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Commentary

Exercising through cancer: Physical activity as medicine for cancer care

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Exercise holds significant potential as an adjunct therapy in cancer, extending beyond quality-of-life improvements to influencing tumor progression, treatment response, and survival. Its clinical integration remains limited by variability in models, heterogenous interventions, and the absence of predictive biomarkers. As the field progresses, identifying molecular effectors of exercise, in addition to emphasizing practical clinical translation, is essential. This commentary highlights the anti-tumor effects of exercise and evaluates how exercise can advance from supportive care to a targeted, evidence-based component of cancer treatment.

Introduction

Approximately 40% of people in North America will be diagnosed with cancer in their lifetime. Epidemiological and clinical studies demonstrate that exercise reduces cancer incidence, improves quality of life (QoL), and mitigates treatment-related side effects such as fatigue and psychological distress. Despite the established benefits, only 30%–40% of cancer patients meet the recommended 150 minutes of moderate-intensity exercise per week set by the American College of Sports Medicine. Similarly, cancer patients spend more time sedentary, which is associated with decreased survival and poorer treatment outcomes. Historically, exercise has been discouraged in cancer care due to concerns around patient fragility, a perception that it induces fatigue, and a lack of mechanistic understanding. In recent years, however, research has highlighted its therapeutic potential, leading to the integration of exercise into oncology guidelines. Numerous randomized controlled trials and preclinical studies suggest that exercise not only enhances treatment tolerance and completion rates but may also exert direct anti-tumor effects. Proposed mechanisms include immune activation, metabolic reprogramming, and myokine secretion, which function interdependently to restore homeostatic control (Figure 1). Despite this, translating exercise into routine cancer treatment remains challenging, primarily due to the complexity of modeling exercise in preclinical settings. Variation in tumor models, mouse strains, housing conditions, and exercise protocols limits reproducibility and restricts progress in clinical research. These issues are particularly prevalent in exercise oncology, where interventions intersect with multiple physiological systems and environmental confounders. Moreover, while exercise is a promising adjunct to therapy, its integration into standard care is complicated by the inherent variability of lifestyle interventions. Unlike traditional pharmacological approaches, exercise is difficult to standardize across patients. This highlights a need not only for personalized exercise prescriptions but also for the identification of molecular mediators of exercise that may be targeted pharmacologically. In this commentary, we explore the emerging mechanistic basis for exercise in oncology, with a focus on its anti-tumor effects and the challenges of modeling, translating, and personalizing these interventions.

Anti-tumorigenic effects of exercise

Immune

Tumor cells exploit immunosuppressive pathways to evade detection, whereas physical activity enhances anti-tumor immunity. Exercise mobilizes and activates cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, increasing their recruitment to the tumor microenvironment. This enhanced immune surveillance has been consistently observed across preclinical models and is considered a central mechanism underpinning the anti-tumor effects of exercise. In models of pancreatic cancer, 3 weeks of low-intensity treadmill running was sufficient to reduce tumor burden by up to 30% by enhancing the mobilization and infiltration of $CD8^+$ T cells.[1] Additionally, voluntary wheel running suppresses tumor growth in multiple mouse models via infiltration of NK cells, highlighting the mechanistic importance of exercise-induced immune signaling.[2]

Exercise-induced improvements in immune surveillance are similarly linked to increased circulation of immune cells. Physical activity promotes the mobilization of various immune cells, including NK cells, CTLs, and dendritic cells, from peripheral tissues into the bloodstream, enhancing their ability to patrol the body and detect cancer cells. The increased circulation is facilitated by the exercise-induced release of chemokines such as CXCL9 and CXCL11 on immune cells and tumor cells. These chemokines guide immune cells to sites of inflammation such as tumors by binding to the CXCR3 receptor, inducing an anti-tumor response.[3]

Exercise also alters the myeloid compartment, primarily by shifting tumor-associated macrophages (TAMs) from an immunosuppressive M2-like state to a more inflammatory antigen-presenting state. Although TAMs are heterogenous and often display a mixed M1/M2 gene signature, this skewing improves antigen presentation and supports CTL priming, providing another pathway through which exercise improves immune surveillance.

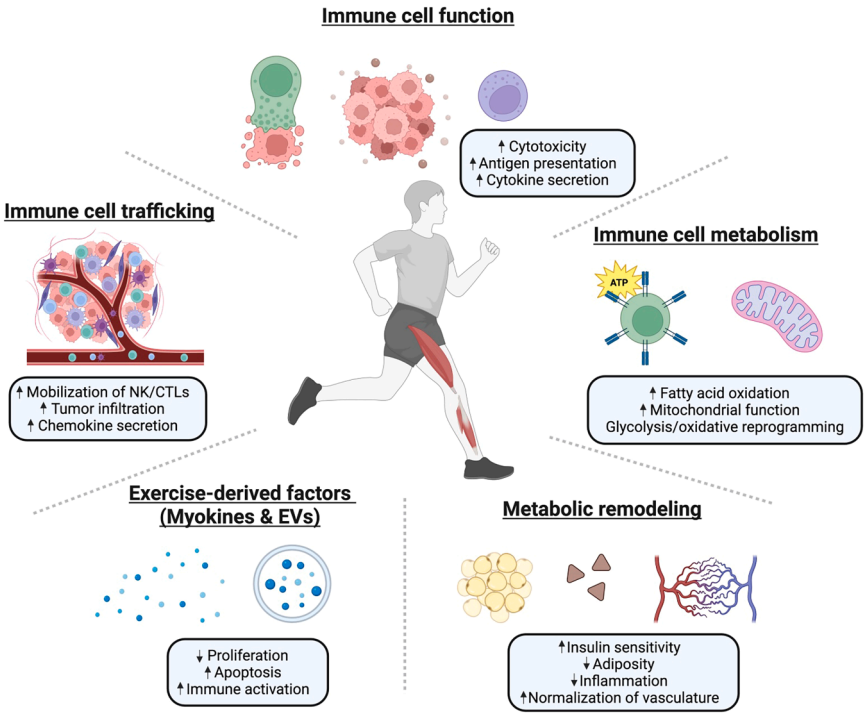

Figure 1. Anti-tumorigenic effects of exercise

Exercise induces a range of systemic and tissue-specific effects that collectively influence tumor progression. Five major categories of effects are illustrated. Immune modulation includes both functional reprogramming (enhanced cytotoxicity, antigen presentation, and cytokine production) and trafficking changes (mobilization and infiltration of effector cells). Immune cell metabolic reprogramming is characterized by increased fatty acid oxidation, enhanced mitochondrial function, and shifts in glycolysis and oxidative metabolism. Exercise-derived signals such as myokines and extracellular vesicles (EVs) directly reduce tumor cell proliferation, promote apoptosis, decrease epithelial-to-mesenchymal transition, and alter immune activity. Exercise-induced metabolic remodeling encompasses improved insulin sensitivity, reduced adiposity and inflammation, and normalization of tumor vasculature. Together, these interdependent adaptations highlight the multifaceted anti-tumor effects of physical activity.

The metabolic fitness of immune cells can be influenced by physical activity, which is increasingly recognized as a key determinant of anti-tumor function. CTLs and NK cells rely on glycolysis to support their proliferation and cytotoxic activity, while memory T cells preferentially rely on oxidative phosphorylation and fatty acid oxidation to maintain long-term tumor control. Exercise training promotes a metabolic profile that supports improved mitochondrial function, glucose uptake, and fatty acid oxidation, believed to enhance the durability and effectiveness of immune responses.

More recently, the gut microbiome has emerged as a juncture of exercise-induced immunity. Beyond its role in metabolite production, the microbiome regulates both innate and adaptive immunity and influences inflammatory cytokine production. Exercise-induced changes in microbial diversity and metabolite profiles serve as upstream regulators of immune engagement in the tumor microenvironment. Recent work has refined this understanding by identifying microbiota-dependent immune responses. A study demonstrated that the beneficial effects of exercise on tumor control and response to immunotherapy were mediated by increased formate production in the gut microbiome.[4] Formate, a one-carbon metabolite usually associated with nucleotide synthesis and tumor growth, has emerged as an unexpected microbiota-derived signal that enhances $CD8^+$ T cell-mediated anti-tumor immunity. Future endeavors to decipher the extent to which the exercise-microbiome-immune axis mediates metabolic health will prove valuable for further elucidating the biology of exercise-associated tumor control.

Metabolic

Altered cellular metabolism is a hallmark of cancer, with tumor cells often relying on aerobic glycolysis (Warburg effect) to support rapid proliferation. Oncogenic drivers such as PI3K and MYC enhance glucose uptake and glycolytic flux, fueling tumor growth and biosynthesis. Exercise can counteract these metabolic adaptations through multiple mechanisms. Aerobic activity downregulates tumor PI3K signaling and activates AMP activated protein kinase (AMPK), a key metabolic sensor that suppresses mTOR and HIF-1 activity, thereby reducing the expression of glycolytic enzymes and glucose transporters. Aerobic training also improves whole-body insulin sensitivity and lowers circulating glucose and insulin levels. These changes may limit glucose availability in the tumor microenvironment, particularly in tumors that rely heavily on aerobic glycolysis. In addition, lower insulin and IGF-1 signaling may reduce growth-promoting signals in insulin-sensitive cancers, such as certain subsets of breast and colorectal cancer.

Exercise further affects oxygen delivery and tumor vasculature, supporting anti-tumor immunity. Preclinical studies have demonstrated that aerobic exercise can remodel the tumor microenvironment by normalizing tumor vasculature and abrogating hypoxic conditions.[5] Specifically, a two-week treadmill running intervention reduced melanoma growth by inhibiting ERK5 S496 phosphorylation in TAMs, an effect that was mimicked by mutating serine to alanine at this site, synthetically preventing phosphorylation.

Acute activation of adrenergic signaling during exercise triggers surges in catecholamines such as epinephrine and norepinephrine. These activate β2-adrenergic receptors (β2-ARs) on a wide range of cells, including immune cells, endothelial cells, and tumor cells. While chronic activation of β2-ARs under psychological stress promotes tumor growth, the intermittent, acute activation induced by exercise appears to have opposing consequences. Exercise-mediated β2-AR activation can transiently modulate glucose and lipid metabolism, enhance blood flow, and mobilize immune cells into circulation. However, the net impact of β2-AR signaling likely depends on tissue context, tumor type, and the duration and frequency of activation.

Additionally, reductions in adiposity induced by exercise may attenuate tumor-promoting signals and modify the

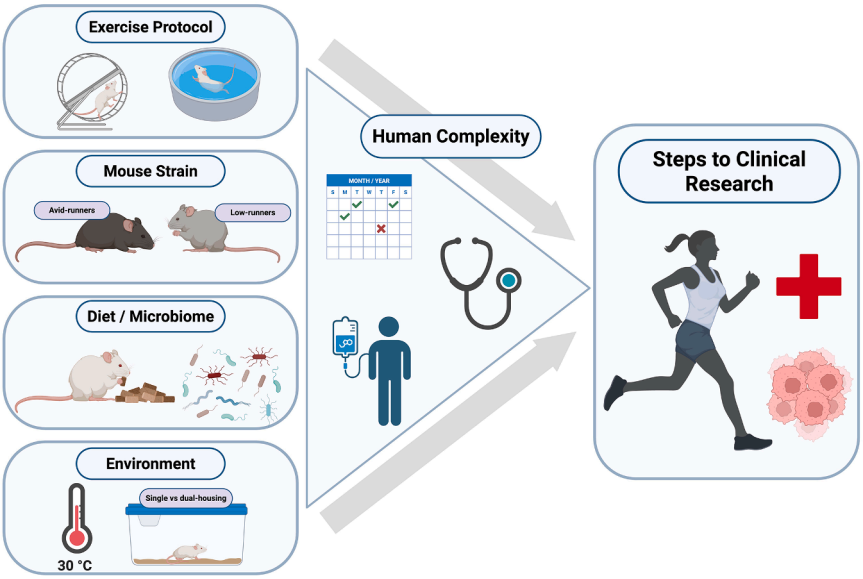

Figure 2. Translational considerations for exercise oncology research
Preclinical studies are influenced by multiple experimental variables, including exercise protocol, mouse strain (and their proclivity to exercise), diet and microbiome composition, and environmental conditions. These factors collectively shape outcomes but only partially capture the heterogeneity of human populations. Translation into clinical research requires accounting for human complexity, including comorbidities, patient condition, and variability in adherence to exercise interventions.

metabolism of immune cells. Obesity is associated with elevated leptin, TNF-α, and estrogen—all linked to cancer progression. In a genetically engineered model of obesity-associated pancreatic cancer, voluntary wheel running suppressed systemic inflammation, improved insulin sensitivity, and delayed tumor development, in part by downregulating pro-inflammatory cytokines in adipose tissue and upregulating IL-15Rα expression.[6] Such adipose remodeling may enhance both metabolic homeostasis and immune-mediated tumor control.

Myokines and EVs

Myokines are a group of cytokines that are produced and released by skeletal muscle during exercise. These molecules can have a variety of effects on the body, including reducing inflammation, improving glucose uptake, and increasing fat metabolism. In recent years, there has been growing interest in the effect of myokines in metabolism-related diseases such as diabetes, dementia, and cancer. These molecules, including IL-6, irisin, decorin, and IL-15, are increasingly implicated in the anti-tumor effects of exercise. Exercise-induced IL-6 acts as an anti-tumor cytokine, mobilizing immune cells and promoting NK cell infiltration into tumors. In the B16 melanoma model, voluntary wheel running reduced tumor burden via an IL-6-noradrenaline axis, highlighting its role in NK cell cytotoxicity.[2] Irisin and decorin have been shown to suppress proliferation and interfere with epithelial-to-mesenchymal transition, reducing metastatic potential. Our laboratory has linked decorin expression in breast cancer with improved survival,[7] while IL-15 enhances CTL activity and maintains metabolic homeostasis.[1]

It is now appreciated that many myokines may be contained within extracellular vesicles (EVs). Initially thought to contain cellular debris, EVs are now considered important carriers of proteins, lipids, and nucleic acids, capable of transferring cargo to other tissues. Recent evidence suggests that exercise-derived EVs represent a means for conferring the protective effects of exercise to tissues via circulation.[8] These EVs contain myokines and microRNAs that can potentially suppress tumor growth by promoting apoptosis, mobilizing immune cells, reprogramming metabolic pathways, normalizing vasculature, and reducing inflammation. A recent study showed that voluntary exercise increased skeletal muscle-derived EVs containing miR-29a-3p.[9] These EVs suppressed type I collagen expression in the tumor extracellular matrix, facilitating $CD8^+$ T cell infiltration and sensitizing tumors to immune checkpoint therapy. These findings highlight EV-mediated reprogramming of the tumor immune microenvironment as a viable mechanism linking exercise to improved cancer outcomes.

Clinically, support for EV research in cancer is growing, as demonstrated by the recent registration of two clinical trials investigating how exercise modulates the concentration and content of EVs in prostate (NCT02730338) and breast cancer (NCT06522971). Despite these promising findings, challenges persist: EV and myokine profiles vary widely depending on exercise modality, intensity, and timing. Moreover, myokine secretion outside of exercise contexts can have opposing effects on tumor biology, complicating translational efforts. A greater mechanistic understanding is required to define optimal exercise protocols and isolate the most therapeutically potent myokines.

Challenges in studying the effects of exercise

Although rodent models have provided unprecedented insight into the antitumorigenic mechanisms of exercise, challenges persist in translating promising results across animal studies and into patient populations (Figure 2). Many effects remain model dependent, and the magnitude of exercise-induced metabolic change likely varies with tumor type, anatomical site, and systemic context.

Syngeneic tumors in immune-competent mice enable readouts of exercise-immune crosstalk but rely on homogeneous cell lines that poorly mimic the heterogeneity of human tumors. Conversely, patient-derived xenografts offer human-relevant insights into certain signaling and metabolic pathways yet are limited in their ability to reflect exercise-induced adaptive immunity. Transgenic models provide disease-relevant progression but show variable exercise responses across background and labs. Mouse strain selection further influences outcomes, with species-specific differences in exercise capacity and behavior affecting tumor growth. For instance, C57BL/6 mice, commonly used in syngeneic and transgenic tumor studies, are avid runners, running up to 10 km per day—distances that far exceed those of other strains.

Exercise modality and dosing significantly shape outcomes and require diligent selection and nuance to avoid the over-generalization of results. Beyond voluntary wheel and conventional treadmill running, swimming and resistance models are alternative interventions that engage distinct physiological systems. Voluntary wheel running preserves naturalistic activity but results in highly variable running distances. Treadmill running allows control of speed and interval structure but often involves aversive stimuli such as electric shocks, which can induce stress and confound physiological adaptations, as does swimming. Resistance models such as the hang-test or ladder climb capture anabolic adaptations but are subject to high variability. Moreover, discrepancies in exercise intensity—ranging from high-intensity interval training (HIIT) to low-intensity to exhaustive protocols—influence distinct immune-metabolic pathways, making it difficult to determine optimal exercise prescriptions for cancer patients. As steps to clinical translation are dependent on observing a dose response, preclinical interventions should be constructed using FITT principles: frequency, intensity, time, and type.

Beyond exercise parameters, environmental factors can impact exercise outcomes. Mice are inherently social animals, and single housing, which is often required for voluntary wheel monitoring, is associated with chronic stress that can alter exercise response.[7] Standard laboratory temperatures (~21°C) fall below the thermoneutral zone of mice (~30°C), leading to chronic cold stress and metabolic adaptations that influence both exercise responses and tumor biology.[10] Furthermore, circadian timing of exercise, diet (macronutrient composition and whether diets are matched for energy intake), and the microbiome (facility variation) warrant consideration given their capacity to modulate both exercise adaptations and anti-tumor immunity. The presence of such confounding environmental considerations reduces the ability to model clinically relevant homeostatic mechanisms; thus, mitigating these factors will reduce barriers to translation.

Exercise-associated benefits for QoL in cancer patients

For many cancer patients, involuntary weight loss is a significant physical burden, which often predicts poor prognosis. Cancer cachexia is a multifactorial syndrome characterized by systemic inflammation and persistent loss of skeletal muscle and adipose tissue. Present in up to 80% of patients with advanced malignancies, particularly pancreatic, lung, and gastrointestinal cancers, cachexia contributes to diminished treatment tolerance and reduced QoL. Distinct from starvation, cachexia persists despite adequate nutritional intake, reflecting dysregulation of metabolic control. Nutritional support alone is insufficient to reverse cachexia, emphasizing the need for multimodal interventions. Exercise has emerged as a unique modality capable of mitigating cachexia through coordinated effects on inflammatory signaling and maintenance of muscle mass.

Systemic inflammation is a hallmark of cancer cachexia that is driven by an interplay of tumor-derived factors, host immune responses, and metabolic dysregulation. Cytokines central to the pathogenesis of cancer cachexia such as TNF-α, IL-6, IL-1β, and IFN-γ drive catabolic pathways in skeletal muscle, particularly the ubiquitin-proteasome system and autophagy. Regular exercise produces an anti-inflammatory response, while decreasing basal circulating levels of TNF-α and IL-6, tempering chronic inflammation and abrogating catabolic effects.[6] Paradoxically, exercise induces the acute secretion of IL-6 from skeletal muscle,[2] which, in turn, stimulates the production of anti-inflammatory cytokines like IL-10 and soluble receptors for TNF-α. This "cytokine crosstalk" results in transient anti-inflammatory responses that mitigate the chronic inflammation in cachexia.

Beyond cachexia, regular exercise improves cardiorespiratory fitness and muscle function; mitigates chemotherapy-associated side effects such as fatigue, nausea, and cognitive decline; and enhances treatment adherence in early-stage cancer. As a neoadjuvant intervention, exercise during the preoperative window has shown promise in maintaining physical function and reducing postoperative complications, particularly in gastrointestinal and breast cancer. This prehabilitative approach may not, however, be feasible in aggressive cancers requiring immediate treatment.

In the context of metastatic and palliative care, the role of exercise is primarily focused on safe application, given the limited potential for impacting disease progression. The PREFERABLE-EFFECT trial found that a supervised, structured, and personalized exercise intervention is well tolerated and improves the QoL in patients with advanced breast cancer.[11] These results suggest that exercise can safely be incorporated into a patient's cancer treatment and provide further evidence of the utility of exercise in cancer treatment across all stages of disease progression.

Clinical integration of exercise into cancer care

Twenty years have passed since the first report that moderate levels of physical activity improved survival rates in women with breast cancer.[12] Long-term prospective studies have reinforced the benefits of exercise, yet the integration of exercise in cancer treatment remains limited.[13]

Barriers to integration are multifaceted. The costs for exercise programs are typically worn by cancer patients, as reimbursement is rarely provided for either supervised or unsupervised exercise interventions. Adherence is limited by the physical condition of the patient and socioeconomic restraints, and comorbidities and previous history of exercising further complicate implementation (Figure 2). Do the patients want to exercise? Are they capable of exercising at all? Given these widespread barriers to implementation, these are necessary considerations for clinical research. While current evidence supports implementation where feasible, broader adoption will depend on larger trials powered for tumor endpoints, in addition to pragmatic implementation studies addressing the inherent human complexity of exercise interventions in oncology.

The current landscape of exercise oncology is shifting toward measuring the efficacy of exercise directly on survival outcomes. Recently completed, one of the largest phase 3 clinical trials, the CHALLENGE trial, enrolled over 800 patients with high-risk colon cancer since 2009.[14] The CHALLENGE trial is one of the very few trials to investigate the long-term benefits of exercise on

cancer-specific mortality across such a large and diverse patient population. The 3-year exercise intervention reduced cancer recurrence by 28% and risk of death by 37% following tumor resection and adjuvant chemotherapy.

There is no set prescription for exercise in cancer treatment. Current therapies including chemotherapy, radiotherapy, and immunotherapy are also adapted based on a patient's individual health. Less is known about how exercise can be prescribed as a specific regimen in a similar manner to conventional therapies. Personalized exercise interventions offer a tailored approach that accounts for the unique needs and conditions of each patient, taking into consideration the frequency, intensity, and duration of exercise. Factors such as a patient's baseline fitness level, type and stage of cancer, and treatment history all influence how they might respond to a given exercise protocol. By adjusting for treatment toxicity and disease progression and tailoring programs to individual fitness levels, these interventions can help manage side effects, improve QoL, and potentially enhance survival.

The future of exercise in oncology

Despite the clear biological rationale for exercise as an adjunct cancer therapy, it remains a vastly underutilized tool in oncology. Its benefits extend beyond symptom management, with emerging evidence suggesting that exercise can influence tumor biology, treatment efficacy, and survival. The field, however, still lacks sufficient mechanistic understanding and precision required to incorporate exercise into mainstream practice.

At the clinical level, the lack of biomarkers to stratify patients and track physiological response remains a major bottleneck. Exercise oncology has largely relied on QoL scores and surrogate fitness metrics, but if exercise is to be treated as a legitimate therapeutic modality, it must be studied with the same rigor as other existing and emerging therapies. This requires establishing exercise guidelines, understanding dose-response dynamics and identifying the patient populations most likely to benefit. Recent advances in multi-omic profiling—including data from large-scale initiatives like MoTrPAC[15]—offer a roadmap for identifying specific molecular effectors of exercise and could enable a biomarker-driven approach to exercise prescription. Efforts to personalize exercise regimens based on genetic, metabolic, and tumor-specific factors may unlock its full therapeutic potential. Such approaches would allow for dynamic adjustment of exercise intensity, duration, and frequency to balance safety and efficacy, particularly for older or advanced-stage patients where standard protocols may not be feasible.

Beyond traditional exercise paradigms, "exercise mimetics" are emerging as promising adjuncts. Molecules that activate exercise-sensitive pathways, such as IC7Fc (a designer IL-6/CNTF chimeric cytokine) or ponsegromab (GDF-15 antibody), demonstrate the potential to recapitulate aspects of exercise biology in patients unable to tolerate physical activity. While these interventions will not fully replicate the systemic benefits of exercise, they highlight the feasibility of targeting discrete molecular mediators of exercise for therapeutic gain.

As the field of exercise oncology continues to emerge, it is essential that preclinical and clinical studies are designed appropriately and shift toward an integrated, precision-based model in which exercise is prescribed not as a one-size-fits-all lifestyle intervention but as a targeted therapy.

DECLARATION OF INTERESTS

M.A.F. is a co-inventor of IC7Fc and holds patents for this molecule (US 60/920,822; WO/2008/119110 A1). He is a founder and shareholder of Celesta Therapeutics and is on the scientific advisory board of Gallant Bio.

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