Effects of physical activity on cell-to-cell communication during type 2 diabetes: A focus on miRNA signaling

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Abstract

Type 2 diabetes (TD2) is a progressive disease characterized by hyperglycemia that results from alteration in insulin secretion, insulin resistance, or both. A number of alterations involving different tissues and organs have been reported to the development and the progression of T2D, and more relevantly, through cell-to-cell communication pathways. Recent studies demonstrated that miRNAs are considerably implicated to cell-to-cell communication during T2D. Physical activity (PA) is associated with decreasing risks of developing T2D and acts as insulin-like factor. Cumulative evidence suggest that this effect could be mediated in part through improving insulin sensitivity in T2D and obese patients and modulating miRNAs synthesis and release in healthy patients. Therefore, the practice of PA should ideally be established before the initiation of T2D. This review describes cell-to-cell communications involved in the pathophysiology of T2D during PA.

Keywords: Type 2 diabetes, physical activity, miRNA, extracellular vesicles, antidiabetic drugs.

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1. Introduction

Diabetes is one of the public health problems and commonly related to metabolic syndrome. It is characterized by hyperglycemia that results from alteration in insulin secretion, insulin resistance, or both [1]. The diagnosis of diabetes is based on a fasting blood glucose concentration above 7.0 mmol/L (126 mg/dL), a random blood glucose concentration above 11.1 mmol/L (200 mg/dL) with symptoms, or an abnormal result from an oral glucose tolerance test. Patients affected by this disease exhibit some symptoms such as fatigue, increased thirst, blurred vision, and frequent urination. The chronic hyperglycemia of diabetes is a major cause mortality resulting long-term failure of various organs and complications such as neuropathy, stroke, arteriopathy, heart attack and chronic kidney disease. Diabetes exists in several forms. The first is called type 1 diabetes (T1D) or insulin-dependent diabetes, usually occurs in childhood hence the name of juvenile diabetes. T1D is a chronic auto-immune disease characterized by insulin secretion deficiency due to pancreatic β-cell loss. More than 40 million people worldwide have T1D as it accounts for 5 – 10% of the total cases of diabetes [2]. The second is called type 2 diabetes (T2D), also known as non-insulin-dependent diabetes, which is the most common diabetes in the world with more than 462 million people affected by the pathology [3]. The global prevalence of T2D is currently estimated around 6000 cases per 100,000 and projected to increase to more than 7000 cases per 100,000 by 2030 [3]. T2D usually occurs after 40 years old and increases in frequency with age [1]. It is characterized by failure and dysfunction of pancreatic β-cells and insulin resistance. Another type is named gestational diabetes which develops commonly during the second or third trimester of pregnancy and usually disappears after delivery [3].

Although pharmacological treatment amelioration is still occurring, a steady rise in the prevalence of diabetes and its related diseases have been observed during past decades [4]. Thus, prophylactic approaches such as weight loss, the practice of physical activity (PA), healthy diet, limitation of alcohol intake, quitting smoking and control of blood pressure are now considered as a major interest. Today, sport in general stands out as a slogan due to its association with health. It is well known that regular PA acts as insulin-like factor and associated to a decrease of T2D incidence [5]. Furthermore, physical inactivity is an essential factor which contributes to the development and the progression of T2D [5].

Due to high socio-economic costs, T2D and its related diseases are actually the subject of particular attention. Therefore, an early prevention based on the practice of PA should ideally be established before the initiation of T2D. This prevention requires more investigations of pathways and mediators involved in the pathophysiology of T2D, particularly those mediated through inter-organ and cell-to-cell communications such as hormones, bioactive lipids, non-coding RNA.

Non-coding RNAs are small RNAs that do not encode for a protein. They include microRNAs (miRNAs), small nucleolar RNAs, long non-coding RNAs, circular RNAs, PIWI-interacting RNAs and other species of regulatory non-coding RNAs [6]. Initially considered to be non-functional, mi-RNAs recently appear to regulate signaling pathways. They are synthesized from primary miRNAs (pri-miRNAs) by two RNase III-family proteins located in the nucleus (Drosha) and in the cytoplasm (Dicer) [6]. The mature miRNAs are then bound by Argonaute subfamily proteins and induce RNA silencing of genes and their post-transcriptional regulations leading to changes in some cellular activities such as the metabolism of their targeted cells, the expression of proteins and

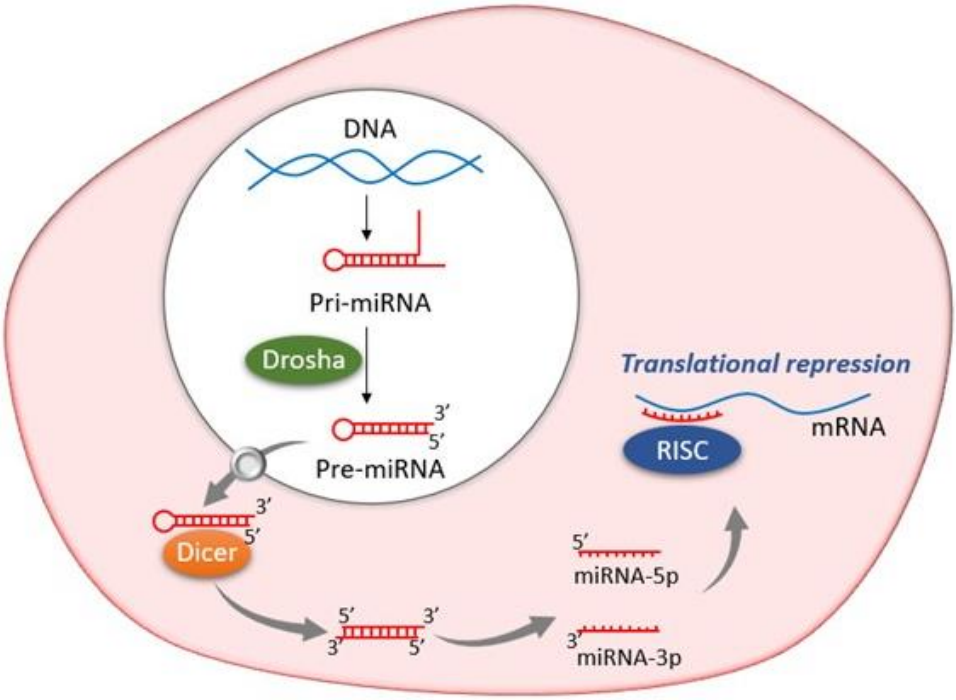

figure 1 : miRNA synthesis : miRNAs are synthesized from primary miRNAs (pri-miRNA) by two RNase III-family proteins located in the nucleus (Drosha) and in the cytoplasm (Dicer). The mature miRNAs are then bound to specific mRNA and lead to gene silencing.

signaling pathways involved in the proliferation, the differentiation, and apoptosis (Figure 1) [6]. This effect is mediated through the activation of large ribonucleoprotein assemblies, known as RNA-induced silencing complexes [7]. To avoid any redundancies or mis-annotations, miRNAs are named using numerical identifier (miRNA-XX) and followed in some cases by -3p or -5p according to which end of the miRNA they are found on. The 3' miRNA would be miRNA-XX-3p and the 5' miRNA would be miRNA-XX-5p [6]. Additional nomenclatures are used to differentiate pri/pre-miRNAs form mature miRNAs. Some circulating miRNA such as miR-28-3p, miR-501, miR-199a are reported to be upregulated in the bloodstream of T2D patients and have been suggested as biomarkers for T2D [8–10].

Most miRNA are carried by a group of cell-derived lipid bound membranous structures called extracellular vesicles (EV) [11,12]. Three subtypes of EVs have been described. Small EVs with a diameter less than 150 nm are called exosomes and released through multivesicular bodies using endosomal pathway in a similar manner to that of retroviruses. Microvesicles or ectosomes are small membrane-enclosed sacs ranging from 50 to 1000 nm in diameter that are thought to be shed from a variety of cell types. During apoptosis, cells release large EVs called apoptotic bodies with various sizes ranging from 0.5 to 10 μm in diameter that are hard to distinguish from other types of EVs. Circulating EV interact with specific target cells where they deliver their cargos including miRNA into the cytosol through ligand-receptor interaction, direct membrane fusion, phagocytosis, and clathrin-mediated endocytosis [11,12]. Proteomic and transcriptomic analysis revealed that EV contain specific proteins and nucleic acids derived from the parent cells and are used as biomarkers to evaluate physiological and pathophysiological responses related to cell and organs activities where they are generated [12,13]. For example, EVs have been suggested to be a biomarker of tumor progression and metastasis, early neurodegenerative

diseases or cardiovascular diseases [12,14,15]. The expression of some proteins such as tetraspanins (CD9, CD63, CD37, CD81, or CD82) are specially enriched in the membrane of exosomes, while β1 integrin receptors and vesicle-associated membrane protein 3 are generally carried by microvesicles [11,16].

In this review, we will (i) describe roles of organs implicated in glycemic control and the physiopathology of T2D, (ii) review the PA-induced modulation of miRNA expression and (iii) discuss the mediators involved in the benefic effects of PA in T2D with a focus on miRNA.

2. Circulating organ-specific miRNAs during T2D

Hundreds of miRNA, bioactive lipids, peptides, and hormones are described to play major roles in the physiopathology of T2D through modulations of molecular targets function, and their activation such as receptors, enzymes, transporters, ion channels, and nucleic acids [17,18]. This section is focused on the most important organs implicated in the physiopathology of T2D: pancreas, skeletal muscle, adipose tissue and liver.

Pancreas

During normal situations, pancreas synthetizes and releases hormones such as insulin, glucagon, somatostatin, and pancreatic polypeptide. Insulin is released by β-cells clustered in the islets of Langerhans and stimulates the storage of glucose in fat, muscle, liver and other body tissues. A progressive decline of insulin synthesis by the pancreas and alteration of insulin cell signaling represent the most causes of the onset of T2D [19]. In addition to insulin, pancreas communicates with other organs through the release of glucagon. This hormone is produced by α-cells present in the islets of Langerhans. It has the opposite effect to insulin, by raising glycemic levels. Glucagon acts on the liver and activates glycogen hydrolysis into glucose [19].

Exposure to some features of the T2D microenvironment was associated with dysregulation of miRNA synthesis in pancreatic β-cells. A part of these miRNA has been shown to act on other cells and organs. Zhang et al. showed that miRNA-29, miRNA-375, miRNA-223, miRNA-26, and miRNA-143 were two to three times increased in the medium of cultured pancreatic β-cells after high glucose stimulation [20]. Among these miRNAs, miRNA-223 secreted by pancreatic β-cells has been identified to stimulate GLUT-4 expression in skeletal muscles and liver tissues of ob/ob mice and consequently favored insulin sensitivity [20]. In addition, Werneck-de-Castro JP et al. recently showed that high glucose treatment up-regulates miRNA-199 expression in β-cells [21]. This miRNA has been shown to negatively impact β-cell function and regulate the myosin heavy chain protein levels in myoblasts [22]. These *in vitro* and *in vivo* data suggest that quantification of serum miRNA released by pancreatic β-cells could be used as biomarker to assess early diabetes-associated β-cell dysfunction before onset of disease[8].

Skeletal muscle

Skeletal muscle is one of the main predominant organ of insulin-mediated glucose uptake, and is thereby directly involved in the physiopathology of T2D. Skeletal muscle synthetizes a group of mediators called myokines [23] that allow to communicate with different organs such as adipose tissue, intestine, liver, and pancreas [24]. Among these myokines, interleukin-6 (IL-6) is produced in response to muscle contractions and regulates glucose intake and energy metabolism [25]. IL-6 has been shown to increase insulin-stimulated glucose disposal, fatty acid oxidation, glucose transport, and GLUT-4 translocation to the plasma membrane in myotubes [26]. Other studies showed a relationship between skeletal muscle and

gut through the release of IL-6. In a murine model, exercise-induced IL-6 has been shown to act on intestinal L cells and stimulated glucagon-like peptide-1 (GLP-1), a hormone inducing insulin secretion [27]. This effect was supported by a clinical study demonstrating that total GLP-1 plasma levels were significantly increased in patients presenting high plasma levels of IL-6 in comparison with healthy control subjects [28].

In addition, irisin hormone mainly released by skeletal muscle has been described to improve glucose homeostasis, lipid profile and metabolic parameters [29]. This observation suggest that the muscle communicates with insulin-sensitive cells such as adipocytes through this hormone. Rana SK et al reported on 79 T2D individuals an increased level of circulating irisin compared to healthy volunteers [30]. In this study, the level of irisin was positively correlated with body mass index, body fat percentage, HbA1c and soluble E-selectin and negatively correlated with visceral adiposity. In addition, they observed a significant increase of E-selectin on human primary endothelial cell treated for 4h with irisin. Overall, these data suggested that irisin was elevated during T2D and may be responsible for the T2D-induced endothelial disturbance. However, in another study, Xiang L et al observed a decrease level of circulating irisin in 188 newly diagnosed T2D Chinese patients compared to healthy subjects [31]. This contradictory effect may probably be due to the exclusion of patients with cardiovascular diseases (microangiopathy, macroangiopathy, neuropathy, retinopathy, cerebrovascular disease and peripheral vascular diseases) in this study while irisin is considered as a biomarker of cardiovascular diseases in T2D patients [30–32]. Some miRNAs, such as miRNA-19b and miRNA-140, have been suggested to downregulate irisin expression and thereby to promote weight loss through reduced energy expenditure [33,34].

Skeletal muscle is one of the tissues most affected during T2D as Andersen et al. showed a significant decrease in muscle strength in patients with 11-year T2D [35]. Volpato S. et al. reported that T2D is associated with lower muscle density, knee and ankle strength, and worse muscle quality [36]. This effect could be related to insulin synthesis since this hormone acts as a potent inhibitor of protein degradation in human skeletal muscle and stimulate muscle mitochondrial function [37]. A recent clinical study demonstrated that high-sensitivity C-reactive protein, an inflammation-related biomarker, is associated with the loss of the muscle strength during T2D [38]. However, the muscle could react to this situation during physical activity through the modulation of inflammatory and oxidative cytokines, and the synthesis of heat shock proteins [39,40].

In addition, it has been described that skeletal muscle synthetizes a group of miRNAs, called myomiRNA [41]. Increasing evidence suggest an involvement of myomiRNAs in the regulation of other organs. For example, myomiRNA-7, myomiRNA-96, and myomiRNA-124a have been recognized to alter pancreatic β-cell [42,43], while myomiRNA-26, myomiRNA-148, myomiRNA-182, and myomiRNA-483 stimulated insulin gene transcription [44,45]. Recently, a short report showed that circulating miRNAs with functions in skeletal muscle (miRNA-106b and miRNA-20b-5p) were associated with development of diabetes [46]. Those data are related to Japanese American cohort as epigenetic marker for diabetes development [46]. Changes in miRNA releases by the muscle could be implicated in pancreas dysfunction and the progression of T2D.

Adipose tissue

Adipose tissue is known as the main organ for energy storage. It is composed of adipocytes and many other cell types such as macrophages, lymphocytes, and fibroblasts embedded in a connective tissue.

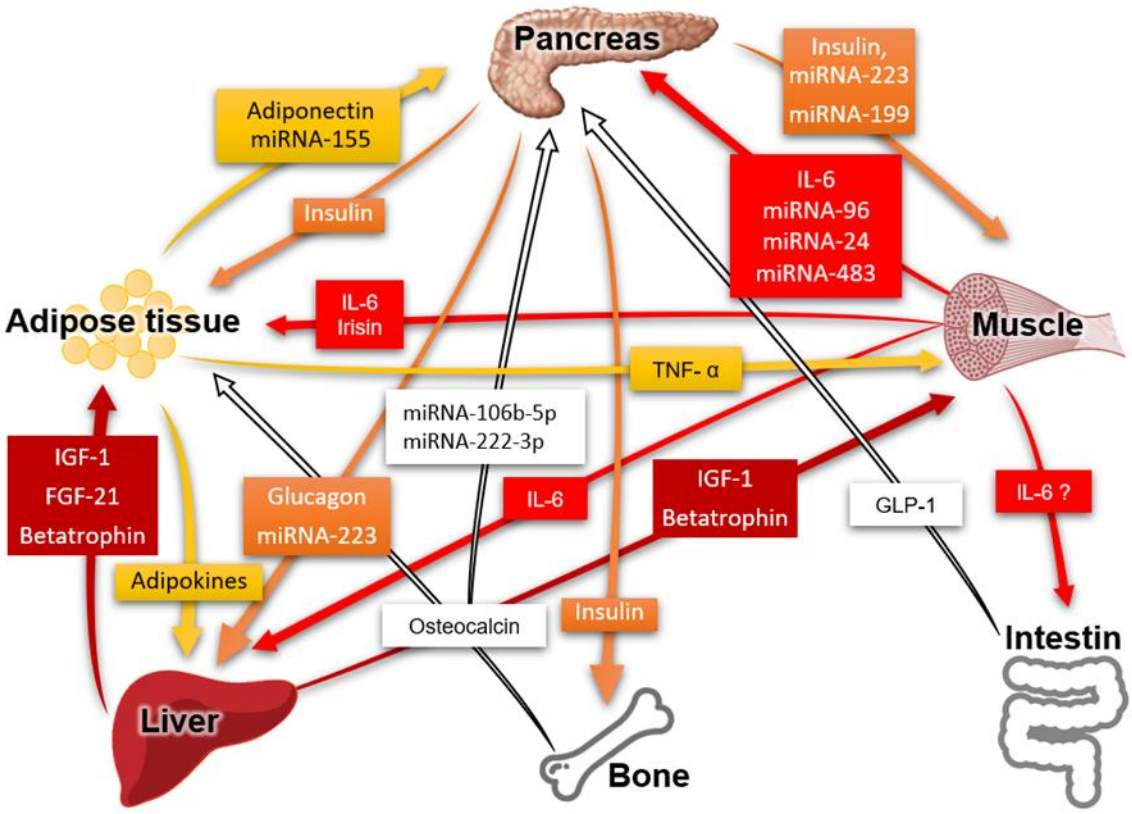

Figure 2: *Representative schema showing major communication pathways implicated in the physiopathology of type 2 diabetes. FGF-21: fibroblast growth factor-21, GLP-1: glucagon-like peptide-1, IGF-1: insulin-like growth factor-1, IL: interleukin, miRNA: microRNA, myomiRNA: muscle-derived microRNA, TNF-α: tumor necrosis factor-α.*

During normal situations, adipose tissue represents about 20% of the body mass in men and about 30% in women. In obese people, this tissue may reach 50% of the body mass. The increase of adipose tissue ratio, especially in obese individuals, gained tremendous scientific interest as a major risk factor for the development of T2D [18].

Additionally, adipose tissue acts as an endocrine organ through the release of several hormones and mediators called adipokines such as leptin and adiponectines. In a case-control study conducted in middle-aged women, it has been shown that high soluble leptin receptor levels were significantly associated with a lower risk of T2D [47]. Furthermore, TNF-α, a pro-inflammatory cytokine mainly derived from adipose tissue macrophages, is associated with insulin resistance. Indeed, TNF-α has been shown to inhibit insulin/Akt signaling in high fat diet-fed mice and upregulate miRNA-494 in cultured skeletal muscle cells leading to insulin resistance [48,49]. Therefore, miRNA-494 could be a relevant target for insulin resistance therapy during T2D. In addition, injection of miRNA-containing exosomes isolated from macrophage associated adipose tissue of obese mice into control ones, induces glucose intolerance and insulin resistance in muscle, visceral adipose tissue and liver [50]. This effect has been identified to be mediated by increased miRNA-155 which then targeted peroxisomal proliferator-associated receptor δ (PPARδ) and decreased insulin sensitivity [50]. These data suggest that miRNA released by adipose tissue could be implicated in the modulation of physiological activities in several organs, especially during T2D.

Liver

The liver synthetizes and releases into the bloodstream a subfamily of mediators called hepatokines such as insulin-like growth factor-1 (IGF-1), angiotensinogen, thrombopoietin, hepcidin, betatrophin, and fibroblast growth factor (FGF)-21.

Lee YS et al. showed that palmitic acid treatment enhanced the production and miRNA 122 and miRNA 192 contents of exosomes released by hepatocytes [51]. Moreover, these exosomes caused an increase in the expression levels of fibrotic genes in other hepatocyte cells. Recently, Wu J et al. showed that hepatic exosome-derived miRNA-130a-3p increased glucose uptake *via* GLUT4 signaling pathway in adipocyte [52]. Altogether, these works suggest that exosomes and miRNA derived from hepatocytes may have important roles in the cell-to-cell communication especially in the progression of T2D.

The table 1 summarizes the most common miRNA released by T2D-related organs and the figure 2 summarizes major communication pathways implicated in the physiopathology of T2D.

Organs	miRNA	Effects	Ref
Pancreas	miRNA-199	Muscle fiber type Conversion	[22]
	miRNA-223	↑ GLUT-4 expression	[20]
Skeletal muscle	miRNA-7	Pancreatic β-cell alteration	[42,43]
	miRNA-24	↑ insulin secretion	[44]
	miRNA-26	↑ insulin gene transcription	[44,45]
	miRNA-96	Pancreatic β-cell alteration	[42,43]
	miRNA-124a	Pancreatic β-cell alteration	[42,43]
	miRNA-148	↑ insulin gene transcription	[44,45]
	miRNA-182	↑ insulin gene transcription ↑	[44,45]
	miRNA-483	insulin secretion	[45]
	miRNA-494	Insulin resistance	[48,49]
Adipose tissue	miRNA-155	↓ insulin sensitivity	[50]
Bone	miRNA-106b-5p	↑ β-cell proliferation	[87]
Hepatocyte	miRNA 122	↑ expression of fibrotic genes	[51]
	miRNA 192	↑ expression of fibrotic genes	[51]

Table 1: Major miRNA released by type 2 diabetes-related organs.

3. Role of PA in patients with T2D

PA is defined as any corporal effort produced by skeletal muscles that involves energy expenditure such as walking, running, and cycling [53]. Three types of PA are generally described depending on the overall effect on the human body: (1) Flexibility exercises such as stretching improve the range of motion of muscles and joints, (2) aerobic exercises such as walking and running cause cardiovascular endurance, and (3) anaerobic exercises such as weight training, functional training or sprinting increase short-term muscle strength [54]. Physical performance is mostly evaluated by the maximal oxygen consumption (VO_2max), the minute ventilation/carbon dioxide production (VE/VCO_2) slope, and the blood lactate concentration. VO_2max is defined as the aptitude to transport and consume oxygen during exhausted work [55]. Cardiac output and the capacity of active muscle to extract oxygen from arterial blood are considered as main factors which could limit VO_2max [54]. Regular PA practice is known to improve VO_2max by increasing cardiac output, aerobic enzyme activity in the muscles, and intramuscular glycogen storage [54]. Whereas, VE/VCO_2 is negatively correlated to cardiac output. The decreased VE/VCO_2 slope could be a result of an enhancement of physical performance through the increase of both ventilation perfusion and diffusion of metabolic gases. While, low lactate concentrations exhibit an enhancement of aerobic metabolic capacity and thereby physical performance [56]. Patients with T2D exhibit a decreased VO_2max [57]. This effect is correlated with loss of insulin sensitivity; endothelial dysfunction, decreased myocardial perfusion, and slowed tissue hemoglobin oxygen saturation and mitochondrial function [57,58]. Impairments in VO_2 kinetics are considered as earliest indicators and important risk factors for T2D progression [57,58].

Several clinical studies demonstrated that PA significantly reduced the incidence of T2D [59,60]. Thus, the type and the intensity of PA could be taken into consideration for improved glycemic control. Recently, Dela et al. demonstrated that high-intensity interval training program (total of eight sessions, each comprised of 10 x 1 minutes ergometer bicycle exercise at > 80% of maximal heart rate, interspersed with one minute of rest) improves skeletal muscle insulin sensitivity in patients with T2D [61].

A clinical randomized trial including 251 adults age 39 to 70 years with T2D demonstrated that aerobic exercise training performed three times per week for 22 weeks significantly decreased hemoglobin A1c, a marker revealing the glycemic control for a long time [60]. Another study investigated the effects of an 8-week aerobic exercise (3 sessions per week, each session 60 to 75 minutes with 60-80% of maximum heart rate) on endogenous levels of GLP-1 and DPP4 on 48 patients with T2D [62]. In this study, aerobic exercises induced an increase in GLP-1 and a decrease in DPP4 blood levels in T2D patients [62]. Thus, glycemic control effects observed after exercise is related to an increase of incretin circulating levels and thereby to insulin secretion in human.

Another clinical study showed that low-intensity exercise (treadmill at 50% of VO_2max) is as effective as high-intensity exercise (treadmill at 75% of VO_2max) to reduce insulin resistance in patient with T2D [63]. This study showed no significant difference between groups, regarding inflammatory and blood lipid profiles, glycated hemoglobin, basal artery diameter, and flow mediated arterial dilation. Furthermore, a recent randomized controlled trial including 44 diabetic elderly patients has compared resistance training group (three times a week) to active control group (stretching workout once per week) after 12 weeks [64]. However, Chen ZP et al. showed that change from low (40% of VO_2max) to medium (60% of VO_2max) intensity exercise increases skeletal muscle AMP-activated protein kinase (AMPK) signaling, whose activation elicits insulin-sensitizing effects [65]. This discrepancy could be related to differences in experimental protocols.

Based on these clinical data, the American Diabetes Association recommends to T2D patients to practice about 30 minutes of moderate-to-vigorous intensity aerobic exercise for 3 to 5 days a week without more than 2 days of inactivity [66,67]. In addition, French physicians can now prescribe PA to type 2 diabetic patients thus considering PA as a part of the treatment of T2D.

At a cellular level, several molecular mechanisms involved in insulin-like effects related to PA have been described. A recent study has shown that treatment with β-aminoisobutyric acid, a substance produced by skeletal muscles which is increased during exercise, attenuates insulin resistance in adipocytes through AMPK-mediated pathway [68]. Meanwhile, it has been demonstrated that repeated exercise bouts by obese patients induced an activation of AMPK and Rab-GTPase-activating proteins pathways in skeletal muscles after biopsy [69]. AMPK signaling have been shown to be involved in mitochondrial biogenesis during exercise through the modulation of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), nitric oxide, and calcium/calmodulin-dependent protein kinase II (CaMKII) synthesis [70]. These molecular adaptations lead to the increase of GLUT-4 expression [71], and thereby to an improvement of insulin sensitivity, explaining the decreased insulin resistance induced by PA in patients suffer from metabolic disorders. However, further investigations are needed in order to clearly decipher the precise molecular mechanisms involved in the PA-induced insulin sensitivity in T2D.

4. PA as a modulator of miRNA expression

Several studies show that miRNA synthesis is modified in response to different exercise programs depending on type, duration and intensity and these miRNAs have been shown to play an important role in cell-to-cell communication through EV during T2D [72]. Recent studies have demonstrated that PA increases miRNA-126 containing EV release into bloodstream [73,74], suggesting that EV could participate in cell-to-cell communication during exercise-mediated adaptation by carrying miRNA to other organs and tissues. This hypothesis is supported by the fact that the majority of the previous reported miRNA, myokines, adipokines, and other mediators implicated

in T2D progression, were found in EV. Recent results related to miRNA expression in cell-to-cell communication have arose novel pathways which can explain the PA antidiabetic effects (Figure 3).

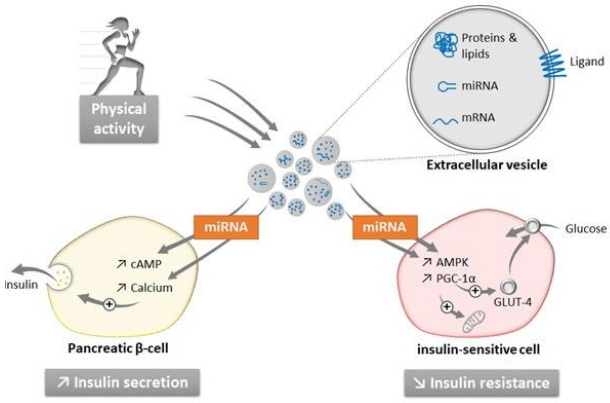

Figure 3: *Proposal of some mechanisms related to physical activity effects during type 2 diabetes through the modulation of miRNA synthesis and extracellular vesicle releases. Physical activity could modify AMPK: AMP-activated protein kinase, GLUT-4: glucose transporter-4, miRNA: microRNA, PGC-1α: peroxisome proliferator-activated receptor-γ coactivator-1α.*

Several studies demonstrated that PA modifies miRNA expression in healthy humans. Radom-Aizik S et al. largely contributed to identify the modifications of circulating miRNA expression after PA in human [75–78]. Tables 2 and 3 summarize the miRNA with up and down regulated expression after PA in healthy human. Whether ten miRNA or precursors (miRNA-15a, miRNA-30e, miRNA-130a, miRNA-151-5p, miRNA-181b, miRNA-223, miRNA-338-3p, miRNA-486, miRNA-499, miRNA-652) present a clear modified expression which is described by three different authors or more, some data remain divergent with a description of both down- and up-regulation of other miRNA (miRNA-1, miRNA-20a, miRNA-21, miRNA-27a-5p, miRNA-107, miRNA-125a-5p, miRNA-126, miRNA-133a, miRNA-133b, miRNA-143-3p, miRNA-145, miRNA-146a, miRNA-206, miRNA-221, miRNA-222, miRNA-363, miRNA-451).

These discrepancies can be explained by the type of PA. Sapp RM et al [79] effectively demonstrated that 30-minute high intensity interval cycling exercise bouts increased the expression of circulating miRNA-126-3p and miRNA-126-5p compared to 30-minute moderate continuous cycling exercise bouts in ten young and healthy men. Similarly, both Mooren FC et al. [80], Baggish AI et al. [81] and Clauss S et al. [82] observed an increased expression of miRNA-133a in the blood circulation of healthy subjects after a marathon while Cui SF et al. [83] observed a decreased expression of the same miRNA-133a after a 30-second intervals intensive sprint cycling in healthy young men. Following the type of PA (aerobic / nonaerobic, endurance training / high intensity training), an opposite effect on the expression of some miRNA can be observed.

In addition, by comparing miRNA expression in muscle of ten young (24.2±0.9 years) and ten old (66.6 ± 1.1 years) males after acute bout of resistance exercise, Zacharewicz E et al. [84] observed

miRNA	Organ	References
miRNA-1	Blood circulation	[80–82, 88–92]
miRNA-7	PBMCs NK cells	[76,77,93]
miRNA-10a-5p	Blood circulation	[94,95]
miRNA-15a	Blood circulation PBMCs Monocytes	[96,97] [77] [78]
miRNA-20a	Blood circulation	[98]
miRNA-21	Blood circulation PBMCs	[98,99] [100]
miRNA-21-5p	Blood circulation	[101]
miRNA-22-3p		[94,102]
miRNA-24		[61,103]
miRNA-24-2-5p		[101]
miRNA-26b	PBMCs	[77]
miRNA-27-a	Blood circulation	[104,105]
miRNA-27a-5p		[101]
miRNA-27b-3p		[106,107]
miRNA-29a	NK cells	[76,108]
miRNA-29b	NK cells Monocyte	[76,105] [78]
miRNA-29c		[76] [78]
miRNA-30a-5p	Blood circulation	[94,109, 110]
miRNA-30d-5p		[94]
miRNA-30e	NK cells Monocytes Blood circulation	[76] [78] [104]
miRNA-96-5p	Blood circulation	[103]
miRNA-98-3p		[111]
miRNA-103		[89,112]
miRNA-107		[89]
miRNA-122		[83,113]
miRNA-125a-5p	Blood circulation Neutrophils	[111] [75]
miRNA-126	Blood circulation PBMCs	[114,115] [116]
miRNA-126-3p	Blood circulation	[79,106]
miRNA-126-5p		[79]
miRNA-128		[94]
miRNA-132	PBMCs	[77,117]
miRNA-133	Blood circulation	[114]
miRNA-133a	Blood circulation Muscle	[80,81,85,88,90–92,118]
miRNA-133b		[88,92, 118]
miRNA-134	Blood circulation	[81]
miRNA-139-5p		[89,109, 119]
miRNA-140-5p	PBMCs Monocytes	[77,78]
miRNA-142-3p	NK cells Blood circulation	[76] [106]
miRNA-142-5p	NK cells	[76]
miRNA-143	Blood circulation	[89,103, 120]
miRNA- 143-3p		[109]
miRNA-145	Neutrophils	[75,121]
miRNA-146a	Blood circulation	[81,92,98,122]
miRNA-146a-5p		[106]
miRNA-149		[123]
miRNA-150		[104,124]
miRNA-181a	PBMCs	[77,125]
miRNA-181a-5p	Blood circulation	[92,101]
miRNA-181a-2	PBMCs	[77]
miRNA-181b	Blood circulation PBMCs Neutrophils	[88,96] [77] [75]
miRNA-181c	PBMCs	[77]
miRNA-186	Blood circulation	[96]
miRNA-192	NK cells	[76]
miRNA-193a-3p	Neutrophils	[75]
miRNA-195-5p	Blood circulation	[109]
miRNA-197	Neutrophils	[75]
miRNA-197-3p	Blood circulation	[109]
miRNA-206	Blood circulation Muscle	[80,90–92,118, 126]
miRNA-208a	Blood circulation	[81]
miRNA-208b		[80,88]
miRNA-212	Neutrophils	[75]
miRNA-214	Blood circulation	[88]
miRNA-221	Blood circulation PBMCs NK cells	[98] [123,127] [89]
miRNA-221-3p	Blood circulation	[106]
miRNA-222		[98,128]
miRNA-223	Blood circulation Neutrophils NK cells	[89] [75] [76]
miRNA-324-3p	Monocyte	[78]
miRNA-330-3p	Blood circulation	[89]
miRNA-338-3p	Blood circulation PBMCs NK cells Monocytes	[89] [77,129] [76] [78]
miRNA-339-3p	Muscle	[84]
miRNA-340	Neutrophils	[75,130]
miRNA-362-3p	Monocyte	[78]
miRNA-362-5p		[78]
miRNA-363	PBMCs	[77]
miRNA-365	Neutrophils	[75]
miRNA-378a-3p	Blood circulation	[94]
miRNA-378a-5p		
miRNA-378f		
miRNA-378g		
miRNA-378i		
miRNA-422a		
miRNA-451	Muscle	[85,131]
miRNA-485-3p	Neutrophils	[75]
miRNA-485-5p	Blood cirulation	[118]
miRNA-494		[104]
miRNA-499		[80,92]
miRNA-499-5p		[81,88,91]
miRNA-505	Neutrophils	[75]
miRNA-509-5p	Blood circulation	[118]
miRNA-517a		
miRNA-518f-3p		
miRNA-520d-3p	Neutrophils	[75]
miRNA-520f	Blood circulation	[118]
miRNA-522		
miRNA-532-3p	Monocytes	[78]
miRNA-532-5p	Monocytes Blood circulation	[78] [94]
miRNA-553	Blood circulation	[118]
miRNA-629	Neutrophils	[75]
miRNA-638		
miRNA-888	Blood circulation	[118]
miRNA-939	PBMCs Neutrophils	[77] [75]
miRNA-940		
miRNA-1202	Monocyte	[78]
miRNA-1225-5p	PBMCs Neutrophils	[77] [75]
miRNA-1238	Neutrophils	[75]
miRNA-1260	Blood circulation	[104]
miRNA-1305	Monocyte	[78]

Table 2: Upregulated miRNAs in healthy human after physical activity. PBMCs: peripheral blood mononuclear cells; NK: natural killer. miRNAs involved in insulin pathway are in bold.

miRNA	Organ	Reference
miRNA-1	Muscle Blood circulation Muscle	[118] [83] [132]
miRNA-7-5p	Blood circulation	[106]
miRNA-16	Blood circulation Neutrophils	[83] [75]
miRNA-17	Neutrophils	[75]
miRNA-18a		
miRNA-18b		
miRNA-20a		
miRNA-20b		
miRNA-21	Blood circulation	[77,89,99,133]
miRNA-22	Neutrophils	[75,134]
miRNA-23b	PBMCs Monocytes	[77,135] [78]
miRNA-24-2p	Blood circulation	[101]
miRNA-25		[89]
miRNA-25-3p		[106]
miRNA-26a	Muscle	[85,108]
miRNA-27a-5p	Blood circulation	[101]
miRNA-29a	Muscle	[85,108]
miRNA-29b-3p	Blood circulation	[105,106]
miRNA-29c-3p		
miRNA-30a		[82]
miRNA-30b		[89]
miRNA-30d-5p		[136]
miRNA-31	PBMCs	[77]
miRNA-92a-3p	Blood circulation	[106]
miRNA-93	Neutrophils	[75,137]
miRNA-93-5p	Blood circulation	[106]
miRNA-96	Blood circulation Neutrophils	[96] [75]
miRNA-99	PBMCs	[77]
miRNA-106a	Blood circulation Neutrophils	[89] [75]
miRNA-107	Neutrophils	[75]
miRNA-125a-5p	PBMCs	[77]
miRNA-126	Neutrophils NK cells	[81,115] [75] [76,77]
miRNA-130a	PBMCs Neutrophils NK cells Monocytes	[77] [75] [76] [78]
miRNA-130b	Neutrophils	[75]
miRNA-133a	Blood circulation Muscle	[83] [132]
miRNA-133b	Blood circulation Muscle	[83] [132]
miRNA-143-3p	Blood circulation	[109]
miRNA-144		[104]
miRNA-145	PBMCs	[77,121]
miRNA-146a	Blood circulation	[123][89]
miRNA-148a		[89]
miRNA-148b		[89]
miRNA-151-5p	PBMCs Neutrophils NK cells Monocytes Muscle	[77] [75] [76] [78] [84]
miRNA-151-3p	Blood circulation PBMCs	[89] [77]
miRNA-151-5p	Blood circulation Neutrophils	[89] [75]
miRNA-181-5p	Blood circulation	[101]
miRNA-185	Blood circulation Neutrophils	[89] [75]
miRNA-194	Neutrophils	[75]
miRNA-199a-3p	NK cells Monocytes	[76] [78]
miRNA-199a-5p	PBMCs NK cells	[77] [76]
miRNA-199b-3p	PBMCs	[77]
miRNA-206	Muscle	[126,132]
miRNA-210	Blood circulation	[100,133]
miRNA-221	Neutrophils Monocytes	[76,77,127] [78]
miRNA-222	Blood circulation	[128] [133]
miRNA-320	PBMCs	[77,138]
miRNA-320b	Blood circulation	[104]
miRNA-320c		
miRNA-320d		
miRNA-320e		
miRNA-326	NK cells	[76]
miRNA-328		
miRNA-342-3p	Blood circulation	[89]
miRNA-363	Neutrophils NK cells	[75] [76]
miRNA-378	Muscle	[85,139]
miRNA-483-5p	Muscle	[84]
miRNA-486	Blood circulation PBMCs Muscle	[140] [77] [139]
miRNA-486-5p	Blood circulation	[106]
miRNA-574-3p	Muscle	[84]
miRNA-584	PBMCs	[77]
miRNA-592-5p	NK cells	[76]
miRNA-652	Blood circulation PBMCs NK cells	[89] [77] [76]
miRNA-660	Neutrophils Monocytes	[75] [78]
miRNA-766	Blood circulation	[89]
miRNA-935	Muscle	[84]
miRNA-3656	Blood circulation	[104]

Table 3 regulated miRNAs in healthy human after physical activity. PBMCs: peripheral blood mononuclear cells; NK: natural killer. miRNAs involved in insulin pathway are in bold.

variations of expression for seven miRNA (miRNA-146a-5p,miRNA-191-5p, miRNA-320a, miRNA-483-5p, miRNA-486-3p, miRNA-539-5p and miRNA-628-5p) with different effects for the two groups. The age should also be considered in the modified expression of miRNA after PA.

The long-term training has also been studied to evaluate whether it can modify the expression of miRNA after a PA. Nielsen S et al. [85] observed an increased expression of miRNA-1 and miRNA-133a after a 60-minute cycle ergometer exercise bout in muscle of ten healthy men while no modification of the expression was observed after 12 weeks of high intensity endurance training in the same subjects. Long term training of subjects has also to be considered suggesting that the physical exertion does not induce the same metabolism for trained subjects compared to non-trained subjects and lead to variations of miRNA expression in these two populations.

It is noteworthy that the majority of the studies reported in tables 2 and 3 indicate miRNA expression in blood circulation or in cells from the blood circulation. Blood samples is easy to perform and in human, biopsies remain very invasive procedures and few data reported level expression of miRNA after PA in specific organs. Even if they are in the blood circulation, miRNA can originate from organs. Because miRNA can be carried by EV and that EV can express specific markers of the organ from which they come from, the organ origin of the circulating miRNA could be partly identified by a co-staining of specific markers of EV. Then, characterization of EV and identification of their organ origin would allow to precise the origin of circulating miRNA. Interestingly, recent studies have demonstrated that PA increased EV release into bloodstream [73,74], suggesting that EV could participate in cell-to-cell communication during exercise-mediated adaptation by carrying miRNA to other organs and tissues. This hypothesis is supported by the fact that the majority of the previous reported miRNA, myokines, adipokines, and other mediators implicated in T2D progression, are found in EV.

More recently, some studies examined the effect of PA on miRNA-contained EV release in specific organs such as liver, muscle, kidney, and adipose tissue. De Mendonça M et al, showed that aerobic training induces a decrease of miRNA-122, miRNA-192, and miRNA-22 levels in the circulating EV of obese mice [86]. In addition, the aerobic exercise reduced adipocyte hypertrophy and increased the expression of adipogenesis markers in this animal model. Furthermore, the expression of adipogenesis and insulin sensitivity markers is negatively correlated with miRNA-22 levels. This study also showed that aerobic training reverted obesity-induced steatohepatitis and adipogenesis markers and were negatively correlated with miRNA-122 levels in the liver. These observations from a murine model suggest that miRNA-contained EV might be involved in communication between liver and adipose tissue during aerobic exercise but need to be confirmed in human.

Interestingly, among miRNAs mainly increased by T2D (table 1), miRNA-96 has also been described to be decreased after PA (table 3). This means that PA can counterbalance some T2D-induced skeletal miRNAs. However, further studies are needed to specifically evaluate if PA can decrease all the overexpressed miRNA in T2D conditions.

5. Conclusion

Regarding its health benefits, physicians generally prescribe PA as first-line therapy for T2D patients. PA causes adjustments in the releases of insulin, myokines, adipokines, hepatokines, and

other mediators, by which it improves cell-to-cell communication during T2D. Some of these mediators including miRNA are released within EV. Additional studies are now needed to determine and to characterize the roles miRNA in these conditions. Determination of miRNA cell origins especially those modified during PA in T2D conditions, is essential to shed the light on pathways implicated in antidiabetic effects of PA. Administration of isolated EV from athletes following exercise or bioengineered EV carrying miRNAs could also be a promising beneficial tool for T2D treatment.

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