



Beyond the treadmill: Exercise oncology as a platform for translational advance

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Abstract

Regular aerobic exercise is associated with increased survival for patients suffering from solid tumor cancers. In the last decade, pre-clinical exercise oncology studies have begun to explore the mechanisms governing the protective effects of exercise, leading to the translation of exercise-based regimens into the clinic. However, many patients with intractable solid tumors or those diagnosed at a late stage may be physically unable to partake in exercise-based regimens, or lack access to them. In this perspective piece, authors argue that the value of pre-clinical exercise oncology work is not limited to direct translation, but should be considered as an additional means of discovery for novel anti-tumor mechanisms. When exercise-based pre-clinical work is considered as a discovery engine, mechanisms identified at the intersection of exercise physiology and tumor biology can be autonomously evaluated for their clinical potential, independent of the exercise intervention.

Keywords: Exercise oncology, cancer immunotherapy, metabolomics, gut microbiome, myokines, translational oncology

1. Introduction

A growing body of clinical and epidemiologic evidence suggests exercise improves quality of life and overall survival for cancer patients^[1,2]. Pre-clinical studies have found exercise is protective against tumor growth in several solid tumor models, invoking anti-tumor mechanisms such as immune modulation, metabolic rewiring, modulation of microbial composition, and vascular remodeling, among others^[3-5]. This body of pre-clinical work has supported the recent translation of many exercise-based regimens into the clinic as adjuvant therapeutic approaches^[6,7]. Unfortunately, patients with advanced cancers are often burdened by profound co-morbidities, cachexia, sarcopenia, and treatment-related toxicities^[8,9]. Expecting such patients to complete a regular or strenuous aerobic exercise regimen may be, for some, unrealistic or unsafe. Herein, we propose that pre-clinical exercise oncology (EO) studies serve not only as justification for the translation of exercise regimens into the clinic, but also as an untapped reservoir of novel anti-tumor mechanisms. These molecular pathways at the intersection of exercise physiology and tumor biology can be independently harnessed to generate creative and potentially non-toxic treatment strategies in difficult-to-treat cancers. Utilizing a case study format, we explore three different mechanistic pre-clinical EO applications to demonstrate how exercise-induced modulation of (i) the metabolome, (ii) the gut microbiome, and (iii) cytokine signaling can lead to the development of innovative therapeutic approaches to cancer treatment, beyond the treadmill.

2. Metabolic Reprogramming and Circulating Exerkines

Bouts of aerobic exercise induce a profound and, in some cases, reproducible shift in systemic metabolites^[10-12]. Several studies have shown that the beneficial effects of exercise are mediated, at least in part, by the release of soluble factors from muscle during exercise, which alter the composition of circulating metabolites, extracellular vesicles, and exosomes^[11,13-15]. For example, blood lactate, acylcarnitine, and branched-chain amino acids rise predictably in circulation with exercise intensity^[12,15,16], and exercise can directly reprogram the proteomic landscape of immune cells in healthy hosts^[17]. Pre-clinical EO studies have begun to examine whether these physiologic perturbations are conserved in the presence of a tumor, and if so, what their potential translational implications are.

In a landmark study, Rundqvist *et al.*^[18] demonstrate this very principle: the metabolic response of host muscle to exercise is



necessary for the observed immunologic rewiring and anti-tumor effects. In murine models of breast, melanoma, and colon cancer, the authors show that exercise induces a significant increase in plasma and splenic lactate levels (in addition to decreases in α -ketoglutarate (α KG), fumarate, and succinate). These metabolic changes were found to directly reprogram cluster of differentiation 8 (CD8) T cells toward a more activated and less exhausted anti-tumor phenotype. The authors show that serial daily administration of L-lactate not only leads to an increase in anti-tumor CD8 T cell infiltration, but also, in the absence of exercise, is sufficient to induce a reduction in tumor growth^[18]. Subsequent pre-clinical studies have further demonstrated that lactate alone can increase the stemness and anti-tumor capacity of CD8 T cells and their responsiveness to checkpoint blockade immunotherapy in several solid tumor models^[19,20].

The work of Rundqvist *et al.*^[18] exemplifies how EO pre-clinical work may allow for the identification of translationally relevant circulating anti-cancer “exerkines”, which can be harnessed into anti-cancer therapies. Administration of exerkines in plasma to harness the benefits of exercise, without needing to undergo exercise itself, has already garnered significant mechanistic support *outside* of the field of oncology. However, within the field of cancer biology, serial metabolite peripheral injection as an adjuvant approach remains largely underexplored. This approach is technologically feasible, as high-throughput multi-omics sequencing techniques are being utilized by large cross-disciplinary study groups like the Molecular Transducers of Physical Activity Consortium (MoTrPAC) to profile the whole-body metabolomic response to exercise in healthy hosts, allowing for more reliable identification of targets^[21]. Horowitz *et al.* demonstrate that direct administration of circulating factors (specifically Gpld1) isolated from the plasma of exercised mice was able to confer many of the neurocognitive and anti-aging benefits of exercise to aged and sedentary mice, without a need for the treadmill^[22]. Studies have also shown that serial lactate injection alone can mimic the exercise-specific metabolic benefits in murine liver and brain^[23,24]. While this work is encouraging, there remains an added layer of complexity in the field of EO, as the metabolic response to exercise, both in the periphery and in the tumor, is highly cancer-type specific. For example, in preclinical pancreatic ductal adenocarcinoma (PDAC) models, lactate has been shown to increase immunosuppressive tumor-associated macrophages (TAMs) and contribute to the lack of response to immunotherapy^[25], while the opposite effect is observed in pre-clinical models of colon adenocarcinoma^[19,20]. For this reason, application of the MoTrPAC approach to a variety of tumor-specific models will be essential to examine how the presence of cancer alters the systemic metabolic milieu and the metabolic response to exercise.

In aggregate, Rundqvist *et al.* identified a single metabolite able to mediate the downstream tumor-reductive and immune-activating benefits of exercise. In-depth multi-omics assessment of circulating factors should be performed in high-fidelity murine models of solid tumors and in human cancer patients undergoing exercise-based interventions to profile the cancer-specific and tumor-type-specific metabolomic responses. Thereafter, bidirectional pre-clinical to translational studies can identify the possible disease-specific circulating mediators of the anti-tumor effects of exercise, and ultimately harness these mediators into possible organically-derived, non-toxic therapeutic approaches to cancer therapy that may synergize with the standard of care.

3. Gut Microbial Rewiring in Response to Exercise and Fecal Microbial Transfer

Over the last decade, the gut (and intra-tumoral) microbiome has emerged as a potent modulator of systemic immunity and, by extension, anti-tumor immune responses^[26,27]. Elegant work has shown that commensal microbial diversity, composition, and particularly the gut-microbial metabolome can mediate the efficacy of checkpoint blockade and dictate clinical response to therapy in patients with advanced solid tumors^[28,29]. In fact, gut microbial phenotype and function correlate with immune checkpoint inhibitor (ICI) response and ICI-related adverse treatment events in melanoma^[30,31]. These phenomena are likely disease specific, as, for example, commensal *Bifidobacterium* is thought to promote anti-tumor immunity in melanoma^[29], while in colorectal cancer *Fusobacterium* species accelerate tumor growth and promote metastases, respectively^[33-35]. Mechanistic work has shown that *Lactobacillus reuteri* (Lr), a common organism in commercially available probiotics, leads to the release of I3A and subsequent AhR signaling activation in CD8 T cells, leading to increased effector and anti-tumor function^[36]. Authors found that oral Lr supplementation alone could induce anti-tumor immunity, reduce tumor growth, and prolong murine survival. This body of work raised the possibility of utilizing fecal microbial transfer (FMT) or supplementation with select oral probiotics (of particular bacterial strains with particular metabolic properties) as a non-invasive adjuvant approach to enhance the efficacy of immunotherapy for solid tumors.

Concurrently, recent exercise physiology studies have demonstrated that regular aerobic exercise can alter intestinal health, digestion, and gut microbiome composition, diversity, and metabolic phenotype^[37-39]. Clinical studies have shown significant differences in the gut microbiome composition of patients with higher levels of physical activity and lower body mass index (BMI)^[40]. The question of whether exercise as a non-invasive intervention can modulate the gut or intra-tumoral microbiome in cancer-bearing hosts, and if so, whether these perturbations can confer anti-tumor benefits, had remained largely underexplored. Phelps *et al.* recently provided compelling mechanistic evidence to this effect. In murine models of melanoma, routine aerobic exercise was found to enhance the efficacy of immune checkpoint inhibition. Authors traced this effect to a rewiring of the metabolic phenotype of indwelling gut microbiota, increasing *pfl* expression, one-carbon metabolism, and their production of formate. Formate, in turn, enhanced the responsiveness of CD8 T cells to ICI therapy through a nuclear factor erythroid 2-related factor 2

(NRF2)-dependent pathway. Critically, the authors identified microbial-derived fecal *pfl* as a potential biomarker of ICI response and serum formate as a biomarker of prolonged survival in human melanoma patients treated with checkpoint blockade^[41]. The work of Phelps *et al.* was the first to identify exercise-induced microbial metabolic rewiring as a means of promoting anti-tumor immunity that may confer increased therapeutic sensitivity in patients.

The work of Phelps *et al.*^[41] opens a conceptually novel framework, whereby patients with advanced cancers who are unable to exercise may undergo FMT from exercised hosts to receive the anti-tumor or immune-activating benefits of exercise, without the need for the treadmill. There is precedent for this concept, as Liu *et al.* elegantly demonstrate that transfer of the microbiome from healthy exercised donor mice who are “exercise responders” (i.e., exercise reduces their metabolic syndrome) is sufficient to reduce insulin resistance in sedentary obese recipients^[42]. This approach is also clinically feasible, as multiple trials are currently evaluating FMT in ICI-refractory solid tumors with minimal safety concerns. Recent trials have even shown that administration of single live bacterial strains (*Clostridium butyricum*) to patients with advanced renal cell carcinoma increased their response to ICI compared to controls^[43-45].

Utilization of in-depth sequencing techniques to profile the microbial composition, diversity, and microbiome-specific metabolome of exercised mice in tumor-bearing hosts could help to identify exercise-associated bacterial signatures or exercise-specific metabolic signatures in bacteria that confer enhanced anti-tumor benefits. Based on these findings, one could envision a host of therapeutic applications for the treatment of patients with solid tumors with significant morbidity who are unable to exercise: (i) autologous FMT (a-FMT)^[46], wherein patients with cancer who are able to undergo regular exercise, perhaps early in the disease course, could then undergo a-FMT, transferring back their “exercised” microbial signature later in the disease course; or (ii) allogeneic FMT from healthy exercised donors into sedentary recipients with cancer prior to initiation of ICI, neoantigen vaccine, or chimeric antigen receptor T-cell (CAR-T)-based regimens in refractory and highly co-morbid solid tumor types like PDAC and glioblastoma, where patients may be unable to exercise from the day of diagnosis.

4. Myokine Signaling and the IL-15 Paradigm

Perhaps the most well-studied downstream physiologic effect of aerobic exercise is modulation of systemic immunity. Studies have shown for decades that exercise can induce a transient but profound mobilization of circulating cytotoxic immune cells (CD8 T cells, natural killer (NK) cells, and B cells) in a phenomenon termed exercise-induced leukocytosis (EIL), which is dependent on sympathetic nervous system tone^[47-49]. Exercise has been well documented to cause the release of specific cytokines from muscle, otherwise called myokines, which themselves promote anatomically specific immune cell activation or immune tolerance, depending on physiologic need^[50]. The most commonly described of these myokines are interleukin (IL)-6, IL-8, IL-10, and IL-15, thought to be responsible for the immunologic reprogramming observed in mobilized immune subsets during exercise^[51-53]. Exercise effects on immunity are complex and are both concentration- and temporally-dependent. For example, extreme exercise to exhaustion such as marathon running can lead to transient and profound immunologic perturbations that may confer an immunosuppressed state^[54,55]. Conversely, the rapid mobilization of cytotoxic immune cells in certain contexts can increase surveillance against infection^[56] and feasibly, as studies have begun to show, against cancer.

Pre-clinical EO studies have since invoked myokine release and EIL not only as physiologic exercise phenomena, but as mechanistic mediators of anti-tumor immunity. In 2016, Pedersen *et al.* found that myokine IL-6 released from skeletal muscle during aerobic exercise can reprogram mobilized NK cells in circulation to a more cytotoxic and anti-tumor phenotype in models of melanoma, reducing tumor growth^[3]. Conversely, in 2022, Kurz *et al.* found that exercise-induced mobilization of CD8 T cells into peripheral blood confers an increased capacity for IL-15 signaling and can mediate anti-tumor immunity and reduction in tumor growth in aggressive models of pancreatic cancer. In this latter work, authors demonstrate that activation of the IL-15 signaling axis is not only necessary to confer the anti-tumor benefits of exercise, but is also sufficient to reduce tumor growth in the absence of exercise. Serial treatment of mice with an IL-15 super-agonist agent mimicked the immunologic effects of aerobic exercise, enhanced mouse survival, and increased sensitivity of tumors to ICI and standard-of-care chemotherapy^[57]. Subsequent work has corroborated that IL-15 activation may hold therapeutic potential in PDAC, demonstrating that the combination of an IL-15 activating complex with CD40 agonism and anti-programmed death-ligand 1 (PDL1) blockade prolonged murine survival, reduced CD8 T cell exhaustion, and prevented orthotopic tumor regrowth^[58].

The work of Pedersen *et al.* and Kurz *et al.* demonstrates that EO studies can be utilized to identify a novel and tumor-type-specific immune signaling axis, targeting of which alone can mimic some of the effects of aerobic exercise and has the potential for use in patient populations for whom exercise may not be feasible. The tumor specificity of the exercise immune response also has great translational implications. While IL-6 is a critical mediator of the exercise-induced anti-tumor immune response in melanoma, there were minimal IL-6/NK cell changes in exercised mice with PDAC^[3,57]. Conversely, IL-15 signaling played a crucial role in the anti-cancer benefits of exercise in PDAC, without any observed response in melanoma. These data suggest that the physiologic response to exercise is altered by the presence of cancer and dictated by a highly specific exercise-to-primary-tumor cross-talk. For this reason, IL-15-based therapeutic approaches may carry more potential in PDAC than melanoma, whereas NK cell-based CARs or NK-activating therapies may benefit patients with melanoma. Exercise oncology studies can therefore not only identify novel

immunologic targets that can be harnessed pharmacologically, but can also help inform the disease-specific translational potential of already existing immune-based therapies.

5. Conclusion/Summary: Pre-Clinical Exercise Oncology as a Discovery Engine

This series of exercise oncology case studies, spanning systemic metabolic rewiring (Figure 1a; top), gut microbial remodeling (Figure 1b; top), and cytokine-directed immune activation (Figure 1c; top), demonstrates that identification of molecular mechanisms that govern exercise-induced tumor protection can have potential as disease-specific pharmacologic or therapeutic approaches, dissociable from exercise itself (Figure 1a,b,c; bottom). The field of EO would benefit from supplementing the focus of pre-clinical work as a means to put patients on the treadmill with the utility of exercise as a discovery engine for therapeutic innovation. Next steps in the field include standardization of pre-clinical exercise models, multi-omics assessment of both pre-clinical and patient samples, and clinical trials that begin to bridge the translational gap. It is important to note that the manifold of physiologic changes associated with aerobic exercise cannot simply be replicated through molecular mimicry or the targeting of specific pathways involved in exercise, no matter how comprehensive. For this reason, this piece is not meant to suggest that exercise based interventions should be replaced in the clinic by the translational applications learned from pre-clinical exercise studies, but rather that they be used to synergize with those findings and maximize possible learning opportunities in the field. Mechanistically grounded extensions of observations made from the study of mice on the treadmill can help to ensure that our most vulnerable patients are not excluded from the anti-cancer benefits of aerobic exercise in the future.

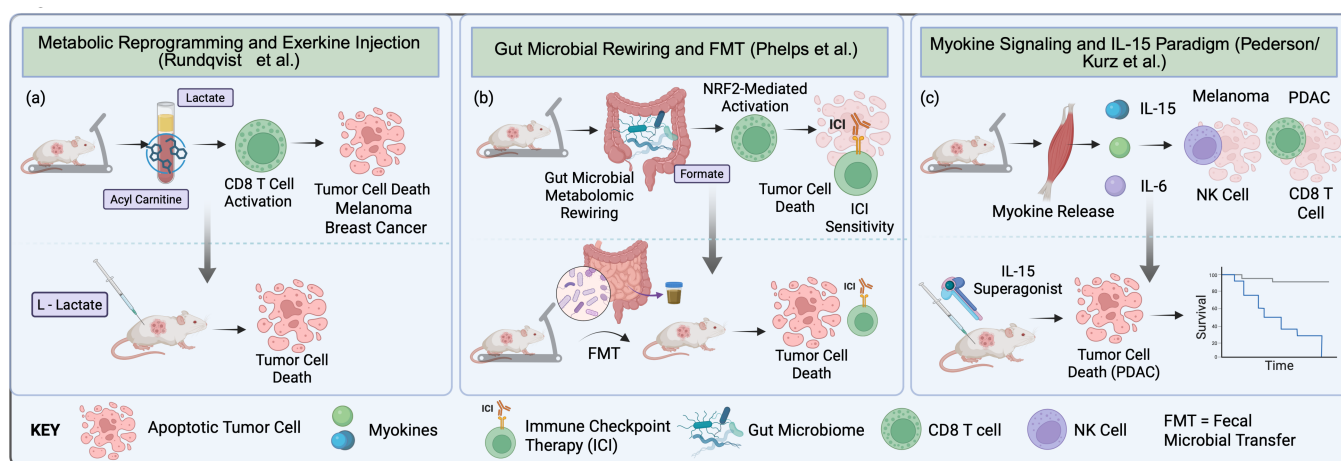


Figure 1. Pre-clinical exercise oncology as a discovery engine: metabolic reprogramming, microbial rewiring, and myokine signaling. In this schematic, pre-clinical mechanistic exercise work (top) is proposed to lead to novel translational advances beyond the treadmill (bottom). (a) Exercise increases circulating levels of specific metabolites, such as lactate, which has been shown to directly activate CD8 T cells, leading to tumor cell death [top]; these data suggest the possibility of serial injection of anti-tumor metabolites (exerkines) like L-lactate to reduce tumor growth [bottom]; (b) Exercise can remodel the phenotype of the gut microbiome, leading to a distinct metabolomic signature (increased microbial formate) that promotes CD8 T cell activation via NRF2, reduced tumor growth, and enhanced responses to cancer immunotherapy (ICI) in pre-clinical melanoma [top]; these data suggest the possibility of utilizing FMT from exercised to non-exercised hosts to promote similar ICI sensitivity and reduced tumor growth [bottom]; (c) Exercise promotes release of myokines (such as IL-6 and IL-15) from muscle, which can reprogram immune cell subsets (NK Cells and CD8 T Cells) and reduce tumor growth (in melanoma and PDAC, respectively) [top]; further data suggest the possibility of using an IL-15 superagonist agent to promote tumor cell death and improve survival in PDAC models, without the need for exercise [bottom]. Created in BioRender. Kurz, E. (2026) <https://BioRender.com/Opiec23>. ICI: immune checkpoint inhibitor; FMT: fecal microbial transfer; CD8: cluster of differentiation 8; NRF2: nuclear factor erythroid 2-related factor 2; IL: interleukin; NK: natural killer; PDAC: pancreatic ductal adenocarcinoma.

Declarations

Authors contribution

Kurz ES, Bar-Sagi D: Conceptualization, investigation, writing-original draft, writing-review & editing.

Conflicts of interest

Dafna Bar-Sagi is an Editorial Board Member of *EXO*. The remaining author declares no conflicts of interest.

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