

# Pathophysiology of Cancer-Related Fatigue

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Cancer-related fatigue (CRF) is influenced and modulated by a number of critical factors, and the mechanism that is both necessary and sufficient to induce development of severe fatigue in patients with cancer has not yet been identified. Specific research efforts to understand the factors that may contribute to CRF development have been made, including studies of the direct effects of tumor burden, the effects of cancer treatment, and other pathophysiologic and psychosocial conditions. Compelling new hypotheses regarding CRF pathophysiology have been proposed, such as the pro-inflammatory hypothesis, the serotonin hypothesis, the vagal-afferent-activation hypothesis, the anemia hypothesis, and the adenosine triphosphate hypothesis; some of these have been tested in both animal models and humans and some in animals only. Gaining an understanding of the specific mechanisms related to the development of fatigue in patients with cancer and survivors requires further investigation. Pathophysiologic research in CRF could be applied in the clinic to improve CRF diagnosis and to enable administration of mechanism-driven interventions. A targeted intervention study with CRF as a primary end point also would be useful.

**C**ancer-related fatigue (CRF) is one of the most common and complex symptoms experienced by patients with cancer, occurring across the spectrum of malignant disease diagnoses and major therapies. Gaining an understanding of the mechanisms underlying this highly prevalent and burdensome symptom is of great interest to researchers and clinicians alike, yet relatively few studies have evaluated the etiology of CRF or the factors that mediate multiple and related physiologic effects (Gutstein, 2001; Wagner & Cella, 2004). The multifactorial and multidimensional nature of CRF has hindered the development of methodologies for evaluating its underlying mechanisms; therefore, the lack of mechanism-driven clinical trials exploring effective pharmacologic therapies has hampered effective CRF management (Lawrence, Kupelnick, Miller, Devine, & Lau, 2004). CRF is a challenging and controversial subject for researchers and clinicians and a significant issue for the many patients with cancer who are unable to get out of bed and function normally. This article will review the clinical correlates of CRF development and propose potential mechanisms underlying the pathophysiology of CRF with support from data related to single and multiple mechanisms.

The pathophysiology of CRF has not been adequately elucidated. Clinical studies have focused on understanding factors that contribute to CRF, including the disease itself, treatments received, and a variety of chronic physical or psychological comorbid conditions, such as anemia, pain, depression, anxiety, cachexia, sleep disturbance, and immobility (see Figure 1). Although several mechanisms for the pathophysiology of CRF have been proposed, little progress has been made toward identifying reliable physiologic markers as objective measures of fatigue.

## At a Glance

- ◆ The pathophysiology of cancer-related fatigue (CRF) has not been adequately elucidated to date.
- ◆ No physiologic markers of CRF have been established from ongoing research with hypotheses proposing underlying mechanisms.
- ◆ A web of causation may be reflected in an interaction of etiology and host susceptibility.

CRF has been analyzed from physiologic, anatomic, and psychological perspectives (St Clair Gibson et al., 2003). The central governor model posits that fatigue develops in the brain and spinal cord (central fatigue as opposed to peripheral fatigue, which occurs in the neuromuscular junctions and muscle tissues) (Ryan et al., 2007; Weir, Beck, Cramer, & Housh, 2006). Central fatigue, defined as difficulty in the initiation or maintenance of voluntary activities, manifests as a failure to complete physical and mental tasks that require self-motivation and internal cues, in the absence of demonstrable cognitive

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