

# Exercise Mediates Myokine Release and Tumor Suppression in Prostate Cancer Independent of Androgen Signaling

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<sup>1</sup>Exercise Medicine Research Institute, Edith Cowan University, Joondalup, Western Australia, Australia; <sup>2</sup>School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia; <sup>3</sup>Department of Urology, Centre Hospitalier de l'Université de Montréal, Montréal, Quebec, Canada; and <sup>4</sup>School of Human Movement and Nutrition Sciences, University of Queensland, St Lucia, Queensland, Australia

KIM, J.-S., D.R. TAAFFE, D.A. GALVÃO, F. SAAD, and R.U. NEWTON. Exercise mediates myokine release and tumor suppression in prostate cancer independent of androgen signaling. *Exerc. Sport Sci. Rev.*, Vol. 51, No. 4, pp. 161–168, 2023. A prominent toxicity of androgen suppression in patients with prostate cancer (PCa) is loss of skeletal muscle. Exercise may induce tumor suppression through the endocrinal function of skeletal muscle; however, this is currently unknown. In this review, we summarize our work demonstrating the acute and chronic myokine response to exercise and the tumor-suppressive effect of circulatory milieu alteration in PCa patients. **Key Words:** exercise medicine, myokines, skeletal muscle, prostate cancer, androgen suppression

## KEY POINTS

- Androgen suppression causes a substantial decline of skeletal muscle mass due to loss of the androgen-activated anabolic signal.
- Despite skeletal muscle deficiencies in patients, circulatory levels of myokines are altered by acute and chronic exercise.
- In the presence of serum collected from patients undertaking androgen suppression, prostate cancer cell growth was reduced after acute and chronic exercise.
- A bout of exercise may provide additional tumor suppression to the anticancer environment established by regular exercise.
- This specific mechanism may explain reduced disease progression and increased survival in patients with prostate cancer who are more physically active.

## INTRODUCTION

Prostate cancer (PCa) has distinctive properties compared with other cancer types because the growth of the tumor is largely dependent on the expression of androgens and recipient receptors (androgen receptors; AR) (1,2). As such, although various active

treatments are available, androgen suppression such as androgen deprivation therapy (ADT) ± androgen receptor-targeted agents (ARTA), have been widely used across all stages of PCa to slow disease progression (3,4). However, androgen suppression causes multiple adverse effects such as obesity, sarcopenia, lipid alteration, insulin resistance, coronary heart disease, and osteoporosis, reducing the quality of life for patients with PCa (5).

In the past two decades, exercise oncology, the application of exercise medicine in cancer, has received increased recognition in the care of patients with cancer (6). Specifically in patients with PCa, reduced disease progression (7) and cancer-specific mortality (8) have been observed in those patients with higher levels of physical activity. Furthermore, a retrospective study showed a positive association between lean body mass and progression-free survival in this patient group (9), suggesting the importance of preventing skeletal muscle mass loss, for example resulting from ADT (6). However, although our recent systematic review and meta-analysis (10) showed an increase in skeletal muscle mass and reduction in fat mass in patients with PCa undergoing exercise, the mechanisms by which such improvement, especially in skeletal muscle mass accrual, contribute to improved clinical outcomes, such as disease progression and survival, are not fully elucidated.

Although multiple hypotheses exist, recent research has shown an effect of exercise-induced alteration of the systemic milieu in supporting an antitumor environment for patients with cancer by applying serum collected after exercise directly to various cancer cell lines (11). Moreover, skeletal muscle has been identified as having a substantial endocrine role by producing and releasing multiple cytokines called myokines, and it has been

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suggested that myokines are a candidate molecular player for cancer cell growth suppression across multiple *in vitro* studies (12–14). However, although myokine response to exercise in noncancer patients is well documented, there has been limited work examining myokine response in patients with PCa (11). This is especially the case for patients with PCa on androgen suppression because androgens have a critical anabolic role in skeletal muscle (15); thus, it is important to understand the exercise-induced myokine response in these patients to improve exercise medicine effectiveness. As such, we recently undertook a series of studies to examine the acute and chronic myokine response to exercise as well as the tumor-suppressive effect of chronic and acute exercise-induced alteration of circulatory milieu in patients with PCa undergoing androgen suppression. This review summarizes the effect of androgen suppression on myokine expression and the tumor-suppressive potential of exercise via the endocrine function of skeletal muscle and the results from our studies in patients undertaking ADT and ARTA.

## EXERCISE IN PATIENTS WITH PROSTATE CANCER UNDERGOING ANDROGEN SUPPRESSION

### Effect of Androgen Suppression on Skeletal Muscle Mass

PCa has a unique requirement because androgens are necessary to grow and avoid apoptosis (16). Due to this necessity, blocking the action of androgens from patients is a widely used approach in patients with PCa across the disease stages. Androgens are produced in the form of testosterone and are generally found in the circulatory system (17) with production controlled by gonadotropin-releasing hormone (GnRH) from the hypothalamus and luteinizing hormone (LH) in gonadotrophs (16,17). As such, therapies targeted to inhibit physiological androgen levels by orchiectomy, injection of LH-releasing hormone analogues (ADT), with or without antiandrogen treatments (flutamide and bicalutamide) are commonly used to treat advanced PCa (16). Furthermore, once castration resistance develops, androgen-targeted agents (ARTA; enzalutamide and abiraterone acetate) are added to ADT as first-line treatment for patients to further reduce AR-activated signaling in PCa cells (16). More recently the combination of ADT + ARTA has been established as a life-prolonging first-line approach for metastatic castrate-resistant prostate cancer (mCRPC) (18).

As with many cancer treatments, androgen suppression therapy is associated with an array of adverse effects, with the loss of skeletal muscle mass a prominent toxicity because androgen signaling involving mTOR/Akt is one of the key pathways for skeletal muscle anabolism (15). Androgens stimulate satellite cell proliferation in skeletal muscle (19,20), and increased satellite cell number is associated with muscle hypertrophy (21). In a murine model, overexpression of AR on mesenchymal stem cells results in a substantial increase in lean mass (22), whereas myocyte-specific AR knockout results in lower skeletal muscle mass (23). A similar observation was made in a clinical trial that examined the effect of different systemic androgen levels on adipose tissue and lean mass in healthy individuals (24). In this study, 54 healthy men were treated with a GnRH agonist and randomized into five groups to receive weekly injections

of 25, 50, 125, 300, and 600 mg of androgen for 20 wk (24). At 20 wk, circulatory androgen levels were below normal levels in groups that received 25 and 50 mg of androgen, were maintained at baseline levels in the group receiving a weekly injection of 125 mg, and were significantly higher in the group that received 300 and 600 mg of androgen (24). Significant reductions in percentage lean mass, appendicular lean mass, and trunk lean mass were observed in groups that showed lower circulatory androgen levels than the group with high androgen levels at 20 wk (24). Specifically in patients with PCa, Smith and coworkers (25) reported an increase in body mass by 2.4%, reduction of lean body mass percentage by 2.7%, and increase in body fat mass percentage by 9.4% after a year of ADT treatment in patients with localized and advanced PCa. Similarly, in one of our cohort studies, we also observed a significant decrease of 2.4% ( $P < 0.01$ ) in whole-body lean mass, with fat mass increasing by 20.7% ( $P < 0.001$ ) in patients with PCa after 36 wk of ADT (26).

### Effect of Exercise in Patients Undergoing Androgen Suppression

Exercise as a medicine has received increased attention in clinical oncology (6), with a range of objective and patient-reported benefits accruing as a result of exercise participation (27–34) and epidemiological studies demonstrating an association between level of physical activity and survival (35). Specifically in PCa, an observational study by Kenfield *et al.* (8) involving 2705 patients with nonmetastatic PCa showed a 61% reduction in PCa-specific mortality for survivors engaging in more than 3 h·wk<sup>-1</sup> of vigorous physical activity. Richman *et al.* (7) also reported a 57% reduction in PCa progression in 1455 patients with localized PCa who participated in moderate- to vigorous-intensity physical activity more than 3 h·wk<sup>-1</sup> compared with those who participated in low-intensity physical activity less than 3 h·wk<sup>-1</sup>.

With the importance of having higher levels of physical activity in improving clinical outcomes in patients with PCa, multiple studies have demonstrated the positive impact of exercise on physiological outcomes in patients. For example, our randomized controlled trial involving 57 patients with nonmetastatic PCa undertaking androgen suppression demonstrated a significant 0.8-kg ( $P < 0.05$ ) adjusted mean difference in whole-body lean mass favoring the exercise group, with improvement in physical function and muscle strength after 12 wk of exercise (27). Furthermore, our recent systematic review and meta-analysis of 21 randomized controlled trials in patients with PCa receiving a range of active treatments showed a 0.5-kg increase in lean body mass and 1.0% reduction in fat mass percentage with exercise, indicating the efficacy of exercise in improving body composition in these patients (10). Despite the loss of androgen signaling due to androgen suppression therapy (*e.g.*, ADT), exercise has been consistently reported as efficacious for improving skeletal muscle mass with substantial improvements in muscle strength and physical function (27–34).

Although these studies provide strong evidence for the positive impact of exercise in patients undergoing androgen suppression, a direct causal relation between exercise and improved clinical outcomes such as disease progression and survival is not fully understood. Nevertheless, a recent retrospective study by Pak and colleagues (9) showed a positive association between skeletal muscle mass and overall survival (high skeletal muscle

mass, 24.1 months vs low skeletal muscle mass, 16.9 months) in 230 patients with PCa undergoing a range of treatments, suggesting that skeletal muscle may be the key linking the impact of exercise causing improved survival and reduced disease progression in patients with PCa.

## ENDOCRINE FUNCTION OF SKELETAL MUSCLE AND TUMOR SUPPRESSION

### Exercise-Induced Systemic Alteration and Tumor Suppression

Although multiple hypotheses have been proposed for exercise-induced tumor suppression, recent research has revealed the potential role of exercise-induced alteration of circulatory factors that may cause tumor suppression (Table, Fig.). This was shown by applying exercise-conditioned serum to various cancer cell lines, including PCa (36–43). For instance, Barnard and colleagues (36) demonstrated a reduction of PCa cell line LNCaP growth and increased cell apoptosis in the presence of serum obtained from healthy individuals who regularly exercised compared with serum from sedentary individuals. Furthermore, after a short-term, intense exercise and dietary intervention, exposing LNCaP cells to serum obtained after the intervention resulted in a substantial reduction of cell growth compared with cells exposed to preintervention serum with significant upregulation of tumor-suppressive p53 protein in the cells (37). Similarly, the tumor-suppressive role of exercise-conditioned serum obtained after a single bout of exercise has been demonstrated in lung, breast, colon, and PCa (11), providing further evidence for the potential tumor-suppressive role of exercise. Rundqvist *et al.* (39) reported a 31% reduction in the viability of LNCaP cells after administering serum collected from healthy individuals immediately after a single 60-min cycling bout of exercise with alteration of serum contents. In addition, Hwang and colleagues (40) demonstrated reduced LNCaP metabolic activity in the presence of serum collected after a single bout of aerobic exercise in older individuals.

Recently, researchers have demonstrated the tumor-suppressive role of exercise-induced circulatory alteration in patients with PCa, adding further evidence for exercise supporting an antitumor environment (Table, Fig.). In 2021, Kang and colleagues (41) reported a significant difference of 5.1% ( $P = 0.020$ ) in LNCaP growth with the presence of serum obtained from patients on active surveillance after 12 wk of high-intensity interval training ( $n = 26$ ) compared with usual care ( $n = 26$ ). Similarly, our work confirms the tumor-suppressive effect of exercise-induced alteration of the circulatory milieu in patients with PCa undertaking ADT and ARTA (42,43). In these studies, we directly applied serum obtained from patients with PCa to the androgen-insensitive PCa cell line DU-145 and evaluated cell growth. In the first study, exercise-conditioned serum from 10 patients with localized PCa on ADT obtained after a 12-wk mixed-mode (resistance + aerobic) exercise intervention resulted in a significant 21.3% ( $P = 0.012$ ) reduction in DU-145 cell growth (42). Likewise, in a randomized controlled trial involving patients with mCRPC undertaking ADT and ARTA, we demonstrated a 20.3% ( $P = 0.029$ ) reduction in DU-145 cells with serum obtained from the exercisers ( $n = 13$ ) compared with the controls ( $n = 12$ ) after 24 wk of mixed-mode exercise training (43). We have also examined the tumor-suppressive

effect of acutely exercise-conditioned serum involving a single bout of exercise in trained patients with mCRPC, and a substantial reduction (17%,  $P < 0.01$ ) of DU-145 cells was found with serum obtained after a 34-min high-intensity interval aerobic exercise session (44). Although there is evidence suggesting the tumor-suppressive effect of exercise-induced circulatory milieu, the molecular players responsible for direct growth reduction of PCa cells remain unclear (44). However, with the identification of skeletal muscle-induced factors (myokines) and the preclinical studies reporting the tumor-suppressive role of these molecules, myokines have been suggested as candidate molecules for these observations (11).

### Tumor-Suppressive Role of Myokines

In the early 2000s, skeletal muscle had been identified as having a substantial endocrine function with its capacity to produce and release myokines into the systemic milieu in response to muscle contraction and elongation (12–14). Released myokines allow skeletal muscle to cross talk with other organs and elicit multiple health-related benefits, consequently reducing the risk of multiple chronic diseases, including cancer (12,14).

In PCa, multiple preclinical studies have reported the potential of myokines, such as secreted protein acidic and rich in cysteine (SPARC), decorin, irisin, and fibroblast growth factor-21 (FGF-21), in PCa suppression, suggesting the endocrine function of skeletal muscle may take a role in reducing PCa cell growth (45–50). In one animal study, researchers examined tumor incidence and aggressiveness in a SPARC-null mouse model and showed a substantial reduction in both tumor incidence and aggressiveness in SPARC-null TRAMP (transgenic adenocarcinoma of mouse prostate) mice compared with TRAMP mice with normal SPARC expression, with increased Ki67 protein and Cyclin D1 levels in the SPARC-null mice (45). However, SPARC-transfected LNCaP, DU-145, and PC-3 PCa cell lines showed reduced Cyclin D1 and increased p21 and p27 protein, suggesting that SPARC may reduce PCa cell proliferation by inducing cell cycle arrest (45). In another study, exogenous SPARC treatment to these cells significantly reduced proliferation and migration of the cells, with a substantial reduction of Akt phosphorylation, while the treatment with integrin  $\beta$ 1-blocking antibody restored proliferation, migration, and Akt phosphorylation in these cells, further confirming a tumor-suppressive role of SPARC (46).

In addition, systemic injection of decorin into Pten (prostate-specific phosphatase and tensin homologue)-null mice reduced tumor size, Ki67 protein levels, and AR activation through epidermal growth factor receptor (EGFR) reduction but increased caspase-3 activity (47). PCa cell lines LNCaP, DU-145, and PC-3 also had significantly reduced proliferation, DNA synthesis, EGFR, and p-EGFR with decorin treatment, demonstrating that decorin reduces PCa cell growth by inhibiting EGFR activation and increasing apoptosis of PCa cells (47). Inhibition of PCa progression by decorin was further confirmed by Xu and colleagues (48), who showed reduced tumor size and an increased number of tumor-free mice in a PC-3 cell inoculated male mouse model injected with adenoviruses overexpressing decorin. Furthermore, treatment with another myokine, irisin, also showed reduced growth of LNCaP, DU-145, and PC-3 in a dose-dependent fashion, suggesting the tumor-suppressive role of irisin (49). A recent

TABLE. Summary of studies of altered prostate cancer cell behavior with exercised serum

Author	Duration	Subjects	Exercise Protocol	Sample	Stimulus	Outcome
<b>Healthy individuals</b>						
Barnard <i>et al.</i> (2003) (36)	Chronic exercise/diet control	34 healthy men (CON, n = 14; Diet+EX, n = 8; EX, n = 12)	Chronic habitual exercise - ≥10 yr of exercise history Exercise + diet control program - average time of 14.2 yr of program adherence	LNCaP	Exercised serum	LNCaP cell viability: Diet+EX 45%↓ (vs FBS control); EX 35%↓ (vs FBS control); CON↔ (vs FBS control); Apoptosis: Diet+EX & EX↑ (vs FBS control)
				Serum	Serum + IGF-1 Exercise/diet control	LNCaP cell viability↔ (vs FBS control) Insulin↓; IGF-1↓; IGFBP-1↑
Ngo <i>et al.</i> (2003) (37)	Short-term exercise/diet control	14 healthy men	11-d exercise and diet control program - low-fat, high-fiber diet - 30–60 min of aerobic exercise daily	LNCaP	Exercised serum Postserum + IGF-1	Cell growth↓ (30%) Cell growth↑
				Serum	Baseline serum + IGFBP-1 Exercise/diet control	Cell growth↓ (20 ng·mL <sup>-1</sup> , 23%; 50 ng·mL <sup>-1</sup> , 29%); Apoptosis↑ IGF-1 ↓; IGFBP-1↑
Leung <i>et al.</i> (2004) (38)	Chronic exercise	22 healthy men (CON, n = 10, EX, n = 12)	Habitual exercise (n = 12) - ≥10 yr of exercise history	LNCaP	Serum	Cell viability↓ (27%); PCNA protein↓ (33%); apoptosis ↑ (371%); p53 ↑ (100%)
				Serum	Exercise	Insulin↓; IGF-1↓; IGFBP-1↑
Rundqvist <i>et al.</i> (2013) (39)	Single bout of aerobic exercise	10 healthy men	65-min electrodynamically loaded cycle ergometer - 20 min at 50% of VO <sub>2max</sub> - 40 min at 65% of VO <sub>2max</sub>	LNCaP	Exercised serum	Cell viability↓ (31%); proliferation↓; cell apoptosis↔
				<i>in vivo</i>	Inoculation of serum-incubated cancer cell	Time tumor incidence↑
				Serum	Exercise	EGF↓; IGFBP-1↑
Hwang <i>et al.</i> (2020) (40)	Single bout of aerobic exercise	12 healthy men 10 healthy aged men	65-min electrodynamically loaded cycle ergometer - 20 min at 50% of VO <sub>2max</sub> - 40 min at 65% of VO <sub>2max</sub>	LNCaP, PC-3	Exercised serum	Young male subjects: LNCaP metabolic activity↔; metabolic activity PC-3↔ Aged male subjects: LNCaP metabolic activity↓; metabolic activity PC-3↔
				Immune cells in the blood	Exercise	Young male subjects: white blood cell ↑; lymphocytes↑; monocyte↔; granulocyte↑ Aged male subjects: white blood cell↑; lymphocytes↑; monocyte↔; granulocyte↑
				Serum	Exercise	Young male subjects: testosterone↑; OSM↑; SPARC↑ Aged male subjects: testosterone↔; OSM↑; SPARC↑
<b>Patients with PCa</b>						
Kang <i>et al.</i> (2021) (41)	Chronic exercise	52 patients on active surveillance (CON = 26, EX = 26)	12 wk of high-intensity interval aerobic training - 3 in-clinic exercises per wk - alternating 2-min high-intensity bouts at 85%–95% VO <sub>2max</sub> and 2-min active rest at 40% VO <sub>2max</sub> for 5–8 rounds	LNCaP	Exercised serum	Proliferation↓ (5.1%) in the exercise group (vs usual care group)
				Serum	Exercise	PSA ↓; PSA velocity↓
Kim <i>et al.</i> (2022) (42)	Chronic exercise	10 patients with PCa on ADT	12 wk of mixed-mode exercise - 300 min of exercise weekly - 3 in-clinic exercises per wk (resistance exercise: 3 sessions per week, 9 exercises, 1–4 sets, 6–12 RM) - self-directed home-based aerobic exercise	DU-145	Exercised serum	DU-145 growth↓ (21.3%); DU-145 growth rate↓
				Serum	Exercise	IGF-1↔; IGFBP-3↔; IGF-1:IGFBP-3 ratio ↔ OSM ↑; SPARC↑; decorin ↔ Positive association between lean mass changes and OSM changes
Kim <i>et al.</i> (2022) (43)	Chronic exercise	25 patients with mCRPC undertaking ADT and ART (CON = 12, EX = 13)	24 wk of mixed-mode exercise - 3 sessions per week for 24 wk - sessions 1 and 3 of the week: resistance exercise (6 exercises, 2–5 sets, 6–12 RM) + high-intensity interval aerobic exercise (6 × 60 s) - session 2: moderate-intensity continuous aerobic training (30–40 min at RPE 6 of 0–10 Borg scale)	DU-145	Exercised serum	DU-145 growth ↓; DU-145 growth area under curve↓ (20.3%)
				Serum	Exercise	IGF-1↔; IGFBP-3↔; IGF-1:IGFBP-3 ratio ↔ OSM ↑; SPARC↑; decorin ↔

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TABLE. (Continued)

Author	Duration	Subjects	Exercise Protocol	Sample	Stimulus	Outcome
Kim <i>et al.</i> (2022) (44)	Single bout of aerobic exercise	9 patients with mCRPC undertaking ADT and ARTA who completed at least 3-month exercise program	34-min high-intensity interval aerobic exercise - alternation of 4-min high-intensity bout (70%–85% maximum HR) and 2-min active rest (50%–65% maximum HR) for 6 rounds	DU-145  Serum	Exercised serum  Exercise	Baseline vs immediately after: DU-145 growth ↓, DU-145 growth area under curve ↓ Baseline vs 30 min after: DU-145 growth ↓, DU-145 growth area under curve ↓ Baseline vs immediately after: OSM ↑, IL-6 ↑, SPARC ↑, IL-15 ↑, decorin ↑ Baseline vs 30 min after: OSM ↔, IL-6 ↔, SPARC ↔, IL-15 ↔, decorin ↔

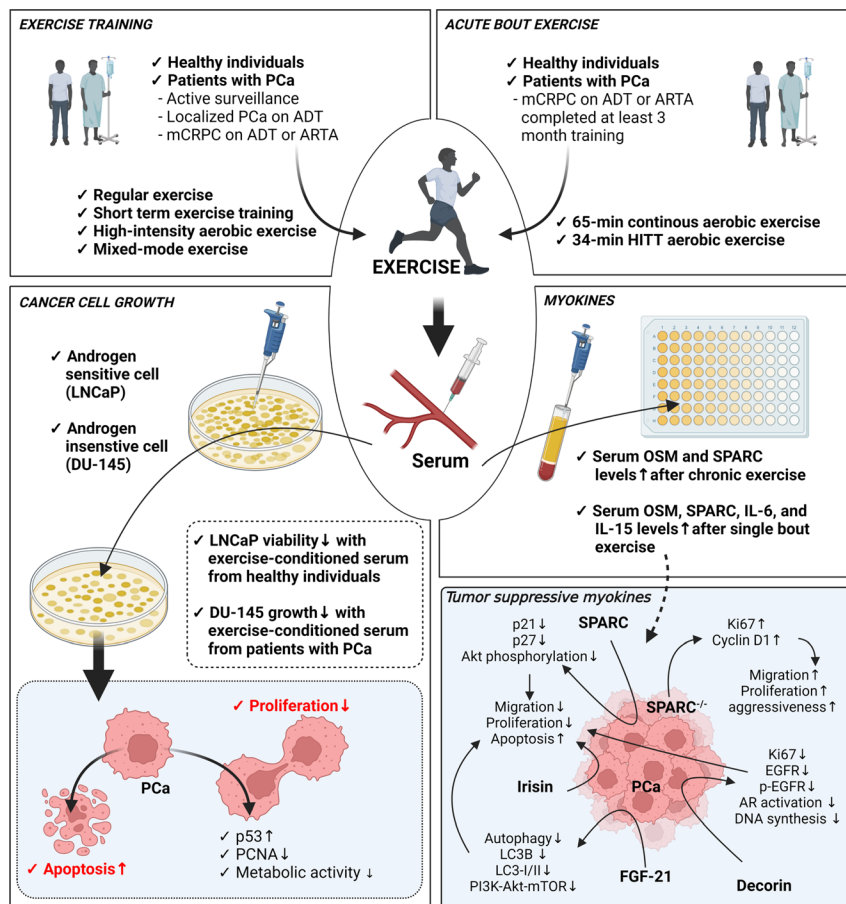
All results are statistically significant ( $P < 0.05$ ). Increased or decreased magnitudes presented in the outcome column with values in parentheses when numbers are presented.

↓, decreased; ↑, increased; ↔, unchanged; CON, control group; Diet+EX, diet control and exercise group; EGF, epidermal growth factor; EX, exercise group; FBS, fetal bovine serum; HR, heart rate; IGF-1, insulin-like growth factor-1; IGF1BP, insulin-like growth factor binding protein; RM, repetition maximum; RPE, rated perceived exertion; TB, tumor-bearing;  $VO_{2max}$ , maximum oxygen consumption.

study by Dai and colleagues (50) showed lower levels of another myokine, FGF-21, and its mRNA levels in PCa cell lines LNCaP, DU-145, and PC-3 compared with normal prostate epithelial cells (RWPE1), whereas FGF-21 transfection in these cell lines resulted in reduced proliferation, migration, and invasion. Apoptosis and autophagy of these cells were significantly increased in this study, with a substantial upregulation of the LC3B autophagy pathway (50).

### Myokine Expression in an Androgen-Deficient Environment

In multiple exercise trials involving healthy individuals and patients with metabolic disease, alteration of circulatory myokine levels after chronic exercise training as well as after a single acute bout of exercise has been well documented (12). However, because androgen deficiency substantially impacts skeletal muscle mass, it is not possible to extrapolate information on myokine



**Figure.** Effect of exercise on serum myokine levels and its tumor-suppressive effect. Application of the serum obtained from healthy individuals and patients with prostate cancer (PCa) on androgen suppression after exercise training and an acute bout of exercise-reduced androgen-sensitive PCa cancer cell line LNCaP and androgen-insensitive PCa cell line DU-145. An increase in apoptosis and reduction of proliferation with increased p53, proliferating cell nuclear antigen, and reduced metabolic activity were observed in PCa cells exposed to exercise-conditioned serum. Moreover, OSM and secreted protein acidic and rich in cysteine (SPARC) levels were increased after exercise training in patients with localized PCa and metastatic castrate-resistant prostate cancer (mCRPC) and undertaking androgen suppression therapy. In addition, serum levels of OSM, SPARC, IL-6, and IL-15 were increased in patients with mCRPC on androgen suppression after a single bout of exercise. The alteration of myokines, such as SPARC, irisin, FGF-21, and decorin, might reduce proliferation and migration and increases apoptosis.

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expression from healthy individuals and patients with metabolic disease to individuals with an androgen-suppressed environment. For instance, in a study examining the effect of myostatin (inhibits muscle hypertrophy) knockout on muscle hypertrophy in a mouse model, muscle hypertrophy was more pronounced in male mice compared with female mice (51), and myostatin overexpression reduced skeletal muscle mass more in female mice compared with male mice (52). This was partially explained in a preclinical study that demonstrated an increase of follistatin by the androgen-induced enhancement of  $\beta$ -catenin signaling, which inhibited myostatin expression in skeletal muscle (53). In addition, Iemura and colleagues (54) recently demonstrated the effect of an androgen-deficient environment on the myokine, irisin, by showing substantially lower serum irisin levels in orchidectomy mice compared with normal mice. Moreover, although the treatments patients received were not specified, a case-control study by Aslan *et al.* (55) demonstrated a significant reduction in serum irisin levels in 50 patients with PCa compared with healthy individuals.

Although the mechanisms by which skeletal muscle responds to exercise under an androgen-deficient environment regarding myokine expression remain unclear, our recent work showed a substantial alteration in serum levels of myokines in patients on ADT after chronic exercise training, resulting in a tumor-suppressive effect from the collected serum (Table, Fig.) (42,43). After 12 wk of mixed-mode exercise training, a significant alteration of resting serum levels of oncostatin M (OSM; 45%,  $P = 0.020$ ) and a trend for an increase in serum SPARC level was observed in 10 patients undertaking ADT with an improvement of body composition, specifically reduction in fat mass and preservation of lean mass (42). Similarly, after 24 wk of exercise in patients with mCRPC undertaking ADT and ARTA, there was a significant increase in serum levels of SPARC (43%;  $P = 0.022$ ) and OSM (17%;  $P = 0.005$ ) in the exercise group compared with the usual care group (43). These two studies indicate that circulatory levels of myokines at rest can be altered as part of exercise adaptation in patients with androgen suppression regardless of disease stage. Furthermore, after an acute bout of exercise in trained patients with mCRPC undertaking androgen suppression (ADT or ADT + ARTA), significant increases in serum levels of myokines, OSM, SPARC, interleukin (IL)-6, and IL-15 were observed immediately after exercise but returned to preexercise levels after 30 min postexercise (44), suggesting exercise acutely alters circulatory myokine levels in patients in an androgen signaling-deprived environment, albeit transitory.

## IMPLICATIONS AND FUTURE RESEARCH DIRECTIONS

In the past 2 decades, the benefits of exercise in reversing/ameliorating androgen suppression adverse effects have been consistently reported (27–34), and along with observational studies reporting an association between levels of physical activity and disease progression (7), exercise has been suggested as a promising treatment in the management of PCa (6). In line with this, detailed exercise recommendations in cancer management have been provided by the American College of Sports Medicine (56) and Exercise and Sports Science Australia (57). However, such exercise recommendations are not universally embedded in cancer management due to limited evidence of the causal link between exercise and improved clinical outcomes,

such as disease progression and survival. As such, a phase III randomized controlled trial, the INTERVAL-GAP4 trial, is currently ongoing to examine whether the association between exercise and cancer-specific survival is causative (58).

As crucial as it is to determine the causality of exercise in improving survival, investigating how exercise impacts tumor biology is also essential in cancer management to enhance our understanding of exercise oncology. With previous experimental studies reporting growth inhibition of cancer cells with application of myokines (36–43) and recent studies demonstrating reduced tumor growth of various cancer-type cell lines in the presence of exercise-conditioned serum (45–50), increasing attention is being given to exercise-induced cell-free/soluble factors as a tumor-suppressive mechanism (11). Furthermore, studies that examined serum myokine levels before and after exercise provide additional evidence for the tumor-suppressive endocrine function of skeletal muscle (42,43). This is important because exercise medicine not only enhances health-related outcomes but also may contribute directly to improvement of clinical outcomes, such as disease progression and survival. Collectively, exercise stimulation of skeletal muscle endocrine function may partially explain the observations of previous epidemiological studies (7,8) for patients with PCa. Furthermore, the consistent alteration of tumor-suppressive myokines, such as OSM and SPARC, in patients with PCa with different disease stages while under androgen suppression should be noted. A substantial loss of skeletal muscle mass is an adverse effect of treatments involving androgen suppression and androgen-signaling blockade (25,26). However, despite this adverse effect, skeletal muscle in patients under an androgen-suppressive environment retains the capacity to function as an endocrine organ by releasing myokines into the circulatory milieu.

Notably, our study involving an acute exercise bout in trained patients with mCRPC provides additional critical insight regarding myokine expression in patients with androgen suppression (44). Previously, we (11) suggested that at least 30 min of continuous moderate- to high-intensity exercise involving major muscle groups is required for an acute myokine response based on a comprehensive review of exercise trials examining myokine expression in healthy individuals and patients with metabolic disease. This period was confirmed in our acute study of patients with mCRPC by demonstrating that previously suggested exercise volume and intensity, more than 30 min of continuous aerobic exercise at moderate intensity ( $\sim 60\% \dot{V}O_{2max}$ ) or high-intensity ( $\dot{V}O_{2max} > 80\%$ ) interval aerobic exercise, is sufficient to drive the myokine response in this patient group (44).

In addition, Dethlefsen and colleagues (59) previously suggested that the accumulation of individual exercise bouts may suppress cancer cell growth in patients with breast cancer. This insight was provided based on their observation that serum obtained after chronic exercise (mixed-mode exercise,  $\sim 90$  min, one session per week) did not reduce cancer cell growth, but an acute exercise bout (high-intensity aerobic interval exercise,  $\sim 120$  min) significantly reduced cancer cell growth in patients with breast cancer. However, in our studies, we observed a significant reduction in PCa cells after applying the serum from both chronic (mixed-mode exercise,  $\sim 60$  min, three sessions per week) (43) and an acute exercise bout (high-intensity aerobic interval exercise,  $\sim 30$  min) (44). This may be due to higher

frequency of exercise bouts in our chronic exercise trials (three times/week vs one time/week), suggesting that the total volume of structured exercise per week is an important factor to elicit the physical and physiological adaptations that could be translated into biological adaptations that influence tumor biology.

Furthermore, our acute exercise study (44) recruited patients from our INTERVAL-GAP4 project (58), which shared the same inclusion criteria with our chronic exercise study (43), but trained for 3 months. This suggests that exercise adaptation may induce tumor suppression, with every bout of exercise potentially an additional “dose” of tumor suppression in the anticancer environment established by regular exercise. However, the threshold or optimal exercise prescription (modes, intensities, volumes, and frequency) to elicit the greatest myokine surge is still unknown. Further exercise trials for patients with PCa examining different exercise prescriptions are required for tailoring appropriate exercise prescriptions in patients undergoing androgen suppression. Moreover, it is not clear whether exercise-induced myokines influence the tumor microenvironment or directly impact tumor cells to suppress growth. In-depth investigations of intercellular signaling pathways in single-cell studies are required to enhance our understanding of the role of exercise-induced alteration of circulatory myokines. This will allow us to improve exercise prescriptions based on physiological evidence with biological insight. Lastly, the potential involvement of other circulatory factors in the anticancer environment established by regular exercise should also be acknowledged and investigated.

## CONCLUSIONS

Exercise is gaining acceptance in clinical oncology as a cancer treatment given the positive effect on patient-reported outcomes as well as physical improvement associated with exercise. Recently, researchers have demonstrated the tumor-suppressive potential of exercise via the endocrinal function of skeletal muscle, providing further necessity for patients with PCa to engage in exercise. Moreover, despite the adverse effects of commonly prescribed treatments for PCa (androgen suppression), we have shown that even patients with advanced disease and long treatment history can elicit a more potent anticancer environment by altering the circulatory milieu, and, thus, tumor microenvironment, in response to exercise. However, further research involving various exercise modes, intensities, volumes, and frequency in patients with PCa to evaluate any differential effects on myokine expression is required to enhance our understanding of the specifics of exercise in creating an anticancer environment. Furthermore, because exercise may have a different impact on skeletal muscle and endocrine function in response to varying treatments, studies investigating the effect of various exercise regimens in patients undergoing different treatments are needed for the tailoring of treatment-related appropriate exercise prescriptions. Finally, accruing knowledge that exercise drives endogenous anticancer medicine may be a powerful motivator for patients to exercise and for clinicians to recommend and support.

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