Original Article

Differential Expression of Genes Related to Mitochondrial Biogenesis and Bioenergetics in Fatigued Prostate Cancer Men Receiving External Beam Radiation Therapy

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Abstract

Objectives. This prospective study explored relationships between expression changes of genes related to mitochondrial biogenesis/bioenergetics and fatigue in men with prostate cancer receiving external beam radiation therapy (EBRT).

Methods. Fatigue and gene expression were measured before (Day 0), at midpoint (Days 19–21), and at completion (Days 38–42) of EBRT using the seven-item Patient-Reported Outcomes Measurement Information System-Fatigue short form and from whole blood cell RNA, respectively. The human mitochondria RT2 Profiler™ PCR Array System was used to identify differential expression of mitochondrial biogenesis/bioenergetics-related genes. Mixed linear modeling estimated the changes in fatigue and gene expression over time and determined significant associations between gene expression and fatigue.

Results. Subjects were 50 men with prostate cancer (scheduled for EBRT = 25, active surveillance as matched controls = 25). The mean Patient-Reported Outcomes Measurement Information System-Fatigue *T*-score (mean = 50 ± 10 in a general population) for study subjects was 44.87 ± 5.89 and for controls was 43.5 ± 2.8 at baseline. Differential expression of two genes inside the mitochondria involved in critical mitochondrial complexes: *BCS1L* ($\beta = 1.30$), *SLC25A37* ($\beta = -2.44$), and two genes on the outer mitochondrial membrane vital for mitochondrial integrity: *BCL2L1* ($\beta = -1.68$) and *FIS1* ($\beta = -2.35$) were significantly associated with changes in fatigue scores of study subjects during EBRT.

Conclusion. Genes related to oxidative phosphorylation, energy production, and mitochondrial membrane integrity are associated with worsening fatigue during EBRT. Further investigation of the pathways involved with this association may explain mechanisms behind the development of fatigue in this

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Key Words
Fatigue, gene expression, mitochondria, biogenesis, bioenergetics, prostate cancer, radiation therapy

Introduction

Prostate cancer is the second leading cause of cancer-related deaths in the U.S. In 2012, 241,740 men were newly diagnosed with the disease and 28,170 men died of it.[1] Approximately 90% of all prostate cancers are low-grade tumors that have not metastasized.[2] Localized external beam radiation therapy (EBRT) is one of the preferred standard, curative treatment options for individuals with nonmetastatic prostate cancer (NMPC).[3] Although EBRT has increased survival rates for these men, adverse effects including fatigue, diarrhea, and cognitive function impairment are frequently reported during and even after completion of the therapy.[4,5] Fatigue severity reported by men during the course of the EBRT has been found to peak at midpoint and decline after completion of the treatment.[6] The pathophysiological mechanisms behind the worsening of fatigue intensity during EBRT remain unknown.

Cancer-related fatigue (CRF) is reported as a distressing, persistent sense of tiredness or exhaustion related to cancer or cancer treatment.[7] Fatigue reported by patients with prostate cancer during EBRT and survivorship has been recognized as a type of CRF.[8] CRF is associated with negative functional status and health outcomes, including depression, impaired cognitive function, sleep disturbance, and decreased health-related quality of life.[9–11] The etiology of CRF remains unclear;[12,13] however, a number of mechanisms related to energy production and expenditure have been proposed. These include decreased generation or utilization of adenosine triphosphate and decline in neuromuscular efficiency.[13–15] Confirmation or negation of these possible causes of fatigue is needed as a step toward identifying possible interventions that can target this prevalent symptom.

Radiation-related cellular damage causes genomic instability and a para-inflammatory response inducing production of reactive oxygen species (ROS).[16] It is also known to alter mitochondrial metabolism, inhibit the mitochondrial respiratory chain, and form highly reactive peroxynitrite (ONO_2^-).[17] Few longitudinal studies have investigated the associations between biological markers and fatigue symptoms experienced by men with NMPC receiving EBRT.[6,18] The hypothesis-generating, exploratory study described here investigates the relationship between differential expression of genes associated with mitochondrial biogenesis and bioenergetics and changes in fatigue experienced by the study participants. The present study expands our initial findings on the association of differential expression of mitochondrial-related genes with fatigue experienced by men with NMPC before, during, and at completion of EBRT.[19]

Methods

Study Samples and Recruitment

A prospective, exploratory, repeated-measures design was used to investigate fatigue in men with NMPC before EBRT (baseline), Days 19–21 (midpoint of EBRT), and Days 38–42 (completion of EBRT). The study (NCT01143467) was approved by the institutional review board of the National Institutes of Health, Bethesda, MD. Recruitment and data collection were conducted at the Hatfield Clinical Research Center, National Institutes of Health, from May 2010 to August 2011.

Informed consent was obtained from all participants before collecting data. Inclusion criteria included males ≥18 years, clinical diagnosis of NMPC, scheduled to receive EBRT using an intensity-modulated radiation therapy technique with or without concurrent androgen deprivation therapy, and able to provide written informed consent. Patients were excluded if they had progressive or unstable disease of a body system causing clinically significant