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Review and Meta-analysis

Exercise and Regulation of PI3K/Akt/mTOR and AMPK Pathways in Cancer: Molecular Mechanisms and Therapeutic Implications: A Narrative Review

Abeer Issa Mohammed	Al-Manara College for Medical Sciences, University of Manara, Iraq, Advanced Medical and Dental Institute, University Sains Malaysia, Kepala Batas, Pulau Penang, Malaysia.
Ochilova Gulrux Saidovna	Department of Clinical Pharmacology, Bukhara State Medical Institute named after Abu Ali ibn Sino, Bukhara, Uzbekistan.
Davron Makhmudov	Department of Children's Infectious Diseases, Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan.
Narkulova Sokhiba	Department of Obstetrics and Gynecology N3, Samarkand State Medical University, Samarkand, Uzbekistan.
Istamov Mirmukhsinjon Bakhodirovich	Department of Psychiatry, Narcology and Medical Psychology, Bukhara State Medical Institute named after Abu Ali ibn Sino, Bukhara Uzbekistan.
Shoista Sultonbekovna	6Department of Obstetrics and Gynecology No. 1, Faculty of Pediatrics, Andijan State Medical Institute, Uzbekistan.
Qobilov Odiljon Rustamovich	Department of Oncology, Pediatric Oncology, and Palliative Care, Tashkent State Medical University, Tashkent, Uzbekistan.
Niyozova Shaxnoza Xamoydinovna	Department of Oncology, Clinical Oncology, Oncohematology, and Radiation Oncology, Tashkent State Medical University, Tashkent, Uzbekistan.
Izrailbekova Kamila Shavkatovna	Department of Republican Oncology Center, Medical Oncologist (Chemotherapist), Tashkent, Uzbekistan.
Achilova Ozoda Farkhodovna	Department of Japanese Philology, Faculty of Oriental Languages, Samarkand State Institute of Foreign Languages, Uzbekistan.
Berdikulova Nigina Mirsoliyevna	Department of Japanese Philology, Faculty of Oriental Languages, Samarkand State Institute of Foreign Languages, Uzbekistan.
Ergasheva Zilolaxon Xasanboy Qizi	Department of Food Technology and Engineering, Faculty of Food Technology and Management, International Institute of Food Technology and Engineering, Uzbekistan.
Azim Akbarzadehkhayavi	Professor of Institute Pasteur of Iran in Department of Nanobiotechnology, Tehran, Iran.
Mohsen Mir	Department of Anatomy, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

Overview: Dysregulation of the PI3K/Akt/mTOR and AMPK pathways is central to cancer development, driving uncontrolled cell growth, metabolic disturbances, and resistance to cell death and therapy. Exercise has emerged as an effective non-drug strategy that can modify these pathways and influence tumor-related cellular processes.

Methods: This review compiles evidence from 2015 to 2025 on how exercise impacts

PI3K/Akt/mTOR and AMPK signaling in cancer.

Results: Findings show that exercise activates AMPK, an energy sensor that boosts glucose uptake, insulin sensitivity, autophagy, and mitochondrial biogenesis. Through AMPK activation, exercise reduces anabolic signaling and excessive protein synthesis, which often promotes tumor growth, while supporting healthier metabolism. At the same time, exercise inhibits the PI3K/Akt/mTOR pathway, reducing cell proliferation, affecting growth factors like insulin and IGF-1, and restoring metabolic balance across tissues. These combined effects improve cellular stability, lessen tumor-promoting mechanisms, and may enhance responsiveness to cancer treatments, making exercise a valuable complement for cancer prevention and therapy. Most current insights come from preclinical studies or epidemiological data, with few clinical trials examining exercise-induced molecular changes in human tumors.

Conclusion: More research is needed to identify optimal exercise regimens, understand pathway-specific effects, and evaluate their clinical relevance to better incorporate exercise into personalized cancer care.

Introduction

Despite progress in detection and treatment, cancer remains a significant public health issue worldwide. In the United States, cancer has consistently been the second leading cause of death since 1937 [1]. During 2020 and 2021, cancer deaths in the USA surpassed those from COVID-19, despite the ongoing pandemic, with about 600,000 cancer deaths in 2020 compared to approximately 350,000 from COVID-19 [2, 3]. Projections for 2024 estimate that the US will see 2 million new cancer cases and over 600,000 deaths [4, 5]. The PI3K/Akt/mTOR pathway is frequently overactive in many solid tumors, including breast and ovarian cancers. In normal cells, this pathway plays a crucial role in supporting growth, proliferation, and survival [6-10]. Research on molecular signaling has advanced our understanding of disease mechanisms and led to the discovery of biomarkers, drug targets, and innovative therapies [11].

As shown in Table 1, In tumor tissues, activation of the PI3K/Akt/mTOR and AMPK pathways can be evaluated using histopathological markers [12].

Pathway Node	Tissue Marker (IHC)	Typical Findings in Cancer	Preclinical / Hypothetical Exercise Response
PI3K/Akt	Phospho-Akt (Ser473/Thr308)	Nuclear/cytoplasmic; correlates with proliferation indices (Ki-67)	Exercise may reduce Akt activation via systemic insulin/IGF-1 reduction; limited direct tumor evidence
mTORC1	Phospho-S6, Phospho-4E-BP1	Elevated in many solid tumors; promotes translation and growth	Exercise inhibits mTORC1 via AMPK activation,suppressing anabolic signaling
mTORC2	Rictor	Regulates cytoskeletal organization; heterogeneous	Modulated indirectly via Akt regulation andsystemic effects of exercise
AMPK	Phospho-AMPK (Thr172)	Variable; context-dependent(tumor-suppressive vs stress-adaptive)	Activated by exercise, adiponectin, and myokines; promotes energy balance, autophagy, andanti-inflammatory signaling
PTEN	PTEN loss (IHC/genetic)	Constitutive PI3K/Akt activation	PTEN-deficient tumors may rely more onAMPK-mediated mTOR inhibition than insulin/ IGF-1 reduction

Table 1. Most Exercise-related Evidence Comes from Systemic Compartments (muscle, liver, adipose tissue)

Rather than Tumor Tissue. Direct human tumor data remain limited.

PI3K/Akt activation is often measured with phospho-Akt antibodies (Ser473/ Thr308) and is linked to nuclear and cytoplasmic localization; it also correlates with proliferation markers like Ki-67. mTORC1 activity can be assessed through phospho-S6 and phospho-4E-BP1 staining, while mTORC2 affects cytoskeletal organization [13]. PTEN loss is a key upstream driver of PI3K signaling [14]. AMPK activity can be tracked using phospho-AMPK (Thr172), which may indicate tumor-suppressive or adaptive responses [15]. These findings highlight the heterogeneity of signaling within tumor regions and underscore the translational importance of preclinical research on exercise-induced modulation of these pathways.

Clinical tissue studies highlight the prevalence and prognostic relevance of key signaling biomarkers. Phospho-AKT is detectable in a substantial proportion of tumors (e.g., ~60 % of colorectal cancers) and is associated with advanced stage and poor outcomes. Elevated phospho-S6 correlates with metastasis and shorter survival in lung adenocarcinoma. Phospho-AMPK is present in colorectal and breast tumors, with higher levels sometimes linked to better prognosis, though context-dependent. While these studies support the relevance of PI3K/AKT/ mTOR and AMPK signaling in human cancers, links to exercise remain to be confirmed [16, 17].

The PI3K/AKT/mTOR pathway, a highly conserved intracellular pathway in eukaryotic cells, is crucial for cell metabolism and regulates processes such as growth, proliferation, survival, motility, adhesion, and differentiation [18]. Its frequent dysregulation in many diseases has made it a key focus for identifying biomarkers and potential therapeutic targets. The phosphoinositide 3-kinase (PI3K) can be activated by receptor tyrosine kinases (RTKs), including platelet-derived growth factor receptor (PDGFR) and epidermal growth factor receptor (EGFR), which promote cell proliferation and migration, as well as the insulin-like growth factor receptor (IGFR), which stimulates growth and survival, and the insulin receptor (IR), which helps maintain metabolic balance [19-21].

The PI3K/AKT/mTOR signaling pathway is a crucial regulator of essential cellular processes such as proliferation, metabolism, survival, and immune response. In cancer, improper regulation promotes malignant transformation, tumor growth, resistance to therapy, and immune evasion. Although many studies have been conducted, a comprehensive understanding of this pathway’s complex role in tumor biology and therapy is still lacking [22]. Exercise has been shown to modulate AMPK and mTOR pathways, restoring signaling balance and improving metabolic regulation.

This review combines insights from aging biology, exercise physiology, and molecular metabolism to underscore the therapeutic potential of targeting AMPK/ mTOR signaling through physical activity to address insulin resistance in older adults [23]. While previous research has largely focused on the effects of exercise in aging skeletal muscle, studies also suggest potential relevance in cancer biology. This article examines the impact of exercise on these pathways in cancer research.

2. Exercise-Induced Molecular Mechanisms

2.1. Adiponectin-mediated AMPK Activation

Exercise and weight loss elevate circulating adiponectin, which binds to AdipoR1/R2 receptors, activating upstream kinases such as LKB1 and CaMKKβ to stimulate AMPK. This pathway enhances fatty acid oxidation, insulin sensitivity, and suppresses anabolic processes that support tumor growth [24, 25]. Exercise and weight loss elevate circulating adiponectin, which activates AMPK via AdipoR1/R2 signaling in multiple tissues. This adipokine-mediated mechanism may contribute to AMPK-dependent effects on tumor metabolism and systemic energy balance.

2.2. Myokines and Cytokine Remodeling

Acute bouts of exercise induce IL-6 release from skeletal muscle, functioning as an anti-inflammatory myokine that activates AMPK and increases glucose uptake. Chronic exercise reduces TNF-α and IL-1β from adipose and myeloid cells, decreasing NF-κB activation and subsequent PI3K/Akt signaling [26]. Regular exercise shifts the systemic cytokine milieu from a pro-inflammatory (TNF-α, IL-1β dominant) to an anti-inflammatory state, reducing NF-κB activation in both tumor and stromal cells. This cytokine remodeling complements dire.

2.3. IRS-1/IRS-2 Feedback Loop

mTORC1 phosphorylates and destabilizes IRS-1/IRS- 2 under nutrient-rich conditions. Exercise-induced AMPK activation inhibits mTORC1, stabilizing IRS-1/2 and potentially increasing PI3K/Akt signaling via feedback loops [27].

2.4. PTEN-Loss Tumors

Tumors with PTEN loss exhibit constitutive PI3K/Akt activation independent of insulin/IGF-1. Exercise benefits in such tumors may rely primarily on AMPK-mediated mTOR inhibition and metabolic reprogramming rather than systemic insulin/IGF-1 reduction [28].

Importantly, mTORC1 normally phosphorylates and destabilizes insulin receptor substrates (IRS-1/IRS-2). When mTORC1 is inhibited either by AMPK activation or pharmacologically IRS-1/2 levels recover, leading to increased PI3K/Akt signaling via a compensatory feedback loop. Exercise-induced AMPK activation may activate both branches (AMPK→mTORC1 inhibition AND enhanced insulin sensitivity), but this dual regulation warrants further investigation in tumor contexts.

EDIT: Contextualized PTEN-loss impact

2.5. HIF-1α and Tumor Perfusion

Exercise improves tumor perfusion and oxygenation, reducing hypoxia-induced HIF-1α stabilization and downstream pro-growth and metabolic adaptations [29]. Exercise-induced improvements in cardiovascular function enhance tumor perfusion and oxygenation, reducing HIF-1α stabilization and attenuating HIF-1α-dependent angiogenic and metabolic adaptations in tumor cells.

EDIT: Added tumor vascular/HIF-1α mechanism

2.6. Autophagy Duality

AMPK-driven autophagy is tumor-suppressive in pre-malignant and early tumors but may support survival in metabolically stressed established tumors. Exercise-induced AMPK activation thus has context-dependent effects on autophagy [25].

While AMPK-driven autophagy is generally tumor-suppressive in pre-malignant and early tumor contexts, in metabolically stressed established tumors, autophagy may conversely support cancer cell survival and drug resistance. The net effect of exercise-induced AMPK activation on autophagy in cancer is therefore context-dependent

EDIT: Clarified dual role of autophagy

Materials and Methods

Search Strategy

For this review, we conducted a comprehensive search of PubMed, Google Scholar, and Scopus databases covering 2015–2025. The keywords used were neoplasm, cancer, signaling, exercise, and PI3K/AKT/ mTOR. Eligible studies included original, peer-reviewed research articles written in English that investigated the molecular or physiological effects of exercise on cancer progression through modulation of these signaling pathways. Exclusion criteria encompassed review articles, meta-analyses, book chapters, editorials, letters to the editor, conference abstracts, non-English publications, and studies not directly related to the research question.

The selection process was conducted in two stages: first, screening titles and abstracts for relevance, and then reviewing the full texts of potentially eligible articles. The Zotero reference management software was used to organize, categorize, and remove duplicate entries, ensuring a systematic and transparent selection of studies.

Results and Discussion

The role of PI3K/Akt/mTOR pathway in the incidence of cancer

Previous studies highlighted the significance of the mTOR pathway in cancer development. PIK3CA is overexpressed in ovarian [30] and cervical cancers [31], with mutations also noted in breast cancer, glioblastoma, and gastric cancer [32]. Overexpression of Akt1 has been identified in gastric carcinoma, while Akt2 overexpression occurs in ovarian and pancreatic cancers [33]. Although Akt mutations are rare, Carpten et al. [34] reported somatic mutations in Akt1 in a small percentage of human breast, ovarian, and colorectal cancers. Additionally, mTOR complex 1 (mTORC1) may promote mRNA translation, protein synthesis, and cellular proliferation [35]. Activation of a second mTOR complex (mTORC2), which regulates the cytoskeleton, likely results from Akt loop feedback [36]. Balsara et al. [37] observed that 74% of non-small cell lung cancer (NSCLC) patient specimens showed positive mTOR staining using tissue microarray (TMA). Rictor, a subunit of mTORc2, enhances mTORC2 assembly and activity, increasing the proliferation and invasion capabilities of glioma cells. Preclinical data indicate that exercise-activated AMPK and mTORC1 suppression may reduce proliferative and anabolic activity in tumor cells, providing a potential complementary approach for cancer prevention or treatment. However, clinical evidence in human tumors remains limited, and more research is necessary [38]. Overall, these findings show that abnormal activation of the PI3K/Akt/mTOR pathway is crucial in tumor formation.

The PI3K-AKT-mTOR signaling pathway is vital for cancer cell growth and survival. Lipid kinases called PI3K are key regulators in many essential cellular processes, such as cell survival, growth, and differentiation [39, 40]. This pathway features several crucial nodes that lead to a variety of functional outcomes. Activation of downstream targets, such as the mammalian target of rapamycin (mTOR), by AKT promotes cell proliferation and controls translation in response to growth factors, primarily through phosphorylation of the protein synthesis machinery [41]. mTOR promotes translation by phosphorylating ribosomal protein S6 kinases (S6K) and 4E-binding protein 1 (4E-BP1). When 4e-BP1 is phosphorylated, it releases eukaryotic translation initiation factor 4E (eIF4E), which has anti-apoptotic effects in vitro [42, 43]. The TSC1-TSC2 complex negatively regulates this process. The TSC1/TSC2 complex inhibits the small GTPase Rheb, thereby suppressing mTORC1 activity and keeping 4E-BP1 in a hypophosphorylated state, in which it binds eIF4E and represses cap-dependent translation. [44, 45]. Additionally, AKT phosphorylates and inhibits TSC2, further complicating this pathway. Interestingly, while rapamycin and its analogues can inhibit mTOR, this

may activate upstream proteins such as AKT via a feedback loop disruption [46, 47]. The PI3K/Akt/mTOR pathway regulates key normal cellular processes such as proliferation, growth, survival, and mobility, all of which are also crucial for tumour development. Abnormalities in this pathway are common in y types of tumors, which makes its components attractive targets for cancer therapy. [10, 14, 20, 48, 49].

In addition to supporting proliferation and survival, this pathway also plays a role in signalling metabolic and angiogenic processes. Additionally, the PI3K-AKT pathway interacts with complex molecular mechanisms that regulate cellular energy and glucose metabolism.

AKT phosphorylates and inhibits targets such as glycogen synthase kinase-3 (GSK3), phosphodiesterase-3 B, protein phosphatase 2A, and Raf-1. The PI3K signaling pathway also plays a role in controlling growth, proliferation, senescence, and angiogenesis, which are regulated by vascular endothelial growth factor (VEGF) transcriptional activation and hypoxia-inducible factor-1 alpha (HIF-1α) expression [50, 51]. This brief overview emphasises the pathway's involvement in critical cell growth processes, underscoring its complexity and importance at multiple nodes [52]. Given the diversity of signaling dependencies across cancer types, the strength of epidemiologic evidence and mechanistic plausibility for exercise varies substantially. Exercise elicits cancer-type-specific effects on PI3K/Akt/mTOR and AMPK pathways. It may modulate hormone-sensitive tumors via the IGF-1/insulin axis, alter responses to targeted therapies such as PI3K/ mTOR inhibitors, and influence immune checkpoint inhibitor efficacy. Stage-specific evidence is strongest for primary prevention, moderate for adjuvant/survivorship settings (particularly breast and colon cancer), and limited in metastatic disease, where the focus is primarily on functional and quality-of-life benefits. General exercise guidance includes ≥150 minutes/week of moderate aerobic activity plus two resistance training sessions per week [53]. For a consolidated cancer-type-specific summary of mechanistic and epidemiologic evidence, see Table 2.

Cancer Type	Epidemiologic Evidence	Mechanistic Plausibility	Clinical Application
Breast	Strong	AMPK activation, IGF-1/insulinmodulation, myokines	Prevention, adjuvant support,survivorship
Colon	Strong	AMPK, mTOR inhibition, cytokine shifts	Prevention, adjuvant support
Lung	Moderate	AMPK, HIF-1α reduction	Prevention, QOL in palliative care
Prostate	Moderate	AMPK, IGF-1 axis	Prevention, survivorship
Ovarian	Limited	AMPK, mTOR	Prevention only
Pancreatic	Limited	AMPK, metabolic reprogramming	Prevention, palliative focus
Glioblastoma	Limited	HIF-1α, perfusion	Palliative support
Melanoma	Limited	AMPK, immune modulation	Prevention
HCC	Moderate	AMPK, mTOR, cytokines	Prevention, survivorship

Table 2. Summary of Exercise-Related Evidence Across Cancer Types: Epidemiologic Support, Mechanistic Plausibility (PI3K/Akt/mTOR, AMPK), and Clinical Utility.

PI3K/AKT/mTOR signaling and exercise

Cancer cells primarily exhibit increased proliferation, decreased apoptosis, and enhanced survival, driven by the regulation of critical signaling molecules and pathways [54, 55]. The activation of phosphatidylinositol 3-kinase (PI3K)-Akt and Ras-ERK (Erk1/2) pathways occurs when growth factors bind to cell surface receptors, promoting cell growth and longevity [56, 57]. Akt activation leads to downstream effectors, including mTOR and S6 kinase, which stimulate protein synthesis and cell growth [58, 59]. Moreover, Akt phosphorylates Bad, inhibiting apoptosis and enhancing

cell survival [60].

Akt, a proto-oncogene, is frequently overexpressed in many cancers, including NSCLC, contributing to resistance to chemotherapy and radiation therapy [37, 57]. Ras signaling is also often activated in cancers like NSCLC, leading to Erk1/2 activation, increased proliferation, and therapy resistance [49-51]. This activation downstream of Erk1/2 promotes cell proliferation and contributes to chemo- and radiation resistance [61]. Thus, targeting or inhibiting the Akt and Ras-Erk1/2 pathways could be an effective strategy for preventing and treating lung cancer. Therefore, targeting the Akt and Ras-ERK pathways may be a promising therapeutic approach for cancers such as NSCLC.

Regular exercise is associated with reduced cancer risk [53], including prostate [53] and breast cancer [62]. Breast cancer patients engaged in light aerobic exercise showed higher survival rates than sedentary patients [63]. Additionally, increasing physical activity to more than 1.8 Mets/day (such as running) was associated with nearly a 90% reduction in cancer mortality risk [64].

While the link between exercise and lung cancer has not been thoroughly studied, evidence suggests that engaging in regular exercise more than 4 hours weekly at a moderate intensity (>4.5 MET) can lower the risk of NSCLC adenocarcinomas in both men and women compared to those exercising less than 4 hours weekly at a low intensity (<4.5 MET) [65, 66]. Additionally, regular exercisers seem to have a 20–40% lower risk of lung cancer relative to sedentary individuals. Nonetheless, despite this epidemiological data, the specific factors and mechanisms through which exercise exerts its anticancer effects remain unclear [67].

Mechanistically, exercise can modulate key signaling pathways involved in tumor growth. Weight loss and exercise reduce IGF-1, insulin, and leptin levels, thereby diminishing activation of Ras-MAPK and PKB/Akt-PI3K pathways, which normally promote proliferation and inhibit apoptosis [68-70]. Furthermore, exercise inhibits mTOR activity in tissues such as liver, brain, fat, and skeletal muscle, contributing to reduced tumor-promoting signaling [68, 71, 72].

The AMPK pathway and its role in cancer inhibition

AMP-activated protein kinase (AMPK) is a highly conserved enzyme made up of a catalytic α subunit and two regulatory subunits, β and γ. This pathway has become a crucial regulator of cellular energy balance and plays a role in cancer suppression. It is found in various tissues, including liver and skeletal muscle [73, 74]. The α-subunit contains a crucial threonine residue (Thr172), where phosphorylation by upstream kinases activates AMPK. These kinases include liver kinase B1 (LKB1), calcium/calmodulin-dependent protein kinase (CaMKK) [75], and transforming growth factor β (TGF-β)-activated kinase (TAK1) [75]. Mutations in these upstream kinases may cause AMPK dysregulation and elevate cancer risk, for example. Individuals with Peutz-Jeghers syndrome who have germline mutations in LKB1 show a higher cancer risk [75]. AMPK can also be triggered by external changes such as ATP depletion, low glucose, or alterations in NADPH levels [76]. Beyond physiological stressors, both pharmacological and natural compounds can activate AMPK, suggesting possible therapeutic strategies. Certain drugs and natural compounds can activate AMPK, including metformin and some NSAIDs [77, 78], polyphenols like resveratrol [79-81], flavonoids such as quercetin [82], and herbal compounds like berberine [83-85]. Activation of AMPK by NSAIDS and anti-inflammatory drugs suggests a role for AMPK in inflammation. Once active, AMPK influences multiple effector proteins involved in regulatory pathways that may lead to cancer development. Regarding cancer metabolism, the mammalian target of Rapamycin (mTOR) is a key target of AMPK, with ongoing efforts to develop clinical interventions [86]. AMPK also regulates p53 [87] and modulates transcription factors and co-regulators that control the cell cycle [88-90]. Through aMPK regulates key targets like mTOR and p53, broadly influencing cell cycle, apoptosis, and tumor metabolism. AMPK frequently exerts tumor-suppressing effects by inhibiting mTORC1 and restricting anabolic metabolism; however, its role depends on the context. In established tumors experiencing metabolic or hypoxic stress, AMPK activation might also support

cell survival through promoting autophagy and metabolic processes adaptation [91].

AMPK has been shown to have tumor-suppressing functions in multiple experimental cancer models; however, evidence at the tissue level in human tumors suggests that its role might be dependent on the context and can differ based on tumor stage and microenvironmental conditions. Together, these mechanisms produce tumor- suppressing effects in various cancer types, as shown by research in NSCLC, CRC, HCC, melanoma, and breast cancer. In NSCLC, its activation correlates with better prognosis and decreased cell proliferation. In CRC, AMPK significantly influences cancer cell survival and promotes apoptosis. In HCC, activating AMPK is linked to hindering tumor growth and enhancing prognosis. In melanoma, AMPK triggers cancer cell death and diminishes tumor expansion. In breast cancer, it suppresses cell growth and supports survival under stressful conditions. While AMPK activation can limit anabolic signaling and support anti-proliferative responses, studies of human tumor tissues suggest that AMPK may also support metabolic adaptation and cell survival under tumor-associated stress conditions [73]. AMPK frequently exerts tumor- suppressing effects by inhibiting mTORC1 and restricting anabolic metabolism; however, its role depends on the context. In established tumors experiencing metabolic or hypoxic stress, AMPK activation might also support cell survival through promoting autophagy and metabolic processes adaptation.

The relationship between AMPK and exercise

AMPK (AMP-activated protein kinase) is an evolutionarily conserved enzyme that senses cellular energy levels and is found in all mammalian cells. It is essential in maintaining cellular energy balance, and its activity can be influenced by physiological triggers such as exercise. In humans, exercise activates AMPK in skeletal muscles, and in rodents, it also activates in adipose tissue, liver, and possibly other organs due to increased AMP/ATP ratios. This tissue-specific activation is fundamental to many of the systemic metabolic changes seen during exercise. When active, like glucose uptake and fatty acid oxidation, while it suppresses energy-consuming processes such as protein and lipid synthesis. Since exercise strongly stimulates AMPK activity, it serves as a natural model for studying these energy regulation mechanisms pathways. Exercise is arguably the most significant natural activator of AMPK and serves as an ideal model for exploring its various physiological roles. Moreover, it enhances metabolic health in rodents displaying metabolic syndrome traits, similar to the effects of AMPK-activating drugs [92-96]. This suggests that the health benefits of regular physical activity may partly stem from AMPK activation [97]. Animal studies show that both acute exercise and regular training boost cardiac AMPK phosphorylation and activity. Overall, these findings imply that activating AMPK alone can promote glucose and fatty acid metabolism [93]. Ultimately, these results suggest that activation of AMPK through exercise plays a crucial role in improving energy metabolism and could be a factor in the overall health advantages of physical activity.

Exercise affects crosstalk between PI3K/Akt/mTOR and AMPK

Dysregulation of nutrient-sensitive pathways like AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR) is key to metabolic imbalance and abnormal cell growth seen in aging and cancer [23]. These pathways work together to regulate energy use, protein production, and glucose metabolism, which also influence cell growth and survival [98]. Exercise influences these kinases, helping improve metabolic signaling. By activating AMPK and regulating mTOR activity, exercise boosts mitochondrial biogenesis, increases glucose uptake, and supports healthy growth processes, thereby preventing out-of-control signaling [99]. In cancer, the interaction between AMPK and mTOR offers therapeutic potential, as activating AMPK can inhibit tumor-promoting mTOR activity, reduce abnormal protein production, and promote autophagy of damaged cell parts. Therefore, targeting how exercise affects the PI3K/Akt/mTOR and AMPK

pathways could be an effective approach to managing cellular metabolism and controlling growth in cancer prevention and treatment [23]. Importantly, the metabolic effects of exercise-induced AMPK activation also contribute to cancer protection by connecting energy regulation with tumor suppression.

Exercise and physical activity can activate AMPK, a tumor suppressor protein linked to numerous cancers [70]. Once activated through exercise, AMPK inhibits cancer cell growth by regulating cellular metabolism, blocking pathways that support cell division, and decreasing insulin resistance and IGF-1 levels [100-102]. Therefore, engaging in exercise not only boosts metabolic health but also acts as a natural method to help prevent cancer and support treatment.

In conclusion, exercise represents a promising, multidimensional intervention in cancer prevention and management. By activating AMPK and simultaneously inhibiting mTOR signaling, exercise restores metabolic balance, improves insulin sensitivity, promotes autophagy, and reduces proliferative signaling in tumor and systemic tissues. Systemic mediators, including adiponectin and myokines, and anti-inflammatory cytokine shifts contribute to these effects. The impact of exercise is influenced by tumor-specific factors such as PTEN status, hypoxia, and stage, underscoring the importance of context in interpreting its anticancer potential. While evidence supports strong benefits in early-stage and prevention settings, clinical trials in human tumors are needed to clarify optimal exercise regimens, dose, and interactions with conventional therapies. In conclusion, regular physical activity should be considered a complementary strategy in oncology, offering metabolic, molecular, and systemic benefits that may enhance the efficacy of standard treatments and contribute to improved patient outcomes.

Ethics approval

This manuscript does not encompass any research involving animals or people.

Conflict and interest

The authors assert no conflict of interest in this work.

Acknowledgments

Not Applicable

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