Does Muscle-Derived Interleukin-6 Mediate Some of the Beneficial Effects of Exercise on Cancer Treatment–Related Fatigue?

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Purpose/Objectives: To review evidence that muscle-derived interleukin-6 (IL-6) mediates some of the beneficial effects of exercise on cancer treatment–related fatigue (CTRF).

Data Sources: Electronic nursing, psychology, and medicine databases.

Data Synthesis: Fatigue is a common and often debilitating symptom associated with cancer treatment. Although the molecular mechanisms underlying CTRF have yet to be fully elucidated, it may be akin to the fatigue associated with "sickness behavior," which is initiated by the production of the proinflammatory cytokines interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α). Physical exercise has been shown to decrease fatigue levels in patients with cancer undergoing treatment. Skeletal muscle selectively produces IL-6 during exercise, and muscle-derived IL-6 can decrease the production and activity of IL-1β and TNF-α. Thus, the anti-inflammatory effects of muscle-derived IL-6 may be a mechanism underlying the observed beneficial effects of exercise on CTRF.

Conclusions: Further studies are needed to determine whether the anti-inflammatory effects of exercise underlie its beneficial effects on CTRF.

Implications for Nursing: Nurses have proven to be leaders in the field of cancer symptom management. An understanding of potential mechanisms underlying the beneficial effects of exercise on CTRF may help to fine-tune exercise interventions to maximize symptom control and to identify new treatment strategies for fatigued patients with cancer who are unable to participate in an exercise program.

Fatigue is a common and often debilitating symptom associated with cancer treatment. Although the molecular mechanisms underlying cancer treatment–related fatigue (CTRF) have yet to be fully elucidated, it may be homologous to the fatigue associated with "sickness behavior," a cluster of symptoms caused by the production of the proinflammatory cytokines interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α). Physical exercise has been shown to decrease fatigue levels in patients with cancer undergoing treatment. Yet the mechanisms underlying this benefit are unclear. This article discusses recent observations regarding the secretion of interleukin-6 (IL-6) by exercising muscle, its anti-inflammatory effects, and its potential relevance to the beneficial effects of exercise on CTRF.

Overview of Concepts

"Cancer-related fatigue is a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (National Comprehensive Cancer Network, 2009, p. FT-1). Fatigue often begins at the start of treatment and is the most common symptom experienced by patients undergoing cancer treatment (Irvine, Vincent, Graydon, Bubela, & Thompson, 1994). Given the effect that CTRF has on physical functioning and quality of life, its management is a crucial component of the cancer treatment plan. Although the cause of CTRF remains unclear, it may be the same as sickness behavior, a normal physiologic response to infection or tissue injury that is initiated by the production of IL-1β and TNF-α by immune cells (Dantzer & Kelley, 2007; Wood, Nail, Gilster, Winters, & Elsea, 2006). In a healthy individual, serum levels of IL-1β and TNF-α are low or undetectable (0–10 pg/ml). However, in response to immune challenge (e.g., infection, tissue damage), serum levels of IL-1β and TNF-α increase 10- to 100-fold, depending on the magnitude of the immune stimulus. IL-1β and TNF-α, in turn, trigger the production of IL-6, leading to an increase in serum levels of the cytokines (Mant et al., 2008). Although a direct role for the cytokines in CTRF has yet to be demonstrated, indirect evidence supports the idea. First, patients with cancer undergoing treatment often experience several symptoms, including anorexia, cachexia, pain, sleep disturbance, and depression, which

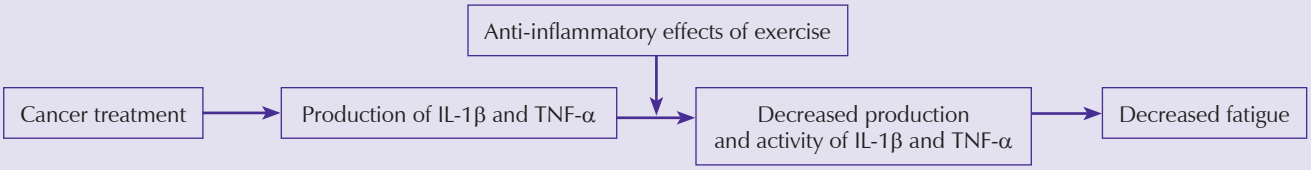
can affect the subjective sensation of fatigue. Considerable evidence has been generated in animal models and in clinical populations that IL-1β, TNF-α, and IL-6 play a significant role in the etiology of those symptoms (Wood, Nail, Gilster, et al., 2006). Second, cytotoxic chemotherapeutic agents and whole-body or localized radiation can induce the production of inflammatory cytokines in isolated immune cells and when administered to experimental animals (Ding, Porteu, Sanchez, & Nathan, 1990; Muhl et al., 1999; White, Martin, Lee, Haskill, & Ting, 1998; Wood, Nail, Perrin, et al., 2006). The stimulus for inflammatory cytokine production may be related, in part, to cancer treatment–mediated activation of p38 mitogen–activated protein kinase (p38 MAPK), a cellular enzyme that plays a central role in the production of inflammatory cytokines and the development of sickness behavior (Badger et al., 1996; Branger et al., 2002; Elsea, Roberts, Druker, & Wood, 2008). Third, increased blood levels of several inflammatory markers, including IL-6, have been demonstrated in fatigued patients with cancer (Schubert, Hong, Natarajan, Mills, & Dimsdale, 2007). Fourth, fatigue is common in chronic inflammatory diseases. For instance, the fatigue associated with Castleman disease (a rare lymphoproliferative disorder in which increased secretion of IL-6 by lymphoid cells is believed to play an important role) can be decreased by administration of monoclonal antibodies that block the activity of IL-6 (Nishimoto et al., 2005). Fatigue also is a common symptom of rheumatoid arthritis (RA). Proinflammatory cytokines such as TNF-α have been implicated in the etiology of RA (Goldblatt & Isenberg, 2005), and monoclonal antibodies that block the activity of the cytokine in the blood and synovial fluid of the affected joint have proven effective in reducing the severity of disease and levels of fatigue (Omdal & Gunnarsson, 2004; Weinblatt et al., 2003). In addition to RA, diabetes and cardiovascular disease are associated with low-grade systemic inflammation. Indeed, chronic production of TNF-α, IL-1β, and IL-6 have been implicated in the etiology of those disorders (Andersen & Pedersen, 2008).

The Role of Physical Exercise

Regular moderate exercise reduces systemic inflammation and, consequently, improves health outcomes in RA, cardiovascular disease, and diabetes (Lundberg & Nader, 2008; Pedersen, 2006). For more than a decade, physical exercise has been known to have similar beneficial effects with regard to fatigue in patients with cancer undergoing treatment (Mock et al., 1997). Although several studies since have supported those earlier findings, others have not (Cramp & Daniel, 2008). Exercise may decrease fatigue by stimulating neuromuscular function and producing hemodynamic changes (Schwartz, 1998), reducing depression and anxiety (Segar et al., 1998), or reducing social isolation (Bower, Ganz, Aziz, & Fahey, 2002; Michael, Kawachi, Berkman, Holmes, & Colditz, 2000). Another explanation for the beneficial effect of exercise on CTRF is that exercise stimulates an anti-inflammatory cascade that decreases the biologic activity of fatigue-causing IL-1β and TNF-α. The relationship among CTRF, IL-1β, TNF-α, and exercise is illustrated in Figure 1. Understanding whether muscle-derived IL-6 mediates the beneficial effects of physical exercise on CTRF by decreasing levels of IL-1β and TNF-α would allow researchers and clinicians to fine-tune future exercise interventions to achieve maximum symptom control. Furthermore, physical exercise may be an unachievable goal for some patients with cancer undergoing treatment. For such individuals, understanding whether exercise reduces fatigue by decreasing the production of fatigue-causing IL-1β and TNF-α could lead to therapeutic strategies using drugs to target the cytokines, thereby decreasing fatigue.

Skeletal Muscle and Interleukin-6

Skeletal muscle is the largest organ in the body that produces IL-6 in response to exercise (Steensberg et al., 2000). Serum levels of IL-6 rise rapidly during exercise, followed by a complete decline to baseline levels soon thereafter. The pattern of expression of IL-6 during non–muscle-damaging exercise is shown in Figure 2A. When the IL-6 response to exercise first emerged, researchers believed that its production was related to exercise-induced muscle damage (Bruunsgaard et al., 1997). In contrast to low-intensity exercise that does not lead to muscle fiber damage, the response to high-intensity or unaccustomed muscle-damaging exercise is typically accompanied by a systemic cytokine response that is similar to infection and includes elevated serum levels of IL-1β and TNF-α and, in turn, IL-6 (Ostrowski, Rohde, Asp, Schjerling, & Pedersen, 1999). The source of these serum cytokines in the context of muscle damage is likely macrophages and neutrophils that rapidly infiltrate the damaged muscle (Tidball, 2005). In addition, muscle cells have the innate ability to produce IL-1β, TNF-α and IL-6 themselves in response to harmful stimuli such as infection (Lang, Silvis, Deshpande, Nystrom, & Frost, 2003). The pattern of expression of IL-1β, TNF-α, and, consequently, IL-6 following muscle-damaging exercise is shown in Figure 2B. Of note is the fact that in contrast to non–muscle-damaging exercise, when IL-6 levels rapidly peak and then fall to baseline levels soon after the end of exercise (see Figure 2A), a second surge of IL-6 is evident following muscle-damaging exercise, usually of decreased magnitude (see Figure 2B). In that case, its production is triggered by IL-1β and TNF-α (see Figure 2B). In addition, creatine kinase, a widely used indirect marker of muscle fiber damage, also is elevated two to



Note. The model proposes that cancer treatment–related fatigue (CTRF) is caused by treatment-induced increases in proinflammatory cytokines interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α). Exercising muscle produces interleukin-6 (IL-6) to trigger an anti-inflammatory cascade to decrease the production and/or activity of IL-1β and TNF-α. Thus, the anti-inflammatory effects of muscle-derived IL-6 may be one mechanism underlying the observed beneficial effects of exercise on CTRF.

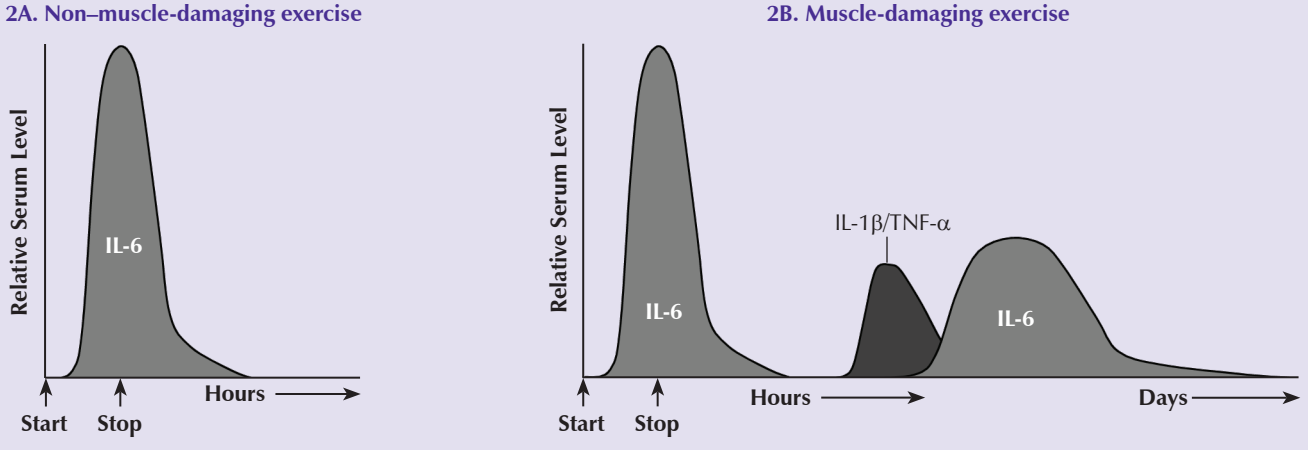
Figure 1. Proposed Mechanism Underlying the Beneficial Effects of Exercise on Cancer Treatment–Related Fatigue

three days following muscle-damaging exercise (Clarkson, Kearns, Rouzier, Rubin, & Thompson, 2006).

Subsequent studies challenged the notion that IL-6 response to exercise was related to muscle damage because the same IL-6 response was evident in its absence (Ostrowski, Hermann, et al., 1998; Ostrowski, Rohde, Zacho, Asp, & Pedersen, 1998; Steensberg et al., 2002). That finding led to the idea that the source of IL-6 produced during non–muscle-damaging exercise is muscle cells responding to contraction and energy depletion (Steensberg et al., 2000). Indeed, IL-6 is an important regulator of glucose and amino acid homeostasis and fat metabolism (for reviews, see Pedersen & Fischer, 2007). Consistent with this idea is the finding that magnitude of the IL-6 response is related to the intensity, duration, and type of exercise (Brenner et al., 1999; Ostrowski, Schjerling, & Pedersen, 2000) but not muscle mass (Toft et al., 2002). In addition, higher levels of IL-6 are released from exercising skeletal muscle in conditions of low- compared to high-glycogen conditions (Keller et al., 2001).

Muscle-Derived Interleukin-6 as a Mediator of the Anti-Inflammatory Effects of Exercise

Exercise-induced increases in IL-6 may mediate the anti-inflammatory effects of exercise. This idea may seem paradoxical because IL-6 often is considered proinflammatory in nature, playing an intimate role with IL-1β and TNF-α in the induction of sickness behavior. Moreover, increased blood levels of IL-6 have been reported in fatigued cancer survivors (Schubert et al., 2007) and in those with atherosclerosis and diabetes (Tilg & Moschen, 2006). Yet substantial evidence shows that IL-6 has anti-inflammatory properties in that it decreases the production or activity of IL-1β and TNF-α. For instance, infusion of IL-6 prior to endotoxin administration in healthy people has been shown to decrease plasma levels of TNF-α (Febbraio et al., 2003). Moreover, exercise-induced IL-6 production can decrease TNF-α levels in muscle of TNF-α transgenic mice (Keller, Keller, Giralt, Hidalgo, & Pedersen,



Note. In healthy, resting individuals, serum levels of these inflammatory markers are low. During exercise, serum levels of IL-6 rise rapidly, peak at the end of exercise, and rapidly return to baseline levels within hours of the end of exercise. If exercise leads to muscle damage, a second surge of IL-6 is evident in the serum, but in this case its production is triggered by the pro-inflammatory cytokines IL-1β and TNF-α.

Figure 2. Approximation of the Kinetics of Interleukin-1 Beta (IL-1β), Tumor Necrosis Factor Alpha (TNF-α), and Interleukin-6 (IL-6) in Serum During Two Types of Exercise

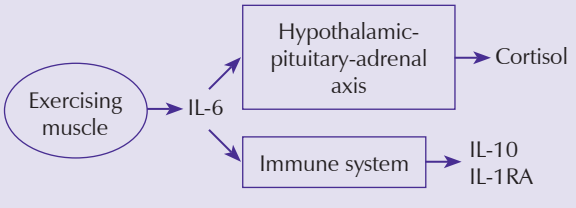
2004). Thus, the observed increase in blood IL-6 levels in CTRF and cardiovascular disease may reflect persistent IL-1β and TNF-α production on a local level that, in turn, triggers the systemic production of IL-6. IL-6 mediates its own anti-inflammatory effects by stimulating both the hypothalamic-pituitary-adrenal (HPA) axis and the immune system, the end result of which is the increased production of several molecules with anti-inflammatory properties, namely growth hormone, cortisol, interleukin-10 (IL-10), and interleukin-1 receptor agonist (IL-1RA) (see Figure 3).

Hypothalamic-Pituitary-Adrenal Axis

Activation of the HPA axis occurs following a stressor, such as high-intensity exercise. Cortisol is a marker of HPA axis activation. At the start of exercise, serum cortisol rises rapidly and peaks just after exercise has stopped (Paiva, Deodhar, Jones, & Bennett, 2002). Within an hour of exercise, serum cortisol levels return to baseline. Thus, the pattern of cortisol secretion during exercise parallels that of IL-6. This observation led to the idea that circulating IL-6 stimulates cortisol release or vice versa. Studies in which IL-6 was infused into healthy, resting adults demonstrated that the former is likely the case. IL-6 infusion triggers the production and release of cortisol from the adrenal cortex, leading to its accumulation in the circulation (Steensberg, Fischer, Keller, Moller, & Pedersen, 2003). Cortisol is believed to exert its anti-inflammatory effects by increasing the production of the anti-inflammatory cytokines IL-1RA and IL-10 (Barber et al., 1995; Dandona, Aljada, Garg, & Mohanty, 1999).

The Immune System

IL-6 infusion in healthy individuals increases serum levels of IL-1RA, which competes with IL-1β for binding to the IL-1β receptor, therefore blocking the activity of IL-1β (Steensberg et al., 2003). Although the source of IL-1RA following IL-6 infusion is unclear, primary sources of this cytokine during infection are monocytes and macrophages. IL-6 also induces the production of IL-10 (Steensberg et al., 2003). IL-10 is another cytokine with potent anti-inflammatory properties (de Waal Malefyt, Abrams, Bennett, Figdor, & de Vries, 1991). It is produced by several types of immune cells, including specific T helper cell lymphocytes, monocytes, and B cells. IL-10 blocks the synthesis of several cytokines, including IL-1β, TNF-α, and IL-6 (Thomassen, Divis, & Fisher, 1996), and its ability to reduce the synthesis of these cytokines likely explains its ability to protect mice from a lethal dose of endotoxin in a mouse model of septic shock (Gerard et al., 1993). Not surprisingly, IL-10–deficient mice display an exaggerated TNF-α response to infection (Holscher et al., 2000). Taken together, substantial evidence suggests an anti-inflammatory role for IL-6 that balances the activity of IL-1β and TNF-α to attain homeostasis.



Note. Interleukin-6 (IL-6) is released from exercising muscle into the circulation, resulting in an increase in blood levels of this cytokine. Circulating IL-6 interacts with the hypothalamic-pituitary-adrenal axis to stimulate the release of growth hormone and cortisol and with the immune system to stimulate the production of interleukin-10 (IL-10) and interleukin-1 receptor agonist (IL-1RA).

Figure 3. Anti-Inflammatory Cascade

Conclusions and Future Research

Compelling evidence exists that proinflammatory cytokines such as IL-1β and TNF-α play a role in the development of CTRF. Exercise is beneficial in the management of CTRF, yet why is unclear. The ability of exercise to decrease the production or activity of fatigue-causing cytokines may be one mechanism underlying the observed beneficial effects of exercise on CTRF. Although strong evidence exists that different cancer treatments can increase the production of inflammatory cytokines, few clinical studies have demonstrated a clear relationship between inflammatory cytokines and CTRF. Emerging longitudinal studies aimed at examining the relationship between changes in blood levels of inflammatory cytokines and changes in fatigue levels may help to support a role for an immunologic basis to CTRF. Such studies also could provide a platform on which to determine whether the anti-inflammatory effects of exercise underlie its beneficial effects on CTRF. Findings from such studies may help further refine exercise interventions for maximal symptom control in patients with cancer and may aid in the identification of biologic factors that mediate the beneficial effects of exercise on CTRF. Importantly, identifying the molecular determinants could lead to new treatment strategies for fatigued patients with cancer who are unable to participate in an exercise program.

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