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Research report

A murine model of peripheral irradiation-induced fatigue

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HIGHLIGHTS

- A novel radiation-induced fatigue mouse model that is not influenced by anemia, anhedonia, intestinal integrity disruption or weight changes.
- Fatigue behavior is most prominent in the last four hours of the dark (active) cycle of the mouse model.
- Voluntary wheel running wheel distance and speed are sensitive measures of fatigue behavior.

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ABSTRACT

Purpose: Fatigue is the most ubiquitous side effect of cancer treatment, but its etiology remains elusive. Further investigations into cancer-related fatigue pathobiology necessitate the expanded use of animal models. This study describes the development of a murine model of radiation-induced fatigue.
Methods: Voluntary wheel running activity measured fatigue in 5–8 week-old, male C57BL/6 mice before and after γ irradiation totaling 2400 cGy (3 consecutive days × 800 cGy daily fractionated doses) to the lower abdominal areas. Three trials confirmed fatigue behavior at this dose. Anhedonia, body weight, and hemoglobin were also measured. Gastrointestinal, skeletal muscle, and bone marrow tissue samples were evaluated for signs of damage.
Results: In two validation trials, irradiated mice (trial 1, n = 8; trial 2, n = 8) covered less cumulative distance in kilometers post-irradiation (trial 1, mean = 115.3 ± 12.3; trial 2, mean = 113.6 ± 21.8) than sham controls (trial 1, n = 5, mean = 126.3 ± 5.7, $p = 0.05$; trial 2, n = 8, mean = 140.9 ± 25.4, $p = 0.02$). Decreased mean daily running distance and speed were observed during the last four hours of the dark cycle in irradiated mice compared to controls for two weeks post-irradiation. There were no differences in saccharin preference or hemoglobin levels between groups, no effect of changes in body weight or hemoglobin on wheel running distance, additionally, histology showed no damage to muscle, bone marrow, or gastrointestinal integrity, with the latter confirmed by ELISA.
Conclusion: We characterized a novel mouse model of fatigue caused by peripheral radiation and not associated with anemia, weight changes, or anhedonia. This model provides opportunities for detailed study of the mechanisms of radiation-induced fatigue.

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1. Introduction

Fatigue is the most distressing, costly, and ubiquitous symptom experienced by patients with cancer, especially during treatment [1–3]. Cancer-related fatigue (CRF) is a complex, multidimensional condition associated with cognitive deficits, persistent tiredness unrelieved by sleep or rest, and weakness not proportional to recent activity [1,4]. It causes disturbances in memory, mood, motivation, and attention, interfering with daily function and negatively affecting patients' quality of life [5,6]. CRF severity varies over the course of the day, usually worsening in the evening [7,8]. Importantly, CRF is a key reason for decreased compliance or discontinuation of potentially life-saving cancer therapies [9–11]. However, definitive mechanisms and treatments for CRF remain elusive [12].

Both peripheral and central inflammatory pathways have important influences on CRF during and after treatment [13–15].

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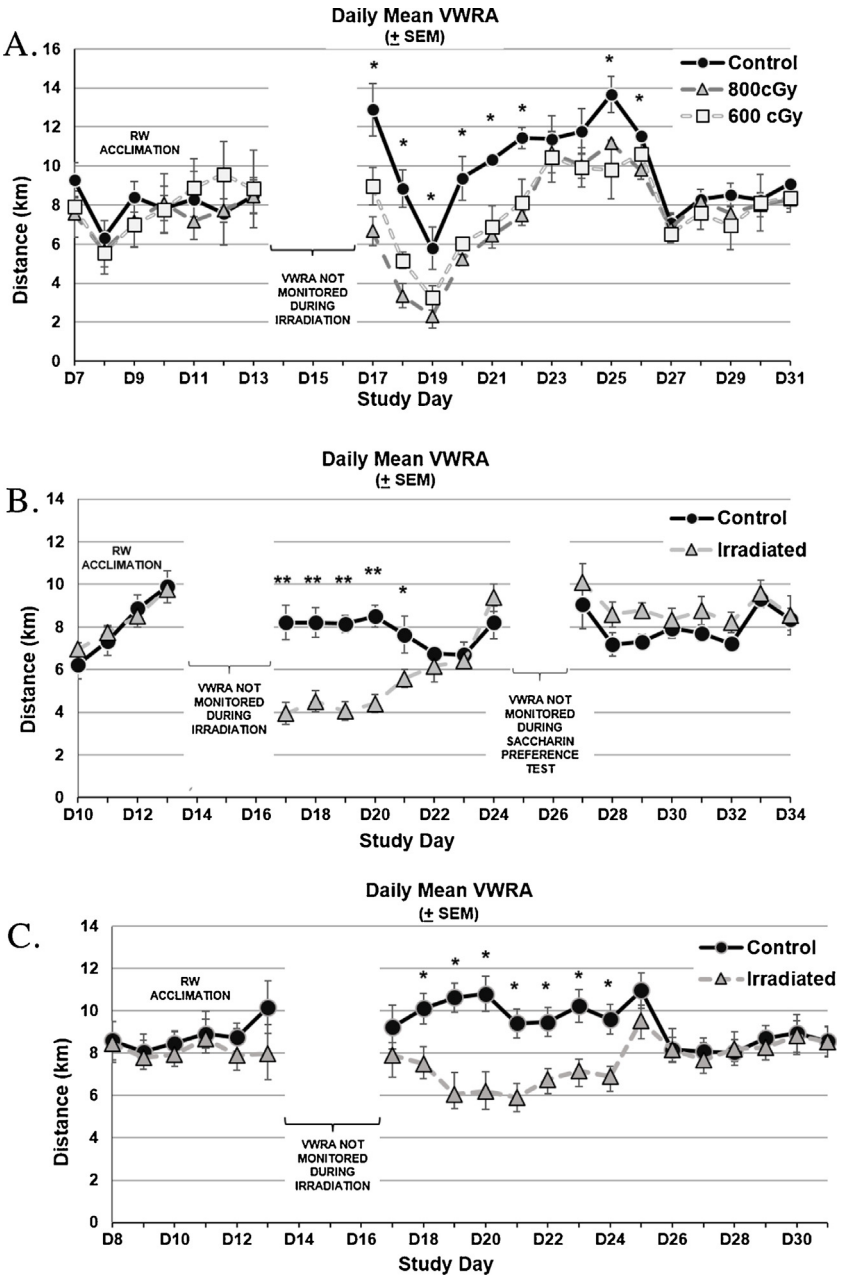

Fig. 1. Daily Voluntary Wheel Running Activity (VWRA) A. 800 cGy daily radiation dose × 3 produced more pronounced fatigue behavior compared to 600 cGy daily radiation dose × 3, and sham controls in pilot trial 2. B. Validation trial 1 revealed significant decrease in distance (kilometers) for mice irradiated with 800 cGy daily radiation dose × 3. C. Validation trial 2 further confirms the development of fatigue behavior following irradiation with 800 cGy daily radiation dose × 3. The daily mean VWRA distance prior to irradiation days (days 13–15) reflect the VWRA distance covered during running wheel (RW) acclimation. Mice were allowed to rest in home cages on days 13–15 and during saccharin preference testing (days 24–26) in validation trial 1. Error bars show standard error of the mean. $^{*}p < 0.05$, $^{**}p < 0.001$.

Our group has observed associations between inflammatory markers and intensification of fatigue in men with non-metastatic prostate cancer receiving external beam radiation therapy (EBRT) [16]. The development of CRF upon treatment initiation and persistence after treatment completion suggests that radiation therapy (RT) triggers CRF initiation. We seek to understand how the physiological responses to localized, peripheral irradiation lead to fatigue development. Clinical studies, which have predominated CRF research to date, rely mainly on patient self-report with results that may be subject to differences in patient genetics, psychological responses to cancer diagnoses/treatment, and other factors that make causation difficult to infer. However, mouse models provide researchers with an ideal system for overcoming such challenges. In addition to allowing strict control of experimental conditions, treatments, genetics, and sample collection for biochemical or histological analysis, behavioral assays can quantify aspects of subjective symptoms to assist in phenotyping the condition of interest. Therefore, a mouse model of radiation-induced fatigue would be instrumental to understanding the pathobiology underlying this debilitating condition.

Existing *in vivo* mouse models examining fatigue-like behavior related to cancer or cancer therapy involve the use of one or more of the following: tumorigenic mice [17], chemotherapeutics [10,18], antigenic challenge such as lipopolysaccharide or cytokine administration [19,20], or brain or total body irradiation [21,22]. These models often show symptoms associated with CRF, including cognitive deficiencies, assessed by learning or memory tests [23], and depressive behaviors, such as anhedonia [20]. However, the