoptosis and autophagy
<i>TGM2</i>	< .001 (3.3)	Regulation of autophagy: co-regulator of apoptosis and autophagy
Necrosis (<i>n</i> = 28 samples)		
<i>GALNT5</i>	.003 (2.4)	TNF-induced necrosis

Note. There were no significant changes in expression from T1 to T2 in the nonfatigued group for unique genes related to cell damage pathways. FDR = false discovery rate; TNF = tumor necrosis factor.

Table 5. Lactate Dehydrogenase (LDH) Concentration [mean (SD)] at T1 and T2 by Study Group.

Fatigue Phenotype	<i>N</i>	Study Time Point		<i>p</i> -value
		T1	T2	
Fatigue	9	143.1 (23.2)	152.6 (59.4)	.64
No Fatigue	9	158.4 (30.4)	154.8 (13.5)	.77
<i>p</i> -value		.25	.92	

nonfatigued group there were no unique genes that were differentially expressed from T1 to T2 (Table 4).

Necrosis. There were no significant differences in the expression of genes related to the necrosis pathway between the fatigued and nonfatigued groups at either time point (T1 or T2) after FDR correction. Within the fatigued group, one gene, *GALNT5*, was differentially expressed from T1 to T2 after FDR correction. Within the nonfatigued group, there were no unique genes that were differentially expressed from T1 to T2 (Table 4).

LDH Concentration

For the group as a whole, there was no significant difference in the LDH concentration from T1 to T2. Likewise, there was no significant differences in the LDH concentration from T1 to T2 within either fatigue group. LDH concentration did not differ significantly between the fatigued and nonfatigued groups at either time point. Additionally, the percent change in LDH concentration from T1 to T2 did not differ significantly between the fatigue groups (Table 5).

Genes Related to Oxidative Stress

There were no significant differences in the expression of genes related to oxidative stress between the fatigued and nonfatigued groups at T1. However, two genes were significantly decreased

in the fatigued group when compared to the nonfatigued group at T2: *TXNRD2* (fold difference -2.9 , $p = .009$) and *PRDX6* (fold difference -2.9 , $p = .02$).

Discussion

RT induces cell death and tissue toxicity through the generation of free radicals and oxidative damage (Mapuskar et al., 2019). This novel, exploratory study is the first, to our knowledge, to investigate the contribution of cell damage pathways (apoptosis, autophagy, and necrosis) to cancer-related fatigue (CRF) in patients undergoing EBRT for nonmetastatic prostate cancer. We observed several genes unique to each cell damage pathway that were significantly upregulated in the fatigued group over time; however, no genes were significantly changed over time in the nonfatigued group. Specifically, we observed significant upregulation of seven genes (*BCL2L1*, *CD70*, *GADD45A*, *GABARAPL2*, *SNCA*, *TGM2*, *GALNT5*) related to three cell damage pathways (apoptosis, autophagy, and necrosis) in the fatigued group from T1 to T2. These results provide preliminary evidence that cell damage might be upregulated in the CRF phenotype, suggesting that changes in behavior, like fatigue, may stem from an inability to adequately respond to the cellular damage caused by radiation. However, we found no significant changes in LDH concentration over time or differences in the concentration between groups, suggesting that LDH may not be the appropriate downstream marker for these differentially expressed genes.

Pathway-Specific Results

Apoptosis. Results indicated that three genes in the apoptotic pathway were upregulated in the fatigued group from T1 to T2: *BCL2L1*, *CD70*, and *GADD45A*. The protein product of *BCL2L1* acts as an anti-apoptotic regulator. The protein product of *CD70* is a tumor necrosis factor (TNF) cytokine and plays a role in T- and B-cell proliferation and activation (National Center for Biotechnology Information, 2020). The transcript of *GADD45A* responds to environmental stress and

DNA damage (National Center for Biotechnology Information, 2019). Although *GADD45A* is often classified as pro-apoptotic, there is evidence that the gene can play an anti-apoptotic role (Portt et al., 2011). Previous literature has shown a relationship between upregulation of *GADD45A* and downstream upregulation of *BCL2L1* for cell protection during exposure to ultraviolet (UV) radiation (Hoffman & Liebermann, 2009). Putting this evidence together, the upregulation of these genes might suggest that the biological compensation to the radiation treatment was altered in patients in the fatigued group compared to those in the nonfatigued group, who had no significant upregulation of these genes.

Autophagy. In the autophagy pathway, there were four genes that were upregulated in the fatigued group from T1 to T2: *BCL2L1*, *GABARAPL2*, *SNCA*, and *TGM2*. The protein product of *GABARAPL2* is involved in autophagy (regulation, vacuole formation, protein transport) as well as in mitophagy, the mitochondrial-specific autophagy (Stelzer et al., 2016). The protein products of *SNCA* and *TGM2* both play a role in regulating apoptosis and autophagy. The upregulation of these autophagy-related genes suggest that either (a) autophagic processes are more active in the CRF phenotype to increase the cellular stress threshold and prevent the need for cell damage pathway activation or (b) these genes may also exhibit apoptotic/necrotic functions and are upregulated via crosstalk between these adaptive pathways (Mariño et al., 2014). Therefore, those in the fatigued group had upregulation of autophagic-relevant genes that either resulted in or was a result of dysfunctional adaptation to the radiation treatment.

Necrosis. Results indicated that only one gene in the necrosis pathway was upregulated in the fatigued group: *GALNT5*. The protein product of this gene plays a role in TNF-induced necrosis. The upregulation of this gene suggests a role for inflammation and cell damage in the fatigued group. The role of inflammation in the pathogenesis of CRF has been heavily studied (Bower, 2014).

Oxidative stress. Our findings show that two genes (*TXNRD2* and *PRDX6*) were significantly downregulated in the fatigued group compared to the nonfatigued group at T2. The protein products of these two genes are antioxidants that are involved in the conversion of the reactive oxygen species hydrogen peroxide to water. Downregulation of both antioxidant genes could result in excess hydrogen peroxide, which then could contribute to increased cellular damage and death. Therefore, downregulation of these genes supports the upregulation observed in the genes related to cell damage.

Interaction of Genes Across Pathways

Several of the genes across the three cell damage pathways tell a consistent story. *BCL2L1* was significantly upregulated in both the apoptosis and the autophagy arrays in the fatigued group. Our finding of upregulation of *BCL2L1* aligns with prior

findings of an association between *BCL2L1* and CRF (Hsiao et al., 2015). Findings of upregulation of *GADD45A* (apoptosis array), *CD70* (autophagy array), and *GALNT5* (necrotic array) in the fatigued group provide preliminary evidence to suggest the potential involvement of TNF in CRF. Prior researchers have reported associations of TNF with fatigue in other conditions such as rheumatoid arthritis and chronic fatigue syndrome (Brenu, et al., 2011; McInnes et al., 2015). The upregulation of these inflammatory-associated genes aligns with a large body of research that has explored the contribution of inflammation to CRF (Bower, 2014).

The upregulation of *SNCA* in the fatigued group aligns with previously reported findings in the literature and further supports the role of inflammation, specifically neuroinflammation, as a potential contributor to CRF (Saligan et al., 2013). Additionally, *SNCA* and *GABARAPL2* were part of a nine-gene signature that researchers found to be associated with poor clinical outcomes in prostate cancer patients (Olmos et al., 2012). Therefore, more research to understand the potential relationship between fatigue and clinical outcomes is warranted.

Strengths and Limitations

The small and relatively homogenous sample size limits the generalizability of study results. Further investigations, using larger samples and more diverse populations, are warranted to investigate potential associations between cell damage pathways and CRF. The strengths of the present study include the novel approach and the fact that it provides preliminary evidence for the contribution of cell damage pathways to CRF. Further research is needed to validate our results and determine the functional significance of the identified genes. Additional research is needed to understand the potential implications of these findings for therapeutic response to treatment and disease control.

Clinical Implications

Findings from the present study enhance our understanding of potential contributions of cell damage pathways and oxidative stress to the experience of CRF as well as provide direction for future larger validation studies. Enhanced understanding of the biologic markers contributing to CRF can help inform the identification of pharmacodynamic therapeutic targets that can be used to develop innovative interventions for the management of CRF.

Conclusions

The present study is one of the first to explore the potential contributions of genes related to cell damage pathways to CRF in men with nonmetastatic prostate cancer receiving EBRT. Our preliminary findings suggest that upregulation of genes related to oxidative stress and cell damage pathways may contribute to the CRF phenotype. Validation of these findings using a larger and more diverse sample is warranted.

Declaration of Conflicting Interests

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ORCID iD

Kristin Dickinson <https://orcid.org/0000-0003-4772-8085>

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