Chapter

A Landscape of Epigenetic Regulation by MicroRNAs to the Hallmarks of Cancer and Cachexia: Implications of Physical Activity to Tumor Regression

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Abstract

In the last decades, there has been a remarkable advance in the treatment of most types of cancer, improving the patient's prognosis. During cancer progression, tumor cells develop several biological changes to support initiation, proliferation, and resistance to death. Nearly 50–80% of all oncologic patients experience rapid weight loss that is related to ~20% of cancer-related deaths. Cancer cachexia is a syndrome characterized by loss of skeletal muscle mass, anorexia, and anemia. A lot of effort in scientific investigation has contributed to the understanding of cancer processes, in which epigenetic changes, as microRNAs, can influence cancer progression. Therefore, useful strategies to control the cancer-induced epigenetic changes in the tumor cells can have a key role in a clinical perspective to decrease the cancer development and aggressiveness. Physical activity has been proposed as a suitable tool to manage tumor growth and cachexia and to improve the deleterious sequelae experienced during cancer treatment. Although the molecular mechanisms involved in these responses are poorly understood, this chapter aims to discuss the role of microRNAs in the cancer-induced epigenetic changes and how physical activity could influence the epigenetic control of tumor cells and cachexia and their potential role in clinical applications for cancer.

Keywords: epigenetic, cancer, hallmarks of cancer, cachexia, physical activity, tumor progression, microRNAs

1. Introduction: hallmarks of cancer, genetics and epigenetics

In the last decades, there has been a remarkable advance in the treatment of most types of cancer, improving the patient's prognosis [1]. However, cancer remains the second major cause of death in the world and major cause of death in the rich countries [2, 3]. Cancer consists in a set of diseases characterized by the progressive accumulation of mutations in the cell. These mutations provide changes in

the intracellular environment that induce advantages for its proliferation as well as greater resistance to mechanisms of cell death. A dysfunctional cluster of these cells is classically known as tumor. Currently, cancer is understood as a microenvironment, in which the interactions between the cellular elements that compose it are determinants for the progression of the disease. For example, such elements would be involved in the interaction of tumor cells with normal cells such as fibroblasts, adipocytes, immune system cells, and endothelial cells [4–6]. All these cellular interactions support the development of cancer cachexia, which affects approximately 50–80% of cancer patients, and more than 25% of cancer deaths are a direct consequence of cachexia [7]. Cancer cachexia is directly related to a reduction in tolerance to physical effort [8], a reduction in tolerance to cancer treatments [9], and a shorter patient survival [10].

During cancer progression, tumor cells develop a number of important biological changes to support initiation, proliferation, and resistance to death known as cancer hallmarks [5, 6]. Hanahan and Weinberg [5, 6] discuss 10 biological capabilities acquired by tumor cells that may be common among the different neoplasms and are important for the development and growth of the tumor mass, namely: (1) sustaining proliferative signaling, (2) loss of growth suppressors, (3) resisting cell death, (4) enabling replicative immortality, (5) inducing angiogenesis, (6) activating invasion and metastasis, (7) genome instability, (8) inflammation, (9) reprogramming of energy metabolism, and (10) loss of immune destruction [5, 6]. Among the 10 cancer-related biological processes, we point out that 6 are of fundamental importance for tumor mass growth.

1. Sustaining proliferative signaling

   In normal tissues, there is a careful control of the release of growth and proliferation factors for the regulation of the cell cycle, which ensures adequate tissue architecture and function. However, tumor cells show abnormal proliferation signaling, which promote exacerbated cell proliferation that generates morphological and functional tissue disarrangement. Some mutations are shown as probable causes of a normal cell to initiate a sustained proliferation and tumorigenesis. For example, mutation of *PIK3CA* gene and tyrosine kinases are mutations well described that promote sustained proliferation of a tumor cell [11].

2. Loss of growth suppressors.

   Tumor cells bypass growth suppressor signals through the escape of mechanisms that negatively control cell proliferation. Usually, tumor cells show loss of *p53*, a well-known tumor suppressor that controls proliferation, senescence, and cellular apoptotic programs, culminating in the uncontrolled growth of tumor cells. Tumor cells must also bypass powerful programs that negatively regulate cell proliferation; many of these programs depend on the actions of tumor suppressor genes [12].

3. Resisting cell death.

   Over the past few decades, the literature has shown that apoptosis-programmed cell death serves as a natural barrier to the development of cancer. Apoptosis is triggered in response to various physiological stresses that tumor cells undergo during the course of tumorigenesis or as a result of antineoplastic therapies. However, tumor cells have the ability to resist apoptosis and subsequently progress to conditions of malignancy and resistance to therapy [5].

4. Enabling replicative immortality.
   In healthy tissues, most normal cells have growth and cell division capacity controlled, but tumor cells have unlimited replicative potential, which favors the development of tumors [5].

5. Inducing angiogenesis.
   In any tissue, the presence of vessels allows both the uptake of nutrients and oxygen and the release of substances not useful for the cells. Moreover, angiogenesis occurs temporarily in response to some stimulation such as healing and the female reproductive cycle, being a transient process. However, this process is sustained and dysfunctional, since new vessels that present less coverage of pericytes appear continuously, favoring tumor growth [5].

6. Activating invasion and metastasis.
   Tissue invasion and metastasis are probably the most relevant features developed by tumor cells, since the major cause of cancer death is associated with the formation of metastatic tumors. Metastasis is the formation of a new tumor, originating from the primary tumor. This is a complex process in which primary tumor cells invade blood and lymphatic circulation, spreading and forming colonies at distant sites from the primary tumor [13].

To reach the circulation and invade distant tissues, tumor cells need to modify their configuration and undergo a process named epithelial-mesenchymal transition (EMT). Thus, tumor cells with epithelial characteristics deactivate the mechanisms of cell adhesion and acquire locomotor properties, becoming able to infiltrate the stroma and have access to blood and lymphatic vessels [14, 15]. Moreover, for the colonization of tumor cells in distant tissues, the preparation of the "*premetastatic niche,*" which corresponds to the preparation of the metastatic tissue target of the tumor cells, is fundamental. The process of formation of the *premetastatic niche* involves an intricate cellular signaling at the systemic and local level, involving tumor-secreted factors and tumor-shed extracellular vesicle interaction [16]. Additionally, although Hanahan and Weinberg [5, 6] demonstrate possible treatments against hallmarks of cancer, the individual response to various treatments is still unpredictable [17, 18], demonstrating the plasticity of tumor cells [19–23]. The understanding of *premetastatic niche* is a new paradigm for the initiation of metastasis that can enable the clinical body to fight metastasis, and would benefit greatly from understanding the pathological processes occurring before the development of macrometastases [24].

2. Epigenetics and cancer

Cancer is considered a typically genetic disease; however, epigenetic modifications play an important role in the development and progression of cancer [5, 6, 25–27].

The term "epigenetics" was originally described by Conrad Waddington to describe hereditary changes in a cell phenotype that were independent of changes in DNA sequence [28].

Epigenetic modifications reflect a complexity of factors that determine the condensation state of chromatin, which determines whether the DNA is accessible to proteins that control gene transcription. A relaxed or "open" chromatin state allows gene transcription, while a condensed or "closed" chromatin condition prevents gene transcription [25, 26, 28–31]. Epigenetic mechanisms currently believed to play a role in the development of cancer include: (1) DNA methylation of cytosine bases

in CG-rich sequences, called CpG islands; (2) posttranslational modification of histones (proteins that form the nucleosomes), which regulate the packaging structure of DNA (called chromatin); and (3) microRNAs (miRs) and noncoding RNAs [25, 26, 28–31].

Although DNA methylation and histone modifications are important components of epigenetic regulation [25, 26, 28–31], here we will focus on the role of alterations in miRs expression, since their expression is regulated through various mechanisms, including epigenetic modifications, and because their functions are aberrant in cancer, boosting the progression of the disease.

3. MicroRNAs

MiRs are a class of molecules that have an important role in the regulation of protein expression, even after the transcription of messenger RNA (mRNA).

MiRs are characterized as small RNAs of approximately 17–22 nucleotides, noncoding proteins, that act by binding to the mRNA, repressing the translation of proteins. MiRs are found in several organisms as animals and plants and control a lot of physiological and pathological processes. Evidence shows that at least one-third of all biological processes are controlled by miRs [32].

This class of molecules was first observed in 1993 by Lee et al., which demonstrated that miR *lin-4* was associated with larval development of *C elegans* [33]. Although the discovery of the first miR occurred in 1993, miRs researches only progressed in the year 2000, when miR *lin-4* was found to participate in the posttranscriptional control of *lin-14* protein through the complementary binding of miR with the 3' untranslated region (3'UTR region) of the protein mRNA [34]. After the pioneering study by Hong et al., many studies have been developed to demonstrate that small RNAs could participate in posttranscriptional controls. Thus, Ambros observed that miR *let-7* had a partially complementary binding to the 3'UTR region of the *lin-4* protein mRNA, negatively controlling its protein expression [34, 35]. These findings led to the discovery of new miRs, and more than 30,000 mature miRs are now known in the most diverse organisms [32].

As mentioned, miRs exert their action through partially or totally binding to the 3'UTR region of the target mRNA. The complete complementarity induces the degradation of the mRNAs, being commonly observed in plants. In mammals, there is partial complementarity, which inhibits the translation of the target transcript [36].

The miRs bind their *seed* region, that in mammals comprises 2–8 nucleotide, with the target mRNA, present in the 3'UTR region, where only some of the base pairs are complementary. Due to the imperfect pairing and small size of these molecules, there is the possibility of an miR presenting various targets [36].

The biogenesis of miRs begins with the action of the enzyme RNA polymerase II that generates a primary transcript called pri-miR. The pri-miR has a hairpin double helix structure with approximately 300 nucleotides. Still in the cell nucleus, the Drosha enzyme and its cofactor DGCR8 cleave the pri-miR, forming its precursor, the pre-miR. The pre-miR is exported to the cytosol by the exportin 5 enzyme. In the cytoplasm, the pre-miR is cleaved by the enzyme dicer, originating two strands together, one being the mature miR and the other called an antisense. Dicer cleaves again and separates the duplex. The mature miR is then incorporated by a multimeric complex named RISC that contains argonaute protein (AGO) as showed in **Figure 1**, while the other strand can be degraded or incorporated in other RISC complex to exert negative regulation of target mRNAs [32].

Recently, the interest in the study of miRs has increased, since they exert a paracrine function and are effective in the tissue communication. Also, an miR can exert the same function on different cell types, as different function in the same cells. In 2008, the presence of miRs in plasma and other biological fluids was discovered, demonstrating that miRs are viable in the extracellular environment and important signaling molecules. There are circulating miRs in almost all biological fluids, including: milk, plasma, serum, saliva, urine, tear, and amniotic fluid [37]. Circulating miRs are remarkably stable, resistant to RNase activity, freeze-thaw cycles as well as extreme pH. This stability is associated with the carriers that carry them and can be secreted by the cells through different vesicles such as exosomes, HDL, or AGO proteins containing apoptotic bodies [37].

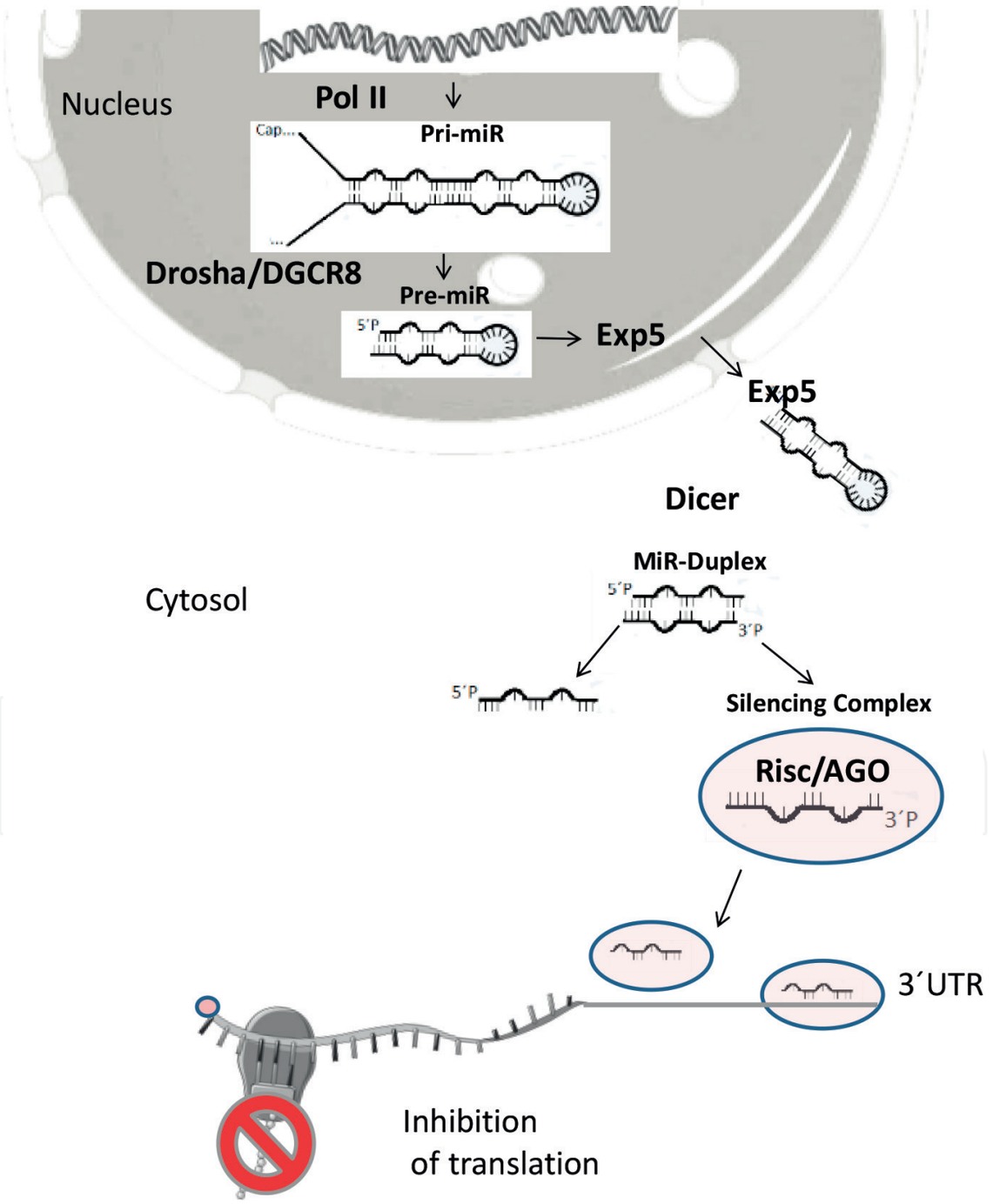

Figure 1.
Canonical pathway of biogenesis of miRs [31]. https://smart.servier.com/image-set-download/.

4. microRNAs and cancer

The miRs play a key role in the control of various physiological and pathological processes. Many studies demonstrate the participation of miRs during the progression of several types of cancer. MiRs present altered expression in tumors, and many studies are being conducted with this new class of molecules to elucidate their role in controlling the pathophysiology of the disease [36, 38, 39].

There is evidence that miRs are also involved in regulation of hallmarks of cancer and thus in the progression of cancer [5, 15]. In view of this, there is an effort by the scientific community to understand the mechanisms involving miRs and the development of cancer aiming to develop cancer-specific gene therapies [40]. The aim of these efforts is to improve responses to conventional drugs for the cancer treatment, specifically suppress oncogenic processes, and improve the prognosis of the disease.

The *miR-124* was one of the first studied miRs involved in the pathogenesis of cancer [41]. *MiR-124* was silenced in more than 10 types of cancer, as breast, colorectal, liver, and lung cancer. This silencing promotes increased expression of *CDK6*, which affects the phosphorylation state of *Rb* protein, favoring tumor progression [42]. Other miRs silenced are *miR-9-1* and *miR-9-3*. When analyzing the expression of *miR-9-3* in primary and metastatic tumors, it was observed that metastatic tumors have a lower expression of *miR-9-3*. Also, patients with lower *miR-9-3* expression in the tumor have a lower survival rate than patients with higher expression of *miR-9-3* [43].

Garzon et al. [40] observed that there is a decrease in *miRs-15a/16* expression in patients with chronic lymphoid leukemia and in chronic lymphocytic leukemia tumor cells CLL23. Thus, the authors ectopically increased the expression of *miRs-15a/16* in CLL23 tumor cells and investigated the processes of proliferation and apoptosis. It was observed that with the increase of *miRs-15a/16* expression in CLL23 tumor cells, there is a higher apoptosis and less cellular proliferation. This response occurs because *miRs-15a/16* target *BCL-2* protein, an important antiapoptotic factor. *BCL-2* is known to be increased in tumors of cancer patients [40].

Moreover, *miR-34* has been shown to be downregulated in pancreatic cancer. The overexpression of *miR-34* in these cells increases apoptosis and inhibition of autophagy, reducing tumor growth [44]. Another example is the miR *Let-7* family, which targets *HRAS* and *HMGA2* as well as participates in the regulation of proliferation and cell cycle. *Let-7* family members are also negatively regulated in various types of cancers, and their overexpression results in inhibition of tumor growth in different cancer models [45, 46]. This is due to the fact that *Let-7* targets the major components of cell cycle progression, such as *KRAS*, *CCDN1*, *CDC34*, *HMGA2*, *E2F2,* and *Lin28* [45, 46].

In contrast, miRs may also be increased in cancer and their biological effects may potentiate the development of the disease. For example, the case of *miR-21* has a high expression in tumors of glioblastoma, pancreatic cancer, breast cancer, and colon cancer. Inhibition of *miR-21* in glioblastoma cells was able to increase caspase activity and promote apoptosis of tumor cells. One possible explanation is that *miR-21* targets *PTEN* protein and *PDCD4* protein, functioning as an antiapoptotic agent in cancer [47].

MiRs are also involved in several other cancer factors, such as in the formation of metastases. Zhou et al. [48] observed that *miR-105* is involved with preparation of the "premetastatic niche." The authors demonstrated that animals with breast cancer exhibit high levels of *miR-105* expression in both tumor and circulation and that elevated *miR-105* levels in the circulation promote the destruction of endothelial barriers and increase vascular permeability in the target metastatic organ. Inhibition of *miR-105* in tumor cells from highly metastatic breast cancer prevented the development of

metastasis [48]. Another miR associated with metastasis formation is the family of *miR-200*. The 200 family plays a role in repress proteins that promote the epithelial-mesenchymal transition. However, its expression is reduced in tumors in response to increased expression of the *long noncoding RNA ATB* that competes with the miRs binding site of the 200 family, reducing its expression and function, which favors the negative regulation of *E-cadherin* and increase of *ZEB* proteins expression [49]. The current involvement of miRs in the hallmarks of cancer is elucidated in **Figure 2**.

4.1 Physical activity as nonpharmacological therapy

Although in recent time cancer treatments have evolved considerably, there are still no responsive patients to the treatments, which suggest the need for strategies to reduce the incidence and aggressiveness of cancer. At same time, *American Cancer Society* recommends to cancer survivors the participation in 150 min of moderate intensity exercise per week. There is evidence that physical activity improves quality of life, treatment response, decreases cancer recurrence due physical fitness improvement of patients, and survivors [50]. In the present moment, there is strong academic effort in clinical trials being performed, investigating about perspective and limitation of inclusion physical activities in the cancer therapy. The main investigations focus in physiological aspects and appropriate modalities and methods [51–53].

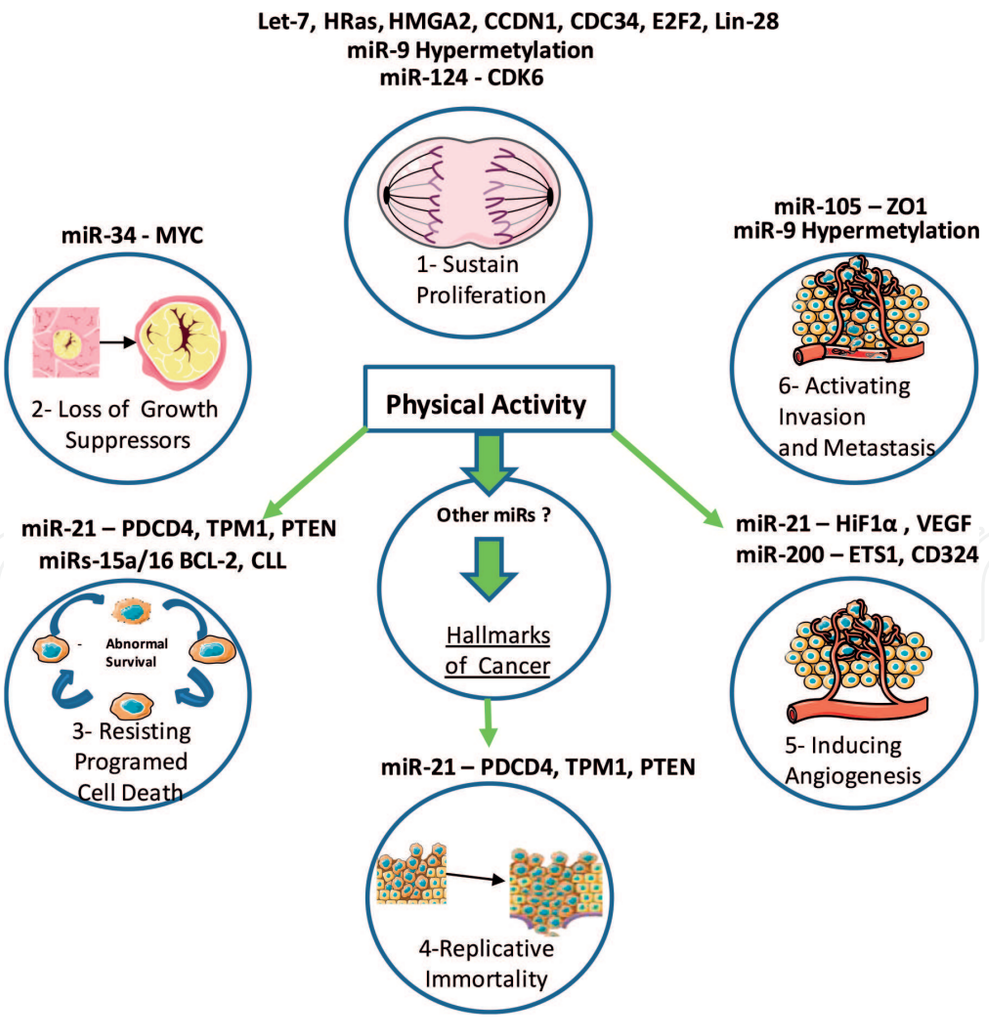

Figure 2.
Landscape of investigative field involving miRs, molecular basis, and the hallmarks of cancer. Currently, among the miRs related to the cancer hallmarks, only miR-21 and its target, the mRNA of PDCD4, PTEN, TPM1, HIF1α and VEGF was established the beneficial relationship with the effects of physical activity in the tumor (thin green arrows) [43–49, 83, 84]. https://smart.servier.com/image-set-download/.

Physical fitness is the ability to perform daily tasks with vigor and alertness, without excessive fatigue and with energy to enjoy leisure activities and to meet unforeseen emergencies [54]. It is known that physical activity induces beneficial adaptations to the body, improving physical fitness [55]. Physical activity encompasses both physical exercise with controlled volume, intensity, and duration or recreational activities [56]. There is evidence that support the importance of maintaining a physically active life for health. Healthy individuals or cardiovascular patients who have low physical capacity tend to have a lower survival rate [57]. Corroborating with these clinical and epidemiological data, experimental results show that rats with high capacity to run present a higher survival (~45%) when compared to those that have low capacity to run [58, 59]. Regular physical activities are recognized as nonpharmacologic preventive approach and treatment for chronic diseases [60–62], including cancer [63–65]. Several studies also demonstrate that aerobic physical activity normalizes the expression of aberrant miRs due to diseases such as myocardial infarction, hypertension, diabetes, and obesity. That these pathologies induce molecular and structural alterations and aerobic physical exercise is a beneficial stimulus for the reversal and control of these deleterious alterations such as muscle mass decrease and microvascular rarefaction [66–69].

4.2 Physical activity, cancer, and microRNAs: new perspectives

There is evidence that aerobic physical activity reduces the incidence of several types of cancer [65]. Moore et al. [65] demonstrated that regular physical activity resulted in decreased incidence of 13 types of cancer in 26 analyzed in 1.44 million adults. The individuals involved with higher daily volumes of physical activity presented decrease in the incidence in esophageal adenocarcinoma, myeloid leukemia, myeloma, liver, lung, kidney, gastric, endometrial, colon, head and neck, rectal, bladder, and breast cancer. The effects of physical activity on reducing the incidence of cancer were independent of other factors such as body mass index (BMI), smoking, geographical region, use of hormonal therapy, and ethnicity [65]. Cancer patients with reduced physical capacity have a worse prognosis [70–72]. Colon cancer patients have a reduction of more than 20% in maximal oxygen consumption (VO_2 máx.) compared to their healthy peers [71]. Patients with lung cancer and colon cancer with greater physical capacity present a higher survival compared to patients with lower physical capacity [73]. Aerobic physical activity attenuates tumor growth in different animal models [74–78]. However, the molecular mechanisms involved in this response are poorly understood. Recently, Pedersen et al. [79] showed that 4 weeks of prior voluntary physical activity was able to delay tumor initiation and attenuate tumor growth in various cancer models in mice and was also efficient in decreasing the formation of metastatic nodules. The authors demonstrated that physical activity increases the mobilization and redistribution of NK cells to the tumor microenvironment due to the systemic increase of *IL-6* and epinephrine induced by physical activity. This increase of immune response in the tumor microenvironment was proposed as the main mechanism induced by aerobic physical activity for the attenuation of tumor growth [79]. Betof et al. [77] also demonstrated that previous aerobic physical activity is capable of attenuating tumor growth in the 4T1 breast cancer model. The authors demonstrated that aerobic physical activity increased the pericytic coverage of tumor vessels and apoptosis of tumor cells, provided a greater functional neo-vascularization on the tumor endothelium, and consequently reduced the hypoxia regions in the tumor microenvironment [77]. Pigna et al. demonstrated that aerobic physical activity is also efficient in increasing the survival of animals injected with C26 (colon cancer) tumor cells lineages [80].

However, it is important to note that only two of the studies that observed attenuation of tumor growth induced by aerobic physical activity investigated the role of miR in this response, both in mice breast cancer injected with MC4-L2. Khori et al. observed that aerobic physical activity was efficient in reducing *miR-21* gene expression in animal tumors, inhibiting proliferation and migration of tumor cells. In addition, the *miR-21* downregulation was associated with increase of gene and protein *PDCD4* expression and *TPM1*, two tumor suppressor genes [81]. Isanejad et al. [82] also demonstrated that aerobic physical activity reduces tumor growth and increased the gene expression levels of *miRs-206* and *let-7* in the mammary tumor. Moreover, exercise-increased expression of *miR-206* and *let-7* decreased in the levels of gene expression of *HIF-1α*, *CD31*, and *VEGF* in mice, suggesting an anti-angiogenic effect, which contributed to the decrease of tumor angiogenesis and growth [82]. Both Khori et al. and Isanejad et al. observed involvement of miRs in the aerobic physical activity response, which enhanced the effects of treatment with tamoxifen and letrozole, respectively, on tumor growth and molecular responses [81, 82].

These results indicate the potential of physical activity in modulating the decompensated miRs in the tumor. Also, we can point to the potential of physical activity to an improved miRs profile in the tumor, and their direct role in the reduction of the tumor growth and aggressiveness. However, currently there is a gap in elucidating about the global molecular mechanisms by which physical activity induces the phenotypical improvement. Therefore, the interaction between cancer, miRs and the effect of physical activity in the several cancer types is a promisor field of investigation that certainly will develop a lot of knowledge about preventive, therapeutic, as well as the mechanisms by which physical activity acts is cancer.

5. Cancer cachexia

Cancer cachexia (CC) is a multifactorial syndrome characterized by continuous loss of muscle mass that can be conjugated or not by loss of fat mass. CC cannot be completely reversed by conventional nutritional support and leads to progressive functional disability [83]. The pathophysiology of CC is characterized by a negative protein balance, anorexia, and metabolic abnormalities [84]. CC individuals usually present with muscle weakness, asthenia and poor response to anticancer treatment, all of these processes contributes to patient mortality [85, 86].

Muscle atrophy in CC results from the imbalance in protein turnover due to exacerbated proteolytic activation, reduction of protein synthesis pathways, and reduced regenerative capacity in skeletal muscle [87, 88].

In this context, it is essential to understand the role of epigenetic factors in the loss of muscle mass in CC. There is massive evidence that epigenetic factors, for example histone acetylation, DNA methylation and miRs orchestrate processes such as muscle proliferation and differentiation, as well as skeletal muscle regenerative capacity [89–92]. To elucidate about the epigenetic factors that lead to the loss of muscle mass in CC also may contribute to the emergence of new therapies for the prevention and treatment of the syndrome.

In this section, we will approach about the role of miRs in the regulation of muscular trophism. Skeletal muscle presents a set of miRs that are enriched in this tissue and mediate mechanisms of proliferation, differentiation, and protein synthesis. These miRs are known as myomiRs [32]. The most studied myomiRs are the *-133a/b*, *–206,* and *–1 miRs*. These miRs are known to display target genes such as *IGF-1R*, known hypertrophic pathway promoters [32] and *PAX3* and *PAX7*, genes that regulates proliferation of satellite cells [93]. In another view, there are many

studies showing the role of several other miRs orchestrating prohypertrophic and procatabolic genes in the skeletal muscle [32, 94].

Interesting advances have been made in studies about the of role skeletal muscle enriched miRs in CC. Lee et al. [95] conducted a study in order to investigate the profile of miRs expressed in skeletal muscle of cachectic mice. The researchers performed a sequencing of the anterior tibial muscle of LLC tumor-bearing mice, animal model of orthotopic lung cancer, and compared them to healthy mice. The *miRs-147-3p*, *–299a-3p*, *1933-3p*, *511-3p*, *3473d*, *233-3p*, *431-5p*, *665-3p*, and *205-3p* were found to be differently expressed. Genetic ontology analyzes of these miRs indicate a relationship with cellular survival pathways, inflammatory response, cell cycle, cell development, and cell morphology through crosstalk of several pathways, with target genes such as *FOXO3*, *HRAS*, *P38*, *MAPK*, *MYC,* and *EIF4E*. We can note that *HRAS* and *MYC* are also related to hallmarks of cancer [95].

Narasimhan et al. [96] conducted another study evaluating the profile of miRs in muscle tissue of CC patients. In this study, human rectal abdominal muscle samples were collected during the tumor resection surgery of colon and pancreatic cancer patients. Sequencing analyzes demonstrated that eight miRs were differentially expressed between cachectic individuals and controls. The miRs let-*7d-3p*, *3184-3p,* and *–1296-5p* were selected and these miRs were increased in cachectic patients relative to controls. The authors performed *in-silico* analyzes and pointed out that these miRs targets genes related to adipogenesis, myogenesis (*SULF1* and *DLK1*), inflammation, and immune response (*RPS6KA6*) [96].

The loss of fat mass is not present in all cases of CC; however, the role in energy metabolism of adipose tissue in CC is important. Therefore, studies are being conducted to understand the function of miRs in maintaining of adipose tissue in cachetic state. Kulyté et al. [97] conducted a sequencing analyzes of miRs in adipose tissue of cachectic and noncachectic gastrointestinal cancer patients, the authors found difference in expression of nine miRs between cachectic and noncachectic patients. *MiR-378* was selected due to an increased expression in the adipose tissue of cachectic patients compared to noncachectic patients. The inhibition and overexpression of *miR-378* on human adipose-derived stem cells were performed; overexpression of *miR-378* decreased expression of the *HSL*, *PLIN1*, and *ATGL* protein and consequently increased lipids catabolism and release of glycerol [97].

MiRs are also present in body fluids such as saliva, tear, and blood. In this sense, studies are being conducted with the purpose of understanding the role of circulating miRs in CC. Okugawa et al. [98] showed that the expression of circulating *miR-21* increases in the patients with cachectic colon cancer; however, the expression of *miR-21* is not different in the skeletal muscle in compared to noncachectic patients [98]. The circulating miRs can be studied as biomarkers for some pathological processes. Studies in humans and animals have looked for miRs that are biomarkers in order to early diagnose CC [94]; however, it should be noted that many of these miRs are not widely accepted as biomarkers by the medical and scientific community and some are not even validated in humans [96].

The role of *miR-21* in CC was also investigated by He et al. [99], which showed that *miR-21*-enriched exosomes were found in the circulation of pancreatic and lung cancer patients. Myoblast cells cultures treated with these *miR-21*-enriched exosomes showed an interaction of the microvesicle with the muscle cells that induced cell death via *TLR8* protein, an endosomal receptor that recognizes single-stranded RNA (ssRNA), and can recognize ssRNA viruses such as Influenza, Sendai, and Coxsackie B viruses. *TLR8* is a protein binding to RNA and is able to recruit *MYD88* and leads to activation of the transcription factor *NF-κB* and an antiviral response. *TLR8* agonists have undergone clinical trials as immune stimulants in combination therapy for some cancers [99].

There are few studies showing a direct association of the action of miRs and their targets about processes involved in the progression or reversal of CC. The issue promises a great field for development of results that can be clinically relevant and useful in the future. Additionally, skeletal muscle is highly responsive to both physical activity and CC, and investigation of skeletal muscle-enriched miRs and the effect of physical activity and exercise in these miRs are promising to elucidate about CC. The next section will cover this topic.

5.1 Relationship between physical exercise and the mediators of cachexia

There is massive evidence that support the importance of maintaining aerobic fitness for health. Low aerobic fitness is an independent indicator of early death in individuals with cardiovascular and/or healthy individuals [57]. The physical training regulates the expression of miRs in a profile that enables endurance performance and physical fitness. Aerobic exercise prevents a number of chronic-degenerative diseases [60], including cancer [65]. Resistance training increases muscle mass and strength and contributes to increased functional capacity [87]. Therefore, aerobic and resistance training are presented as a therapeutic potential for CC patients and presents an interesting field of investigation to clarify clinically relevant process related to CC. However, due to clinical difficulties and poor safety conditions, there is a lack in human studies about the role of physical exercise in CC patients. In this context, the use of animal models in well-controlled studies has shown that physical training may be promising in the treatment of CC. Oh et al. demonstrated that the C26, orthotopic colon cancer cachectic mice, when submitted to resistance training and aerobic training protocols presented lower muscle mass loss [100]. Partial preservation of muscle mass due to physical training is associated with higher expression of proteins such as *mTOR*, *IGF,* and *myogenin* in the trained C26 mice when compared to sedentary C26 mice [100]. Pigna et al. demonstrated that voluntary aerobic activity in C26 mice also improves the autophagy flow preventing skeletal muscle loss in association with autophagy regulatory drugs [80]. Baggish et al. showed for the first time that *miRs-21*, *miR-146a,* and *-133a* are candidates to be biomarkers of aerobic physical training in the circulation [101].

Skeletal muscle trophism is regulated by the action of some miRs, and exercise controls the expression of these miRs. As example, *IGF-IR* mRNA encodes *IGF1* receptor protein and is a target of *miR-133*. A study shows that *IGF-IR* overexpression results in increased PI3K-AKT-mTOR pathway that mediated muscle hypertrophy, in myocyte cell culture, and that knockdown of *IGF-IR* decreases the hypertrophic signal. *MiR-133* decreases the expression of *IGF-IR*, and consequently decreases *AKT* and *mTOR* phosphorylation, regulating the development of skeletal muscle [102]. Furthermore, aerobic physical exercise decreases the expression of *miR-133a* [103].

In conclusion, many studies show that both aerobic and resistance physical exercise control the expression of miRs that are dysregulated by diseases as hypertension, diabetes, and obesity [68, 69, 104, 105]. Physical exercise rebalances the expression of the miRs involved with those alterations reverses structural deleterious changes in the skeletal muscle and restores tissue or prevents deterioration [66]. However, there are no studies designing an miR profile from CC skeletal muscle and the prevention of muscle catabolism by physical exercise, which is interesting for future investigation.

6. Conclusions

The effects of physical activity as nonpharmacological adjuvant for cancer patients are effective to the disease and survivorship in cancer, since it improves

quality of life and decreases the recurrence of cancer. Currently, there are massive efforts to include exercise in the therapeutic approach to patients. Furthermore, studies show several benefits of aerobic physical activity in reducing the risk of incidence of cancer. Physical activity also reduces expenditures for public health agencies, both by decrease of cancer incidence and can attenuate the side effects or resistance related to anticancer treatment. However, little is known about the epigenetic, molecular, and cellular mechanisms involved in this response, both related to hallmarks of cancer, to cachexia process, and the comprehension about physical training effect in oncologic patients remains incipient.

Recently, the attentions of several areas of the scientific community have turned to miRs, epigenetic regulators in different cellular processes, as in tumorigenesis. To date, studies postulating the effects of aerobic physical activity on the modulation of decompensated miRNAs in the tumor and its potential as cancer gene therapy in cancer are rare. Thus, the identification of miRs modified by cancer of sedentary animals in comparison with trained animals can lead to the identification of miRs with therapeutic potential and elucidate about epigenetic mechanisms involved in physical activity therapy. However, it is necessary to better understand these mechanisms both in cell culture and in animal models of cancer in order to transpose into translational medicine in a whole approach. In this sense, extensive basic research is needed to elucidate these mechanisms in order to establish relationships about the role of miRs, the 10 biological capacities, the hallmarks of cancer, and if how these processes can be reversed by physical activity. Another interesting issue to be investigated is about the involvement of the miRs regulated by the physical activity in the CC and how these miRs are related to the 10 capacities and the hallmarks of cancer. These approaches can extensively clarify about cancer mechanisms and improve future physical activity therapy.

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Conflict of interest

No disclosures.

Abbreviations

3'UTR region	3' untranslated region
AKT	AKT serine/threonine kinase
AGO	argonaute protein
ATGL	patatin-like phospholipase domain-containing protein 2
BCL2	B-cell lymphoma 2
BMI	body mass index
CC	cancer cachexia
CCDN1	cyclin D1

CD324	cadherin 1
CDC34	cell division cycle 34
CDK6	cell division protein kinase 6
DGCR8	DiGeorge syndrome critical region gene 8 microprocessor protein
DLK1	delta like non-canonical Notch ligand 1
DNA	deoxyribonucleic acid
E2F2	E2F transcription factor 2
EIF4E	eukaryotic translation initiation factor 4E
EMT	epithelial-mesenchymal transition
ETS1	ETS proto-oncogene 1
FOXO3	forkhead box O3
HDL	high-density lipoprotein
HiF1α	hypoxia inducible factor 1 alpha
HMGA2	high-mobility group AT-hook 2
HRAS	HRas proto-oncogene
HSL	hormone-sensitive lipase
IGF	insulin-like growth factor
IGF-1R	insulin like growth factor 1 receptor
IL-6	interleukin 6
MAPK	mitogen-activated protein kinase
$VO_{2máx}$	maximal oxygen consumption
mRNA	messenger RNA
miR	microRNA
mTOR	mechanistic target of rapamycin kinase
MYC	Myc proto-oncogene
MyD88	myeloid differentiation primary response
NK cells	natural killer cells
P38	mitogen-activated protein kinase 14
PAX3	paired box 3
PAX7	paired box 7
PDCD4	programmed cell death protein 4
PTEN	phosphatase and tensin homolog
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PI3K	phosphatidylinositol-4,5-bisphosphate 3-kinase
PLIN1	perilipin 1
PDCD4	programmed cell death 4
RISC	RNA induced silencer complex
RPS6KA6	ribosomal protein S6 kinase A6
SULF1	sulfatase 1
TLR8	toll like receptor 8
TPM1	tropomyosin 1
VEGF	vascular endothelial growth factor
ZO1	tight junction protein 1

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