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Perspective

Molecular Mechanisms Linking Exercise to Cancer Prevention and Treatment

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The benefits of exercise training for cancer patients are becoming increasingly evident. Physical exercise has been shown to reduce cancer incidence and inhibit tumor growth. Here we provide the status of the current molecular understanding of the effect of exercise on cancer. We propose that exercise has a role in controlling cancer progression through a direct effect on tumor-intrinsic factors, interplay with whole-body exercise effects, alleviation of cancer-related adverse events, and improvement of anti-cancer treatment efficacy. These findings have wide-ranging societal implications, as this understanding may lead to changes in cancer treatment strategies.

Introduction

Epidemiological studies demonstrate that leisure-time physical activity reduces the risk of at least 13 different cancer types (Moore et al., 2016), and furthermore provide evidence for an exercise-dependent reduction in the risk of disease recurrence for breast, colon, and prostate cancer (Holmes et al., 2005; Kenfield et al., 2011; Meyerhardt et al., 2006). Likewise, numerous preclinical exercise studies show similar exercise-dependent protection against cancer. Utilizing a variety of exercise interventions, including voluntary wheel running, treadmill running, and swimming, it has repeatedly been shown in rodents that exercise training can reduce tumor incidence, tumor growth, and metastasis across a wide range of transplantable, genetic, and chemical-induced tumor models (Ashcraft et al., 2016; Pedersen et al., 2015). Some evidence suggests that cancers of different genetic background may display differential sensibility to exercise training (Jones et al., 2016; Morikawa et al., 2011). For instance, the genetic p53-deficient MMTV-*Wnt* mouse breast cancer model demonstrates no regulation with exercise training (Colbert et al., 2009), which might reflect a very strong oncogenic driver mutation initiating this tumor model. Likewise, epidemiological evidence suggests that women with postmenopausal hormone-sensitive breast cancer displayed a larger risk reduction by physical activity than women with premenopausal hormone-insensitive breast cancer (Jones et al., 2016). Despite these differences, we propose that regular exercise in general decreases the risk of cancer and can control tumor growth, and that this effect is unrelated to the specific cancer diagnoses. These tumor growth-inhibitory effects are probably mediated by several different mechanisms, and their individual contributions to the inhibitory effect of exercise may vary in importance across different cancer diagnoses.

Exercise as Cancer Medicine

The nature of exercise training involves repetitive bouts of exercise that challenge whole-body homeostasis, leading to widespread adaptations in cells, tissues, and organ systems (Gabriel and Zierath, 2017; Hawley et al., 2014). While biomechanical and metabolic adaptations have been extensively studied in skeletal muscle, heart, adipose tissue, and the vasculature, much less is known about other tissues, including tumors (Neufer et al., 2015). Despite this, exercise training has been proposed to target and improve almost every conceivable outcome in cancer patients. Notwithstanding a considerable heterogeneity in the more than 100 published exercise intervention studies in cancer patients, exercise is generally acknowledged to be associated with positive changes in objective physiological measures (e.g., cardiopulmonary fitness, physical function, and body composition), as well as in patient-reported outcomes (e.g., fatigue, sleep quality, and sense of empowerment) (Ballard-Barbash et al., 2012; Sasso et al., 2015) (Table 1). These parameters are, of course, of direct significance to cancer patients, but emerging evidence indicates that exercise is also directly linked to control of tumor biology and thus may ultimately improve the clinical outcome.

In 2008, McTiernan published a seminal paper suggesting that physical activity was linked to cancer protection through exercise-dependent reductions in cancer risk factors, such as sex hormones, insulin/IGF, and inflammatory markers (McTiernan, 2008), and subsequent research has focused on providing a proof-of-concept for this hypothesis. In parallel, solid mechanistic investigations have outlined additional mechanisms that may link physical activity and exercise to cancer control. This detailed insight into the underlying mechanistic effects is warranted in order to pursue exercise as cancer medicine. With such knowledge, exercise training in cancer patients may potentially move from a "one fits all" approach toward individualized approaches based on extensive physiological knowledge of the molecular effects on cancer outcomes that different amounts, intensities, and modes of exercise will induce.

Evidence is emerging from murine studies showing that exercise training (1) controls cancer progression through direct effects on tumor intrinsic factors (growth rate, metastasis, tumor metabolism, and immunogenicity of the tumor), (2) regulates tumor growth through interplay with systemic factors, (3) alleviates adverse events related to cancer and its treatment, and (4) improves cancer treatment efficacy. Here, we aim to review the

Table 1. Adaptive Responses to Endurance and Resistance Training in Cancer Patients

Exercise Adaptions		Aerobic Training	Resistance Training
Whole-Body Adaptations			
Cardio-pulmonary exercise test (CPET)			
	Fitness ($Watt_{max}$)	↑↑	↑
	VO_{2peak}	↑↑	↔ ↑
Walking capacity (6 min/400 m)		↑↑	↑↑
Body mass index		↔	↔
Fat mass		↓ ↔	↔
Bone mineral density		↔	↔ ↑
Muscle Adaptations			
Muscle strength (1-RM)		↑	↑↑↑
Muscle mass		↔	↑
Muscle fiber size (cross-sectional area)		NA	↔ ↑
Muscle fiber type composition		NA	↔
Capillary density		NA	↔
Mitochondrial function and density		NA	NA
Neural adaptations		NA	NA
Systemic Adaptations			
Glucose		↔	↔
Lipids		↓ ↔	↔
Inflammatory markers			
	CRP	↓[a]	↔
	TNF-α	↔	↔
	IL-6	↔	↔
Sex hormones		↓ ↔	↔
Metabolic hormones			
	Insulin	↓ ↔[b]	↔
	Leptin	↓ ↔[b]	↔
Growth factors (GH, IGF-1)		↔	↔
Health-Related Quality of Life			
Symptom status (e.g., lower fatigue)		↑↑↑	↑↑↑
Functional status (e.g., lower depression)		↑↑	↑↑
General health perception (e.g., improved life satisfaction)		↑	↑

The table summarizes the adaptive responses to endurance and resistance training in cancer patients based on the large amount of literature available from clinical training intervention studies. ↑ indicates an increasing effect on the parameter, ↓ indicates a decreasing effect on the parameter, and ↔ indicates no effect. The number of arrows represents the magnitude of the effect. NA, not assessed.

[a]Changes in inflammatory markers are primarily seen after long (>16 weeks) interventions.

[b]Changes in metabolic hormones are primarily seen if the interventions are associated with weight loss.

current molecular understanding of the influence of exercise at the various levels of the cancer continuum and, when available, seek to include mechanistic data from human interventions.

Tumor-Intrinsic Effects of Exercise

Intratumoral signaling networks are highly modifiable and modulated by numerous extrinsic factors (Schneider et al., 2017). In the case of exercise, these extrinsic factors include both physical effects (i.e., increase in blood flow, shear stress on the vascular bed, pH regulation, heat production, and sympathetic activation) and endocrine effects (i.e., stress hormones, myokines, and circulating exosomes) (Hawley et al., 2014), all of which have the potential to regulate cancer progression and biology. The effect of these physiological factors may regulate tumor growth kinetics, metastatic potential, tumor metabolism, and the immunogenic profile of the tumor. Here, we discuss these general mechanisms with little emphasis on the different cancer histologies, though it should be highlighted that individual cancer histologies differ markedly in their growth kinetics, metabolism, and immunogenicity. These differences stem from the basal and mutational profile of the tumors, and the effect of exercise on the individual mechanisms might therefore vary in importance between the individual cancer diagnostic groups.

Tumor Growth Kinetics and Tumor Formation

Across the vast majority of preclinical studies investigating the effect of exercise on cancer outcomes, the most common outcome is a reduction in the rate of tumor growth (Ashcraft et al., 2016; Pedersen et al., 2015). Strikingly, this omnipresent inhibitory effect is evident across most investigated cancer histologies (Table 2). The control of tumor growth by exercise training in established tumors may be as high as a 67% reduction in growth rate (Pedersen et al., 2016), but exercise in itself is not capable of directly eradicating tumors. So far, no preclinical studies have shown that exercise interventions are able to eliminate or markedly reduce already established tumors. To further explore the growth-inhibitory effect of exercise, several studies have utilized exercise-conditioned serum to incubate cancer cells of different origins (breast, prostate, and lung cancer). In these *in vitro* studies, evaluation of cancer cell proliferation demonstrates an inhibition of around 10%–15% compared to the control setting, but no direct eradication of cancer cells compared to baseline levels (Dethlefsen et al., 2016; Hojman et al., 2011; Rundqvist et al., 2013). This inhibition does not reach the same level of suppression as seen with *in vivo* exercise interventions lasting several weeks, which may be explained by the fact that the *in vitro* studies reflect the effect of only one single bout of exercise. However, if exercise is performed at the recommended level, such 10%–15% inhibition might be striking the tumors several times a week and may thus accumulate to a clinically significant inhibition (Dethlefsen et al., 2017b).

A very important but often overlooked finding from these serum incubation studies is that exposure to exercise-conditioned serum strongly affects the seeding and clonogenic potential of cancer cells. It has been shown that colony formation is reduced with 80% after pre-incubation with exercise-conditioned serum (Kurgan et al., 2017). Similarly, pre-incubation of cancer cells with exercise-conditioned serum more than halves tumor incidence when tumor cells are injected into sedentary mice (Dethlefsen et al., 2017a; Rundqvist et al., 2013). Thus,

Table 2. Voluntary Wheel Running Reduced Tumor Growth across a Range of Histologies

Tumor Type	Reduction in Tumor Growth
Murine Tumors in Immuno-Competent Mice	
B16 melanoma	−67%
Lewis lung cancer	−58%
C26 colon cancer	−33%
E0771 breast cancer	−43%
Transgenic melanoma (Grm^{-})	−31%
DEN-inducible hepatocarcinoma	−59%
Human Tumors in Immuno-Incompetent Mice	
MCF7 hormone-sensitive breast cancer	−36%
MDA-MB-231 triple negative breast cancer	−66%
UTSCC45 head and neck cancer	−54%

For comparison, we have investigated the effect of voluntary wheel running on tumor growth in nine different mouse models of tumors. For the fast-growing tumors, i.e., murine B16 melanoma, Lewis lung cancer, C26 colon cancer, and E0771 breast cancer, the running wheels were placed in the cages 4 weeks prior to tumor inoculation, in order to accustom the mice to running, and the wheel remained in the cages throughout tumor challenge. For the remaining tumor models, the running wheels were placed in the cages concurrent with tumor inoculation. Data are summarized from Pedersen et al., 2016; Dethlefsen et al., 2017a; and unpublished data.

exposure to exercise-induced molecular factors may interfere with molecular signaling events in the cancer cells that are involved in tumor formation. One such pathway, which is essential for organ formation and has been implicated in tumor formation, is the Hippo signaling pathway (Tremblay et al., 2014; Zanconato et al., 2016). Recent studies have demonstrated that this pathway is downregulated by exercise and catecholamines (Gabriel et al., 2016; Yu et al., 2012). In addition, exercise and exercise-conditioned serum have been shown to deactivate Hippo/YAP signaling in breast cancer cells through an epinephrine-dependent mechanism, and blockade of adrenergic signaling blunted the suppressive effect of exercise-conditioned serum on both tumor formation and cell viability (Dethlefsen et al., 2017a). These data suggest that exercise at intensities associated with increases in catecholamine levels can reduce the ability of cancer cells to form tumors in distant tissues, e.g., through regulation of the Hippo signaling pathway. On a broader scale, the collected evidence of the effect of exercise on tumor growth implicates that exercise may have a more potent effect on the metastatic potential than on the direct control of cancer cell viability.

Tumor Metabolism

Tumors are recognized for having an altered cellular metabolism, favoring aerobic glycolysis in order to support high energy turnover and rapid cell proliferation (Martinez-Outschoorn et al., 2017). This reprogramming is driven by distinct oncogenic mutations, as seen in the PI3K pathway, or through a more general upregulation of the metabolic machinery with c-Myc mutations (DeBerardinis et al., 2008; Mitsuishi et al., 2012; Tarrado-Castellarnau et al., 2016). Exercise is an energy-consuming activity that induces marked changes in whole-body and intracellular metabolism. Acknowledging that tumors are not isolated entities detached from the rest of the body, it must be expected that intratumoral metabolism is affected during exercise performance. Preclinical studies suggest that tumors with an inherent high metabolism are more susceptible to exercise-induced energy stress, in line with their increased susceptibility to other stress factors such as fasting and caloric restriction (Higgins et al., 2014; Jiang et al., 2013; Lee et al., 2010; Lu et al., 2006). Simplistically, this might be interpreted as a redirection of energy substrates from the energy-demanding tumors to competing metabolically active tissue, leaving the tumors vulnerable due to the lack of energy delivery. However, this one-dimensional view may not reflect the full picture, as extensive regulation of metabolic signaling pathways also contributes to exercise-dependent metabolic reprogramming.

Numerous preclinical studies have highlighted the Akt/mTOR signaling pathway that is found to be differentially regulated during exercise in many tumor studies, as reviewed in Thompson et al., 2009. This pathway is central for control of growth and protein synthesis and plays a pivotal role in the muscular response to resistance training (Nair and Ren, 2012; Schiaffino et al., 2013). In contrast, the Akt/mTOR pathway has been shown to be deactivated with endurance exercise in several models of murine tumors (Thompson et al., 2009). Despite the fact that many studies have demonstrated associations between exercise interventions and reduced mTOR signaling, none have so far proven mTOR signaling's causative effect on tumor growth or fully elucidated the exercise-dependent mechanisms underlying this induction. Various metabolic pathways convene at mTOR, e.g., AMPK signaling. AMPK has been described as the master regulator of energy metabolism, and AMPK is highly induced by exercise in other organs (Atherton et al., 2005). Consequently, AMPK is, as might be expected, also induced in tumors during exercise (Piguet et al., 2015; Theriau et al., 2016). Taken together, intratumoral metabolism is unquestionably regulated during exercise, but how this affects tumor growth and metastatic rate is currently not mechanistically understood.

Immunological Profile of the Tumor

Immune recognition and eradication are potent intrinsic weapons against cancer, and the immunological profile of tumors is accordingly tightly linked to cancer prognosis. Thus, high levels of infiltrating natural killer (NK) cells and cytotoxic T cells in tumors of cancer patients are associated with a better prognosis (Ferrone and Dranoff, 2010; Nelson, 2008; Pagès et al., 2010; Strauss and Thomas, 2010). To avoid immune cell-driven eradication, tumor cells have developed ways of paralyzing infiltrating cytotoxic immune cells. Hence, tumor cells can express inhibiting receptor ligands (PD-L1, B7.1, etc.) that regulate the activity of the cytotoxic immune cells, or tumor cells may secrete TGF-β or other immunosuppressive factors that suppress the function of the infiltrating immune cells (Sharma and Allison, 2015).

We have recently shown that voluntary wheel running decreases tumor growth through an exercise-dependent mobilization and redistribution of cytotoxic immune cells (Pedersen et al., 2016). In particular, the last step of redirecting the cytotoxic immune cells to the tumor is dependent on the immunological profile of the tumor. We found that exercise increased the levels of immune-attractant chemokines, NK cell-activating receptor

ligands, and immune check-point blockade ligands (unpublished data), and studies are emerging, aiming to elucidate which upstream events are inducing this enhanced tumor immunogenicity. Here, type I interferon signaling may play an important role, as it has the potential to elicit the full immuno- and chemoattractant array of pathways, leading to improved immune recognition (Müller et al., 2017). It is worth mentioning in this context that cellular senescence, but not quiescence, has been shown to provoke tumor immunogenicity, type I interferon signaling, and increased infiltration of cytotoxic NK and T cells (Tasdemir et al., 2016). There are few studies investigating the effect of exercise on these pathways, but those available suggest the exercise might actually decrease the level of cellular senescence, as based on regulation of telomere lengths in immune cells (Arsenis et al., 2017).

Metabolic byproducts may also play a role in exercise-mediated regulation of tumor immunogenicity. Due to the high levels of aerobic glycolysis derived from the altered cellular metabolism of most tumors, high levels of lactate will accumulate within the tumors. Such elevated levels of lactate may inhibit the function of cytotoxic immune cells, including T cells (Angelin et al., 2017; Fischer et al., 2007). However, this suppression may be relieved by exercise training, as exercise has been demonstrated to lower intratumoral levels of lactate, an effect that was associated with regulation of LDH levels (Aveseh et al., 2015). In continuation, this regulation may have direct clinical implications, as intratumoral LDH levels are currently used to stratify melanoma patients into high- and low-risk groups, with high levels of LDH being associated with poor prognosis (Hersey et al., 2009). Together, these studies indicate that events triggering immune infiltration, and partly alleviating immunosuppressive metabolites, may act to promote enhanced immunogenicity within tumors from exercising mice.

Exercise-Dependent Tumor-Organ Crosstalk

Immunological Control of Tumor Growth

Exercise has extensively been shown to regulate the cellular immune system, as cytotoxic immune cells are mobilized to the circulation during exercise through mechanisms involving blood-flow-induced shear stress and adrenergic signaling (Idorn and Hojman, 2016). These mobilized cytotoxic immune cells survey the body to identify and eradicate transformed cells. We have shown a marked exercise-mediated suppression of tumor growth, which could be attributed to an epinephrine-dependent mobilization of NK cells, followed by increased immune cell infiltration into tumors from wheel-running mice (Pedersen et al., 2016). Through treatment with the beta-blocker propranolol, it was demonstrated that adrenergic signaling was driving the exercise-dependent suppression in tumor growth, as beta-blocker treatment blunted the suppression of tumor growth as well as NK cell mobilization and intratumoral immune cell infiltration (Pedersen et al., 2016). Numerous studies have shown that immune cell mobilization during exercise is a common phenomenon, independent of age, gender, or presence of morbidities (Idorn and Hojman, 2016). The exercise-mediated mobilization of immune cells has been examined in only one study with cancer patients, but here it was also convincingly shown that breast cancer survivors were able to mobilize NK cells to the circulation to the same degree as age-matched healthy controls (Evans et al., 2015a).

Other exercise-related physical factors are also able to increase immune cell trafficking and function, with increased body temperature as a prominent example (Evans et al., 2015b). It is well documented that hyperthermia can control and delay tumor growth through enhancement of intratumoral NK cell infiltration (Chen et al., 2006; Fisher et al., 2011). The increased body temperature enhances immune cell trafficking by increasing the diameter of the intratumoral blood vessels. In addition to this physical effect, increased body temperature modifies the tumor vasculature by inducing IL-6 trans-signaling, making the vasculature more permissible for cytotoxic T cell trafficking into the tumors (Fisher et al., 2011). Hyperthermia is currently being used in treatment of certain cancers (Gao et al., 2016). Still, the hyperthermia induced in such treatments is higher than what is typically reached with exercise training (González-Alonso, 2012).

In these studies, both transplantable and genetic mouse tumor models were used (Chen et al., 2006; Fisher et al., 2011; Pedersen et al., 2016). For the transplantable models, a strong effect of training prior to tumor cell inoculation was observed, suggesting that part of the exercise response includes a priming of the immune system to recognize the artificially introduced tumor cells. However, immune recognition also occurs in genetic tumor models, indicating that in addition to the first clearance of inoculated tumor cells, additional immunological control may mediate the exercise effect. Furthermore, transplantable murine tumor models tend to grow very quickly; thus the full immunological response might not have time to unfold (Idorn and Hojman, 2016). In mice, an exercise-dependent accumulation of NK cells was observed, and these are known to promote the adaptive immune response with infiltration of cytotoxic T cells (Gross et al., 2013). In human cancers, this extended immunological response will have time to develop, and thus while the initial events are similar for mice and humans, the human cancers might demonstrate a more complex immunological response to exercise. However, this needs to be investigated further.

Muscle-to-Tumor Crosstalk

Skeletal muscle releases peptides during muscle contractions, and these myokines comprise a conceptual basis for muscle-to-organ crosstalk (Pedersen and Febbraio, 2012). The list of exercise-induced myokines is continuously growing, and large-scale omics-based strategies are aiming at elucidating the entire muscle secretome (Whitham and Febbraio, 2016). Currently, predictions estimate that there are around 600 potential myokines, with the best-characterized candidate being IL-6 (Henningsen et al., 2010). Generally, these myokines are released from muscles during exercise to regulate energy exchange and promote metabolic adaptations in muscles and other organs (Pedersen and Febbraio, 2012). Evidence on the role of myokines in cancer protection is still limited; however, a few preclinical studies have demonstrated that muscle-derived Oncostatin M (OSM) and Irisin inhibit breast cancer cell viability *in vitro* (Gannon et al., 2015; Hojman et al., 2011), while the myokine SPARC has been shown to reduce tumorigenesis in the colon of exercising mice (Aoi et al., 2013). In general, myokines belong to a number of distinct protein classes, and their potential in the regulation of cancer development and progression is reflected by their ability to either directly control cell proliferation or antagonize cellular ligands involved in cell proliferation and

differentiation. This includes candidates that are acknowledged for their roles as antagonists for TGF-β or Wnt signaling.

In a more indirect manner, exercise-induced myokines may affect immune cell activity through the release of immune regulatory cytokines. These exercise-induced immune regulatory cytokines include IL-6, IL-7, and IL-15 (Pedersen and Febbraio, 2012). Numerous studies have documented the importance of IL-15 in promotion of NK and T cell proliferation, differentiation, and maturation (Marçais et al., 2014; Satoh-Takayama et al., 2010). Accordingly, the potential of IL-15 to boost immune responses in cancer patients is currently being pursued (Conlon et al., 2015). Far less is known regarding the role of IL-6 in controlling immune cell function, yet in our recent study we demonstrated that IL-6 was involved in facilitating intratumoral immune cell infiltration during exercise. In humans, IL-6 increases in an exponential manner with exercise, and the magnitude of this IL-6 increase is dependent on duration, intensity, and amount of muscle mass engaged in the exercise (Pedersen and Febbraio, 2008). Blockade of IL-6 signaling by anti-IL-6 antibodies during wheel running was shown to diminish the exercise-mediated suppression of tumor growth (Pedersen et al., 2016). This effect could not be mimicked by direct IL-6 administration, suggesting that prior exercise-dependent mobilization and priming of the immune cells were needed for IL-6 to impose its regulatory role.

Taken together, exercise may target tumor development and progression through several mechanisms (Figure 1). During exercise performance, release of several systemic factors (i.e., catecholamines, myokines, etc.), sympathetic activation, increased blood flow, shear stress, and increased temperature exert immediate stress on tumor metabolism and homeostasis. Following long-term training, these acute effects lead to intratumoral adaptations of improved blood perfusion, enhanced immunogenicity, and metabolism adjustments, which contribute to slower tumor progression.

Exercise May Modify Symptoms of Cancer and Therapy-Related Adverse Effects

From the point of diagnosis and throughout the cancer trajectory, cancer patients are subjected to a myriad of interrelated pathophysiological effects with potential adverse prognostic impact. Pre-existing comorbidities, poor conditioning, and metabolic disorders are common in newly diagnosed cancer patients and constitute negative prognostic factors. Significant loss of muscle mass (sarcopenia/cachexia), metabolic derangements, and depression are among the most prevalent and serious cancer-related symptoms and are strongly correlated to impaired prognosis (Caruso et al., 2017; Christensen et al., 2014; Klil-Drori et al., 2017). Yet emerging evidence suggests that these conditions may be targetable by exercise training.

Prevention of Muscular Impairments and Cancer Cachexia

Muscular fitness, as evaluated by muscle mass, strength, or metabolic function, is strongly associated with cancer-specific and overall mortality risk, treatment tolerance, and risk of complications during surgery in patients with cancer (Christensen et al., 2014). This impairment of muscle function goes beyond cachexia, which is a state of marked weight loss that cannot be reversed by nutritional support (Fearon et al., 2013). Within certain diagnoses (e.g., gastro-intestinal, lung, and pancreatic cancer), loss of muscle mass can be caused by tumor-derived factors, which are secreted from the tumor to the circulation and drive muscle degradation. Comprehensive preclinical studies have shown that mouse models of colon cancer (C26) and lung cancer (Lewis lung cancer, LLC) drive muscle wasting and weight loss through release of tumor-derived factors such as PTHrP and myostatin (Gallot et al., 2014; Kir et al., 2014, 2016). We have verified this tumor-induced muscle wasting in the LLC model, and in our study access to running wheels was sufficient to completely eliminate the tumor-induced loss of body weight and muscle mass, independent of tumor size in the LLC model (Pedersen et al., 2016). Thus, there is a large potential for maintaining muscle mass and function, if the molecular mechanisms underlying the tumor-induced muscle wasting are elucidated.

For other cancer diagnoses, muscle wasting is mainly caused by anti-cancer treatment. Various chemotherapy regimens are known to cause significant muscle wasting through a combination of treatment-induced anorexia, physical inactivity, and direct induction of muscular protein degradation, including factors such as the ubiquitin ligases Atrogin-1 and MuRF. In mice, voluntary wheel running has been shown to prevent cisplatin-induced muscle wasting, which was associated with attenuated intramuscular protein degradation and systemic inflammation (Hojman et al., 2014). In addition, wheel running restored normal levels of food intake, which was linked to a training-dependent induction of the appetite-regulating hormone ghrelin. From clinical experience, androgen deprivation treatment (ADT) for prostate cancer is known to cause marked loss of muscle mass, concurrent with accumulation of body fat. Numerous exercise intervention studies in these patients suggest that exercise training has beneficial effects on adiposity and insulin sensitivity (Galvão et al., 2010; Hvid et al., 2013; Wall et al., 2017). In contrast, the muscular response is highly variable, with prostate cancer patients showing large adaptations in muscle mass while others have a minimal response (Nilsen et al., 2016). The mechanisms behind these highly individual muscular responses to training remain to be determined.

Obesity, Metabolic Health, and Systemic Inflammation

While some cancer patients struggle with involuntary weight loss and cachexia, another large group of cancer patients experience significant weight gains during anti-cancer therapy (Demark-Wahnefried et al., 2012). These typically include early-stage breast cancer patients and prostate cancer patients in ADT. This metabolic imbalance may lead to increased systemic levels of obesity-related risk factors for cancer (Park et al., 2014). Much research has focused on whether exercise training is able to reduce cancer incidence and development through reductions in systemic low-grade inflammation and other known risk factors, including sex hormone levels and factors involved in insulin signaling (McTiernan, 2008), as these are correlated with poor cancer outcomes, i.e., disease progression and reduced survival (McTiernan, 2008). Exercise disrupts the vicious cycle of chronic inflammation, both directly through induction of anti-inflammatory cytokines during each bout of exercise and indirectly by improving comorbidities and cardiovascular risk factors, in particular by decreasing the amount of visceral fat (Benatti and Pedersen, 2015). As a consequence, several clinical exercise

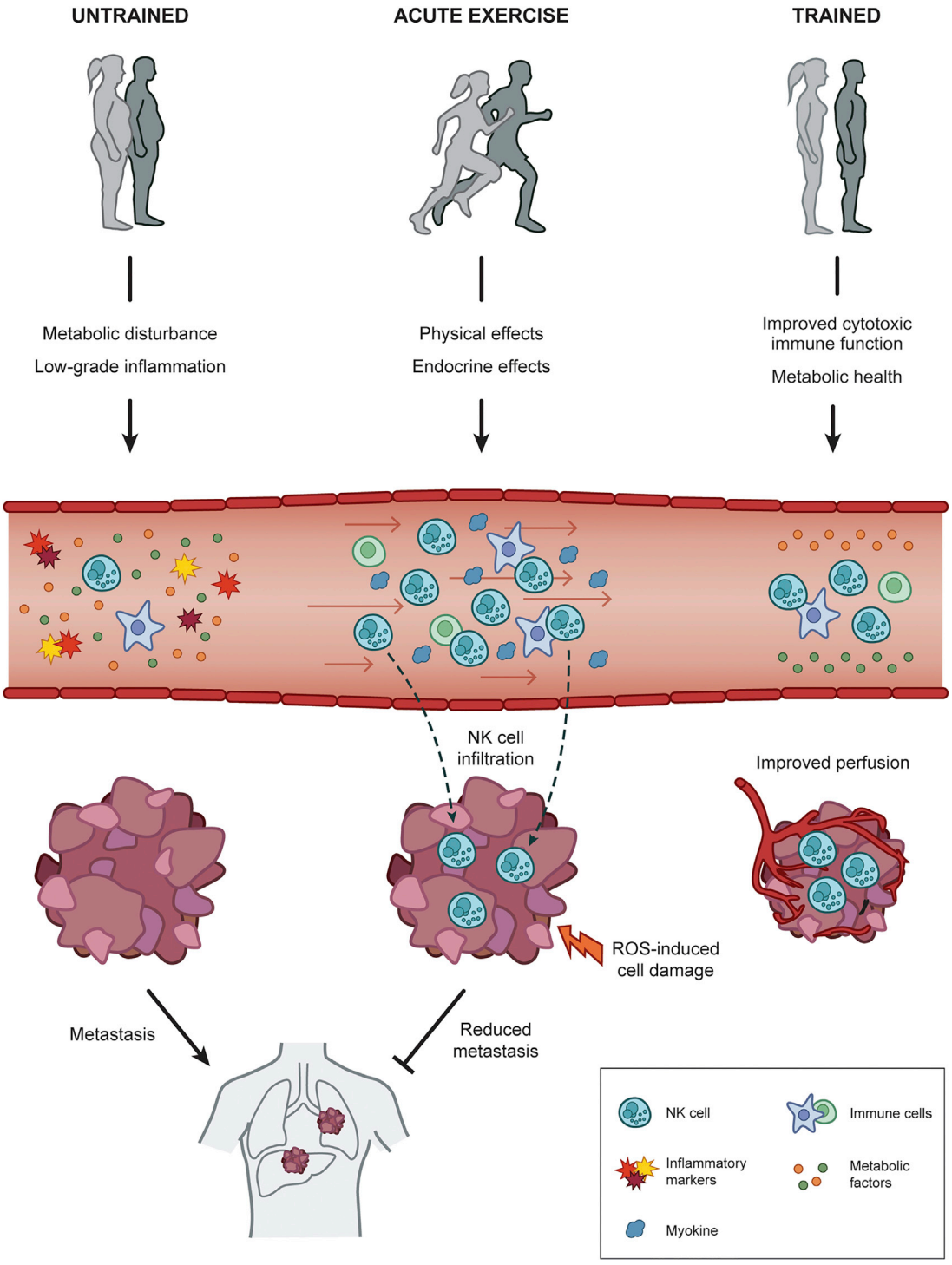

Figure 1. Molecular Mechanisms Linking Exercise to Cancer Protection

Exercise consists of: (1) Acute sessions leading to physical (increased blood flow, shear stress on the vascular bed, temperature increases, sympathetic activation) and endocrine (release of catecholamines and exercise hormones, myokine secretion) regulation that results in increased tumor perfusion, oxygen delivery, intratumoral metabolic stress, cellular damage, and ROS production. These acute changes are able to elicit signaling pathways that prevent metastasis. (2) Chronic training adaptations comprising systemic alterations with improved immune function, reduced systemic inflammation, and improved metabolic health, as well as intratumoral changes in the form of enhanced blood perfusion, immunogenic profile, and immune cell infiltration.

intervention studies have aimed at reducing the levels of inflammatory markers in cancer survivors or in people at high risk of cancer (Ballard-Barbash et al., 2012; Friedenreich et al., 2016; Imayama et al., 2012; Jones et al., 2013). Results from these studies show that long-term exercise training may reduce systemic levels of CRP, TNF-α, IL-6, and other pro-inflammatory factors, but the interventions are typically needed to last longer than the usual 12–16 weeks of training intervention used in most studies (Dethlefsen et al., 2017b). In parallel, numerous exercise intervention studies in women at high risk of breast cancer or breast cancer survivors have aimed at reducing circulating sex hormone level, e.g., estrogen, given the strong rationale that this hormone drives hormone-sensitive breast cancer. Taken together, these studies indicate that it is possible to reduce systemic sex hormone levels, but this regulation is tightly linked to training-induced weight loss (Dethlefsen et al., 2017b; van Gemert et al., 2017).

Depression and Cognitive Function

Depression, anxiety, and cognitive problems are common side effects of anti-cancer therapy. These adverse effects have direct clinical importance, as patients with depression tend to have lower compliance to their anti-cancer therapy (Lin et al., 2017). Numerous exercise intervention studies have shown that exercise training, in particular endurance training, can alleviate these symptoms in the cancer patient population, where depression is a major problem (Cooney et al., 2013; Mishra et al., 2012a, 2012b; Newby et al., 2015). A molecular link between exercise and depression was recently demonstrated in mice. Tryptophan metabolism results in the production of the circulating metabolite kynurenine that is able to cross the blood-brain barrier and induce depression (Agudelo et al., 2014). Circulating levels of this metabolite are upregulated and associated with depression and cancer-related fatigue in cancer patients (Kim et al., 2015). Skeletal muscles were shown to metabolize kynurenine into kynurenic acid, which cannot cross the blood-brain barrier, thereby protecting against depression. The increased conversion of kynurenine was dependent on activation of the PGC-1α transcription factor, which is upregulated with endurance training (Agudelo et al., 2014). In line with this, a recent study in healthy individuals demonstrated that kynurenine is indeed metabolized in muscles during exercise training, and this involves upregulation of the catabolic enzymes kynurenine aminotransferases within the muscles (Schlittler et al., 2016). Whether these results can be translated into cancer patients for exercise-mediated alleviation of their depression symptoms remains to be determined.

Exercise May Improve the Efficacy of Anti-cancer Therapy

With very few exceptions, patients with a measurable cancer burden are treated with one or more anti-cancer treatment modalities (e.g., surgery, chemotherapy, radiotherapy, immunotherapy, and/or anti-hormonal therapy), and it is therefore imperative to consider the concurrent pathophysiological interplay of these various treatments. Traditionally, administration of anti-cancer medicine has been regarded as a reason to preclude exercise training, given the major impact these treatments have on the cancer patients' wellbeing. However, this view might be changing with the accumulating literature, showing that exercise training not only attenuates treatment toxicity (Schmitz et al., 2010), but may also have the potential to augment the potency and efficacy of traditional cancer therapies.

Radiotherapy requires sufficient oxygen delivery to tumors, which is essential for promoting the generation of reactive oxidative species that facilitate the therapeutic effect (Chen and Kuo, 2017). Exercise training strongly affects blood circulation and oxygen delivery to peripheral tissues. Blood circulation during exercise is controlled by the sympathetic nervous system, driving elevation in heart rate and blood pressure and thus regulating vascular tension. In concert, these biophysical adaptations have the potential to increase tumor perfusion and, over time, increase angiogenesis and intratumoral vascularization. Evidence from rodent studies has demonstrated that enhanced perfusion counteracts hypoxia-related intratumoral stress (Betof et al., 2015; Garcia et al., 2016; McCullough et al., 2013, 2014; Pedersen et al., 2015). Initiatives are currently being undertaken to investigate if exercise performance immediately prior to radiotherapy may enhance treatment response and affect tumor biology.

Similarly, the efficacy of both chemotherapy and immunotherapy relies on adequate intratumoral blood perfusion in order to deliver the cytotoxic drugs and immune cells to the interior of tumors. Both enhanced blood perfusion and temperature increases due to a higher energy production play important biophysical roles in improving drug and immune cell delivery. This combinatory effect is also important in the long-term efficacy of chemotherapy, which depends on engaging the patient's memory immune response during the resolution of the acute tumor clearance for future tumor protection. A few preclinical studies have investigated the combined effect of chemotherapy and wheel running. These studies demonstrated an increased treatment effect when combining cytostatic treatment with an exercise intervention (Betof et al., 2015; Schadler et al., 2016). On the other hand, compromising blood flow to a tumor can also be a treatment strategy in itself, as illustrated by anti-angiogenic therapies that are being utilized in the treatment of, e.g., colorectal cancer (De Palma et al., 2017). In this case, exercise and anti-angiogenic therapy might be working in opposite directions, as exercise studies in mice all indicate that exercise increases blood perfusion and normalizes the capillary network within tumors (Betof et al., 2015; Garcia et al., 2016; McCullough et al., 2014).

For most solid malignancies, surgery is the first-line treatment, and radical tumor resection is currently considered the most efficient curative treatment. Exercise training is starting to gain momentum as a potent supportive strategy in the pre-operative period, where clinical studies have focused on the potential of exercise training to improve physical capacity of frail patients in order to lower post-operative morbidities and the associated extended length of hospitalization (Cavalheri and Granger, 2017; Singh et al., 2013). Recent insights indicate that maladaptive responses in paracrine, endocrine, and immune-related factors during surgery are key determinants of long-term risk of tumor progression and metastases (Horowitz et al., 2015). Given the potential of acute and chronic exercise to modulate these processes, including regulation of tumor metastasis and immune function, and improved tolerance to hormonal and metabolic

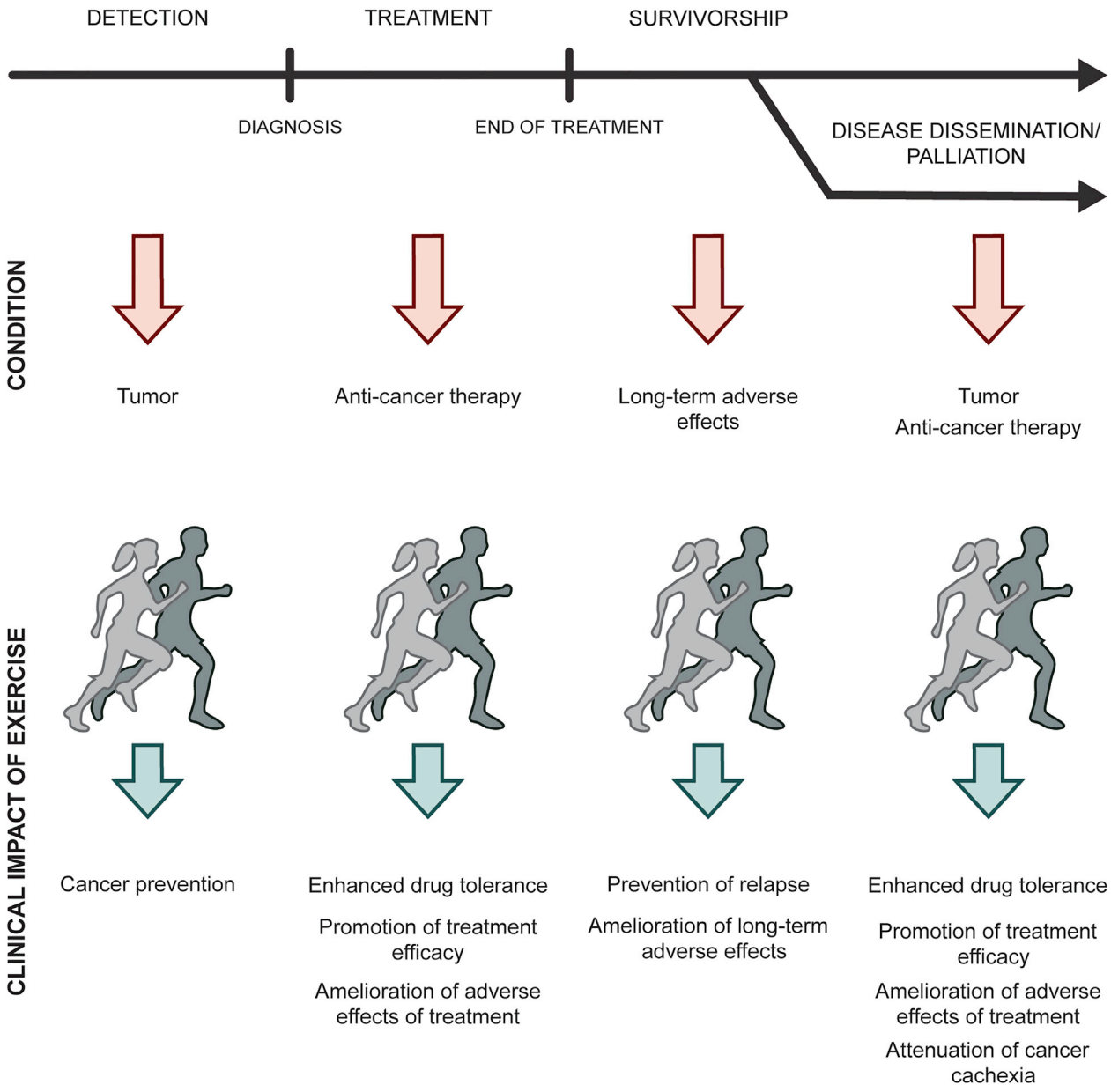

Figure 2. Running from Cancer at All Stages

The cancer continuum comprises detection, treatment, survivorship, and disease dissemination and palliation. Each stage is characterized by different pathological conditions (presence of tumor, anti-cancer therapy, long-term adverse effect, and those in combination), and exercise training may play different roles across the cancer continuum: reducing the risk of cancer in the pre-diagnostic period; improving drug tolerance and efficacy during treatment; preventing relapse, controlling adverse effects post-primary anti-cancer treatment, and reducing risk of comorbidities; and doing all of the above in advanced-stage cancer patients.

stress, exercise training may at the same time both lower the risk of postoperative complications and reduce the risk of residual disease. Yet the mechanistic effects of exercise in relation to surgical outcomes are largely unknown; thus further investigations are warranted to fully explore the potential of exercise training in the perioperative period.

These examples demonstrate how insight into the mechanistic effects of exercise might govern the use of targeted exercise. Still, as our current insight stems from rodent studies, much more research is needed to fully understand the synergistic effects of exercise and conventional anti-cancer therapies. In particular, targeted clinical studies are warranted.

Running from Cancer at All Stages of the Cancer Continuum

Clearly, exercise training is associated with numerous health benefits, most of which are obtainable in cancer patients (Table 1). The evidence-based foundation for prescribing exercise as medicine has been described for several chronic diseases, such as type 2 diabetes and cardiovascular disease (Pedersen and Saltin,

2015). Likewise, exercise may protect cancer patients from comorbidities. In addition to the general health benefits, the available evidence indicates that exercise training also has direct cancer-specific effects. Thus, cancer patients should not just exercise because it improves their overall health, but exercise training should be implemented as a targeted approach in order to regulate cancer progression and formation, ameliorate cancer-associated adverse events, and improve anti-cancer treatment efficacy (Figure 2). If exercise does indeed drive such direct anti-cancer effects, it seems imperative to incorporate exercise training into standard treatments for cancer patients, from surgery to radiotherapy, chemotherapy, immunotherapy, and likely also other treatment modalities.

In the future, knowledge about the molecular mechanisms will allow prescription of the optimal dose, intensity, and mode of exercise training. Current evidence indicates that moderate to high-intensity endurance exercise is superior to light exercise, when aiming to target tumor intrinsic factors. This stems from the identified roles of sympathetic activation, catecholamine signaling, and mobilization of cytotoxic immune cells with high-intensity endurance training. Resistance training should be explored to prevent cancer cachexia, as this training modality provides the strongest regulation of muscular de- and regeneration processes. In addition to selecting the most appropriate mode of exercise, it is important to prescribe exercise at the right intensity. Here, it is critical to recognize that exercise intensity is a relative term that depends on the patient's basal fitness level and physical performance status.

Second, awareness of the beneficial effects of exercise training in cancer patients should be promoted globally and within healthcare systems. Despite the fact that more than 100 clinical exercise intervention studies have been performed in cancer patients, proving the safety, feasibility, and efficacy of exercise training, even in the most fragile and advanced-stage cancer patients (Schmitz et al., 2010), exercise plays a strikingly limited role in clinical oncology at present. This might be due to a lack of recognition of the positive effects of exercise on cancer. However, an even larger challenge is the current lack of clarity regarding the organizational setup required for successful clinical execution of exercise interventions. By envisioning exercise as an integrated part of cancer treatment, it follows that exercise training should be prescribed by the responsible physician in parallel with conventional anti-cancer therapy. The delivery of exercise training should be conducted by trained exercise therapists, in particular when targeting fragile patients, and this may preferably be performed in a hospital-based setting in communication with the clinical department. An important goal would be to define and implement simple physical tests that may reliably evaluate the physical state of the patient. These should document that patients are actually receiving and responding to the intervention, as well as enable individualization and proper progression in training load.

Conclusion

In conclusion, current evidence shows that physical exercise reduces cancer incidence, lowers the risk of recurrence, and secures longer lives with better quality to patients with disseminated disease. Moreover, exercise inhibits tumor growth across cancer histologies and at all stages of tumor development. Here, we have summarized the current insight into the underlying mechanisms for this protection, a fundamental basis for the increasing recognition of the beneficial effects of exercise training in prevention and treatment of cancer. Although exercise has shown positive effects in large epidemiological studies, as well as in laboratory studies, the role of exercise in the treatment of specific cancer diagnoses and at specific disease stages is far from elucidated at this time. Looking at the level of the individual cancer patient, physical exercise may for many reasons remain an overall recommendation, but this must be seen in the context of the general condition of the individual patient and the planned treatment.

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