MiRNAs link Metabolic Reprogramming to Oncogenesis

Maria Hatziapostolou[1-3*], Christos Polytarchou[1-3*] & Dimitrios Iliopoulos[1-3#]

[1]Center for Systems Biomedicine, [2]Division of Digestive Diseases, [3]Institute for Molecular Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA

*These authors have equally contributed.

[#]**Corresponding author**: Dimitrios Iliopoulos, Ph.D., Center Systems Biomedicine, Division of Digestive Diseases, David Geffen School of Medicine, University of California at Los Angeles, 650 Charles E Young Dr., CHS 44-133, Los Angeles, CA 90095-7278. Tel: 310-825-8856; E-mail: diliopoulos@mednet.ucla.edu; Phone: 310-825-8856

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Abstract

The most profound biochemical phenotype of cancer cells is their ability to metabolize glucose to lactate, even under aerobic conditions. This alternative metabolic circuitry is sufficient to support the biosynthetic and energy requirements for cancer cell proliferation and metastasis. Alterations in oncogenes and tumor suppressor genes are involved in the metabolic switch of cancer cells to aerobic glycolysis, increased glutaminolysis and fatty acid biosynthesis. MiRNAs mediate fine-tuning of genes involved directly or indirectly in cancer metabolism. In this review, we discuss the regulatory role of miRNAs on enzymes, signaling pathways and transcription factors involved in glucose and lipid metabolism. We further consider the therapeutic potential of metabolism-related miRNAs in cancer.

Keywords: miRNAs, metabolism, cancer, therapy

Highlights:

Metabolic reprogramming is a central hallmark of oncogenesis.

Metabolic pathway alterations in cancer are tightly regulated by microRNAs.

MicroRNAs regulating metabolic pathways are frequently silenced or overexpressed in cancer.

MicroRNAs targeting the metabolic reprogramming cascade possess value for cancer therapy.

Metabolic reprogramming in cancer

Cancer is a disease where cells have lost their normal checks on cell proliferation. Intrinsic and extrinsic molecular mechanisms converge to alter core cellular metabolism and provide support for the three basic needs of proliferating cells: rapid ATP generation to maintain energy status; increased biosynthesis of macromolecules; and maintenance of appropriate redox status [1]. To meet these needs, cancer cells often display fundamental changes in pathways of energy metabolism and nutrient uptake. Similar alterations are also observed in rapidly proliferating normal cells, representing responses to physiological growth signals [2, 3].

In comparison to normal cells, malignant transformation is associated with excessive glucose uptake, aerobic glycolysis, glutaminolysis, altered lipid metabolism, *de novo* fatty acid synthesis and increased generation of reactive oxygen species (ROS) (**Figure 1**). These bioenergetics and metabolic features allow cancer cells to proliferate and survive under adverse conditions such as hypoxia, and enable their progression, invasiveness, and subsequent distant metastasis [4].

The best characterized metabolic phenotype that distinguishes cancer from normal cells is the aerobic glycolysis, also termed the Warburg effect (Box 1). The fundamental finding of Warburg's studies was that cancer cells metabolize glucose to lactate under aerobic conditions, despite the fact that this metabolic pathway is much less energy efficient when compared to oxidative phosphorylation. The Warburg phenomenon has been observed across several tumor types and is often associated with a high rate of glucose uptake [5]. However, since these alterations are also observed in the proliferating normal cells it is not clear whether this metabolic profile is specific to cancer or just cell proliferation. Moreover, the Warburg effect alone cannot explain all the metabolic alterations that are necessary for cell growth requirements [6]. Instead, the importance of other nutrients in fueling cell growth, such as glutamine, has gained much attention the recent years [7]. The metabolic interactions between tumor and stroma add more complexity to the understanding of metabolic reprogramming of cancer. Tumors with the same genetic lesions have different metabolic profiles depending on the tissue they arise in [8], suggesting that

the tissue microenvironment strongly affects the metabolic activity of cancer cells. Another mechanism that is not explained by the Warburg effect and still remains unclear is how cancer cells maintain the balance between enhanced glycolytic activity and the need for antioxidant production. ROS can directly suppress aerobic glycolysis, through inhibition of the glycolytic enzyme pyruvate kinase (PKM2), and induce the production of NADPH for anti-oxidant synthesis by allowing the accumulation of glycolytic intermediates [9]. In conclusion, although the Warburg phenomenon has become synonymous with the hallmark designation attributed to altered cancer metabolism, still remains unclear whether it plays a causal role in cancer or it is just an epiphenomenon.

MiRNAs and Cancer

MicroRNAs (miRNAs) are endogenous small non-coding RNAs, 18 to 25 nucleotides in length, which regulate gene expression [10]. The mechanism of miRNA biogenesis is described in Box 2. MiRNA-mediated regulation of gene expression may take place either through mRNA degradation or inhibition of translation. MiRNAs bind to the 3'-untranslated region (3'-UTR) of the target mRNA through imperfect base-pairing, thus are able to regulate a large number of genes simultaneously [11-13]. Therefore, miRNAs act as master gene regulators, similar to transcription factors and the two may cooperate and ultimately determine gene expression patterns in the cell [14, 15].

MiRNAs are involved in a number of biological processes, such as development. differentiation, proliferation, apoptosis or pluripotency [10, 16]. Recent studies have shown that miRNAs control different aspects of energy metabolism including insulin production and signaling, glucose transport and metabolism, cholesterol and lipid homeostasis and amino-acid biogenesis [17, 18]. MiRNAs regulate cell metabolic processes either directly by targeting key molecules of metabolic pathways (transporters, enzymes and kinases) or indirectly by modulating the expression of important transcription factors [16-18].

The full spectrum of miRNAs expressed in a specific cell type (the miRNAome) varies between normal and pathologic tissues and specific signatures of deregulated miRNAs harbor diagnostic and prognostic implications [16, 17]. Deregulation of miRNA expression is involved in the initiation and progression of tumorigenesis and has been investigated in almost all types of human cancer [19]. Some miRNAs act mainly as tumor suppressors while others have a well-established role as oncogenes, depending upon their target genes. Multiple studies have revealed that the altered metabolic pathways in cancers are tightly regulated by miRNAs. The downstream targets of a number of miRNAs are directly or indirectly connected to metabolic regulation [18, 20]. In this review, we discuss the regulatory role of miRNAs on essential cancer metabolism molecular mechanisms.

MiRNAs and Metabolic Reprogramming

Regulation of glucose uptake receptors by miRNAs

Glucose transport across the plasma membrane of eukaryotic cells is mediated by two different types of membrane-associated carrier proteins, the Na^+-coupled glucose transporters (SGLT) and glucose transporter facilitators (GLUT) (**Figure 1**). The SGLT family members function as sugar transporters (SGLT1 and SGLT2) or sensors (SGLT3) [21]. Eleven out of the 14 members of the GLUT family in humans facilitate glucose transport and exhibit differential regulation, tissue-specific expression and substrate specificity. The levels of GLUT1, GLUT2 and GLUT3 are found elevated in most malignant tissues, while the mRNA of GLUT4 and GLUT5 are below sensitivity [22]. Presumably, the deregulation of GLUTs may increase glucose uptake, satisfy the high glucose requirements and accelerate metabolism in cancer cells.

Among the different mechanisms regulating GLUTs, miRNAs may regulate glucose uptake via affecting GLUTs expression or indirectly through effects on other regulatory mechanisms (**Table 1**). MiR-195-5p, which is downregulated in bladder cancer, has been identified as a direct regulator of GLUT3 [23]. A protein with glucose transporter function, SLC45A3, is directly regulated by miR-32 [24]. GLUT4 expression is indirectly upregulated by miR-223 and

downregulated by miR-133 [25, 26]. Other examples of indirect regulation of glucose transport include miR-23a, which regulates SMAD4 and subsequently GLUT4 translocation [27] and miR-21, which affects GLUT4 translocation in adipocytes [28]. However, the direct links between miRNA deregulation and glucose transport in cancer are largely unknown.

Functions of miRNAs in glycolysis

Recent studies have emphasized the miRNA regulation of the irreversible steps in glycolysis (**Table 1**). Hexokinases catalyze the first and irreversible step of glucose metabolism, the ATP-dependent phosphorylation of glucose to yield glucose-6-phosphate (**Figure 1**) [29]. Hexokinase 2 (HK2) is overexpressed in tumors and contributes to aerobic glycolysis. Thus, it is characterized as a pivotal player in the Warburg effect and an emerging target for cancer metabolism therapeutics [30, 31]. MiR-143 inhibits HK2 expression in head and neck squamous cell carcinoma (HNSCC) cell lines. In accord, miR-143 inversely correlates with HK2 expression in HNSCC and lung tumors [32, 33]. Similarly, targeting of HK2 by miR-143 affects glucose metabolism in colon cancer cells [34]. Importantly, the 5q–syndrome a common subtype of the Myelodysplastic syndrome, is defined by an isolated interstitial deletion of chromosome 5q, where the *MIR-143* gene resides [35]. This locus is often deleted in other malignancies [36], while miR-143 has also been found down-regulated in a number of cancers [37, 38]. The miRNA-dependent regulation of hexokinase expression is not limited to HK2 as miR-138 targets HK1 [32]. Other important intermediate steps in the glycolysis pathway may be regulated by or regulate microRNAs. Aldolase A is a direct target of miR-122 in liver cells [39]. Phosphoglucose isomerase (PGI) has been associated with invasion and metastasis of cancer cells. PGI regulates the expression of the miR-200 family of microRNAs and subsequently the Epithelial-Mesenchymal Transition (EMT) in breast cancer cells [40].

Cancer cells re-express the embryonic isoform of pyruvate kinase (PK), PKM2, which dephosphorylates phosphoenolpyruvate (PEP) to pyruvate (**Figure 1**). PKM2 provides a metabolic advantage in that it allows the tumor cells to use phosphometabolites upstream of

pyruvate as precursors for the synthesis of amino acids, nucleic acids and lipids [41, 42]. MiR-326 has been shown to target PKM2 and suppress cell growth. As a result, in glioblastoma cell lines, the upregulation of PKM2 correlates with low levels of miR-326 [43]. Likewise, miR-122 targets PKM2 and inhibits hepatocellular carcinoma (HCC) proliferation. Significantly, the increased miR-122 promoter methylation in HCC inhibits its expression and relieves PKM2 suppression [44]. PKM2 overexpression in tongue SCC has been associated with the downregulation of miR-133a and miR-133b [45]. A set of microRNAs, deregulated in colorectal cancer, miR-124, miR-137 and miR-340 are proposed to regulate the switch of PKM gene expression from PKM2 to PKM1 [46]. Under hypoxic conditions, miR-210 represses ISCU1/2 and thus, decreases the activity of proteins controlling mitochondrial metabolism, including Complex I and aconitase [47]. Hence, miR-210 represses mitochondrial respiration and might indirectly facilitate aerobic glycolysis in cancer.

MiRNAs involved in lactate metabolism

In normal cells, when oxygen is available, pyruvate undergoes oxidative phosphorylation in mitochondria, through the tricarboxylic acid (TCA) cycle. When oxygen levels are low, pyruvate is converted to lactate in the cytoplasm by lactate dehydrogenase (LDH) (**Figure 1**). LDHB is a target of miR-375 which is downregulated in maxillary sinus and esophageal SCC (**Table 1**). This contributes to the increased levels of LDHB and correlates with increased tumor aggressiveness [48, 49].

Most of the lactate is secreted and can be taken up by the liver where it is converted into glucose and recycled to the bloodstream and back to the tumors. The ability of cells to secrete lactate depends on the monocarboxylate transporters (MCTs) (**Figure 1**). MCT1 is targeted by miR-29a, miR-29b and miR-124 (**Table 1**) [50]. During the progression of malignant melanoma, the highly expressed protein basigin (Bsg) interacts with MCT1 and 4. Let-7b has been shown to target Bsg and inhibit the invasiveness of melanoma cells, potentially through the disruption of this interaction (**Table 1**) [51].

Glutamine Metabolism

Apart from glucose, cancer cells exhibit increased glutamine intake and glutamine metabolism (glutaminolysis). This adaptive accelerated glutamine metabolism by cancer cells seems to provide substrates for increased lipogenesis and nucleic acid biosynthesis that are critical to the proliferative phenotype of the cancer cell. It has been demonstrated that cell transformation stimulates glutaminolysis and that many cancer cells are tightly dependent on this amino acid [52, 53].

Cancer cells are known to overexpress mitochondrial phosphate dependent and phosphate independent glutaminase, the enzyme that catalyzes the degradation of glutamine to glutamate and ammonia [54]. Glutamate can be converted directly into GsH, by the enzyme glutathione cysteine ligase (GCl), one of the most abundant antioxidants in mammalian cells important in controlling the redox state of all subcellular compartments [55]. Glutamate can also further oxidized to α-ketoglutarate and enter the TCA cycle to produce ATP. It has been documented that the ammonia produced following glutaminolysis stimulates autophagy, suggesting that when glucose-depleted cells become more dependent on glutamine via glutaminase and glutamate dehydrogenase to produce α-ketoglutarate, the excess ammonia triggers autophagy to provide sufficient energy to survive a period of glucose deprivation [56]. One of the major regulators of glutaminolysis is MYC, further supporting the concept that MYC promotes not only cell proliferation but also the generation of macromolecules and antioxidants required for growth. In the same line, the suppression of *MIR-23A/B* by MYC enhances mitochondrial glutaminase expression and glutamine metabolism [53].

MiRNA regulation of insulin secretion and signaling

In response to increased nutrient levels in the blood, pancreatic β-cells synthesize and secrete insulin. The effects of insulin secretion include glucose uptake in muscles and adipocytes, inhibition of glucose production in the liver and increased storage of nutrients in forms of fat,

glycogen and protein. MicroRNAs have been implicated in insulin secretion regulation through effects on pancreatic development and insulin exocytosis. MiR-375 and miR-124a decrease insulin exocytosis through the repression of myotrophin [57, 58]. Additionally, miR-9 regulate insulin secretion through inhibition of the transcription factor one cut homeobox 2 [59].

Other miRNAs act in target tissues to regulate responses to insulin and glucose homeostasis. The let-7 tumor suppressor microRNAs are known for their regulation of oncogenes, while the RNA-binding proteins Lin28a/b promote malignancy by blocking let-7 biogenesis. In studies using transgenic mice, it has been demonstrated that the Lin28/let-7 pathway is a central regulator of mammalian glucose metabolism. Both Lin28a and LIN28B promoted an insulin-sensitized state that resisted high fat diet-induced diabetes, whereas muscle-specific loss of Lin28a and overexpression of let-7 resulted in insulin resistance and impaired glucose tolerance. These phenomena occurred in part through let-7-mediated repression of multiple components of the insulin-PI3K-mTOR pathway [60]. Furthermore, it was recently shown that Lin28 restores glucose metabolism in obese adipocyte stem cells through repression of let-7 expression [61]. MiR-29a and miR-29b, have been linked to insulin resistance, through the down-regulation of proteins that promote insulin signaling like caveolin 2 and phosphatidylinositol 3-kinase (PI3K) regulatory subunit-α [62, 63]. The inhibition of insulin receptor substrate-1 (IRS1) by miR-126 also promotes insulin resistance [64], while miR-33a and miR-33b affect insulin signaling and glucose regulation by targeting IRS2, SIRT6 and AMPKα1 [65]. Additionally, miR-33a may regulate Pim-1, a kinase that possesses overlapping functions with Akt [66]. In this context, it has been demonstrated that miR-33a may be an efficient strategy for microRNA replacement therapy [67]. IRS-2 is a target of miR-7-5p in melanoma cells. MiR-7-5p is downregulated in metastatic melanoma-derived cell lines and regulates melanoma cell migration and invasion through upregulation of IRS-2 and induction of Akt [68].

Obesity is an established risk and progression factor for many cancers. In obesity models, several miRNAs are overexpressed and exert regulatory effects on insulin signaling and glucose homeostasis. MiR-103, miR-107 and miR-143 are overexpressed and reduce insulin sensitivity

[69, 70]. Protein tyrosine phosphatase 1B (PTP1B), a target of miR-122, inhibits hepatic insulin signaling by dephosphorylating insulin receptor and IRS. In high-fat-diet-fed mice and hepatocyte models with insulin resistance, the expression of miR-122 is downregulated [71].

MiRNAs and Lipid Metabolism

Lipids form a diverse group of water-insoluble molecules and include triglycerides, phospholipids, sterols and sphingolipids. Triglycerides are mainly used for energy storage while phospholipids, together with sterols and sphingolipids, represent the major structural components of biological membranes. Lipids can also act as signaling molecules, functioning as second messengers (e.g. sphingolipids) and as hormones (e.g. steroid hormones) [72]. Lipids such as cholesterol and fatty acids are taken up in the diet and are synthesized *de novo*, predominantly in the liver. Regulation of the biosynthesis of cholesterol, fatty acids and phospholipids is mediated by transcription factors such as sterol regulatory element binding proteins (SREBPs) [73]. A major transcription factor of the liver that regulates lipid homeostasis and controls the expression of 12% of the genes expressed is hepatocyte nuclear factor α (HNF4α) [74]. Interestingly, adult liver-specific knockout mice of the *HNF4A* gene exhibit fatty liver and greater than 70% mortality by 8 weeks of age [75]. A more broad effect of HNF4α on metabolism is reflected on the finding that mutations on the *HNF4A* gene contribute to several forms of maturity-onset diabetes in children [76].

Changes in lipid metabolism can affect numerous cellular processes, including proliferation, differentiation and cell motility. There is increasing evidence that cancer cells show specific alterations in different aspects of lipid metabolism. One characteristic is that irrespective of the concentration of extracellular lipids, fatty acids are mainly synthesized *de novo* [72]. Another characteristic is that some tumor types, instead of exhibiting a high rate of glucose uptake they exhibit increased dependence on lipid oxidation as their main energy source. One such example is prostate cancer, which generally displays a low rate of glucose utilization, showing increased uptake of fatty acids and overexpression of some β-oxidation enzymes [77, 78]. The increased availability of lipids in cancer cells contributes to several aspects of tumor biology such as cell

growth and proliferation, survival under oxidative and energy stress, chemoresistance, support of a high-glycolytic rate by promoting redox balance and stimulation of signaling pathways that lead to invasion and metastasis [72, 79].

MiR-122 was the first miRNA to be linked to metabolic control. It is expressed primarily in the liver and was initially shown to affect hepatic cholesterol and lipid metabolism [80]. Antisense targeting of miR-122 in the whole animal results in a vast reduction in plasma cholesterol by affecting the expression of genes involved in cholesterol biosynthesis [81], and inducing fatty acid β-oxidation [82]. However, the genes affected by miR-122 in the liver and are involved in cholesterol and lipid metabolism, do not seem to be direct targets of miR-122 [81]. Interestingly, miR-122 was successfully targeted by antisense inhibitors using locked nucleic acid (LNA) chemistry in non-human primates, resulting in lowered circulating cholesterol [83]. Regarding cancer, deletion of miR-122 in mice causes several key phenotypes of chronic human liver diseases and eventually liver cancer [84, 85]. This lack of mechanistic understanding of miR-122 and the carcinogenic effect of miR-122 suppression raised questions about the development of miR-122 antisense technologies as therapeutic approaches.

Several recent studies have reported miR-33a/b as a regulator of cholesterol/lipid metabolism and energy homeostasis. *MIR-33A/B* embeds within intron sequences of the human *SREBF* genes and controls the levels of ATP-binding cassette transporter ABCA1, a cholesterol efflux pump [86, 87]. Thus, Srebp and miR-33 may cooperate to regulate cell proliferation and cell cycle progression [88]. MiR-33a/b also acts in the lipid homeostasis pathway by controlling the expression of fatty acid β-oxidation genes and energy homeostasis regulators like AMPK and SIRT6 [65].

There's evidence that miRNAs are involved in the differentiation of adipocytes and the development of obesity [89, 90]. MiR-335 is up-regulated in the white adipose tissue of obese mice and is associated with elevated hepatic triglycerides and cholesterol [90]. Additionally, miR-370 acting via miR-122 may accumulate hepatic triglycerides by modulating initially the

expression of SREBP-1c, DGAT2, and Cpt1α and, subsequently, the expression of other genes that affect lipid metabolism [91].

It was recently demonstrated that miR-24 and miR-629 suppress directly HNF4α expression inducing hepatocellular cancer initiation and growth. Furthermore, we have shown that miR-24 and miR-629 are upregulated in HCC and their expression is mediated by STAT3. We have further demonstrated that HNF4α controls the expression of miR-124, a miRNA suppressed in HCC. Our findings suggest that transient inhibition of HNF4α initiates hepatocellular transformation through a feedback loop circuit that consists of miR-124, miR-24, miR-629 and STAT3. Once this circuit is activated it maintains suppression of HNF4α and sustains oncogenesis [15].

MiRNA regulation of signaling pathways

The fact that a plethora of the predominant mutations observed in cancer also regulate cell metabolism led to the theory that oncogene and tumor suppressor networks influence the metabolic shift in cancer. Accordingly, the interrelation between deregulated microRNAs and imbalanced signaling pathways largely contributes to abnormal cell metabolism and carcinogenesis (**Table 2**). Major factors and pathways involved in metabolic reprogramming include HIF1A, MYC, AKT, AMPK, and p53 (**Figure 2**).

*HIF1 and MYC transcription factors***:** The hypoxia-inducible factor (HIF) complexes are transcription factors regulating gene expression upon oxygen deprivation. HIF1α or HIF2α subunits are stabilized upon exposure to hypoxia and form heterodimers of the HIF1β. These two transcription factors increase the cell capacity to carry out glycolysis, through the activation of genes encoding glucose transporters and most glycolytic enzymes, and reinforce the glycolytic phenotype through activation of the pyruvate dehydrogenase kinases (PDKs) which reduce the flow of pyruvate into the TCA cycle (**Figure 2**) [1]. MiR-199a downregulation upon oxygen deprivation is required for the rapid upregulation of its target, HIF1α [92]. In chronic lymphocytic

leukemia (CLL), the stabilization of HIF1 under normoxia is mediated by miR-92-1. MiR-92-1 targets the von Hippel-Lindau (VHL) tumor suppressor [93], an E3 ubiquitin ligase which marks HIF1α for degradation in the presence of oxygen. Under hypoxia, miR-424 upregulation in endothelial cells stabilizes HIF1α through the targeting of cullin 2, a scaffolding protein critical to the assembly of ubiquitin ligase system [94]. Glycerol-3-phosphate dehydrogenase 1-like (GPD1L), an inhibitor of HIF-1α stability is a direct target of miR-210. Importantly, miR-210, a transcriptional target of HIF-1α is overexpressed in multiple cancers and reinforces HIF-1α activity [95]. The oncogenic transcription factor MYC collaborates with HIF in the activation of several glucose transporters, glycolytic enzymes, LDHA and PDK1. In parallel, MYC regulates glutamine metabolism and mitochondrial function through the activation of genes involved in mitochondrial biogenesis [4, 52]. *MYC* increases glutamine uptake by directly inducing the expression of the glutamine transporters slC5A1 and slC7A1 (also known as CAT1) [53]. MiR-33b has been identified as a negative regulator of c-MYC. Thus, in medulloblastomas loss of the 17p11.2 genomic locus, where *MIR-133b* resides, results in c-Myc overproduction [96]. MYC directly up-regulates a pro-tumorigenic group of miRNAs known as the miR-17-92 cluster (Figure 2) [97]. This cluster leads to inhibition of tumor suppressor PTEN, an antagonist of PI3K/Akt/mTOR pathway which plays important roles in facilitating aerobic glycolysis in cancer cells [98].

*The PI3K/AKT/mTOR pathway***:** The AKT pathway, commonly activated in human cancers, is a key regulator of survival and apoptosis, cell cycle and growth, protein synthesis and glucose metabolism [99]. AKT, which lies downstream of PI3K, stimulates glycolysis by increasing the expression and membrane translocation of glucose transporters and by phosphorylating key glycolytic enzymes, such as hexokinase [100, 101] (**Figure 2**). Through the inhibition of forkhead box subfamily O (FOXO) transcription factors, AKT increases the glycolytic capacity and lipid genesis [102, 103]. In addition, AKT strongly stimulates mTOR by phosphorylating and inhibiting its negative regulator tuberous sclerosis 2 (TSC2). Activated mTOR stimulates protein and lipid biosynthesis and cell growth in response to sufficient nutrient and energy conditions [103]. Finally,

sustained activation of the PI3K/AKT/mTOR pathway in cancer regulates metabolism partly through HIF-1α induction under normoxic conditions (**Figure 2**) [1, 99]. MiR-126, frequently lost in colorectal cancers, impedes tumor cell growth by targeting the p85b subunit of PI3K [104]. MiR-21, a microRNA increased in multiple cancers, activates AKT through the inhibition of PTEN and induces the tumor cell migration, proliferation and invasiveness [105]. It has been demonstrated that AKT2, one of the three isoforms of AKT, under hypoxic conditions regulates miR-21 and promotes resistance to hypoxia through activation of all isoforms [106]. It was recently shown that AKT isoforms differentially regulate microRNA expression. In specific, through the downregulation of miR-200 family of microRNAs, AKT signals may govern EMT and cancer stem cell-like properties [107]. On the other hand, miR-143 upregulation in the liver of obese mice results in downregulation of oxysterol-binding-protein-related protein 8 and thus impaired ability of insulin to induce AKT activation [70]. In liver cancer the upregulation of miR-221 negatively correlates to the expression of DNA damage-inducible transcript 4 (DDIT4), a modulator of mTOR [108]. In addition, miR-100 was found to target mTOR and its downregulation in ovarian cancer cell lines enhanced mTOR signaling [109]. MiR-199a-3p, downregulated in several human malignancies, inversely correlates with its target mTOR in hepatocellular carcinomas [110].

*AMP-activated protein kinase***:** The AMPK pathway couples energy status to growth signals. It functions as a metabolic checkpoint, regulating the cellular responses to energy availability [111]. LKB1 a kinase that lies upstream of AMPK, in the presence of AMP, when intracellular levels of ATP are low, phosphorylates and activates AMPK (**Figure 2**) [112]. Thus, during periods of energetic stress, AMPK becomes activated in response to an increased AMP/ATP ratio, and is responsible for shifting cells to an oxidative metabolic phenotype and inhibiting cell proliferation. In tumor cells uncoupling the fuel signals from growth signals, allows them to divide under abnormal nutrient conditions. In fact, many cancer cells exhibit a loss of appropriate AMPK signaling which may also contribute to their glycolytic phenotype [1, 111]. Interestingly, miR-451 promotes glioma cell adaptation to metabolic stress through suppression of the LKB-1-associated

protein CAB39 and indirect activation of mTOR signaling [113]. Recently, miR-195 has been found to also target CAB39 and regulate mTOR [114].

*The p53 pathway***:** Tumor suppressor p53, best known for its functions in the DNA damage response and apoptosis, it is also an important regulator of metabolism. p53 activates the expression of HK2 [115], TP53-induced glycolysis and apoptosis regulator (TIGAR) [116], PTEN [117] and SCO2 [118]. TIGAR decreases the levels of the glycolytic activator fructose-2,6-bisphosphate and PTEN inhibits the PI3K pathway, and collectively suppress the glycolytic pathway, while SCO2 increases mitochondrial metabolism (**Figure 2**). Hence, loss or suppression of p53, an event common in cancers, might function as a major force behind the acquisition of the glycolytic phenotype. Several studies have identified miRNAs as regulators of p53 activity as well as its downstream effectors (**Table 2**). The 3'-UTR of p53 mRNA contains a conserved response element for miR-125b [119]. MiR-504 acts as a negative regulator of human p53, decreases p53 protein levels and promotes tumorigenicity [120]. A library screen identified a group of microRNAs regulating p53 activity. Among them, miR-30d downregulate p53 protein levels and inhibit p53-transcriptionally activated genes [121]. A screen for microRNAs against p53 activity, reported to be deregulated in human tumors, revealed the positive regulation of p53 by the miR-29 family members. This effect was attributed to direct suppression of the p85 regulatory subunit of PI3K and CDC42, a Rho family GTPase, both of which negatively regulate p53 [122]. The oncogenic role of miR-122 loss in the liver has been attributed to the indirect regulation of p53. In specific, by modulating cyclin G1, miR-122 influences p53 protein stability and transcriptional activity [123]. MiR-25 and miR-32 are also indirect regulators of p53 by targeting directly Mdm2 and TSC1, which are negative regulators of the p53 and the mTOR pathway. MiR-25 and miR-32 induce accumulation of p53 and subsequently inhibition of glioblastoma cell growth [124]. MiR-7 has been found to target YY1, a p53 suppressor. Hence, downregulation of miR-7 in a subset of colorectal cancers correlates with repression of p53 [125]. In another subset of colorectal cancers miR-218 downregulation has been correlated with inhibition of p53, through derepression of its

target BMI1 [126]. Downstream of p53, a p53 response element in the promoter of miR-145 provides the link between this tumor suppressor miRNA and its direct target, c-Myc [127]. It has also been shown that under genetic stress, p53 may interact with the Drosha processing complex and thus enhance the post-transcriptional maturation of several miRNAs with growth-suppressive function, including miR-16-1, miR-143 and miR-145 [128]. The members of the pro-apoptotic miR-34 family are expressed at very low levels in several types of cancers [129, 130] and have been characterized as direct transcriptional targets of p53 [131-133]. However their role as downstream effectors of p53 is currently under debate. A recent report investigating the role of miR-34 in the intact mouse showed that mir-34 knockouts remain healthy with no spontaneous tumors [134].

Therapeutic Potential of Metabolism-Related MiRNAs

MiRNA Therapeutics in Cancer Metabolism

The possibility that agents targeting cell metabolism could be effective across diverse cancer types has historical precedent. For example, antifolate drugs were developed before there was an understanding of how folic acid contributes to nucleic acids generation. Today, the antimetabolite class of nucleoside analogues — among them 5-fluorouracil and gemcitabine — is widely used in the treatment of diverse human tumors [135]. Although these drugs are not considered ‘targeted therapies’, they have clear targets in metabolism and remain effective therapies for many human cancers. Considering the recent increase in our understanding of cancer metabolism the question arises: could metabolism be cancer’s Achilles heel? Are there differences between normal and cancer cell metabolism that provide clinically relevant therapeutic windows? These questions have been addressed by recent recommendable reviews [6, 136, 137], and here we focus on the therapeutic potential of metabolism-related miRNAs.

It has been identified through gain- and loss-of-function studies that miRNA deregulation could have therapeutic effects by suppressing the growth of cancer cells without affecting the growth of normal cells [138]. These findings have enforced the development of miRNA-based therapeutics in the last few years. To overcome delivery challenges innate with small RNA

therapeutics, chemical modifications, nanoparticles, liposomes, polymers are being exploited for effective delivery of miRNAs to targeted sites.

Different chemical modifications in antisense-miRNAs have been developed aiming to enhance the specificity and potency of these inhibitors [138]. The LNA modification increases the stability of antisense miRNAs, which could be delivered by intratumoral, intraperitoneal and intravenous injections. A Phase 2 trial of the LNA anti-miR-122 is being carried out in human subjects in Denmark [139]. In addition to the LNA technology, cholesterol-modified miRNAs (chol-anti-miRs) exhibit improved pharmacokinetics and anti-tumor efficacy. For example, chol-anti-miR-221 suppresses effectively liver tumor growth *in vivo* [140].

Regarding miRNA mimics, they are administered either directly by injection or indirectly through systemic adenoassociated viral (AAV) delivery [141]. It was recently demonstrated that systemic administration of miR-124 suppresses liver cancer growth *in vivo*, through suppression of the IL6/STAT3 inflammatory pathway [15]. Furthermore, AAV-delivery of miR-26a or miR-122 suppresses *MYC*-driven liver carcinogenesis *in vivo* without affecting normal hepatocytes [84, 142]. One recent study proposes the systemic delivery of miRNA mimics in complex with neutral lipid emulsion, showing therapeutic benefits in mouse models of lung cancer. Therapeutic delivery was demonstrated for the two well-characterized families of tumor suppressor miRNAs let-7 and miR-34: let-7 targets *RAS* and *MYC* oncogenes while miR-34 is directly transcribed by p53 [143].

Metformin: From Diabetes to Cancer Therapy

Links between cancer and metabolic disorders such as diabetes have long been suspected [144]. Metabolic disorders cause alterations in glucose metabolism and could be associated with increased cancer risk. As a result antidiabetic drugs such as metformin, which is currently taken by 100 million people worldwide, are being explored for anti-tumor activity [144-146]. Multiple epidemiological studies show that diabetic patients treated with metformin have reduced incidence of cancer and reduced cancer mortality [145]. In addition, metformin affects the progression and relapse of breast, prostate and lung cancer, when combined with suboptimal

doses of standard chemotherapeutic agents [147-149]. Metformin activates AMPK that leads to suppression of mTOR and stimulation of the p53 axis, hence affecting metabolic and carcinogenic processes. The anticancer activity of metformin on different types of cancer suggests the existence of a broader mechanism of action for this drug. This was further supported by a recent study demonstrating that miRNA modulation underlies the anticancer metabolic actions of metformin [112]. Metformin-modulated miRNAs were predicted to impinge mainly on the energy metabolism and insulin signaling pathways. In addition, it was shown that metformin affects the mRNA levels of c-MYC, IRS-2 and HIF1α as well [146].

Concluding remarks and future perspectives

Over recent years, miRNAs have emerged as major players in the complex network of gene regulation and have been implicated in various aspects of human disease. The fact that miRNAs can be found circulating in the blood, either inside exosomes or as “free” molecules, not only points to their potential use as biomarkers, but also suggests that circulating miRNAs may be actively secreted from cells to act as signaling molecules that alter the gene expression output of distant target cells. The involvement of miRNAs in carcinogenesis has been well documented for almost a decade and scientists have roughly categorized those miRNAs to oncogenic and tumor suppressor miRNAs. For years now, cancer researchers have been seeking molecular mechanisms underlying the Warburg effect in an effort to model cancer metabolism and select target combinations for possible therapeutic intervention. The recent finding that miRNAs are important regulators of cell metabolism makes clear that it is particularly significant to complement these models with the function of miRNAs in cancer cells. This approach will provide new insight into which enzymes, miRNAs or their combination represent promising targets for cancer therapy.

Table 1. Glucose metabolism-regulating microRNAs deregulated in cancer

microRNA	Target	Up/Down	Disease
Glucose uptake			
miR-133	GLUT4	▬	bladder cancer, pancreatic ductal adenocarcinoma, oesophageal squamous cell carcinoma of the tongue, hepatocellular carcinoma, lung carcinoma
miR-223	GLUT4	▬	chronic lymphocytic leukemia, osteosarcoma, peripheral nerve sheath tumors, hepatocellular carcinoma, acute lymphoblastic leukemia
miR-32	SLC45A3	▬	bronchial squamous cell carcinoma, lung adenocarcinoma
miR-195-5p	GLUT3	▬	bladder cancer, gastric cancer, colorectal cancer, glioblastoma, adrenocortical carcinoma
miR-23a	SMAD4	▬	colorectal cancer, hepatocellular carcinoma, pancreatic cancer, oral squamous cell carcinoma, bladder cancer
Glycolysis			
miR-143	Hexokinase 2	▬	esophageal squamous cell carcinoma, lung cancer, colorectal cancer, cervical carcinoma, liposarcoma, bladder cancer, osteosarcoma, gastric cancer
miR-138	Hexokinase 1	▬	nasopharyngeal carcinoma, hepatocellular carcinoma, papillary thyroid carcinoma, tongue squamous cell carcinoma, head and neck/oral cancer
miR-122	Aldolase A / PKM2	▬	hepatocellular carcinoma
miR-326	PKM2	▬	glioblastoma, pituitary GH adenoma
miR-133a/b	PKM2	▬	*see above*
miR-210	ISCU1/2	▬	lung cancer , adrenocortical carcinoma, clear-cell kidney cancer, pancreatic cancer, clear cell renal cell carcinoma, breast cancer
Lactate metabolism and secretion			
miR-375	LDHB	▬	maxillary sinus-esophageal squamous cell carcinoma, laryngeal squamous cell carcinoma, nonsmall cell lung cancer, rectal cancer, gastric cancer
miR-29a/b	MCT1	▬	B-cell lymphoma, acute myelogeneous leukemia, hepatocellular carcinoma, cutaneous melanoma
miR-124	MCT1	▬	hepatocellular carcinoma, gastric cancer, pancreatic cancer, colorectal cancer, cervical cancer, haematological malignancies, medulloblastoma
let-7b	Basigin	▬	breast cancer, colorectal cancer, ovarian serous carcinoma, head and neck squamous cell carcinoma

Table 2. MicroRNAs deregulated in cancer, targeting signals involved in metabolism.

microRNA	Target	Up/Down	Disease
HIF1 and MYC			
miR-199a	HIF1A	▼	osteosarcoma, small cell cervical carcinoma, testicular cancer, hepatocellular carcinoma, ovarian cancer
miR-92-1	VHL	▼	chronic lymphocytic leukemia, multiple myeloma, lung cancer
miR-424	CULLIN1	▼	colorectal cancer
miR-210	GPD1L	▼	*see Table 1.*
miR-429	CMYC	▼	renal cell carcinoma, gastric cancer, nasopharyngeal carcinoma
miR-135a	CMYC	▼	renal cell carcinoma, gastric cancer, glioma, Hodgkin lymphoma
miR-33b	CMYC	▼	medulloblastoma
miR-223	CMYC	▼	*see Table 1.*
PI3K/AKT/mTOR			
miR-126	PI3K	▼	colorectal cancer, lung cancer, pancreatic cancer, malignant pleural mesothelioma, breast cancer, gastric cancer, cervical cancer
miR-21	PTEN	▼	breast cancer, glioblastoma, hepatocellular carcinoma, chronic myelogeneous leukemia, cervical cancer, stomach cancer, colorectal cancer, prostate cancer, cholangiocarcinoma, lung cancer, esophageal cancer
miR-143	ORP8	▼	*see Table 1.*
miR-100	MTOR	▼	lung cancer, esophageal cancer, ovarian cancer, head and neck squamous cell carcinoma, cervical cancer, bladder cancer
miR-199a-3p	MTOR	▼	*see above*
miR-223	FOXO1	▼	*see Table 1.*
LKB1/AMPK			
miR-451	CAB39	▼	pancreatic cancer, glioma, head and neck squamous cell carcinoma
miR-195	CAB39	▼	chronic lymphocytic leukemia, gastric cancer
P53			
miR-125b	P53	▼	endometrial carcinoma, hepatocellular carcinoma, thyroid cancer, acute lymphoblastic leukemia
miR-30	P53	▼	anaplastic thyroid carcinoma, medulloblastoma, hepatitis B virus-associated hepatocellular carcinoma
miR-122	CYCLIN G1	▼	*see Table 1.*
miR-29	PI3K/CDC42	▼	*see Table 1.*
miR-7	YY1	▼	breast cancer, gastric cancer, glioblastoma
miR-218	BMI1	▼	cervical cancer, gastric cancer, lymphoma, bladder cancer, lung cancer, medulloblastoma

Box 1 – The Warburg effect

In the 1920s, Otto Warburg first proposed the theory that cancer cells exhibit atypical metabolic characteristics. Specifically, Warburg found that in contrast to normal cells cancer cells metabolize glucose into lactate under aerobic conditions [251, 252]. Normal cells, in the presence of oxygen, metabolize glucose to pyruvate which in turn is completely oxidized to carbon dioxide in mitochondria through oxidative phosphorylation (Ref). The metabolism of glucose to lactate is far less efficient, in terms of ATP generation per molecule of glucose, (2 ATPs) when compared to oxidative phosphorylation (36 ATPs). A possible explanation for this seemingly paradoxical phenomenon is the necessity for a cell to produce metabolic products that extend beyond the ATP. Acetyl-coA is necessary for fatty acid biosynthesis, glycolytic intermediates for non-essential amino acids and ribose for nucleotides [2, 253]. The Warburg phenomenon has been supported by multiple studies in a variety of tumor types, and is now exploited in the clinic for diagnostic purposes. Fluorodeoxyglucose positron emission tomography imaging is used today for the detection of primary tumors and metastases of several types of cancer [254]. Emerging understanding on the molecular mechanisms responsible for the Warburg effect indicate that the hypoxic altered tumor microenvironment, activation of proto-oncogenes (c-*MYC*) and kinases (AKT, AMPK), activation and/or stabilization of transcription factors (HIF-1), as well as the inactivation of tumor suppressors (p53), induce the glycolytic phenotype of cancer cells [2].

Box 2 – The canonical miRNA biogenesis pathway

A canonical pathway driven by RNAse III enzymes generates the majority of animal miRNAs. MiRNA genes are either independent genes (intergenic) or portions of introns of protein-coding genes (intragenic) [255]. RNA polymerase II transcribes miRNA genes, generating long primary transcripts (pri-miRNAs). Subsequently, the process to yield mature miRNAs involves two consecutive cleavages by two RNase-III enzymes and the companion of double-stranded RNA-binding proteins. In the nucleus, the single strand-double strand junction of the pri-miRNA hairpin is recognized by DGCR8, which positions the catalytic site of the RNase III enzyme Drosha. This cleavage yields hairpin precursors (pre-miRNAs), consisting of approximately 70 nucleotides, that are exported to the cytoplasm [256, 257]. The pre-miRNA hairpins are cleaved toward the terminal loop by the RNase III enzyme Dicer. This process gives rise to unstable, miRNA/miRNA duplex structures of 19-25 nucleotides length [258, 259]. The miRNA/miRNA* duplexes are loaded into miRNA-class Argonaute effectors (in mammals, Ago1–4). One of the duplex strands is preferentially retained in Ago to form the functional RNA-induced silencing complex (RISC) [260, 261]. The RISC–miRNA assembly is then guided to specific target sequences in mRNAs. The initial recognition of mRNAs by the RISC–miRNA complex is driven primarily by Watson–Crick base-pairing of nucleotides 2 to 8 in the mature miRNA (seed sequence) with specific mRNA target sequences chiefly located in the 3′-untranslated region (3’-UTR).

Figures

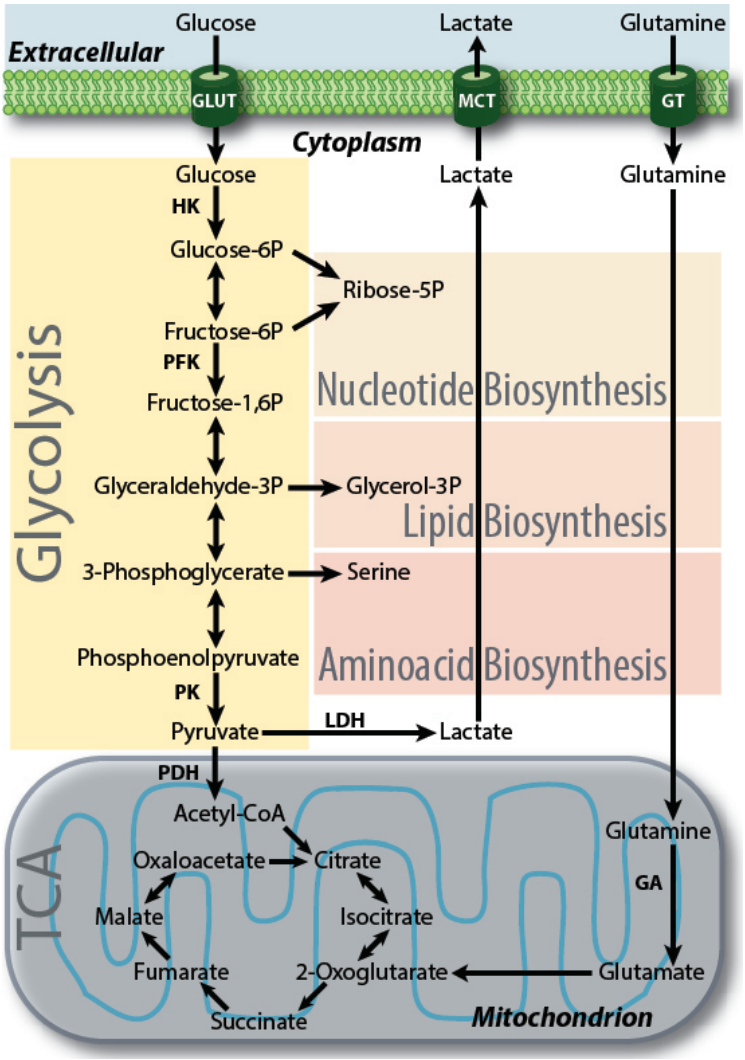

Figure 1: The biochemistry of cancer cell metabolism

Exemplified schematic representation of our current understanding of the biochemical pathways involved in metabolic reprogramming. On entering the cell through GLUTs, glucose is converted to pyruvate by glycolysis. Under normoxic conditions, in normal cells, pyruvate undergoes oxidative phosphorylation in mitochondria, through the TCA cycle. However, upon oxygen deprivation, pyruvate is metabolized to lactate in the cytoplasm. In cancer cells both glycolysis and glutaminolysis are modified. Pyruvate conversion to lactate dominates, even in the presence of oxygen. In parallel, increased glycolysis contributes to anabolic pathways for the production of building materials (such as lipids and amino acids) for the formation of new cells. GLUT, glucose transporter; MCT, monocarboxylate transporter; GT, glutamine transporters; HK, hexokinase; PFK, phosphofructokinase; PK, pyruvate kinase; LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase; GA, glutaminase.

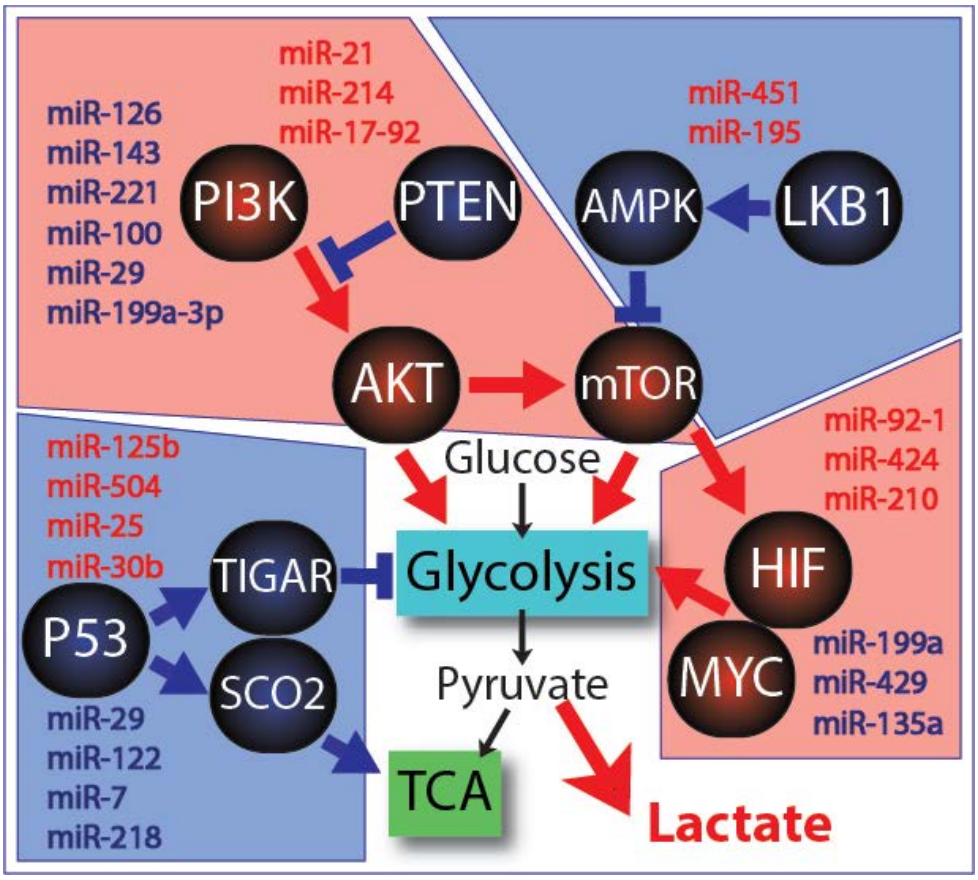

Figure 2: Regulation of signaling pathways involved in cancer metabolism by miRNAs The shift to aerobic glycolysis in cancer cells may be driven or enhanced by miRNAs through the deregulation of signaling pathways and/or transcription factors. AKT activation downstream of PI3K, upregulates several glycolytic enzymes and activates mTOR. In turn, mTOR enhances the activity of HIF. HIF cooperates with MYC in the transcriptional activation of genes encoding glycolytic enzymes. Activation of the PI3K/AKT/mTOR pathway or HIF- and MYC-dependent transcription (red quadrangles) through suppression of inhibitory miRNAs (blue) or upregulation of the oncogenic microRNAs (red), support increased glycolysis and inhibit the TCA cycle. Conversely, LKB1/AMPK signals inhibit mTOR and p53 suppresses glycolysis through TIGAR and increases mitochondrial metabolism through SCO2 (blue quadrangles). Therefore, miRNAs targeting elements of these two pathways, or loss of miRNAs that reinforce them, enhance the glycolytic phenotype. Red and blue indicate molecules and interactions with a positive and negative role in the metabolic reprogramming of cancer cells, respectively.

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