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The Impact of Oxidoreductases-Related MicroRNAs in Glucose Metabolism of Renal Cell Carcinoma and Prostate Cancer

Mariana Gomes Morais, Francisca Guilherme Carvalho Dias, João Alexandre Velho Prior, Ana Luísa Pereira Teixeira and Rui Manuel de Medeiros Melo Silva

Abstract

The reprogramming of metabolism is one of cancer hallmarks. Glucose's metabolism, as one of the main fuels of cancer cells, has been the focus of several research studies in the oncology field. However, because cancer is a heterogeneous disease, the disruptions in glucose metabolism are highly variable depending of the cancer. In fact, Renal Cell Carcinoma (RCC) and Prostate Cancer (PCa), the most lethal and common urological neoplasia, respectively, show different disruptions in the main pathways of glucose catabolism: glycolysis, lactate fermentation and Krebs Cycle. Oxidoreductases are a class of enzymes that catalyze electrons transfer from one molecule to another and are present in these three pathways, posing as an opportunity to better understand these catabolic deregulations. Furthermore, nowadays it is recognized that their expression is modulated by microRNAs (miRNAs), in this book chapter, we selected the known miRNAs that directly target these oxidoreductases and analyzed their deregulation in both cancers. The characterization of these miRNAs opens a new door that could be applied in patients' stratification and therapy monitorization because of their potential as cancer biomarkers. Additionally, their delivery to cancer cells, using glucose capped NPs could help establish new therapeutic strategies that would improve RCC and PCa management.

Keywords: oxidoreductases, urological cancers, glucose metabolism, biomarkers, therapeutic targets, nanoparticles

1. Introduction

Cancer is one of the current main public health problems in the world, accounting for, according to GLOBOCAN, approximately 18.1 million new cases and 9.6 million deaths, worldwide in 2018 [1]. It arises from genetic and environmental interactions that cause the deregulation of signaling pathways involved in fundamental cellular processes. Being a heterogeneous disease with multiple etiologies, cancer shows different pathological evolutions and treatment approaches [2].

Renal Cell Carcinoma (RCC) and Prostate Cancer (PCa) represent the most lethal and common urological cancers, respectively [1].

Kidney cancer represents 403,000 new cases and 175,000 deaths worldwide, with RCC accounting for 90% of these cases [1]. Because of kidney's anatomic location, these tumors only become symptomatic in the late stages of the disease. Even though about 60% of RCCs are incidentally detected in an early stage because of routine imaging, about 30% are still diagnosed at the symptomatic phase, which is usually associated with worse prognosis [3]. Additionally, most of the patients continue to be diagnosed with locally advanced disease, with about 17% of them presenting distant metastasis at the diagnosis [4]. Apart from these, approximately 40% of patients submitted to surgery with curative intent will also relapse in a 5-year period [5]. Because of its radio and chemo-resistance, targeted therapies are the only agents available to manage metastatic patients, but one fourth of the patients never respond to them, and the ones who do, typically develop resistance in a median of 5–11 months of treatment [6].

On the other hand, with a world estimate of 1.2 million cases and more than 350 thousand deaths in 2018, PCa is the second most frequent cancer in men and the fifth cause of death [1]. Its treatment depends on the grade, stage and age of the patients, being the androgen deprivation therapy (ADT) one of the main therapy options because of its high dependence on the androgen pathway [7]. Despite the initial high response rates, nearly all men that undergo ADT develop resistance within 2 to 3 years, progressing to Castration Resistant PCa (CRPC) [8]. In the last few years new drugs came up as alternatives to these patients, but they present limited time benefits and patients eventually relapse [9].

The late diagnosis, the lack of accurate prognosis and disease follow up biomarkers, as well as the resistance to the existing therapies are some of the major current challenges in both prostate and renal cell carcinoma [10, 11]. Thus, there is an urgent need of more accurate and sensitive biomarkers as well as alternative therapeutic approaches in these tumor models.

Almost 10 years ago, in 2011, the reprogramming of energy metabolism was considered a hallmark of cancer and in the last few years the scientific community has devoted their time to better understand it in order to develop new therapeutic approaches and biomarkers [2]. Oxidoreductases (enzymes that catalyze electrons transfer from one molecule to another) play an important part in these deregulations since they are present in the different pathways involved in cells metabolism, namely in glucose's metabolism [12].

Glucose, as one of the major “fuels” of any cell, has its metabolism altered in most tumor models [13]. However, because cancer is a heterogeneous disease, this deregulation depends on the type of cells that the tumor arises from, being RCC and PCa a good example of such differences.

2. Glucose metabolism in renal cell carcinoma

RCC is a heterogeneous group of cancers with different genetic and molecular alterations, and histological and clinical characteristics [14]. Clear cell RCC (ccRCC) accounts for about 80% of RCC cases and the most common genetic event involved in its beginning is the copy number deletion, inactivating mutation and/or epigenetic silencing of *von Hippel–Lindau* (VHL) [3]. Its loss or inactivation leads to an increase of Hypoxia Inducible Factor alpha (HIF- α), triggering a hypoxic response, even in normoxic conditions, from the cell and a consequent induction of its target genes transcription [15]. These genes are

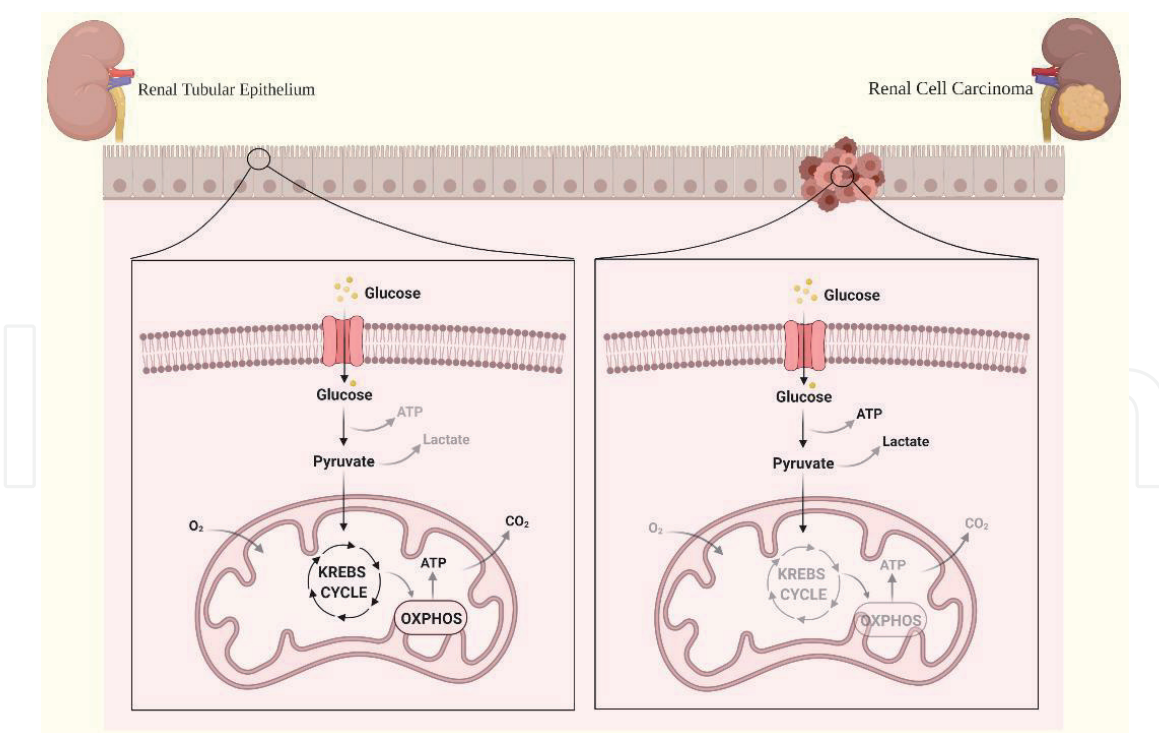


Figure 1.
RCC's glucose metabolic switch. In RCC cells, pyruvate is transformed in lactate, with the production of ATP instead of undergoing Krebs cycle and oxidative phosphorylation (Warburg effect). Created by BioRender.com.

involved in several cellular processes including glucose metabolism (*GLUT-1* and *GLUT-4*) and pH regulation (*CAIX*). Thus, ccRCC is from a very early beginning in a state of constant pseudo hypoxia [16].

This is the most likely cause of the well-known Warburg Effect which is widely documented in ccRCC [17, 18]. The Warburg Effect, or aerobic glycolysis, was firstly described in 1920 by Otto Warburg and describes cancer cells' preference to metabolize glucose through glycolysis followed by lactate fermentation instead of oxidative phosphorylation, even in the presence of oxygen (**Figure 1**) [19]. Very common in many tumors, there are several possible explanations to why cancer cells undergo these alterations, even though the energy resulting from it is significantly lower when compared to oxidative phosphorylation. Using aerobic glycolysis, cancer cells are able to obtain ATP in a faster way and this pathway supports better their high biosynthetic needs [18]. Moreover, the consequent acidification of the microenvironment due to the lactate fermentation is of great advantage to cancer cells since it has been shown to boost their invasiveness and metastatic capacity as well as to inhibit immune rejection [20, 21].

In ccRCC, besides *VHL* loss, *HIF- α* can also be stabilized by mechanisms like *RAS* activation or accumulation of Krebs cycle substrates [22]. Moreover, this effect can also be driven by the interruption of the Krebs Cycle and mutations in genes that encode enzymes like Fumarate Hydratase or Succinate Dehydrogenase, increased levels of reactive oxygen species and activation of pathways such as *NRF2/KEAP1* and *PI3K/mTOR* [18].

In addition to that, the deregulation of the expression of several enzymes involved in the glucose metabolic pathways has already been reported in ccRCC, including several oxidoreductases, such as glyceraldehyde-3-phosphate dehydrogenase (*G3PD*), lactate dehydrogenase (*LDHA*) which belong to the glycolysis pathway; pyruvate dehydrogenase (*PD*) and isocitrate dehydrogenase (*IDH*) involved in the Krebs Cycle and succinate dehydrogenase (*SDH*) which is part of the oxidative phosphorylation pathway [16, 23–26].

3. Glucose metabolism in prostate cancer

Due to its organ's function, prostatic tissue shows a unique metabolic activity under normal conditions, which will reflect in the disruptions presented by its cancer cells. One of the key functions of the prostate gland is to produce large amounts of citrate that is secreted as part of the seminal liquid [27]. Thus, normal prostate epithelial cells undergo a very inefficient energy metabolism.

In most organs, glucose is metabolized through glycolysis in pyruvate, which is decarboxylated in the mitochondria to generate Acetyl-CoA. This metabolite reacts with oxalacetate to generate citrate which is oxidized and undergoes the Krebs Cycle where a large amount of NADH is produced (that will be used in oxidative phosphorylation to produce ATP), as well as precursors of several amino acids [28]. In normal prostate epithelial cells, there is an impairment of the mitochondrial aconitase, responsible for citrate oxidization, granting this metabolite accumulation, which is needed in the seminal liquid composition [27]. Aconitase's inhibition is triggered by an accumulation of zinc in these cells due to the overexpression of the zinc-regulated transporter/iron-regulated transporter-like protein 1 (ZIP1) [29]. Thus, in these cells, citrate is the final product of glucose metabolism and oxaloacetic acid (which normally is regenerated in the Krebs cycle) is produced through aspartate imported from the plasma through a specific carrier [30]. Because of Krebs cycle inhibition, and consequent oxidative phosphorylation impairment, these cells show a higher glycolytic rate [28].

Prostate cancer cells, however, have increased energy demands. Franklin and Costello have concluded that an early event in PCa carcinogenesis is the completion of the Krebs cycle and subsequent ability to produce much more ATP [31]. In fact, PCa cells show dramatically reduced levels of zinc, and consequent reactivation of m-aconitase and of Krebs cycle [32]. Interestingly, zinc has also been shown to induce apoptosis and inhibit invasion and angiogenesis in PCa cells [33, 34].

Nevertheless, it is important to take into consideration that cells need to readjust their bioenergetics and metabolism according to their energetic needs, during cancer progression. Thus, in its metastatic stage, PCa has been shown to switch to Warburg Effect [35]. The exact mechanisms behind this switch are not yet fully understood, but the microenvironment in the metastatic sites seems to play a key

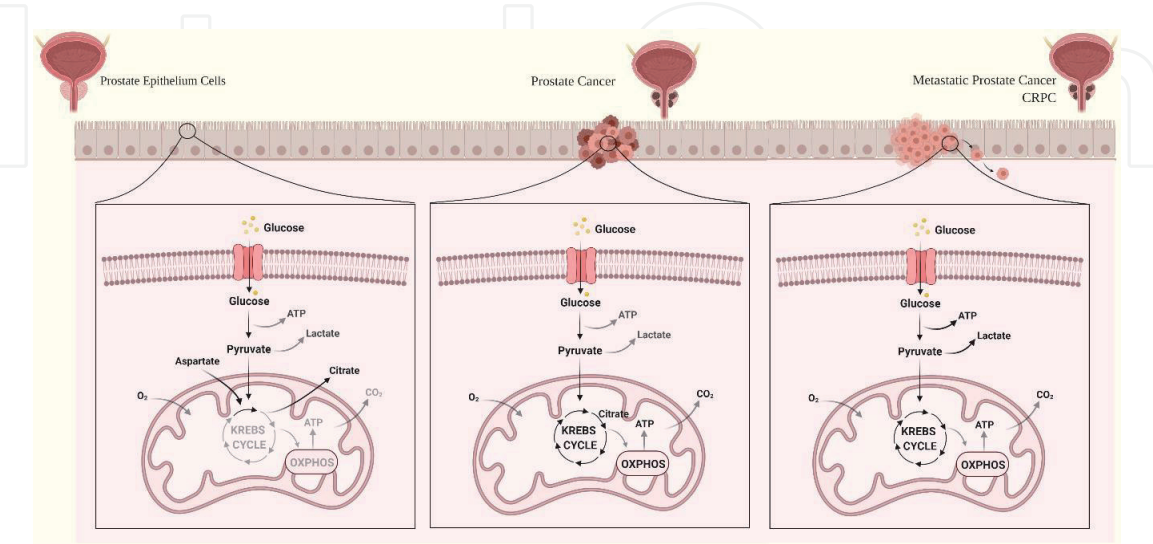


Figure 2. PCa's glucose metabolic switch. Normal prostate epithelial cells have the Krebs cycle interrupted because of their need to secrete citrate as part of seminal fluid. In prostate cancer, Krebs cycle is resumed because of the increased demand for energy. Warburg effect is only observed in the more advanced stages of the tumor. Created by BioRender.com.

role, whether through the neighboring adipocytes or through the immune system. These seem to be able to increase HIF1 α 's production inducing aerobic glycolysis and blocking oxidative phosphorylation (**Figure 2**) [36, 37].

Several oxidoreductases involved in the glucose metabolic pathways have already been studied in PCa and reported as deregulated, such as glyceraldehyde-3-phosphate dehydrogenase (G3PD) and lactate dehydrogenase (LDHA) which belong to the glycolysis pathway and pyruvate dehydrogenase (PD) and isocitrate dehydrogenase (IDH) involved in the Krebs Cycle [38–41].

4. miRNAs as glucose metabolism regulators

The deregulation of the oxidoreductases as well as other enzymes involved in the glucose metabolism pathways is necessary for its reprogramming. This deregulation has already been connected with microRNAs (miRNAs), both in RCC and in PCa [18, 42].

miRNAs are short non-coding RNAs (~19 to 25 nucleotides) which regulate gene expression at a post-transcriptional level. Through binding to the 3' untranslated region (3' UTR) of mRNAs, miRNAs induce their degradation or translation repression [43]. These molecules are important modulators of cellular behavior being involved in different biological processes such as cell development, differentiation, apoptosis, proliferation, and metabolism. This is due to their dynamic expression since each miRNA regulates up to 100 different mRNAs and more than 10,000 mRNAs are regulated by miRNAs [44].

There are different characteristics that make miRNAs good biomarkers' candidates. Firstly, miRNAs have different expression patterns in normal cells when compared with tumoral ones, and even among different subtypes or in different stages of the disease, which shows their potential as biomarkers' candidates [45]. Secondly, there has been cumulating evidence regarding the fact that miRNAs are secreted into several body fluids, such as serum, plasma, saliva or urine [46]. Finally, miRNAs circulate in these fluids incorporated into protein complexes or extracellular vesicles, which protect them from RNase degradation and make them resistant to extreme conditions like temperature or pH differences [47].

In fact, in previous studies circulating miRNAs profiles have already been associated with histology, staging and clinical endpoints, including patients' survival and therapy response both in ccRCC and in PCa [48–50].

Thus, the study of miRNAs whose targets are involved in the glucose metabolism in tumor models such as RCC and PCa is highly important, not only because it can help to better understand the differences in metabolic deregulations of the different tumors, but also because this knowledge can be applied in designing new-targeted therapies and biomarkers.

5. Literature review and data collection

This chapter is focused on the three main glycolytic pathways: glycolysis, Krebs cycle and Lactate Fermentation. Since oxidoreductases are present in these three pathways, we chose this type of enzymes to select miRNAs that directly regulate them (**Table 1**).

Following, we used miRTarBase (version 8.0), the largest known online database of validated miRNA:mRNA target interactions, to select the miRNAs that directly target these enzymes [51]. Only studies featuring hsa-miRNAs and functional miRNA Target Interaction (MTI) evidence were considered. The selected miRNAs and the respective validated targets are displayed in **Figure 3**.

Glycolysis	Lactate fermentation	Krebs cycle
GAPDH	LDHA	PDH
		IDH
		KGDH
		SDH
		MDH

Table 1.
Oxidoreductases in glycolysis, lactate fermentation and Krebs cycle.

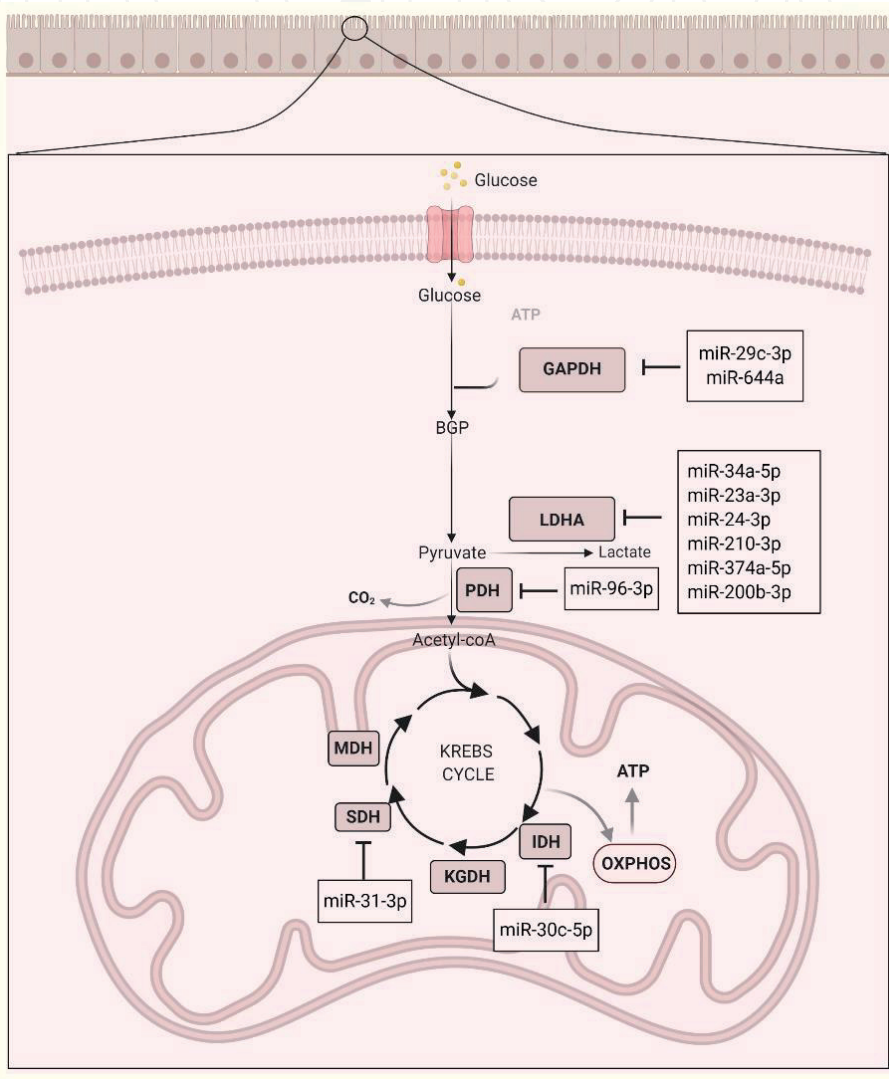


Figure 3.
miRNAs that directly regulate the oxidoreductases involved in the main pathways of glucose catabolism.
Created by BioRender.com.

A systematic search in Pubmed was then conducted regarding the existing evidence for each miRNA in both ccRCC and in PCa, in order to get a deeper knowledge of these miRNAs expression in these tumor models. To do so, we combined each miRNA with the following keywords: “renal cell carcinoma”, “RCC”, “Kidney Cancer”; “Prostate Cancer”. The obtained scientific papers were manually curated to determine the association between the miRNA and either RCC or PCa. The criteria of exclusion were the following: 1) scientific papers that do not report results from human samples; 2) scientific papers that do not directly correlate the miRNA with the disease. From the 56 papers initially found, 23 were excluded. For each

selected paper, we extracted information regarding the deregulation of the miRNA's expression in each tumor model (upregulated ↑/downregulated ↓) and gathered it in the following tables, according to the metabolic processes involved.

5.1 Glycolysis

Glycolysis is the pathway responsible for converting glucose in pyruvate and it is constituted by a series of enzymatic reactions. Its sixth step is catalyzed by an oxido-reductase - Glyceraldehyde_3-phosphate_dehydrogenase (GAPDH) – responsible for transforming glyceraldehyde 3-phosphate in D-glycerate 1,3-biphosphate. According to miRTarBase (version 8.0), GAPDH is directly targeted by miR-29c-3p and miR-644a [51]. The studies regarding these miRNAs in both RCC and PCa are scarce, and miR-644a's expression is still not described in RCC nor miR-29c-3p's expression is described in PCa (**Tables 2** and **3**).

In both tumor models, the miRNAs targeting GAPDH are downregulated, which may partly explain the upregulation of GAPDH already observed in PCa [52, 53]. There is, in fact, an increase of glucose consumption in cancer due to the bigger energetic needs of tumoral cells. Since glycolysis is the basis of glucose catabolism, either by following Krebs Cycle or Lactate Fermentation, the upregulation of the expression of this pathway's enzymes will help ensure cancer cells' catabolic demands.

5.2 Lactate fermentation

Lactate fermentation is the metabolic process in which the pyruvate resulting from glycolysis is transformed in lactate with ATP production. This reaction is catalyzed by an oxidoreductase – Lactate Dehydrogenase (LDHA), whose mRNA, according to miRTarBase (version 8.0), is directly targeted by miR-34a-5p, miR-23a-3p, miR-24-3p, miR-210-3p, miR-374a-5p and miR-200b-3p [51]. To the best of our knowledge, there are still no studies regarding miR-24-3p and miR-374a-5p's expression in RCC as well as miR-374a-5p's expression in PCa. The studies regarding the other miRNA's expression in RCC are summarized in **Table 4** and the ones regarding miRNA's expression in PCa are summarized in **Table 5**.

In RCC, the available studies for the selected miRNAs are controversial. This may be result of lack of standardized procedures but also of the different types of samples analyzed. Moreover, it is interesting to look at the studies of miR-210-3p's expression. This miRNA was significantly increased in ccRCC patients at the time of surgery, when compared to healthy donors, but significantly decreased in follow-up disease-free ccRCC patients of the same cohort [62, 64]. These studies show, not only this miRNA potential as follow-up biomarker but are also an example

Enzyme	miRNA	Sample type	Outcome	References
GAPDH	miR-29c-3p	Tissues and Cell lines	↓	[52]

Table 2.
Deregulation of the miRNAs that directly target the glycolysis' oxidoreductases in RCC.

Enzyme	miRNA	Sample type	Outcome	References
GAPDH	miR-644a	Tissues	↓	[53]

Table 3.
Deregulation of the miRNAs that directly target the glycolysis' oxidoreductases in PCa.

Enzyme	miRNA	Sample type	Outcome	References
LDHA	miR-34a-5p	Cell lines	↑	[54]
		Tissues and cell lines	↑	[55]
		Tissues	↓	[56]
	miR-23a-3p	Cell lines	↓	[57]
		Tissues and cell lines	↑	[58]
	miR-210-3p	Tissues	↑	[59]
		Cell lines	↓	[60]
		Cell lines	↓	[61]
		Tissues and urine	↑↓	[62]
		Tissues	↑	[63]
		Tissues and urine	↑↓	[64]
		Tissues	↑	[65]
		Cell lines and plasma	↑	[66]
		Cell lines	↓	[67]

Table 4.
Deregulation of the miRNAs that directly target the lactate Fermentation’s oxidoreductases in RCC.

of miRNAs dynamic expression. In PCa, one can notice that hormonal resistant and metastatic PCa show a decrease in miR-34a-5p and miR-200b-3p, which may traduce in an increase of LDHA and the switch to Warburg Effect which is only observed in these stages of PCa [68, 79].

5.3 Krebs cycle

Krebs Cycle, also known as the tricarboxylic acid cycle, follows glycolysis in the glucose catabolism when oxygen is present. It is preceded by the transformation of pyruvate in acetyl-coA, which will enter the cycle – a series of reactions that provide precursors of amino acids as well as the reducing agent NADH which will be used in the oxidative phosphorylation pathway and lead to ATP production.

Pyruvate oxidation in acetyl-coA is catalyzed by an oxidoreductase – Pyruvate dehydrogenase (PDH), whose mRNA is, according to miRTarBase (version 8.0) directly targeted by miR-96-3p [51]. However, there are still no studies regarding this miRNA in both RCC and in PCa.

In the series of reactions of Krebs Cycle, there are 4 reactions catalyzed by 4 oxidoreductases – Isocitrate dehydrogenase (IDH), α-ketoglutarate dehydrogenase (KDGH), Succinate dehydrogenase (SDH) and Malate dehydrogenase (MDH). According to miRTarBase (version 8.0), miRNAs directly targeting KDGH and MDH were not yet identified. Moreover, SDH is directly targeted by miR-31-3p, which, to the best of our knowledge, has not yet been studied in RCC and in PCa [51].

IDH is directly targeted by miR-30c-5p. There are few studies regarding this miRNA both in RCC (**Table 6**) and in PCa (**Table 7**).

In these studies, the expression of miR-30c-5p in RCC is downregulated which would suggest an upregulation of IDH’s mRNA expression. However, this protein was shown to be downregulated in this tumor model [85]. In fact, a single mRNA can be regulate by several miRNAs, making the miRNA:mRNA expres- sion not always inversely correlated. Nevertheless, the fact that miR-30-c-5p was

Enzyme	miRNA	Sample type	Outcome	References
LDHA	miR-34a-5p	Cell lines (resistant vs. hormonal sensitive)	↓	[68]
		Urinary exosomes and tissues	↓	[69]
		Cell lines	↓	[70]
	miR-23a-3p	Tissues	↑	[71]
	miR-24-3p	Urine	↓	[72]
		Urine	↓	[73]
		Tissues and cell lines	↓	[74]
	miR-210-3p	Tissues	↑	[75]
		Tissues	↑	[76]
	miR-200b-3p	Tissues	↑	[77]
		Cell lines	↓	[78]
		Metastatic tissues	↓	[79]
		Chemo-resistant cells	↑	[80]

Table 5.
Deregulation of the miRNAs that directly target the lactate fermentation’s oxidoreductases in PCa.

Enzyme	miRNA	Sample type	Outcome	References
IDH	miR-30c-5p	Urinary exosomes	↓	[81]
		Tissues	↓	[82]

Table 6.
Deregulation of the miRNAs that directly target the Krebs cycle’s oxidoreductases in RCC.

Enzyme	miRNA	Sample type	Outcome	References
IDH	miR-30c-5p	Tissues	↓	[83]
		Urine	↑	[73]
		Tissues	↑	[84]

Table 7.
Deregulation of the miRNAs that directly target the Krebs Cycle’s oxidoreductases in PCa.

downregulated in urinary exosomes shows its potential as a biomarker in a liquid biopsy approach [81].
In PCa the results regarding this miRNA are scarce and controversial, showing the need of more studies to clarify its expression levels.

6. Discussion

miRNAs potential in the oncology field has been widely recognized and there has been an increase of studies regarding their deregulation in cancer in the last few years. However, there are many genes whose mRNA have not been identified as direct targets of any miRNA. In this book chapter, both KGDH and MDH, key enzymes in the Krebs Cycle, have not been directly associated with any miRNAs. Moreover, there are several miRNAs that directly target the mRNA of key enzymes of glucose catabolism but

have not yet been studied in RCC (miR-644a, miR-24-3p, miR-374a-5p, miR-96-3p and miR-31-3p) and in PCa (miR-29c-3p, miR-374a-5p, miR-96-3p, miR-31-3p). Additionally, some miRNAs present controversial results which shall be subject of more studies to confirm their deregulation. Nevertheless, two miRNAs have been identified as downregulated (miR-29c-3p and miR-200b-2p) in RCC and three miRNAs have been identified as downregulated (miR-644a, miR-34a-5p and miR-24-3p) and two as upregulated (miR-23a-3p and miR-210-3p) in PCa. Their potential as biomarkers of both RCC and PCa could be increased if combined as a profile, which could pose as an advance to establish a successful liquid biopsy approach.

Because of their influence in their target genes' expression, the reestablishment of miRNAs' levels may have a great impact in the regulation of glucose metabolism. Restoring the levels of the downregulated miRNAs in both RCC and PCa could benefit the current cancer therapies and one possible way to do so is through a nanomedicine approach. Nanoparticles (NPs) are small organized structures with sizes between in size 1 and 100 nm that show very specific chemical and physical properties due to their size and composition [86]. Even though the existing research is scarce, NPs can improve the specificity of miRNAs delivery to target cells (thus reducing side effects) and allow for controlled miRNA release [87]. They also can protect them from degradation and prevent their clearance by the reticuloendothelial system. Moreover, they avoid unfavorable immune cell stimulation [87]. NPs highly depend on their capping which acts prevents their agglomeration and stops uncontrolled growth. The choice of capping will highly influence NPs properties. To effectively deliver the miRNAs selected in this chapter, a glucose capping could be an interesting choice. As stated above, both in RCC and PCa, tumoral cells show an increased glucose consumption when compared with their counterpart normal cells. Thus, glucose as NP's capping could favor the selective delivery of miRNAs and would likely not be recognized as antagonist by the immune system.

7. Conclusions

The deregulation of glucose metabolism as a great influence in the pathophysiology of cancer, with the oxidoreductases involved in its pathways posing as both an opportunity to better comprehend the disease and finding not only strategies of detecting and monitoring it but also new therapeutic strategies. miRNAs could be part of these strategies since they influence the expression of these enzymes. Both in RCC and PCa, there are studies regarding miRNAs that target these oxidoreductases, showing their impact in patients' prognosis. In the future, more studies are needed, regarding the identification of more miRNAs that target for example KGDH and MDH and their validation in RCC and PCa. Moreover, exploring the potential of glucose capped NPs carrying these miRNAs could help establish new therapeutic strategies that would benefit RCC and PCa management.

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Conflict of interest

The authors declare no conflict of interest.

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