How does cancer cell metabolism affect tumor migration and invasion?

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Keywords: cancer cell metabolism, cell migration, metastasis, glycolysis, glutamine

Cancer metastasis is the major cause of cancer-associated death. Accordingly, identification of the regulatory mechanisms that control whether or not tumor cells become “directed walkers” is a crucial issue of cancer research. The deregulation of cell migration during cancer progression determines the capacity of tumor cells to escape from the primary tumors and invade adjacent tissues to finally form metastases. The ability to switch from a predominantly oxidative metabolism to glycolysis and the production of lactate even when oxygen is plentiful is a key characteristic of cancer cells. This metabolic switch, known as the Warburg effect, was first described in 1920s, and affected not only tumor cell growth but also tumor cell migration. In this review, we will focus on the recent studies on how cancer cell metabolism affects tumor cell migration and invasion. Understanding the new aspects on molecular mechanisms and signaling pathways controlling tumor cell migration is critical for development of therapeutic strategies for cancer patients.

Introduction

Tumor metastasis involves a series of interrelated events. Briefly, the initial steps involve vascularization of the primary tumor for aggressive growth through secretion of angiogenic factors, increased motility, and invasion of the tissue stroma through secretion of matrix metalloproteinases, and other changes in the tumor cells, such as the epithelial–mesenchymal-like transition (EMT-like). The invasive tumor cells penetrate blood vessels (intravasation) to enter the circulation or migrate through the lymphatic channels. The tumor cells also associate with bone marrow-derived cells, endothelial cells, stromal cells, and others, which provide a supportive microenvironment for the tumor cells. The circulating tumor cells extravagate into the parenchyma of a distal organ, where they undergo metastatic growth. Although tumor cell migration is a complicated procedure, the basic steps are similar to normal cell migration. For example, Rho GTPase-regulated cytoskeletal remodeling and PI-3K-defined leading edge are critical steps in both tumor cell migration and normal cell migration (Fig. 1).

The alternation of cancer cell metabolism was first observed by Otto Warburg in early 1921. He found that glucose carbons were mainly converted to lactate in proliferating ascites tumor cells, even with supply of abundant oxygen, a phenomenon known as the “Warburg effect.” He hypothesized that the metabolic alteration arose from the defects of mitochondria that lost their ability to effectively oxidize glucose carbon to CO₂. Advances in cancer metabolism research over the last decade have enhanced our understanding of how aerobic glycolysis and other metabolic alterations observed in cancer cells support the anabolic requirements associated with cell growth and proliferation. High glycolytic rate allows cells to use the most abundant extracellular nutrient, glucose, to produce abundant ATP. Glucose degradation provides cells with intermediates needed for biosynthetic pathways, including ribose sugars for nucleotides; glycerol and citrate for lipids; nonessential amino acids; and, through the oxidative pentose phosphate pathway, NADPH. Therefore, the Warburg effect benefits both bioenergetics and biosynthesis necessary for cell growth and proliferation. A consequence of this changed metabolism is to increase acid production in tumor cells. This leads to normal cell death, and extracellular matrix degradation by proteolytic enzymes, these enhance cancer cell’s capability for migration and invasion.

Decreased oxygen availability (hypoxia) in cancer cells is coordinated by the hypoxia-inducible factor 1 (HIF-1). HIF-1’s targets include genes encoding glucose transporters, glycolytic enzymes, and LDH-A. HIF-1 also can activate Myc, then
Myc targets glutaminases for high activities in proliferating breast cancer cells. Experiments from carbon labeling metabolic studies demonstrated that glycolysis, glutaminolysis, the Kreb’s cycle, the pentose phosphate pathway, and nucleotide biosynthesis are all coordinately enhanced in tumor cells (Fig. 2). Therefore, in this review, we will focus on the effects of glycolysis, glutamine metabolism, and pentose phosphate pathway on tumor cell migration and invasion.

How Does the Glycolysis Pathway Affect Tumor Cell Migration and Invasion?

The most cancer cells use glucose at high level and convert it to lactate instead of relying on mitochondrial oxidative phosphorylation to generate energy even with adequate oxygen, a phenomenon termed “Warburg effect.” Aerobic glycolysis is an inefficient way to generate ATP, but the inefficiency of the anaerobic pathway can be compensated by increased glucose flux. Switching to the aerobic metabolism of glucose to lactate is substantially less efficient than oxidation to CO₂ and H₂O, tumor cells maintain ATP production by increasing glucose flux. A critical consequence of this altered metabolism is to increase lactate production in tumor cells. This leads to normal cell death via caspase-mediated activation of p53-dependent apoptotic pathway, whereas cancer cells are well equipped to export lactate by MCTs transporters resulting in the acidification of microenvironment. A low pH created by extracellular acidification provides a favorable microenvironment for the activation of proteases, including MMPs, urokinase-type plasminogen activator, and cathepsins B, D, and L, which induce extracellular matrix (ECM) degradation and facilitate tumor cells to metastasis. Goetze et al. found that sodium L-lactate but not D-lactate or changes in intracellular pH induced a time- and dose-dependent migration of human SQ20B squamous larynx carcinoma cells in a chemo-attractive experiment. Therefore, tumor cells become migratory and invasive because they disturb the environment so that it is optimal for their proliferation and toxic to the normal cells with which they compete for space and substrate.

Although no clinical diagnostic application has been developed to date, elevated levels of lactate have shown a correlation with poor patient prognosis and overall survival in different cancers. Lactate is not only a metabolic intermediate but also acts as a signaling molecule. Lactate has been reported to activate hypoxia-inducible factor (HIF). The underlying pathway was shown to require lactate oxidation into pyruvate (LDH-1 reaction) in order to support a functional competition between pyruvate and 2-oxoglutarate (a by-product of the TCA cycle) for the control of HIF PHD activity. Pyruvate functionally competes with 2-oxoglutarate leading to PHD inactivation and, consequently, HIF-1 protein stabilization. HIF, as a transcription factor, drives the induction or repression of a myriad of genes controlling multiple cell functions such as angiogenesis, metabolism, invasion/metastasis, and
apoptosis/survival. HIF activation by acidic microenvironment contributes to tumorigenesis and metastasis. Disruption of cell–cell and cell–extracellular matrix contacts promotes cell migration. A substantial number of proteins induced by HIF are involved in these processes, which includes vimentin, fibronectin, keratins 14, 18, 19, matrix metalloproteinase 2, cathepsin D. The loss of E-cadherin, a hallmark in invasion, is also linked to HIF activation and, thus, metastasis. Hypoxic environments select for tumor cells with stabilized HIF1 α, which enhances invasion of tumor cells. An increase in environmental oxygen in combination with a mitochondrial-targeted catalase mimetic and a metabolism booster may be of interest to investigate as a treatment strategy for invasive cancer.

Anoikis resistance, or the ability for cells to live detached from the extracellular matrix, is a property of epithelial cancers. A recent study focused on metabolic alterations in ovarian cancer cells with varying invasive capability under anoikis conditions found that pyruvate uptake was significantly higher for the highly invasive ovarian cancer cells compared with the less invasive ovarian cancer cells. These differences in metabolism would have an effect on cell migration, and pyruvate may be used by highly invasive ovarian cancer cells to migrate in attached conditions and, thus, may enhance metastatic potential.

The enzymes in glycolysis also play important roles in tumor migration and invasion. Phosphoglucose isomerase (PGI, also known as glucose-6-phosphate isomerase or phosphohexose isomerase) is a housekeeping cytosolic enzyme that catalyzes the conversion of glucose-6-phosphate into fructose-6-phosphate in the second step of glycolysis. PGI is a secreted protein that behaves as a potent cytokine in extracellular environment. It has been demonstrated that PGI is an autocrine motility factor (AMF), and a tumor-secreted cytokine that stimulates cell migration in vitro and metastasis in vivo. PGI/AMF stimulates cell migration through binding to its seven-transmembrane receptor gp78 on the surface of target cells. PGI/AMF is critical for migration, invasion, metastasis of tumor cells, and contains anti-apoptotic effects on malignant tumor cells and its multiple roles in tumor progression are mediated by certain downstream pathways and effectors. A previous study showed that PGI/AMF induced interleukin (IL)-8 production and by which it induced tumor cell migration. IL-8 is a potent pro-inflammatory cytokine, which is expressed in various tumor cells, especially those with high metastatic indexes, such as melanoma cells and breast carcinoma cells. It was reported that PGI/AMF could increase IL-8 expression at both mRNA and protein levels in the early stage of melanoma cells and the migratory ability of melanoma cells could be inhibited by an anti-IL-8-neutralizing antibody. It was also reported that PGI/AMF directly stimulated tumor cell migration through RhoA and Rac1 pathways. However, the relationship of these pathways remains to be further defined.

Increasing evidence suggested that the conversion of epithelial cells to more mesenchymal-like cells facilitated cell migration,
invasion, and metastasis. Molecular analysis showed that PG1/AMF suppressed epithelial marker expression and enhanced mesenchymal marker expression. The acquisition of migratory and invasive properties by epithelial cells may be associated with the gain of mesenchymal characteristics and the loss of epithelial features. PG1/AMF induce epithelial-to-mesenchymal transition (EMT) by decreasing the E-cadherin expression through NFκB pathway, which is activated by RhoA and Rac1 pathways. It has been reported that PG1/AMF-induced EMT was regulated by miR-200s in breast cancer cells. MiR-200s negatively regulated expression of ZEB1/ZEB2, a mesenchymal marker and target gene of NFκB. MiR-200s can alter the relative expression of epithelia and mesenchymal markers, and decrease aggressiveness and migration of tumor cells (Fig. 3).

Fructose-1,6-bisphosphatase (FBP1), a gluconeogenesis enzyme, which catalyzes the splitting of fructose-1,6-bisphosphate (F-1,6-BP) into fructose 6-phosphate, also plays an important role in EMT. This metabolic reprogramming is intertwined with the development of basal-like breast cancer, because loss of FBP1 is required for EMT induction and enhanced cancer invasiveness.

Pyruvate kinase (PK) mediates the final rate-limiting step of glycolysis by catalyzing the dephosphorylation of phosphoenolpyruvate (PEP) to pyruvate. Studies have found that cancer cells exclusively express PKM2, but there might be different expressing patterns and roles of PKM2 in different tumors. As PKM2 expression is strongly correlated with gastric cancer differentiation, it may play different roles in differently differentiated gastric cancer cell types. In differentiated gastric cancer cells, knockdown of PKM2 can decrease the expression of E-cadherin and, thus, activate downstream signaling pathway of EGFR, such as PLC-1 and ERK1/2, and promote cell migration and invasion. While in undifferentiated gastric cancer cells that lack E-cadherin, PKM2 can enhance EGFR downstream signaling activation and promote cell migration and invasion. In colorectal cancer, the PKM2 expression is increased and increased PKM2 expression was associated with later stage and lymph metastasis of the tumors. Knocking-down of PKM2 suppressed the proliferation and migration of colon cancer RKO cells.

Lactate dehydrogenase (LDH) is a key metabolic enzyme catalyzing the transition of pyruvate to lactate. There are two types of subunits of LDH, designated M (muscle-type; LDHA gene product) and H (heart-type; LDHB gene product). Normal cells contain five different LDH isozymes with different substrate reactivities as a result of the five different combinations of the two different subunits: LDH1 (H4); LDH2 (MH3); LDH3 (M2H2); LDH4 (M3H); LDH5 (M4). The expression levels of LDHA and LDHB determine the cell’s isozyme pattern. LDH5 effectively catalyzes the conversion of pyruvate to lactate, and an isozyme shift to LDH5 has been linked with metastatic cancer. This shift is mediated by increased LDHA expression via HIF-1α. LDHA induction via HIF-1α is critical for maintaining glycolysis in cancer cells and increasing its invasive activity. In glioma cells, lactate metabolism regulates TGF-β2-mediated migration. Transforming growth factor-β2 (TGF-β2) is an important regulator for invasion of high-grade gliomas. TGF-β2 plays an important role in glioma cell motility and migration via several mechanisms that involve certain extracellular matrix (ECM) proteins such as versican and ECM-degrading enzymes such as MMPs. LDHA and lactate can regulate TGF-β2 expression in glioblastoma cells and increase MMP-2 expression, resulting in enhanced glioma cell migration. Conversely, downregulation of LDH-A can decrease TGF-β2 protein levels and result in reduced glioma cell migration.

Another study showed that suppressed LDHB expression plays a critical role in hepatoma cell invasiveness by inducing claudin-1 (Cln-1), a tight junction protein. The increased lactate production was due to LDH isozyme shifts to LDH5 by LDHB downexpression rather than LDHA induction. The ectopic expression of LDHB attenuated the invasiveness of both SNU 354 and 449 cells, whereas LDHB knockdown significantly augmented the invasiveness of Chang cells with Cln-1 induction.

Beside the glycolysis enzymes we discussed above, other glycolytic enzymes also play a potential role in the process of tumor cell migration. Hexokinase 2 (HK2) and 6-phosphofructo-2-kinase (PFKFB) have been reported to be transcriptional targets of HIF-1α. Based on these findings, drugs have been developed to inhibit glycolysis pathways and small molecule inhibitors of HIF are being actively sought. Other strategies like manipulation of the extracellular and/or intracellular pH of tumors may also have considerable potential in cancer therapy.

**How Does Glutamine Metabolism Affect Tumor Cell Migration and Invasion?**

Along with increased aerobic glycolysis, enhanced metabolism of glutamine is now recognized as a key feature of the metabolic pathways.
profile of cancer cells. As the most abundant amino acid in plasma, glutamine is consumed and utilized by most tumors at much higher rates than other amino acids.70 Once transported into cells, glutamine could be used as an amino acid for protein synthesis or as a nitrogen donor for nucleic acid synthesis. In actively growing cells, glucose is secreted as a lactate, which will cause a dramatic decrease of intermediates in the tricarboxylic acid (TCA) cycle. Glutamine can replenish the TCA cycle by a process termed glutamine-dependent anaplerosis,71 in which glutamine is transported into mitochondria and catabolized to glutamate by the mitochondrial enzyme glutaminase. Glutamate is then catabolized by glutamate dehydrogenase to α-ketoglutarate to feed the TCA cycle.

Recent studies suggested that glutamine metabolism contributed to cancer cell migration. Transformed fibroblasts and the highly invasive MDA-MB231 and SKBR3 breast cancer cells showed significantly higher glutaminase activity, compared with non-transformed cells and normal human mammary epithelial cells (HMECs), indicating the importance of glutamine metabolism. In screening for inhibitors of Rho GTPase-mediated cell transformation, a small molecule inhibitor 968 was found to be a potent inhibitor of Rho GTPases-mediated cell transformation. Further experiments identified glutaminase as the direct target of 968. In cell invasion assays, the migratory activity of the transformed fibroblasts and cancer cells was severely compromised when they were treated with 968, suggesting the contribution of glutamine metabolism to cancer cell migration.72 In prostate cancer cell line PC3, the c-Myc oncogenic transcription factor represses miR-23a and miR-23b, resulting in greater expression of their target protein, mitochondrial glutaminase (GLS). This leads to upregulation of glutamine catabolism. Knocking-down c-Myc by siRNA also repressed miR-23a and miR-23b expression. Importantly, PC3 cell proliferation is markedly attenuated by siGLS but not by control siRNA, indicating that GLS is necessary for cell proliferation.73 Moreover, glutamine restriction inhibits attachment, spreading, and migration of melanoma cell lines via inhibition of specific integrin expression and modulation of actin cytoskeleton remodeling.74 In addition, glutamine catabolism, leading to glutamate formation, plays specific role in neoplastic phenotype. It was reported that high extracellular concentration of glutamate favors glioma cell migration.75 Glutamate was also observed to increase the invasion and migration of pancreatic cancer cells via AMPA receptor activation and kRas-MAPK signaling.76 On the other hand, glutamate antagonists decreased motility and invasive activities of adenocarcinoma and breast and lung carcinoma cells.77

Glutamine is hydrolyzed by different isoforms of glutaminases in different tissues/cells: liver-type glutaminase (LGA) and kidney-type glutaminase (KGA).78 Normally, the expression of KGA in cancer cells promotes their growth and migration. However, stable transfection of T98G cells with a vector carrying human LGA sequence resulted in increased LGA protein activity, and the transfected cells showed a 45% reduction of cell

![Figure 4. The PPP is directly connected to glycolysis, as fructose-6-phosphate and glyceraldehyde-3-phosphate are the intermediates in both pathways. We hypothesized that TKTL1 could increase the production of fructose-6-phosphate and glyceraldehydes-3-phosphate, increasing aerobic glycolysis.](image-url)
migration compared with non-transfected cells. LGA was also identified as a novel target of p53 and plays an important role in energy metabolism and antioxidant function. Taken together, glutamine plays an important role in contributing to the core metabolism of proliferating cells by supporting energy production and biosynthesis. Glutamine availability and metabolism can also modulate activity of signal transduction pathways and then regulates cancer cell growth and migration (Fig. 2).

Cancer cells metabolic reprogramming includes a shift in energy production from oxidative phosphorylation to less efficient glycolysis even in the presence of oxygen (Warburg effect) and use of glutamine for increased biosynthetic needs. This necessitates greatly increased glucose and glutamine uptake, both of which enter the hexosamine biosynthetic pathway (HBP). The HBP end product UDP-N-acetylglucosamine (UDP-GlcNAc) is used in enzymatic post-translational modification of many cytosolic and nuclear proteins by O-linked β-N-acetylglucosamin (O-GlcNAc). A number of these targeted proteins are implicated in cancer. The increased HBP flux and hyper-O-GlcNAcylation were observed in human pancreatic ductal adenocarcinoma (PDAC). Reducing hyper-O-GlcNAcylation had no effect on non-transformed pancreatic epithelial cell growth, but inhibited PDAC cell proliferation, anchorage-independent growth, orthotopic tumor growth, and triggered apoptosis. Therefore, targeting HBP should be a potential therapeutic strategy in the treatment of cancer.

How Does Pentose Phosphate Pathway Affect Tumor Cell Migration and Invasion?

The pentose phosphate pathway (PPP) is involved in the degradation of glucose in which glucose is catalyzed by different enzymes through oxidative and non-oxidative ways, leading to production of lactate and more nucleotides. Because the PPP provides two substrates—ribose5-phosphate and NADPH—necessary for dividing cells and buffering the ROS damage, it is not surprising that changes in PPP activity usually occur during cancer development and progression. An upregulation of the PPP is generally associated with invasive and metastasizing tumors. Overexpression of the oxidative branch enzyme-G6PD was found in the central nervous system metastases of breast cancer. An increased activation of the non-oxidative branch seems functional to provide increased energetic needs of a highly invasive renal cancer. In light of these results, some studies have proposed that the activation of the non-oxidative branch of the PPP can be a hallmark of metastatic tumors. The non-oxidative branch of pentose phosphate pathway is catalyzed by transketolases (TKT). TKT is a ubiquitous thiamin diphosphate and Me2+-dependent enzyme that catalyzes the reversible transfer of two-carbon ketol units between ketose and aldose phosphates in the non-oxidative part of the pentose phosphate pathway (PPP). TKT, along with transaldolase (TAL), which transfers three-carbon units, a reversible connection between glycolysis, and the PPP. A mutated transketolase transcript (TKTL1) is upregulated in human malignancies, and the overexpression of TKTL1 has been reported in different cancers. TKTL1 is responsible for around 60% or 70% of transketolase activity in human hepatoma and colon-cancer cells. It has been demonstrated that knockdown of TKTL1 by RNAs in human HCT116 colon carcinoma cells resulted in reducing cancer cell migration along with a significantly low glucose consumption and lactate production. As one of the five lactate dehydrogenase (LDH) isoenzymes, LDH5 plays an important role in catalyzing pyruvate into lactate. Kayser et al. found that overexpression of TKTL1 led to overexpression of LDH5, thereby enhanced the production of pyruvate and lactate. High lactate concentration could induce the necrosis and apoptosis of normal tissues and release of cathepsin B and other proteolytic enzymes, which results in the degradation of extracellular matrix and initiates cancer cell migration. It is reported that metastasis of tumors is promoted by lactate-induced secretion of hyaluronan that creates a milieu favorable for migration. Intriguingly, lactate itself has been found to induce the migration of cancer cells. The data from patients also suggest that TKTL1 plays a critical role in cancer migration. Langbein and his co-workers found that strong TKTL1 activity was observed in invasive tumors, whereas no or weak activity of TKTL1 was detected in non-invasive colon carcinomas. They also found that increased TKTL1 protein expression was observed in tumor tissue of all patients with metastasized kidney cancer, whereas no expression or weak expression in non-progressing tumors. Finally, a recent study showed that overexpression of TKTL1 induced the expression of HIF-1α in vivo and in vitro. Conversely, gene silence of TKTL1 by siRNA significantly decreased the HIF-1α level. HIF-1, a transcriptional factor, regulates the transcription of hundreds of genes that encode proteins involved in every aspect of cancer biology, including cell proliferation, division, migration, invasion, and metastasis (Fig. 4). Taken together, the enzymes that function in pentose phosphate pathway may affect tumor cell migration and tumor invasion through multiple mechanisms.

Conclusion and Future Directions

In this review, we provide an overview of recent experimental studies that investigate the effects of cancer cell metabolism on tumor cell migration and invasion. These experimental studies have provided great insight into how the enzymes that control cancer metabolisms affect tumor cell migration and invasion. The ability to switch from a predominantly oxidative metabolism to glycolysis and the production of lactate even when oxygen is plentiful is a key characteristic of cancer cells. This metabolic switch, known as the Warburg effect, was first described in the 1920s, and not only affected tumor cell growth but also affected tumor cell migration. In general, there are several pathways including glycolysis, glutamine metabolism, and pentose phosphate pathway that are involved in cancer cell metabolism. There is a concomitantly increase of glucose metabolism in tumor cells, leading to generation of ATP, NADPH, lactate, and nucleic acids. Emerging studies suggest that not only the key enzymes that control cancer metabolism but also the metabolic products from cancer cells significantly affect tumor cell migration and
invasion. However, the detailed molecular mechanisms on how cancer metabolism regulates tumor cell migration and cancer metastasis are not clear.

While anaerobic glycolysis promotes energy production under hypoxia, aerobic glycolysis, the Warburg effect, is favorable not only for cancer cell growth, but also tumor migration and invasion. These metabolic switches in cancer cells lead to the changes of HIF1 activation, lactate release, and redox production, which all link the development of invasive phenotype of cancers. A recent mathematical model provided a hypothesis of acid-mediated tumor invasion. In this model, increased acid production due to altered glucose metabolism serves as a key intermediate by producing H+ flow alone concentration gradients into adjacent normal tissue. This chronic exposure of peritumoral normal tissue to an acidic microenvironment induces normal cell death and extracellular matrix degradation through the release of cathepsin B and other proteolytic enzymes, which permits cancer cells to invade the damaged adjacent normal tissue despite the acid gradient. However, this model is still needed to be proven by more in vivo experimental evidence. In addition, the underlying mechanisms of lactate acidosis and metastasis, lactate shuttle, the influence of lactate on redox homeostasis, lactate signaling, and lactate-activated angiogenesis in the cancer context are still needed to be further investigated in the future.

In summary, we are here summarizing the recent advances in the effects of cancer cell metabolism on its invasive phenotype. Targeting the cancer cell metabolism may provide novel strategies for inhibiting tumor cell migration and cancer metastasis and make cancer treatable.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Acknowledgments
We thank Dr Ceshi Chen (Kunming Institute of Zoology, Chinese Academy of Science) for discussion and reading of the manuscript. This work was supported by a starting fund from Nanchang University.

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