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Glycolysis in human cancers: Emphasis circRNA/glycolysis axis and nanoparticles in glycolysis regulation in cancer therapy

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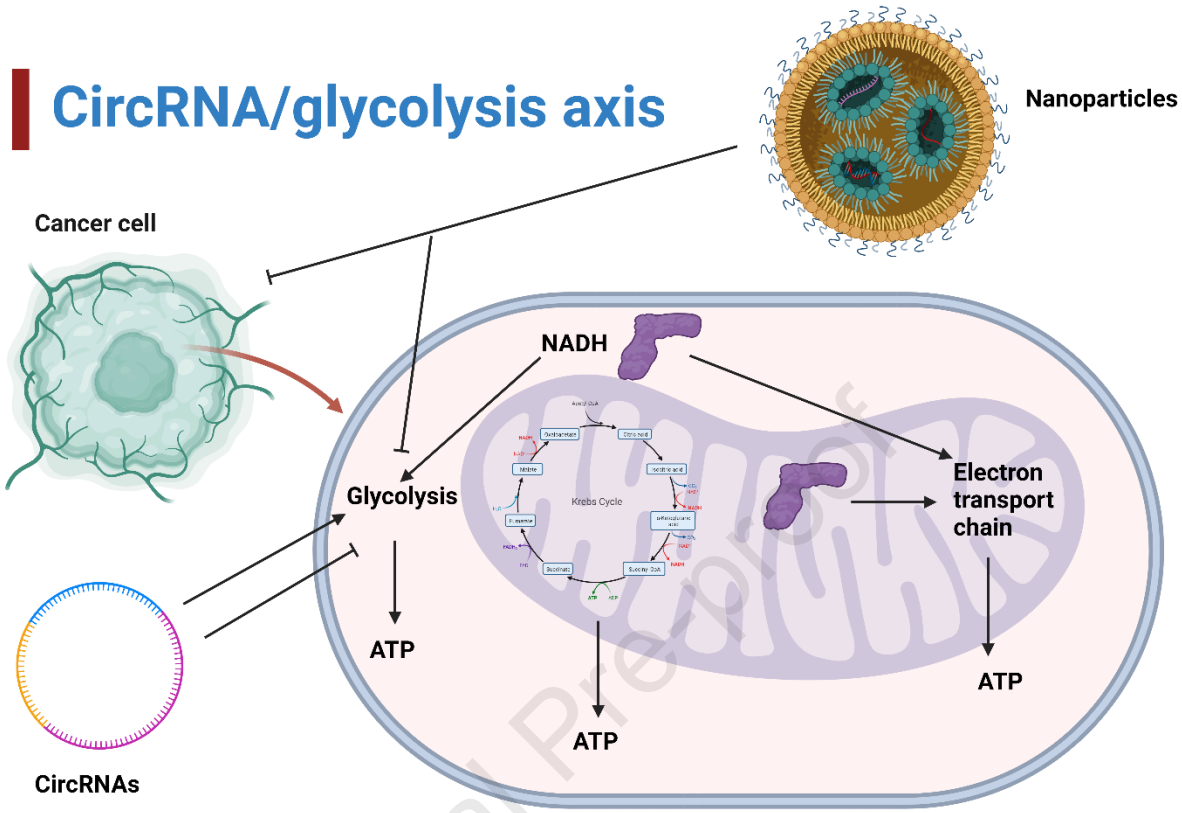
Graphical abstract:



Abstract:

The metabolism of cancer has been an interesting hallmark and metabolic reprogramming, especially the change from oxidative phosphorylation in mitochondria to glucose metabolism known as glycolysis occurs in cancer. The molecular profile of glycolysis, related molecular pathways and enzymes involved in this mechanism such as hexokinase have been fully understood. The glycolysis inhibition can significantly decrease tumorigenesis. On the other hand, circRNAs are new emerging non-coding RNA (ncRNA) molecules with potential biological functions and aberrant expression in cancer cells which have received high attention in recent years. CircRNAs have a unique covalently closed loop structure which makes them highly stable and reliable biomarkers in cancer. CircRNAs are regulators of molecular mechanisms including glycolysis. The enzymes involved in the glycolysis mechanism such as hexokinase are regulated by circRNAs to modulate tumor progression. Induction of glycolysis by circRNAs can significantly increase proliferation rate of cancer cells given access to energy and enhance metastasis. CircRNAs regulating glycolysis can influence drug resistance in cancers because of theirimpact on malignancy of tumor cells upon glycolysis induction. TRIM44, CDCA3, SKA2 and ROCK1 are among the downstream targets of circRNAs in regulating glycolysis in cancer. Additionally, microRNAs are key regulators of glycolysis mechanism in cancer cells and can affect related molecular pathways and enzymes. CircRNAs sponge miRNAs to regulate glycolysis as a main upstream mediator. Moreover, nanoparticles have been emerged as new tools in tumorigenesis suppression and in addition to drug and gene delivery, then mediate cancer immunotherapy and can be used for vaccine development. The nanoparticles can delivery circRNAs in cancer therapy and they are promising candidates in regulation of glycolysis, its suppression and inhibition of related pathways such as HIF-1α. The stimuli-responsive nanoparticles and ligand-functionalized ones have been developed for selective targeting of glycolysis and cancer cells, and mediating carcinogenesis inhibition.

Keywords: Circular RNAs, glycolysis, cancer metabolism, chemoresistance, nanoparticles, gene delivery

Contents

1. Introduction

As endogenous ncRNAs, circRNAs were recognized in 1990s with one of their features being their scrambled exon order [1]. Attempts were made to understand the structure, mechanism of action, and their roles in diseases in recent years [2-5]. The conventional linear RNA molecules have 5'caps and 3'tails, while circRNAs have closed loop structures [6]. The highly conserved ncRNA family in mammals has other members such as miRNAs and lncRNAs, with circRNAs having higher stability because of their nuclease resistance characteristics [7, 8]. The expression of circRNAs has been mentioned in various species from humans and animals to plants [9-11]. Therefore, circRNAs are evolutionary conserved in a time-dependent, cell type and gene-specific manner. Because of advances in biology and high-throughput sequencing technologies, a high number of circRNAs have been identified with roles in cardiovascular diseases, neurological disorders, cancer and other diseases [12-14]. Since circRNAs are evolutionary conserved with high stability and expression in tissues and body fluids, they can be used for diagnosis and treatment of diseases [15, 16]. The biogenesis of circRNAs was reported by Jeck and colleagues in two models [17] including intron-pairing-driven circularization and lariat-driven circularization. Intron circRNA was discovered in recent years and consists of an 11-nucleotide C-rich element and a 7-nucleotide G-rich element in the parent gene which are mixed to generate a circular structure that can undergo splicing by spliceosome [18]. The spliceosome is a vital mechanism in the biogenesis of circRNAs and relies on trans-acting factors and cis-regulatory elements [19].

CircRNAs play various roles in cells that one of them is miRNA sponging. miRNAs have the capacity of reducing gene expression at mRNA levels [20]. The intracellular mobility of miRNAs determines their sponging ability and is featured as an intermittent active transport type [21]. Hanssen's lab was one of the leaders in studying the complexity of gene expression regulation and discovered circRNA and miRNA interactions [22]. Since circRNAs have unique structures, they can be protected from destabilization and degradation by miRNA-induced deadenylation [23]. Protein binding, transcription regulation, coding for proteins and peptides are other functions of circRNAs [24]. The role of cicRNAs in cancer progression regulation has been of importance in recent years. In the oncology field, circRNAs are divided into two categories including oncogenic and onco-suppressor circRNAs [25, 26]. Circ-PTCD3 is a driver of breast cancer progression and by sponging miR-198, it increases growth and colony formation of tumor cells [27]. Overexpression of circ-SEPT9 in endometrial cancer is associated with induction of methylation of miR-186 to decrease its level and enhance cancer malignancy [28]. In lung cancer, circ-CPA4 promotes TIGF2 expression via miR-214-3p inhibition thereby increasing tumorigenesis [29]. On the other hand, onco-suppressor circRNAs induce apoptosis thereby reducing cancer progression [30]. Finally, circRNAs are cancer hallmark modulators which can interact with components of tumor microenvironment such as macrophages in regulating tumor progression [31-37]. The current review focuses on the role of circRNAs in regulating EMT mechanism in various cancers and provides new insights on their role in regulation of cancer metastasis.

2. Glycolysis mechanism: An overview

Among the various metabolic pathways in cancer, glycolysis or Warburg effect has been investigated in detail [38, 39]. Otto Warburg introduced a hypothesis as a fundamental basis for cancer in 1920s which explains a metabolic shift towards glycolysis [40]. Based on this hypothesis, cancer is a multifactorial malignancy and despite showing a high number of alterations, there is a major change in replacement of oxygen respiration with sugar fragmentation. This hypothesis is called Warburg effect in which cancers transform glucose into lactate, even at the presence of oxygen also called aerobic glycolysis. In contrast, anaerobic glycolysis occurs during hypoxia and acts as an energetic adaptation to hypoxia [41-43]. In normal cells during normal conditions when there is enough oxygen, glucose is utilized for generation of pyruvate. Glucose is then oxidated in mitochondria in the TCA cycle to carbon dioxide, known as oxidative phosphorylation [44]. On the other hand, the process of glycolysis occurs in cytoplasm where glucose is transformed into pyruvate and lactate is produced. HK, PFK and PK are other regulators of glycolysis [45, 46].

Remarkably, the induction of glycolysis increases progression of cancer. ENO1-IT1 upregulation by F. nucleatum can result in stimulation of glycolysis and increase in colorectal cancer growth [27]. The neutrophils present in tumor microenvironment can secrete extracellular vesicles and lead to an increase in mRNA levels of SPI1 which mediates glycolysis and enhances colon cancer progression [47]. ISLR inhibition suppresses JAK/STAT3 and impairment of glycolysis in lung cancer [48]. NEDD4L can enhance ubiquitination of ENO1 and inducing its degradation thereby inhibiting glycolysis in oral tumor [49]. SIRT6 stimulates glycolysis in lung cancer and in turn, α-hederin reduces SIRT6 expression to prevent glycolysis [50]. Penfluridol reduces PFKL expression to inhibit AMPK/FOXO3a axis, induce apoptosis, and interfere with glycolysis in esophageal cancer [51]. Interestingly, with glycolysis induction in cancer, tumor cells show more resistance to apoptosis [52] and this may be considered as a factor for development of therapy resistance. This idea has been confirmed by the function of POU2F1-ALDOA axis in glycolysis induction which leads to mediation of resistance to chemotherapy [53]. Therefore, interaction of molecular pathways can determine glycolysis status in cancer [54, 55] and the purpose of current review is to find interactions between circRNAs and glycolysis in cancers.

3. Climate, environment and cancer: A brief discussion

It is obvious that changes in climate can cause development of cancer. Now, there is no doubt that climate change can change health of humanity [56]. Currently, world is facing climate change and various international organization had predicted that disruption in planetary ecology can impact human health [57]. Researchers have shown that changes in climate can affect prevalence of infectious diseases and alter access to healthy water and food [58]. However, there is little focus on the cancer, since it is a chronic disease and does not bring suddenly after close temporal proximity to the exposures mediated by climate change. The exposure to tobacco products, ultraviolet irradiation, infection diseases, HPV, environmental toxics, chemicals and changes in lifestyle can lead to cancer development [59]. Based on these risk factors of cancer, when climate change occurs, it is obvious that increase in incidence rate of cancer is observed. The climate change can alter the plans of cancer control through air pollution, ultraviolet irradiation, food and water supply disruption, industrial toxics and chemicals and infection

disease-related cancer. Therefore, there is strong correlation between climate change, environmental factors and cancer development, and effective control of cancer requires an international law for controlling and preventing climate change.

4. Nanoparticles in cancer therapy: An overview

Nanomaterials are promising candidates in cancer therapy. The use of nanostructures is not limited only to delivery of drugs and progresses in field of nanoengineering and nanomedicine have resulted in development of nanocarriers with multiple and versatile functions. The nanoparticles are opening their way to be used significantly in cancer immunotherapy. The BTO nanoparticles have been functionalized with cell membrane to deliver PD-L1 antibody. The engineered membranes are sensitive to MMP-2 enzyme in tumors and undergo cleavage and by increasing ROS generation, they promote CTLs infiltration and increase potential of PD-L1 immunotherapy [60]. Due to immunosuppression activity of tumor cells, application of nanoparticle-mediated immunotherapy is increasing. The PLGA nanoparticles with biodegradable feature are able to stimulate cGAS/STING axis to mediate IL-15-induced NK cell induction and enhancing cancer immunotherapy [61]. Furthermore, nanoparticles can be employed for purpose of vaccine development and improving immune system [62]. The selenium nanomaterials are able to modulate innate immune system through direct interaction with macrophages, dendritic and NK cells, and such immunotherapy can increase chemotherapy potential in cancer suppression [63]. The silver nanostructures can be stabilized by PVP and they decrease IL-6 secretion in impairing prostate cancer [64]. The targeted delivery of drugs by nanocarriers is the most common use in cancer therapy; doxorubicin has been loaded on hybrid magnetic nanostructures and then, they have been functionalized with chitosan and folic acid. These nanoparticles increase cell internalization of doxorubicin and release drug in response to pH-sensitive manner for tumor suppression [65]. The polymeric nanoparticles can co-deliver both elesclomol (ES) and Cu, and release cargo in response to ROS. When the drugs and cargo are released, they mediate cuproptosis to reduce viability of tumor cells and can stimulate anti-cancer immune responses. Moreover, they reprogram tumor microenvironment and reduce bladder cancer progression [66]. Interestingly, the identification and determination of anti-cancer drugs by nanostructures can also be performed [67, 68]. The nanoparticles are able to deeply penetrate into cancer cells and they are promising in tumor disruption [69]. In the field of chemotherapy, the application of nanoparticles is highly suggested due to their potential in improving cellular uptake of drugs [70]. Furthermore, nanoparticles can stimulate phototherapy in tumor ablation [71]. In addition, self-assembled peptide nanomaterials can target tumor microenvironment and prevent immunosuppression [72]. Hence, nanoparticles are extensively used in cancer therapy [73, 74]. However, the toxicity and biocompatibility of nanoparticles should also be considered; for instance, high concentration of glycol chitosan nanoparticles mediate cardiotoxicity [75]. **Table 1** displays application of nanoparticles in cancer therapy.

Table 1: Nanoparticles as promising tools in cancer therapy.

Nanoparticles	**Aim of application**	**Reference**
Albumin-based nanocarriers	High biocompatibility and biosafety Disrupting tumor vasculature	[76]

	Photothermal-mediated tumor ablation	
Polymeric nanoparticles	Increase in cellular uptake Oxidative damage HSP70 down-regulation	[77]
Mesoporous silica nanoparticles	pH-sensitive release of drug Increasing ROS generation Stimulation of chemodynamic therapy	[78]
Organosilica nanostructures and Au nanoparticles	Proliferation suppression Cell death induction	[79]
Lipid nanoparticles	Development of mRNA vaccines for cancer immunotherapy	[80]
Chondroitin sulfate-based prodrug nanomaterials	Targeting Golgi apparatus to mediate photodynamic immunotherapy	[81]
Core-shell nanoparticles	Development of biocompatible nanocarriers with chlorin e6-polydopamic in cancer phototherapy	[82]
PEGylated iron oxide nanoparticle-loaded liposomes	Ferroptosis induction Delivery of doxorubicin and chemotherapy	[83]
Polydopamine-coated gold nanoparticles	ROS overgeneration in photodynamic therapy Apoptosis induction	[84]
Hydroxyapatite nanomaterials	Delivery of altretamine and apoptosis induction	[85]
Metal-organic frameworks	Modification of nanocomposites with GST-Afb to protect the surface and preventing the interactions in biological media	[86]
Worm-like nanoparticles	Reduction-responsive system Delivery of curcumin and also, stimulation of phototherapy by IR820 delivery	[87]
Gold nanoparticles	Gadolinium chelate-coated nanoparticles to impair metastasis of glioblastoma cells	[88]

5. Nanoparticles in regulation of glycolysis in cancer

Based on the previous discussions, it was revealed that glycolysis induction in tumor cells promotes their growth. Therefore, inhibition of glycolysis using pharmacological compounds or gene therapy methods can prevent carcinogenesis. Notably, nanoparticles have been emerged as new tools in glycolysis regulation. The delivery of zoledronic acid by nanoparticles impairs isoprenoid synthesis and prevents upregulation of HIF-1α through modulation of Ras/ERK1/2 and finally, suppresses glycolysis enzymes and glucose flux in reducing tumorigenesis [89]. Such nanoparticles have been extensively used for treatment of various human cancers and they are not specific to a certain kind of tumor. A recent experiment has revealed that albumin nanostructures containing bevacizumab can suppress glycolysis and reduce metabolism in tumor in a higher capacity compared to drug alone in suppression of colorectal tumor [90]. Since biological aspect of glycolysis and molecular pathways regulating this mechanism have been identified, gene delivery by nanoparticles can be also beneficial. A study on breast tumor has mentioned that RNAi-loaded iron oxide nanocarriers can reduce MCT4 expression to disrupt glycolysis and mediate acidosis in cancer cells to enhance oxidative damage [91]. Notably, phototherapy of tumor can also direct the aim for regulation of glycolysis and tumor metabolism.

The polypyrrole nanostructures can deliver dl-Menthol and can function as a diclofenac nanoplatform stimulate photothermal therapy that suppresses glycolysis in cancer [92]. Importantly, the charge of cancer cells is distinct ogf normal cells. The stimulation of glycolysis can change the charge of cell membrane to negative charge and therefore, positively charged nanocarriers have been developed in cancer therapy [93]. The glycolysis regulation by nanoparticles can also improve cancer immunotherapy; the nanogels have been loaded with doxorubicin and after intracellular accumulation, such nanocarriers release doxorubicin in response to GSH and by impairing glycolysis metabolism, they reduce ATP generation. Moreover, they can stimulate immunogenic cell death and promote maturation of DC cells [94]. One of the regulators of glycolysis in cancer is HIF-1α that increases RNF146 expression in glycolysis stimulation and elevating proliferation [95]. HIF-1 down-regulation by cryptolepine impairs glycolysis in breast cancer [96]. A recent experiment has focused on development of a nanococktail comprised of dendrimer and polymer that is redox-responsive and by reducing HIF-1α suppression, it disrupts glycolysis in tumor cells [97]. **Table 2** summarizes the function of nanoparticles in glycolysis regulation.

Table 2: Affecting the metabolism of cancer cells through nanoparticles.

Nanoparticle	**Mechanism of action**	**Reference**
Zinc-Carnosine Metallodrug Network	Cu-sensitive drug release Inducing Cu depletion Suppressing glycolysis and oxidative phosphorylation	[98]
JX06 nanostructures	A combination of nanoparticles and metformin decrease PDK1 expression in disrupting metabolic plasticity	[99]
Liposome hybrid nanoparticles	Surface modification with cancer cell membrane pH-responsive release of siRNA and docetaxel Glycolysis inhibition	[100]
Liposomes	Loading EDTA and ICG in nanoparticles Deep tumor penetration and glycolysis inhibition	[101]
Iron oxide nanoparticles	Glycolysis mediates negative charge of cancer cells and positively charged nanocarriers suppress tumorigenesis	[102]
Self-assembled nanoparticles	Co-application of berberine and BACH1 inhibitor hermin in preparation of nanoparticles Glycolysis inhibition	[103]
BPTES nanoparticles	A combination of metformin and nanostructures suppress glutaminase After glutaminase inhibition, tumor cells rely on glycolysis for survival	[104]
MOF nanoparticles	Delivery of dihydroartemisinin and down-regulation of PI3K/Akt in glycolysis suppression	[105]
Two-in-One nanoformulation	Delivery of miR-125 and tyrosine kinase inhibitor in glycolysis inhibition	[106]
Bioresponsive nanotherapeutics	Apoptosis and autophagy induction Glycolysis inhibition Targeted delivery of quercetin	[107]

6. CircRNAs induce glycolysis mechanism

The ability of circRNAs in regulating glycolysis mechanism has resulted in a significant impact on progression of tumor cells. Due to two distinct functions of circRNAs including tumor-promoter and tumor-suppressor functions, circRNAs can induce/suppress glycolysis. Circ-DONSON promotes expression level of SOX4 transcription factor to elevate gastric cancer progression [108]. Furthermore, circ-0001829 enhances SMAD2 expression via miR-155-5p sponging to avoid apoptosis in gastric tumor [109]. Besides, circ-0023409 stimulates PI3K/Akt thereby increasing gastric cancer malignancy [110]. Circ-UBE2Q2 stimulates autophagy and glycolysis thereby enhancing gastric cancer progression and to this end, circ-UBE2Q2 triggers STAT3 signaling through miR-370-3p down-regulation [111]. The expression level of oncogenic circRNAs increase in gastric cancer. Circ-0000592 has been positively associated with growth, invasion, and glycolysis. Circ-0000592 suppresses miR-1179 to elevate ANXA4 expression thereby triggering glycolysis and promoting malignancy [112].

Another life-threatening tumor malignancy is bladder cancer. Development of bladder cancer and its malignancy depend on alterations in genetic and epigenetic factors as well as environmental exposures. Despite various therapeutics for bladder cancer, prognosis of patients remains poor [113]. Epigenetic factors are key players in the development of bladder cancer [114-116]. Circ-SEMA5A is an inducer of bladder cancer progression associated with triggering glycolysis. Circ-SEMA5A reduces miR-330-5p to elevate levels of ENO1 and SMEA5A as downstream targets to accelerate tumor progression partially via inducing glycolysis [117]. One of the factors that significantly enhances progression of bladder tumor is hypoxia in tumor microenvironment. Presence of hypoxia can lead to activation of autophagy in bladder cancer and trigger cisplatin resistance [118]. Notably, expression level of circRNAs in bladder cancer can be affected by hypoxia to enhance drug resistance [119]. Hypoxia can result in upregulation of LDHA as one of the enzymes of glycolysis to increase tumor progression. Hypoxia enhances expression level of circ-403658 through HIF-1α-dependent manner and increases LDHA expression which leads to glycolysis induction and bladder tumor progression [120]. In addition to bladder tumor, prostate tumor is also a leading cause of death among men and is associated with a decrease in life quality of patients. Chemotherapy, radiotherapy, surgery, and targeted delivery systems are currently applied in treatment of prostate tumor [121, 122]. Similarly, ncRNAs modulate prostate tumor hallmarks such as proliferation and metastasis as well as response to therapy [123-125]. Circ-MID1 is involved in evoking glycolysis and elevating the progression. Upregulation of IGF1R and YTHDC2 is essential for carcinogenesis. Circ-MID1 enhances the expression level of IGF1R and YTHDC2 via miR-330-3p sponging which leads to glycolysis induction in prostate cancer [126]. Another malignancy of urogenital tract is renal cancer. Circ-VAMP3 can trigger glycolysis in renal cancer. The induction of glycolysis in renal cancer which enhances cancer growth through LDHA overexpression. Circ-VAMP3 is involved in inducing the phosphorylation of LDHA at tyrosine 10 and is mediated by interacting with FGFR1 [127].

Colorectal tumor is a common cancer of digestive system and is still a major healthcare problem worldwide [128]. Colorectal cancer has the third highest incidence rate among cancers and is the

second leading cause of death among patients [129]. Radiotherapy, surgery, chemotherapy, and adjuvant therapies are used for colorectal cancer suppression but prognosis remains poor [130]. Circ-PLCE1 accounts for increasing the progression and malignancy. Circ-PLCE1 functions as a sponge for miR-485-5p to upregulate ACTG1 which induces glycolysis, increases glucose uptake and metabolism, and promotes lactic acid and pyruvate production [131]. The upregulation of circRNAs such as circ-NOX4 induce glycolysis and mediate poor prognosis in colorectal tumor. Circ-NOX4 promotes progression and proliferation of colorectal via inducing glycolysis. To do this, circ-NOX4 promotes CDC28 level via miR-485-5p inhibition [132].

7. CircRNAs suppress glycolysis mechanism

In the previous section, the function of oncogenic circRNAs in inducing glycolysis and promoting malignancy of tumor cells was discussed. However, there are also several circRNAs that can suppress glycolysis and reduce carcinogenesis. Although the focus of experiments is on oncogenic circRNAs, this section aims in highlighting the function of tumor-suppressor circRNAs in glycolysis inhibition. CircRNF13 is an inhibitor of tumor progression with reduced expression levels in lung cancer. Restoring circRNF13 expression leads to sponging miR-93-5p which leads to its downregulation and interference in lung tumor progression [133]. In nasopharyngeal tumor, circRNF13 is considered as an inhibitor of glycolysis. At first, circRNF13 binds to 3'-UTR of *SUMO2* gene to increase protein levels of SUMO2.Then, SUMO2 enhances SUMOylation and degradation of GLUT1 thereby suppressing glycolysis [134]. Circ-0086414 is another pivotal player in tumors and its level is decreased in oral cancer [135]. Crc-0086414 disrupts tumorigenesis via inhibiting glycolysis. Circ-0086414 decreases miR-1290 expression via sponging and such reverse relationship between circ-0086414 and miR-1290 is necessary for upregulating SPARCL1 mediating glycolysis suppression and diminution in growth and metastasis of esophageal tumor [136].

One of the important regulators of glycolysis mechanism in cancer is PI3K/Akt. PER1 suppresses glycolysis mechanism in oral tumor via suppressing PI3K signaling [137]. Furthermore, PLOD1 induces PI3K/Akt signaling via SOX9 upregulation thereby triggering glycolysis and promoting gastric cancer progression [138]. On the other hand, increasing evidence suggests that PI3K/Akt signaling is an oncogenic pathway and a driver of ovarian cancer progression [139, 140]. PI3K/Akt signaling stimulates glycolysis to increase progression of ovarian cancer. However, circ-RHOBTB3 suppresses PI3K/Akt signaling thereby prevents glycolysis, minimizes proliferation and metastasis, and reduces ovarian cancer malignancy [141].

CircFADS2 has been considered as a driver of lung cancer progression via miR-498 sponging [142]. Furthermore, circFADS2 is used as a biomarker in colorectal cancer [143]. However, one of the complexities of circRNAs is their dual function in cancer. For instance, a previous experiment demonstrated the role of circFADS2 to increase lung cancer progression. However, another experiment shows that circFADS2 is an inhibitor of cutaneous cancer progression via glycolysis inhibition. CircFADS2 increases HOXA9 expression via miR-766-3p down-regulation thereby suppressing glycolysis-mediated cancer progression [144]. Notably, the capacity of circRNAs in regulating glycolysis and cancer progression has been confirmed *in vitro* and *in vivo*. Circ-0001777 down-regulates miR-942-5p expression to enhance PRICKLE2

expression, resulting in glycolysis inhibition and lung tumor reduction *in vitro* and *in vivo* [145]. Therefore, more studies are needed to delineate the role of circRNAs in suppressing glycolysis in cancer (**Figure 1**).

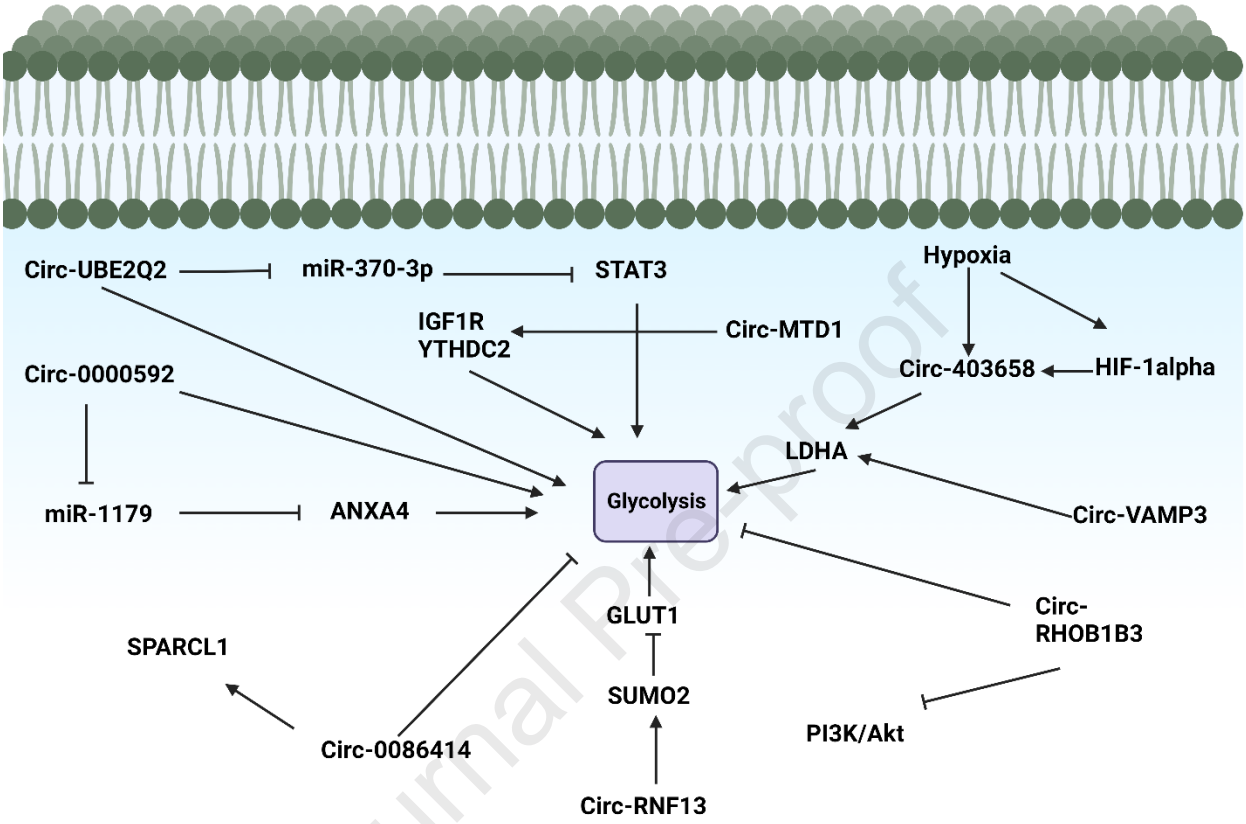


Figure 1: The role of CircRNAs in regulating glycolysis in cancer.

8. CircRNAs regulate drug resistance via glycolysis regulation

Accumulating data has shown that circRNAs are involved in two important aspects of cancer progression including metabolic reprogramming (e.g., Glycolysis) and mediating drug resistance. Circ-CUX1 can interact with EWSR1 to increase MAZ expression thereby triggering glycolysis and increasing proliferation [146]. Besides, circ-0008039 increases SKA2 expression via miR-140-3p sponging leading to glycolysis induction and tumorigenesis promotion in breast cancer [147]. Therefore, circRNAs are critical regulators of glycolysis in cancer [148]. On the other hand, increasing evidence has shown that circ-0,007,331 promotes ANLN expression via miR-200b-3p down-regulation to induce paclitaxel resistance in breast tumor [149]. CircNRP1 is suggested to be a key player in the process of developing resistance to 5-flouoruracil (5-FU) chemotherapy [150]. Although 5-FU is commonly used in treatment of gastric cancer, the development of hypoxia in tumor microenvironment can result in an increase in progression of gastric tumor due to activation of HIF-1α signaling. After overexpression of HIF-1α during hypoxia, glycolysis and glucose metabolism pave the way to increased proliferation of gastric tumor cells and 5-FU resistance. However, miR-138-5p is an inhibitor of HIF-1α signaling

associated with suppression of gastric tumor progression. Notably, circNRIP1 stimulates HIF-1α signaling via miR-138-5p sponging thereby triggering 5-FU resistance in gastric cancer [150]. Therefore, therapeutic targeting of circNRIP1/miR-138-5p/HIF-1α axis is of importance in suppressing glycolysis and reversing 5-FU resistance in gastric cancer [150]. More importantly, 5-FU is utilized for the treatment of colorectal cancer and its anti-invasion activity is based on suppressing EMT mechanism [151]. However, overexpression of tumor-promoting factors and increase in stemness of colorectal cancer cells can result in development of 5-FU resistance [152]. On the other hand, glycolysis is implicated in increasing progression of colorectal cancer. LINRIS can increase stability of IGF2BP2 thereby triggering aerobic glycolysis and mediating colorectal cancer progression [153]. Besides, inhibition of glycolysis by fasting via suppression of Akt/mTOR/HIF-1α axis results in significant reduction in growth of colorectal tumor cells [154]. CircSAMD4A has been implicated in developing 5-FU resistance in colorectal cancer. Upregulation of PFKFB3 induces glycolysis and increases proliferation of colorectal tumor cells thereby triggering 5-FU resistance. CircSAMD4A increases PFKFB3 expression via miR-545-3p sponging to induce glycolysis and 5-FU resistance in colorectal tumor [155].

Paclitaxel belongs to the family of taxanes and its mechanism of action in cancer therapy is based on disrupting the balance of microtubules via inhibiting depolymerization of microtubules to induce cell cycle arrest. Due to the development of paclitaxel resistance in cancer, nanoscale delivery systems have been contemplated on to increase paclitaxel potential for cancer suppression and reversing drug resistance [156]. Circ-RNF111 is involved in triggering paclitaxel resistance in breast tumor. miR-140-5p is capable of reducing expression level of E2F3 to inhibit paclitaxel insensitivity in breast tumor. However, circ-RNF111 promotes E2F3 expression via miR-140-5p down-regulation thereby promote progression and colony formation in breast cancer cells and induce paclitaxel resistance. Notably, the capacity of circ-RNF111 in developing paclitaxel resistance is partially mediated by glycolysis induction via affecting miR-140-5p/E2F3 axis [157]. Lung cancer is another malignant tumor in humans and non-small cell lung cancer (NSCLC) is the most prominent type [158, 159]. In spite of significant efforts in treatment of NSCLC, prognosis and survival rate of patients remain poor [160]. The gold standard of treatment for NSCLC is paclitaxel [161]. Upregulation of circ-0011298 in NSCLC can render paclitaxel resistance in tumor cells. miR-486-3p functions as a tumor-suppressor factor in NSCLC and increases paclitaxel sensitivity via CRABP2 inhibition. However, NSCLC cells show increased malignancy and glycolysis which reduce their sensitivity to paclitaxel chemotherapy. Circ-0011298 sponges miR-486-3p to upregulate CRABP2 thereby induce glycolysis and inhibit apoptosis to develop paclitaxel resistance in NSCLC cells [162].

miR-543 is a new emerging target in cancer therapy and accumulating data suggests its onco-suppressor function. Therefore, increasing miR-543 expression is key in cancer therapy. miR-543 reduces the expression levels of VCAN and UBE2T thereby suppress breast cancer progression [163, 164]. Besides, miR-543 induces apoptosis via suppressing STAT3 signaling in liver cancer [165]. However, a recent experiment has shown that miR-543 can induce cisplatin resistance in NSCLC. Notably, circ-FOXO3 reduces miR-543 expression to inhibit glycolysis and enhance cisplatin sensitivity of NSCLC cells [166]. CircRNAs induce glycolysis and prevent apoptosis to aid in developing drug resistance in cancer [167]. Therefore, future studies are

needed to investigate the regulation of apoptosis by circRNA/glycolysis axis in regulating therapy resistance in cancers.

Another important malignant tumor in humans is hepatocellular carcinoma. Hepatocellular carcinoma is a subtype of liver cancer and the second leading cause of cancer-related death [168, 169]. Despite advances in treatment of hepatocellular carcinoma, metastasis and recurrence are still major challenges [170, 171]. Furthermore, molecular pathways play a significant role in the progression of hepatocellular carcinoma [172-174]. Circ-UBE2D2 promotes the expression level of LDHA via reducing miR-889-3p which leads to glycolysis and sorafenib resistance [175]. In addition to regulating LDHA in glycolysis, circRNAs can also modulate expression level of HK2. Upregulation of HK2 results in glycolysis and mediates cisplatin resistance in NSCLC. Circ-0008928 promotes HK2 expression by miR-488 inhibition leading to glycolysis induction and cisplatin resistance in NSCLC [176]. More importantly, expression level of circRNAs can be regulated by astragalus IV in breast cancer. Astragalus IV is involved in reversing drug resistance in breast cancer. It promotes the expression levels of circ-0001982 which leads to down-regulation of miR-206/miR-613 to suppress drug resistance in breast cancer [177].

Small extracellular vesicles are known as exosomes. These minute structures are used for cell-to-cell communication. Bioactive molecules, RNA molecules, DNA, proteins, and lipids are among the factors that can be loaded in exosomes. Recently, much attention has been directed towards understanding the role of exosomes in cancer progression and therapy resistance [178-181]. Exosomal circRNAs have been considered as regulators of glycolysis that impact drug resistance. Exosomes can deliver circ-0005963 which induces glycolysis via increasing PKM2 expression. Additionally, exosomal circ-0005963 reduces miR-122 expression. Subsequently, PKM2 upregulation during glycolysis leads to drug resistance in colorectal cancer [182]. However, exosomal circ-0094343 increases drug sensitivity in colorectal cancer. Exosomal circ-0094343 promotes TRIM67 expression via miR-766-5p down-regulation to suppress glycolysis thereby promoting drug sensitivity in colorectal cancer [183].

miR-143 is a tumor-suppressor factor capable of inhibiting metastasis of tumor cells and impairing cancer invasion via EMT inhibition [184, 185]. CircRNAs are regulators of miR-143 in cancer progression [186, 187]. Down-regulation of miR-143 can induce glycolysis thereby trigger drug resistance in cancers. Exosomal circ-DLGAP4 can induce glycolysis and mediate chemoresistance in neuroblastoma. Exosomal circ-DLGAP4 increases HK2 expression by miR-143 down-regulation which triggers chemoresistance [188]. Therefore, exosomal circRNAs also regulate glycolysis in cancer therapy resistance [189]. One of the limitations of current studies is the lack of assessments of the role of circRNAs in modulating radio-resistance via glycolysis. **Table 3** summarizes circRNA/miRNA axis in cancer drug resistance.

Table 3: The role of circRNAs in regulating glycolysis and mediating drug resistance.

CircRNA	Molecular pathway	Cancer type	Drug	Remark	Ref

Circ-NRIP1	miR-138-5p/HIF-1α	Gastric cancer	5-Flourouracil	miR-138-5p sponging by circ-NRIP1 Increase in HIF-1α expression Glycolysis induction Drug resistance development	[150]
Circ-SAMD4A	miR-545-3p/PFKFB3	Colorectal cancer	5-Flourouracil	Increase in expression of PFKFB3 by circ-SAMD4A via miR-545-3p sponging Stimulating glycolysis and promoting drug resistance	[155]
Circ-RNF111	miR-140-5p/E2F3	Breast cancer	Paclitaxel	Circ-RNF111 increases E2F3 expression by miR-140-5p sponging in developing paclitaxel resistance	[157]
Circ-0011298	miR-486-3p/CRABP2	NSCLC	Taxol	Circ-0011298 increases CRABP2 expression by miR-486-3p down-regulation in taxol resistance	[162]
Circ-0080145	miR-326/PPFIA1	Leukemia	Imatinib	Circ-0080145 increases PPFIA1 expression via miR-326 down-regulation for inducing imatinib resistance	[167]
Circ-UBE2D2	miR-889-3p/LDHA	Hepatocellular carcinoma	Sorafenib	Circ-UBE2D2 promotes LDHA expression via miR-889-3p sponging for triggering drug resistance	[175]
Circ-0005963	miR-122/PKM2	Colorectal cancer	Oxaliplatin	Circ-0005963 increases PKM2 expression via miR-122 down-regulation for drug resistance development	[182]
Circ-0094343	miR-766-5p/TRIM67	Colorectal cancer	5-flourouracil	Circ-0094343 increases TRIM67 expression via miR-766-5p inhibition for glycolysis inhibition and mediating drug sensitivity	[183]

9. CircRNA/miRNA axis and glycolysis

Up to 75% of the human genome is transcribed to RNAs. There are two types of RNAs including protein-coding and non-coding RNAs (ncRNAs) [190]. microRNAs (miRNAs) are another type of ncRNAs with lengths of less than 24 nucleotides. MicroRNAs are pre-maturely produced in the nucleus and are transferred to the cytoplasm by exportin 5. In the cytoplasm, they undergo maturation and gain their function by loading into RNA-induced silencing complex (RISC) [191, 192]. miRNAs reduce the expression levels of target genes by binding to UTR regions to prevent translation or mediate degradation of mRNAs. Dysregulation of miRNAs is observed in cancers

and can increase/decrease tumor progression. Targeting miRNAs is key in regulating tumor malignancy and affecting cancer progression. miRNAs can regulate cancer hallmarks including proliferation, metastasis, and therapy resistance [193-196]. Furthermore, miRNAs have been considered as important regulators of glycolysis in cancer [197, 198]. CircRNA/miRNA axis can also regulate glycolysis in cancers. CircRNF20 is an inducer of Warburg effect in breast tumor. Upregulation of HIF-1α can lead to an increase in progression of breast cancer and stimulation of glycolysis via enhancing expression level of HK2. However, miR-487a reduces HK2 expression by inhibiting HIF-1α signaling thereby interfering with glycolysis in breast cancer. Notably, CircRNF20 stimulates HIF-1α/HK2 axis by miR-487a sponging which triggers glycolysis and favors breast cancer progression [199]. Similarly, HIF-1α signaling has been implicated in increasing the progression of gastric cancer. HIF-1α upregulation by CTHRC1 is involved in increasing CXCR4 expression to promote invasion of gastric tumor cells [200]. Besides, PI3K/Akt signaling enhances HIF-1α expression which aggravates gastric cancer progression [201]. miR-515-5p suppresses HIF-1α signaling to inhibit glycolysis in gastric cancer. However, gastric tumor cells use molecular pathway switching which increases their progression via glycolysis induction. Gastric tumor cells increase expression level of circ-MAT2B which increases HIF-1α expression via miR-515-5p sponging in cytoplasm leading to glycolysis-mediated gastric cancer progression [202].

miR-98 is another new emerging target in cancer which impairs tumor progression. Hence, restoring miR-98 expression is of importance for cancer therapy. miR-98 reduces the expression level of BCAT1 to reduce self-renewal capacity of cancer stem cells and avoid paclitaxel resistance in gastric cancer [203]. miR-98-5p reduces TGFBR1 and suppresses PI3K/Akt signaling which impair cancer proliferation and invasion [204, 205]. However, lung tumor cells prefer to reduce miR-98 expression in enhancing their progression. Circ-0006349 is involved in triggering glycolysis and promoting the progression of lung cancer. miR-98 reduces MKP1 expression which inhibits lung cancer progression. On the other hand, circ-0006349 increases MKP1 expression via miR-98 down-regulation leading to glycolysis induction and cancer progression [206]. Besides, circ-0091579 and CASC3 are increased in expression in hepatocellular carcinoma, while miR-490-5p is decreased. Knock-down of circ-0091579 is beneficial in preventing progression of tumor cells. Circ-0091579 sponges miR-490-5p to increase CASC3 expression. Then, glycolysis is induced and a significant increase is observed in progression of hepatocellular carcinoma cells [207].

The process of glycolysis is dependent on glucose delivery to cancer cells to be used as a valuable source of energy. Increasing evidence has shown that overexpression of GLUT1 as a cell surface transporter is vital for the process of cancer progression. S100A2 promotes GLUT1 expression to induce glycolysis in colorectal cancer [208]. SALL4 enhances GLUT1 expression via interacting with HP1α to induce glycolysis [209]. Therefore, GLUT1 is an inducer of glycolysis and cancer acceleration. Circ-DENND4C is an inducer of glycolysis in colorectal tumors. Upregulation of GLUT1 has been considered as a pre-requisite of glycolysis induction in colorectal cancer. Circ-DENND4C promotes GLUT1 expression via miR-760 inhibition leading to glycolysis induction and cancer progression [210]. Therefore, glycolysis and proliferation of tumor cells are tightly regulated by circRNA/miRNA axis in cancers. For instance, circ-0001421

aggravates lung cancer progression by promoting CDCA3 expression via miR-4677-3p inhibition thereby triggering glycolysis and accelerating proliferation of lung tumor [211].

Hepatoma-derived growth factor (HDGF) is an oncogenic factor and its upregulation by ZEB1 can lead to increase in invasion of tumor cells [212]. Non-coding RNAs are regulators of HDGF which suppress carcinogenesis [213, 214]. Upregulation of HDGF can lead to glycolysis induction and lung tumor progression. Circ-MAGI3 is involved in facilitating glycolysis and increasing tumor progression in lung cancer. Circ-MAGI3 promotes HDGF expression via miR-515-5p sponging to increase lung cancer growth and glycolysis [215]. miR-106a is an oncogenic factor in different cancers, especially ovarian cancer [216, 217]. Upregulation of miR-106a can pave the way for growth and invasion of prostate tumor cells [218]. In a number of cancers such as colorectal tumor, miR-106a demonstrates tumor-suppressor activity [219] and modulates c-Jun signaling to impair cervical cancer progression [220]. Circ-ITCH is an inhibitor of ovarian cancer progression which reduces miR-106a expression to elevate CDH expression, resulting in glycolysis inhibition and reduction in progression of ovarian tumor cells [221]. Previously, it was mentioned that GLUT1 is involved in increasing the transportation of glucose into tumor cells and triggering glycolysis in cancer cells [222]. Notably, GLUT3 is also involved in the tumorigenesis process and its activation by YAP signaling promotes colorectal cancer progression [223]. Stimulation of tumor cells by IL-8 can lead to an increase in GLUT3 expression [224]. Besides, upregulation of GLUT3 increases glucose uptake and mediates drug resistance in cancer [225]. Circ-MYLK is involved in glycolysis via promoting glucose uptake in NSCLC cells. Silencing circ-MYLK impairs proliferation and glycolysis in NSCLC cells. Circ-MYLK enhances GLUT3 expression via miR-195-5p sponging thereby elevating glucose uptake and mediating glycolysis in tumor cells [226]. Based on these discussions, circRNAs are potential regulators of miRNAs that can impact glycolysis in tumor cells (**Figure 2, Table 4**).

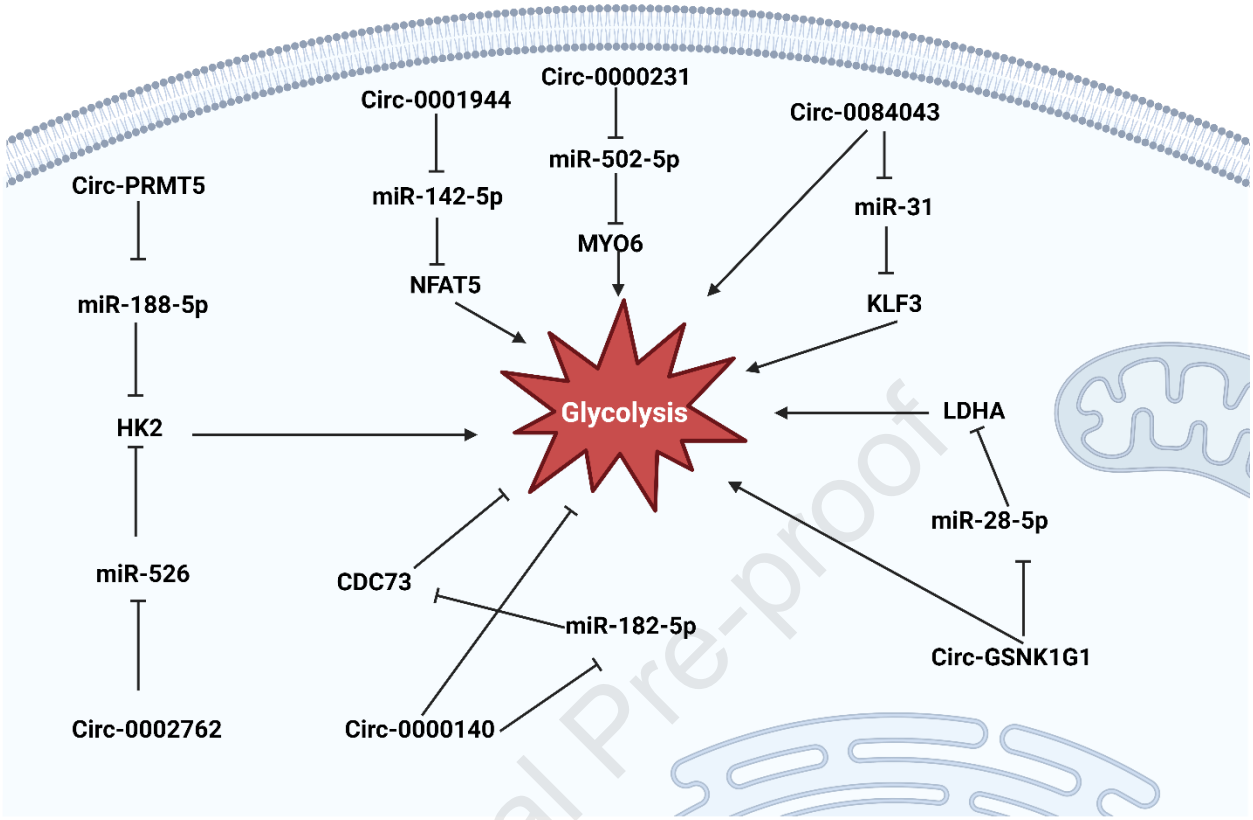


Figure 2: Role of CircRNA/miRNA axis in regulating glycolysis in cancer.

Table 4: An overview of circRNAs' role in regulating glycolysis in cancers.

CircRNA	Molecular pathway	Cancer type	Remark	Ref
Circ-0000231	miR-502-5p/MYO6	Colorectal cancer	Circ-0000231 increases MYO6 expression via miR-502-5p sponging for glycolysis induction	[227]
Circ-0001944	miR-142-5p/NFAT5	Lung cancer	Circ-0001944 increases NFAT5 expression via miR-142-5p inhibition for glycolysis induction	[228]
Circ-PRMT5	miR-188-5p/HK2	Hepatoma	Circ-PRMT5 increases HK2 expression by miR-188-5p down-regulation for glycolysis stimulation	[229]
Circ-0084043	miR-31/KLF3	Melanoma	Circ-0084043 increases KLF3 expression via miR-31 inhibition in increasing cancer progression Glycolysis induction	[230]
Circ-0002762	miR-526b-5p/HK2	Cervical cancer	Circ-0002762 increases HK2 expression via miR-526b-5p sponging for glycolysis induction	[231]

Circ-0000140	miR-182-5p/CDC73	Oral cancer	Circ-0000140 increases CDC73 expression via miR-182-5p sponging in glycolysis inhibition and preventing tumorigenesis	[232]
Circ-CSNK1G1	miR-28-5p/LDHA	Breast cancer	Circ-CSNK1G1 positively regulates LDHA expression via miR-28-5p down-regulation for glycolysis stimulation	[233]
Circ-0000735	miR-940/BMPER	Lung cancer	Circ-0000735 increases BMPER expression by miR-40 sponging for glycolysis induction	[234]
Circ-0009910	miR-361-3p/SNRPA	Gastric cancer	Circ-0009910 enhances SNRPA expression by miR-361-3p sponging Glycolysis induction Tumorigenesis acceleration	[235]
Circ-0000442	miR-1229-3p/ZBTB1	Breast cancer	Circ-0000442 promotes ZBTB1 expression via miR-1229-3p inhibition Suppressing carcinogenesis via glycolysis inhibition	[236]
Circ-0016760	miR-4295/E2F3	Lung cancer	Sponging miR-4295 by circ-0016760 Increasing E2F3 expression Inducing glycolysis	[237]
Circ-0047921	miR-1287-5p/LARP1	Lung cancer	Circ-0047921 increases LARP1 expression by miR-1287-5p sponging for carcinogenesis and glycolysis induction	[238]
Circ-0001982	miR-1287-5p/MUC19	Breast cancer	Circ-0001982 increases MUC19 expression via miR-1287-5p down-regulation for increasing cancer progression during hypoxia and inducing glycolysis	[239]
Circ-0099999	miR-330-5p/FSCN1	Pancreatic cancer	Circ-0099999 increases FSCN1 expression by miR-330-5p sponging for glycolysis induction and facilitating tumorigenesis	[240]
Circ-0136666	miR-383/CREB1	Colorectal cancer	Circ-0136666 promotes CREB1 expression via miR-383 sponging thereby triggering glycolysis and enhancing tumorigenesis	[241]
Circ-0039411	miR-423-5p/SOX4	Thyroid cancer	Circ-0039411 increases SOX4 expression via miR-423-5p sponging for glycolysis induction	[242]
Circ-0002346	miR-582-3p/STXBP6	Lung cancer	Circ-0002346 increases STXBP6 expression via miR-582-3p to suppress glycolysis	[243]

Circ-PITX1	miR-1248/CCND2	Lung cancer	Circ-PITX1 increases CCND2 expression via miR-1248 sponging leading to glycolysis induction	[244]
Circ-0078710	miR-431-5p/TXNDC5	Liver cancer	Circ-0078710 increases TXNDC5 expression by miR-431-5p inhibition Glycolysis induction Apoptosis inhibition	[245]
Circ-0072995	miR-149-5p/SHMT2	Breast cancer	Circ-0072995 increases SHMT2 expression by miR-149-5p down-regulation leading to glycolysis induction	[246]
Circ-TFF1	miR-338-3p/FGFR1	Breast cancer	Circ-TFF1 sponges miR-338-3p to increase FGFR1 expression Facilitating tumor progression via glycolysis induction	[247]
Circ-0001721	miR-372-3p/MAPK7	Osteosarcoma	Glycolysis induction Circ-0001721 promotes MAPK7 expression via miR-372-3p down-regulation	[248]
Circ-RPPH1	miR-328-3p/HMGA2	Breast cancer	Circ-RPPH1 increases HMGA2 expression via miR-328-3p sponging leading to glycolysis induction and increase in proliferation and invasion	[249]
Circ-0001495	miR-526b-3p/TMBIM6	Cervical cancer	Circ-00001495 induces glycolysis in cancer via increasing TMBIM6 expression through miR-526b-3p sponging	[250]
Circ-0026134	miR-3619-5p/CHAF1B	Lung cancer	Circ-0026134 increases CHAF1B expression via miR-3619-5p down-regulation to accelerate tumorigenesis via glycolysis induction	[251]
Circ-0000467	miR-330-5p/TYRO3	Colorectal cancer	Circ-0000467 sponges miR-330-5p to increase TYRO3 expression thereby triggering glycolysis	[252]
Circ-0045932	miR-873-5p/HK2	Colorectal cancer	Circ-0045932 sponges miR-873-5p in increasing HK2 expression and promoting tumorigenesis via glycolysis induction	[253]
Circ-0018289	miR-1294/ICMT	Cervical cancer	miR-1294 sponging by circ-0018289 to increase ICMT expression towards glycolysis induction	[254]
Circ-0001955	miR-1299/GLUT1	Breast cancer	Circ-0001955 decoys miR-1299 to increase GLUT1 expression thereby triggering glycolysis and increasing tumorigenesis	[255]

Circ-0008717	miR-217/FBX017	Renal cancer	Circ-0008717 enhances FBX017 expression via miR-217 sponging thereby glycolysis induction	[256]
Circ-0000376	miR-1182/NOVA2	Lung cancer	Circ-0000376 sponges miR-1182 to increase NOVA2 expression, stimulating glycolysis	[257]
Circ-0003221	miR-892b/DHCR24	Bladder cancer	Circ-0003221 increases DHCR24 expression via miR-892b sponging thereby triggering glycolysis and enhancing tumorigenesis	[258]

10. Anti-cancer agents regulating circRNA/glycolysis axis

One of the important aspects related to glycolysis is the ability of anti-tumor agents in impacting this mechanism. A question is ifcircRNAs can regulate glycolysis, can anti-tumor agents regulate glycolysis to affect tumorigenesis? Several studies have evaluated the role of anti-tumor agents in regulating glycolysis via affecting circRNAs. Bupivacaine is a local anesthetic agent that is commonly used in gastric cancer surgery [259]. Increasing evidence shows that bupivacaine is beneficial in cell death induction and limiting growth rate of cancer cells [260, 261]. Notably, bupivacaine is a regulator of circRNA expression for gastric cancer therapy. Bupivacaine decreases the expression level of circ-0000376 to pave the way for upregulation of miR-145-5p thereby suppressing glycolysis, increasing invasion of gastric tumor cells, triggering apoptosis, and reducing viability of cancer cells [262]. Propofol is another anesthetic agent that it is administered intravenously and is a short-acting agent effective for treating pathophysiological mechanisms of diseases [263, 264]. Propofol treatment of cancer is associated with STAT3 signaling suppression and induction of ferroptosis in tumor cells [265]. Furthermore, propofol inhibits SHH and PI3K/Akt molecular pathways thereby impairing cancer progression [266]. One of the important aspects related to propofol is its impact on circRNAs and regulation of glycolysis. Propofol administration results in a decrease in expression level of circ-ERBB2 which leads to upregulation of miR-7-5p. Subsequently, FOXM1 expression decreases in lung cancer, leading to glycolysis suppression [267].

Propofol has been increasingly used in the treatment of ovarian cancer. Propofol increases drug sensitivity of ovarian tumor cells and suppresses various molecular pathways such as STAT3 to impair ovarian cancer progression [268-270]. Propofol administration results in a decrease in expression level of circ-ZER. Then, expression level of miR-212-5p is enhanced to suppress SOD2, resulting in glycolysis inhibition in ovarian cancer [271]. The ability of propofol in decreasing tumor progression and suppressing glycolysis can be disrupted by increasing expression level of circ-MUC16 [272], suggesting that circRNAs are targets of propofol in cancer therapy. In addition, natural products are also promising candidates in treatment of cancer. Tanshinone I has been increasingly applied for the treatment of cancer and is capable of suppressing PI3K/Akt/mTOR axis in reducing ovarian cancer progression [273]. Furthermore, tanshinone I induces apoptosis and suppresses STAT3 signaling in cancer therapy [274, 275]. Tanshinone I has been beneficial in impairing the progression of osteosarcoma. For this purpose,

tanshinone I decreases circ-0000376 expression to upregulate miR-432-5p, resulting in Bcl-2 down-regulation and glycolysis and metastasis suppression [276]. Therefore, circRNA is a "druggable target" and its expression level can be regulated by anti-cancer agents in suppressing glycolysis for tumor treatment.

11. Conclusion and remarks

The tumor microenvironment is characterized by several features such as redox imbalance and low pH levels. The acidic pH of tumor microenvironment is because of high proliferation of cancer cells while colony formation can be attributed to glycolysis induction. There are several enzymes involved in glycolysis such as LDHA, HK2, and others, whose activity induces glycolysis and increase carcinogenesis. The regulation of glycolysis in cancer cells has been of interest and circRNAs are considered as potent modulators of glycolysis in cancer. Due to pleiotropic function of circRNAs and their capacity in modulating molecular pathways as well as their functions as epigenetic factors, increasing evidence has shown that aberrant expression of circRNAs can lead to dysregulation of glycolysis in cancer. The purpose of the current review is to show how circRNAs can affect glycolysis mechanism directly and indirectly in cancers. There are two types of circRNAs, those that induce glycolysis and those that suppress it. The circRNAs regulating glycolysis mechanism can be transferred in tumor microenvironment and among tumor cells via exosomes and therefore, modulating biogenesis of exosomes can control progression and glycolysis in cancer cells. The interaction of circRNAs with glycolysis can determine the response of tumor cells to chemotherapy. Furthermore, circRNAs primarily regulate glycolysis via affecting miRNAs. HK2, LDHA, and PKM2 are mainly regulated by circRNAs thereby affecting glycolysis. HMGA2, SOX4, and CREB1 are among the downstream targets indirectly affected by circRNAs in regulating glycolysis in cancer. More importantly, propofol, tanshinone I, and bupivacaine have been used as regulators of circRNA expression in suppressing glycolysis-mediated cancer progression.

Although significant efforts have been made in revealing the potential of circRNAs and downstream targets in glycolysis regulation, there are several gaps and limitations that should be considered in future studies. The first gap is that there is no experiment on the role of circRNA/glycolysis axis in radio-resistance development in cancer and since radiotherapy is one of the major arms in treatment of cancer, future studies should focus on this aspect. Additionally, two key entities, i.e., exosomal circRNA and tumor-suppressor circRNAs have been ignored for their role in regulating of glycolysis in cancer. Although there are experiments related to them, more studies on their role in tumor progression regulation are required. Another limitation is that only the efficacy of three anti-cancer agents including propofol, bupivacaine, and tanshinone I in regulating circRNA/glycolysis axis in cancer has been investigated and more anti-cancer agents need to be tested. Another major gap is the lack of studies related to using nanostructures for delivery of anti-tumor agents or genetic tools to manipulate levels of circRNAs and targeted therapy of cancer. Future studies can translate these findings into clinic for treatment of patients.

Although the molecular profile of glycolysis and its regulation by circRNA have been understood with details, it is vital to use agents for targeting glycolysis in human cancers. The section 10 of current paper displayed application of pharmacological compounds and anti-cancer

drugs in glycolysis suppression for tumor therapy, but they lack specific accumulation at cancer site. Therefore, nanoparticles for specific targeting and removal of tumor cells have been developed. In section 4, it was discussed that nanoparticles can suppress growth and metastasis of tumor cells. Nanoparticles can impair immunosuppression and induce tumor microenvironment remodeling. Nanoparticles are used for vaccine development and they can deliver both drugs and genes in cancer therapy. Moreover, nanoparticles induce phototherapy in cancer removal. Due to progresses in field of biology, nanoengineering and their combination, there have been efforts that focused on nanoparticle application in glycolysis inhibition. In section 5, it was discussed that nanoparticles can suppress pathways related to glycolysis such as HIF-1α and enzymes of glycolysis pathway such as HK2. Moreover, nanoparticles can deliver drugs and genes suppressing glycolysis in cancer therapy. Therefore, targeted regulation of glycolysis in cancer therapy has been conducted and in order to increase specific targeting of cancer cells, the functionalization of nanoparticles with ligands has been conducted. Moreover, nanoparticles can mediate phototherapy for preventing glycolysis in cancer. However, we are still at the beginning way of using nanoparticles in cancer therapy and more advanced experiments regulating glycolysis in cancer should be conducted. Furthermore, the role of circRNA/glycolysis axis in human cancers was discussed properly and an impornat part is capacity of nanoparticles for delivery of circRNAs in cancer therapy [277]. Therefore, use of circRNA-loaded nanoparticles in glycolysis suppression in human cancers can be examined in future studies.

Conflict of interest:

The authors declare no conflict of interest.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: