REVIEW

miRNA-guided reprogramming of glucose and glutamine metabolism and its impact on cell adhesion/migration during solid tumor progression

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Abstract

MicroRNAs (miRNAs) are small, non-coding RNAs about 22 nucleotides in length that regulate the expression of target genes post-transcriptionally, and are highly involved in cancer progression. They are able to impact a variety of cell processes such as proliferation, apoptosis and differentiation and can consequently control tumor initiation, tumor progression and metastasis formation. miRNAs can regulate, at the same time, metabolic gene expression which, in turn, influences relevant traits of malignancy such as cell adhesion, migration and invasion. Since the interaction between metabolism and adhesion or cell movement has not, to date, been well understood, in this review, we will specifically focus on miRNA alterations that can interfere with some metabolic processes leading to the modulation of cancer cell movement. In addition, we will analyze the signaling pathways connecting metabolism and adhesion/migration, alterations that often affect cancer cell dissemination and metastasis formation.

Keywords miRNAs · Metabolism · Cancer · Metastasis · Adhesion

Introduction

MicroRNAs (miRNAs) are small non-coding RNAs that, at a post-transcriptional level silence their target mRNAs via translational repression or mRNA degradation. They are mainly located in introns or exons of protein-coding genes, as well as in intergenic regions. Most of them are transcribed in the nucleus by RNA polymerase II, generating a long primary miRNA (pri-miRNA), which is then processed by the DROSHA-DGCR8 complex to release a precursor-miRNA (pre-miRNA). Exportin 5 subsequently translocates the pre-miRNA to the cytoplasm where it is cleaved by the RNase III Dicer to form a mature miRNA. It is eventually loaded onto Argonaute family (AGO) proteins to form the effector RNA-induced silencing complex (RISC) [1]. miRNAs are master regulators of protein-coding gene expression: indeed, more than 60% of human genes have, at least, one conserved miRNA binding site [2]. Moreover, each miRNA may have hundreds of targets and a single mRNA may be regulated by several miRNAs. Therefore, alterations in their expression are often associated with diseases, including cancer in which they act as tumor suppressors or oncomiRs. The first link between miRNAs and tumors refers to the miR-15/16 cluster in Chronic Lymphocytic Leukemia [3]. Up to now, a many alterations in miRNA expression have been identified in tumors [4] and have been related to cancer hallmarks [5]. In particular, miRNAs are well-known regulators of adhesion, invasion, metastatic process [6] and recently, emerging evidence supports their role in the regulation of cancer metabolism.
Cell metabolism is the sum of reactions supporting cell survival, proliferation, migration, resiliency to noxious stresses and the control of oxido-reductive balance. One century ago, Warburg observed that cancer cells use glycolysis as the main energetic pathway, either in the presence or absence of oxygen [7]. Consequently, the reprogramming of cell metabolism depending on the environmental conditions is considered a cancer hallmark [8]. Although the Warburg effect fuels cancer cells to metastasize [9], mitochondrial-related metabolic pathways are not necessarily defective in neoplasia. Many cancers rely on oxidative phosphorylation (OXPHOS) and aerobic mitochondrial metabolism [10], based on a tricarboxylic acid (TCA) cycle and fatty acid β-oxidation (FAO). Moreover, to survive in poor nutrient and hypoxic conditions, cancer cells use opportunistic nutrient acquisition strategies as, for example, the uptake of amino acids via micropinocytosis or apoptotic bodies [11]. Since histone acetylation alters the expression of oncosuppressors, epigenetic alterations are also associated with changes in metabolism. Acetyl-CoA (Ac-CoA) is the substrate for histone acetylases [12] and proteins controlling tumor progression [13]. Thus, a metabolic drift towards increased cytosolic Ac-CoA production may increase histone acetylation and confers proliferative/promigratory phenotypes in cancer cells [14]. It is important to note that tumors are characterized by metabolic plasticity: cancer cells may process the same substrate in different ways and use distinct energy sources to adapt to the tumor microenvironment (TME). In addition, metabolic heterogeneity within the same tumor mass further complicates the picture. As it has been demonstrated, metabolic rewiring in cancer cells is driven both by intrinsic and extrinsic factors, and affects not only energy production and biomolecule synthesis, but also cancer biology extensively [15]. Figure 1 highlights the main metabolic pathways in cancer cells.

In healthy tissues, homeostasis mainly depends on adhesion between cells and the extracellular matrix (ECM). These interactions are mediated by a large group of transmembrane receptors, generically defined as Cell Adhesion Molecules (CAMs), which include the calcium-dependent integrins, cadherins and selectins as well as the calcium-independent Immunoglobulin superfamily CAMs [16]. The same adhesion receptors control proliferation, tissue integrity and cell migration and are able to activate signaling cascades and mechano-signals [17]. Therefore, any abnormal change in cell adhesion can lead to malignant transformation and tumor progression [18]. In this context, miRNAs are pivotal regulators of adhesion receptor expression, which impacts tumor progression.

The aim of the present review is to discuss how miRNAs are involved in the regulation of glucose and glutamine metabolism and in the expression of adhesion molecules during cancer progression. In addition, we dissect the interplay between adhesion/migration and metabolism in malignancy and finally we discuss how miRNAs interfere with these hallmarks of cancer.

**How miRNAs tightly regulate cell metabolism**

The metabolic reprogramming of cancer cells is tightly regulated at transcriptional or post-transcriptional levels, where miRNAs play important roles [19]. Notably, both tumoral or stromal miRNAs may operate here, making the metabolic crosstalk within the TME highly variegate [20]. Since glucose and glutamine metabolism strongly promotes cancer cells, a high amount of lactate and their derivatives are released in the extracellular milieu, affecting the TME composition and favoring angiogenesis and tumor progression [21]. A research that used over 6000 tumors revealed miR-34a-5p, miR-106b-5p, miR-146a-5p and miR-155-5p as the universal controllers of cancer metabolism, thus defining them as metabomiRs [22]. However, other miRNAs have been found involved in the control of cancer metabolic pathways. Here, we focus on the link between glucose-related pathways or glutaminolysis and miRNAs in cancer cells (Fig. 2 and Table 1).

**Glucose uptake and glucose-related pathway**

Cancer cells show an enhanced glucose uptake and an alteration of glucose-related pathways including glycolysis, pentose phosphate pathway (PPP), gluconeogenesis and glycogenolysis compared to their normal counterparts. These aspects will be reviewed in the next paragraphs.

**Glucose uptake**

The glucose transporters (GLUTs) move the glucose through the plasma membrane by means of facilitated diffusion. GLUT1 is the predominant carrier and its overexpression is associated with malignancy and poor prognosis in cancer [23, 24], where it can be controlled by miRNAs. For instance, in renal cell carcinomas (RCC), GLUT1 is down-regulated by miR-1291 [25]. Since miR-1291 levels are lower in tumors compared to those in surrounding normal tissues, this phenotype confers a metabolic advantage to RCC cells. In gliomas, GLUT1 is inhibited by miR-451, which targets the calcium-binding protein 39 (CAB39), thereby arresting glucose uptake and metabolism, as well as lactate production. In addition, glioma xenografts pre-treated with miR-451 show a reduced GLUT1 expression compared to controls [26]. In the same tumor type, GLUT1 is also an indirect target of miR-181b. Histological analyses on miR-181b overexpressing xenografts revealed a decrease
of GLUT1 expression and vice versa for miR-181b depleted tumors [27]. In oral squamous cell carcinomas (OSCC), GLUT1 is up-regulated by the oncogenic miR-10a which promotes glucose uptake and glucose metabolism leading to increased cell proliferation, indicating that glucose is required to sustain cancer proliferation and aggressiveness [28]. Similarly, miR-1204 levels and GLUT1 are positively correlated in biopsies of ovarian squamous cell carcinomas and not in non-transformed ovarian tissue, suggesting a specific pathway for ovarian cancer [29]. Several oncosuppressor miRNAs downregulate GLUT1 as, for example miR-132 in prostate cancer (PC), where GLUT1 is also regulated by cucurbitacin D (Cuc D), an anti-cancer plant steroid [30], thus indicating that metabolic effects may be manipulated not only with miRNA mimics or anti-miRNAs/sponges, but also with pharmacological or natural products. In addition, an inverse correlation between miR-22 and GLUT1 expression was found in breast cancer samples. Low miR-22 and high GLUT1 levels are significantly associated with a shorter disease-free survival or overall survival, thus impacting prognosis [31]. Although GLUT1 is the predominant isoform in tumors, other GLUT isoforms can also be modulated by miRNAs. In fact, Kim and colleagues showed that miR-155 knock-out leads to reduced GLUT1, GLUT3 and GLUT4 expression (32). Besides modulating GLUT1 levels, miRNAs may also relocate it. For instance, miR-361-5p regulates the translocation of GLUT1 from the plasma membrane to the cytoplasm, thus reducing anaerobic glycolysis, proliferation and invasion. In contrast, fibroblast growth factor receptor 1 (FGFR1), a miR-361-5p target, reverses...
GLUT1 subcellular translocation [33]. Overall, the effects of miRNAs on glucose uptake are particularly variegated.

Glycolysis

Glycolysis is one of the main energetic pathways in tumors, which produces 2 adenosine triphosphate (ATP) molecules when glucose is metabolized into lactate, or, a higher number of ATP units when it generates pyruvate. miRNAs control some of the main glycolytic enzymes, such as those mentioned in the following paragraphs.

The hexokinase (HK), a key glycolytic enzyme and the branching point of PPP, converts glucose into glucose-6-phosphate (G6P), so it is not surprising that HK expression is controlled by miRNAs. Indeed, in liver cancer, miR-199a-5p directly targets HK2, decreasing glucose consumption, lactate production, G6P and ATP levels. In patients with liver tumors, HK2 is upregulated and miR-199a-5p is deregulated [34]. In OSCC, miR-143 directly targets HK2, thus suppressing glycolysis and decreasing lactate dehydrogenase A (LDHA) levels and activity. Moreover, a negative correlation between miR-143 [35] or miR-98 [36] and HK2 has been detected in oral tumor tissues and in colorectal cancer (CRC), respectively. Likewise, HK2 levels negatively correlate with miR-185 [37].
and miR-497 [38] in osteosarcoma samples, suggesting a multiple miRNA control within the same tumor type.

Pyruvate kinase (PK) catalyzes the transfer of a phosphate group from phosphoenolpyruvate (PEP) to ADP with the consequent formation of pyruvate and ATP. The isof orm M2 (PKM2) is a direct target of miR-338-3p in ovarian cancer [39] and miR-139-5p in gallbladder carcinoma [40].

LDHA is the last glycolytic enzyme of the glycolytic pathway and is closely controlled by miRNAs. Since LDHA is a miR-34a direct target, it is negatively correlated with such miRNA in breast cancer. In addition, LDHA-induced glycolysis can be inhibited by miR-34a [41]. In the same tumor type, LDHA, is downregulated by miR-34a-5p, together with PKM2. In human breast cancer samples or

| miRNA   | Direct target | Pathway          | Cancer type                                      | Reference  |
|---------|--------------|------------------|-------------------------------------------------|------------|
| miR-1291 | GLUT1        | Glucose uptake   | Renal cell carcinoma                             | [25]       |
| miR-451 | CAB39        | Glucose uptake   | Glioma                                          | [26]       |
| miR-181b| SP1          | Glucose uptake   | Glioma                                          | [27]       |
| miR-10a | SP1          | Glucose uptake   | Oral squamous cell carcinoma                     | [28]       |
| miR-1204| SP1          | Glucose uptake   | Ovarian squamous cell carcinoma                  | [29]       |
| miR-132 | GLUT1        | Glucose uptake   | Prostate cancer                                  | [30]       |
| miR-22  | GLUT1        | Glucose uptake   | Breast cancer                                    | [31]       |
| miR-155 | PI3K3R1, FOXO3a | Glucose uptake | Breast cancer                                    | [32]       |
| miR-361-5p | FGFR1     | Glucose uptake   | Breast cancer                                    | [33]       |
| miR-199a-5p | HK2     | Glycolysis       | Liver cancer                                     | [34]       |
| miR-143 | HK2          | Glycolysis       | Oral squamous cell carcinoma                     | [35]       |
| miR-98  | HK2          | Glycolysis       | Colorectal cancer                                | [36]       |
| miR-185 | HK2          | Glycolysis       | Glioma                                           | [37]       |
| miR-497 | HK2          | Glycolysis       | Osteosarcoma                                     | [38]       |
| miR-338-3p | PKM2    | Glycolysis       | Ovarian cancer                                   | [39]       |
| miR-139-5p | PKM2    | Glycolysis       | Gallbladder carcinoma                            | [40]       |
| miR-34a | LDHA         | Glycolysis       | Breast cancer                                    | [41]       |
| miR-34a-5p | LDHA    | Glycolysis       | Breast cancer                                    | [42]       |
| miR-124 | MCT1         | Glycolysis       | Pancreatic ductal adenocarcinoma                 | [43]       |
| miR-150-5p | SIX1    | Glycolysis       | Melanoma                                         | [44]       |
| miR-3662 | HIF-1α    | Glycolysis       | Hepatocellular carcinoma                        | [45]       |
| miR-106b| PLK3         | Glycolysis       | Prostate cancer                                  | [46]       |
| miR-1  | G6PD, PGD, TKT | Pentose phosphate pathway | Lung cancer, cervical cancer, pituitary cancer, hepatocellular carcinoma | [48, 50–51] |
| miR-206 | G6PD, PGD, TKT | Pentose phosphate pathway | Lung cancer                                       | [48–49]    |
| miR-122 | G6PD         | Pentose phosphate pathway | Hepatocellular carcinoma                        | [50, 51]   |
| miR-23a | PGC-1α, G6PC | Gluconeogenesis   | Hepatocellular carcinoma                        | [51]       |
| miR-133a-3p | PYGB   | Glycogenolysis   | Ovarian cancer                                   | [52]       |
| miR-137 | ASCT2        | Glutaminolysis   | Glioblastoma, colorectal cancer, pancreatic ductal adenocarcinoma, prostate cancer | [53]       |
| miR-153 | GLS          | Glutaminolysis   | Glioblastoma                                     | [54]       |
| miR-203 | GLS          | Glutaminolysis   | Melanoma                                         | [55]       |
| miR-145 | c-Myc        | Glutaminolysis   | Ovarian cancer                                   | [56]       |
| miR-18a | GCLC         | Glutaminolysis   | Liver cancer                                     | [57]       |
| miR-9-5p | GOT1        | Glutaminolysis   | Pancreatic cancer                                | [58]       |
| miR-105 | MXI1         | Glutaminolysis, glycolysis | Breast cancer                                    | [59]       |
TCGA datasets, low miR-34a-5p expression correlates with high LIN28B levels and, together with high MYC levels, it predicts poor survival. Interestingly, the LIN28B/MYC/miR-34a-5p pathway can be therapeutically exploited: in fact, when using LIN28B inhibitors, miR-34a-5p increases and PKM2 decreases while tumor growth and lung metastasis are suppressed [42]. In conclusion, miR-361-5p inhibits glycolysis in breast cancer cells and FGFR1, a miR-361-5p target, reverts the anti-glycolytic function of those small RNAs and represses OXPHOS by upregulating LDHA and pyruvate dehydrogenase kinase-1 (PDHK1) function. An inverse expression between miR-361-5p and FGFR1 is present in clinical samples [33]. The modulation of LDHA by miRNAs may also be coordinated by the monocarboxylate transporter 1 (MCT1), which transports lactate out of cancer cells. Indeed, miR-124 inhibits glycolysis and lactate export by targeting MCT1 in pancreatic ductal adenocarcinoma (PDAC). As a consequence, intracellular acidification slows down the glycolytic flux and LDHA activity, thus reducing tumor growth and invasion [43].

Lastly, miRNAs may also act on transcription factors (TFs) involved in aerobic glycolysis, such as sine oculis homeobox 1 (SIX1), targeted by miR-150-5p. As a matter of fact, as a consequence of SIX1 down-modulation, glycolysis is reduced due to a decrease in glucose uptake, lactate and ATP production, extracellular acidification rate (ECAR) and an increase in oxygen consumption rate (OCR) [44]. Similar results are observed for miR-3662 which suppresses glycolysis by directly targeting Hypoxia-inducible factor 1-alpha (HIF-1α) in hepatocellular carcinoma (HCC) [45]. Another TF involved in glycolysis and in the promotion of invasive behavior is STAT3 that in PC cells is indirectly regulated by miR-106b, suppressing HK2 transcription [46].

**Pentose phosphate pathway (PPP)**

Glycolysis can be directed to the PPP that supplies cells with nicotinamide adenine dinucleotide phosphate (NADPH), maintaining a reserve of reduced glutathione (GSH) and ribose-5-phosphate, a precursor for nucleotide synthesis [47]. Controlling both glycolysis and the flux toward the PPP is of paramount importance for the survival and/or malignancy of cancer cells. In particular, the diversion of G6P toward PPP increases tumor aggressiveness by proving ribose 5-phosphate and reductive equivalents as NADPH that are exploited in lipid biosynthesis as well as in the protection from oxidative stress. This linkage with the protection from oxidative damage is demonstrated by reduced levels of the ROS-sensitive nuclear factor erythroid 2-related factor 2 (Nrf2) in cells with high levels of glucose-6-phosphate-dehydrogenase (G6PD), the rate-limiting enzyme of the PPP pathway. The increase of G6P and the consequent decrease in Nrf2 activity is mediated by miR-1 and miR-206 in lung cancers [48]. In tumors, G6PD levels increase with tumor grade and the enzyme is targeted by miR-206 [49] and miR-1 [50] in cervical cancers associated with papillomavirus infections, whereas it is downregulated by miR-1 in pituitary tumors [51]. Moreover, in HCC samples, G6PD levels negatively correlate with miR-1 and the liver-specific miR-122, while loss of expression of these two miRNAs promotes tumor growth [52].

**Gluconeogenesis and glycogenolysis**

Gluconeogenesis is a mechanism used to maintain proper blood glucose levels, thus generating glucose from non-carbohydrate carbon molecules. It mainly occurs in the liver, and it may, therefore, be altered during liver tumorigenesis. To study gluconeogenesis in HCC, Wang et al. used a choline-deficient diet in mice and found a dramatic inhibition of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and glucose-6-phosphatase (G6PC) at the expense of miR-23a direct targeting. Relevantly, a negative expression correlation of PGC-1α and G6PC with miR-23a was also found in human specimens [53]. Alternatively, the excess of glucose may be stored as glycogen and its metabolism can be critical for cancer development. Indeed, glycogen phosphorylase B (PYGB), the rate-limiting enzyme in glycogenolysis, is involved in various tumors, including ovarian cancer where its levels are upregulated and correlate with poor prognosis. Mechanistically, PYGB is targeted by miR-133a-3p, and an indirect correlation between miRNA and enzyme is present in ovarian cancer samples [54]. Overall, as presented, miRNAs are able to affect glucose-related pathways at different levels.

**Glutaminolysis**

Glutamine is the preferred amino acid of cancer cells, which fuels the TCA cycle via its oxidative metabolism [55]. It represents a key source of carbon and nitrogen for the de novo biosynthesis of nucleotides, non-essential amino acids, lipids [56, 57] and anaplerotic metabolites for the TCA cycle, lipids, nucleotides and precursors of GSH. Indeed, proliferating cancer cells display a high glutamine demand [58]. Multiple tumor cells and TME-related molecules, including miRNAs, control glutamine uptake and metabolism. Glutamine enters the cells mainly through the alanine, serine, cysteine, and glutamate transporter (ASCT2), targeted by the oncosuppressor miR-137, which inversely correlates with ASCT2 in glioblastoma, CRC, PDAC and PC. The epigenetic downregulation of miR-137 results instead in an increased glutamine uptake, enabling cancer cells to survive in an adverse environment thanks to the favorable supply of glutamine [59]. Upon entry, glutamine is converted to glutamate by glutaminase
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miRNAs as relevant regulators of adhesion/migration/invasion processes

Integrins are a large family of adhesion receptors and the main components of focal adhesions (FAs), large molecular complexes that transmit a signal bidirectionally, from the outside to the inside of the cells and vice versa [69]. Importantly, FAs are highly dynamic structures that undergo continuous reorganization in response to TME stimuli including ECM alterations, growth factors and nutrient availability [70]. Changes in migration are mainly driven by the cytoskeleton, crucial for FA turnover, and composed of microtubules, actin and intermediate filaments [71]. Integrins and their associated complexes form the adhesome, consisting of ~200 proteins [72], whose deregulation is tightly associated with several diseases [73]. Interestingly, the adhesome components may be targeted by miRNAs, thus resulting in alteration of adhesion or motility.

Adhesome formation

Adhesive components are divided into distinct functional categories: adhesion receptors responsible for the ECM–cell signal transmission; actin regulating proteins controlling the communication between integrins and actin network remodeling; adaptor proteins that serve as hubs; kinases, phosphatases, mainly responsible for the phosphorylation or dephosphorylation of adhesome proteins, including GTPase activating proteins (GAPs) and guanine nucleotide exchange factors (GEFs) [73, 74]. All these proteins are regulated by miRNAs, as discussed below and summarized in Fig. 3.

Adhesion receptors

Among integrin heterodimers, the role of α5β1, αvβ3 or αVβ5 in the formation of fibronectin-dependent or independent adhesion complexes in cancer cells has been well explored [75, 76]. Various miRNAs target the single subunits of integrins: for example, miR-98 and miR-92b directly target ITGB3 and ITGAV in non-small cell lung cancer (NSCLC) and esophageal squamous cell carcinoma (ESCC), respectively [77, 78]. Sometimes, a single miRNA may target several heterodimers, as is the case of miR-30, capable of affecting α2β1, α5β1, α4β1 and αvβ3 integrins, thus influencing bone metastasis formation [79]. In HCC, ITGβ5 stabilizes β-catenin by enhancing its stability and here, miR-185 directly targets ITGβ5. Relevantly, in these tumors, miR-185 expression is decreased compared to normal tissues while ITGβ5 and β-catenin are increased [80]. Similarly, other pathways linked to integrins are involved in cancer progression, i.e., the miR-92b/
ITGα6/Akt axis in ESCC [81] or the miR-214/miR-148b/ITGα5 axis in melanomas and breast cancers [82]. miR-214 is a pro-metastatic miRNA, while miR-148b exerts an anti-metastatic function in tumor progression even though they both act on adhesion receptors. As a matter of fact, miR-148b targets ITGA5 and ALCAM leading to dissemination inhibition. Conversely, miR-214 overexpression reverts the miR-148b-dependent phenotype by inducing miR-148b downregulation with the consequent derepression of ITGA5 and ALCAM [82]. These results suggest that adhesion receptors may be the final effectors of miRNA-mRNA pathways.

### Adhesion complex regulators

When integrins bind to ECM proteins, the involvement of large protein complexes and signal transduction occur leading to the formation of various evolving complexes, such as primitive adhesions, focal complexes, FAs and fibrillar adhesions [83]. Several adaptor proteins, which regulate cell signaling and trafficking inside the cells, are able to localize in these complexes and to participate in the stabilization of signaling proteins [84]. Their loss of function leads to an upregulation of signal transduction, which can be detrimental for tumor progression.
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Interestingly, various miRNAs modulate GTPases such as Rac2, a regulator of various proteins involved in actin remodeling and miR-608 has been found to be linked to conformational changes which, in turn, allow specific protein–protein interactions, therefore any alteration of the Actin-related proteins (Arp2/3) complex. Therefore, a reduction of miR-198 allows for an increase of actin filament branching and elongation, consequently enhancing migration and metastasis dissemination [103]. Similarly, miR-382 downregulation was observed by analyzing 200 melanoma samples and its depletion in melanoma cells revealed its anti-metastatic function. In fact, reduced levels of miR-382 in cells led to an increased expression of CTTN, Rac1 and ARPC2, all players of actin cytoskeleton remodeling. In particular, CTTN regulates lamellipodia and invadopodia formation and its depletion mimics the beneficial effects of miR-382 overexpression [104]. Another component of the Arp2/3 complex, ARPC5, is silenced by miR-133a and decreased in human patients with Head and neck squamous cell carcinoma (HNSCC) compared to controls [105], miR-141 has also been identified as an ARPC5 regulator. Analysis of human xenograft prostate tumors in mice revealed a decrease in miR-141 related to higher amounts of the pro-metastatic Cdc42, Rac1 and ARPC5 [106]. Overall, studies investigating transcriptional and protein levels of Arp2/3 components in pancreatic, colorectal and breast carcinomas have shown contradictory results and in many cases an increase in gene expression has been reported which is directly related to tumor invasiveness. Other investigations however, revealed opposite results [107], suggesting that Arp2/3 upregulation occurs only in specific steps of tumor progression [108]. On the other hand, fascin overexpression is frequently accompanied by specific miRNA downregulation in cancer cells. For instance, miR-145, which is able to target fascin is significantly reduced in CRC, where metastases inversely correlates with miR-145 [109]. Malignant cells also need to degrade ECM in order to metastatize and this comes about by the release of metalloproteinases (MMPs) that are also regulated by miRNAs. For instance, MMP2 and MMP9 activity is enhanced by miR-590-5p overexpression in CRC xenografts, and its inhibition leads to decreased liver metastases. Moreover, miR-590-5p is upregulated in CRC patients and induced by the hypoxic TME [110]. By contrast, miR-584-3p inhibits gastric cancer (GC) progression by suppressing Yin Yang 1 (YY1), which binds to...
MMP14 promoter to improve its expression [111]. In breast cancer, miR-361-5p directly targets MMP1, thus reducing cancer cell invasion and is downregulated in tumor samples [33]. Additionally, miR-182 exerts an anti-metastatic role in NSCLC by targeting CTTN, thus affecting invadopodia formation [112]. Overall miRNAs play an essential role in the regulation of cellular protrusions and ECM degradation.

The crosstalk between metabolism and adhesion in tumor progression

While the involvement of metabolism or adhesion components in cancer progression has been widely studied, their crosstalk still needs better investigation. Here, we discuss how alterations in the adhesion process may influence metabolic pathways and vice versa.

Changes in adhesion can alter metabolic pathways in cancer

FAK interacts with integrins and growth factor receptors, thus affecting motility, growth and, ultimately, cancer progression. Growing evidence supports the link between FAK hyperactivation and aberrant metabolism in tumorigenesis which may promote glucose consumption, lipogenesis, and glutamine dependency [113]. In addition, its activation can promote aerobic glycolysis and tumorigenesis in PDACs by increasing the glycolytic genes enolase, PKM2, LDHA and reducing the OXPHOS. Conversely, FAK inhibition resensitizes cancer cells to growth factors, decreases cell viability and reduces tumor growth [114]. In GC, FAK, together with ITGB4, SOX2 and HIF1α, is part of a signaling pathway induced by the Extracellular Matrix Protein 1 (ECM1), which controls metastases and glucose metabolism [115]. In lung adenocarcinomas, FAK1 is negatively regulated by NeuroFibromin 1 (NF1), leading to metabolic rewiring. NF1 loss specifically causes FAK1 hyperactivation and accelerates murine Kras-driven tumorigenesis. Tumors with NF1 mutations, addicted to glutamine, are susceptible to glutaminase and phosphoserine aminotransferase 1 (Psat1) inhibitors. This strategy could also be applied to other tumors with alterations in the NF1-FAK1 pathway [116]. All this evidence demonstrates the modulation of a panel of adhesion and migration-related genes in the absence of FAK inhibition. On the other hand, Demircioglu et al. showed that FAK depletion in CAFs enhances malignant cell glycolysis and tumor growth, thus indicating that FAK modulation in stroma cells may also affect cancer metabolism and progression [117].

The detachment of cancer cells from the ECM is also able to influence cell metabolism. In fact, Jeon et al. reported that matrix detachment of lung cancer cells induces a decrease in glucose uptake, activates LKB1 and AMPK, inhibits Ac-CoA carboxylases 1 and 2 which in turn, decreases NADPH consumption in fatty acid synthesis (FAS) while increasing NADPH generation through FAO fueling [118]. Similarly, also cell–cell adhesion, mediated by cadherins, is widely known to be critical for tissue homeostasis and maintenance of cell polarity. In particular, E-cadherin, which inhibits invasion, is lost during the EMT, in which a switch from E-Cadherin to N-Cadherin is observed. The presence of E-cadherin is typical of an epithelioid and well-differentiated phenotype and functional cell–cell junctions [119]. While EMT is responsible for cancer metabolic reprogramming towards an increase of glucose metabolism, the specific role of E-cadherin in cancer metabolism is not clear [120]. For instance, in breast cancer, E-cadherin has an unexpected regulatory ability in tumorigenicity and hypoxia responses: E-cadherin loss is associated with slower tumor growth and loss of hypoxia response genes, which lead to reduced glycolytic capacity. Moreover, high levels of E-Cadherin in basal breast cancers are linked to a poor clinical outcome [121].

The papers presented so far described how adhesion molecule alterations affect metabolism in cancer cells.

Changes in metabolism can alter cell adhesion in cancer

Adhesion may not only alter metabolic pathways as described in the previous paragraph, but could itself be affected by tumor metabolism, which adds to the complexity of the cancer scenario. An example is represented by Ac-CoA, which alters adhesion genes in glioblastoma. Its changes affect the epigenetic modification H3K27ac, resulting in cell adhesion modulation through the activation of Ca2⁺–NFAT signaling, as demonstrated by Lee et al. Analysis of xenografts have confirmed the modulation of a panel of adhesion and migration-related genes in the absence of ATP citrate lyase (ACLY) [122]. We previously discussed how FAK may coordinate tumor progression by promoting glycolysis, but, in turn, glycolysis can modulate FAK via PEP which acts as a phospho-donor for histidine-58 in ESCC. Consequently, the PI3K-AKT signaling pathway is activated. Interestingly, ESCCs, but not esophageal adenocarcinoma cancer (EAC) cells, use the described pathway to induce growth factor-independent proliferation and, at the same time, to avoid growth factor signaling targeting therapeutics [123]. FAK may also be controlled by long-chain fatty acid CoA synthetase 4 (ACSL4), an enzyme involved in the conversion of fatty acids to fatty acid-Coenzyme A esters that may affect FAK protein stability. In GC, the expression of ACSL4 is downregulated in cancer tissues when compared to the adjacent mucosa and its decrease corresponds to FAK increase, while the levels of PTEN, vimentin, β-catenin remained unchanged [124]. Specific metabolic changes involving glucose, amino acid and lipid...
metabolism may alter E-cadherin expression, thus inducing EMT in cancer cells [125]. As a matter of fact, in laryngeal squamous cell carcinoma tissues, EMT markers are controlled by GLUT1, whose expression is positively correlated with vimentin and N-cadherin levels and negatively correlated with E-cadherin. These modulations could also have a prognostic value: in fact, high GLUT1. Vimentin and N-cadherin expression lead to a shorter survival rate in patients and those which, on the contrary, display high E-cadherin levels have a longer survival rate [126]. In NSCLC, EMT-associated genes, including E and N-cadherins, are regulated by alpha-enolase (ENO1), a key glycolytic enzyme, whose expression is increased in NSCLC tissues compared to normal ones, thus favoring glycolysis. Conversely, ENO1 down-regulation increases E-cadherin expression [127]. Another pathway involved in the control of EMT is the TCA cycle. In nasopharyngeal carcinoma, TCA metabolites may cause IKKα recruitment to the promoter of EMT genes with the consequent decrease of E-cadherin and ZO-1 expression and an increase of vimentin, thus favoring EMT and metastases [128]. In PC, NAD, involved in glycolysis and TCA, controls EMT by influencing SIRT1, a NAD-dependent histone deacetylase capable of controlling epithelial morphology, E-cadherin transcription and mesenchymal marker levels, thus influencing cell adhesion [129]. In recent years, metformin, a common anti-diabetic drug, has shown its potential as a tumor protective drug. To dissect the anti-cancer mechanism, Banerjee et al. studied its involvement in EMT modulation, revealing an induction of MET and an upregulation of epithelial markers. In particular, metformin activates AMP-activated protein kinase (AMPK), leading to Snail and Slug suppression and E-cadherin upregulation. Interestingly, these results were also confirmed in the blood of diabetic patients undergoing metformin therapy, thus underlying the therapeutic relevance of a highly used metabolic drug useful in controlling tumor progression [130].

In conclusion, the papers presented so far show the existence of a crosstalk between metabolic pathways and the adhesion machinery in cancer. However, further in vivo investigations are necessary to better demonstrate these mutual regulations and their therapeutic value.

**The interplay between miRNAs, metabolism and adhesion/migration/invasion-mechanistic approach**

The alteration of energetic pathways are well-known hallmarks of cancer regulated by miRNAs as described previously. Here, we discuss miRNAs affecting players important both for metabolism and adhesion/invasion that impair tumor progression (Fig. 4).

miRNA modulation of glycolysis is able to influence dissemination in several ways. miR-455-3p, controlled by taurine upregulated gene 1 (TUG1), represses AMPKb2 expression and contributes to increased levels of Snail and HK2, thus leading to enhanced motility and invasion and glycolysis of hepatoma cells [131]. Interestingly, breast cancer cells may impair the utilization of nutrients by other cell types to favor themselves. As a matter of fact, tumor cells at the primary site may suppress glucose uptake in non-tumor cells of the metastatic niche through the secretion of vesicles with high miR-122 levels that target PK. Consequently, when miR-122 is inhibited, glucose uptake is restored in distant organs and the incidence of metastasis is reduced [132].

Also in breast cancer, miR-30a-5p acts through the inhibition of LDHA expression, leading to a decreased glucose uptake, lactate production, ATP generation, and ECAR as well as an increased OCR. Lung metastatization is strongly impaired following miR-30a-5p expression or LDHA knockdown in mouse tumors. Moreover, in breast cancer patients,
miR-30a-5p negatively correlates with LDHA expression and increases FDG uptake [133].

In HNSCC, miR-203 blocks post-extravasation events during lung dissemination without affecting carcinoma differentiation in vivo. miR-203 controls metastasis through the regulation of 3 different players, including the metabolic gene NUAK1, a member of the AMPK catalytic subunit family involved in the maintenance of glycolysis [134]. miR-181d promotes aerobic glycolysis by protecting c-Myc from FBXL3 and CRY2-mediated degradation, which is responsible for CRC metastases. c-Myc, in turn, upregulates miR-181d and inhibits the expression of FBXL3 and CRY2, giving rise to a feed-forward loop [135]. To survive in a harsh environment characterized by hypoxia, starvation and reduced vascularization, PDAC cells increase their glycolysis and lactate production. Meanwhile these prohibitive conditions could activate autophagy. miR-7 represses autophagy and reduces the source of intracellular glucose to feed aerobic glycolysis by upregulating LKB1-AMPK-mTOR signaling, thus reducing proliferation and dissemination of cancer cells [136].

As previously said, miRNAs may act on TFs including SIX1, directly targeted by miR-489-3p, which, in turn, impairs glycolysis, decreases glucose uptake, lactate production, ATP generation, and ECAR, and increases OCR. This axis is relevant for melanoma dissemination in animal models as well as in patients who display an inverse correlation between miR-489-3p and SIX1, increased glucose uptake and metastases [137]. miR-155 activates STAT3, thus promoting HK2 transcription in breast cancer cells. The activation of this axis leads to higher glycolysis and a subsequent increase in the ability of cancer cells to disseminate [138].

The TCA cycle occurs in the mitochondria and oxidizes the Ac-CoA derived from carbohydrates, fats and proteins, thus combining several metabolic ways. In GC, the production of Ac-CoA depends on the decarboxylation of pyruvate by the pyruvate dehydrogenase (PDH) whose levels may be restored after PDHK2 repression by miR-422a in GC. miR-422a overexpression in GC impairs malignancy and leads to a metabolic shift from aerobic glycolysis to oxidative phosphorylation. In addition, the miR-422a–PDHK2 axis promotes de novo lipogenesis and elevates the reactive oxygen species (ROS), arrests cell cycle in G1 phase and influences dissemination [139]. High miR-146b-5p levels promote cell growth, invasion and glycolysis. miR-146b-5p targets pyruvate dehydrogenase B (PDHB), whose overexpression leads to the termination of miR-146b-5p-mediated effects on growth, invasion and glycolysis [140].

Overall, miRNAs effect on both metabolism and adhesion of tumors or tumor-associated cells has a deep impact on multiple aspects of cancer biology, including cancer dissemination.

**Conclusions**

Growing evidence supports the relationship between miRNAs and metabolism or metabolism and adhesion or miRNAs and adhesion. Here, we discussed the interconnections between the three different aspects, miRNAs/metabolism/adhesion, and how the different players may affect tumor progression based on the in vitro and in vivo data. The numerous tumor and stroma cell modifications and their connections occurring during cancer progression were highlighted. In particular, we presented data relative to miR-455-3p, miR-122, miR-30a-5p, miR-203, miR-181d, miR-7, miR-489-3p, miR-155, miR-422a and miR-146b-5p. Interestingly, the main control of these non-coding RNAs focuses on the glycolytic pathways, thus emphasizing the strong involvement of glucose metabolism in cancer. Nevertheless, further studies need to be performed to reinforce the connection between miRNAs, metabolism and adhesion/metastases in patients. The analyzed papers have demonstrated the relevance of miRNAs in this intricate network and these small non-coding RNAs consequently emerge as promising therapeutic candidates. In fact, miRNA expression and activity can be successfully modulated through miRNA mimics or inhibitors to replenish tumor suppressor miRNAs or inhibit oncomiRs, respectively. Moreover, considering the relevance of the discussed adhesion molecules and metabolic players, additional therapeutic interventions must be considered. Thus, from the content of this review new combinatorial therapies to reduce or eliminate cancer dissemination can be envisaged.

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**Data availability** Supplementary data to this article can be found available in the online version. The data underlying this article will be shared on reasonable request to the corresponding author.
Declarations

Conflict of interest The authors have no financial or non-financial interests to disclose.

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References

1. Annese T, Tamma R, De Giorgis M, Ribatti D (2020) microRNAs biogenesis, functions and role in tumor angiogenesis. Front Oncol 10:581107
2. Friedman RC, Farh KK, Burge CB, Bartel DP (2009) Most mammalian mRNAs are conserved targets of microRNAs. Genome Res 19(1):92–105
3. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E (2005) Frequent deletions and down-regulation of microRNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci USA 99(24):15524–15529
4. Ali Syeda Z, Langden SSS, Munkhzul C, Lee M, Song SJ (2020) Regulatory mechanism of MicroRNA expression in cancer. Int J Mol Sci. https://doi.org/10.3390/ijms21051723
5. Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100(1):57–70
6. Grzywa TM, Klicka K, Wlodarski PK (2020) Regulators at every step-how microRNAs drive tumor cell invasiveness and metastasis. Cancers (Basel). https://doi.org/10.3390/cancers12123709
7. VaupeL P, Schmidberger H, Mayer A (2019) The Warburg effect: essential part of metabolic reprogramming and central contributor to cancer progression. Int J Radiat Biol 95(7):912–919
8. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144(5):646–674
9. Lu J (2019) The Warburg metabolism fuels tumor metastasis. Cancer Metastasis Rev 38(1–2):157–164
10. Zheng J (2012) Energy metabolism of cancer: glycolysis versus oxidative phosphorylation (review). Oncol Lett 4(6):1151–1157
11. Palm W, Thompson CB (2017) Nutrient acquisition strategies of mammalian cells. Nature 546(7657):234–242
12. Trefely S, Doan MT, Snyder NW (2019) Crosstalk between cellular metabolism and histone acetylation. Methods Enzymol 626:1–21
13. Narita T, Weinert BT, Choudhary C (2019) Functions and mechanisms of non-histone protein acetylation. Nat Rev Mol Cell Biol 20(3):156–174
14. Feron O (2017) The many metabolic sources of acetyl-CoA to support histone acetylation and influence cancer progression. Ann Transl Med 7(Suppl 8):S277
15. Faubert B, Solmonson A, DeBerardinis RJ (2020) Metabolic reprogramming and cancer progression. Science. https://doi.org/10.1126/science.aaw5473
16. Janiszewska M, Primi MC, Izard T (2020) Cell adhesion in cancer: beyond the migration of single cells. J Biol Chem 295(8):2495–2505
17. Eben K (2017) Functional adhesion molecules (JAMs): cell adhesion receptors with pleiotropic functions in cell physiology and development. Physiol Rev 97(4):1529–1554
18. Hamidi H, Ivaska J (2018) Every step of the way: integrins in cancer progression and metastasis. Nat Rev Cancer 18(9):533–548
19. Taelehshokr S, Taelehshokr N, Hemmat N, Hajazizamian S, Isazadeh A, Dadebighlu P et al (2021) The pivotal role of MicroRNAs in glucose metabolism in cancer. Pathol Res Pract 217:153314
20. Virga F, Quirico L, Cucinelli S, Mazzone M, Taverna D, Orso F (2021) MicroRNA-mediated metabolic shaping of the tumor microenvironment. Cancers (Basel). https://doi.org/10.3390/cancers13010127
21. Perez-Tomas R, Perez-Guillen I (2020) Lactate in the tumor microenvironment: an essential molecule in cancer progression and treatment. Cancers (Basel). https://doi.org/10.3390/cancers12113244
22. Boguszewska J, Poplawski P, Alseekh S, Koblowska M, Iwanicka-Nowicka R, Rybicka B et al (2019) MicroRNA-mediated metabolic reprogramming in renal cancer. Cancers (Basel). https://doi.org/10.3390/cancers11121825
23. Oh S, Kim H, Nam K, Shin I (2017) Glut1 promotes cell proliferation, migration and invasion by regulating epidermal growth factor receptor and integrin signaling in triple-negative breast cancer cells. BMB Rep 50(3):132–137
24. Zhang B, Xie Z, Li B (2019) The clinicopathologic impacts and prognostic significance of GLUT1 expression in patients with lung cancer: a meta-analysis. Gene 689:76–83
25. Yamasaki T, Seki N, Yoshino H, Itsako T, Yamada Y, Tatarano S et al (2013) Tumor-suppressive microRNA-1291 directly regulates glucose transporter 1 in renal cell carcinoma. Cancer Sci 104(11):1411–1419
26. Guo H, Nan Y, Zhen Y, Zhang Y, Guo L, Yu K et al (2016) miRNA-451 inhibits glioma cell proliferation and invasion by downregulating glucose transporter 1. Tumour Biol 37(10):13751–13761
27. Yin J, Shi Z, Wei W, Lu C, Wei Y, Yan W et al (2020) MiR-181b suppresses glioblastoma multiforme growth through inhibition of SPI-mediated glucose metabolism. Cancer Cell Int 20:69
28. Chen YH, Song Y, Yu YL, Cheng W, Tong X (2019) miRNA-10a promotes cancer cell proliferation in oral squamous cell carcinoma by upregulating GLUT1 and promoting glucose metabolism. Oncol Lett 17(6):5441–5446
29. Xu J, Gu X, Yang X, Meng Y (2019) MiR-1204 promotes ovarian squamous cell carcinoma growth by increasing glucose uptake. Biosci Biotechnol Biochem 83(1):123–128
30. Sikander M, Malik S, Chauhan N, Khan P, Kumari S, Kashyap VK et al (2019) Curcubitacin D reprograms glucose metabolic network in prostate cancer. Cancers (Basel). https://doi.org/10.3390/cancers11030364
31. Chen B, Tang H, Liu X, Liu P, Yang L, Xie Y et al (2015) miR-22 as a prognostic factor targets glucose transporter protein type 1 in breast cancer. Cancer Lett 356(2 Pt B):410–417
32. Kim S, Lee E, Jung J, Lee JW, Kim HJ, Kim J et al (2018) microRNA-155 positively regulates glucose metabolism via PIK3R1-FOXO3a-cMYC axis in breast cancer. Oncogene 37(22):2982–2991
33. Ma F, Zhang L, Ma L, Zhang Y, Zhang J, Guo B (2017) MiR-361-5p inhibits glycolytic metabolism, proliferation and invasion of breast cancer by targeting FGFR1 and MMP-1. J Exp Clin Cancer Res 36(1):158
34. Guo W, Qiu Z, Wang Z, Wang Q, Tan N, Chen T et al (2015) MiR-199a-5p is negatively associated with malignancies and
35. Sun X, Zhang L. MicroRNA-143 suppresses oral squamous cell carcinoma cell growth, invasion and glucose metabolism through targeting hexokinase 2. Biosci Rep 2017;37(3).
36. Zhu W, Huang Y, Pan Q, Xiang P, Xie N, Yu H (2017) MicroRNA-98 suppresses warburg effect by targeting HK2 in colon cancer cells. Dig Dis Sci 62(3):660–668.
37. Liu C, Cai L, Li H (2019) miR-185 regulates the growth of osteosarcoma cells via targeting Hexokinase 2. Mol Med Rep 20(3):2774–2782.
38. Song J, Wu X, Liu F, Li M, Sun Y, Wang Y et al (2017) Long non-coding RNA PVT1 promotes glycolysis and tumor progression by regulating miR-497/HK2 axis in osteosarcoma. Biochem Biophys Res Commun 490(2):217–224.
39. Zhang Y, Shi B, Chen J, Hu L, Zhao C (2016) MiR-338-3p targets pyruvate kinase M2 and affects cell proliferation and metastasis of ovarian cancer. Am J Transl Res 8(7):3266–3273.
40. Chen J, Yu Y, Chen X, He Y, Hu Q, Li H et al (2018) MiR-139-5p is associated with poor prognosis and regulates glycolysis by repressing PKM2 in gallbladder carcinoma. Cell Prolif 51(6):e12510.
41. Xiao X, Huang X, Ye F, Chen B, Song C, Wen J et al (2016) The miR-34a-LDHA axis regulates glucose metabolism and tumor growth in breast cancer. Sci Rep 6:21735.
42. Chen C, Bai L, Cao F, Wang S, He H, Song M et al (2019) Targeting LIN28B reprograms tumor glucose metabolism and acidic microenvironment to suppress cancer stemness and metastasis. Oncogene 38(23):4527–4539.
43. Wu DH, Liang H, Lu SN, Wang H, Su ZL, Zhang L et al (2018) miR-124 suppresses pancreatic ductal adenocarcinoma growth by regulating monocarboxylate transporter 1-mediated cancer lactate metabolism. Cell Physiol Biochem 50(3):924–935.
44. Yang X, Zhao H, Yang J, Ma Y, Liu Z, Li C et al (2019) MiR-150-5p regulates melanoma proliferation, invasion and metastasis via SIX1-mediated Warburg Effect. Biochem Biophys Res Commun 515(1):85–91.
45. Chen Z, Zuo X, Zhang Y, Han G, Zhang L, Wu J et al (2018) MiR-3662 suppresses hepatocellular carcinoma growth through inhibition of HIF-1α-mediated Warburg effect. Cell Death Dis 9(5):549.
46. Ou B, Sun H, Zhao J, Xu Z, Liu Y, Feng H et al (2019) Polonol kinase 3 inhibits glucose metabolism in colorectal cancer by targeting HSP90/STAT3/HK2 signaling. J Exp Clin Cancer Res 38(1):426.
47. Riganti C, Gazzano E, Polimeni M, Aldieri E, Ghigo D (2012) The pentose phosphate pathway: an antioxidant defense and a crossroad in tumor cell fate. Free Radic Biol Med 53(3):421–436.
48. Singh A, Happe C, Mannia SK, Acquah-Mensah G, Carrerero J, Kumar S et al (2013) Transcription factor NRF2 regulates miR-1 and miR-206 to drive tumorigenesis. J Clin Invest 123(7):2921–2934.
49. Cui J, Pan Y, Wang J, Liu Y, Wang H, Li H (2018) MicroRNA-206 suppresses proliferation and predicts poor prognosis of HR-HPV-positive cervical cancer cells by targeting G6PD. Oncol Lett 16(5):5946–5952.
50. Hu T, Chang YF, Xiao Z, Mao R, Tong J, Chen B et al (2016) miR-1 inhibits progression of high-risk papillomavirus-associated human cervical cancer by targeting G6PD. Oncotarget 7(52):86103–86116.
51. He C, Yang J, Ding J, Li S, Wu H, Xiong Y et al (2018) Downregulation of glucose-6-phosphate dehydrogenase by microRNA-1 inhibits the growth of pituitary tumor cells. Oncol Rep 40(6):3533–3542.
52. Barajas JM, Reyes R, Guerrero MJ, Jacob ST, Motiwala T, Ghoshal K (2018) The role of miR-122 in the dysregulation of glucose-6-phosphate dehydrogenase (G6PD) expression in hepatocellular cancer. Sci Rep 8(1):9105.
53. Wang B, Hsu SH, Frankel W, Ghoshal K, Jacob ST (2012) Stat3-mediated activation of microRNA-23a suppresses glucocorticosterone in hepatocellular carcinoma by down-regulating glucose-6-phosphatase and peroxisome proliferator-activated receptor gamma, coactivator 1 alpha. Hepatology 56(1):186–197.
54. Zhou Y, Jin Z, Wang C (2019) Glycogen phosphorylase B promotes ovarian cancer progression via Wnt/b-catenin signaling and is regulated by miR-133a-3p. Biomed Pharmacother 120:109449.
55. Yoo HC, Yu YC, Sung Y, Han JM (2020) Glutamine reliance in cell metabolism. Exp Mol Med 52(9):1496–1516.
56. Altman BJ, Stine ZE, Dang CV (2016) From Krebs to clinic: glutamine metabolism to cancer therapy. Nat Rev Cancer 16(10):619–634.
57. Metallo CM, Gameiro PA, Bell EL, Mattaini KR, Yang J, Hiller K et al (2011) Reductive glutamine metabolism by IDH1 mediates lipogenesis under hypoxia. Nature 481(7381):380–384.
58. Jin L, Alesi GN, Kang S (2016) Glutaminolysis as a target for cancer therapy. Oncogene 35(38):3619–3625.
59. Dong J, Xiao D, Zhao Z, Ren P, Li C, Hu Y et al (2017) Epigenetic silencing of microRNA-137 enhances ASCT2 expression and tumor glutamine metabolism. Oncogenesis 6(7):e356.
60. Liu Z, Wang J, Li Y, Fan J, Chen L, Xu R (2017) MicroRNA-153 regulates glutamine metabolism in glioblastoma through targeting glutaminase. Tumour Biol 39(2):101042317691429.
61. Chang X, Zhu W, Zhang H, Lian S (2017) Sensitization of melanoma cells to temozolomide by overexpression of microRNA 203 through direct targeting of glutaminase-mediated glutamine metabolism. Clin Exp Dermatol 42(6):614–621.
62. Li J, Li X, Wu L, Pei M, Li H, Jiang Y (2019) miR-145 inhibits glutamine metabolism through c-myc/GLS1 pathways in ovarian cancer cells. Cell Biol Int 43(8):921–930.
63. Anderton B, Camarda R, Balakrishnan S, Balakrishnan A, Kohrn RA, Lim L et al (2017) MYC-driven inhibition of the glutamate-cysteine ligase promotes glutathione depletion in liver cancer. EMBO Rep 18(4):569–585.
64. Son J, Lyssiotis CA, Ying H, Wang X, Hua S, Ligorio M et al (2013) Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. Nature 496(7443):101–105.
65. Wang J, Wang B, Ren H, Chen W (2019) miR-9-5p inhibits pancreatic cancer cell proliferation, invasion and glutamine metabolism by targeting GOT1. Biochem Biophys Res Commun 509(1):241–248.
66. Sengupta D, Cassel T, Teng KY, Aljubhani M, Chowdhary VK, Hu P et al (2020) Regulation of hepatic glutamine metabolism by miR-122. Mol Metab 34:174–186.
67. Yan W, Wu X, Zhou W, Fong MY, Cao M, Liu J et al (2018) Cancer-cell-secreted exosomal miR-105 promotes tumour growth through the MYC-dependent metabolic reprogramming of stromal cells. Nat Cell Biol 20(5):597–609.
68. Ren L, Ruiz-Rodado V, Dowdy T, Huang S, Issaq SH, Beck J et al (2020) Glutaminase-1 (GLS1) inhibition limits metastatic progression in osteosarcoma. Cancer Metab 8:4.
69. Chastney MR, Conway JRW, Ivaska J (2021) Integrin adhesion complexes. Curr Biol 31(10):R536–R542.
70. Fletcher DA, Mullins RD (2010) Cell mechanics and the cytoskeleton. Nature 463(7280):485–492.
71. Seetharaman S, Etienne-Manneville S (2020) Cytoskeletal crosstalk in cell migration. Trends Cell Biol 30(9):720–735.
72. Horton ER, Humphries JD, James J, Jones MC, Askari JA, Humphries MJ (2016) The integrin adhesion network at a glance. J Cell Sci 129(22):4159–4163.
miRNA-guided reprogramming of glucose and glutamine metabolism and its impact on cell…

73. Winograd-Katz SE, Fässler R, Geiger B, Legate KR (2014) The integrin adhesome: from genes and proteins to human disease. Nat Rev Mol Cell Biol 15(4):273–288

74. Zaidel-Bar R, Itzkovitz S, Ma’ayan A, Iyengar R, Geiger B (2007) Functional atlas of the integrin adhesome. Nat Cell Biol 9(8):858–867

75. Horton ER, Byron A, Askari JA, Ng DH, Millon-Frémillon A, Robertson J et al (2015) Definition of a consensus integrin adhesome and its dynamics during adhesion complex assembly and disassembly. Nat Cell Biol 17(12):1577–1587

76. Paradžik M, Humphries JD, Stojanović N, Nestić D, Majhen D, Dekanić A et al (2020) KANK2 links αvβ5 focal adhesions to microtubules and regulates sensitivity to microtubule poisons and cell migration. Front Cell Dev Biol 8:125

77. Ni R, Huang Y, Wang J (2015) miR-98 targets ITGB3 to inhibit proliferation, migration, and invasion of non-small-cell lung cancer. Onco Targets Ther 8:2689–2697

78. Ma G, Jing C, Li L, Huang F, Ding F, Wang B et al (2016) MicroRNA-92b represses invasion-metastasis cascade of esophageal squamous cell carcinoma. Oncotarget 7(15):20209–20222

79. Croset M, Pantano F, Kan CWS, Bonnelle E, Descotes F, Alix-Panabières C et al (2018) miRNA-30 family members inhibit breast cancer invasion, osteomimcry, and bone destruction by directly targeting multiple bone metastasis-associated genes. Cancer Res 78(18):5259–5273

80. Lin Z, He R, Luo H, Lu C, Ning Z, Wu Y et al (2018) Integrin-β5, a miR-185-targeted gene, promotes hepato-cellular carcinoma tumorigenesis by regulating β-catenin stability. J Exp Clin Cancer Res 37(1):17

81. Ma G, Jing C, Huang F, Li X, Cao X, Liu Z (2017) Integrin α6 promotes esophageal cancer metastasis and is targeted by miR-92b. Oncotarget 8(4):6681–6690

82. Orso F, Quirico L, Virga F, Penna E, Dettori D, Cimino D et al (2016) miR-214 and miR-148b targeting inhibits dissemination of melanoma and breast cancer. Cancer Res 76(17):5151–5162

83. Bachmann M, Kukkurainen S, Hytonen VP, Wehrle-Hall B (2019) Cell adhesion by integrins. Physiol Rev 99(4):1655–1699

84. Shaw AS, Filbert EL (2009) Scaffold proteins and immune-cell signalling. Nat Rev Immunol 9(1):47–56

85. Naudin C, Chevalier C, Roche S (2016) The role of small actin binding proteins: their ups and downs in neurodegeneration and cancer. FEBS Lett 585(19):2998–3005

86. Gross SR (2013) Actin binding proteins: their ups and downs in metastatic life. Cell Adh Migr 7(2):199–213

87. Hanniford D, Segura MF, Zhong J, Philips E, Jirau-Serrano A et al (2007) Functional atlas of the integrin adhesome. Nat Cell Biol 9(8):858–867

88. Zhang W, Mao YQ, Wang H, Yin WJ, Zhu SX, Wang WC (2015) miRNA-145 suppresses cell migration and invasion by targeting talin 1 in prostate cancer cells. Cancer Cell Int 15:49

89. Qin J, Tang Q, Qiu M, Lang N, Li M, Zheng Y et al (2011) miR-21 targets the tumor suppressor RhoB and regulates proliferation, invasion and apoptosis in colorectal cancer cells. FEBS Lett 585(19):2998–3005

90. Kinoshita T, Nohata N, Omo M, Katsuda T, Yoshioka Y, Tamura H, Fujimura L et al (2001) Cortactin promotes and stabilizes Arp2/3-induced actin filament network formation. Curr Biol 11(5):370–374

91. Kaneda A, Kaminishi M, Sugimura T, Ushijima T (2004) The p140Cap adaptor protein as a molecular hub to block cancer aggressiveness. Cell Mol Life Sci 78(4):1355–1367

92. Weaver AM, Karginov AV, Kinley AW, Weed SA, Li Y, Parsons JT et al (2001) Cortactin promotes and stabilizes Arp2/3-induced actin filament network formation. Curr Biol 11(5):370–374

93. Morellato A et al (2007) PAXillin promotes tumor progression and predicts survival and relapse in oral cavity squamous cell carcinoma by microRNA-181c-containing extracellular vesicles capable of destructing blood-brain barrier. Nat Commun 6:6716

94. Zaidel-Bar R, Clément I, Guertin L, Ayad T, Bissada E et al (2017) Four PTEN-targeting co-expressed miRNAs and ACTN4- targeting miR-548b are independent prognostic biomarkers in human squamous cell carcinoma of the oral tongue. Int J Cancer 141(11):2318–2328

95. Di Stefano P, Damiano L, Cabodi S, Aramu S, Tordella L, Praduroux A et al (2007) p140Cap protein suppresses tumour progression by targeting a cohort of pro-metastasis genes. Nat Commun 8:14270

96. Kinoshita T, Nohata N, Omo M, Katsuda T, Yoshioka Y, Tamura H, Fujimura L et al (2001) Cortactin promotes and stabilizes Arp2/3-induced actin filament network formation. Curr Biol 11(5):370–374

97. Cheng HC, Qi RZ, Paudel H, Zhu HJ (2011) Regulation and function of protein kinases and phosphatases. Enzyme Res 2011:794089
Demircioğlu F, Wang J, Candido J, Costa ASH, Casado P, de Wang X, Min S, Liu H, Wu N, Liu X, Wang T et al (2019) Hypoxia-induced microRNA-590-5p promotes colorectal cancer progression by modulating matrix metalloproteinase activity. Cancer Lett 416:31–41

Zheng L, Chen Y, Ye L, Jiao W, Song H, Mei H et al (2017) miRNA-584-3p inhibits gastric cancer progression by repressing Yin Yang 1- facilitated MMP-14 expression. Sci Rep 7(1):8967

Li Y, Zhang H, Gong H, Yuan Y, Li Y, Wang C et al (2018) miR-182 suppresses invadopodia formation and metastasis in non-small cell lung cancer by targeting cortactin gene. J Exp Clin Cancer Res 37(1):141

Zhang J, Hochwald SN (2014) The role of FAK in tumor metabolism and therapy. Pharmacol Ther 142(2):154–163

Zhang J, Gao Q, Zhou Y, Dier U, Hempel N, Hochwald SN (2016) Focal adhesion kinase-promoted tumor glucose metabolism is associated with a shift of mitochondrial respiration to glycolysis. Oncogene 35(15):1926–1942

Gan L, Meng J, Xu M, Liu M, Qi Y, Tan C et al (2018) Extracellular matrix protein 1 promotes cell metastasis and glucose metabolism by inducing integrin β4/FAK/SOX2/HIF-1α signaling pathway in gastric cancer. Oncogene 37(6):744–755

Wang X, Min S, Liu H, Wu N, Liu X, Wang T et al (2019) Nf1 loss promotes Kras-driven lung adenocarcinoma and results in Psat1-mediated glutamate dependence. EMBO Mol Med 11(6):e9856

Demircioğlu F, Wang J, Candido J, Costa ASH, Casado P, de Luxan DB et al (2020) Cancer associated fibroblast FAK regulates malignant cell metabolism. Nat Commun 11(1):1290

Jeon SM, Chandel NS, Hay N (2012) AMPK regulates NADPH homeostasis to promote tumour cell survival during energy stress. Nature 485(7400):661–665

Paredes J, Figueiredo J, Albergaria A, Oliveira P, Carvalho J, Ribeiro AS et al (2012) Epithelial E- and P-cadherins: role and clinical significance in cancer. Biochim Biophys Acta 1826(2):297–311

Georgakopoulos-Soares I, Chartoumpekis DV, Kyriazopoulos V, Zaravinos A (2020) EMT factors and metabolic pathways in cancer. Front Oncol 10:499

Chu K, Boley KM, Moraes R, Barsky SH, Robertson FM (2013) A novel miR-155/miR-143 cascade controls glycolytic Potential. Mol Ther Oncolytics 16:30–40

Lin YH, Wu MH, Huang YH, Yeh CT, Cheng ML, Chi HC et al (2018) Taurine up-regulated gene 1 functions as a master regulator to coordinate glycolysis and metastasis in hepatocellular carcinoma. Hepatology 67(1):188–203

Gu DN, Jiang MJ, Mei Z, Dai J, Dai CY, Fang C et al (2017) microRNA-7 impairs autophagy-derived pools of glucose to suppress pancreatic cancer progression. Cancer Lett 400:69–98

Yang X, Zhu X, Hong Y, Zhang M, Qiu X, Wang Z et al (2017) miR-181d and c-myc-mediated inhibition of CRY2 and FBXL3 reprograms metabolism in colorectal cancer. Cell Death Dis 8(7):e2958

Gu DN, Jiang MJ, Tan Z, Dai J, Dai CY, Fang C et al (2017) microRNA-7-impairs autophagy-derived pools of glucose to suppress pancreatic cancer progression. Cancer Lett 400:69–78

Yang X, Zhu X, Yan Z, Li C, Zhao H, Ma L et al (2020) miR-489-3p/SIX1 Axis Regulates Melanoma Proliferation and Glycolytic Potential. Mol Ther Oncolytics 16:30–40

Jiang S, Zhang LF, Zhang HW, Hu S, Lu MH, Liang S et al (2012) A novel miR-155/miR-143 cascade controls glycolysis by regulating hexokinase 2 in breast cancer cells. Embo j 31(8):1985–1998

He Z, Li Z, Zhang X, Yin K, Wang K, Xu Z et al (2018) miR-422a regulates cellular metabolism and malignancy by targeting pyruvate dehydrogenase kinase 2 in gastric cancer. Cell Death Dis 9(5):505

Zhu Y, Wu Y, Yan W, Zhan H, Sun P (2017) miR-146b-5p regulates cell growth, invasion, and metabolism by targeting PDHB in colorectal cancer. Am J Cancer Res 7(5):1136–1150

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