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Exercise as adjunct therapy in cancer

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Abstract

Data from observational studies indicate that both physical activity as well as exercise (i.e., structured physical activity) is associated with reductions in the risk of recurrence and cancer mortality after a diagnosis of certain forms of cancer. Emerging evidence from pre-clinical studies indicate that physical activity / exercise paradigms regulate intratumoral vascular maturity and perfusion, hypoxia, and metabolism and augments the anti-tumor immune response. Such responses may, in turn, enhance response to standard anticancer treatments. For instance, exercise improves efficacy of chemotherapeutic agents, and there is rationale to believe that it will also improve radiotherapy response. This review overviews the current preclinical as well as clinical evidence supporting exercise modulation of therapeutic response and postulated biological mechanisms underpinning such effects. We also examine the implications for tumor response to radiation, chemotherapy and immunotherapy.

Introduction

Over the past two decades, increased research and clinical attention has focused on the efficacy of exercise therapy as an adjunct strategy following a cancer diagnosis [1, 2]. Randomized trials demonstrate structured exercise therapy is a feasible adjunct strategy associated with significant improvements in symptom-related outcomes including exercise tolerance[3, 4] as well as multiple patient-reported end points such as fatigue, quality of life, and physical functioning both during conventional adjuvant therapy. We have previously reviewed the pre-clinical literature to assess the role of exercise in tumor incidence, progression and metastasis [5]. A critical corollary is whether exercise impacts the antitumor efficacy of cancer treatment. Such a notion is biologically plausible, as emerging evidence suggests exercise modulates several factors inherent in cancer treatment sensitivity, including radiotherapy. Arguably, some of the most relevant are alterations in the tumor

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microenvironment (TME) include tumor hypoxia, perfusion, tumor cell metabolism, and the anti-tumor immune phenotype.

In this review, we outline how exercise-mediated changes in the TME and anti-tumor immune response may influence the radiation response. We further explore the impact of exercise on additional treatment modalities such as chemotherapy and immunotherapy.

Reduction in systemic levels of oxidative stress may play a role in improved neurocognitive function after chemotherapy. Several studies have shown increases in levels of circulating inflammatory markers in women with breast cancer who underwent adjuvant chemotherapy [6, 7]. Changes in systemic levels of several inflammatory markers are associated with reduced neurocognitive performance. Importantly, patients who undergo exercise in conjunction with chemotherapy exhibit reduced levels of inflammatory biomarkers and retain neurocognitive function. However, cancer patients participating in a thrice-weekly exercise program demonstrated reduced blood 8-OhDG levels [8], a significant (41%) increase in systemic antioxidant capacity, and a significant (36%) decrease in protein oxidation; these changes correlated with reduced cancer-related fatigue [9]. It is not known whether the systemic changes in oxidative stress caused by exercise extend to effects on tumor. We previously reported that physical activity improves perfusion and reduces hypoxia in the 4T1 breast tumor model [10]. Not reported was our observation that levels of oxidative stress in the tumor, as depicted by 8-OHDG levels within tumor, were reduced by nearly three-fold in tumors of mice that engaged in physical activity (running wheel) vs. sedentary controls (Figure 1). It is not known is whether changes in oxidative stress within the tumor were a consequence of alteration in systemic levels of oxidative stress or whether they were secondary to local alterations in the tumor microenvironment induced by physical activity. Furthermore, the consequences of reduced oxidative stress associated with exercise on treatment response are not defined. Additionally, in order to fully understand how exercise affects oxidative stress, a more comprehensive set of studies with more in-depth assessment of the oxidative stress environment within the host and the tumor would need to be conducted [11].

1. Exercise regulation of the host milieu

The direct effects of exercise on the respiratory, cardiovascular, and musculoskeletal systems are well-described[12]. In response to repeated bouts of exercise, multiple organ systems adapt, resulting in improved oxygen delivery and utilization, VO_2 max and mitochondrial biogenesis.

These exercise-induced physiologic adaptations (i.e. changes in glucose metabolism, circulating insulin levels, mitochondrial biogenesis, angiogenesis signaling pathways and cytokine release) are not confined to the skeletal muscle. They have broad-reaching systemic implications that affect the overall health of the host. It is now becoming apparent that systemic exercise-induced changes influence growing tumor tissue as well, and have the potential to profoundly impact the tumor microenvironment and treatment response, as will be detailed below.

2. Tumor angiogenesis and vascular function

Solid tumor growth is dependent on angiogenesis, supported by optimized levels of vascular endothelial growth factor (VEGF) and other pro-angiogenic cytokines in the TME. VEGF expression is increased under hypoxic conditions, driven by signaling through the hypoxia-inducible factor-1 (HIF-1) pathway [13]. However, the pressure to create new blood vessels able to serve an ever-evolving mass results in chaotic and immature vessel structure. Consequently, most tumors feature tortuous and leaky vasculature, characterized by shunts, low microvessel density and poor pericyte coverage [14]. Aberrant tumor vasculature causes mismatch between oxygen supply and demand, resulting in pockets of hypoxia. Hypoxic regions are intensified by a decreased microvessel density, which results in regions too far from a vessel to receive adequate oxygen [15]. Finally, poor pericyte coverage is associated with leaky tumor vessels and contributes to invasion and metastasis [16].

Tumor angiogenesis and vascular normalization are targets of anti-tumor therapeutics [17]. “Normalization” of tumor vasculature refers to several steps, including improvement in vascular maturity (reduced permeability, increased pericyte coverage and reduced microvessel diameter), combined with pruning of redundant or non-functional microvessels. The normalization process, by definition, therefore, results in a lowered vascular density. However, efficient normalization increases oxygen and drug delivery because of improvement in the orientation and network structure of the resulting normalized vascular network.

Initial trials with anti-angiogenic agents were promising, but clinical use of anti-angiogenic agents became problematic in many tumor types due to treatment resistance, vascular rarefaction and re-emergence of hypoxia following prolonged use of such agents [18, 19]. Some of the negative effects of angiogenesis inhibitors have been avoided by using lower doses of antiangiogenic agents [18]. This approach prolongs the period of normalization, which could prove beneficial for optimizing drug delivery or enhancing radiotherapy. Nevertheless, alternative approaches to altering tumor vascularity / angiogenesis may have clinical promise – exercise is one such potential strategy.

Vascular changes are perhaps the most well-documented effects of exercise on solid tumor physiology in pre-clinical studies. Several reports have shown that exercise increases tumor VEGF levels [10, 20, 21], vessel density and perfusion [10, 22]. In addition to VEGF, platelet derived growth factor receptor-beta (PDGFRβ) is involved in endothelial cell recruitment during angiogenesis [23]. Interestingly, one report showed that exercise increased tumor VEGF expression occurred in conjunction with a reduction in PDGFRβ expression [10] leading to an overall increase in tumor angiogenesis, which dramatically reduces tumor hypoxia through increased microvessel density and perfusion.

The increased tumor microvessel density [10] and perfusion [22] may have implications for drug delivery and are associated with reduced tumor hypoxia (discussed in more detail below). Importantly, we have also shown that exercise increases HIF-1 expression, which is regulated by oxidative stress [22, 24]. Therefore, the observed differences in microvessel

density and perfusion may reflect how exercise either reduces oxidative stress, or improves the tumors' ability to deal with oxidative stress.

Functional vasculature that can effectively deliver blood, oxygen, and systemic therapies requires mature, long vessels with visible lumens and few non-functional sprouts. Emerging data suggests that exercise may improve vascular function / maturity. Increased sheer stress during exercise results in vascular remodeling, as defined by increased number of visible vessel lumens and longer average vessel length [25]. Exercise-induced shear stress activates the transcription factor, NFAT (nuclear factor of activated T-cells), which in turn increases transcription of thrombospondin 1 (TSP-1), thereby promoting vascular maturity. These changes have important implications for delivery and potential efficacy of systemic anticancer agents. For instance, two studies have demonstrated improved efficacy of chemotherapy in combination with exercise. Our group demonstrated that voluntary running improved response to cyclophosphamide in mice bearing syngeneic mammary tumors [10]. Three doses of cyclophosphamide significantly slowed tumor growth compared in exercising mice compared to sedentary control mice. Similarly, Schadler et al. found that gemcitabine was significantly more efficacious at slowing tumor growth in a mouse pancreatic ductal adenocarcinoma model when administered to mice running at 60%−70% of exercise capacity using a forced exercise paradigm, compared to sedentary mice [25]. This effect was abrogated in thrombospondin-1 knockout mice, suggesting that exercise-mediated vascular normalization is an important mechanism underpinning the exercise – chemotherapy efficacy relationship. Schadler et al. quantified tumor doxorubicin concentrations twenty minutes post-treatment and found that when doxorubicin administration was preceded by two weeks of treadmill running (45 minutes of 12 m/min, 5 days/week) doxorubicin concentrations increased in murine PDAC allografts nearly two-fold [25]. Further, doxorubicin was more efficacious at slowing B16F10 melanoma growth in exercising vs. sedentary mice.

The underlying mechanisms for improved tumor growth delay with the combination of exercise and chemotherapy is likely multifold. First, and perhaps the most logical, is that the increase in functional tumor microvessels increases chemotherapy exposure to a higher portion of tumor cells. Normalization of the tumor vasculature also may promote homogeneous blood flow throughout the tumor, eliminating shunts that leave certain regions unexposed to drug. Using MR perfusion imaging, Betof at al. showed that exercise-mediated increases in uniformity of blood flow [10]. Additionally, by improving vascular maturity, exercise may decrease interstitial fluid pressure (IFP). Decreasing IFP could improve macromolecular and nanoparticle drug transport (>1000MW), because transport of these sized drugs is dominated by the pressure gradient across the vessel wall. The pressure gradient is a consequence of the extent of vascular permeability [26]. Elevated IFP directly impedes large drug and nanoparticle transport from tumor blood vessels into the tumor tissue.

Changes in tumor angiogenesis may influence alternative mechanisms of tumor control, including anti-tumor immunity. Tumors use a variety of mechanisms to diminish T-cell infiltration and recognition, thereby attempting to evade immune surveillance and contributing to decreased anti-tumor immunity [27, 28]. Interleukin-6 (IL6) can overcome this checkpoint, to facilitate T-call trafficking into tumors [28]. Lack of pericyte coverage

facilitates myeloid-derived suppressor cell (MDSC) trafficking [29]. This contributes further to an immune suppressed phenotype within the tumor microenvironment.

Both local and systemic effects of exercise may contribute to enhanced T-cell infiltration into tumors. First, exercise increases circulating levels of IL6, which can promote upregulation of adhesion molecules on tumor vascular endothelium, thereby promoting T-cell trafficking. Further, exercise causes redistribution of NK cells in an epinephrine and IL-6 dependent manner, and these mature effector NK cells have cytotoxic activity against cancer cells in vitro [30, 31]. "Exercise-induced leukocytosis" is the phenomenon by which a single bout of exercise mobilizes vascular, pulmonary, hepatic, and splenic white blood cells into peripheral circulation [32]. A 45–60 minute bout of vigorous exercise increases NK cell concentrations 10-fold and $CD8^+$ T cells approximately 2.5-fold [33]. Dynamic changes in blood pressure, shear force, and epinephrine-mediated stimulation of beta-2-adrenergic receptors on the surface of lymphocytes collaborate to cause leukocyte demargination and circulation [34, 35, 36]. This intensity-dependent mobilization occurs in proportion to the expression of beta-2-adrenergic receptors on lymphocytes, with NK cells and $CD8^+$ T cells responding more strongly than B cells and $CD4^+$ T cells [33, 37, 38].

On a systemic level, immune cells exhibit a characteristic bi-phasic response to exercise, in which acute leukocytosis (during or immediately following exercise treatment) is followed by leukopenia within 1–2 hours after cessation [37, 39, 40]. Stromberg et al. reported that an hour of exercise transiently increased ICAM-1 and VCAM-1 in skeletal muscle vasculature [41], while Santos et al. reported increased neutrophil ICAM-1 and L-selectin expression in marathon runners following the race [42]. Lymphocyte counts generally nadir below baseline and then normalize within 24 hours [37, 39, 40]. This has led to speculation of an "open-window" following vigorous exercise in which the individual is particularly susceptible to infection due to immunosuppression [43]. However, recent evidence force re-evaluation of this hypothesis. In a rodent model, Kruger et al. demonstrated that the leukopenia following exercise reflects a redistribution of T lymphocytes to peripheral tissues (i.e. the lung and Peyer's patches) [36]. This is now known as the acute stress/exercise immune-enhancement hypothesis [44, 45]. It is unclear at this time how these time-dependent systemic changes in circulating immune cells affect local infiltration of the tumor.

3. Tumor hypoxia

Tumor hypoxia is the result of a discrepancy between oxygen supply and demand. Although proliferating tumor cells have high oxygen requirements, immature tumor vasculature and low microvessel density results in hypoxia [46]. Vaupel et al. reviewed 125 clinical studies and determined that tumor tissue generally is poorly oxygenated compared to normal tissue, and that all types of solid tumors include regions with clinically relevant hypoxia (<10 mmHg O_2) [47]. Tumor hypoxia is associated with poor radiotherapy outcome [48] as well as an increased propensity toward metastasis. The impact of hypoxia on prognosis has been reported in multiple trials. For example, a multi-center study stratified head and neck cancer patients based on median pre-treatment tumor oxygen tension (pO2) and fraction of tumors with pO2 of ≤2.5 mmHg ($HP_{2.5}$) and reported significantly worse survival in patients with

"more hypoxic" ($HP_{2.5}$ >19%) tumors compared to those with "less hypoxic" ($HP_{2.5}$ ≤19%) tumors, regardless of treatment approach.

McCullough et al. found that a single bout of aerobic treadmill training increased oxygen delivery three-fold in rat prostate tumors by decreasing vascular resistance and increasing blood flow to the tumor [49]. Wiggins et al. postulated that although exercise redirects blood flow from splanchnic organs to the active skeletal muscles, tumor vessels are uniquely unable to respond to vasoconstrictive signals [49], and therefore benefit from exercise-induced increases in cardiac output [50]. These physiological effects of exercise reduce tumor hypoxia, as has been shown by multiple researchers [10, 49, 51]. Betof et al. reported that voluntary running throughout tumor development reduced the hypoxic fraction by nearly 50%, and McCullough et al. reported that a single bout of treadmill running halved the hypoxic tumor fraction.

Hypoxic cells are 3-fold more resistant to radiation, compared with aerobic cells [52]. Nearly all solid cancers contain some hypoxic cells, and the severity and extent of hypoxia is associated with poor prognosis [47]. A number of different strategies have been attempted to alleviate the impact of hypoxia, including increasing oxygen delivery or reducing oxygen consumption rate. Despite some successes, there is no accepted standard of care for reducing hypoxia [53].

Against this background, several groups have shown that exercise reduces tumor hypoxia [10, 49, 51, 54]. The chronic effects of exercise in reducing hypoxia may make it an attractive means of increasing tumor radiosensitivity. Our group sought to test the hypothesis that exercise would improve the tumor response to radiation, in preclinical murine models [51]. Indeed, in unpublished data from our group mice bearing either 4T1 mammary or MC38 colorectal carcinomas, exercise prior to and during radiation improved tumor response, characterized by slowed tumor growth and delayed metastasis [51]. The addition of voluntary exercise to fractionated radiation treatment increased time to 4T1 tumor volume quintupling from 5.4 days in sedentary/RT mice to 11.6 days in exercising/RT mice. Importantly, we also showed that at the time that RT was applied, the tumor hypoxic fraction averaged 8.8% in sedentary mice, compared to 2.8% in tumors from exercising mice.

Hypoxia is also a well-known mediator of chemoresistance. The same mechanisms that cause hypoxia, such as low microvessel density and vascular shunts limit the delivery of of chemotherapy to the tumor [26]. Another key mechanism of drug resistance is upregulation of the transcription factor HIF-1 and its downstream targets, including key protein and miRNA mediators of proliferation, drug efflux, metabolism, and autophagy [55]. Notably, HIF-1 activation increases expression of *MDR1*, which confers multidrug resistance by increasing drug efflux. For example, targeted downregulation of HIF-1α showed a dose-dependent increase in cisplatin-mediated apoptosis in oral squamous cell carcinoma cells [56]. Hypoxia may also abrogate the apoptotic effects of chemotherapy [57]. Thus, it is possible that the reduction of tumor hypoxia associated with exercise will be accompanied by improved response to chemotherapy.

An exercise-induced decrease in tumor hypoxia may affect the efficacy of immunotherapy. Infiltration of various immune cells is affected by hypoxic conditions. Hatfield et al. showed that $CD8^+$ tumor infiltrating lymphocytes (TILs) have a decreased presence in hypoxic tumor regions [58]. Hypoxic microenvironments also limit the efficacy of TILs by inhibiting their activation by dendritic cells [59] and increasing tumor expression of PD-L1, a key modulator of the immune checkpoint mechanisms [60, 61]. Housing mice in hyperoxic chambers (60% oxygen) increased the numbers of $CD8^+$ TILs more than three-fold [58]. The potential clinical implications of this finding are staggering, as Adams et al., postulated that for every 10% increase in $CD8^+$ TILs would translate to a 19% decrease in patient mortality [62]. Yet the sobering reality is that Hatfield's findings have limited clinical scope, as patients cannot be sequestered in 60% oxygen environments at the time of tumor development. However, exercise may be an effective way to increase TIL numbers, in part by creating a more favorable, normoxic tumor.

The effects of hypoxia extend beyond TILs. Dendritic cells are suppressed by hypoxia-inducible genes including VEGF [55]. Additionally, tumor-associated macrophages (TAMs) respond to the hypoxia-induced cytokines IL-4 and IL-10 by differentiating into an immunosuppressive M2 phenotype [63]. Indoleamine 2,3-dioxygenase (IDO), a tryptophan metabolism enzyme expressed by most tumors, is garnering interest for its immunomodulatory role in T cell suppression and tumor tolerance [64, 65]. IDO expression correlates with reduced TILs and poor prognosis in numerous cancer types [66, 67, 68, 69, 70]. Notably, IDO production by dendritic cells increases when cultured in a hypoxic environment [71]. Thus far, no one has reported the effects of exercise on IDO levels in tumors. However, it is a logical hypothesis that as exercise reduces tumor hypoxia, IDO production may be reduced, thereby reducing immunosuppression. Expanding this hypothesis, exercise may improve tumor response to immunotherapy by removing one of the roadblocks to an effective anti-tumor immune response.

The combination of radiation and immunotherapy creates the perfect storm of augmenting the immune response's potential and increasing tumor cells' susceptibility to immune cell killing [72]. Immunogenic cell death (ICD) occurs when an injured cell increases presentation of damage associated molecular patterns (DAMPs) such as calreticulin and high-mobility group box 1 protein (HMGB1) [73]. These changes promote dendritic cell activation and facilitate an anti-tumor T-cell response. Radiation therapy is a means of inducing ICD in tumor cells. In addition, radiation increases tumor cell expression of MHC Class I [74] and Fas [75]. Together, these changes have been viewed as using the tumor to create an *in situ* vaccine [76] and contribute to abscopal effects, in which the immune response extends beyond the primary irradiated tumor to target distant metastases. However, although the reported radiation-mediated "abscopal effects" against metastatic lesions [77, 78, 79] have sparked much excitement, abscopal effects in humans remain rare [80]. Nevertheless, it is worth considering how exercise may further prime the anti-tumor immune response for an abscopal effect. As detailed above, many of these changes will stem from exercise-mediated modulations in hypoxia (increased T cell infiltration [58]) or changes to tumor vascular maturity (decreased MDSC trafficking [29]). Hypoxia also reduces tumor MHC class I expression [81]; by removing this blockade, antigen recognition and immunogenic cell death may be enhanced.

4. Tumor cell metabolism

One of the emerging “hallmarks of cancer” is deregulated cellular energetics, or altered metabolism [82] which influences radiosensitivity [83, 84, 85]. Many cancer cells increase glucose consumption rate and preferentially utilize glycolysis over aerobic respiration; this may be due to hypoxia or a high rate of cell proliferation and oxidative stress [86, 87]. A downstream consequence of glycolysis is increased lactate concentration within tumors via the Pasteur effect – increased lactate stabilizes HIF-1 [88], which promotes VEGF expression [88], increases metastasis, and correlates with worse prognosis [89, 90]. Exercise may regulate metabolic reprogramming of tumor cells. For example, Bacurau et al. reported that treadmill running (at 60% VO_2 max) decreased carcinoma glucose consumption and decreased lactate production [91, 92]. Lu et al. showed that metabolic responses to exercise were associated with tumor response to exercise (unpublished data [93]). Specifically, comparison of exercise-responsive and non-responsive patient-derived colorectal xenograft (PDX) models revealed that phosphocreatinine metabolism was predictive of tumor growth delay. Tumors that showed growth delay in response to exercise had significantly lower phosphocreatinine compared to sedentary controls, whereas there was no difference in phosphocreatinine levels between sedentary or exercising mice with tumors whose growth was not affected by exercise. Metabolomics data reported by Glass et al. showed that nucleotide metabolism, which correlates with increased cell proliferation, was increased in a murine tumor cell line that showed accelerated tumor growth following exercise, compared to an exercise-responsive tumor that showed growth delay following exercise [94].

Our group also found preliminary evidence that exercise increased long chain acyl carnitines, consistent with fatty acid metabolism, elongation and oxidation (Ashcraft et al., unpublished data). The effects of fatty acid oxidation (FAO) versus glycolysis on oxygen consumption rate relate to the respiratory exchange ratio (RER), or the ratio of ATP molecules gleaned per molecule O_2 consumed. While the RER for glycolysis is 6.3 ATP/O_2, the RER for FAO is 5.6 ATP/O_2, indicating that equivalent energy is produced by FAO, with ~10% less oxygen consumption. Mathematical modeling by Secomb et al. predicted that a 30% decrease in oxygen consumption rate in the R3230Ac mammary carcinoma would completely abolish tumor hypoxia [95]; thus even a modest decrease in oxygen consumption rate induced by exercise could prove important in dictating radiotherapy response. It is also important to note that hypoxia suppresses FAO by regulating medium and long-chain acyl carnitines through the hypoxia-inducible transcription factor, HIF-1 [96], meaning that the cascade of events leading to improved tumor oxygenation is likely bi-directional. Tumors that increase HIF-1 expression following exercise also demonstrate accelerated tumor growth compared to tumors that do not express HIF-1 [94]. The results with metabolism suggest that exercise can exert a diversity of effects on tumor metabolism and radiosensitivity. If exercise pushes metabolism toward aerobic metabolism, radiosensitivity may be improved [97, 98]. If the opposite occurs, namely a push toward anaerobic metabolism radiosensitivity will decrease.

The observed exercise-mediated improvement in chemotherapy efficacy [10, 25] may have metabolic underpinnings, possibly, by reducing the tumors’ reliance on glycolysis [91, 92]. If exercise does reduce tumor glucose reliance, resultant metabolic changes could improve

efficacy of cytotoxic agents. Pharmacologically inhibiting glycolysis (via either 2-deoxyglucose or 3-bromopyruvate) improved etoposide efficacy against lymphoma [99], rapamycin efficacy against neuroblastoma [100] and tamoxifen efficacy against mammary carcinoma [101]. Cantelmo et al. showed that glycolysis inhibition within tumor vessel endothelial cells normalized tumor vasculature and improved perfusion, thereby increasing cisplatin delivery causing inhibition of tumor growth [102].

Finally, we can link shifts in tumor metabolism to potential improvement in immunotherapy. Immune responses become sub-optimal when they develop in acidic microenvironments (reviewed in [103]). Deficient immune responses begin with poor immune cell infiltration into acidic tumor environments. *In vitro* lymphocyte [104] and neutrophil [105] migration is reduced as their environment becomes increasingly acidic. In addition, cells that are able to gain entry into the tumor are less effective. Increased lactate concentrations impede NK cell function in two ways [106]. First, NK cells cytotoxic potential is decreased under acidic conditions. Second, exogenous lactate promotes *ex vivo* differentiation of MDSCs. Lactate increases tumor cell PD-L1 expression [107]. Inhibiting the lactate/PD-L1 cascade within the tumor augments cytotoxic T cell numbers [108]. Currently, there are no reports on how exercise affects tumor pH. However, given that lactate levels are decreased with exercise, it is likely that pH levels are reduced.

5. Concluding remarks

Oxidative stress is present in untreated tumors, and may increase following some treatment modalities. Oxidative stress, along with closely associated tumor hypoxia and acidic microenvironments, contributes to tumor aggressiveness and cancer fatigue. While pharmaceutical means of reducing oxidative stress have been pursued, exercise may provide a non-pharmacological therapy of regulating oxidative stress thereby alleviating these factors. Additionally, emerging evidence shows that exercise exerts other effects on tumor physiology including alterations in hypoxia, vascular normalization, metabolic reprogramming, and immune cell mobilization (summarized in Figure 2). We and others have begun to show that these changes translate to improved response to tumor therapy. Clinical studies that use functional imaging to monitor tumor hypoxia and perfusion in exercising vs. sedentary patients would be helpful in whether changes might influence response to therapy. Although additional work is needed to optimize exercise prescriptions (i.e. frequency, duration, and intensity), current studies suggest that human trials should be considered. For example, exercise could be evaluated as a means to improve treatmant response to established cancer treatment modalities.

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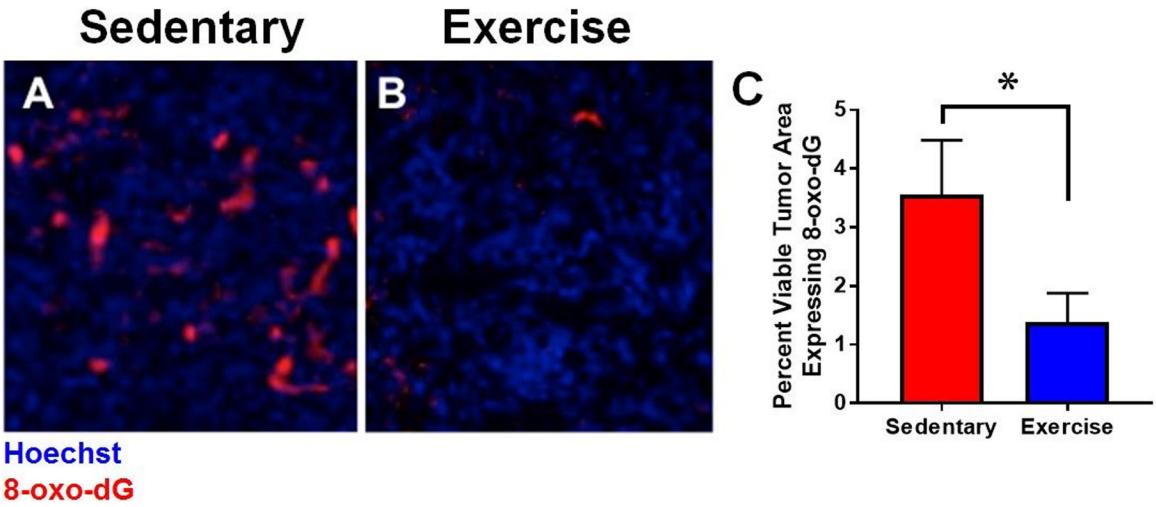

Figure 1.

4T1 tumor sections were immunostained for 8-oxo-dG (red), a marker of oxidative damage to DNA. Cellular nuclei were stained with Hoechst 33342 (blue). (A) and (B) show representative tumors taken from sedentary (A) or running (B) mice (5x objective, magnificantion 100%). Panel C shows quantification of 8-oxo-dG+ pixels per square millimeter of viable tumor area. Error bars represent SEM, N=23, 20, * indicates $p<0.05$, Mann Whitney U test.

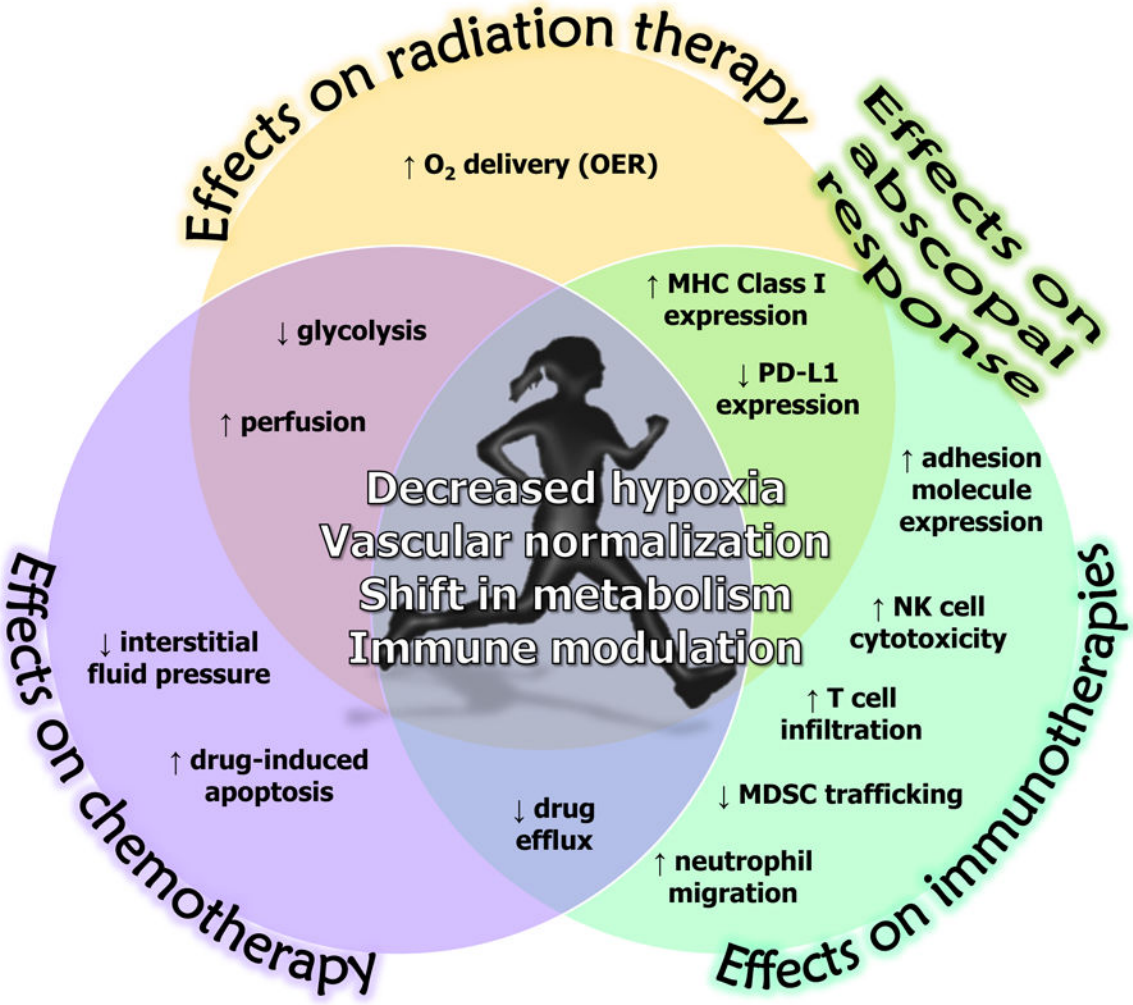

Figure 2.

Exercise oncology studies have demonstrated that exercise modulates both the tumor microenvironemnt and the robustness of the anti-tumor immune response. Pre-clinical studies have already reported that in these changes are sufficient for exercise to play an anti-tumor role in tumor incidence, progression and metastasis when adminsitered as a monotherapy. In this paper, we have described how the exercise-mediated changes may potentiate tumor sesitvity to radiation, chemotherapy or immunotherapy. Furthermore, we hypothesize that some changes may increase potency of abscopal responses, when radiation and immunotherapy are applied concurrently.