

# Skeletal Muscle as a Trainable Anticancer Endocrine Organ: Integrating Myokines, Exercise-Derived Extracellular Vesicles, and Immunometabolic Reprogramming in Exercise Oncology

Jingyu Chen\*

School of Sports Economics and Management, Xi'an Physical Education University, Xi'an 710068, Shaanxi, China

*\*Author to whom correspondence should be addressed.*

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**Abstract:** Exercise oncology has moved from epidemiological association to mechanistic science, yet contracting skeletal muscle is still treated in most oncological models as a bystander rather than as an active regulator of tumour biology. This review integrates evidence from prospective cohorts, controlled exercise trials, tumour-bearing animal models and human ex vivo serum and extracellular vesicle (EV) studies into a single three-level muscle-tumour crosstalk axis. At the first level, repeated contraction remodels the muscle secretome, releasing soluble myokines and EV cargo that act directly on neoplastic cells. At the second level, each exercise bout—and, cumulatively, its chronic repetition—reshapes systemic immunometabolic conditions: immune-cell trafficking, catecholamine and substrate availability, insulin signalling and low-grade inflammation. At the third level, these systemic changes converge on the tumour microenvironment, altering immune infiltration, vascular function, hypoxia, drug delivery and proliferative signalling. The same axis is supported in reverse by the consistent prognostic weight of sarcopenia and cancer cachexia. The 2025 CHALLENGE trial, which improved disease-free survival after adjuvant therapy for colon cancer, supplies the first survival-grade clinical evidence. The review closes with a mechanism-informed prescription framework and a ranked set of unresolved questions concerning EV standardisation, dose-response, tumour-type specificity and synergy with immunotherapy.

**Keywords:** Cancer survivorship; Tumour microenvironment; Exerkines; Natural killer cells; Sarcopenia; Exercise prescription; Immunotherapy

**Online publication:** October 15, 2026

# 1. Introduction

For most of its short history, exercise oncology asked a public-health question: whether physically active people developed cancer less often and lived longer after diagnosis. The answer, replicated across cohorts and continents, was broadly affirmative <sup>[1,2]</sup>. A more demanding question has since taken its place. If physical activity changes the trajectory of a disease defined by autonomous cell proliferation, then something that leaves the working muscle during and after exercise must reach a tumour, or reach the systems that control one. Identifying that “something” has turned exercise from a supportive-care recommendation into a problem of molecular oncology <sup>[3,4]</sup>.

Skeletal muscle is well suited to this role. It is the largest organ in most adults; it is highly plastic, and during contraction it behaves as an endocrine and paracrine organ rather than as a passive motor. The myokine concept, formalised by Pedersen and Febbraio <sup>[5]</sup> and extended by Severinsen and Pedersen <sup>[6]</sup>, holds that muscle fibres secrete several hundred peptides and small proteins whose combined profile depends on contraction type, intensity and training status. Exercise also mobilises a second, less widely appreciated signal pool: extracellular vesicles (EVs) carrying proteins, messenger and microRNAs, and mitochondrial-derived material that can enter distant tissues <sup>[7,8]</sup>. Superimposed on both are the classical systemic responses to exercise—catecholamine surges, altered substrate flux, haemodynamic shear and the repeated, orderly mobilisation and redistribution of leucocytes <sup>[9,10]</sup>.

Three observations motivate integrating these lines of evidence rather than reviewing them in parallel. First, no single mediator accounts for the epidemiological signal: candidate myokines, EV cargo, immune mechanisms and metabolic hormones each explain a part, and their effects converge on the same set of cancer hallmarks <sup>[11,12]</sup>. Second, several apparent contradictions in the field—above all the opposing behaviour of interleukin-6 (IL-6) released during a workout and IL-6 sustained in chronic inflammation—dissolve once timing, source and context are distinguished <sup>[13,14]</sup>. Third, clinical exercise science and tumour biology still speak different languages: prescription trials report quality of life and fitness, whereas mechanistic studies report signalling pathways, and neither side routinely maps its outcomes onto the other.

This review develops a three-level crosstalk framework in which a trainable muscle secretome (Level 1) acts through a remodelled systemic immunometabolic environment (Level 2) to reprogramme the tumour microenvironment (Level 3; Figure 1). We then read the population and clinical evidence—including the first phase III trial to show an exercise effect on cancer-free survival—through that framework, and use it to derive a mechanism-informed approach to prescription. The aim is not to claim that exercise treats cancer; it is to specify, as precisely as current evidence allows, how a contracting muscle could, where the evidence is firm, and where the mechanistic chain remains speculative.

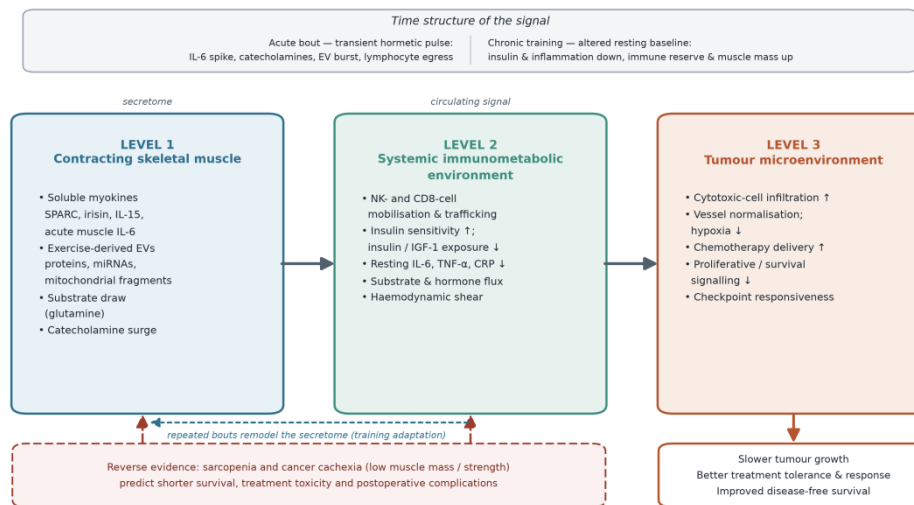


**Figure 1.** The three-level muscle-tumour crosstalk axis.

## 2. Literature search and evidence selection

This is a narrative, mechanistically oriented integrative review, not a systematic review, and the methods below are reported so that the scope and limits of the evidence base are explicit. Peer-reviewed literature was identified through PubMed/MEDLINE, Web of Science, Scopus and the Cochrane Library from inception to August 2025. Search strings combined terms for exercise, physical activity, aerobic training and resistance training with terms for neoplasia, tumour microenvironment, myokines, exerkinases, extracellular vesicles, exosomes, immune surveillance, natural killer cells, sarcopenia, cachexia and cancer survival. Reference lists of retrieved articles and relevant guidelines were hand-searched forward and backward.

We gave priority to prospective pooled cohorts and meta-analyses for population claims; randomised controlled trials and multidisciplinary consensus statements for clinical claims; and controlled tumour-bearing models, human ex vivo exercise-conditioned serum studies and characterised EV experiments for mechanistic claims. Preprints and conference abstracts were not used as primary support. Where mechanistic evidence derives almost entirely from cell lines or rodent models, this is stated in the text, because the inferential step from a wheel-running C57BL/6 mouse to a patient receiving chemotherapy is long and should be visible to the reader. Evidence from exercise-conditioned human serum and EV transfer experiments is treated as an intermediate tier: it uses human biology but removes tissue architecture and immune context. Claims that could not be supported by at least two independent groups, or by one group with convergent model systems, are phrased as hypotheses rather than findings.

## 3. Population-level evidence: From risk reduction to survival

### 3.1. Primary prevention: Activity, fitness and cancer risk

The preventive case rests on a scale of association that individual confounders have struggled to explain. The pooled analysis of 1.44 million US and European adults by Moore et al<sup>[1]</sup> linked leisure-time physical activity to a statistically significant lower risk of 13 of 26 cancer sites examined after multivariable adjustment;

inverse associations were strongest for oesophageal adenocarcinoma, liver, lung, kidney, endometrial and colon cancers, with adjusted risk reductions of roughly 10-40%. The 2018 US Physical Activity Guidelines expert evaluation and the American College of Sports Medicine (ACSM) roundtable converged on a core list of cancers—bladder, breast, colon, endometrial, oesophageal, renal and gastric cardia—for which the evidence of lower risk was judged strong<sup>[15]</sup>. Sedentary behaviour shows a complementary pattern: prolonged sitting is associated with risk and mortality partly, though not entirely, independent of structured exercise<sup>[2]</sup>.

These associations survive adjustment for adiposity, diet, smoking and socioeconomic position, but residual confounding cannot be excluded in observational data, and effect sizes are modest at the individual level. Cardiorespiratory fitness, measured objectively rather than recalled, narrows this weakness: higher fitness is associated with lower incidence and mortality across several cancers with steeper gradients than self-reported activity, a finding consistent with a biological rather than a purely behavioural pathway<sup>[2]</sup>. The mechanistic question—what mediates a risk reduction recorded over decades—cannot be answered by cohorts, but it sets the target that molecular studies must hit.

### **3.2. Post-diagnosis activity and survival**

After diagnosis, the evidence sharpens, because the comparison is between patients who share a disease. In the Nurses' Health Study, women with stage I-III breast cancer who accumulated about nine metabolic-equivalent hours of activity per week, roughly half an hour of brisk walking each day, showed approximately half the risk of death from any cause, and from breast cancer specifically, relative to the least active women, with a gradient across activity categories rather than a threshold<sup>[16]</sup>. Comparable associations between post-diagnosis activity and lower total and cancer-specific mortality have since been reported for colorectal and prostate cancer and in pooled analyses. Observational survival data remain vulnerable to reverse causation—sicker patients exercise less—and statistical adjustment for disease stage and performance status reduces, but does not eliminate, the association.

A randomised trial with a survival endpoint was therefore the missing piece. The Colon Health and Life-Long Exercise Change (CHALLENGE) trial randomised 889 patients with stage III colon cancer after adjuvant chemotherapy to a structured, supervised aerobic and resistance programme or to general health materials. At a median follow-up approaching five years, the exercise arm achieved a five-year disease-free survival of 80.3% against 73.9% in controls (hazard ratio 0.72; 95% confidence interval 0.55-0.94), with an eight-year overall survival of 90.3% versus 83.2%<sup>[17]</sup>. CHALLENGE is the first phase III trial to demonstrate that a structured exercise intervention improves a cancer endpoint, and it converts a long-standing observational signal into an interventional one. A single trial in one disease stage does not establish generality, but it does establish proof of principle that a behavioural intervention delivered through skeletal muscle can alter the natural history of resected malignancy.

### **3.3. The mirror image: Sarcopenia, cachexia and adverse outcomes**

If preserving and training muscle is protective, losing it should be harmful, and the sarcopenia and cachexia literature supplies exactly this reverse image. Cancer cachexia is defined by an international consensus as a multifactorial syndrome of ongoing skeletal-muscle loss (with or without fat loss) that cannot be fully reversed by nutrition and leads to progressive functional impairment, operationally anchored on weight loss greater than 5% or equivalent low body-mass index with depletion<sup>[18]</sup>. Sarcopenia, redefined by the European

Working Group on Sarcopenia in Older People as low muscle strength with low muscle quantity or quality, is measured in oncology chiefly through computed tomography cross-sectional muscle area at the third lumbar vertebra <sup>[19]</sup>.

Across solid tumours, radiologically defined sarcopenia at diagnosis is associated with shorter survival, higher postoperative complication rates, greater dose-limiting chemotherapy toxicity and reduced functional reserve. The meta-analysis by Shachar et al. <sup>[20]</sup> found sarcopenia roughly doubled the hazard of death across solid-tumour cohorts and consistently predicted treatment toxicity and postoperative infection; a disease-specific synthesis in lung cancer reached the same conclusion <sup>[21]</sup>. Sarcopenia is not synonymous with thinness: patients with normal or even elevated body mass index can be sarcopenic, and body-composition phenotype outperforms weight as a prognostic marker. The two lines of literature—exercise training improving outcomes and muscle depletion worsening them—are usually cited separately, but they describe the same axis from opposite ends. A mechanistic account of exercise in oncology that ignores muscle mass is therefore incomplete in both directions.

## **4. Axis Level 1: The contracting muscle secretome**

### **4.1. Soluble myokines as direct tumour regulators**

A myokine is a cytokine or other peptide produced and released by skeletal-muscle fibres in response to contraction, with autocrine, paracrine or endocrine effects. The contraction-induced secretome differs qualitatively from the inflammatory secretome of sedentary adipose tissue: it is transient, it is coupled to energy status through AMP-activated protein kinase and calcium signalling, and trained muscle releases a broader and better-timed profile than untrained muscle. Several members of this profile act directly on neoplastic cells, and these offer the shortest mechanistic route from a contraction to a tumour.

Secreted protein acidic and rich in cysteine (SPARC) is the clearest genetically anchored example. Aoi et al. <sup>[22]</sup> showed that regular exercise raises muscle and circulating SPARC, that SPARC suppresses the formation of aberrant crypt foci and azoxymethane-induced colon tumourigenesis in mice by inducing caspase-8-dependent apoptosis in dysplastic cells, and that anti-SPARC antibody abolishes the protective effect of exercise. Because SPARC also restrains extracellular-matrix remodelling, the same molecule links exercise to two early carcinogenic processes, dysregulated cell survival and stromal remodelling. Irisin, the cleaved product of the exercise- and PGC-1 $\alpha$ -responsive membrane protein FNDC5, illustrates both the promise and the complexity of this class. In vitro, irisin reduced viability and motility in malignant breast epithelial cells while sparing their non-malignant counterparts <sup>[23]</sup>, and it slowed pancreatic cancer-cell expansion through activation of AMP-activated protein kinase and inhibition of mammalian target of rapamycin signalling <sup>[24]</sup>. Other contraction-responsive factors—including oncostatin M, decorin, follistatin and IL-15—constrain proliferation, restrain epithelial-mesenchymal transition or support cytotoxic lymphocytes, and are reviewed in detail elsewhere <sup>[25]</sup>. The shared logic is that a single bout produces a pulse of factors that individually are weak and pleiotropic but that, repeated thousands of times across training, exert a sustained selective pressure against transformed cells.

### **4.2. The acute-versus-chronic IL-6 paradox resolved**

No molecule has caused more confusion than IL-6. Tumour biology generally treats IL-6 as an adverse, tumour-promoting cytokine that drives signal transducer and activator of transcription 3 signalling,

suppresses local immunity and correlates with poor prognosis, yet exercise releases IL-6 in quantities orders of magnitude above resting levels without apparent pro-tumour effect. The paradox is resolved by source, timing and molecular context rather than by the ligand itself.

Contracting muscle fibres transcribe and release IL-6 in an intensity- and duration-dependent manner, in the absence of a preceding tumour-necrosis-factor or IL-1 $\beta$  signal. The pulse is brief, peaking at exercise cessation and clearing within hours, and it is followed by a counter-regulatory rise in IL-1 receptor antagonist and IL-10—the anti-inflammatory arm of the acute response. Chronic, tumour-or adipose-derived IL-6 differs in every relevant respect: it is sustained, embedded in a pro-inflammatory cytokine milieu, and acts on a tissue in which soluble IL-6 receptor and downstream inflammatory circuits are already primed. Repeated training does not raise baseline IL-6; it lowers it, while preserving the acute pulse. The clinical implication is that circulating IL-6 measured in a resting patient and IL-6 measured minutes after a workout are biologically different signals and should not be conflated. This distinction also explains why exercise can simultaneously suppress chronic low-grade inflammation and exploit acute IL-6 as a signalling intermediate, most notably in immune-cell mobilisation (Section 6.1) and in the DNA-damage response of colon cancer cells exposed to post-exercise serum (Section 5.3).

### **4.3. Substrate competition between muscle and tumour**

Beyond secreted signals, a contracting muscle competes with a tumour for metabolic substrates. Many tumours are glutamine-addicted, using glutamine for the tricarboxylic-acid cycle, nucleotide synthesis and redox defence. Pedersen et al. <sup>[26]</sup> reported that exercise lowered glutamine availability to tumour cells in mice, suppressed tumour growth and simultaneously attenuated cancer-driven muscle wasting; supplementing glutamine reversed the suppression. The result reframes the tumour-muscle relationship as a zero-sum metabolic contest in which a trained, substrate-demanding muscle deprives the tumour of a conditionally essential nutrient. The work is preclinical and effector lymphocytes also require glutamine, so therapeutic substrate restriction must be approached carefully, but the study supplies a mechanism that is independent of immune or hormonal signalling and that directly couples systemic metabolism to tumour anabolism.

### **4.4. Catecholamine-dependent tumour-suppressor signalling**

Acute exercise is also a controlled sympathetic stimulus, and the resulting catecholamine surge reaches tumour cells through  $\beta$ -adrenergic receptors. Dethlefsen et al. <sup>[27]</sup> found that exercise-conditioned serum, and epinephrine or norepinephrine alone, activated the Hippo tumour-suppressor pathway in breast cancer cells: large tumour suppressor kinases 1 and 2 phosphorylated the transcriptional co-activator yes-associated protein (YAP), retaining it in the cytoplasm and denying the nucleus a driver of proliferation and organ growth. Inhibition of  $\beta$ -adrenergic signalling or knockdown of Hippo kinases abolished the effect, while voluntary running lowered tumour burden in vivo. These data sit in productive tension with a separate observational literature linking chronic stress signalling—and pharmacological  $\beta$ -blockade—to cancer outcomes, and again the resolution lies in pattern: intermittent, physiological catecholamine pulses coupled to muscle signalling differ from sustained adrenergic drive in a sedentary, stressed host. The contrast between acute hormetic exposure and chronic stress biology runs throughout exercise oncology and offers a useful organising principle for findings that otherwise look contradictory.

## **5. Axis level 2: Exercise-derived extracellular vesicles and the circulating signal**

### **5.1. Kinetics and cellular origins of the exercise EV burst**

EVs—lipid-bilayer vesicles released by most cell types, encompassing small EVs (exosome-scale, roughly 30-150 nm) and larger microvesicles—offer muscle a vector that proteins alone cannot provide: protected, targeted, multi-cargo delivery across the circulation. A single bout of incremental cycling raises circulating small-EV counts within minutes, with a rapid post-exercise decline <sup>[28]</sup>. Cellular origin is heterogeneous: platelets, endothelial cells and leucocytes all contribute to the exercise-triggered burst, and platelet-derived vesicles account for a substantial fraction of the acute signal <sup>[29]</sup>. In a proteomic study of healthy men before and after treadmill exercise, Whitham et al. identified hundreds of vesicular proteins whose composition changed acutely, including proteins traceable to contracting muscle, and demonstrated uptake of exercise-derived vesicles by the liver, placing EVs among the carriers of inter-organ crosstalk. The field has moved from asking whether exercise releases EVs—it does, reproducibly and dose-dependently—to asking what their cargo does to a recipient tumour cell.

### **5.2. Cargo: Proteins, microRNAs and mitochondrial-derived material**

EV cargo is selectively packaged rather than a random sample of the parent cytoplasm, and exercise changes the packaging. Systematic review of in vivo and ex vivo models confirms that acute and chronic training alter vesicular protein and small-RNA profiles in a modality-dependent fashion, with aerobic and resistance exercise producing distinguishable signatures <sup>[30]</sup>. In humans, an acute exercise bout remodelled extracellular plasma microRNAs, including miR-206 and miR-30c, whose predicted targets cluster in cancer-related pathways <sup>[31]</sup>. Vesicles also carry mitochondrial-derived constituents—mitochondrial proteins and fragments of mitochondrial DNA—consistent with the emerging view that exercise mobilises mitochondrial material for intercellular quality control and signalling <sup>[32]</sup>. Whether intact, functional mitochondria transfer into the circulation after exercise in humans remains under active debate and should not yet be stated as established; vesicular mitochondrial fragments are the better-supported observation.

### **5.3. Direct anti-tumour actions: EV transfer and exercise-conditioned serum**

The most direct test of Level 2 asks whether blood taken after exercise changes the behaviour of cancer cells. Two experimental designs converge on the same answer. In the first, vesicles harvested from exercised donors are transferred to tumour systems. Sadovska et al. <sup>[33]</sup> isolated EVs from exercise-trained rats and showed that repeated intravenous injection slowed prostate-cancer xenograft growth—primary tumours were roughly one-third smaller—while suppressing migration, invasion and mesenchymal markers in vitro, an effect absent with vesicles from sedentary animals. In the second design, whole post-exercise serum or plasma is applied to cancer cells ex vivo. Serum drawn after exercise inhibited human lung-cancer cell proliferation and survival in association with reduced phosphorylation of Akt, mammalian target of rapamycin and extracellular-signal-regulated kinase <sup>[34]</sup>. A systematic review and meta-analysis pooling these human studies found a consistent, moderate reduction in cancer-cell growth after exposure to acute-exercise serum <sup>[35]</sup>, and a later controlled experiment attributed part of the anti-proliferative effect in colon cancer cells to IL-6-dependent regulation of the DNA-damage response <sup>[36]</sup>—the same acute IL-6 pulse discussed in Section 4.2, now placed downstream of a measurable tumour-cell phenotype. Metcalfe et al. <sup>[37]</sup> review the design requirements of these “window-of-opportunity” serum studies and note effect sizes that vary with exercise intensity, sampling time and cell line. The convergence across donor species, tumour types and

laboratories is unlikely to be artefactual, although the ex vivo setting removes immune and stromal context and cannot establish in vivo tumour shrinkage.

#### **5.4. Methodological cautions**

The EV literature is younger than the myokine literature and its methods are less settled. Bulk cell-free DNA is released during exercise independently of vesicles, so post-exercise plasma effects cannot be attributed to EVs without adequate isolation and depletion controls<sup>[38]</sup>. Pre-analytical variables—venepuncture order, platelet activation, centrifugation protocols, freeze-thaw cycles, vesicle-size gates and protein quantification—materially change reported particle counts and cargo, and terminology still mixes exosomes, microvesicles and the broader class of extracellular particles<sup>[32]</sup>. Claims that exercise EVs carry a specific tumour-suppressive microRNA require, at minimum, donor-matched controls, vesicle-depleted plasma controls and demonstration that the cargo is intravesicular rather than co-isolated. These are not pedantic objections: the therapeutic translation of exercise EVs, whether as biomarkers of training response or as engineered “exercise mimetics”, depends on the cargo being identifiable and reproducible.

### **6. Axis level 3: Systemic immunometabolic Reprogramming of the tumour microenvironment**

#### **6.1. Immune surveillance: NK-cell and CD8+ T-cell mobilisation**

The most thoroughly characterised link between an exercise bout and a tumour runs through cytotoxic lymphocytes. In the foundational experiment, mice with voluntary wheel access showed slower melanoma and lung-cancer xenograft growth and fewer experimental metastases than sedentary controls<sup>[39]</sup>. Running induced a marked epinephrine-dependent mobilisation of natural killer (NK) cells into the circulation, followed by IL-6-dependent redistribution and increased NK-cell infiltration of the tumour. Either  $\beta$ -adrenergic blockade or IL-6 blockade abolished both the immune-cell trafficking and the tumour suppression, establishing a causal chain from contraction to catecholamine and IL-6 release, to lymphocyte trafficking, to tumour immune infiltration. The same mobilisation logic applies to CD8+ T cells and monocytes, which are recruited from marginal pools during exercise and survey peripheral tissues in the recovery window<sup>[14]</sup>.

The older exercise-immunology literature described this transient lymphocytosis, and the corresponding fall below baseline some hours later, as an “open window” of infection risk. In the oncology context the interpretation inverts: successive bouts repeatedly redeploy cytotoxic cells to tissues that sedentary physiology surveys far less often, and trained individuals show higher circulating cytotoxic-cell counts and function at rest. The effect is not unlimited—tumours with profoundly immunosuppressive microenvironments may exclude infiltrating cells—but it supplies a biologically plausible route by which exercise could complement immunotherapy.

#### **6.2. Myokine–lymphocyte crosstalk and checkpoint-inhibitor synergy**

Muscle-derived signals do more than move lymphocytes around; they shape lymphocyte state. IL-15 is a myokine with non-redundant roles in CD8+ memory and NK-cell maintenance, and contraction raises its bioavailability<sup>[25]</sup>. Kurz et al.<sup>[40]</sup> exploited this in the KPC mouse model of pancreatic ductal adenocarcinoma, an immunologically “cold” tumour. Aerobic exercise training engaged the IL-15/IL-15 receptor- $\alpha$  axis,

expanded tumour-infiltrating CD8<sup>+</sup> T cells with an effector, less exhausted phenotype, slowed tumour growth and extended survival; when exercise was combined with anti-programmed-death-1 therapy the two acted synergistically, an effect lost after CD8<sup>+</sup> depletion. This is among the strongest mechanistic arguments that exercise can convert an immunologically inert tumour into one more responsive to checkpoint blockade.

The enthusiasm generated by such findings needs a counterweight. Buss et al. <sup>[41]</sup> combined exercise with anti-PD-1 across tumour models and found the interaction to be tumour-type dependent: the microenvironmental changes induced by training were not uniformly favourable, and in one model the added benefit over checkpoint blockade alone was limited. Human data are still preliminary: small neoadjuvant and peri-immunotherapy studies are underway, but adequately powered randomised trials with response and survival endpoints have not yet been reported. Exercise is therefore best framed at present as a candidate immune-adjuvant with strong preclinical support and promising early human signals, not as a proven enhancer of checkpoint response.

### **6.3. Vascular normalisation, hypoxia and treatment delivery**

A solid tumour typically contains chaotic, poorly perfused vessels that create hypoxic regions; hypoxia selects for aggressive clones, drives angiogenesis and impedes the delivery of chemotherapy and radiotherapy efficacy. Exercise acts on this component of the microenvironment through repeated haemodynamic and shear stress. In an orthotopic murine breast-cancer model, voluntary wheel running increased tumour vessel density and pericyte coverage, reduced hypoxic fraction, increased intratumoural doxorubicin concentration and chemotherapeutic response, and slowed tumour growth relative to sedentary controls <sup>[42]</sup>. The pattern resembles a partial vascular normalisation rather than the pro-angiogenic stimulation a naïve reading might predict: better organised, better perfused vessels rather than more chaotic ones <sup>[43,44]</sup>. Improved perfusion also raises oxygen availability during radiotherapy and may reduce the hypoxic fraction of surviving clonogens. These findings provide a mechanistic rationale for timing exercise around treatment sessions, although the precise scheduling that maximises drug delivery in patients—same-day versus recovery-day exercise—has not been established.

### **6.4. Systemic metabolism, hormones and chronic inflammation**

Tumours are bathed in the host's metabolic milieu, and training improves several of its oncogenic features. Chronically elevated insulin and bioavailable insulin-like growth factor 1 activate proliferative and anti-apoptotic signalling in many tumours, and sedentary, insulin-resistant states sustain them; repeated exercise increases insulin sensitivity, lowers post-prandial insulin exposure and reduces hepatic growth-factor output <sup>[3]</sup>. Adipose-driven chronic inflammation supplies a second systemic input: tumour-necrosis-factor  $\alpha$ , resting IL-6 and C-reactive protein are elevated in inactive, obese hosts and fall with training, narrowing the inflammatory background against which tumours progress <sup>[14]</sup>. These pathways are slower and less dramatic than acute immune mobilisation, but they operate continuously across years of survivorship, which is the timescale on which recurrence risk is expressed.

### **6.5. Mapping the three-level axis onto the cancer hallmarks**

Read together, the three levels map onto the organising framework of cancer hallmarks without forcing a one-to-one correspondence <sup>[11, 12]</sup>. Soluble myokines and substrate competition address sustained proliferative signalling and deregulated cellular energetics. Immune-cell mobilisation and myokine–lymphocyte crosstalk

address evasion of immune destruction. Vascular normalisation addresses angiogenesis induction and tumour-promoting inflammation, while catecholamine-driven Hippo activation and irisin signalling address resistance to cell death and proliferative survival. EV cargo potentially acts across several of these at once. No single mediator is decisive, and that is precisely the point: exercise is a pleiotropic intervention that applies modest, convergent pressure against several hallmarks simultaneously rather than a strong pressure against one. This multi-target profile is a weakness for reductionist proof—blocking one pathway rarely abolishes the whole effect—and a strength for an adjunctive strategy intended to complement surgery, cytotoxic therapy, targeted therapy and immunotherapy rather than replace them. The principal contraction-derived signals, their reported anti-tumour actions and the tier of evidence supporting each are summarised in **Table 1**.

**Table 1.** Representative contraction-derived signals with reported anti-tumour actions and the supporting evidence tier

| Signal                         | Exercise-responsive source                     | Reported anti-tumour action                                                                                      | Evidence tier                              |
|--------------------------------|------------------------------------------------|------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| SPARC                          | Contracting muscle; raised by regular training | Caspase-8 apoptosis in dysplastic colonocytes; restraint of matrix remodelling                                   | Animal model with blockade rescue          |
| Irisin (FND5)                  | Muscle, PGC-1 $\alpha$ dependent               | Reduced viability of malignant but not normal breast epithelium; AMPK–mTOR inhibition in pancreatic cancer cells | In vitro                                   |
| Acute muscle IL-6              | Transient fibre-derived pulse                  | NK and CD8-cell mobilisation; regulation of DNA-damage response in colon cancer cells                            | Animal plus human ex vivo                  |
| IL-15 and IL-15R $\alpha$      | Muscle and immune cells                        | Maintenance of effector CD8 cells; synergy with PD-1 blockade in pancreatic cancer                               | Animal model                               |
| Epinephrine and norepinephrine | Sympathetic activation during exercise         | Hippo–LATS activation and cytoplasmic retention of YAP in breast cancer cells                                    | Cell plus animal model                     |
| Glutamine withdrawal           | Substrate uptake by working muscle             | Deprivation of glutamine-addicted tumours; concurrent sparing of muscle                                          | Animal model                               |
| EV protein and microRNA cargo  | Multisource exercise EV burst                  | Slower prostate xenograft growth after vesicle transfer; shifts in cancer-pathway microRNAs                      | Animal transfer plus human cross-sectional |

## 7. From mechanism to prescription: Clinical translation

### 7.1. Guideline-grade evidence for symptoms, function and survival

Clinical exercise oncology has matured to the point of multidisciplinary guidelines. The 2019 ACSM roundtable concluded that exercise training is safe during and after cancer treatment and has strong evidence for reducing anxiety, depressive symptoms, cancer-related fatigue and lymphedema exacerbations, and for improving quality of life and physical function<sup>[45]</sup>; the companion preventive evaluation graded the evidence for incidence and post-diagnosis mortality<sup>[15]</sup>. Meta-analytic evidence points the same way: an early synthesis of 56 randomised trials found that exercise improves fitness, physical function and quality of life without raising the rate of adverse events<sup>[46]</sup>, and a comparative network analysis pooling 113 trials and more than 11,000 patients found exercise more effective than either pharmaceutical or psychological treatment for cancer-related fatigue<sup>[47]</sup>. Comparisons of prescription types indicate that combined aerobic and resistance programmes, supervised delivery and programmes continued beyond active treatment yield the most consistent gains in function and patient-reported outcomes<sup>[48]</sup>. CHALLENGE extends this evidence tier from symptoms to disease-free survival<sup>[17]</sup>, and replication trials in other tumour types are now the field's

central clinical priority.

## 7.2. A mechanism-informed FITT-VP framework and treatment timing

Guidelines generally prescribe 150 minutes per week of moderate aerobic exercise plus two resistance sessions, but a mechanistic reading suggests that the prescription should be phased by treatment context and dominant biological target. **Table 2** sets out such a framework across the care continuum. Pre-treatment prehabilitation exploits vascular and cardiorespiratory adaptation to build reserve before surgery or chemoradiation. During active treatment, moderate, regularly repeated aerobic bouts sustain immune mobilisation and insulin sensitivity while respecting recovery; supervised combined training preserves the muscle mass that sarcopenia data identify as prognostic. In extended survivorship the emphasis shifts to long-term metabolic and inflammatory control and recurrence-risk reduction. In advanced disease, adapted exercise preserves function, counters cachexia and supports treatment tolerance, with goals reset toward function rather than volume. Acute scheduling—exercise on the day of chemotherapy or immunotherapy—has a mechanistic rationale in perfusion and lymphocyte trafficking but remains experimental and should be tested rather than assumed.

## 7.3. Resistance training as the specific countermeasure to muscle depletion

Aerobic training dominates the mechanistic literature, but the sarcopenia and cachexia evidence identifies resistance exercise as the modality with the specific stimulus for muscle mass and strength. In a randomised trial among overweight, predominantly minority breast-cancer survivors, 16 weeks of supervised combined aerobic and resistance training produced large reductions in metabolic-syndrome prevalence and sarcopenic obesity and lowered circulating insulin, leptin and resting IL-6 <sup>[49]</sup>. Mechanistically, progressive mechanical loading activates anabolic signalling in muscle that aerobic exercise does not fully reproduce, directly countering the catabolic drivers of cancer cachexia identified in Section 3.3. The practical conclusion is that “exercise” in oncology should not default to walking programmes: resistance training at least twice weekly, adapted to surgical sites, bone metastases and treatment-related neuropathy, is an independent and mechanistically justified prescription component.

**Table 2.** A mechanism-informed exercise-prescription framework across the cancer-care continuum

| Care phase                          | Dominant mechanistic target                                              | Aerobic component                                                                              | Resistance component                                       | Evidence grade                                         |
|-------------------------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------|--------------------------------------------------------|
| Pre-treatment prehabilitation       | Cardiorespiratory reserve and perfusion before surgery or chemoradiation | 3–5 sessions weekly, moderate intensity, progressing toward 150 min weekly                     | Two full-body sessions weekly, machine-assisted as needed  | Moderate clinical evidence                             |
| Active chemotherapy or radiotherapy | Immune mobilisation, insulin sensitivity and fatigue control             | 2–5 sessions weekly at self-paced moderate intensity; same-day scheduling remains experimental | Two sessions weekly, adjusted for cytopenia and neuropathy | Strong for symptoms; mechanistic for treatment synergy |
| Post-treatment survivorship         | Metabolic and inflammatory control and recurrence-risk reduction         | At least 150 min moderate or 75 min vigorous weekly, progressing volume                        | At least two progressive-loading sessions weekly           | Strong guideline evidence; survival signal emerging    |
| Advanced or metastatic disease      | Physical function, cachexia countermeasure and treatment tolerance       | Frequent short bouts at low-to-moderate intensity                                              | Two low-load sessions weekly, adapted to bone lesions      | Low to moderate; function-focused                      |

Note: Intensity and progression should follow the frequency, intensity, time, type, volume and progression (FITT-VP) principle and

be individualised to performance status, comorbidity and treatment toxicity. Evidence grades distinguish replicated trial evidence from mechanistic or preclinical rationale.

## 8. Unresolved questions and research priorities

Despite this convergence, several links in the axis remain open, and stating them precisely is more useful than declaring the case closed. First, the dose-response relationship is poorly resolved. Most mechanistic animal studies use voluntary wheel running, which is self-selected and closer to high-volume endurance activity than to guideline prescriptions, while human studies vary widely in intensity; whether high-intensity interval training offers mechanistic advantages over moderate continuous training, and at what risk, is not settled. Second, tumour-type and molecular-subtype specificity is real: the divergent checkpoint-blockade results warn against assuming a universal effect, and cancers with different dominant hallmarks may require different prescriptions <sup>[41]</sup>.

Third, EV causality is not yet established in humans. The field has moved from association to donor-transfer experiments in animals, but rigorous vesicle-depletion and cargo-add-back rescue experiments, standardised isolation and reporting aligned with extracellular-vesicle guidelines, and identification of the specific cargo molecules responsible are still needed before exercise EVs can be treated as therapeutic agents or surrogate endpoints. Fourth, the leap from acute ex vivo serum effects to chronic tumour control in patients has not been directly made; window-of-opportunity trials that biopsy tumours before and after a defined exercise period are the appropriate design. Fifth, exercise-immunotherapy combinations require adequately powered human trials that specify timing relative to infusion and measure immune kinetics, response rate and survival rather than fitness alone.

Sixth come questions of implementation and equity: older adults, patients with advanced disease, inpatients and those with sarcopenia, bone metastases or treatment-related toxicity are precisely the groups with most to gain, yet they remain under-represented in trials. Finally, the prospect of “exercise mimetics”—drugs or engineered vesicles that reproduce selected myokine or EV effects without contraction—is scientifically attractive but should not be allowed to displace the behavioural intervention, whose multi-target nature and safety record no single molecule currently matches.

## 9. Conclusion

The evidence now supports a view of skeletal muscle as a trainable endocrine and immune organ whose repeated contraction communicates with a tumour along three connected levels: a remodelled secretome of myokines and vesicular cargo, a systemic immunometabolic environment of mobilised lymphocytes, improved substrate and hormone profiles, and a reprogrammed tumour microenvironment of better perfusion, greater immune infiltration and reduced proliferative signalling. The mirror-image prognostic burden of sarcopenia, and the first phase III demonstration that structured exercise improves disease-free survival after colon cancer, anchor this mechanistic picture at both ends. Much of the molecular detail remains preclinical, and tumour-type specificity, dose-response and vesicle causality demand rigorous work. Nevertheless, the trajectory is coherent enough to act on: exercise prescription in oncology should be mechanism-informed, phase-specific and explicit about resistance training, while the next decade of trials tests whether the biology of the trainable muscle translates into reproducible survival benefit across the breadth of human cancer.

## Disclosure statement

The author declares no conflict of interest.

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