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miR-126: a bridge between cancer and exercise

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Abstract

The microRNA miR-126 supports endothelial cells and blood vessel integrity. Recent research has shown that it also serves as a key link between exercise and cancer. This article delves into how exercise affects the expression of miR-126, impacting cardiovascular well-being and metabolic control. The article also examines the various contributions of miR-126 in cancer, acting as both a suppressor and an enhancer depending on the particular context. Regular aerobic exercises, including HIIT, consistently increase levels of miR-126, leading to enhanced angiogenesis, endothelial repair, and improved vascular function through mechanisms involving VEGF, HIF-1α, and EPC mobilization. Resistance training affects similar pathways, but does not cause a significant change in miR-126 levels.

MiR-126 involves in cancer by suppressing tumor growth and controlling key pathways such as PI3K/Akt, ERK/MAPK, and EMT. Lower levels are associated with negative outcomes, later stages of the disease, and increased spread of different types of cancer like glioblastoma, CRC, ovarian, esophageal, gastric, and prostate cancer.

The relationship between exercise and cancer suggests a possible therapeutic approach, where the regulation of miR-126 through exercise could help improve vascular function and slow tumor growth. Further studies should focus on understanding the specific molecular pathways through which miR-126 connects these areas, leading to potential interventions that utilize its regulatory network to promote cardiovascular well-being and enhance cancer treatment.

Keywords Exercise, Cancer, MicroRNA, MiR-206

Introduction

Cancer is a highly dangerous illness, with one of the highest rates of sickness and death among noncommunicable diseases [1]. In 2018, cancer rates and deaths have been on the rise due to the growing population and aging demographics. The global data from that year reported a staggering 9.55 million fatalities and 18.08 million new cases of cancer [2]. Over the years, advancements have been achieved in cancer treatment. However, the outlook for cancer patients remains grim, especially for those in advanced stages of the spread of the disease. It is important to better understand the molecular pathways that cause tumor growth and develop more effective methods for treating cancer in clinical settings [3].

High-income countries had a 36.8% inactivity rate among adults in 2016, a significant difference from low-income countries (16.2%). Inactivity tends to be more common among women, particularly in the Eastern Mediterranean and the US [4]. In contrast, the development of cancer has been linked to a combination of genetic and environmental elements. Studies in controlled and

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real-life situations show that certain controllable behaviors, like smoking, physical inactivity, diet, and alcohol consumption, can affect cancer recurrence and prognosis [5].

Globally, many adults are not physically active. The WHO found that 64% of adults are inactive for over 4 h a day, which is a leading cause of non-communicable illnesses like cancer. 10% of breast and colon cancer cases have been attributed to a sedentary lifestyle [5].

Numerous studies, including retrospective, epidemiological, case-control research, and prospective, have demonstrated the potential advantages of physical activity and exercise in regard to reducing cancer risk [6–8] including breast cancer in menopausal women, endometrial, colon cancer, lung, pancreatic cancer, and prostate [9, 10], decreasing the prevalence of these types of cancer by 40% [11]. Studies have indicated that individuals with sedentary lifestyles may have a higher risk of developing colon cancer (RR = 2.0) and breast cancer (RR = 1.5). Conversely, Regular exercise reduces breast cancer risk by 75% and CRC risk by 22% [12, 13]. The CDC states that staying physically active reduces the risk of developing lung, breast, colon, and endometrial cancer [14].

Studies have consistently found physical activity to be safe during cancer treatment and can lower the risk and development of cancer in certain areas of the body [12, 14]. Exercise's ability to prevent cancer is being researched. It has been observed that physical activity can greatly enhance physical capabilities and muscle strength, as well as positively impact mental well-being in patients. Exercise may decrease tumor growth by improving blood flow, boosting the immune system, changing tumor metabolism, and affecting the relationship between cancer and muscles cells [15]. There is growing evidence of these mechanisms, however, further intervention studies are needed to establish a clear link between them and the regulation of tumor development and progression [15].

A recent focus of research is the impact of exercise on bodily functions, specifically in relation to miRNAs. These are naturally occurring short RNAs, typically 21–25 nucleotides long [16]. Over 2000 miRNAs is discovered in humans [17], They have significant functions in different biological processes, including differentiation, metabolism, proliferation, division and apoptosis [18, 19]. They have a suppressive effect on target gene expression by breaking down mRNA and preventing its translation into a functional protein [20]. In addition, they are believed to make up approximately 1–2% of the entire genome and have the ability to control 30% of genes that encode proteins [16]. Physical activity is believed to alter miRNA levels, which in turn control long-term changes in skeletal muscle, cardiovascular function, and aerobic capacity [21, 22], they could potentially serve as biomarkers to enhance exercise prescription for the purpose of promoting health or enhancing performance.

Dr. Croce et al. first discovered the connection between miRNA and human cancer while investigating potential tumor suppressors in BCLL cells located at chromosome 13q14 [23]. Scientists discovered that a specific region, often missing in BCLL, holds two miRNA genes - miR-16-1and miR-15a. These genes are frequently absent or reduced in most cases of this type of leukemia. Further research showed that these miRNAs function as tumor suppressors by inhibiting Bcl-2, is typically overproduced in cancerous non-dividing B cells and various solid tumors [24, 25]. The removal of the miR-16-1 and miR-15 cluster in mice reproduced the characteristics of chronic lymphocytic leukemia seen in humans, providing strong evidence for the significant impact of these two miRNAs on inhibiting tumors [26]. In subsequent years, the use of miRNA profiling and deep sequencing has revealed that cancer is associated with altered miRNA expression. These changes can be utilized to classify, diagnose, and predict the outcome of tumors.

The increasing attention towards the connection between cancer and physical activity has provided a fresh perspective on comprehending the fundamental molecular processes involved in preventing and treating cancer. In this context, miRNAs have gained significance as key controllers of gene expression in different pathological and physiological conditions. Of these, miR-126 is noteworthy for its impact on both vascular function and tumor development [27, 28]. MiR-126 shows potential in uncovering these links due to its capacity to control endothelial function, inflammation, and tumor cell growth. Exploring the impact of miR-126 in relation to exercise can provide insights into how physical activity affects cancer biology and potentially lead to innovative treatment approaches that utilize the advantages of exercise.

Furthermore, studying the function of miR-126 presents a chance to connect lifestyle changes with molecular aspects of cancer. With exercise being increasingly incorporated into cancer treatment and post-treatment plans, identifying molecular markers such as miR-126 could aid in tailoring individualized interventions, monitoring patient progress, and potentially influencing the creation of exercise-simulating medications.

The hypothesis of this article is that miR-126 acts as a molecular link between exercise and cancer by regulating key signaling pathways involved in tumor suppression, angiogenesis, and tissue repair. It proposes that miR-126 could serve as both a therapeutic target and a biomarker for personalized interventions in cancer prevention and treatment, particularly through exercise-induced modulation. This article summarizes the link between miR-126

and cancer, and how it may connect exercise to preventing and treating cancer.

Role of exercise in prevention of cancers

The impact of exercise on cancer risk differs based on the specific type of cancer. Although there is no definitive evidence, research indicates that making healthier lifestyle choices may reduce the chances of cancer onset. Engaging in moderate to intense physical activity for 3–5 h per week has been associated with a reduced risk of developing cancer. This is especially true for women who participate in vigorous activities like strenuous household chores and dancing, which are known to be effective in lowering the risk of breast cancer [29]. A study discovered that regular exercise significantly decreased the risk of developing breast cancer by 15–20% and colorectal cancer by 24% [30]. Studies have shown that participating in physical exercise can greatly lower the risk of breast cancer in postmenopausal women [31] and its effective in preventing autonomic nervous system dysfunction among them [32]. Also, it has beneficial effect on the occurrence of colorectal cancer. In 126 studies examining this relationship, individuals with higher levels of physical activity had a 19% lower risk of developing colorectal cancer compared to those with lower levels [33]. Regular participation in physical exercise has been scientifically proven to positively impact the reduction of colorectal cancer risk. An extensive review of 126 studies on this topic revealed that individuals who engaged in higher levels of physical activity had a 19% lower chance of developing colorectal cancer compared to those who were less active [30]. Studies have demonstrated that being above a healthy weight greatly increases the chance of developing endometrial cancer [34, 35]. Research on 33 different studies demonstrated that physical activity was effective in decreasing obesity and lowering the risk of endometrial cancer by 20% in women who engaged in high levels of exercise compared to those with low levels [36]. A thorough examination of studies on esophageal cancer, including 15 case-control and 9 cohort studies, determined that individuals who participated in significant amounts of physical activity were 21% less likely to develop the disease compared to those with low levels of physical activity [37]. Research involving over 1 million individuals found that engaging in physical activity during leisure time decreased the likelihood of bladder cancer by 13% and kidney cancer by 23% [38]. After analyzing 11 cohort and 4 case-control studies, it was determined that individuals with higher levels of physical activity had a 15% lower risk of bladder cancer compared to those with lower levels [39]. A thorough analysis of 25 studies indicates that smokers who participated in physical activity had a lower probability of developing lung cancer than those who did not engage in regular exercise. On the other hand, the risk of lung cancer appeared to be similar for nonsmokers, regardless of whether they engaged in physical activity or not [40]. Physical activity may not have a significant effect in decreasing the likelihood of developing specific forms of cancer, including pancreatic, blood-related, thyroid, hepatic, and ovarian cancer.

The primary factor that affects cancer risk is the specific type of cancer, with the way various cancers and subtypes respond to physical activity differing. For example, the effect that exercise has on hormone receptor levels varies between different types of breast cancer. Individuals with HER2-negative/ER-positive/PR-positive/low grade subtype are especially responsive to exercise, resulting in a decreased risk of recurrent breast cancer. However, this effect may not be observed in patients with other genetic backgrounds [41] A study utilizing mice exhibiting p53-deficient MMTV-WNT-1 breast cancer showed that administering exercise did not lead to a noteworthy rise in survival rate or reduction in the incidence of cancer. This could be attributed to the dominant influence of the genetic mutation on exercise response [42]. The research showed that exercise sensitivity varied based on hormone receptors and driving genes, and other factors limited its ability to prevent cancer.

The communication pathways within tumors are easily influenced by external factors and can be changed significantly [43]. When it comes to physical activity, external factors play a significant role in the body. These factors can impact blood flow, put stress on the vascular system, regulate pH levels, produce heat, and activate the sympathetic nervous system. Additionally, they can also affect hormone levels, release myokines, and circulate exosomes [44], each of these can control the advancement and characteristics of cancer. Physiological factors can impact various aspects of tumor development, such as growth rate, ability to spread, metabolic processes, and immune response. While these mechanisms apply broadly to all types of cancer, it is important to note that different cancer types can vary significantly in terms of their specific growth patterns, immunogenicity, and metabolism. The variations in these groups are a result of the tumors' basal and mutational characteristics. The impact of physical activity on each individual mechanism may differ in significance based on the specific type of cancer being diagnosed.

Most research studies examining the relationship between exercise and cancer outcomes primarily find a significant reduction in tumor growth rates [45, 46]. Exercise training is found to significantly decline tumor growth by up to 67% [45], but cannot directly eliminate tumors. Research has not yet demonstrated that exercise interventions can effectively remove or significantly decrease existing tumorsTo gain a better understanding

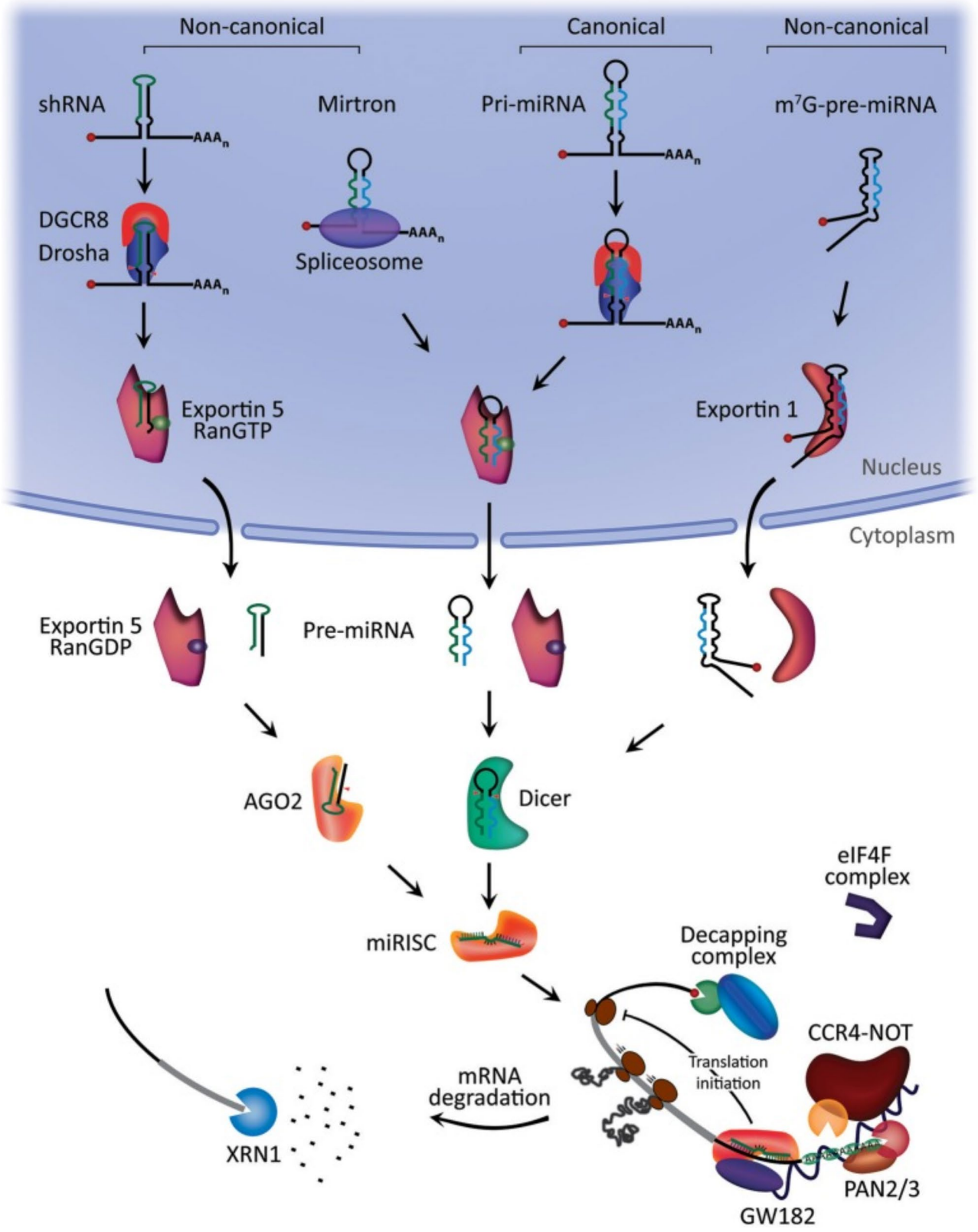

Fig. 1 (See legend on next page.)

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Fig. 1 The process of creating and using miRNAs involves several steps. It starts with producing a pri-miRNA, which is then cut by the microprocessor complex made up of Drosha and DGCR8. This forms a pre-miRNA, which is moved to the cytoplasm and turned into a mature miRNA duplex. One of the strands is then loaded onto an Argonaute protein to make a miRISC. Non-canonical pathways may also be used, where small hairpin RNAs are cut by the microprocessor complex and sent to the cytoplasm for further processing. These can be cleaved by AGO2 without Dicer's involvement. Mirtrons and m7G-pre-miRNAs have distinct processes for maturation in the cytoplasm, with mirtrons utilizing Exportin5/RanGTP and m7G-pre-miRNAs using Exportin1. However, both pathways result in the formation of a functional miRISC complex, which hinders translation by disrupting the eIF4F complex. Additionally, GW182 proteins recruit PAN2/3 and CCR4-NOT to cause deadenylation of the target mRNA. The remaining m7G cap is removed by the decapping complex, allowing for degradation by XRN1

of the potential of exercise in inhibiting tumor growth, some studies have exposed cancer cells from various sources (such as breast, prostate, and lung cancer) to serum conditioned by exercise. These laboratory experiments show that cancer cell growth is reduced by approximately 10–15% when compared to the control group. However, there is no complete elimination of cancer cells compared to their initial levels [47–49]. Completely paraphrased: In vitro studies show lower levels of inhibition compared to longer in vivo interventions. This discrepancy may be because in vitro studies only assess the outcomes of one exercise session. However, consistently engaging in exercise at the recommended intensity can lead to significant overall inhibition of tumors, with potential effects reaching up to 10-15% [50].

miRNA126: biogenesis and their role in cancer and exercise

MiRNAs: biogenesis and mechanisms of the action

The process of miRNA production involves making changes to RNA polymerase II/III transcripts, which can be done either after or during transcription [51]. Around 50% of identified miRNAs are derived from within genes, primarily from introns and a small number from exons in protein-coding genes [52, 53]. The other half are located outside of genes, being produced independently from their host gene and regulated by their own promoter [54]. MiRNAs can be transcribed as a single cluster, with shared seed regions, and are classified as a family in such cases [55]. The production of miRNA can be divided into two pathways: canonical and non-canonical (Fig. 1). The primary method for processing miRNA is through the canonical pathway. This involves the transcription of pri-miRNAs from miRNA genes, which are then processed by a complex consisting of Drosha, a ribonuclease III enzyme, and DGCR8, an RNA-binding protein [19, 56]. DGCR8 recognizes specific patterns, such as N6-methyladenylated GGAC sequences, on the primary microRNA. Afterwards, Drosha divides the paired structure at the bottom of the folded RNA, producing pre-miRNAs with an overhang of 2 nucleotides at the 3' end. These pre-miRNAs are then carried to the cytoplasm by a complex involving exportin 5 (XPO5) and RanGTP. Once in the cytoplasm, Dicer takes off the end portion of the pre-miRNA to create a fully formed miRNA double-stranded molecule [57–60].

The two segments of the duplex, 5p and 3p, are labeled according to their source from the pre-miRNA hairpin's 5′ or 3′ end. These portions are incorporated into AGO proteins, with the selected strand being designated as the dominant one due to factors like diminished thermodynamic stability at the 5′ terminal or the presence of 5′ uracil. The remaining strand, referred to as the non-dominant strand, is separated and disintegrated either through AGO2 cleavage or in instances of mismatches in the middle [57, 61].

Apart from the standard pathway, there are several alternative ways in which miRNA can be produced. These pathways may not involve the usual components and can be divided into two types: those that do not require Drosha or DGCR8, and those that do not involve Dicer [57].

In certain pathways not involving Drosha and DGCR8, pre-miRNAs are generated from spliced introns or from m7G-capped transcripts. These pre-miRNAs do not undergo cleavage by Drosha and are instead transported to the cytoplasm through exportin 1. The presence of an m7G cap can cause a preference for the 3p strand to be loaded into AGO proteins, rather than the 5p strand [62, 63].

In pathways that do not involve Dicer, Drosha converts shRNAs into pre-miRNAs that are too brief to be cleaved by Dicer. These pre-miRNAs are then inserted into AGO2, where they undergo further maturation through the slicing of the 3p strand and trimming of the 5p strand, both of which are facilitated by AGO2 [19, 56, 64].

MiRNAs can regulate gene expression through various mechanisms such as translational repression, mRNA degradation, and transcriptional control. There is consensus that miRNAs bind to specific sequences in the 3′ UTR of target mRNAs, leading to translational repression and subsequent deadenylation and decapping of the mRNA [65, 66]. In addition, miRNA binding sites is detected in various regions of mRNAs, including the coding regions, 5′ UTR, and promoter regions. When bound to the 5′ UTR or coding regions, gene expression is typically inhibited, whereas binding to promoter regions can stimulate transcription [67, 68].

Although the majority of research centers on miRNAs causing gene suppression, they can also trigger gene expression in certain circumstances [57]. During periods of serum starvation or cell cycle arrest, AGO2 and

FXR1 bind to AU-rich elements (AREs) in the 3′ UTR to promote translation. This has been observed with miRNAs such as let-7. In cells that are not actively dividing, miRNAs can increase translation through the involvement of AGO2 and FXR1, rather than GW182 [69, 70]. Furthermore, it is proved that miRNAs can enhance protein production by binding to the 5′ UTR of mRNAs that code for ribosomal proteins during amino acid scarcity [71]. miRNAs can also operate in the nucleus, with AGO2 moving back and forth between the nucleus and cytoplasm through TNRC6A, a protein from the GW182 family [72, 73]. In the nucleus, AGO2 and miRISC interact with active chromatin at gene loci, suggesting their participation in co-transcriptional and post-transcriptional mechanisms. miRISC can either promote mRNA degradation or impact transcriptional activity by binding to promoter regions [74, 75].

miR-126 and its role in cancer

MiR-126, found in intron 7 of the EGFL7 gene on chromosome 9q34.3, is essential for endothelial cell function, maintaining vascular integrity, promoting angiogenesis, and inhibiting tumor growth [76]. This particular miRNA was found in the heart of Mus musculus and is prominently present in endothelial cells and vascular tissues, including the heart, liver, and lungs [76–79]. There are two fully developed versions of miR-126, known as miR-126–3p and miR-126–5p. These forms play a critical role in regulating different genes and signaling pathways [80, 81]. MiR-126 is associated with diseases like diabetes, stroke, Parkinson's, cancer, and viral myocarditis [82, 83].

MiR-126 has been found to have a protective role in metabolic and neurological diseases, such as diabetes, ischemic stroke, and Parkinson's disease. However, excessive levels of this molecule may also make individuals more vulnerable to viral myocarditis [82, 83]. The multifaceted nature of miR-126's function reveals the intricacy of its regulatory effects on human well-being. Studies have demonstrated a notable decrease in miR-126 levels in cancerous tissues across different body systems, such as the respiratory systems, digestive, reproductive, and endocrine. This decline implies its potential as a suppressor of tumors by impeding oncogenes and altering signaling pathways [84–86].

Glioblastoma patients with high miR-126 expression levels tend to have better survival outcomes compared to those with lower levels [87]. The amount of miR-126 are lower in both hepatocellular carcinoma and metastatic ccRCC tissues, indicating a more favorable prognosis when the levels are higher [88]. MiR-126 can differentiate between papillary and clear cell subtypes of renal cell carcinoma [89]. The declined expression of miR-126 in osteosarcoma is linked to more advanced clinical stages and metastasis, potentially caused by the increased levels of ADAM-9 [90]. MiR-126–3p overexpression has been found to suppress vasculogenesis, invasion, migration, and cellular proliferation in TNBC [91]. MiR-126–5p impacts lung adenocarcinoma and increases response to radiation by controlling the EZH2/KLF2/BIRC5 pathway. This ultimately results in cell death and reduces tumor aggressiveness [92].

MiR-126 is found to have a notable impact on various types of cancer. In ovarian cancer, its levels are decreased, leading to increased aggressiveness and a negative prognosis [93]. MiRNA can target specific pathways, such as the Notch-1/Akt pathway in thyroid cancer. Its main function is to hinder tumor growth and movement, while also triggering cell death [94]. Overexpression of miR-126 in ER-positive breast cancer has been shown to decrease cell proliferation and the formation of mammospheres, underscoring its role as a tumor suppressor [95]. Through computational analyses, researchers have identified SLC7A5 and PLXNB2 as potential targets. The decrease in their expression levels upon miR-126 overexpression has been linked to improved overall survival [95].

Epithelial-to-mesenchymal transition (EMT) is a cellular process where epithelial cells lose their characteristic features, such as tight junctions and apical-basal polarity, and acquire mesenchymal properties, including increased motility and invasiveness [96, 97]. EMT plays a crucial role in cancer progression, particularly in metastasis. During EMT, cancer cells gain the ability to detach from the primary tumor, migrate through the extracellular matrix, and invade surrounding tissues, contributing to the spread of cancer to distant sites [98].

Jia et al., investigated the role of miR-126 in the process of EMT in lung cancer cells. Their result showed that miR-126 act as a tumor suppressor via inhibition of EMT. Further exploration in the underlying mechanisms revealed that miR-126 regulated PI3K/AKT/Snail pathway as western blot confirmed reduction of Snail in miR-126 transfected cells [99].

In another study the role of ERK/MAPK pathway and the role of miR-126 in EMT were investigated. Results showed significant reduction of miR-126 in ovarian cancer and inverse association between miR-126 and ovarian cancer patients' prognosis. Further experiments revealed that miR-126 targeted the epidermal growth factor-like domain 7 (EGFL7) 3' untranslated region (3'UTR) as well as ERK/MAPK pathway and regulated EMT process in ovarian cancer [100].

MiR-126 is necessary for both facilitating the angiogenesis and preserving vascular stability, as well as its contribution to cancer. Its expression is elevated in EPCs, and inhibiting it can impede cell proliferation, migration, and invasion, disrupt the cell cycle, and trigger apoptosis. The

results emphasize the critical role of miR-126 in controlling vascular biology [81].

In terms of mechanism, miR-126 directly affects various genes and pathways related to the development of tumors, such as PIK3R2, IRS, VEGF, and mTOR [101]. It alters the way cells communicate with each other, specifically in colitis-associated cancer, by regulating the CXCL12-IL-6 signaling pathway, resulting in inhibition of tumor growth [102]. MiR-126 is found to suppress AKT2 in NSCLC, indicating its potential as a viable treatment option [103].

Regulation of angiogenesis and its related mechanisms which are important in cancer metastasis and progression are other proposed mechanisms in which miR-126 plays an important role in them. This miRNA not only regulates the response of endothelial cells to VEGF but also directly inhibits Sprouty-related protein, SPRED1, and phosphoinositol-3 kinase regulatory subunit 2 (PIK3R2). Furthermore, a study showed that inhibition of this miRNA disrupts vascular integrity and led to the hemorrhage [104].

ADAM9 (A Disintegrin and Metalloproteinase 9) is a member of the ADAM family, which is involved in various cellular processes such as adhesion, migration, and signaling. In cancer, ADAM9 has been implicated in tumor progression, metastasis, and angiogenesis. The enzyme is a membrane-bound metalloprotease that can cleave and release several extracellular matrix components and cell surface proteins, influencing cell behavior [105, 106]. In Hamada and colleagues work, the expression of miR-126 was reduced while the ADAM9 increased in pancreatic cancer cell lines. After the transfection of pancreatic cancer cells with miR-126 and induced overexpression of this miRNA in them, they found significant inhibition of ADAM9 expression as well as upregulation of E-cadherin expression along with reduction of malignant behavior [107].

miR-126 as a mediator of exercise effects

Research has consistently shown that the positive impacts of exercise can be attributed to the involvement of miR-126. Findings from limited research suggest that regular aerobic exercise Both healthy individuals and those with health conditions can experience an increase in myocardial and circulating miR-126 levels. A study has revealed that four weeks of intense exercise can lead to a rise in circulating miR-126 levels in individuals without health conditions [108, 109]. In Wister rats, a 10-week period of moderate and high levels of swimming leads to a notable rise in circulating miR-126. This increase is directly linked to exercise-induced cardiac angiogenesis and follows a dose-dependent pattern [110]. Consistent running leads to an increase in the expression of miR-126 in the heart of STZ rats and db/db mice [111, 112], however, it does not affect the levels of miR-126 in circulation [111]. In the same manner, the levels of miR-126 in the plasma of hypertensive rats do not change after ten weeks of swimming. Yet, the protein PIK3R2, which is influenced by miR-126, decreases from a 51% increase to a normal state [113]. A study conducted on mice with diabetes, aged 8 and 16 weeks, found that initiating exercise at an early stage can increase levels of myocardial miR-126 and VEGF, thereby improving the management of diabetic heart disease [111]. A six-week program of exercise and diet control in obese adolescents increases levels of serum miR-126 and enhances diastolic functions of the vascular endothelium [114]. The results indicate that miR-126 may be the key factor affected by regular aerobic exercise in a dose-dependent manner, potentially playing a role in early cardiac protection.

It has been demonstrated that four weeks of aerobic exercise could increase the level of miR-126 in both serum and myocardium of healthy individuals [108, 109]. Silva et al., reported the significant increase of circulating miR-126 following ten weeks of swimming in male Wistar rats as well as increase of cardiac angiogenesis due to the exercise in a dose– dependent manner [115].

Lew and colleagues investigated chronic aerobic exercise on diabetic mice and found significant increase of VEGF and miR-126 as well as prognosis of diabetes in these mice [111]. Wahl et al. reported significant increase of miR-126 following high-volume training (HVT) with cycling for 130 min at 55% peak power output (PPO) [116]. Also, one session of HVT with 90 min cycling also produced the same results in 60% of PPO [117].

$VO2_{max}$ refers to the highest quantity of oxygen that can be utilized during intense physical activity within a specific period. This is typically measured through a symptom-limited exercise test, such as cycling, It results in a rise of miR-126 levels in the blood of individuals without any health issues [118]. Following a 30-minute aerobic workout at 75% of their $VO2_{max}$, obese individuals experience an increase in circulating miR-126 levels, which continues to rise for an hour after the exercise [119]. Intense physical activity can lead to tissue hypoxia, which may result in an upregulation of miR-126. This is caused by the activation of Ets-1and HIF-1α, both of which can control the expression of miR-126 in vascular endothelial cells [120, 121]. During a marathon, professional runners showed a rise in the number of EPCs containing miR-126, which may have a positive impact on blood pressure and heart rate [122].Diabetic patient, there is a rise in circulating EPC-EVs, but a decrease in both the transported miR-126 and the presence of VEGFR-2 [123]. Our research demonstrated that mice engaged in moderate exercise for a long period had elevated levels of EPC-exosomes in their bloodstream. These exosomes were found

Table 1 Role of miR-126 in cancer and exercise

Context	Type	miR-126 Expression	Molecular Mechanism	Reference
Exercise	Chronic Aerobic Exercise	Increased	Dose-response, induces VEGF, EPC mobilization	[27, 109]
	Acute Aerobic Exercise	Increased	Hypoxia-induced HIF-1α, Ets-1 regulation	[120, 121]
	HIIT	Increased	Influenced by training level and exercise duration	[116, 145]
cancer	Glioblastoma	Decreased	Associated with improved survival with higher levels	[87]
	Hepatocellular Carcinoma	Decreased	Tumor suppression by oncogene inhibition	[88]
	Prostate Cancer	Decreased	Targets ADAM9 to inhibit proliferation and metastasis	[146]
	Colorectal Cancer	Decreased	Regulates CXCR4, decreases metastasis and stage severity	[147]
	Non-Small Cell Lung Cancer	Decreased	Inhibits PI3K-Akt pathway, enhances chemotherapy sensitivity	[148]
	Ovarian Cancer	Decreased	Inhibits ERK/MAPK signaling and EMT	[93]

to improve the function of damaged ECs by reducing SPRED1 and increasing VEGF [124].

miR-126 in a cross-talk between cancer and exercise, limitations and future direction

MiR-126 is a significant factor in cancer biology and the positive effects of physical activity, potentially connecting these two fields at a molecular level. In cancer, miR-126 is well-known for its ability to suppress tumors by targeting oncogenes and influencing important signaling pathways like VEGF, IRS, and mTOR [81, 125, 126]. The expression of this protein is frequently declined in different types of cancer, such as glioblastoma, HCC, and TNBC. This decrease is associated with negative outcomes, including a worse prognosis, higher rates of metastasis, and more aggressive tumor characteristics [87, 88, 91]. On the contrary, increased levels of miR-126 are linked to better survival rates and decreased tumor development [81, 127].

In contrast, miR-126 can enhance the positive effects of physical activity on well-being. Studies have demonstrated that regular aerobic and high-intensity exercise can increase levels of miR-126 in both the bloodstream and specific tissues, leading to improved angiogenesis, better endothelial function, and overall cardiovascular well-being [128, 129]. Physical activity-induced lack of oxygen in the tissues triggers the activation of HIF-1α, a crucial factor in the expression of miR-126. This, in turn, facilitates the angiogenesis and repair of damaged endothelial cells [128, 129]. The dual role of miR-126 is emphasized by these mechanisms, connecting its ability to prevent tumor growth with the positive effects of exercise on the body.

The correlation between cancer and exercise through miR-126 is highly interesting. Consistent physical activity can potentially create a hostile environment for tumors by altering the conditions in which they grow, decreasing inflammation, boosting immune function, and promoting healthy blood vessels [130, 131]. MiR-126 has a significant impact on cancer progression and exercise benefits. It can both hinder harmful pathways and promote tissue repair and vascular health when upregulated through exercise. This highlights its potential as a biomarker for tailoring exercise interventions in cancer prevention and treatment, aiding in personalized regimens and monitoring treatment progress. Table 1 summarizes the how miR-126 acts in cancer and exercise.

Several specific signaling pathways regulated by miR-126 in both cancer and exercise offer deeper insight into this molecular connection. The MAPK/ERK pathway plays a significant role in cell proliferation, differentiation, and survival, all of which are critical in cancer progression [132, 133]. MiR-126 has been shown to modulate the MAPK/ERK pathway by regulating key proteins involved in the signal transduction process. In the context of exercise, this pathway is crucial for adaptive responses such as muscle repair and growth. In cancer, dysregulation of MAPK/ERK signaling often leads to uncontrolled cell growth and survival, contributing to tumorigenesis. By modulating this pathway, miR-126 may help suppress tumor cell proliferation while promoting the reparative effects of exercise on tissues.

Another important pathway influenced by miR-126 is the PI3K/Akt pathway, which regulates cell metabolism, survival, and angiogenesis. In cancer, the overactivation of the PI3K/Akt pathway is commonly associated with enhanced tumor growth and resistance to therapy [134, 135]. MiR-126's ability to suppress PI3K and Akt expression can hinder cancer progression by inhibiting these pro-survival and pro-metastatic signals [125, 136]. In the context of exercise, PI3K/Akt signaling is involved in skeletal muscle adaptation, including muscle growth and vascular remodeling, which supports improved tissue oxygenation and function [137, 138]. Therefore, miR-126-mediated regulation of this pathway highlights its potential to balance the promotion of tissue repair through exercise and the suppression of tumorigenic signals in cancer.

The Notch signaling pathway, which is vital for maintaining cellular differentiation and tissue homeostasis, also plays a significant role in both cancer and exercise. In cancer, aberrant activation of Notch signaling can contribute to tumor cell proliferation and metastasis [139, 140]. MiR-126 has been shown to regulate Notch signaling, potentially inhibiting its pro-tumorigenic effects

while supporting the reparative processes involved in endothelial function during exercise [141]. This pathway is critical in angiogenesis, and miR-126's regulation of Notch could help balance angiogenic responses, enhancing exercise-induced vascular repair and limiting tumor-associated angiogenesis in cancer.

Furthermore, the TGF-β (Transforming Growth Factor Beta) pathway is involved in cancer metastasis through EMT, which allows cancer cells to gain migratory and invasive properties [142, 143]. MiR-126's involvement in regulating the TGF-β signaling pathway, particularly through the modulation of Smad proteins, could be pivotal in preventing EMT in cancer cells, thereby hindering metastasis [142, 144]. During exercise, TGF-β signaling also plays a role in tissue remodeling and repair, and miR-126's ability to regulate this pathway may facilitate the repair of endothelial damage caused by physical activity.

Although there have been some promising findings, current research still has notable shortcomings. The impact of miR-126 on various types and stages of cancer is not yet fully comprehended, and the inconsistency in exercise methods used in studies makes it difficult to apply the results broadly. Additionally, while animal studies have shed light on the mechanisms involved, applying these findings to humans is complicated by physiological and biological distinctions. A major drawback is the lack of extended research that can definitively prove the relationship between miR-126 expression induced by exercise and its impact on cancer prevention or treatment.

To tackle these obstacles, future studies should prioritize thoroughly examining the expression of miR-126 in various cancers, at various stages and with diverse genetic compositions. Additionally, it is crucial to establish standardized exercise routines that cater to individual fitness levels, cancer conditions, and coexisting health issues in order to attain reliable and consistent outcomes. Furthermore, there is a limited clinical and in human studies in this field which limits the utility of this miRNA as a biomarker or therapeutic target. Conducting cohort and clinical trial studies for investigating the changes in the expression of miR-126 in cancer and exercise, respectively, are suggested for better implementation of these findings in human.

More research is required to fully comprehend the specific molecular processes that connect miR-126, physical activity, and cancer. Emphasis should be placed on their effects on TME and immune reactions. Conducting comprehensive clinical trials is essential to determine whether miR-126 can be a reliable indicator for exercise interventions, including its ability to predict treatment outcomes and track disease progression. Furthermore, examining the possibility of using miR-126-targeted treatments or gene therapies as alternatives to exercise may provide choices for those who are unable to engage in physical activity due to advanced cancer or other limitations.

Combining various methods of studying genes and proteins, along with long-term observations, can improve our knowledge of how exercise and miR-126 interact with cancer. As we continue to study this, miR-126 may be recognized as a key factor connecting healthy habits and cancer at the molecular level. MiR-126 has the potential to bridge existing knowledge gaps and open up new possibilities for personalized approaches in cancer prevention and treatment. These approaches could incorporate both exercise and molecular interventions, leading to improved outcomes for patients.

Conclusion

In conclusion, miR-126 serves as a pivotal link between exercise and cancer, influencing key signaling pathways involved in tumor suppression, angiogenesis, and tissue repair. This miRNA holds potential as both a biomarker for monitoring cancer progression and a therapeutic target for personalized treatment strategies. Future research should focus on mechanistic studies, clinical trials, and standardized exercise protocols to further elucidate miR-126's role in cancer prevention and treatment. As our understanding of miR-126 deepens, it may offer valuable opportunities to combine lifestyle interventions with molecular oncology, ultimately leading to improved patient outcomes.

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Declarations

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