

Therapeutic Properties of Aerobic Training After a Cancer Diagnosis: More Than a One-Trick Pony?

Lee W. Jones, Mark W. Dewhirst

Correspondence to: Lee W. Jones, PhD, Memorial Sloan-Kettering Cancer Center, Department of Cardiology, New York, NY, 10065 (e-mail: jonesl3@mskcc.org).

Until recently there was a prevailing dogma that cancer patients may be unable to safely participate in, benefit from, or tolerate structured exercise training/rehabilitation. Nevertheless, two factors pointed to the potential benefit of exercise in cancer patients: 1) the robust efficacy of exercise to favorably impact multiple physiological and psychosocial outcomes in noncancer clinical populations with similar symptomatology and limitations to exercise and 2) the emergence and importance of cancer survivorship. These factors provided the ideal platform and rationale to launch initial studies testing the safety, tolerability, and efficacy of exercise in patients with cancer (1). The past decade has witnessed a relative explosion in research, as well as clinical interest, in the application of exercise, as well as more general physical activity, in the context of cancer control efforts (1).

The vast majority of prior and ongoing exercise-oncology research efforts have focused on the efficacy of exercise to attenuate and/or improve symptom control outcomes (1). However, in recent years a new branch of this field has emerged investigating whether exercise modulates tumor-specific outcomes (eg, biology, progression, modification of therapeutic response) (2). This exciting subdiscipline germinated after the emergence of epidemiological studies that indicated, in general, a statistically significant inverse relationship between physical activity and cancer-specific mortality or recurrence/progression after a diagnosis of breast, colorectal, or prostate cancer (2,3). Not unexpectedly, these provocative findings have, in turn, stimulated initial interest from basic and translational scientists to establish whether exercise directly impacts tumor progression and growth kinetics. Although no doubt important, these endpoints do not capture the intricate and subtle alterations in the highly complex and integrated pathways that govern tumor cell behavior or the tumor microenvironment.

The tumor microenvironment is a major contributor to tumor progression and treatment failure in solid cancers. Solid tumors have an abnormal vascular system that impairs effective oxygen and drug transport (4,5). The resultant hypoxia and associated byproducts, such as lactate (6,7), induce resistance to locoregional and systemic therapies (4,8), as well as promotion of metastasis (9,10). Further, stromal cells, such as macrophages (11) and fibroblasts (12) also contribute to tumor progression. Intriguingly, aerobic exercise training exerts multiple physiologic provascular/angiogenic effects, both in the systemic host vasculature and regionally in heart and skeletal muscle, in patients with ischemic disease (13–18). As such, if exercise can significantly modulate vascular function throughout the cardiovascular system, it appears biologically plausible that it could be a promising strategy to modulate solid tumor physiology.

In this issue of the Journal, McCullough and colleagues (19) directly investigate this notion by examining the effects of acute aerobic exercise on markers of tumor physiology/vascularity in an orthotopic rat model of prostate cancer. Prostate tumor blood flow, vascular resistance, patent vessel number, and hypoxia were evaluated *in vivo* in conscious rats at rest and during a 5-minute acute bout of forced aerobic exercise (performed on a motorized treadmill; the intensity of exercise was not described). Intriguingly, measures of tumor blood flow and microvessel density increased during exercise; these effects occurred in conjunction with a concomitant decrease in tumor hypoxia. The findings of McCullough et al. extend previous work that has demonstrated favorable improvements in intratumoral perfusion/vascularization and hypoxia in orthotopic mouse models of breast and prostate cancer after exposure to chronic exercise (20,21). Taken together, these initial findings indicate that both acute and chronic exercise promote a shift toward a more “normalized” tumor microenvironment (possibly through upregulation of regional and local physiologic angiogenesis) (Figure 1).

Such findings may have important clinical implications in the oncology setting. First, the abnormal tumor vasculature and resulting hypoxia are major drivers of all steps of the metastatic cascade (22). Therefore, exercise-induced favorable alterations of the tumor microenvironment may be an important mechanism underpinning the inverse relationship between physical activity and cancer-specific outcomes (2,3). In recent work, our group found that chronic exercise-induced improvements in tumor physiology occurred in conjunction with reductions in distant metastasis and primary tumor volume in orthotopic models of prostate (23) and breast cancer (24), respectively. As a corollary, it will be important to also evaluate the effects of exercise on modulation of distant organ niches that may be harboring quiescent disseminated tumor cells. The inverse relationship between exercise and disease outcomes reflects, for the most part, exercise exposure after primary therapy, indicating alteration of the final steps in the metastatic cascade (ie, extravasation and metastatic colonization) (25).

Second, the tumor microenvironment poses a formidable barrier to the efficacy of systemic and locoregional anticancer therapies (26), suggesting that exercise, through its “normalizing” properties, may act as a therapeutic sensitizer. In initial work, we found that the combination of exercise and chemotherapy (cyclophosphamide) was associated with statistically significantly prolonged tumor growth delay compared with chemotherapy alone in a mouse model of murine breast cancer

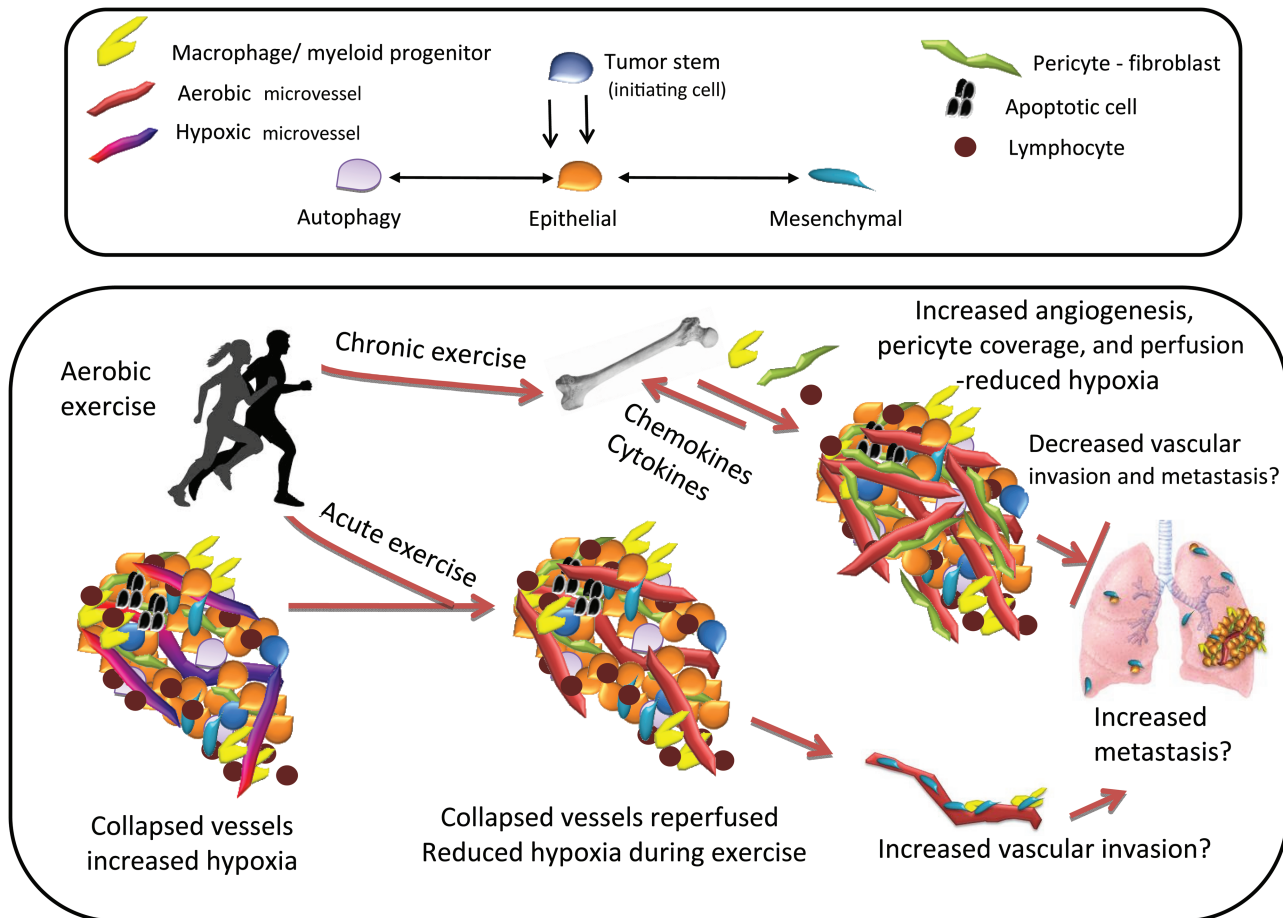


Figure 1. Comparison of acute vs chronic effects of aerobic exercise on the tumor microenvironment. Acute exercise reperfuses collapsed vessels in tumor, leading to increased perfusion and reduced hypoxia during exercise. In response to acute exercise, skeletal muscle cells secrete several cytokines (known as myokines, including vascular endothelial growth factor, tumor necrosis factor alpha, interleukin 6, etc) into the peripheral circulation that, in a paracrine-like manner, trigger responses in nonmuscle tissues (eg, the bone marrow) to induce a proangiogenic host phenotype. This phenotype also may recruit tumor inhibitory factors to the normoxic tumor microenvironment that, through the production of nitric oxide (NO) and accumulation of hypoxia inducible factor-1

alpha, enhance immunoregulatory function and apoptosis. Chronic exercise causes a sustained production and bioavailability of NO, leading to global cardiovascular physiologic adaptations, as well as upregulation of endogenous antioxidant machinery, which together reduce circulating levels of proinflammatory cytokines. This, in turn, alters ligand availability in the tumor microenvironment, leading to an increase in angiogenesis and vascular maturity (augmentation of pericyte coverage). The consequent increase in perfusion reduces hypoxia, resulting in a less aggressive phenotype (decreased invasion and metastasis). Currently, the effects of aerobic exercise on other cells in the microenvironment, such as macrophages, lymphocytes, and fibroblasts, are unknown.

(L. W. Jones and M. W. Dewhirst, personal communication). In a related exploratory clinical trial, we found that supervised exercise training in combination with neoadjuvant doxorubicin-cyclophosphamide chemotherapy, compared with neoadjuvant doxorubicin-cyclophosphamide chemotherapy only, improved host cardiovascular function, which occurred in conjunction with alterations in circulating levels of select angiogenic factors and tumor gene expression in women with operable breast cancer (27). Although the biological and clinical implications remain to be determined, this work also provides clear initial evidence that exercise can modulate host and tumor-related pathways implicated in progression and therapeutic efficacy.

As the result of careful and well-conducted research, exercise oncology has started to gain a foothold as a legitimate field of oncology research and practice. There is little doubt that ongoing work will continue to demonstrate the efficacy of exercise as an effective symptom management therapy in numerous

oncology scenarios. However, the timely work of McCullough et al. (19), as well as that of others (3), is beginning to challenge the current perception of exercise as a “soft” intervention that “cannot hurt.” The potential promise of exercise to modulate tumor physiology/microenvironment is exciting, but much more work is required. Exercise is a pleiotropic intervention that induces a plethora of gene expression changes in multiple organ systems, leading to fundamental changes in the systemic host milieu (28). On the other hand, solid tumors exhibit considerable heterogeneity (29). As such, mechanistically driven preclinical investigations in conjunction with biomarker-driven clinical studies will be required to unravel the complex and dynamic relationship between exercise, the host-tumor interaction, and response to therapy. Although the results of future studies are eagerly anticipated, it is clear that, when correctly prescribed, exercise possesses potent pleiotropic drug-like effects that can dramatically alter host and tumor phenotypes. If correctly tested

and harnessed, exercise therapy may prove to be far more than a one-trick pony in cancer control.

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Affiliation of authors: Memorial Sloan-Kettering Cancer Center, Department of Cardiology, New York, NY (LWJ); Duke Cancer Institute, Duke University Medical Center, Durham, NC (MWD).