10-31-2023

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Jin-Soo Kim
Edith Cowan University

Dennis R. Taaffe
Edith Cowan University

Daniel A. Galvão
Edith Cowan University

Fred Saad
Edith Cowan University

Robert U. Newton
Edith Cowan University

10.1249/JES.0000000000000323
This is a non-final version of an article published in final form in (Kim, J. S., Taaffe, D. R., Galvão, D. A., Saad, F., & Newton, R. U. (2023). Exercise mediates myokine release and tumor suppression in prostate cancer independent of androgen signaling. *Exercise and Sport Sciences Reviews, 51*(4), 161-168. https://doi.org/10.1249/JES.0000000000000323)
Kim, J. S., Taaffe, D. R., Galvão, D. A., Saad, F., & Newton, R. U. (2023). Exercise mediates myokine release and tumor suppression in prostate cancer independent of androgen signaling. *Exercise and Sport Sciences Reviews, 51*(4), 161-168. https://doi.org/10.1249/JES.0000000000000323

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

Jin-Soo Kim[1,2], Dennis R. Taaffe[1,2], Daniel A. Galvão[1,2], Fred Saad[3], Robert U. Newton[1,2,4]

[1] Exercise Medicine Research Institute, Edith Cowan University, Joondalup, WA, 6027, Australia
[2] School of Medical and Health Sciences, Edith Cowan University, Joondalup, WA, 6027, Australia
[3] Department of Urology, Centre Hospitalier de l'Université de Montréal, Montréal, Quebec, Canada
[4] School of Human Movement and Nutrition Sciences, University of Queensland, St Lucia, 4072, QLD, Australia

Corresponding Author
Robert U. Newton, PhD, DSc, FACSM
Exercise Medicine Research Institute
Edith Cowan University
270 Joondalup Drive, Joondalup, WA 6027
AUSTRALIA
[redacted]

Short Title: Role of myokines in prostate cancer

Disclosure of Funding Sources: N/A

Conflict of Interest: Authors have no conflict of interest to declare.

Character Count: Abstract page: 1,375; Text: 28,121; Reference list: 11,505; Table: 5,242; Figure legend: 1,164; Total: 47,407 (limit: 45,885)

Table and Figures: Tables: 1; Figures: 1

ABSTRACT

A prominent toxicity of androgen suppression in prostate cancer patients 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 summarise our work demonstrating the acute and chronic myokine response to exercise and the tumor-suppressive effect of circulatory milieu alteration in prostate cancer patients.

SUMMARY

Exercise alters circulatory myokine levels and elicits tumor-suppressive effects in patients with prostate cancer undertaking androgen suppression therapy.

KEYWORDS

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 anti-cancer 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 to other cancer types since the growth of the tumor is largely dependent on the expression of androgens and recipient receptors (androgen receptors; AR) (1, 2). As such, while 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 cancer patients (6). Specifically in patients with PCa, reduced disease progression (9) and cancer-specific mortality (10) 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 (11), suggesting the importance of preventing skeletal muscle mass loss, for example resulting from ADT (6). However, although our recent systematic review and meta-analysis (8) 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, is not fully elucidated.

While multiple hypotheses exist, recent research has shown an effect of exercise-induced alteration of the systemic milieu in supporting an anti-tumor environment for patients with cancer by applying serum collected after exercise directly to various cancer cell lines (12). Moreover, skeletal muscle has been identified as having a substantial endocrine role by

producing and releasing multiple cytokines called myokines, and it has been suggested that myokines are a candidate molecular player for cancer cell growth suppression across multiple in-vitro studies (13-15). However, although myokine response to exercise in non-cancer patients is well documented, there has been limited work examining myokine response in patients with prostate cancer (12). This is especially the case for patients with prostate cancer on androgen suppression, as androgens have a critical anabolic role in skeletal muscle (16); 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 prostate cancer undergoing androgen suppression. This review summarises 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

Prostate cancer has a unique requirement as androgens are necessary to grow and avoid apoptosis (17). Due to this necessity, blocking the action of androgens from patients is a widely used approach in patients with prostate cancer across the disease stages. Androgens are produced in the form of testosterone and are generally found in the circulatory system (18) with production controlled by gonadotropin-releasing hormone (GnRH) from the hypothalamus and luteinizing hormone (LH) in gonadotrophs (17, 18). 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 prostate cancer (17). 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 prostate cancer cells (17). More recently the combination of ADT+ARTA has been established as a life-prolonging first-line approach for metastatic castrate-resistant prostate cancer (mCRPC) (19).

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 as androgen-signaling involving mTOR/Akt is one of the key pathways for skeletal muscle anabolism (16). Androgens stimulate satellite cell proliferation in skeletal muscle (20, 21) and increased satellite cell number is associated with muscle hypertrophy (22). In a murine model, overexpression of AR on mesenchymal stem cells results in a substantial increase in lean mass (23), while myocyte-specific AR knockout results in lower skeletal muscle mass (24). A similar observation was made in a clinical trial which examined the effect of different systemic androgen levels on adipose tissue and lean mass in healthy individuals (25). 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 weeks (25). At 20 weeks, 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 (25). A significant reduction in percent 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 weeks (25). Specifically in patients with prostate cancer, Smith and co-workers (26) 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 prostate cancer. 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 prostate cancer following 36 weeks of ADT (27).

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 (7, 28-34) and epidemiological studies demonstrating an association between level of physical activity and survival (35). Specifically in prostate cancer, an observational study by Kenfield et al. (10) involving 2,705 patients with non-metastatic prostate cancer showed a 61% reduction in prostate cancer-specific mortality for survivors engaging in more than 3 hours per week of vigorous physical activity. Richman et al. (9) also reported a 57% reduction in prostate cancer progression in 1,455 patients with localized prostate cancer who participated in moderate- to vigorous-intensity physical activity more than 3 hours per week compared to those who participated in low-intensity physical activity less than 3 hours per week.

With the importance of having higher levels of physical activity in improving clinical outcomes in patients with prostate cancer, multiple studies have demonstrated the positive impact of exercise on physiological outcomes in patients. For example, our randomized controlled trial involving 57 patients with non-metastatic prostate cancer 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 weeks of exercise (7). Furthermore, our recent systematic review and meta-analysis of 21 randomized controlled trials in patients with prostate cancer 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 (8). 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 (7, 28-34).

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 (11) 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 prostate cancer 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 prostate cancer.

ENDOCRINE FUNCTION OF SKELETAL MUSCLE AND TUMOR SUPPRESSION

Exercise-Induced Systemic Alteration and Tumor Suppression

While 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 1 & Figure 1)**. This was shown by applying exercise-conditioned serum to various cancer cell lines, including prostate cancer (36-43). For instance, Barnard and colleagues (36) demonstrated a reduction of prostate cancer cell line LNCaP growth and increased cell apoptosis in the presence of serum obtained from healthy

individuals who regularly exercised compared to 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 to cells exposed to pre-intervention 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 prostate cancer (12), 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 administrating serum collected from healthy individuals immediately post 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 prostate cancer, adding further evidence for exercise supporting an anti-tumor environment (**Table 1 & Figure 1**). 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 weeks of high-intensity interval training (n=26) compared to usual care (n=26). Similarly, our work confirms the tumor-suppressive effect of exercise-induced alteration of the circulatory milieu in patients with prostate cancer undertaking ADT and ARTA (42, 43). In these studies we directly applied serum obtained from patients with prostate cancer to the androgen-insensitive prostate cancer cell line DU-145 and evaluated cell growth. In the first study, exercise-conditioned serum from 10 patients with localized prostate cancer on ADT obtained after a 12-week 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 to the controls (n=12) after 24 weeks 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-minute 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 prostate cancer 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 (12).

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 (13-15). Released myokines allow skeletal muscle to crosstalk with other organs and elicit multiple health-related benefits, consequently reducing the risk of multiple chronic diseases, including cancer (13, 15).

In prostate cancer, 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 prostate cancer suppression, suggesting the endocrine function of skeletal muscle may take a role in reducing prostate cancer cell growth (45-50). In one animal study researchers examined tumor incidence and aggressiveness in a SPARC-null mice model and showed a substantial reduction in both tumor incidence and aggressiveness in SPARC-null TRAMP (transgenic adenocarcinoma of mouse prostate) mice compared to

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 prostate cancer cell lines showed reduced Cyclin D1 and increased p21 and p27 protein, suggesting that SPARC may reduce prostate cancer 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 β1 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 EGFR reduction but increased caspase-3 activity (47). Prostate cancer cell lines LNCaP, DU-145, and PC-3 also had significantly reduced proliferation, DNA synthesis, EGFR, and p-EGFR with decorin treatment, demonstrating decorin reduces prostate cancer cell growth by inhibiting EGFR activation and increasing apoptosis of prostate cancer cells (47). Inhibition of prostate cancer 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 mice 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 study by Dai and colleagues (50) showed lower levels of another myokine, FGF-21, and its mRNA levels in prostate cancer cell lines LNCaP, DU-145, and PC-3 compared to 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 up-regulation 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 (13). However, as androgen deficiency substantially impacts skeletal muscle mass, it is not possible to extrapolate information on myokine 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 mice model, muscle hypertrophy was more pronounced in male mice compared to female mice (51), and myostatin overexpression reduced skeletal muscle mass more in female mice compared to male mice (52). This was partially explained in a preclinical study that demonstrated an increase of follistatin by the androgen-induced enhancement of β-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 to 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 prostate cancer compared to 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 1 & Figure 1)** (42, 43). After 12 weeks 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, following 24 weeks 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 to 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, following 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, IL-6, and IL-15 were observed immediately after exercise but returned to pre-exercise levels after 30 minutes post-exercise (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 two decades, the benefits of exercise in reversing/ameliorating androgen suppression adverse effects have been consistently reported (7, 28-34), and along with observational studies reporting an association between levels of physical activity and disease progression (9), exercise has been suggested as a promising treatment in the management of prostate cancer (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 (12). 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 as 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 (9, 10) for patients with prostate cancer. Furthermore, the consistent alteration of tumor-suppressive myokines, such as OSM and SPARC, in prostate cancer patients 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 (26,27). 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 (12) suggested that at least 30 min of continuous moderate-

intensity 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 time period was confirmed in our acute study of mCRPC patients by demonstrating that previously suggested exercise volume and intensity, more than 30 minutes of continuous aerobic exercise at moderate intensity (~60% VO2 max) or high-intensity (VO2 max > 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, ~90 minutes, 1 session per week) did not reduce cancer cell growth, but an acute exercise bout (high-intensity aerobic interval exercise, ~120 minutes) significantly reduced cancer cell growth in patients with breast cancer. However, in our studies, we observed a significant reduction in prostate cancer cells after applying the serum from both chronic (mixed mode exercise, ~60 minutes, 3 sessions per week) (43) and an acute exercise bout (high-intensity aerobic interval exercise, ~30 minutes) (44). This may be due to higher frequency of exercise bouts in our chronic exercise trials (3 times/week vs 1 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.

Further, 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 anti-cancer environment established by regular exercise. However, the threshold or optimal exercise

prescription (modes, intensities, volumes, and frequency) to illicit the greatest myokine surge is still unknown. Further exercise trials for patients with prostate cancer 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 micro-environment 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 anti-cancer environment established by regular exercise should also be acknowledged and investigated.

CONCLUSION

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 prostate cancer to engage in exercise. Moreover, despite the adverse effects of commonly prescribed treatments for prostate cancer (androgen suppression), we have shown that even patients with advanced disease and long treatment history can elicit a more potent anti-cancer 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 prostate cancer to evaluate any differential effects on myokine expression is required to enhance our understanding of the specifics of exercise in creating an anti-cancer environment. Furthermore, as 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 anti-cancer medicine may be a powerful motivator for patients to exercise and for clinicians to recommend and support.

Additional information

Author contribution

J-S Kim, D. R. Taaffe, D. A. Galvao, and R.U. Newton researched data for the article, J-S Kim wrote the first draft of the manuscript. J-S Kim, D. R. Taaffe, D. A. Galvao, F. Saad and R. U. Newton made a substantial contribution to the discussion of the content of the manuscript. J-S Kim, D. R. Taaffe, D. A. Galvao, F. Saad and R.U. Newton reviewed and edited the manuscript prior to submission.

REFERENCES

1. Culig Z, Hobisch A, Cronauer MV, et al. Androgen receptor activation in prostatic tumor cell lines by insulin-like growth factor-I, keratinocyte growth factor, and epidermal growth factor. Cancer Res. 1994;54(20):5474-8.

2. Feldman BJ, Feldman D. The development of androgen-independent prostate cancer. Nat Rev Cancer. 2001;1(1):34-45.

3. Datta D, Aftabuddin M, Gupta DK, Raha S, Sen P. Human prostate cancer hhallmarks map. Sci Rep. 2016;6:30691.

4. Mostaghel EA, Montgomery B, Nelson PS. Castration-resistant prostate cancer: targeting androgen metabolic pathways in recurrent disease. Urol Oncol. 2009;27(3):251-7.

5. Saylor PJ, Smith MR. Adverse effects of androgen deprivation therapy: Defining the problem and promoting health among men with prostate cancer. J Natl Compr Canc Netw. 2010;8(2):211-23.

6. Schmitz KH, Campbell AM, Stuiver MM, et al. Exercise is medicine in oncology: Engaging clinicians to help patients move through cancer. CA Cancer J Clin. 2019;69(6):468-84.

7. Galvão DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: A randomized controlled trial. J Clin Oncol. 2010;28(2):340-7.

8. Lopez P, Taaffe DR, Newton RU, Galvao DA. Resistance exercise dosage in men with prostate cancer: Systematic review, meta-analysis, and meta-regression. Med Sci Sports Exerc. 2021;53(3):459-69.

9. Richman EL, Kenfield SA, Stampfer MJ, Paciorek A, Carroll PR, Chan JM. Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. Cancer Res. 2011;71(11):3889-95.

10. Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. J Clin Oncol. 2011;29(6):726-32.

11. Pak S, Kim MS, Park EY, Kim SH, Lee KH, Joung JY. Association of body composition with survival and treatment efficacy in castration-resistant prostate cancer. Front Oncol. 2020;10:558.

12. Kim J-S, Galvão DA, Newton RU, Gray E, Taaffe DR. Exercise-induced myokines and their effect on prostate cancer. Nat Rev Urol. 2021;18(9):519-42.

13. Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. Physiology (Bethesda). 2013;28(5):330-58.

14. Pedersen BK. The physiology of optimizing health with a focus on exercise as medicine. Annu Rev Physiol. 2019;81:607-27.

15. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol. 2012;8(8):457-65.

16. Dubois V, Laurent M, Boonen S, Vanderschueren D, Claessens F. Androgens and skeletal muscle: cellular and molecular action mechanisms underlying the anabolic actions. Cell Mol Life Sci. 2012;69(10):1651-67.

17. Grossmann ME, Huang H, Tindall DJ. Androgen receptor signaling in androgen-refractory prostate cancer. J Natl Cancer Insit. 2001;93(22):1687-97.

18. Lindzey J, Kumar MV, Grossman M, Young C, Tindall DJ. Molecular mechanisms of androgen action. Vitam Horm. 1994;49:383-432.

19. Saad F, Efstathiou E, Attard G, et al. Apalutamide plus abiraterone acetate and prednisone versus placebo plus abiraterone and prednisone in metastatic, castration-resistant prostate cancer (ACIS): a randomised, placebo-controlled, double-blind, multinational, phase 3 study. Lancet Oncol. 2021;22(11):1541-59.

20. Joubert Y, Tobin C. Satellite cell proliferation and increase in the number of myonuclei induced by testosterone in the levator ani muscle of the adult female rat. Dev Biol. 1989;131(2):550-7.

21. Joubert Y, Tobin C, Lebart MC. Testosterone-induced masculinization of the rat levator ani muscle during puberty. Dev Biol. 1994;162(1):104-10.

22. Sinha-Hikim I, Roth SM, Lee MI, Bhasin S. Testosterone-induced muscle hypertrophy is associated with an increase in satellite cell number in healthy, young men. Am J Physiol Endocrinol Metab. 2003;285(1):E197-205.

23. Semirale AA, Zhang XW, Wiren KM. Body composition changes and inhibition of fat development in vivo implicates androgen in regulation of stem cell lineage allocation. J Cell Biochem. 2011;112(7):1773-86.

24. Ophoff J, Van Proeyen K, Callewaert F, et al. Androgen signaling in myocytes contributes to the maintenance of muscle mass and fiber type regulation but not to muscle strength or fatigue. Endocrinology. 2009;150(8):3558-66.

25. Woodhouse LJ, Gupta N, Bhasin M, et al. Dose-dependent effects of testosterone on regional adipose tissue distribution in healthy young men. J Clin Endocrinol Metab. 2004;89(2):718-26.

26. Smith MR, Finkelstein JS, McGovern FJ, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab. 2002;87(2):599-603.

27. Galvão DA, Spry NA, Taaffe DR, Newton RU, Stanley J, Shannon T, Rowling C, Prince R. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. BJU Int. 2008; 102(1):44-7.

28. Cormie P, Newton RU, Spry N, Joseph D, Taaffe DR, Galvao DA. Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases. Prostate Cancer Prostatic Dis. 2013;16(4):328-35.

29. Cormie P, Galvão DA, Spry N, et al. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. BJU International. 2015;115(2):256-66.

30. Nilsen TS, Raastad T, Skovlund E, et al. Effects of strength training on body composition, physical functioning, and quality of life in prostate cancer patients during androgen deprivation therapy. Acta Oncol. 2015;54(10):1805-13.

31. Wall BA, Galvão DA, Fatehee N, et al. Exercise improves V˙O2max and body composition in androgen deprivation therapy–treated prostate cancer patients. Med Sci Sports Exerc. 2017;49(8):1503-10.

32. Gilbert SE, Tew GA, Fairhurst C, et al. Effects of a lifestyle intervention on endothelial function in men on long-term androgen deprivation therapy for prostate cancer. Br J Cancer. 2016;114(4):401-8.

33. Newton RU, Galvão DA, Spry N, et al. Exercise mode specificity for preserving spine and hip bone mineral density in prostate cancer patients. Med Sci Sports Exerc. 2019;51(4):607-14.

34. Dawson JK, Dorff TB, Todd Schroeder E, Lane CJ, Gross ME, Dieli-Conwright CM. Impact of resistance training on body composition and metabolic syndrome variables during androgen deprivation therapy for prostate cancer: a pilot randomized controlled trial. BMC Cancer. 2018;18(1):368.

35. Gunnell AS, Joyce S, Tomlin S, et al. Physical activity and survival among long-term cancer survivor and non-cancer cohorts. Front Public Health. 2017;5:19.

36. Barnard RJ, Ngo TH, Leung PS, Aronson WJ, Golding LA. A low-fat diet and/or strenuous exercise alters the IGF axis in vivo and reduces prostate tumor cell growth in vitro. Prostate. 2003;56(3):201-6.

37. Ngo TH, Barnard RJ, Leung PS, Cohen P, Aronson WJ. Insulin-like growth factor I (IGF-I) and IGF binding protein-1 modulate prostate cancer cell growth and apoptosis: possible mediators for the effects of diet and exercise on cancer cell survival. Endocrinology. 2003;144(6):2319-24.

38. Leung PS, Aronson WJ, Ngo TH, Golding LA, Barnard RJ. Exercise alters the IGF axis in vivo and increases p53 protein in prostate tumor cells in vitro. J Appl Physiol (1985). 2004;96(2):450-4.

39. Rundqvist H, Augsten M, Stromberg A, et al. Effect of acute exercise on prostate cancer cell growth. PLoS One. 2013;8(7):e67579.

40. Hwang JH, McGovern J, Minett GM, et al. Mobilizing serum factors and immune cells through exercise to counteract age-related changes in cancer risk. Exerc Immunol Rev. 2020;26:80-99.

41. Kang DW, Fairey AS, Boule NG, Field CJ, Wharton SA, Courneya KS. Effects of exercise on cardiorespiratory fitness and biochemical progression in men with localized prostate cancer under active surveillance: The ERASE randomized clinical trial. JAMA Oncol. 2021;7(10):1487-95.

42. Kim JS, Wilson RL, Taaffe DR, Galvao DA, Gray E, Newton RU. Myokine expression and tumor-suppressive effect of serum following 12 weeks of exercise in prostate cancer patients on ADT. Med Sci Sports Exerc. 2021;54(2):197-205.

43. Kim JS, Taaffe DR, Galvão DA, et al. Exercise in advanced prostate cancer elevates myokine levels and suppresses in-vitro cell growth. Prostate Cancer Prostatic Dis. 2022;25(1):86-92.

497 44. Kim J-S, Taaffe DR, Galvão DA, et al. Acute effect of high-intensity interval aerobic exercise on serum
498 myokine levels and resulting tumour-suppressive effect in trained patients with advanced prostate cancer.
499 Prostate Cancer Prostatic Dis. Epub 2022 Nov 29. Doi: 10.1038/s41391-022-00624-4.

500 45. Said N, Frierson HF, Jr., Chernauskas D, Conaway M, Motamed K, Theodorescu D. The role of SPARC in
501 the TRAMP model of prostate carcinogenesis and progression. Oncogene. 2009;28(39):3487-98.

502 46. Shin M, Mizokami A, Kim J, et al. Exogenous SPARC suppresses proliferation and migration of prostate
503 cancer by interacting with integrin β1. Prostate. 2013;73(11):1159-70.

504 47. Hu Y, Sun H, Owens RT, et al. Decorin suppresses prostate tumor growth through inhibition of epidermal
505 growth factor and androgen receptor pathways. Neoplasia. 2009;11(10):1042-53.

506 48. Xu W, Neill T, Yang Y, et al. The systemic delivery of an oncolytic adenovirus expressing decorin inhibits
507 bone metastasis in a mouse model of human prostate cancer. Gene Ther. 2015;22(3):247-56.

508 49.Tekin S, Erden Y, Sandal S, Yilmaz B. Is Irisin an Anticarcinogenic Peptide? Med-Science. 2015;4(2):2172-
509 80.

510 50. Dai H, Hu W, Zhang L, et al. FGF21 facilitates autophagy in prostate cancer cells by inhibiting the PI3K-
511 Akt-mTOR signaling pathway. Cell Death Dis. 2021;12(4):303.

512 51. McPherron AC, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new TGF-beta
513 superfamily member. Nature. 1997;387(6628):83-90.

514 52. Reisz-Porszasz S, Bhasin S, Artaza JN, et al. Lower skeletal muscle mass in male transgenic mice with
515 muscle-specific overexpression of myostatin. Am J Physiol Endocrinol Metab. 2003;285(4):E876-88.

516 53. Singh R, Bhasin S, Braga M, et al. Regulation of myogenic differentiation by androgens: cross talk between
517 androgen receptor/ beta-catenin and follistatin/transforming growth factor-beta signaling pathways.
518 Endocrinology. 2009;150(3):1259-68.

519 54. Iemura S, Kawao N, Okumoto K, Akagi M, Kaji H. Role of irisin in androgen-deficient muscle wasting and
520 osteopenia in mice. J Bone Miner Metab. 2020;38(2):161-71.

521 55. Aslan R, Alp HH, Eryilmaz R, et al. Can the irisin be a biomarker for prostate cancer? A case control study.
522 Asian Pac J Cancer Prev. 2020;21(2):505-9.

523 56. Campbell KL, Winters-Stone KM, Wiskemann J, et al. Exercise guidelines for cancer survivors: Consensus
524 statement from international multidisciplinary roundtable. Med Sci Sports Exerc. 2019;51(11):2375-90.

525 57. Hayes SC, Newton RU, Spence RR, Galvão DA. The Exercise and Sports Science Australia position
526 statement: Exercise medicine in cancer management. J Sci Med Sport. 2019;22(11):1175-99.

527 58. Newton RU, Kenfield SA, Hart NH, et al. Intense exercise for survival among men with metastatic castrate-
528 resistant prostate cancer (INTERVAL-GAP4): a multicentre, randomised, controlled phase III study protocol.
529 BMJ open. 2018;8(5):e022899.

530 59. Dethlefsen C, Lillelund C, Midtgaard J, et al., Exercise regulates breast cancer cell viability: systemic
531 traning adaptations verses acute exercise reponses. Breast Cancer Res Treat. 2016;159:469-769.

Table 1. Summary of studies of altered prostate cancer cell behaviour with exercised serum.

Author	Duration	Subjects	Exercise protocol	Sample	Stimulus	Outcome
Healthy individuals						
Barnard et al. (2003) (36)	Chronic exercise/diet control	34 healthy males (CON, n=14; Diet+EX, n=8; EX, n=12)	Chronic habitual exercise - ≥10 years of exercise history Exercise + Diet control program - average time of 14.2 years 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 + IGF-1	LNCaP cell viability↔ (vs. FBS control)
				Serum	Exercise/diet control	Insulin↓; IGF-1↓; IGFBP-1↑
Ngo et al. (2003) (37)	Short-term exercise/diet control	14 healthy males	11-day exercise and diet control program - low-fat, high-fiber diet - 30-60 min aerobic exercise daily	LNCaP	Exercised serum	Cell growth↓ (30%)
					Post serum + IGF-1	Cell growth↑
					Baseline serum + IGFBP-1	Cell growth↓ (20 ng/ml, 23%; 50 ng/ml; 29%); Apoptosis↑
				Serum	Exercise/diet control	IGF-1 ↓; IGFBP-1↑
Leung et al. (2004) (38)	Chronic exercised	22 healthy males (CON, n=10, EX, n=12)	Habitual exercise (n=12) - ≥ 10 years of exercise history	LNCaP	Serum	Cell viability↓ (27%); PCNA protein↓ (33%); apoptosis ↑ (371%); p53 ↑ (100%)
				Serum	Exercise	Insulin↓; IGF-1↓; IGFBP-1↑
Rundqvist et al. (2013) (39)	Single bout aerobic exercise	10 healthy males	65-min electro-dynamically loaded cycle ergometer - 20-min at 50% VO2max - 40-min at 65% of VO2max	LNCaP	Exercised serum	Cell viability↓ (31%); proliferation↓; cell apoptosis↔
				in vivo	Inoculation of serum-incubated cancer cell	Time tumor incidence↑
				Serum	Exercise	EGF↓; IGFBP-1↑
Hwang et al. (2020) (40)	Single bout aerobic exercise	12 healthy males 10 healthy aged males	65-min electro-dynamically loaded cycle ergometer - 20-min at 50% VO2max - 40-min at 65% of VO2max	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↑
Patients with prostate cancer						
Kang et al. (2021) (41)	Chronic exercise	52 patients on active surveillance	12 weeks of high-intensity interval aerobic training - 3 in-clinic exercises per week	LNCaP	Exercised serum	Proliferation↓ (5.1%) in the exercise group (vs. usual care group)

		(CON=26, EX=26)	- alternating 2-min high-intensity bouts at 85-95% VO_2max and 2-min active rest at 40% VO_2max for 5-8 rounds			
				Serum	Exercise	PSA ↓; PSA velocity↓
Kim et al. (2022) (42)	Chronic exercise	10 patients with prostate cancer on ADT	12 weeks of mixed-mode exercise - 300 min of exercise weekly - 3 in-clinic exercises per week (resistance exercise: 3 sessions/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 et al. (2022) (43)	Chronic exercise	25 patients with mCRPC undertaking ADT and ART (CON=12, EX=13)	24 weeks of mixed-mode exercise - 3 sessions/week for 24 weeks - sessions 1 and 3 of the week: resistance exercise (6 exercises, 2-5 sets, 6-12 RM) + high-intensity interval aerobic exercise (6 x 60 sec) - session 2: moderate-intensity continuous aerobic training (30-40 minutes 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 ↔
Kim et al. (2022) (44)	Single bout 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	Exercised serum	Baseline vs. immediately after: DU-145 growth ↓, DU-145 growth area under curve ↓ Baseline vs. 30-min post: DU-145 growth ↓, DU-145 growth area under curve ↓
				Serum	Exercise	Baseline vs. immediately after: OSM ↑, IL-6 ↑, SPARC ↑, IL-15 ↑, decorin ↑ Baseline vs. 30-min post: OSM ↔, IL-6 ↔, SPARC ↔, IL-15 ↔, decorin ↔

CON, control group; Diet+EX, diet control and exercise group; EX, exercise group; FBS, fetal bovine serum; TB, tumor-bearing; IGF-1, insulin-like growth factor-1; IGFBP, insulin-like growth factor binding protein; EGF, epidermal growth factor; OSM, oncostatin M, SPARC, secreted protein acidic and rich in cysteine; VO_2max, maximum oxygen consumption; ADT, androgen deprivation therapy; RM, repetition maximum; CON, control group; EX, exercise group; RPE, rated perceived exertion; ARTA, androgen receptor targeted agent; IL-6, interleukin 6; IL-15, interleukin 15; HR, heart rate; ↑Indicate increased; ↓ indicate decreased; ↔ indicate unchanged. 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.

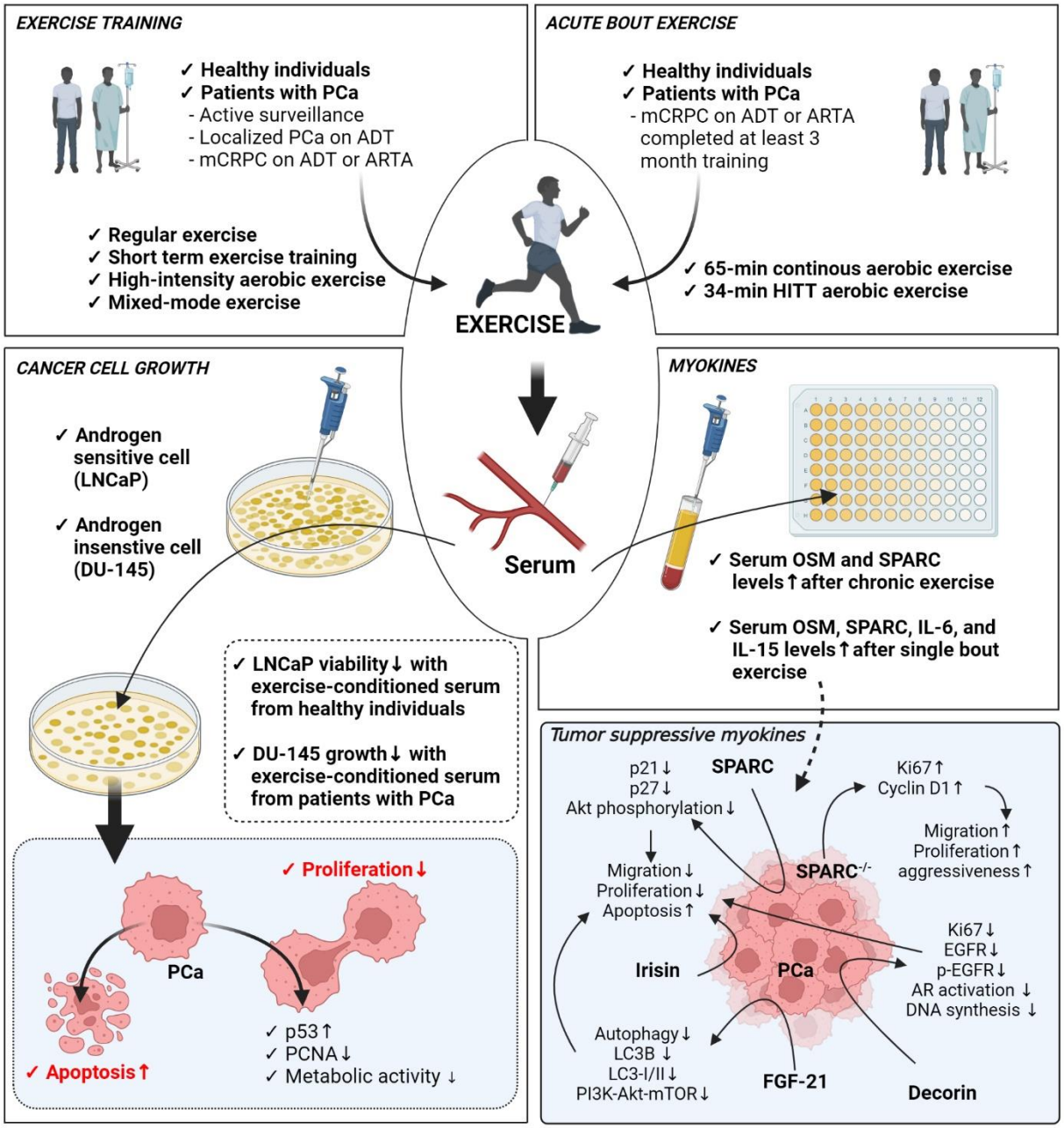

Figure 1. Effect of exercise on serum myokine levels and its tumor-suppressive effect.

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, serum oncostatin M (OSM) and secreted protein acidic and rich 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, interleukin-6 (IL-6), interleukin-15 (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.