Exercise-Induced Metabolic Reprogramming and Immune Modulation: A Novel Strategy for Cancer Therapy

Anqi He[1#], Sha Wang[1#], Tianjie Bao[1], Shunzi Rong[2], Chong Li[1], Min Luo[3], Chengqi He[1], Yonghong Yang[1], Yong Xia[1*]

[1] Rehabilitation Medicine Center and Institute of Rehabilitation Medicine, Key Laboratory of Rehabilitation Medicine in Sichuan Province, West China Hospital, Sichuan University, Chengdu, 610041, China
[2] West China School of Pharmacy, Sichuan University, Chengdu 610041, China
[3] Department of Biotherapy, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China

ABSTRACT

Exercise represents a non-pharmacological strategy capable of concurrently modulating tumor metabolism and immunity. Regular physical activity reprograms systemic and tumor-localized metabolic networks, including glucose, lactate, amino acid, and lipid pathways, while enhancing innate and adaptive immune responses. Exercise-induced myokines (e.g., IL-6, IL-15, irisin, SPARC) and improved vascularization contribute to reshaping the tumor microenvironment (TME), mitigating immunosuppressive metabolite accumulation, and promoting T cell and NK cell infiltration. Mechanistically, exercise activates integrated signaling networks including AMPK–mTOR–HIF1α, PGC-1α–ERRα, and IL-6/STAT3 axes, supporting metabolic flexibility and anti-tumor immunity. Translational and clinical studies suggest exercise can enhance chemotherapy and immunotherapy efficacy, while precision exercise prescriptions based on FITT principles, biomarkers, and patient-specific tolerance may maximize therapeutic benefits. This review summarizes the molecular and systemic mechanisms of exercise-induced metabolic-immune reprogramming and outlines strategies for clinical translation in oncology.

INTRODUCTION

Cancer is a multifactorial disease driven by intricate genetic, epigenetic, and environmental influences. Among its hallmarks, metabolic reprogramming and immune evasion are recognized as key contributors to tumor initiation, progression, and resistance to therapy (1, 2). Tumor cells undergo profound metabolic adaptations to sustain rapid proliferation and survive under nutrient-deprived, hypoxic conditions. These changes—encompassing glycolysis, amino acid metabolism, and lipid utilization—reshape the TME and directly impair the function of various immune cell types, including $CD8^+$ T cells, Natural killer (NK) cells, and dendritic cells (DCs), thereby facilitating immune escape (3-5).

Central to tumor metabolic reprogramming is the Warburg effect, wherein cancer cells favor aerobic glycolysis, leading to excessive lactate production and acidification of the TME (6, 7). Lactate accumulation not only suppresses effector T and NK cell function but also promotes regulatory T cell differentiation and tumor-associated macrophage polarization (8). Similarly, altered amino acid metabolism (e.g., glutamine, serine, tryptophan) and lipid metabolism contribute to immune dysfunction and support tumor growth (4, 9, 10).

The immunosuppressive TME created by these metabolic shifts represents a major barrier to effective anti-tumor immunity and limits the efficacy of immunotherapies (11-14). As a result, targeting the metabolism-immunity axis is gaining traction as a promising therapeutic strategy (15).

Exercise, a well-established modulator of systemic metabolism and immune function, has recently emerged as a potential non-pharmacological intervention to disrupt tumor metabolic networks and restore immune competence (16-20). Studies suggest that exercise may improve glucose and lipid metabolism, reduce lactate accumulation, and reprogram amino acid utilization within tumors. Concurrently, exercise enhances the mobilization and cytotoxicity of immune effector cells, modulates immune checkpoint expression, and may synergize with immunotherapy (16-20).

**Corresponding author:*
[#]These authors contributed equally to this work.
[*]Correspondence:
Yong Xia (yxia4@scu.edu.cn).

However, important knowledge gaps remain. The impact of exercise varies across tumor types and individual patients due to molecular and physiological heterogeneity (21, 22). Moreover, the optimal parameters of exercise—type, duration, intensity—required to achieve therapeutic benefits in cancer contexts are not yet fully defined (22, 23).

This review aims to provide a comprehensive overview of how tumor metabolic reprogramming drives immune suppression and how exercise may counteract these effects through systemic and tumor-local immunometabolic modulation. We further explore emerging evidence supporting the integration of exercise into anti-cancer strategies and highlight directions for future research focused on precision exercise oncology.

HALLMARKS OF TUMOR METABOLISM: MECHANISMS AND IMPACT OF METABOLIC REPROGRAMMING

Tumor cells are distinguished by their profound metabolic alterations, a phenomenon first noted by Warburg, where cancer cells preferentially produce energy via glycolysis rather than relying on mitochondrial oxidative phosphorylation (OXPHOS)—even under aerobic conditions (24). This metabolic shift, commonly known as the Warburg effect, leads to an increased rate of glucose uptake and lactate production, providing the essential building blocks and energy required for rapid proliferation (24-27). The excessive lactate accumulation in the TME not only fuels tumor growth but also contributes to acidification, which in turn supports immune evasion and promotes angiogenesis (7, 8).

Beyond glycolysis, tumors exhibit extensive reprogramming of other metabolic pathways. Alterations in amino acid metabolism—such as the enhanced utilization of glutamine, serine, and glycine—enable cancer cells to replenish substrates for biosynthesis and sustain energy production even under nutrient-limited conditions (28-30). Similarly, modifications in lipid metabolism, including increased uptake and oxidation of fatty acids (FAs) and cholesterol, further support the structural and energetic needs of malignant cells (28, 29). These adaptive changes collectively not only meet the metabolic demands of tumor cells but also reshape the surrounding microenvironment to favor tumor survival and progression.

Moreover, the metabolic reprogramming of cancer cells has broader implications. The interplay between altered cancer cell metabolism and the diverse cell types within the TME—ranging from immune cells to stromal cells—creates a competitive landscape for nutrients. This competition can exacerbate immune suppression by depriving effector cells of vital metabolic substrates, thereby reinforcing mechanisms of immune escape (31, 32). Understanding these metabolic adaptations is therefore critical, as they reveal potential targets for therapies aimed at disrupting the tumor's metabolic network and restoring anti-tumor immunity (13-15).

IMMUNOMETABOLIC INTERACTIONS: HOW TUMOR-DERIVED METABOLITES REGULATE TUMOR PROGRESSION AND IMMUNE FUNCTION

Mounting evidence indicates that tumor metabolic reprogramming not only facilitates malignant cell survival and proliferation under hostile microenvironmental conditions but also promotes immune evasion, thereby accelerating tumor progression (15, 33, 34). Within the TME, cancer cells and immune cells coexist in a metabolically competitive and often suppressive landscape. Tumor-derived metabolites, such as glucose, lactate, and amino acids, play dual roles: they sustain cancer cell metabolism while simultaneously impairing anti-tumor immunity.

In this section, we examine how these metabolites influence immune cell function, alter metabolic pathways within the TME, and contribute to immunosuppression. We further explore strategies that may restore immune function by targeting these metabolic vulnerabilities (Figure 1 and Table 1).

GLUCOSE AND LACTATE: DUAL ROLES IN FUELING TUMORS AND SUPPRESSING IMMUNITY

Glucose metabolism: Competition between tumor and immune cells in the TME

Glucose is a critical energy substrate for both tumor cells and immune cells. Cancer cells reprogram their glucose metabolism by enhancing glycolysis, the tricarboxylic acid (TCA) cycle, the pentose phosphate pathway (PPP), and the serine synthesis pathway (SSP), thereby supporting biosynthesis and proliferation (68). This metabolic flexibility enables tumor cells to adapt to hypoxia and nutrient stress, in part by maintaining transcriptional programs such as the yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) axis that drive oncogenic growth and invasiveness (69).

However, immune cells within the TME—particularly $CD8^+$ T cells and tumor-associated macrophages (TAMs)—also depend on glucose to sustain their effector functions (34, 70). Studies have shown that TAMs, especially the M2-like subtype, consume substantial amounts of glucose, promoting pro-tumoral behavior via O-GlcNAcylation of cathepsin B and facilitating chemoresistance and metastasis (70). In addition, tumor-derived metabolites such as D-2-hydroxyglutarate (D-2HG), produced through mutant isocitrate dehydrogenase (IDH), can impair glycolysis in $CD8^+$ T cells, suppressing their proliferation and cytotoxicity (71).

Pharmacologic or genetic interventions that inhibit glycolysis in tumor cells can, paradoxically, restore immune surveillance. For instance, inhibition of Glucose Transporter 1 (Glut1) enhances Cytotoxic T Lymphocyte (CTL) -mediated Tumor Necrosis Factor-alpha (TNFα) release and tumor cell lysis (39). Moreover, GLUT10 has been identified as a selective regulator of glucose uptake and effector function in $CD8^+$ T cells, making it a potential therapeutic target (35).

Table 1. Immunosuppressive effects of tumor-associated metabolites and their molecular targets in preclinical studies.

Metabolites	Immune Cells	Immune-Metabolic Interaction Targets	Effects/Mechanism on Immune-Metabolic Interaction	References
Glucose	CD8+ T cells	GLUT10	GLUT10 regulates glucose uptake and is essential for $CD8^+$ T-cell proliferation, effector function, and anti-tumor immunity.	(35)
Glucose	CD8+ T cells	NSUN2	Deletion of the glucose/NSUN2/TREX2 axis activates cGAS/STING signaling, increases $CD8^+$ T-cell infiltration, and enhances anti–PD-L1 response.	(36)
Glucose	MDM	GLUT1	PERK-driven glucose metabolism enhances macrophage immunosuppressive activity via histone lactylation, inhibiting T-cell function and promoting tumor growth.	(37)
Glucose	NK cell	MICA/B	High glucose inhibits MICA/B expression through the AMPK–Bmi1–GATA2 axis, reducing NK cell-mediated cytotoxicity.	(38)
Glucose	CTL	Glut1 and Gpi1	Deficiency of Glut1 or Gpi1 enhances cytotoxic T-cell–mediated killing of tumor cells.	(39)
Glucose	DC	STING signal	Glycolysis activates STING signaling in dendritic cells, enhancing their anti-tumor activity in lung cancer.	(40)
Glucose	DC	NCoR1	NCoR1 regulates the balance between tolerance and inflammation by modulating glycolysis and fatty acid oxidation in dendritic cells.	(41)
Glucose	B Cells	PP2A	PP2A redirects glucose metabolism from glycolysis to the PPP to protect B cells from oxidative stress.	(42, 43)
LA	CD8+ T cells	GLUT10	High lactate binds GLUT10 and blocks glucose uptake, suppressing $CD8^+$ T-cell activation and effector function.	(35)
LA	MDM, T cells	PERK-ATF4 axis	Lactate induces histone lactylation and IL-10 expression in macrophages, suppressing T-cell anti-tumor activity.	(37)
LA	Treg	MCT1	Lactate enhances PD-1 expression on Tregs, reducing effector T-cell function and promoting immune escape.	(44)
LA	B cells, T cells	mTOR signaling pathway	Tumor-derived lactate enhances glycolysis and OXPHOS in B cells, leading to glucose deprivation and T-cell inhibition.	(45)
LA	M2 macrophages, CD8 T cells	Myc	Myc promotes lactate-induced Gpr132-dependent M2 polarization and suppresses $CD8^+$ T-cell function in ovarian cancer.	(46)
LA	NK cell	CaMKK2	Lactate regulates CaMKK2 expression, promoting NK cell survival and proliferation within tumors.	(47)
LA	NK cell	MCT1/4, GLUT1	Tumor-derived lactate lowers NK-cell intracellular pH, induces mitochondrial stress, and promotes apoptosis, impairing anti-tumor immunity.	(48)
Lactate	DC	SREBP2	Lactate activates the SREBP2 pathway in DCs, driving their transition to a regulatory phenotype and suppressing anti-tumor immunity.	(49)
Lactate	T cell	MCT4	Lactate accumulation through MCT4 inhibits T-cell function and anti-tumor responses.	(50)
Lactate	T+ ex cells	MCT11	Upregulation of MCT11 by lactate increases T-cell sensitivity to high-lactate TME, leading to T-cell exhaustion.	(51)
Sodium lactate	CD8+ T cell	Histone deacetylase	Sodium lactate enhances $CD8^+$ T-cell stemness and anti-tumor immunity in a pH-independent manner.	(52)
D-Lactate	macrophage	PI3K/AKT pathway	D-lactate interacts with TLR2/TLR9, inhibits PI3K–AKT, activates NF-κB, and promotes M1 polarization.	(53)
Asn	CD8+ T cell	NRF2	Asparagine restriction activates NRF2, enhances $CD8^+$ T-cell proliferation, and boosts anti-tumor immunity.	(54)
Leucine	T cell	LRIG1, VISTA	LRIG1 binds VISTA, suppressing TCR signaling and CTL amplification, leading to immune evasion.	(55)
Valine	CD8+ T cell	HLA-A2	Valine enhances $CD8^+$ T-cell recognition of tumor cells lacking TAP function via improved HLA-A2 binding.	(56)
Glutamine	CD8+ T cells	CircTRPS1/miR-141-3p/GLS1 axis	Tumor exosomal circTRPS1 modulates glutamine metabolism and ROS homeostasis, limiting $CD8^+$ T-cell exhaustion.	(57)
Glutamine	cDC1s, CD8 T cell	SLC38A2	Glutamine supports cDC1–$CD8^+$ T-cell metabolic crosstalk to sustain anti-tumor immunity.	(58)
Glutamine	T cell and NK cell	TNF-α, IL2	Glutamine supplementation enhances T-cell activation, NK-cell cytotoxicity, and apoptosis in tumor-bearing mice.	(59)
Kynurenine	T cell	D-kynurenine	D-kynurenine modulates T-cell metabolism and proliferation, limiting immunosuppression.	(60)
Tryptophan	CD8+ T cell	AhR	Intratumoral I3A from tryptophan metabolism activates AhR and enhances the efficacy of immune checkpoint therapy.	(61)
Serine	Regulatory T Cell	GSH	Serine regulates GSH synthesis and one-carbon metabolism, modulating Treg suppressive capacity.	(62)
Arginine	TAM, CD8+ T cell	Collagen	Arginine depletion by TAMs promotes fibrosis and suppresses $CD8^+$ T-cell responses, reducing immunotherapy efficacy.	(63)
Fatty acid	Regulatory T Cells	PI3K-AKT-mTOR signaling pathway	RHOA mutations increase fatty acid production, enhancing Treg accumulation and immune suppression.	(64)
Fatty acid	CTL	FAO, CPT1A	Fatty acids inhibit CPT1A, reducing T-cell cytotoxicity and promoting immune evasion.	(65)
Cholesterol	Mφ	ABCA1	Cholesterol accumulation promotes immunosuppressive macrophage differentiation in tumors.	(66)

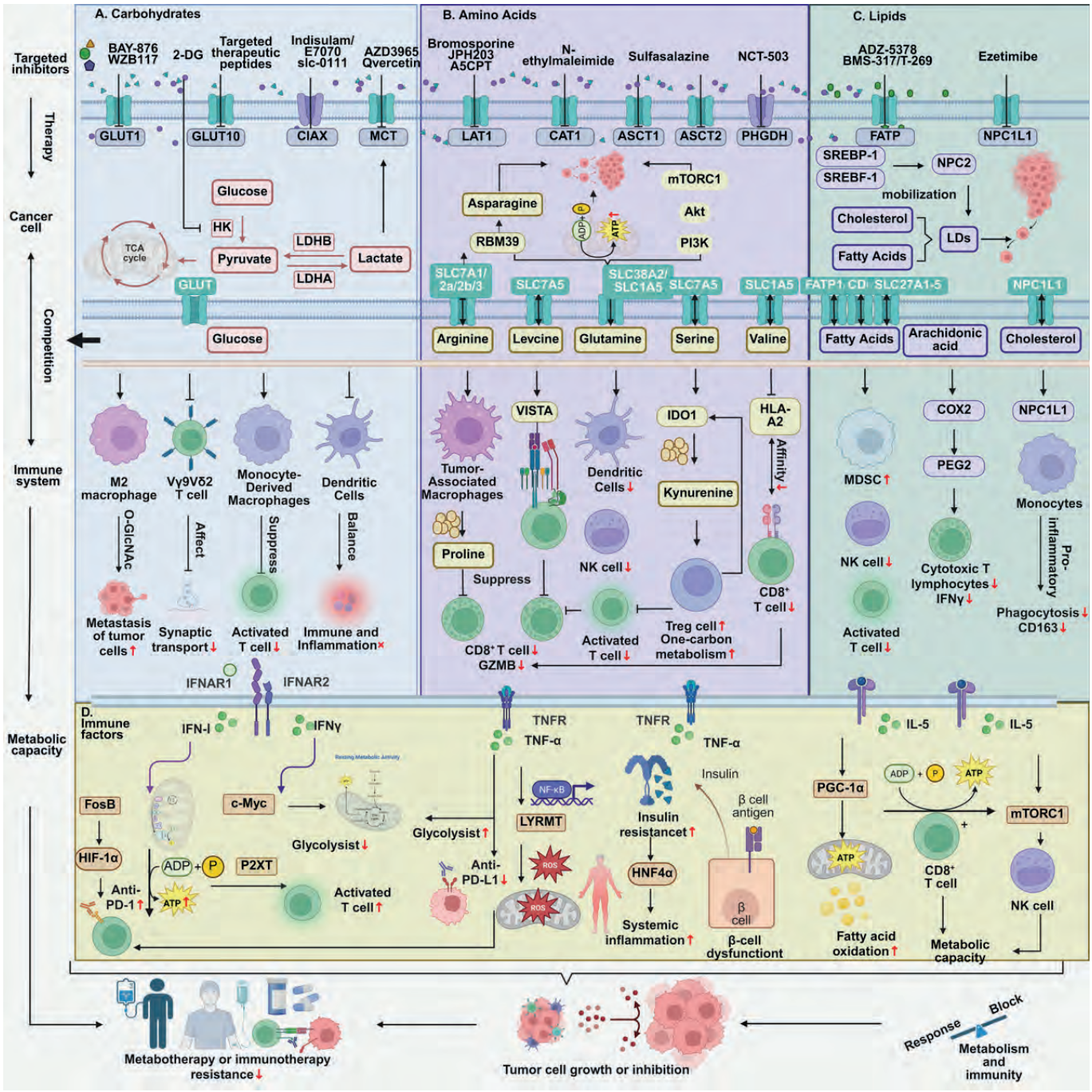

Figure 1. Metabolic reprogramming in tumors and its bidirectional crosstalk with the immune system.
(A) Carbohydrate metabolism: Tumor cells consume excessive glucose via GLUT transporters, converting it to lactate through aerobic glycolysis. Lactate suppresses T and NK cell function, promotes M2 macrophage polarization, and facilitates immune evasion. Inhibitors such as 2-DG and BAY-876 target glycolysis and glucose transport. (B) Amino acid metabolism: Tumor cells exploit glutamine, arginine, and tryptophan to support proliferation and evade immunity. Enzymes like IDO1 degrade tryptophan to kynurenine, activating Tregs and suppressing CD8+ T cells. Targeted therapies (e.g., Sulfasalazine, NCT-503) aim to restore immune function.
(C) Lipid metabolism: Tumor cells uptake fatty acids and cholesterol to fuel membrane synthesis and survival under stress. Lipid byproducts suppress NK and T cell activity through pathways such as COX2/PGE2. Inhibitors like Ezetimibe and other lipid regulators can improve immune responses.
(D) Immune Factors: Cytokines such as IFNγ, TNF, and IL-6 reshape cellular metabolism, which in turn modulates immune function. For instance, IFNγ enhances glycolysis in effector T cells, TNF affects lipid metabolism in macrophages, and IL-6 drives tumor glycolytic flux—all contributing to the balance between anti- and pro-tumor immune responses
Abbreviations: GLUT1: Glucose Transporter 1; GLUT10: Glucose Transporter 10; CAIX: Carbonic Anhydrase IX; MCT: Monocarboxylate Transporter; LAT1: L-type Amino Acid Transporter 1; CAT1: Cationic Amino Acid Transporter 1; ASCT1: Alanine: Serine: Cysteine Transporter 1; ASCT2: Alanine: Serine: Cysteine Transporter 2; PHGDH: 3-Phosphoglycerate Dehydrogenase; FATP: Fatty Acid Transport Protein; NPC1L1: Niemann-Pick C1-Like 1 Protein; SREBP-1: Sterol Regulatory Element-Binding Protein 1; SREBF-1: Sterol Regulatory Element-Binding Factor 1; LDs: Lipid Droplets; COX2: Cyclooxygenase 2; M2 macrophage: M2-Type Macrophage; Vγ9Vδ2 T cell: Vγ9Vδ2 T cell; DCs: Dendritic Cells; NK cell: Natural Killer Cell; Treg cell: Regulatory T Cell; CD8+ T cell: CD8 Positive T Cell; HLA-A2: Human Leukocyte Antigen A2; IDO1: Indoleamine 2,3-Dioxygenase 1; GZMB: Granzyme B; IFNγ: Interferon Gamma; PGE2: Prostaglandin E2; MDSCs: Myeloid-Derived Suppressor Cells; TCA cycle: Tricarboxylic Acid Cycle (Krebs Cycle); HK: Hexokinase; LDHA: Lactate Dehydrogenase A; LDHB: Lactate Dehydrogenase B; PI3K: Phosphoinositide 3-Kinase; mTORC1: Mammalian Target of Rapamycin Complex 1; Akt: Protein Kinase B; TNF: Tumor Necrosis Factor; IL-5: Interleukin-5

Future studies should explore how exercise impacts glucose availability and utilization in both tumor and immune cells, particularly regarding GLUT transporter expression, glycolytic flux, and nutrient competition in the TME (36-38, 40-43).

Lactate:
A key mediator of immune suppression and tumor survival
Lactate, the terminal product of aerobic glycolysis, has emerged as a multifunctional metabolite central to tumor growth and immune evasion. Tumor cells produce lactate primarily via lactate dehydrogenase A (LDHA), and extracellular lactate is imported through monocarboxylate transporters such as Monocarboxylic acid transporter 1 (MCT1) and MCT4 (8). Far from being a mere waste product, lactate supports cancer cell survival as a metabolic substrate and functions as a signaling molecule that shapes the TME.

One of the most critical roles of lactate is its capacity to regulate protein function through post-translational modification. Accumulated lactate can enter the nucleus and participate in lactylation, a novel epigenetic modification that influences protein stability, DNA repair, and transcriptional regulation (72, 73). In lung cancer cells, lactate-induced lactylation of autophagy-related proteins such as Unc-51 Like Autophagy Activating Kinase 1 (ULK1), Phosphatidylinositol 3-Kinase Catalytic Subunit Type 3 (PIK3C3), and UV Radiation Resistance Associated Gene (UVRAG) promotes endosomal-lysosomal degradation pathways, contributing to tumor adaptation and growth under stress conditions (74).

Lactate also plays a major role in shaping the immunosuppressive TME. It impairs the cytotoxic function of $CD8^+$ T cells by disrupting pyruvate metabolism, reduces NK cell viability, and promotes polarization of TAMs toward an M2 phenotype (35, 50, 52). Additionally, lactate can upregulate immunosuppressive cytokines like IL-10 and TGF-β, further reinforcing immune evasion. These effects collectively contribute to diminished anti-tumor immune surveillance and enhanced tumor progression.

Interestingly, the immunoregulatory effects of lactate appear to vary depending on pH. In tumor tissues, cancer cells highly express LDHA and produce large amounts of lactate through glycolysis. This process is accompanied by H^+ extrusion, leading to acidic lactate accumulation that acidifies the TME and suppresses anti-tumor immunity (75). Among these factors, acidity is a dominant feature of the TME—it can inhibit cytosolic extracellular signal–regulated kinase (ERK) activity, block oncogene-induced mitochondrial fragmentation, and promote mitochondrial fusion. Consequently, it enhances mitochondrial respiration and supports cancer cell adaptation to various metabolic stresses, allowing sustained proliferation even under harsh conditions (76). At physiological pH, lactate primarily exists in its anionic form ($lactate^-$), and sodium lactate does not contribute to acidification. Notably, lactate can serve as a metabolic substrate for $CD8^+$ T cells, promoting oxidative metabolism and thereby enhancing T cell stemness and persistence (77). For instance, sodium lactate—administered in a neutral-pH form—has been shown to promote $CD8^+$ T cell stemness and improve anti-tumor immunity in preclinical models (52). Intraperitoneal injection of sodium lactate (2 g/kg) in mice reduces tumor growth in breast cancer, cutaneous melanoma, Lewis lung cancer (LLC) and colon adenocarcinoma models, and this effect is dependent on T cells (78). Helene et al. also reported that in a mouse breast cancer model, 2 g/kg sodium lactate treatment increased the number of tumor-infiltrating immune cells, specifically $CD3^+$ T cells, including $CD4^+$ and $CD8^+$ T cells (79). In contrast, administration of a lower dose (1 g/kg) of sodium lactate shortened the survival of tumor-bearing mice (79). Therefore, it is essential to distinguish between the immunosuppressive effects driven by acidic lactate accumulation and the immunoenhancing effects induced by neutral sodium lactate supplementation (44-49, 51, 53).

In summary, lactate is a central mediator linking tumor metabolism with immune dysfunction (Figure 2). Future studies should investigate how exercise modulates lactate dynamics, particularly its influence on lactylation, immune cell metabolism, and lactate transporter expression (e.g., MCT1/MCT4). Understanding these mechanisms may provide new opportunities to exploit exercise as an adjuvant strategy in metabolic-immunotherapy.

Amino acid metabolism: Modulating tumor growth and immune cell activity
Amino acids are essential substrates for cell growth, functioning as both nitrogen and carbon donors in biosynthetic pathways, signal transduction, and epigenetic regulation. Tumor cells exploit amino acid metabolism to bypass nutrient limitations and sustain rapid proliferation. Key amino acids involved include glutamine, arginine, tryptophan, serine, glycine, and asparagine (Asn), all of which contribute to tumor biosynthesis and redox balance (80, 81). Glutamine, although classified as non-essential, becomes conditionally essential for many tumors, especially under hypoxic conditions where it replaces glucose as a primary carbon source in the TCA cycle (82). Altered glutamine metabolism activates oncogenic pathways such as PI3K/AKT/mTOR, promoting tumor progression, as shown in hepatocellular carcinoma models (83). Similarly, high arginine levels drive metabolic remodeling and support tumor proliferation (84).

Immune cells also depend on amino acids for survival, proliferation, and effector function. $CD8^+$ T cells, macrophages, and neutrophils require distinct amino acid pools to execute anti-tumor responses (55-63) . For example, restricting Asn triggers NRF2-mediated stress responses that reduce glucose and glutamine consumption while boosting nucleotide synthesis, thereby enhancing $CD8^+$ T cell proliferation and cytotoxicity (54). Moreover, tryptophan catabolism via kynurenine—a ligand for the aryl hydrocarbon receptor (AhR)—promotes differentiation of immunosuppressive regulatory T cells (Tregs), dampening inflammation and immune surveillance (61).

Future research should examine how exercise influences amino acid metabolism in both tumor and immune compartments. Understanding exercise-induced changes in glutamine, arginine, and tryptophan pathways may provide novel opportunities to overcome metabolic suppression and improve anti-tumor immunity.

Lipid metabolism:
Supporting tumor adaptation and immune escape
Lipids serve multiple biological functions including energy stor-

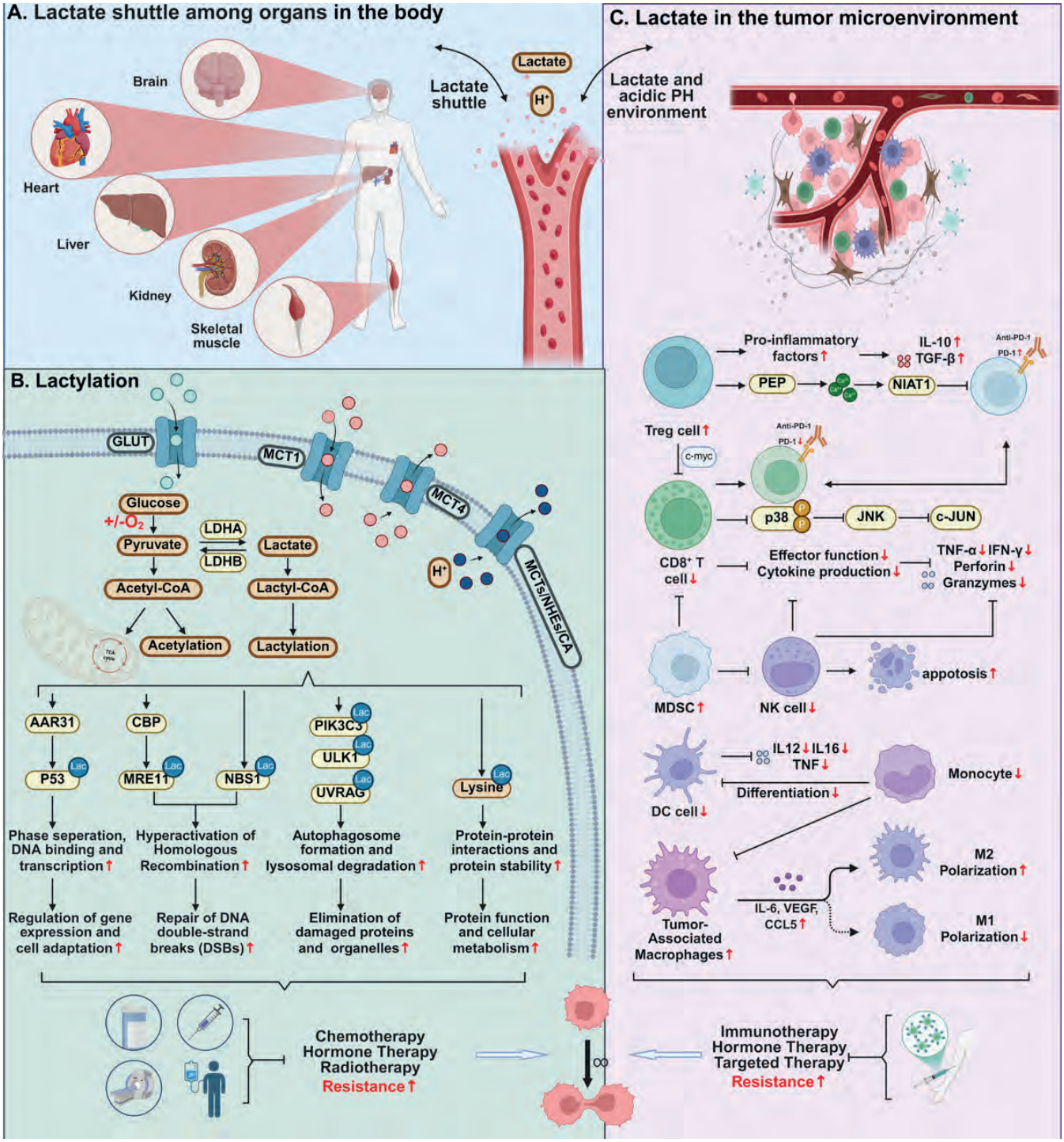

Figure 2. Multifaceted roles of lactate in tumor progression and immune suppression.
This figure summarizes the pleiotropic effects of lactate in the TME, highlighting its metabolic, signaling, and immunoregulatory functions.
(A) Lactate shuttle. Tumor cells generate lactate via LDHA and export it through MCT1/4 transporters. Lactate circulates between cells and organs, serving as a substrate and signaling molecule.
(B) Lactylation modification. Lactate-mediated protein lactylation represents a novel post-translational modification mechanism that extensively participates in critical biological processes including gene expression regulation, DNA damage repair, and protein stability maintenance. This modification not only provides survival and proliferation advantages for tumor cells but more importantly, induces resistance to chemotherapy, radiotherapy, and targeted therapies, thereby significantly enhancing tumor immune evasion. Research indicates that lactylation modification can alter the immunogenicity of tumor cells through epigenetic regulation, serving as a crucial molecular bridge connecting aberrant tumor metabolism with immunosuppressive microenvironments.
(C) Lactate in the TME. High lactate concentrations acidify the TME, upregulate immunosuppressive cytokines (e.g., IL-10, TGF-β), and impair $CD8^+$ T cell and NK cell function. Lactate also promotes polarization of tumor-associated macrophages (TAMs) toward an M2 phenotype and increases Treg recruitment.
Overall, lactate acts as a central mediator of metabolic-immune crosstalk, shaping an immune-suppressive and tumor-promoting environment.
Abbreviations: GLUT: Glucose Transporter; MCT1: Monocarboxylate Transporter 1; MCT2: Monocarboxylate Transporter 2; MCT4: Monocarboxylate Transporter 4; LDHA: Lactic Acid Dehydrogenase A; LDHB: Lactic Acid Dehydrogenase B; Acetyl-CoA: Acetyl Coenzyme A; Lactyl-CoA: Lactyl Coenzyme A; AARS1: Alanyl-tRNA Synthetase 1 ; CBP: CREB Binding Protein; NBS1: Nibrin Protein 1; PIK3C3: Phosphoinositide 3-Kinase Catalytic Subunit 3; UVRAG: UV Radiation Resistance-Associated Gene Protein; IL-10: Interleukin 10; TGF-β: Transforming Growth Factor Beta; TNF-α: Tumor Necrosis Factor Alpha; IFN-γ: Interferon Gamma; IL-12: Interleukin 12; IL-16: Interleukin 16; IL-6: Interleukin 6; VEGF: Vascular Endothelial Growth Factor; ROS: Reactive Oxygen Species; SOD1: Superoxide Dismutase 1; SOD2: Superoxide Dismutase 2.

age, membrane synthesis, and intracellular signaling. In cancer, dysregulated lipid metabolism—particularly involving FAs and cholesterol—is a hallmark of tumor progression (85). Tumor cells exploit lipid pathways to meet increased energy demands, enhance membrane biosynthesis, and support metastatic potential under fluctuating nutrient availability in the TME (86). Upregulation of lipid-regulatory transcription factors such as SREBF1 and SREBP-1 promotes autophagy-mediated lipid droplet breakdown, enabling efficient mobilization of cholesterol and FAs for membrane synthesis and rapid growth (87).

Lipid metabolism is also reprogrammed in stromal and immune cells within the TME. FAs enhance OXPHOS in resting DCs, skew macrophage polarization, suppress cytokine production in NK cells, and contribute to T cell exhaustion (65, 66). Cholesterol accumulation in the TME further promotes immune dysfunction by inducing T cell depletion (64, 67).

Despite increasing insights, the precise mechanisms through which lipid metabolism affects immune modulation remain poorly defined. Future studies should explore how exercise modifies lipid metabolic pathways in both tumors and immune cells. Investigating fatty acid oxidation (FAO), lipid signaling, and membrane remodeling in response to physical activity could reveal novel therapeutic strategies for restoring immune competence in cancer.

IMMUNOMETABOLIC INTERACTIONS: IMPACT OF IMMUNE-DERIVED FACTORS ON TUMOR METABOLISM.

Immune-derived factors, such as interferons (IFNs), TNF-α, and interleukin-15 (IL-15), act as key mediators of immunometabolic reprogramming within the TME. These signaling molecules not only modulate immune responses but also remodel tumor cell metabolism, collectively influencing tumor progression and therapeutic outcomes.

IFN:
Driven Crosstalk Between Tumor Metabolism and Immune Editing

IFNs are broadly classified into type I and type II families. Type I IFNs include IFN-α, IFN-β, and IFN-ω, which all signal through a common cell-surface receptor, whereas IFN-γ is the sole type II interferon that engages a distinct receptor complex (88). Type I interferons (IFN-Is) are central coordinators of tumor–immune interactions(88). One preclinical study has shown that persistent IFN-I signaling and the chronic activation of interferon-stimulated genes (ISGs) may paradoxically promote tumor progression. For instance, the ISG mediates the pro-tumorigenic effects of IFN-I by enhancing mRNA translation and reprogramming lipid metabolism, thereby driving cancer growth (89). Conversely, IFN-I can also induce tumoricidal metabolic responses. One study demonstrated that IFN-I promotes OXPHOS and triggers autophagy-dependent Adenosine triphosphate (ATP) release, with extracellular ATP subsequently activating P2X7-dependent dendritic cell signaling, leading to enhanced anti-tumor T cell responses (90). Beyond its classic immune-modulatory roles, IFN-α has been shown to suppress the key metabolic regulator FBJ murine osteosarcoma viral oncogene homolog B (FosB) in an Interferon regulatory factor 1 (IRF1)-dependent manner, concurrently inhibiting downstream HIF-1α signaling. This downregulation of glycolysis-related genes sensitizes hepatocellular carcinoma cells to anti–PD-1 immunotherapy, providing a promising combinatorial strategy for advanced liver cancer (91). IFN-γ, a hallmark cytokine produced by activated T cells, profoundly shapes tumor metabolic phenotypes. In melanoma models, T cell–derived IFN-γ upregulates c-Myc expression in tumor cells, driving metabolic reprogramming that favors immune evasion (92). Intriguingly, recent evidence suggests that IFN-γ signaling may paradoxically activate tumor-intrinsic compensatory pathways during immune checkpoint blockade. IFN-γ–induced secretion of fibroblast growth factor 2 (FGF2) promotes PKM2 phosphorylation, inhibits glycolysis, and lowers intracellular NAD^+ levels. The resulting IFNγ–FGF2–β-catenin axis integrates immune, metabolic, and proliferative pathways, representing a potential biomarker and therapeutic target to prevent hyperprogressive disease (HPD) during immunotherapy (93).

TNF-α:
Linking inflammation, mitochondrial bioenergetics, and immune suppression

TNF-α acts as a central regulator of both metabolism and inflammation within the TME, where it exhibits paradoxical roles. Preclinical research indicates that TNF-α–mediated activation of NF-κB regulates the expression of LYRM7, affecting mitochondrial supercomplex assembly and reactive oxygen species (ROS) production—key drivers of metabolic reprogramming (94). Moreover, TNF-α derived from TAMs can enhance tumor glycolysis and upregulate PD-L1 expression, thereby diminishing the efficacy of PD-L1 blockade therapy (95). Beyond cancer, macrophage-secreted TNF-α and IL-1β contribute to insulin resistance and β-cell dysfunction, establishing a mechanistic link between systemic metabolic disorders and chronic inflammation (96). In early-stage breast cancer, infiltration of innate immune cells secreting IL-6 and TNF-α into the liver suppresses HNF4α, leading to hepatic metabolic reprogramming and systemic inflammation that together promote tumor initiation (97).

IL-15:
Sustaining lymphocyte metabolic fitness and therapeutic persistence

IL-15, a γc-family cytokine produced by bone marrow, dendritic, and muscle cells, is a master regulator of T cell and NK cell homeostasis, effector function, and memory formation. In addition to these immunologic roles, IL-15 enhances mitochondrial biogenesis through activation of the PGC-1α pathway, increases spare respiratory capacity (SRC), and promotes FAO via upregulation of CPT1A, collectively favoring oxidative metabolism over glycolysis (98). IL-15–induced memory-like $CD8^+$ T cells display enhanced OXPHOS and mitochondrial fusion mediated by cardiolipin remodeling (98, 99). In adoptive cell therapy, IL-15–expanded CAR-T cells (CAR-T/IL15) retain a stem cell–like memory phenotype (Tscm) characterized by $CD62L^+CD45RA^+CCR7^{+-}$ expression, reduced exhaustion, and improved mitochondrial fitness. Mechanistically, IL-15–mediated suppression of mTORC1 activity maintains metabolic quiescence while enhancing in vivo antitumor efficacy.

IL-15 also modulates NK cell metabolism and anti-cancer

activity. High IL-15 levels stimulate NK cell metabolism through mTOR activation, boosting cytotoxic function (100). However, dosing strategies are critical: continuous IL-15 exposure induces NK cell exhaustion, functional decline, and reduced fatty acid metabolism (101). Together, these findings highlight IL-15 as a pivotal regulator of immune cell metabolic resilience, offering a promising avenue for optimizing next-generation immunotherapies (102).

EXERCISE-INDUCED REGULATION OF TUMOR METABOLISM AND IMMUNE RESPONSES: MECHANISMS AND THERAPEUTIC POTENTIAL

Emerging evidence highlights the capacity of exercise to modulate both systemic and tumor-localized metabolism, while simultaneously reprogramming immune responses. These dual effects position exercise as a promising adjunctive approach to cancer therapy (103, 104). Regular physical activity has been shown to inhibit tumor growth by altering tumor cell metabolic networks, enhancing immune surveillance, and improving treatment responsiveness (105).

Mechanistically, exercise impacts tumor progression through three major pathways: (1) regulation of tumor metabolite availability (e.g., glucose, lactate, FAs), (2) enhancement of innate and adaptive immune cell function, and (3) modulation of immune-metabolic interactions within the TME. Exercise reprograms systemic energy metabolism and modulates cytokines involved in tumor biology, such as interleukin-6 (IL-6) (106-108). The exercise-induced modulation of metabolic hormones and their impact on tumor signaling pathways are discussed in the following section.

Moreover, endurance training has been shown to alter expression of lactate metabolism-related factors (e.g., MCT1, LDHA, Estrogen-Related Receptor Alpha (ERRα)), reduce tumor acidity, and restore immune cell infiltration (109). Myokines such as IL-6, irisin, and Secreted Protein Acidic And Cysteine Rich (SPARC), secreted by skeletal muscle during exercise, further modulate tumor metabolism, epithelial–mesenchymal transition (EMT), and immune activation (110, 111).

As such, understanding the mechanisms of exercise-induced metabolic reprogramming may lead to novel intervention strategies that reshape the TME, limit nutrient competition, and restore anti-tumor immunity. This section explores how these systemic and local effects translate into potential clinical benefits.

Systemic effects of exercise on organ metabolism and immune homeostasis

The anti-tumor effects of exercise are partly attributable to its ability to induce metabolic and immune remodeling across multiple organs. Key systems—including skeletal muscle, cardiovascular system, liver, and gastrointestinal tract—respond to exercise through metabolic reprogramming and immune regulation, which in turn can influence tumor progression (20, 112, 113). We have compiled a summary of this research in Figure 3.

As the primary site for nutrient storage and energy utilization, skeletal muscle plays a central role in the physiological adaptations to exercise, particularly in the regulation of metabolism, angiogenesis, and immune responses (114). A single bout of exercise can directly enhance amino acid and glucose uptake in skeletal muscle, while during the recovery phase, it promotes muscle protein synthesis and improves insulin-stimulated glucose disposal (115).

Exercise-induced improvements in cardiorespiratory fitness (CRF) are mediated by multiple mechanisms, including modulation of sympathetic nerve activity, increased myocardial contractility, reduced oxidative stress, promotion of physiological cardiac hypertrophy, enhancement of stroke volume and heart rate, and regulation of non-coding RNAs and their signaling pathways (116, 117). A preclinical study demonstrated that exercise elevates the abundance and/or activity of antioxidant enzymes—such as superoxide dismutases (SOD1, SOD2), glutathione peroxidase, and catalase—in mitochondria isolated from ventricular cardiomyocytes. These changes reduce myocardial ROS and enhance cardiac antioxidant capacity (118)

The liver, as the major metabolic organ, also exhibits significant adaptive responses to exercise. Accumulating evidence indicates that regular physical activity improves systemic metabolism and insulin sensitivity, induces adaptations in glucose and lipid metabolism, and markedly reduces the risk of chronic metabolic diseases such as alcoholic fatty liver and metabolic dysfunction–associated fatty liver disease (MAFLD) (119-121). Exercise-induced fibronectin (FN1) acts as a circulating metabolic factor that triggers hepatic autophagy and systemic insulin sensitization via the hepatic α5β1 integrin–IKKα/β–JNK1–BECN1 signaling pathway, thereby promoting protein and organelle turnover and systemic metabolic adaptation (122).

The gut is a dynamic environment, and the gut microbiota plays an important role in human biology, including metabolism, endocrine, neuronal, and immune functions (123, 124). A recent study found that proper exercise can increase the diversity of gut microbes and the number and activity of beneficial bacteria, indirectly affecting the body's metabolism and immunity, thereby having a positive impact on health (123, 125).

Exercise regulation of tumor-associated metabolites and enzymes: pathways to enhanced anti-tumor immunity

Exercise represents a powerful, non-pharmacologic intervention capable of reshaping the tumor metabolic landscape and restoring immune competence. Tumor cells display altered metabolic profiles, with enhanced glycolysis, glutaminolysis, and lipid metabolism that facilitate rapid proliferation and immune evasion (6, 8, 28, 86). These same pathways, however, can be modulated by exercise to limit nutrient availability to tumor cells while supporting immune cell activation. The dual impact of exercise on metabolism and immunity makes it a unique tool in anti-cancer strategies, particularly in the context of immunotherapy (16, 103, 104) .

This section outlines how exercise regulates tumor metabolism (5.2.1), reshapes immune function (5.2.2), and exercise and immune-metabolic crosstalk: mechanistic integration of tumor suppression (5.2.3), highlighting the mechanistic foundations and therapeutic relevance of these interactions. We have compiled a

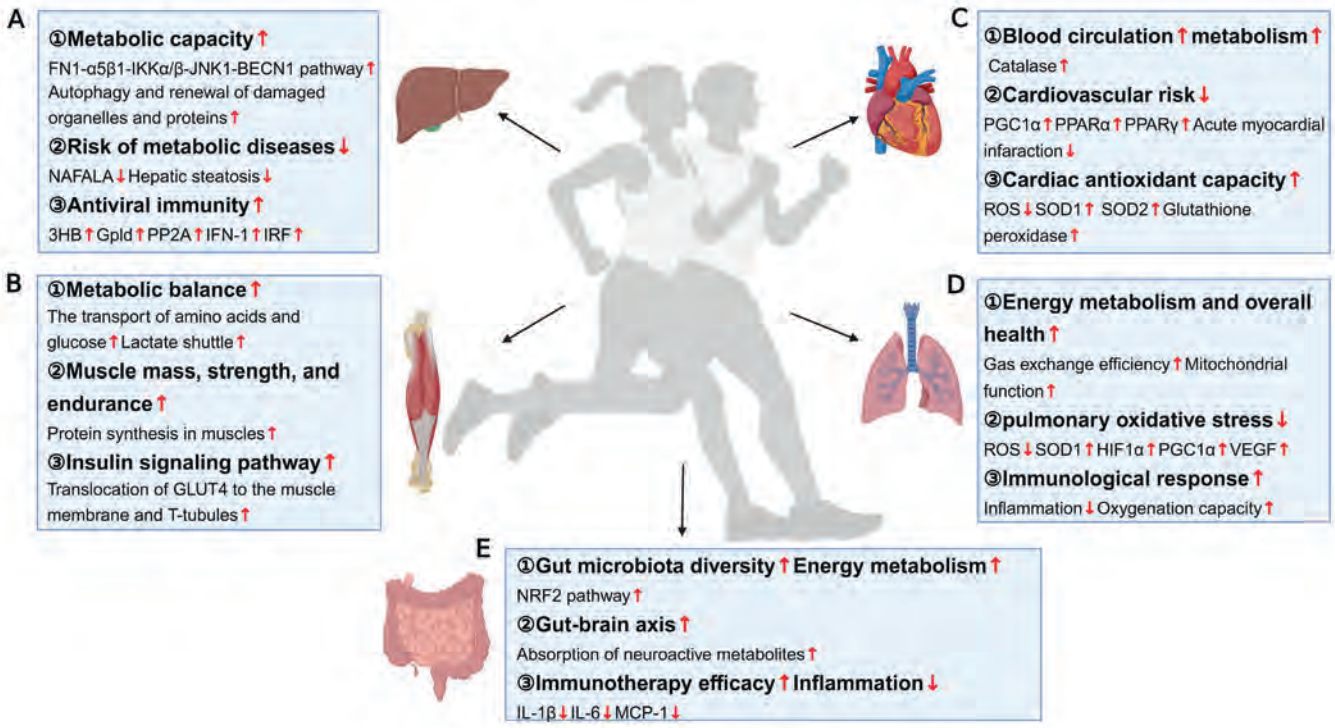

Figure 3. The effects of exercise on different organs.
(A) Exercise might improve liver metabolic function, promotes metabolic balance, and enhances gluconeogenesis and lipid metabolism.
(B) Exercise could enhance muscle metabolic function, improves energy metabolism and insulin sensitivity, and helps maintain muscle mass.
(C) Exercise probably improves blood circulation and metabolic capacity of the heart, promoting cardiovascular health.
(D) Exercise can improve lung function, increasing oxygen intake and carbon dioxide expulsion efficiency.
(E) Exercise may promote gut microbiome diversity, improves gut health and immune function, and reduces the risk of metabolic diseases.
Abbreviations: FN1-α5β1- IKKα/β-JNK1-BECN1 pathway: Fibronectin 1-α5β1-KKα/β-JNK1-Beclin1 autophagy-related protein pathway; Hepatic steatosis: Liver fat degeneration; 3HB: 3-Hydroxybutyrate; Gpld: Glycosylphosphatidylinositol-specific Phospholipase D; PP2A: Protein Phosphatase 2A; IFN-1: Interferon 1; IRF: Interferon Regulatory Factor; PGC1α: Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 Alpha; PPARα: Peroxisome Proliferator-Activated Receptor Alpha; PPARγ: Peroxisome Proliferator-Activated Receptor Gamma; Acute myocardial infarction: Acute myocardial infarction (heart attack); ROS: Reactive Oxygen Species; SOD1: Superoxide Dismutase 1; SOD2: Superoxide Dismutase 2; Glutathione peroxidase: Glutathione Peroxidase; HIF1α: Hypoxia-Inducible Factor 1 Alpha; VEGF: Vascular Endothelial Growth Factor; IL-1β: Interleukin 1 Beta; IL-6: Interleukin 6; MCP-1: Monocyte Chemoattractant Protein 1; NRF2 pathway: Nuclear Factor E2-Related Factor 2 pathway

summary of this research in Table 2 and Figure 4.

Reprogramming tumor metabolism through exercise: Glucose, lactate, and growth factor pathways

Tumor cells rely on a high rate of aerobic glycolysis, consuming excessive glucose and secreting lactate into the TME. This metabolic phenotype—known as the Warburg effect—not only supports anabolic processes but also creates a hostile, acidic microenvironment that suppresses immune activity (6, 7). Lactate impairs T and NK cell functions, enhances regulatory T cell expansion, and polarizes macrophages toward immunosuppressive phenotypes (8, 35, 50).

Exercise can reverse several aspects of this metabolic imbalance. Endurance and moderate-intensity exercise improve whole-body glucose homeostasis, lower insulin and IGF-1 levels, and reduce the availability of metabolic substrates to tumors (106-108). GLUT4-mediated glucose uptake in skeletal muscle is enhanced during exercise, effectively reducing systemic glucose concentrations and limiting tumor access to this critical nutrient (134). Additionally, exercise modulates lactate dynamics within the TME (109). Furthermore, exercise may offer a non-pharmacologic strategy to mitigate lactate-mediated immune suppression. Preclinical studies have shown that endurance training reduces lactate accumulation in tumors by enhancing systemic lactate clearance and downregulating key lactate transport and metabolic regulators such as LDHA, MCT1, and ERRα (109). These adaptations can shift the TME from immunosuppressive to immune-permissive.

Beyond glycolysis, exercise also affects amino acid and lipid metabolism. For example, exercise reduces tumor glutamine uptake by downregulating glutamine transporters and modulating MYC- and mTOR-dependent pathways that drive glutaminolysis (82-84). These changes impair nucleotide synthesis and antioxidant defense in cancer cells. Similarly, exercise enhances FAO in multiple tissues and reduces lipid accumulation within tumors, decreasing the metabolic flexibility and survival advantage of cancer cells under stress (86, 87).

As a systemic modulator, exercise influences metabolic hormones, including insulin and IGF-1. Downregulation of the insulin/IGF-1 axis leads to inhibition of the PI3K/AKT/mTOR pathway, reducing cancer cell proliferation and resistance to apoptosis (107). These systemic effects synergize with local metabolic changes in the TME, collectively creating a metabolically hostile environment for tumors while preserving immune cell function.

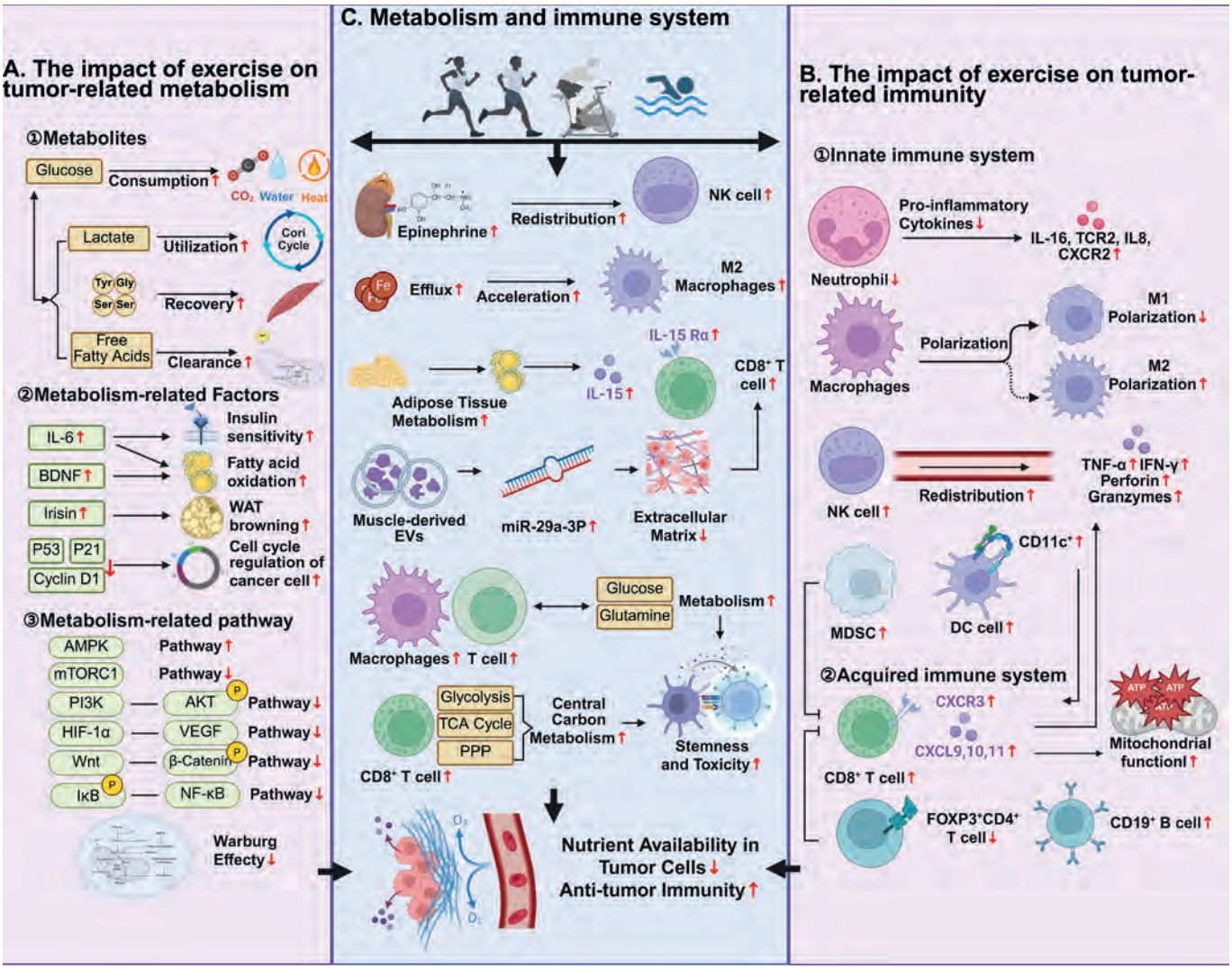

Figure 4. The potential mechanisms through which exercise affects tumors by regulating metabolism and immunity.
(A) Exercise Modulates Metabolic Pathways Exercise regulates the levels of metabolites such as glucose, lactate, and fatty acids, thereby increasing the metabolic rate of tumor-associated organs. This limits nutrient availability to tumors, reducing their risk and progression. Exercise also influences metabolism-related growth factors or cytokines, modulating tumor-related metabolic pathways to inhibit tumor cell proliferation and survival. (B) Exercise Modulates Immune Responses Exercise enhances tumor-associated immune responses by modulating the number and function of immune cells in both the innate and adaptive immune systems. This improvement strengthens anti-tumor immunity. In the innate immune system, exercise increases the activity of NK cells, neutrophils, macrophages, and dendritic cells. In the adaptive immune system, exercise enhances the function of T cells and B cells, promoting anti-tumor immune responses. (C) Exercise Modulates Immune-Metabolic Interactions Exercise reduces tumor immune escape and suppresses tumor progression by modulating immune-metabolic interactions. For instance, in animal models of pancreatic cancer, exercise promotes immune cell mobilization and tumor infiltration, enhancing the immune system's anti-tumor effects. Furthermore, exercise may affect tumor progression by modulating iron metabolism and tumor extracellular matrix. This includes selectively targeting tumor cells and promoting muscle-derived extracellular vesicles, such as miR-29a-3p, to inhibit the tumor extracellular matrix and facilitate immune cell infiltration.
Abbreviations: NK cell: Natural Killer Cell; M2 Macrophages: M2 Type Macrophages; CD8+ T cell: CD8 Positive T Cell; IL-15 Raβ: Interleukin 15 Receptor Alpha Chain; IL-15: Interleukin 15; miR-29a-3p: MicroRNA-29a-3p; EVs: Extracellular Vesicles; WAT: White Adipose Tissue; BDNF: Brain-Derived Neurotrophic Factor; P21: Cyclin-Dependent Kinase Inhibitor 1A; AMPK: AMP-Activated Protein Kinase; mTORC1: Mammalian Target of Rapamycin Complex 1; PI3K: Phosphoinositide 3-Kinase; HIF-1β: Hypoxia-Inducible Factor 1 Alpha; VEGF: Vascular Endothelial Growth Factor; Wnt: Wnt Signaling Pathway;β-Catenin: Beta-Catenin; IkB: Inhibitor of Nuclear Factor Kappa B; NF-βB: Nuclear Factor Kappa B; MDSCs: Myeloid-Derived Suppressor Cells; CXCR3: CXC Chemokine Receptor 3; CXCR9,10,11: CXC Chemokine Receptor 9, 10, 11; FOXP3+CD4+ T cell: Forkhead Box Protein P3 Positive CD4 Positive T Cell; CD19+ B cell: CD19 Positive B Cell; TNF-β: Tumor Necrosis Factor Alpha; IFN-β: Interferon Gamma

Table 2. Summary of the potential regulatory mechanisms of exercise on metabolic and immune function in preclinical models.

Cancer type	Research subject	Parameters of exercise	Metabolites	Immune cells	The effect of exercise on metabolic-immune regulation	References
NSCLC	Mouse	Voluntary wheel running	Collagen, miR-29a-3p	T cells	Voluntary exercise could increase T cell infiltration via the collagen inhibition orchestrated inflammatory TIME.	(126)
Melanoma Liver cancer, Lewis, Lung Cancer	Mouse	Voluntary wheel running	Epinephrine	NK cells	Regular exercise probably enhances immune function through epinephrine - and IL-6-mediated NK cell mobilization and infiltration, thereby inhibiting tumor growth and reducing tumor incidence and risk of recurrence.	(127)
Pancreatic cancer	Rat	Moderate Intensity Training Program (8 weeks)	Glucose and glutamine	Lymphocytes and macrophages	Moderate-intensity exercise can improve the survival of tumor-bearing rats by modulating glucose and glutamine metabolism in immune cells (e.g., lymphocytes and macrophages), promoting increased aerobic metabolism, and improving immune function.	(128)
Breast cancer	Mouse	Running wheels	TCA Metabolites	CD8 T cell	Exercise could alter the central carbon metabolism of CD8+ T cells by inducing the production and secretion of metabolites in skeletal muscle, which in turn enhances their antitumor effects.	(129)
Pancreatic cancer	Rat	High-intensity treadmill training (10 weeks, 5 days/week, 30 minutes/day, 85% VO2 max)	Glucose and glutamine	Lymphocytes and macrophages	High-intensity exercise would promote anti-tumor effects by modulating immune function and tumor cell metabolism (e.g., glucose and glutamine metabolism), and thus may be an effective strategy against cancer.	(130)
Lymphoma	Mouse	Voluntary wheel running	Epinephrine	NK cell	Voluntary wheel running could mobilize cytotoxic immune cells and prevents tumor progression through β2-adrenergic receptor signaling, suggesting that combining physical activity with adrenergic modulation can enhance anti-tumor immune responses.	(131)
GvL	Mouse	Voluntary wheel running	Genes related to metabolic processes	Lymphocytes	Voluntary wheel running could downregulates genes related to mitochondrial function, protein synthesis, and metabolism in tumors, and improves donor lymphocyte infusion outcomes by enhancing graft-versus-leukemia effects while reducing graft-versus-host disease, partially through metabolic reprogramming of leukemia cells	(132)
PDA	Mouse	Treadmill, 30min, per day at 15cm/s, 5days/week.	Epinephrine	CD8+ T cells	Exercise possibly promotes immune mobilization and accumulation of tumor-infiltrating IL15Ra+ CD8 T cells and inhibits tumor growth.	(133)

Collectively, these adaptations suggest that exercise reprograms the tumor's metabolic network, reducing nutrient access and interfering with biosynthetic pathways essential for malignant progression.

Modulation of innate and adaptive immunity by exercise

Exercise exerts robust immunomodulatory effects, influencing both the quantity and functionality of innate and adaptive immune cells. Acute exercise mobilizes immune cells into circulation, including NK cells, monocytes, neutrophils, and DCs, while chronic training induces sustained enhancements in immune surveillance and anti-tumor immunity (126-128, 131, 132) .

In the adaptive compartment, exercise improves the cytotoxicity of $CD8^+$ T cells by increasing granzyme B, perforin, and IFN-γ production, while reducing the expression of exhaustion markers like Programmed Death-1 (PD-1), TIM-3, and LAG-3 (19, 108). These functional improvements translate to enhanced killing of tumor cells and improved responsiveness to immune checkpoint blockade therapies. Exercise has also been shown to promote $CD8^+$ memory T cell differentiation and expansion, thereby establishing long-term immune protection (108, 110, 111).

NK cells are particularly sensitive to exercise stimuli. Physical activity increases NK cell mobilization and infiltration into tumors, improves their activation status, and enhances the release of cytolytic molecules such as FasL and TRAIL (126, 129). These changes contribute to both early detection and control of tumor growth.

Exercise also impacts myeloid cell populations in the TME. It can reduce the accumulation of immunosuppressive myeloid-derived suppressor cells (MDSCs), which otherwise inhibit T cell responses through arginase production and ROS generation (130). Moreover, exercise skews macrophage polarization from the M2 phenotype toward an M1-like, pro-inflammatory phenotype, enhancing antigen presentation and promoting anti-tumor immunity (126).

Importantly, exercise also improves the trafficking and infiltration of immune cells into tumors, a process often hindered by the dense extracellular matrix and abnormal vasculature. Exercise-induced vascular remodeling and reduced tumor fibrosis facilitate immune cell access and improve immune–tumor engagement (110, 111, 129).

These immunological benefits collectively enhance immune readiness and support long-term tumor control, particularly when combined with immunotherapies.

EXERCISE AND IMMUNE-METABOLIC CROSSTALK: MECHANISTIC INTEGRATION OF TUMOR SUPPRESSION

Macro-functional overview: Exercise reshapes tumor metabolism and immunity

The functional outcomes of anti-tumor immunity are intimately linked to metabolic support. Within the TME, nutrient competition between tumor and immune cells often leaves effector lymphocytes functionally impaired. For example, glucose depletion impairs T cell proliferation and cytokine secretion, while tryptophan degradation via IDO1 leads to Treg induction and $CD8^+$ T cell suppression (61).

Exercise can shift this metabolic competition in favor of the immune system. By reducing tumor consumption of glucose, glutamine, and lipids, exercise helps preserve these nutrients for immune cell activation (133). Moreover, exercise activates AMPK signaling in immune cells, enhancing their metabolic flexibility and mitochondrial function, allowing them to sustain cytotoxicity even under nutrient stress (135).

Exercise also attenuates tumor-derived suppressive metabolites such as lactate and kynurenine. Reduced lactate levels in the TME improve $CD8^+$ T cell viability, increase effector cytokine secretion, and inhibit lactate-mediated polarization of TAMs (8, 52). Meanwhile, suppression of tryptophan catabolism and kynurenine production by exercise may limit AhR signaling, reducing Treg differentiation and restoring immune surveillance (61).

Myokines secreted during physical activity—including IL-6, IL-7, IL-15, irisin, and SPARC—further modulate immune metabolism and function (110, 111). For example, IL-15, a key regulator of lymphocyte metabolic fitness as detailed in section 4.3, may mediate several exercise-induced benefits on immune cells. Irisin has been shown to inhibit tumor cell proliferation and EMT, and may play a role in modifying stromal cell behavior (110, 111).

Exercise-induced improvement in tumor vasculature, perfusion, and oxygenation also plays a vital role in immune–metabolic synergy. Better oxygen delivery reduces hypoxia-driven immunosuppression and restores OXPHOS in T cells. Combined with improved immune cell trafficking, these effects enhance the depth and durability of anti-tumor responses.

Together, these findings illustrate how exercise simultaneously remodels the metabolic and immunological landscape of tumors. A deeper understanding of this bidirectional regulation may facilitate the development of individualized exercise regimens as adjuncts to immunotherapy or metabolic-targeted cancer treatments.

AMPK–mTOR–HIF1α axis

AMPK serves as a central energy sensor and regulator of cellular homeostasis. The AMPK–mTOR–HIF1α signaling axis not only governs tumor metabolic plasticity but also enhances mitochondrial function in T cells and NK cells, thereby supporting immune effector activity and energy supply (136). One preclinical study demonstrates that regular exercise markedly activates AMPK and its downstream phosphorylation targets, leading to the suppression of tumor proliferation (137). Mechanistically, exercise-induced AMPK activation suppresses mTOR signaling, reduces tumor glycolysis and HIF1α-driven lactate accumulation, and enhances mitochondrial oxidative capacity in T and NK cells—forming a core framework of "energy sensing–metabolic reprogramming–immune activation"(138). In melanoma models, exercise improves tumor vascular architecture and oxygenation via an ERK5-dependent mechanism, which increases $CD8^+$ T-cell infiltration, reprograms myeloid cell phenotypes, and destabilizes HIF1α under reduced hypoxic stress (139). Similarly,

aerobic exercise improves tumor perfusion and oxygen supply while decreasing mitochondrial ROS accumulation, further promoting HIF1α inactivation (140). In breast cancer models, inhibition of the mTOR pathway by exercise reverses metabolic reprogramming, limits glucose and glutamine utilization, and induces tumor cell apoptosis (141).

At the systemic level, exercise also counteracts the proliferative stimulus of a high-fat diet. For instance, in MCF7 cells, exercise-activated AMPK upregulates p27, downregulates pAkt, and increases AdipoR1 expression, thereby promoting cell-cycle arrest in an intensity-dependent manner—high-intensity training (>3 km/day) completely abolishes HFD-induced proliferation (142). Furthermore, exercise enhances NK cell activity accompanied by upregulation of PIK3R1, which supports NK cell maturation, trafficking, and cytotoxic functions (143).

PGC-1α–ERRα axis

The PGC-1α–ERRα axis represents a crucial molecular bridge connecting exercise, mitochondrial function, and immunometabolic adaptation (144). PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha) is a master transcriptional coactivator regulating mitochondrial biogenesis and oxidative metabolism, and it plays a central role in muscle fiber type switching (145). Acting as a metabolic sensor of environmental stress (146), exercise-induced activation of PGC-1α enhances mitochondrial health, promotes OXPHOS, and maintains energy homeostasis (147). Beyond its direct metabolic role, PGC-1α regulates the secretion of myokines such as irisin and IL-15, which convey systemic signals that reshape the metabolic flexibility of tumor and immune cells (148). Through this endocrine-like mechanism, exercise not only improves systemic energy balance but also indirectly enhances the metabolic fitness of immune effectors. Within tumor cells, PGC-1α enhances OXPHOS and restrains glycolysis (149), while in skeletal muscle it contributes to whole-body metabolic stability (150).

Meanwhile, ERRα functions downstream of PGC-1α to control oxidative gene networks. Genetic enhancement of ERRα increases exercise endurance and fatigue resistance by globally remodeling DNA binding and transcriptional programs, leading to increased oxidative fiber proportion, mitochondrial biogenesis, FAO, and lactate homeostasis (151). Targeting ERRα has thus emerged as a strategy to develop exercise mimetics, which can improve mitochondrial respiration and mitigate age-related or disease-induced muscle dysfunction(152). Importantly, ERRα also regulates lactate and energy metabolism in tumors; exercise can inhibit its aberrant activation, reduce TME acidification, and restore immune cell function (153).

Together, these findings define the PGC-1α–ERRα axis as a mechanistic bridge between exercise, mitochondrial function, and immune metabolism, serving as a central node of exercise-mediated metabolic regulation in cancer.

IL-6/STAT3 axis

The IL-6/STAT3 pathway constitutes another key interface between exercise and immunometabolic regulation. In non-small cell lung cancer (NSCLC), sustained activation of IL-6–STAT3 signaling contributes to $CD8^+$ T-cell exhaustion and tumor progression (154). However, exercise modulates this pathway in an opposite, transient, and beneficial manner.

One clinical study has shown that resistance training increases plasma levels of anti-inflammatory cytokines and simultaneously activates STAT3 signaling in peripheral blood mononuclear cells (PBMCs), highlighting a potential mechanism by which resistance exercise enhances immune anti-inflammatory capacity (155). Exercise-induced IL-6 primarily acts as a myokine—a cytokine secreted from skeletal muscle—whose short-term elevation improves insulin sensitivity, activates STAT3-dependent mobilization pathways, and promotes the trafficking of NK and $CD8^+$ T cells from circulation to tissues (156). This transient cytokine surge represents a rapid immunometabolic mobilization mechanism underlying the systemic benefits of exercise.

During exercise, both skeletal muscle and stromal or immune cells within the TME release IL-6. Short-term elevations of myokine-derived IL-6 improve insulin sensitivity, stimulate anti-inflammatory cytokine production, recruit cytotoxic immune cells, and transiently activate IL-6 signaling within the TME. Long-term regular exercise lowers basal intratumoral IL-6, correlating with smaller tumor size, while maintaining metabolic and immune homeostasis (157-159).

The biological outcome of IL-6 signaling thus depends critically on exercise intensity and duration: moderate, transient IL-6 elevations are immunometabolically beneficial, whereas chronic or pathologically sustained IL-6 activation may promote tumor progression (160).

EXERCISE PRESCRIPTION PARAMETERS INFLUENCING TUMOR METABOLISM AND IMMUNITY

According to the FITT principle (Frequency, Intensity, Time, and Type), the design of exercise interventions should comprehensively consider key parameters such as exercise type, intensity, frequency, and duration. However, some patients with advanced malignancies may not tolerate evidence-based FITT protocols; therefore, exercise prescriptions should be adjusted according to individual physical capacity and treatment tolerance (161).

Different exercise types can activate distinct metabolic and immune signaling pathways to exert anticancer effects. Forced treadmill running—a common modality in preclinical studies—can regulate gut microbiota-derived metabolites such as formate, thereby enhancing tumor antigen-specific $CD8^+$ T-cell effector functions and improving the efficacy of immune checkpoint inhibitors (ICIs) through an Nrf2-dependent mechanism in melanoma (162).In contrast, voluntary wheel running elevates the level of skeletal muscle–derived extracellular vesicle (EV) miR-29a-3p, which targets COL1A1 to suppress collagen deposition in the tumor stroma, promoting T-cell infiltration and augmenting immunotherapy response (163).Resistance training improves metabolic health in cancer survivors by reducing adiposity and preserving lean muscle mass (164).In addition, traditional Eastern exercise modalities such as Taoist Qigong and Yoga also show immune-modulatory potential: Qigong alters B-cell and monocyte proportions, while Yoga reduces pro-inflammatory cytokines (TNF-α, IL-6), increases IL-10, and ameliorates oxidative stress (165).

Among the FITT components, intensity appears to be the most critical determinant of anticancer efficacy. Based on the percentage of maximal running capacity in mice, exercise can be classified as low (~30%), moderate (~60%), or high (~90%) intensity. Both low- and moderate-intensity training promote tumor vascular normalization; however, only moderate-intensity exercise significantly enhances intratumoral $CD8^+$ T-cell infiltration and effector molecule expression (CD69, IFNγ, GzmB) (166).A systematic review further demonstrated that a single bout of moderate-to-vigorous aerobic exercise could suppress tumor cell proliferation via increased secretion of myokines and hormones (167).Nonetheless, the benefits of intensity follow a U-shaped curve: excessive or exhaustive training may blunt immune surveillance. In a comparative preclinical study, high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) both improved cardiovascular fitness and quality of life in breast cancer patients, but no significant differences were observed in metabolic or inflammatory biomarkers (168).However, prolonged exhaustive high-intensity exercise (HIE) was shown to elevate anti-inflammatory cytokines and Treg proportions, potentially increasing infection susceptibility and impairing antitumor immunity (169).Collectively, these findings suggest that moderate-intensity exercise maximizes immune activation while minimizing immunosuppression, thereby representing the optimal balance for anticancer effects.

Exercise frequency also shapes metabolic and immune outcomes by regulating skeletal muscle circadian genes such as PPARδ. Regular training reinforces the synchronization between muscle clocks and metabolic pathways, improving glucose–lipid balance, mitochondrial efficiency, and redox homeostasis, while reducing tumor-related metabolic dysregulation (170).Epidemiological evidence indicates that total weekly exercise duration exceeding 280 minutes more effectively improves systemic inflammatory markers such as TNF-α and IL-8 (171).Moderate-to-high frequency programs (2–4 sessions per week) with moderate total load appear most efficient in eliciting short- to mid-term immune cell mobilization and metabolic benefits (171).After a single bout of training, leukocyte and NK-cell mobilization are positively correlated with intensity, and frequent repetition of such transient responses can lead to cumulative enhancement—an "EX-BOOST" phenomenon. Therefore, at least two sessions of moderate-to-vigorous exercise per week are recommended to maintain sustained immune activation (172).

Exercise duration determines whether adaptations remain transient or consolidate into long-term immunometabolic remodeling. A comprehensive review showed that short-term (4–12 weeks), medium-term (13–24 weeks), and long-term (>24 weeks) interventions each exert distinct physiological impacts (167).Short-term exercise primarily triggers acute leukocyte and NK-cell mobilization pathways (172) enhances glucose–lipid metabolism, and modulates myokine secretion (e.g., irisin, myostatin) (173). In contrast, long-term, regular training stabilizes immune homeostasis, reduces chronic inflammation, and enhances chemotherapy tolerance and efficacy (171).Immediately after acute exercise, serum IL-4, IL-6, and IL-10 levels rise transiently and return to baseline within one hour. Chronic moderate-to-high intensity training, however, decreases TNF-α, IL-6, and CD4/CD8 ratio, while increasing IL-10 after 24 weeks (174).These patterns suggest that long-term exercise establishes a persistent "immunometabolic memory" at the organ and systemic levels, and interventions lasting over 24 weeks may produce durable antitumor immune adaptations (175).

Overall, optimization of exercise prescription following the FITT framework is essential for achieving maximal therapeutic benefit in oncology. Exercise type defines the molecular entry point (e.g., Nrf2, myokine, or collagen remodeling pathways), intensity dictates the immune activation threshold, frequency governs rhythmic and cumulative adaptations, and duration determines the persistence of immunometabolic reprogramming. Properly calibrated, these parameters synergize to transform exercise into a form of precision metabolic–immune modulation, offering a non-pharmacological strategy to complement chemotherapy and immunotherapy in cancer treatment.

TRANSLATIONAL AND CLINICAL PERSPECTIVES: TOWARD PRECISION EXERCISE ONCOLOGY

With the rapid advancement of data analytics and personalized medicine, Precision Exercise Oncology is emerging as an important component of cancer rehabilitation and adjuvant therapy. The core principle is to design precise and dynamic exercise prescriptions based on tumor type, metabolic phenotype, immune status, and individual physiological characteristics, leveraging big data and intelligent monitoring to maximize patients' metabolic homeostasis and immune function (176).

Extensive clinical studies consistently indicate that exercise is safe and beneficial for most cancer patients, including those undergoing chemotherapy or radiotherapy (16-20).In parallel, preclinical evidence increasingly suggests that exercise combined with metabolic or immunotherapy can significantly enhance antitumor efficacy (133, 135).Currently, several clinical trials are investigating the synergistic effects of exercise with immuno- or metabolic therapies (Table 3), and a systematic review evaluating the role of exercise in modulating immunity and immunotherapy outcomes in cancer is forthcoming (177).However, most trials are ongoing, and the definitive therapeutic outcomes remain to be established.

Despite its potential benefits, exercise interventions must consider patients' physical capacity and metabolic reserve. Patients with cachexia, anemia, or immunosuppression may not tolerate standard exercise regimens. Given the variability in cancer types, treatment modalities, and potential cardiovascular risks, medical evaluation and clearance are generally required prior to initiating exercise programs.

For cachectic patients, a systematic review of randomized and non-randomized controlled trials indicated that exercise interventions are overall safe and can improve body composition and muscle strength (178). However, excessive whole-body exercise may exacerbate energy imbalance and weight loss in this population (179).Therefore, low-intensity resistance training combined with high-protein, energy-dense nutritional support, and dynamic adjustment of training loads based on body weight and muscle mass is recommended to ensure safety (180, 181).

For anemic patients, multiple studies demonstrate that aerobic exercise can maintain red blood cell levels and oxygen-carrying

Table 3. Summary of Ongoing Clinical Trials on Exercise Interventions Targeting Immune-Metabolic Regulation in Cancer.

Cancer Type	NCT Number	Immune-Metabolic Interaction	Exercise Intervention	Planned Enrollment	Expected Outcome / Endpoint
Melanoma	NCT06627595	Immunotherapy	Self-reported physical activity	160	Adverse events at treatment initiation and 6 months, assessed via IPAQ questionnaire
Urological Cancers	NCT06152926	Immunotherapy (e.g., ICI)	Regular physical activity or planned exercise	12	Exploratory study on patient perspectives and experiences regarding exercise during immunotherapy
Metastatic NSCLC	NCT04676009	Immunotherapy + Chemotherapy	Acute 35-min physical exercise	26	Feasibility of acute exercise immediately before immunotherapy and chemotherapy
Triple-Negative Breast Cancer	NCT06672120	Chemotherapy + Immunotherapy (checkpoint inhibitors)	24-week home-based, video-supervised endurance & resistance training	120	Incidence of CTRCD and ICI-related myocarditis at 24 and 52 weeks
Melanoma	NCT05358938	Checkpoint blockade immunotherapy	30-min moderate exercise	22	Exercise to enhance response to checkpoint blockade therapy
Lung Cancer	NCT06993896	Chemo- and/or Immunotherapy	Steps per week (walking)	38	Evaluate predictors and correlation with patient-reported outcomes (pain, distress, fatigue)
Cutaneous Cancers	NCT06008977	Checkpoint blockade immunotherapy	Moderate pace, 30 min/day	20	Feasibility of exercise intervention; preliminary data on day-of-therapy exercise effects
Hematological Malignancies	NCT05763563	CAR-T Cell Immunotherapy	Resistance training 30 min ×2/week + moderate aerobic ≥3 days/week	20	Evaluate exercise program for patients preparing for CAR-T therapy
Lung Cancer	NCT06026111	Immunotherapy	12-week training: HIIT, MICT, or usual care	30	Feasibility and comparison of immune activity, cardiorespiratory fitness, physical function, immunotherapy-related adverse events, and patient-reported outcomes
NSCLC	NCT06983899	Immunotherapy	Aerobic interval training	100	Aerobic interval training to improve oxygen utilization and immune activity, enhancing treatment response
Prostate Cancer	NCT03440879	ADT	Strength training	23	Assess ADT effects on basal muscle protein turnover and strength training response; secondary: postprandial glucose/insulin differences
Breast Cancer	NCT06928701	Nutritional supplement	Physical activity per WHO and EUSOMA criteria	160	Impact of targeted nutrition + exercise on metabolic and immune-related gene expression in early breast cancer patients undergoing neoadjuvant therapy
Prostate Cancer	NCT04870515	ADT	Aerobic + strength/ resistance exercise	40	Diet and exercise intervention to mitigate metabolic and physiologic changes caused by ADT and radiotherapy

capacity during breast cancer chemoradiotherapy. Moderate-intensity, regular aerobic exercise improves treatment-related anemia and encourages participation (182-186).Nevertheless, anemia severity, cancer type, treatment regimen, and exercise type and intensity all influence safety and tolerance (182).A systematic review suggested that platelet counts $>20 \times 10^9$/L are generally safe for exercise and daily activities, whereas $<10 \times 10^9$/L warrants caution or contraindication; hemoglobin <70–80 g/L may increase the risk of adverse events during exercise (187).Thus, pre-exercise evaluation of cardiopulmonary function and symptoms is essential for anemic patients, and HIE should be delayed if Hb <7–8 g/dL or hypoxic symptoms are present, with preference for static, breathing, or functional training modalities to ensure safety (161, 181).

Exercise has been shown to regulate the TME and enhance immune cell function, potentially ameliorating cancer-associated immunological dysfunction (188-190). Nevertheless, infection risk must be considered, particularly in immunocompromised patients such as those with HIV or post-transplant status (191). In these populations, exercise programs should be professionally supervised, prioritize low-intensity, progressive training, and adopt home-based or one-on-one formats, avoiding high-exposure environments while dynamically adjusting exercise load to optimize immune and metabolic benefits safely (192, 193).

Achieving truly precision exercise interventions requires the development of a biomarker-based framework that dynamically reflects metabolic and immune status, guiding exercise frequency, intensity, type, and duration, and predicting individual responsiveness. Although no standardized system exists, several candidate markers have been proposed:

Metabolic biomarkers: Lactate levels and LDHA expression may serve as immediate indicators of exercise intensity and tumor metabolic response, helping to avoid excessive acidification of the TME (194, 195). Circulating insulin concentrations provide long-term assessment of exercise tolerance and metabolic benefits (196). Exercise-induced changes in tryptophan metabolites (kynurenine) and gut microbiota-derived formate reflect modulation of $CD8^+$ T-cell function and immunosuppressive metabolic environment (162, 197). Mitochondrial regulator PGC-1α is implicated in the protective effects of physical activity on colorectal cancer, as its activity is positively stimulated by exercise and inversely correlated with cancer risk (144).

Immune biomarkers: Neutrophil-to-lymphocyte ratio (NLR), $CD4^+$, $CD8^+$, NK cells, Treg, and MDSCs—both absolute and relative levels—can identify patients suitable for exercise intervention and serve as dynamic predictors of response (198). Short-term exercise-induced immune activation can be monitored via IFN-γ, Granzyme B, and Perforin (199). Exercise mobilizes IL-15-dependent immune cells and promotes accumulation of tumor-infiltrating IL-15Rα^9 $CD8^+$ T cells, which exhibit potent antitumor activity, highlighting IL-15 as a potential therapeutic target in exercise oncology (133). Concurrently, exercise-induced IL-6 enhances insulin sensitivity, stimulates anti-inflammatory factor secretion, mobilizes immune cells, and reduces DNA damage, synergistically preventing tumor initiation and progression (200). Moreover, circulating NK cell activity, intratumoral NK cell infiltration, and IL-6 levels can serve as biomarkers of exercise-induced antitumor immune activation and may be used to monitor and optimize exercise interventions in cancer models (127).

In summary, precision exercise oncology offers a viable strategy for rehabilitation and adjuvant therapy in cancer patients, while providing new avenues for individualized optimization of metabolic and immune therapies. Future research should integrate multi-omics, physiological monitoring, and AI algorithms to construct a biomarker-feedback–based closed-loop exercise intervention system, achieving truly personalized and dynamically adaptive exercise prescriptions for cancer therapy.

CONCLUSION AND FUTURE PERSPECTIVES: EXERCISE AS A METABOLIC-IMMUNE MODULATOR IN CANCER THERAPY

Tumor metabolic reprogramming and immune evasion are two central hallmarks that synergistically sustain cancer progression and therapeutic resistance. As highlighted in this review, exercise represents a promising, low-cost, and non-pharmacological strategy capable of concurrently modulating tumor metabolism and enhancing anti-tumor immunity. By reshaping the tumor metabolic microenvironment—including reducing lactate accumulation, reprogramming amino acid and lipid metabolism, and improving systemic glucose homeostasis—exercise may indirectly restore immune function and strengthen host anti-tumor defenses.

Importantly, the influence of exercise extends beyond skeletal muscle to organs such as the liver, heart, and gut, each contributing to the metabolic and immune landscape of the TME. These systemic effects offer a unique opportunity to leverage exercise as an adjunct therapy in oncology.

However, significant challenges remain. Current knowledge on how exercise influences immune-metabolic pathways in different tumor types and molecular subtypes is still limited. Moreover, the optimal parameters of exercise—such as type, intensity, frequency, and duration—may vary significantly across patients, cancer types, and stages of treatment. Future studies should aim to establish precision exercise prescriptions that consider tumor heterogeneity, host fitness levels, and treatment context (e.g., immunotherapy vs. chemotherapy). Additionally, integrating wearable technology and real-time metabolic monitoring may enable dynamic adjustment of exercise protocols for individual patients.

In conclusion, exercise has the potential to become an integral component of personalized cancer therapy by targeting the immunometabolic vulnerabilities of tumors. Advancing this field requires translational and clinical research that bridges molecular mechanisms with practical implementation, ultimately enabling evidence-based, individualized exercise strategies in oncology care.

AUTHOR CONTRIBUTIONS

Anqi He and Sha Wang prepared tables and figures. Anqi He and Yong Xia conceptualized and wrote the manuscript. Shunzi Rong, Chong Li, Tianjie Bao, Min Luo, Chengqi He, and Yonghong Yang helped with conceptualization of the manuscript. All authors participated in manuscript editing and read and approved the final version.

FUNDING

This work was supported by Sichuan Science and Technology Program (Grant No. 2025ZNSFSC0559), Sichuan University Young Faculty Science and Technology Innovation Capability Enhancement Project (2024SCUOJTX046) and the National Natural Science Foundation of China (Grant No. 82573560).

Availability of data and materials
Not applicable.

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

REFERENCES

1. Stine ZE, Schug ZT, Salvino JM, and Dang CV. Targeting cancer metabolism in the era of precision oncology. Nature reviews Drug discovery 21: 141-162, 2022.
2. Galassi C, Chan TA, Vitale I, and Galluzzi L. The hallmarks of cancer immune evasion. Cancer cell 42: 1825-1863, 2024.
3. Faubert B, Solmonson A, and DeBerardinis RJ. Metabolic reprogramming and cancer progression. 368: eaaw5473, 2020.
4. Liu Y, Zhao Y, Song H, Li Y, Liu Z, Ye Z, Zhao J, Wu Y, Tang J, and Yao M. Metabolic reprogramming in tumor immune microenvironment: Impact on immune cell function and therapeutic implications. Cancer letters 597: 217076, 2024.
5. Bai R, Meng Y, and Cui J. Therapeutic strategies targeting metabolic characteristics of cancer cells. Critical reviews in oncology/hematology 187: 104037, 2023.
6. Huang K, Han Y, Chen Y, Shen H, Zeng S, and Cai C. Tumor metabolic regulators: key drivers of metabolic reprogramming and the promising targets in cancer therapy. Molecular cancer 24: 7, 2025.
7. Kooshan Z, Cárdenas-Piedra L, Clements J, and Batra J. Glycolysis, the sweet appetite of the tumor microenvironment. Cancer letters 600: 217156, 2024.
8. Wang ZH, Peng WB, Zhang P, Yang XP, and Zhou Q. Lactate in the tumour microenvironment: From immune modulation to therapy. EBioMedicine 73: 103627, 2021.
9. Wang Y, and Patti GJ. The Warburg effect: a signature of mitochondrial overload. Trends in cell biology 33: 1014-1020, 2023.
10. Chen J, Cui L, Lu S, and Xu S. Amino acid metabolism in tumor biology and therapy. Cell death & disease 15: 42, 2024.
11. Chew V, Toh HC, and Abastado JP. Immune microenvironment in tumor progression: characteristics and challenges for therapy. Journal of oncology 2012: 608406, 2012.
12. Lei X, Lei Y, Li JK, Du WX, Li RG, Yang J, Li J, Li F, and Tan HB. Immune cells within the tumor microenvironment: Biological functions and roles in cancer immunotherapy. Cancer letters 470: 126-133, 2020.
13. Viel S, Vivier E, Walzer T, and Marçais A. Targeting metabolic dysfunction of CD8 T cells and natural killer cells in cancer. Nature Reviews Drug Discovery 2024.
14. Kao KC, Vilbois S, Tsai CH, and Ho PC. Metabolic communication in the tumour-immune microenvironment. Nature cell biology 24: 1574-1583, 2022.
15. Bader JE, Voss K, and Rathmell JC. Targeting Metabolism to Improve the Tumor Microenvironment for Cancer Immunotherapy. Molecular cell 78: 1019-1033, 2020.
16. He A, Pu Y, Jia C, Wu M, He H, and Xia Y. The Influence of Exercise on Cancer Risk, the Tumor Microenvironment and the Treatment of Cancer. Sports medicine (Auckland, NZ) 2024.
17. Hojman P, Gehl J, Christensen JF, and Pedersen BK. Molecular Mechanisms Linking Exercise to Cancer Prevention and Treatment. Cell metabolism 27: 10-21, 2018.
18. Buss LA, and Dachs GU. Effects of Exercise on the Tumour Microenvironment. Advances in experimental medicine and biology 1225: 31-51, 2020.
19. Miao S-N, Chai M-Q, Liu X-Y, Wei C-Y, Zhang C-C, Sun N-N, Fei Q-Z, Peng L-L, and Qiu H. Exercise accelerates recruitment of CD8+ T cell to promotes anti-tumor immunity in lung cancer via epinephrine. BMC cancer 24: 474, 2024.

20. Zhu C, Ma H, He A, Li Y, He C, and Xia Y. Exercise in cancer prevention and anticancer therapy: Efficacy, molecular mechanisms and clinical information. Cancer letters 544: 215814, 2022.
21. Sparks LM. Exercise training response heterogeneity: physiological and molecular insights. Diabetologia 60: 2329-2336, 2017.
22. Wang Z, Wang Z, Chen H, Li S, Yang J, Ma Y, Zhou C, Jin X, Liu J, and Wang X. Exercise therapy: Anti-tumor and improving chemotherapy efficacy. Journal of Holistic Integrative Pharmacy 5: 185-194, 2024.
23. Neufer PD, Bamman Marcas M, Muoio Deborah M, Bouchard C, Cooper Dan M, Goodpaster Bret H, Booth Frank W, Kohrt Wendy M, Gerszten Robert E, Mattson Mark P, Hepple Russell T, Kraus William E, Reid Michael B, Bodine Sue C, Jakicic John M, Fleg Jerome L, Williams John P, Joseph L, Evans M, Maruvada P, Rodgers M, Roary M, Boyce Amanda T, Drugan Jonelle K, Koenig James I, Ingraham Richard H, Krotoski D, Garcia-Cazarin M, McGowan Joan A, and Laughlin Maren R. Understanding the Cellular and Molecular Mechanisms of Physical Activity-Induced Health Benefits. Cell metabolism 22: 4-11, 2015.
24. Warburg O. On the origin of cancer cells. Science (New York, NY) 123: 309-314, 1956.
25. Hönigova K, Navratil J, Peltanova B, Polanska HH, Raudenska M, and Masarik M. Metabolic tricks of cancer cells. Biochimica et biophysica acta Reviews on cancer 1877: 188705, 2022.
26. Liao M, Yao D, Wu L, Luo C, Wang Z, Zhang J, and Liu B. Targeting the Warburg effect: A revisited perspective from molecular mechanisms to traditional and innovative therapeutic strategies in cancer. Acta pharmaceutica Sinica B 14: 953-1008, 2024.
27. Ni X, Lu CP, Xu GQ, and Ma JJ. Transcriptional regulation and post-translational modifications in the glycolytic pathway for targeted cancer therapy. Acta pharmacologica Sinica 2024.
28. Du A, Wang Z, Huang T, Xue S, Jiang C, Qiu G, and Yuan K. Fatty acids in cancer: Metabolic functions and potential treatment. 2: e25, 2023.
29. Du D, Liu C, Qin M, Zhang X, Xi T, Yuan S, Hao H, and Xiong J. Metabolic dysregulation and emerging therapeutical targets for hepatocellular carcinoma. Acta pharmaceutica Sinica B 12: 558-580, 2022.
30. Bergers G, and Fendt SM. The metabolism of cancer cells during metastasis. Nature reviews Cancer 21: 162-180, 2021.
31. Arner EN, and Rathmell JC. Metabolic programming and immune suppression in the tumor microenvironment. Cancer cell 41: 421-433, 2023.
32. Bejarano L, Jordão MJC, and Joyce JA. Therapeutic Targeting of the Tumor Microenvironment. Cancer discovery 11: 933-959, 2021.
33. Kroemer G, and Pouyssegur J. Tumor cell metabolism: cancer's Achilles' heel. Cancer cell 13: 472-482, 2008.
34. De Martino M, Rathmell JC, Galluzzi L, and Vanpouille-Box C. Cancer cell metabolism and antitumour immunity. Nature reviews Immunology 24: 654-669, 2024.
35. Liu Y, Wang F, Peng D, Zhang D, Liu L, Wei J, Yuan J, Zhao L, Jiang H, Zhang T, Li Y, Zhao C, He S, Wu J, Yan Y, Zhang P, Guo C, Zhang J, Li X, Gao H, and Li K. Activation and antitumor immunity of CD8(+) T cells are supported by the glucose transporter GLUT10 and disrupted by lactic acid. Science translational medicine 16: eadk7399, 2024.
36. Chen T, Xu ZG, Luo J, Manne RK, Wang Z, Hsu CC, Pan BS, Cai Z, Tsai PJ, Tsai YS, Chen ZZ, Li HY, and Lin HK. NSUN2 is a glucose sensor suppressing cGAS/STING to maintain tumorigenesis and immunotherapy resistance. Cell metabolism 35: 1782-1798.e1788, 2023.
37. De Leo A, Ugolini A, Yu X, Scirocchi F, Scocozza D, Peixoto B, Pace A, D'Angelo L, Liu JKC, Etame AB, Rughetti A, Nuti M, Santoro A, Vogelbaum MA, Conejo-Garcia JR, Rodriguez PC, and Veglia F. Glucose-driven histone lactylation promotes the immunosuppressive activity of monocyte-derived macrophages in glioblastoma. Immunity 57: 1105-1123. e1108, 2024.
38. Duan Q, Li H, Gao C, Zhao H, Wu S, Wu H, Wang C, Shen Q, and Yin T. High glucose promotes pancreatic cancer cells to escape from immune surveillance via AMPK-Bmi1-GATA2-MICA/B pathway. Journal of experimental & clinical cancer research : CR 38: 192, 2019.
39. Wu L, Jin Y, Zhao X, Tang K, Zhao Y, Tong L, Yu X, Xiong K, Luo C, Zhu J, Wang F, Zeng Z, and Pan D. Tumor aerobic glycolysis confers immune evasion through modulating sensitivity to T cell-mediated bystander killing via TNF-α. Cell metabolism 35: 1580-1596.e1589, 2023.
40. Hu Z, Yu X, Ding R, Liu B, Gu C, Pan XW, Han Q, Zhang Y, Wan J, Cui XG, Sun J, and Zou Q. Glycolysis drives STING signaling to facilitate dendritic cell antitumor function. The Journal of clinical investigation 133: 2023.
41. Sen K, Pati R, Jha A, Mishra GP, Prusty S, Chaudhary S, Swetalika S, Podder S, Sen A, Swain M, Nanda RK, and Raghav SK. NCoR1 controls immune tolerance in conventional dendritic cells by fine-tuning glycolysis and fatty acid oxidation. Redox biology 59: 102575, 2023.
42. Xiao G, Chan LN, Klemm L, Braas D, Chen Z, Geng H, Zhang QC, Aghajanirefah A, Cosgun KN, Sadras T, Lee J, Mirzapoiazova T, Salgia R, Ernst T, Hochhaus A, Jumaa H, Jiang X, Weinstock DM, Graeber TG, and Müschen M. B-Cell-Specific Diversion of Glucose Carbon Utilization Reveals a Unique Vulnerability in B Cell Malignancies. Cell 173: 470-484.e418, 2018.
43. Ehm PAH, Horn S, Hoffer K, Kriegs M, Horn M, Giehler S, Nalaskowski M, Rehbach C, Horstmann MA, and Jücker M. Ikaros sets the threshold for negative B-cell selection by regulation of the signaling strength of the AKT pathway. Cell communication and signaling : CCS 22: 360, 2024.
44. Kumagai S, Koyama S, Itahashi K, Tanegashima T, Lin YT, Togashi Y, Kamada T, Irie T, Okumura G, Kono H, Ito D, Fujii R, Watanabe S, Sai A, Fukuoka S, Sugiyama E, Watanabe G, Owari T, Nishinakamura H, Sugiyama D, Maeda Y, Kawazoe A, Yukami H, Chida K, Ohara Y, Yoshida T, Shinno Y, Takeyasu Y, Shirasawa M, Nakama K, Aokage K, Suzuki J, Ishii G, Kuwata T, Sakamoto N, Kawazu M, Ueno T, Mori T, Yamazaki N, Tsuboi M, Yatabe Y, Kinoshita T, Doi T, Shitara K, Mano H, and Nishikawa H. Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments. Cancer cell 40: 201-218.e209, 2022.
45. Imahashi N, Basar R, Huang Y, Wang F, Baran N, Banerjee PP, Lu J, Nunez Cortes AK, Uprety N, Ensley E, Muniz-Feliciano L, Laskowski TJ, Moyes JS, Daher M, Mendt M, Kerbauy LN, Shanley M, Li L, Lim F, Shaim H, Li Y, Konopleva M, Green M, Wargo J, Shpall EJ, Chen K, and Rezvani K. Activated B cells suppress T-cell function through metabolic competition. Journal for immunotherapy of cancer 10: 2022.
46. Liu X, Wang X, Zhang J, Tian T, Ning Y, Chen Y, Li G, and Cui Z. Myc-mediated inhibition of HIF1a degradation promotes M2 macrophage polarization and impairs CD8 T cell function through lactic acid secretion in ovarian cancer. International immunopharmacology 141: 112876, 2024.

47. Juras PK, Racioppi L, Mukherjee D, Artham S, Gao X, Akullian D'Agostino L, Chang CY, and McDonnell DP. Increased CaMKK2 Expression Is an Adaptive Response That Maintains the Fitness of Tumor-Infiltrating Natural Killer Cells. Cancer immunology research 11: 109-122, 2023.
48. Harmon C, Robinson MW, Hand F, Almuaili D, Mentor K, Houlihan DD, Hoti E, Lynch L, Geoghegan J, and O'Farrelly C. Lactate-Mediated Acidification of Tumor Microenvironment Induces Apoptosis of Liver-Resident NK Cells in Colorectal Liver Metastasis. Cancer immunology research 7: 335-346, 2019.
49. Plebanek MP, Xue Y, Nguyen YV, DeVito NC, Wang X, Holtzhausen A, Beasley GM, Theivanthiran B, and Hanks BA. A lactate-SREBP2 signaling axis drives tolerogenic dendritic cell maturation and promotes cancer progression. Science immunology 9: eadi4191, 2024.
50. Babl N, Decking SM, Voll F, Althammer M, Sala-Hojman A, Ferretti R, Korf C, Schmidl C, Schmidleithner L, Nerb B, Matos C, Koehl GE, Siska P, Bruss C, Kellermeier F, Dettmer K, Oefner PJ, Wichland M, Ugele I, Bohr C, Herr W, Ramaswamy S, Heinrich T, Herhaus C, Kreutz M, and Renner K. MCT4 blockade increases the efficacy of immune checkpoint blockade. Journal for immunotherapy of cancer 11: 2023.
51. Peralta RM, Xie B, Lontos K, Nieves-Rosado H, Spahr K, Joshi S, Ford BR, Quann K, Frisch AT, Dean V, Philbin M, Cillo AR, Gingras S, Poholek AC, Kane LP, Rivadeneira DB, and Delgoffe GM. Dysfunction of exhausted T cells is enforced by MCT11-mediated lactate metabolism. Nature immunology 2024.
52. Feng Q, Liu Z, Yu X, Huang T, Chen J, Wang J, Wilhelm J, Li S, Song J, Li W, Sun Z, Sumer BD, Li B, Fu YX, and Gao J. Lactate increases stemness of CD8+T cells to augment anti-tumor immunity. Nature communications 13: 4981, 2022.
53. Han S, Bao X, Zou Y, Wang L, Li Y, Yang L, Liao A, Zhang X, Jiang X, Liang D, Dai Y, Zheng QC, Yu Z, and Guo J. d-lactate modulates M2 tumor-associated macrophages and remodels immunosuppressive tumor microenvironment for hepatocellular carcinoma. Science advances 9: eadg2697, 2023.
54. Gnanaprakasam JNR, Kushwaha B, Liu L, Chen X, Kang S, Wang T, Cassel TA, Adams CM, Higashi RM, Scott DA, Xin G, Li Z, Yang J, Lane AN, Fan TW, Zhang J, and Wang R. Asparagine restriction enhances CD8(+) T cell metabolic fitness and antitumoral functionality through an NRF2-dependent stress response. Nature metabolism 5: 1423-1439, 2023.
55. Ta HM, Roy D, Zhang K, Alban T, Juric I, Dong J, Parthasarathy PB, Patnaik S, Delaney E, Gilmour C, Zakeri A, Shukla N, Rupani A, Phoon YP, Liu C, Avril S, Gastman B, Chan T, and Wang LL. LRIG1 engages ligand VISTA and impairs tumor-specific CD8(+) T cell responses. Science immunology 9: eadi7418, 2024.
56. Marijt KA, Griffioen L, Blijleven L, van der Burg SH, and van Hall T. Cross-presentation of a TAP-independent signal peptide induces CD8 T immunity to escaped cancers but necessitates anchor replacement. Cancer immunology, immunotherapy : CII 71: 289-300, 2022.
57. Yang C, Wu S, Mou Z, Zhou Q, Dai X, Ou Y, Chen X, Chen Y, Xu C, Hu Y, Zhang L, Zou L, Jin S, Hu J, Mao S, and Jiang H. Exosome-derived circTRPS1 promotes malignant phenotype and CD8+ T cell exhaustion in bladder cancer microenvironments. Molecular therapy : the journal of the American Society of Gene Therapy 30: 1054-1070, 2022.
58. Guo C, You Z, Shi H, Sun Y, Du X, Palacios G, Guy C, Yuan S, Chapman NM, Lim SA, Sun X, Saravia J, Rankin S, Dhungana Y, and Chi H. SLC38A2 and glutamine signalling in cDC1s dictate anti-tumour immunity. Nature 620: 200-208, 2023.
59. Li LB, Fang TY, and Xu WJ. Oral glutamine inhibits tumor growth of gastric cancer bearing mice by improving immune function and activating apoptosis pathway. Tissue & cell 71: 101508, 2021.
60. Siska PJ, Jiao J, Matos C, Singer K, Berger RS, Dettmer K, Oefner PJ, Cully MD, Wang Z, Quinn IW, Oliff KN, Wilkins BJ, Christensen LM, Wang L, Hancock WW, Baur JA, Levine MH, Ugele I, Mayr R, Renner K, Zhou L, Kreutz M, and Beier UH. Kynurenine induces T cell fat catabolism and has limited suppressive effects in vivo. EBioMedicine 74: 103734, 2021.
61. Bender MJ, McPherson AC, Phelps CM, Pandey SP, Laughlin CR, Shapira JH, Medina Sanchez L, Rana M, Richie TG, Mims TS, Gocher-Demske AM, Cervantes-Barragan L, Mullett SJ, Gelhaus SL, Bruno TC, Cannon N, McCulloch JA, Vignali DAA, Hinterleitner R, Joglekar AV, Pierre JF, Lee STM, Davar D, Zarour HM, and Meisel M. Dietary tryptophan metabolite released by intratumoral Lactobacillus reuteri facilitates immune checkpoint inhibitor treatment. Cell 186: 1846-1862.e1826, 2023.
62. Kurniawan H, Franchina DG, Guerra L, Bonetti L, Baguet LS, Grusdat M, Schlicker L, Hunewald O, Dostert C, Merz MP, Binsfeld C, Duncan GS, Farinelle S, Nonnenmacher Y, Haight J, Das Gupta D, Ewen A, Taskesen R, Halder R, Chen Y, Jäger C, Ollert M, Wilmes P, Vasiliou V, Harris IS, Knobbe-Thomsen CB, Turner JD, Mak TW, Lohoff M, Meiser J, Hiller K, and Brenner D. Glutathione Restricts Serine Metabolism to Preserve Regulatory T Cell Function. Cell metabolism 31: 920-936.e927, 2020.
63. Tharp KM, Kersten K, Maller O, Timblin GA, Stashko C, Canale FP, Menjivar RE, Hayward MK, Berestjuk I, Ten Hoeve J, Samad B, Ironside AJ, di Magliano MP, Muir A, Geiger R, Combes AJ, and Weaver VM. Tumor-associated macrophages restrict CD8(+) T cell function through collagen deposition and metabolic reprogramming of the breast cancer microenvironment. Nature cancer 5: 1045-1062, 2024.
64. Kumagai S, Togashi Y, Sakai C, Kawazoe A, Kawazu M, Ueno T, Sato E, Kuwata T, Kinoshita T, Yamamoto M, Nomura S, Tsukamoto T, Mano H, Shitara K, and Nishikawa H. An Oncogenic Alteration Creates a Microenvironment that Promotes Tumor Progression by Conferring a Metabolic Advantage to Regulatory T Cells. Immunity 53: 187-203.e188, 2020.
65. Liu Z, Liu W, Wang W, Ma Y, Wang Y, Drum DL, Cai J, Blevins H, Lee E, Shah S, Fisher PB, Wang X, Fang X, Guo C, and Wang XY. CPT1A-mediated fatty acid oxidation confers cancer cell resistance to immune-mediated cytolytic killing. Proceedings of the National Academy of Sciences of the United States of America 120: e2302878120, 2023.
66. Li Z, Wang Y, Xing R, Zeng H, Yu XJ, Zhang YJ, Xu J, and Zheng L. Cholesterol Efflux Drives the Generation of Immunosuppressive Macrophages to Promote the Progression of Human Hepatocellular Carcinoma. Cancer immunology research 11: 1400-1413, 2023.
67. Liao P, Wang W, Wang W, Kryczek I, Li X, Bian Y, Sell A, Wei S, Grove S, Johnson JK, Kennedy PD, Gijón M, Shah YM, and Zou W. CD8(+) T cells and fatty acids orchestrate tumor ferroptosis and immunity via ACSL4. Cancer cell 40: 365-378.e366, 2022.
68. Zhu L, Zhu X, and Wu Y. Effects of Glucose Metabolism, Lipid Metabolism, and Glutamine Metabolism on Tumor Microenvironment and Clinical Implications. Biomolecules 12: 2022.

69. Enzo E, Santinon G, Pocaterra A, Aragona M, Bresolin S, Forcato M, Grifoni D, Pession A, Zanconato F, Guzzo G, Bicciato S, and Dupont S. Aerobic glycolysis tunes YAP/TAZ transcriptional activity. The EMBO journal 34: 1349-1370, 2015.
70. Shi Q, Shen Q, Liu Y, Shi Y, Huang W, Wang X, Li Z, Chai Y, Wang H, Hu X, Li N, Zhang Q, and Cao X. Increased glucose metabolism in TAMs fuels O-GlcNAcylation of lysosomal Cathepsin B to promote cancer metastasis and chemoresistance. Cancer cell 40: 1207-1222.e1210, 2022.
71. Notarangelo G, Spinelli JB, Perez EM, Baker GJ, Kurmi K, Elia I, Stopka SA, Baquer G, Lin JR, Golby AJ, Joshi S, Baron HF, Drijvers JM, Georgiev P, Ringel AE, Zaganjor E, McBrayer SK, Sorger PK, Sharpe AH, Wucherpfennig KW, Santagata S, Agar NYR, Suvà ML, and Haigis MC. Oncometabolite d-2HG alters T cell metabolism to impair CD8(+) T cell function. Science (New York, NY) 377: 1519-1529, 2022.
72. Wang T, Ye Z, Li Z, Jing DS, Fan GX, Liu MQ, Zhuo QF, Ji SR, Yu XJ, Xu XW, and Qin Y. Lactate-induced protein lactylation: A bridge between epigenetics and metabolic reprogramming in cancer. Cell proliferation 56: e13478, 2023.
73. Chen S, Xu Y, Zhuo W, and Zhang L. The emerging role of lactate in tumor microenvironment and its clinical relevance. Cancer letters 590: 216837, 2024.
74. Jia M, Yue X, Sun W, Zhou Q, Chang C, Gong W, Feng J, Li X, Zhan R, Mo K, Zhang L, Qian Y, Sun Y, Wang A, Zou Y, Chen W, Li Y, Huang L, Yang Y, Zhao Y, and Cheng X. ULK1-mediated metabolic reprogramming regulates Vps34 lipid kinase activity by its lactylation. Science advances 9: eadg4993, 2023.
75. Oseguera M, and Yau AA. Lactic acidosis in a patient with cancer. Clinical medicine (London, England) 23: 615-617, 2023.
76. Groessl S, Kalis R, Snaebjornsson MT, Wambach L, Haider J, Andersch F, Schulze A, Palm W, and Zuber J. Acidosis orchestrates adaptations of energy metabolism in tumors. Science (New York, NY) 390: eadp7603, 2025.
77. Apostolova P, and Pearce EL. Lactic acid and lactate: revisiting the physiological roles in the tumor microenvironment. Trends in immunology 43: 969-977, 2022.
78. Wen J, Cheng S, Zhang Y, Wang R, Xu J, Ling Z, Ma L, Ai X, and Sun B. Lactate anions participate in T cell cytokine production and function. Science China Life sciences 64: 1895-1905, 2021.
79. Rundqvist H, Veliça P, Barbieri L, Gameiro PA, Bargiela D, Gojkovic M, Mijwel S, Reitzner SM, Wulliman D, Ahlstedt E, Ule J, Östman A, and Johnson RS. Cytotoxic T-cells mediate exercise-induced reductions in tumor growth. eLife 9: e59996, 2020.
80. Chen J, Cui L, Lu S, and Xu S. Amino acid metabolism in tumor biology and therapy. Cell death & disease 15: 42, 2024.
81. Lieu EL, Nguyen T, Rhyne S, and Kim J. Amino acids in cancer. Experimental & molecular medicine 52: 15-30, 2020.
82. Zhang J, Pavlova NN, and Thompson CB. Cancer cell metabolism: the essential role of the nonessential amino acid, glutamine. The EMBO journal 36: 1302-1315, 2017.
83. Yoo HC, Park SJ, Nam M, Kang J, Kim K, Yeo JH, Kim JK, Heo Y, Lee HS, Lee MY, Lee CW, Kang JS, Kim YH, Lee J, Choi J, Hwang GS, Bang S, and Han JM. A Variant of SLC1A5 Is a Mitochondrial Glutamine Transporter for Metabolic Reprogramming in Cancer Cells. Cell metabolism 31: 267-283.e212, 2020.
84. Mossmann D, Müller C, Park S, Ryback B, Colombi M, Ritter N, Weißenberger D, Dazert E, Coto-Llerena M, Nuciforo S, Blukacz L, Ercan C, Jimenez V, Piscuoglio S, Bosch F, Terracciano LM, Sauer U, Heim MH, and Hall MN. Arginine reprograms metabolism in liver cancer via RBM39. Cell 186: 5068-5083. e5023, 2023.
85. Martin-Perez M, Urdiroz-Urricelqui U, Bigas C, and Benitah SA. The role of lipids in cancer progression and metastasis. Cell metabolism 34: 1675-1699, 2022.
86. Broadfield LA, Pane AA, Talebi A, Swinnen JV, and Fendt SM. Lipid metabolism in cancer: New perspectives and emerging mechanisms. Developmental cell 56: 1363-1393, 2021.
87. Geng F, and Guo D. SREBF1/SREBP-1 concurrently regulates lipid synthesis and lipophagy to maintain lipid homeostasis and tumor growth. Autophagy 20: 1183-1185, 2024.
88. Platanias LC. Mechanisms of type-I- and type-II-interferon-mediated signalling. Nature Reviews Immunology 5: 375-386, 2005.
89. Li SB, Yuan L, Zhu QY, Zhang G, Liu YT, Gao MH, Han F, Lin ZR, Zhang H, Tang LQ, Sun L, He QY, Song EW, Young LS, Li YC, Mai HQ, Zeng MS, and Zhong Q. OASL enhances mRNA translation and reprograms lipid metabolism to promote cancer progression. Cell reports 44: 115901, 2025.
90. Zhou H, Wang W, Xu H, Liang Y, Ding J, Lv M, Ren B, Peng H, Fu YX, and Zhu M. Metabolic reprograming mediated by tumor cell-intrinsic type I IFN signaling is required for CD47-SIRPα blockade efficacy. Nature communications 15: 5759, 2024.
91. Hu B, Yu M, Ma X, Sun J, Liu C, Wang C, Wu S, Fu P, Yang Z, He Y, Zhu Y, Huang C, Yang X, Shi Y, Qiu S, Sun H, Zhu AX, Zhou J, Xu Y, Zhu D, and Fan J. IFNα Potentiates Anti-PD-1 Efficacy by Remodeling Glucose Metabolism in the Hepatocellular Carcinoma Microenvironment. Cancer discovery 12: 1718-1741, 2022.
92. Tsai CH, Chuang YM, Li X, Yu YR, Tzeng SF, Teoh ST, Lindblad KE, Di Matteo M, Cheng WC, Hsueh PC, Kao KC, Imrichova H, Duan L, Gallart-Ayala H, Hsiao PW, Mazzone M, Ivanesevic J, Liu X, de Visser KE, Lujambio A, Lunt SY, Kaech SM, and Ho PC. Immunoediting instructs tumor metabolic reprogramming to support immune evasion. Cell metabolism 35: 118-133.e117, 2023.
93. Li G, Choi JE, Kryczek I, Sun Y, Liao P, Li S, Wei S, Grove S, Vatan L, Nelson R, Schaefer G, Allen SG, Sankar K, Fecher LA, Mendiratta-Lala M, Frankel TL, Qin A, Waninger JJ, Tezel A, Alva A, Lao CD, Ramnath N, Cieslik M, Harms PW, Green MD, Chinnaiyan AM, and Zou W. Intersection of immune and oncometabolic pathways drives cancer hyperprogression during immunotherapy. Cancer cell 41: 304-322.e307, 2023.
94. Shinde A, Chandak N, Singh J, Roy M, Mane M, Tang X, Vasiyani H, Currim F, Gohel D, Shukla S, Goyani S, Saranga MV, Brindley DN, and Singh R. TNF-α induced NF-κB mediated LYRM7 expression modulates the tumor growth and metastatic ability in breast cancer. Free Radical Biology and Medicine 211: 158-170, 2024.
95. Jeong H, Kim S, Hong BJ, Lee CJ, Kim YE, Bok S, Oh JM, Gwak SH, Yoo MY, Lee MS, Chung SJ, Defrêne J, Tessier P, Pelletier M, Jeon H, Roh TY, Kim B, Kim KH, Ju JH, Kim S, Lee YJ, Kim DW, Kim IH, Kim HJ, Park JW, Lee YS, Lee JS, Cheon GJ, Weissman IL, Chung DH, Jeon YK, and Ahn GO. Tumor-Associated Macrophages Enhance Tumor Hypoxia and Aerobic Glycolysis. Cancer research 79: 795-806, 2019.
96. Taranto D, Kloosterman DJ, and Akkari L. Macrophages and T cells in metabolic disorder-associated cancers. Nature reviews Cancer 24: 744-767, 2024.
97. Goldman O, Adler LN, Hajaj E, Croese T, Darzi N, Galai S, Tishler H, Ariav Y, Lavie D, Fellus-Alyagor L, Oren R, Kuznetsov Y, David E, Jaschek R, Stossel C, Singer O, Malitsky S, Barak R, Seger R, Erez N, Amit I, Tanay A, Saada A, Golan T, Rubinek T, Sang Lee J, Ben-Shachar S, Wolf I, and Erez A. Early Infiltration of Innate Immune Cells to the Liver Depletes HNF4α and Promotes Extrahepatic Carcinogenesis. Cancer discovery 13: 1616-1635, 2023.

98. van der Windt GJ, Everts B, Chang CH, Curtis JD, Freitas TC, Amiel E, Pearce EJ, and Pearce EL. Mitochondrial respiratory capacity is a critical regulator of CD8+ T cell memory development. Immunity 36: 68-78, 2012.
99. Buck MD, O'Sullivan D, Klein Geltink RI, Curtis JD, Chang CH, Sanin DE, Qiu J, Kretz O, Braas D, van der Windt GJ, Chen Q, Huang SC, O'Neill CM, Edelson BT, Pearce EJ, Sesaki H, Huber TB, Rambold AS, and Pearce EL. Mitochondrial Dynamics Controls T Cell Fate through Metabolic Programming. Cell 166: 63-76, 2016.
100. Marçais A, Cherfils-Vicini J, Viant C, Degouve S, Viel S, Fenis A, Rabilloud J, Mayol K, Tavares A, Bienvenu J, Gangloff YG, Gilson E, Vivier E, and Walzer T. The metabolic checkpoint kinase mTOR is essential for IL-15 signaling during the development and activation of NK cells. Nature immunology 15: 749-757, 2014.
101. Felices M, Lenvik AJ, McElmurry R, Chu S, Hinderlie P, Bendzick L, Geller MA, Tolar J, Blazar BR, and Miller JS. Continuous treatment with IL-15 exhausts human NK cells via a metabolic defect. JCI insight 3: 2018.
102. Alizadeh D, Wong RA, Yang X, Wang D, Pecoraro JR, Kuo CF, Aguilar B, Qi Y, Ann DK, Starr R, Urak R, Wang X, Forman SJ, and Brown CE. IL15 Enhances CAR-T Cell Antitumor Activity by Reducing mTORC1 Activity and Preserving Their Stem Cell Memory Phenotype. Cancer immunology research 7: 759-772, 2019.
103. Matthews CE, Moore SC, Arem H, Cook MB, Trabert B, Håkansson N, Larsson SC, Wolk A, Gapstur SM, Lynch BM, Milne RL, Freedman ND, Huang WY, Berrington de Gonzalez A, Kitahara CM, Linet MS, Shiroma EJ, Sandin S, Patel AV, and Lee IM. Amount and Intensity of Leisure-Time Physical Activity and Lower Cancer Risk. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 38: 686-697, 2020.
104. Moore SC, Lee IM, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, Keadle SK, Arem H, Berrington de Gonzalez A, Hartge P, Adami HO, Blair CK, Borch KB, Boyd E, Check DP, Fournier A, Freedman ND, Gunter M, Johannson M, Khaw KT, Linet MS, Orsini N, Park Y, Riboli E, Robien K, Schairer C, Sesso H, Spriggs M, Van Dusen R, Wolk A, Matthews CE, and Patel AV. Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults. JAMA internal medicine 176: 816-825, 2016.
105. Torregrosa C, Chorin F, Beltran EEM, Neuzillet C, and Cardot-Ruffino V. Physical Activity as the Best Supportive Care in Cancer: The Clinician's and the Researcher's Perspectives. Cancers 14: 2022.
106. Koelwyn GJ, Zhuang X, Tammela T, Schietinger A, and Jones LW. Exercise and immunometabolic regulation in cancer. Nature metabolism 2: 849-857, 2020.
107. Sheinboim D, Parikh S, Manich P, Markus I, Dahan S, Parikh R, Stubbs E, Cohen G, Zemser-Werner V, Bell RE, Ruiz SA, Percik R, Brenner R, Leibou S, Vaknine H, Arad G, Gerber Y, Keinan-Boker L, Shimony T, Bikovski L, Goldstein N, Constantini K, Labes S, Mordechai S, Doron H, Lonescu A, Ziv T, Nizri E, Choshen G, Eldar-Finkelman H, Tabach Y, Helman A, Ben-Eliyahu S, Erez N, Perlson E, Geiger T, Ben-Zvi D, Khaled M, Gepner Y, and Levy C. An Exercise-Induced Metabolic Shield in Distant Organs Blocks Cancer Progression and Metastatic Dissemination. Cancer research 82: 4164-4178, 2022.
108. Mika A, Macaluso F, Barone R, Di Felice V, and Sledzinski T. Effect of Exercise on Fatty Acid Metabolism and Adipokine Secretion in Adipose Tissue. Frontiers in physiology 10: 26, 2019.
109. Aveseh M, Nikooie R, and Aminaie M. Exercise-induced changes in tumour LDH-B and MCT1 expression are modulated by oestrogen-related receptor alpha in breast cancer-bearing BALB/c mice. The Journal of physiology 593: 2635-2648, 2015.
110. Davis AR, Goodenough CG, Westerlind KC, Strange R, Deaver JW, Ryan PJ, Riechman SE, and Fluckey JD. Myokines derived from contracting skeletal muscle suppress anabolism in MCF7 breast cancer cells by inhibiting mTOR. Frontiers in physiology 13: 1033585, 2022.
111. Huang Q, Wu M, Wu X, Zhang Y, and Xia Y. Muscle-to-tumor crosstalk: The effect of exercise-induced myokine on cancer progression. Biochimica et biophysica acta Reviews on cancer 1877: 188761, 2022.
112. Nieman DC, and Pence BD. Exercise immunology: Future directions. Journal of sport and health science 9: 432-445, 2020.
113. Mohr AE, Jäger R, Carpenter KC, Kerksick CM, Purpura M, Townsend JR, West NP, Black K, Gleeson M, Pyne DB, Wells SD, Arent SM, Kreider RB, Campbell BI, Bannock L, Scheiman J, Wissent CJ, Pane M, Kalman DS, Pugh JN, Ortega-Santos CP, Ter Haar JA, Arciero PJ, and Antonio J. The athletic gut microbiota. Journal of the International Society of Sports Nutrition 17: 24, 2020.
114. Smith JAB, Murach KA, Dyar KA, and Zierath JR. Exercise metabolism and adaptation in skeletal muscle. Nature reviews Molecular cell biology 24: 607-632, 2023.
115. Egan B, and Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. Cell metabolism 17: 162-184, 2013.
116. Isath A, Koziol KJ, Martinez MW, Garber CE, Martinez MN, Emery MS, Baggish AL, Naidu SS, Lavie CJ, Arena R, and Krittanawong C. Exercise and cardiovascular health: A state-of-the-art review. Progress in cardiovascular diseases 79: 44-52, 2023.
117. Chen H, Chen C, Spanos M, Li G, Lu R, Bei Y, and Xiao J. Exercise training maintains cardiovascular health: signaling pathways involved and potential therapeutics. Signal transduction and targeted therapy 7: 306, 2022.
118. Powers SK, Sollanek KJ, Wiggs MP, Demirel HA, and Smuder AJ. Exercise-induced improvements in myocardial antioxidant capacity: the antioxidant players and cardioprotection. Free radical research 48: 43-51, 2014.
119. Gao Y, Zhang W, Zeng LQ, Bai H, Li J, Zhou J, Zhou GY, Fang CW, Wang F, and Qin XJ. Exercise and dietary intervention ameliorate high-fat diet-induced NAFLD and liver aging by inducing lipophagy. Redox biology 36: 101635, 2020.
120. Thyfault JP, and Bergouignan A. Exercise and metabolic health: beyond skeletal muscle. Diabetologia 63: 1464-1474, 2020.
121. Keating SE, Sabag A, Hallsworth K, Hickman IJ, Macdonald GA, Stine JG, George J, and Johnson NA. Exercise in the Management of Metabolic-Associated Fatty Liver Disease (MAFLD) in Adults: A Position Statement from Exercise and Sport Science Australia. Sports medicine (Auckland, NZ) 53: 2347-2371, 2023.
122. Kuramoto K, Liang H, Hong JH, and He C. Exercise-activated hepatic autophagy via the FN1-α5β1 integrin pathway drives metabolic benefits of exercise. Cell metabolism 35: 620-632. e625, 2023.
123. Clark A, and Mach N. Exercise-induced stress behavior, gut-microbiota-brain axis and diet: a systematic review for athletes. Journal of the International Society of Sports Nutrition 13: 43, 2016.
124. Markandey M, Bajaj A, Ilott NE, Kedia S, Travis S, Powrie F, and Ahuja V. Gut microbiota: sculptors of the intestinal stem cell niche in health and inflammatory bowel disease. Gut microbes 13: 1990827, 2021.

125. Gubert C, Kong G, Renoir T, and Hannan AJ. Exercise, diet and stress as modulators of gut microbiota: Implications for neurodegenerative diseases. Neurobiology of disease 134: 104621, 2020.
126. Luo Z, Mei J, Wang X, Wang R, He Z, Geffen Y, Sun X, Zhang X, Xu J, Wan R, Feng X, Jiao C, Su X, Sun J, Chen S, Chen J, Mao W, Yang Y, and Sun Y. Voluntary exercise sensitizes cancer immunotherapy via the collagen inhibition-orchestrated inflammatory tumor immune microenvironment. Cell reports 43: 114697, 2024.
127. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, Johannesen HH, Becker JC, Pedersen KS, Dethlefsen C, Nielsen J, Gehl J, Pedersen BK, Thor Straten P, and Hojman P. Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. Cell metabolism 23: 554-562, 2016.
128. Bacurau RF, Belmonte MA, Seelaender MC, and Costa Rosa LF. Effect of a moderate intensity exercise training protocol on the metabolism of macrophages and lymphocytes of tumour-bearing rats. Cell biochemistry and function 18: 249-258, 2000.
129. Rundqvist H, Veliça P, Barbieri L, Gameiro PA, Bargiela D, Gojkovic M, Mijwel S, Reitzner SM, Wulliman D, Ahlstedt E, Ule J, Östman A, and Johnson RS. Cytotoxic T-cells mediate exercise-induced reductions in tumor growth. eLife 9: 2020.
130. Bacurau AV, Belmonte MA, Navarro F, Moraes MR, Pontes FL, Jr., Pesquero JL, Araújo RC, and Bacurau RF. Effect of a high-intensity exercise training on the metabolism and function of macrophages and lymphocytes of walker 256 tumor bearing rats. Experimental biology and medicine (Maywood, NJ) 232: 1289-1299, 2007.
131. Smith KA, Batatinha H, Niemiro GM, Baker FL, Zúñiga TM, Diak DM, Mylabathula PL, Kistner TM, Davini D, Hoffman E, Colombo JN, Seckeler MD, Bond RA, Katsanis E, and Simpson RJ. Exercise-induced β(2)-adrenergic receptor activation enhances effector lymphocyte mobilization in humans and suppresses lymphoma growth in mice through NK-cells. Brain, behavior, and immunity 128: 751-765, 2025.
132. Batatinha H, Peña NA, Hoskin GA, Kistner TM, Diak DM, Niemiro GM, Katsanis E, and Simpson RJ. Exercise Delays Human Leukemia Progression and Mitigates Graft-Versus-Host Disease After Donor Lymphocyte Infusion in Xenogeneic Mice. Cancers 17: 2025.
133. Kurz E, Hirsch CA, Dalton T, Shadaloey SA, Khodadadi-Jamayran A, Miller G, Pareek S, Rajaei H, Mohindroo C, Baydogan S, Ngo-Huang A, Parker N, Katz MHG, Petzel M, Vucic E, McAllister F, Schadler K, Winograd R, and Bar-Sagi D. Exercise-induced engagement of the IL-15/IL-15Rα axis promotes anti-tumor immunity in pancreatic cancer. Cancer cell 40: 720-737.e725, 2022.
134. Flores-Opazo M, McGee SL, and Hargreaves M. Exercise and GLUT4. Exercise and sport sciences reviews 48: 110-118, 2020.
135. Orange ST, Jordan AR, Odell A, Kavanagh O, Hicks KM, Eaglen T, Todryk S, and Saxton JM. Acute aerobic exercise-conditioned serum reduces colon cancer cell proliferation in vitro through interleukin-6-induced regulation of DNA damage. International journal of cancer 151: 265-274, 2022.
136. Zhu C, Ma H, He A, Li Y, He C, and Xia Y. Exercise in cancer prevention and anticancer therapy: Efficacy, molecular mechanisms and clinical information. Cancer letters 544: 215814, 2022.
137. Piguet AC, Saran U, Simillion C, Keller I, Terracciano L, Reeves HL, and Dufour JF. Regular exercise decreases liver tumors development in hepatocyte-specific PTEN-deficient mice independently of steatosis. Journal of hepatology 62: 1296-1303, 2015.
138. Hojman P, Gehl J, Christensen JF, and Pedersen BK. Molecular Mechanisms Linking Exercise to Cancer Prevention and Treatment. Cell metabolism 27: 10-21, 2018.
139. Savage H, Pareek S, Lee J, Ballarò R, Conterno Minussi D, Hayek K, Sadullozoda M, Lochmann BS, McQuade JL, LaVoy EC, Marmonti E, Patel H, Wang G, Imanishi M, Kotla S, Abe JI, and Schadler K. Aerobic Exercise Alters the Melanoma Microenvironment and Modulates ERK5 S496 Phosphorylation. Cancer immunology research 11: 1168-1183, 2023.
140. Schadler KL, Thomas NJ, Galie PA, Bhang DH, Roby KC, Addai P, Till JE, Sturgeon K, Zaslavsky A, Chen CS, and Ryeom S. Tumor vessel normalization after aerobic exercise enhances chemotherapeutic efficacy. Oncotarget 7: 65429-65440, 2016.
141. Thompson HJ, Jiang W, and Zhu Z. Candidate mechanisms accounting for effects of physical activity on breast carcinogenesis. IUBMB life 61: 895-901, 2009.
142. Theriau CF, Shpilberg Y, Riddell MC, and Connor MK. Voluntary physical activity abolishes the proliferative tumor growth microenvironment created by adipose tissue in animals fed a high fat diet. Journal of applied physiology (Bethesda, Md : 1985) 121: 139-153, 2016.
143. Llavero F, Alejo LB, Fiuza-Luces C, López Soto A, Valenzuela PL, Castillo-García A, Morales JS, Fernández D, Aldazabal IP, Ramírez M, Santos-Lozano A, Zugaza JL, and Lucia A. Exercise training effects on natural killer cells: a preliminary proteomics and systems biology approach. Exercise immunology review 27: 125-141, 2021.
144. de Souza-Teixeira F, Alonso-Molero J, Ayán C, Vilorio-Marques L, Molina AJ, González-Donquiles C, Dávila-Batista V, Fernández-Villa T, de Paz JA, and Martín V. PGC-1α as a Biomarker of Physical Activity-Protective Effect on Colorectal Cancer. Cancer Prevention Research 11: 523-534, 2018.
145. Neto IVS, Pinto AP, Muñoz VR, de Cássia Marqueti R, Pauli JR, Ropelle ER, and Silva A. Pleiotropic and multi-systemic actions of physical exercise on PGC-1α signaling during the aging process. Ageing research reviews 87: 101935, 2023.
146. Bost F, and Kaminski L. The metabolic modulator PGC-1α in cancer. American journal of cancer research 9: 198-211, 2019.
147. Neto IVdS, Pinto AP, Muñoz VR, de Cássia Marqueti R, Pauli JR, Ropelle ER, and Silva ASRd. Pleiotropic and multi-systemic actions of physical exercise on PGC-1α signaling during the aging process. Ageing research reviews 87: 101935, 2023.
148. Memme JM, Erlich AT, Phukan G, and Hood DA. Exercise and mitochondrial health. The Journal of physiology 599: 803-817, 2021.
149. Handschin C, and Spiegelman BM. The role of exercise and PGC1α in inflammation and chronic disease. Nature 454: 463-469, 2008.
150. Li L, Pan R, Li R, Niemann B, Aurich AC, Chen Y, and Rohrbach S. Mitochondrial biogenesis and peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) deacetylation by physical activity: intact adipocytokine signaling is required. Diabetes 60: 157-167, 2011.
151. Xia H, Scholtes C, Dufour CR, Guluzian C, and Giguère V. ERRα fosters running endurance by driving myofiber aerobic transformation and fuel efficiency. Molecular metabolism 78: 101814, 2023.

152. Billon C, Sitaula S, Banerjee S, Welch R, Elgendy B, Hegazy L, Oh TG, Kazantzis M, Chatterjee A, Chrivia J, Hayes ME, Xu W, Hamilton A, Huss JM, Zhang L, Walker JK, Downes M, Evans RM, and Burris TP. Synthetic ERRα/β/γ Agonist Induces an ERRα-Dependent Acute Aerobic Exercise Response and Enhances Exercise Capacity. ACS chemical biology 18: 756-771, 2023.
153. Fiuza-Luces C, Valenzuela PL, Gálvez BG, Ramírez M, López-Soto A, Simpson RJ, and Lucia A. The effect of physical exercise on anticancer immunity. Nature Reviews Immunology 24: 282-293, 2024.
154. Li S, Lin J, Huang L, Hu S, Wang M, Sun W, and Sun S. STK31 drives tumor immune evasion through STAT3-IL-6 mediated CD8+ T cell exhaustion. Oncogene 44: 1452-1462, 2025.
155. Tsai SH, Cheng HC, Little JP, Islam H, and Liu HW. Elevated Plasma IL-6 Coincides with Activation of STAT3 in PBMC After Acute Resistance Exercise. Medicine and science in sports and exercise 56: 2117-2124, 2024.
156. Wei L-Y, Lin H-C, Tsai F-C, Ko J-Y, Kok S-H, Cheng S-J, Lee J-J, and Chia J-S. Effects of Interleukin-6 on STAT3-regulated signaling in oral cancer and as a prognosticator of patient survival. Oral Oncology 124: 105665, 2022.
157. Shalamzari SA, Agha-Alinejad H, Alizadeh S, Shahbazi S, Khatib ZK, Kazemi A, Saei MA, and Minayi N. The effect of exercise training on the level of tissue IL-6 and vascular endothelial growth factor in breast cancer bearing mice. Iranian journal of basic medical sciences 17: 231-258, 2014.
158. Fischer CP. Interleukin-6 in acute exercise and training: what is the biological relevance? Exercise immunology review 12: 6-33, 2006.
159. Wiig H, and Swartz MA. Interstitial fluid and lymph formation and transport: physiological regulation and roles in inflammation and cancer. Physiological reviews 92: 1005-1060, 2012.
160. Nash D, Hughes MG, Butcher L, Aicheler R, Smith P, Cullen T, and Webb R. IL-6 signaling in acute exercise and chronic training: Potential consequences for health and athletic performance. Scandinavian journal of medicine & science in sports 33: 4-19, 2023.
161. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, Zucker DS, Matthews CE, Ligibel JA, Gerber LH, Morris GS, Patel AV, Hue TF, Perna FM, and Schmitz KH. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. Medicine and science in sports and exercise 51: 2375-2390, 2019.
162. Phelps CM, Willis NB, Duan T, Lee AH, Zhang Y, Rodriguez J DM, Pandey SP, Laughlin CR, Rosen ABI, McPherson AC, Shapira JH, Randhawa SK, Hedden L, Richie TG, Wiechman HM, Bender MJ, Nemet I, Zöhrer PA, Gottschalk RA, Schmitz KH, Mullett SJ, Gelhaus SL, Davar D, Zarour HM, Hinterleitner R, Mossington T, Badger JH, Rodrigues RR, McCulloch JA, Lee STM, Wagner K-H, Winter MG, Winter SE, Das J, Pierre JF, Trinchieri G, and Meisel M. Exercise-induced microbiota metabolite enhances CD8 T cell antitumor immunity promoting immunotherapy efficacy. Cell 188: 5680-5700.e5628, 2025.
163. Luo Z, Mei J, Wang X, Wang R, He Z, Geffen Y, Sun X, Zhang X, Xu J, Wan R, Feng X, Jiao C, Su X, Sun J, Chen S, Chen J, Mao W, Yang Y, and Sun Y. Voluntary exercise sensitizes cancer immunotherapy via the collagen inhibition-orchestrated inflammatory tumor immune microenvironment. Cell reports 43: 2024.
164. Clifford B, Koizumi S, Wewege MA, Leake HB, Ha L, Macdonald E, Fairman CM, and Hagstrom AD. The Effect of Resistance Training on Body Composition During and After Cancer Treatment: A Systematic Review and Meta-Analysis. Sports medicine (Auckland, NZ) 51: 2527-2546, 2021.
165. Niu N, Huang R, Zhao J, and Zeng Y. Health benefits of yoga for cancer survivors: An updated systematic review and meta-analysis. Asia-Pacific journal of oncology nursing 11: 100316, 2024.
166. Gomes-Santos IL, Kumar AS, Hausmann F, Meyer MN, Shiferaw SZ, Amoozgar Z, Jain RK, and Fukumura D. Exercise intensity governs tumor control in mice with breast cancer. Frontiers in immunology 15: 1339232, 2024.
167. Bettariga F, Taaffe DR, Galvão DA, Bishop C, Kim JS, and Newton RU. Suppressive effects of exercise-conditioned serum on cancer cells: A narrative review of the influence of exercise mode, volume, and intensity. Journal of sport and health science 13: 484-498, 2024.
168. Isanejad A, Nazari S, Gharib B, and Motlagh AG. Comparison of the effects of high-intensity interval and moderate-intensity continuous training on inflammatory markers, cardiorespiratory fitness, and quality of life in breast cancer patients. Journal of sport and health science 12: 674-689, 2023.
169. Wang J, Song H, Tang X, Yang Y, Vieira VJ, Niu Y, and Ma Y. Effect of exercise training intensity on murine T-regulatory cells and vaccination response. Scandinavian journal of medicine & science in sports 22: 643-652, 2012.
170. Martin RA, Viggars MR, and Esser KA. Metabolism and exercise: the skeletal muscle clock takes centre stage. Nature reviews Endocrinology 19: 272-284, 2023.
171. Wang J, He Y, Wang Z, Wang Z, Miao Y, and Choi JY. Effects of different exercise prescription parameters on metabolic and inflammatory biomarkers in cancer patients: a systematic review, meta-analysis, and meta-regression. Frontiers in immunology 16: 1663560, 2025.
172. Koivula T, Lempiäinen S, Rinne P, Rannikko JH, Hollmén M, Sundberg CJ, Rundqvist H, Minn H, and Heinonen I. The effect of acute exercise on circulating immune cells in newly diagnosed breast cancer patients. Scientific reports 13: 6561, 2023.
173. Amare F, Kiflu A, and Taddese A. Effects of concurrent continuous aerobic and short rest resistance exercise training on metabolic biomarkers in type 2 diabetes patients: a systematic review and meta-analysis. Diabetology & metabolic syndrome 17: 290, 2025.
174. Teodoro TH, Costa KPM, Prestes J, Campanholi J, Navalta J, and Pereira GB. The effects of acute and chronic exercise on immune markers of TH1/TH2 cells in older adults: a systematic review. Frontiers in physiology 16: 1453747, 2025.
175. Zhang N, Wang X, Feng M, Li M, Wang J, Yang H, He S, Xia Z, Shang L, Jiang X, Sun M, Wu Y, Ren C, Zhang X, Li J, and Gao F. Early-life exercise induces immunometabolic epigenetic modification enhancing anti-inflammatory immunity in middle-aged male mice. Nature communications 15: 3103, 2024.
176. Liu M, and Ren T. Impact of personlized exercise prescription on muscle mass, physical function, and quality of life in postoperative pancreatic cancer patients undergoing da Vinci robotic surgery: a randomized controlled trial protocol. Trials 26: 420, 2025.
177. Gundakaram S, Sirigireddy S, McDonald A, King E, and Goparaju P. Evaluating the role of exercise in modulating immunity and immunotherapy outcomes in cancer: A systematic review. 43: 2646-2646, 2025.
178. Cheung C, Boocock E, Grande AJ, and Maddocks M. Exercise-based interventions for cancer cachexia: A systematic review of randomised and non-randomised controlled trials. Asia-Pacific journal of oncology nursing 10: 100335, 2023.
179. Allan J, Buss LA, Draper N, and Currie MJ. Exercise in People With Cancer: A Spotlight on Energy Regulation and Cachexia. Frontiers in physiology 13: 836804, 2022.

180. Peyrachon R, Lièvre A, and Rébillard A. The role of aerobic and resistance exercise for cancer cachexia management – A systematic scoping review. Asia-Pacific journal of oncology nursing 12: 100748, 2025.
181. Shaver AL, Sharma S, Nikita N, Lefler DS, Basu-Mallick A, Johnson JM, Butryn M, and Lu-Yao G. The Effects of Physical Activity on Cancer Patients Undergoing Treatment with Immune Checkpoint Inhibitors: A Scoping Review. Cancers 13: 2021.
182. Avancini A, Belluomini L, Tregnago D, Trestini I, Milella M, Lanza M, and Pilotto S. Exercise and anemia in cancer patients: could it make the difference? Expert review of hematology 14: 979-985, 2021.
183. Dolan LB, Gelmon K, Courneya KS, Mackey JR, Segal RJ, Lane K, Reid RD, and McKenzie DC. Hemoglobin and aerobic fitness changes with supervised exercise training in breast cancer patients receiving chemotherapy. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 19: 2826-2832, 2010.
184. Mohamady HM, Elsisi HF, and Aneis YM. Impact of moderate intensity aerobic exercise on chemotherapy-induced anemia in elderly women with breast cancer: A randomized controlled clinical trial. Journal of advanced research 8: 7-12, 2017.
185. Drouin JS, Young TJ, Beeler J, Byrne K, Birk TJ, Hryniuk WM, and Hryniuk LE. Random control clinical trial on the effects of aerobic exercise training on erythrocyte levels during radiation treatment for breast cancer. Cancer 107: 2490-2495, 2006.
186. Furrer R, Jauch AJ, Nageswara Rao T, Dilbaz S, Rhein P, Steurer SA, Recher M, Skoda RC, and Handschin C. Remodeling of metabolism and inflammation by exercise ameliorates tumor-associated anemia. Science advances 7: eabi4852, 2021.
187. Houston JL, Boyd KP, Gittings PM, and Cavalheri V. What are safe hemoglobin, neutrophil and platelet counts for people with hematological malignancies to participate in exercise and activities of daily living: a scoping review. Supportive Care in Cancer 33: 605, 2025.
188. Hassing Johansen S, Reinertsen KV, Wisløff T, Sæter M, Sarvari SI, Kiserud CE, Strandos N, Edvardsen E, Grydeland M, Nilsen TS, and Thorsen L. Effects of aerobic exercise on late effects and quality of life in Long-Term breast cancer survivors: a randomized controlled trial. JNCI cancer spectrum 2025.
189. Wang S. Run to boost your gut microbiome that can help fight cancer. Cell host & microbe 33: 1464-1465, 2025.
190. McTiernan A. In Motion: Experimental Evidence on Exercise and Breast Cancer in Women and Mice. Clinical cancer research : an official journal of the American Association for Cancer Research 31: 3353-3355, 2025.
191. Nates JL, Pène F, Darmon M, Mokart D, Castro P, David S, Povoa P, Russell L, Nielsen ND, Gorecki GP, Gradel KO, Azoulay E, and Bauer PR. Septic shock in the immunocompromised cancer patient: a narrative review. Critical care (London, England) 28: 285, 2024.
192. Cortiula F, Hendriks LEL, van de Worp W, Schols A, Vaes RDW, Langen RCJ, and De Ruysscher D. Physical exercise at the crossroad between muscle wasting and the immune system: implications for lung cancer cachexia. Journal of cachexia, sarcopenia and muscle 13: 55-67, 2022.
193. Chen X, Li Z, and Zhang J. A novel approach to cancer rehabilitation: assessing the influence of exercise intervention on postoperative recovery and survival rates. International journal of surgery (London, England) 111: 3373-3385, 2025.
194. Wen H, Zhang P, Zhao J, Liu Y, Wan L, Li H, Yi J, and Li X. Metabolic alterations driven by LDHA in CD8+T cells promote immune evasion and therapy resistance in NSCLC. Scientific reports 15: 24440, 2025.
195. Miao R, Liu C, Wang Y, Li H, Han C, Wang C, Tian Z, and Liu J. Exercise-induced lactate suppresses ccRCC via CNDP2-mediated depletion of intracellular amino acids. Cell Death Discovery 11: 356, 2025.
196. Navarro-Ledesma S, Hamed-Hamed D, González-Muñoz A, and Pruimboom L. Physical Activity, Insulin Resistance and Cancer: A Systematic Review. Cancers 16: 2024.
197. Rangel M, Lopes KG, Qin X, and Borges JP. Exercise-induced adaptations in the kynurenine pathway: implications for health and disease management. Frontiers in sports and active living 7: 1535152, 2025.
198. Gustafson MP, Wheatley-Guy CM, Rosenthal AC, Gastineau DA, Katsanis E, Johnson BD, and Simpson RJ. Exercise and the immune system: taking steps to improve responses to cancer immunotherapy. Journal for immunotherapy of cancer 9: 2021.
199. Koelwyn GJ, Wennerberg E, Demaria S, and Jones LW. Exercise in Regulation of Inflammation-Immune Axis Function in Cancer Initiation and Progression. Oncology (Williston Park, NY) 29: 908-920, 922, 2015.
200. Orange ST, Leslie J, Ross M, Mann DA, and Wackerhage H. The exercise IL-6 enigma in cancer. Trends in endocrinology and metabolism: TEM 34: 749-763, 2023.