Review

Cancer Research

Metabolic Plasticity as a Determinant of Tumor Growth and Metastasis

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Abstract

Cancer cells must adapt their metabolism to meet the energetic and biosynthetic demands that accompany rapid growth of the primary tumor and colonization of distinct metastatic sites. Different stages of the metastatic cascade can also present distinct metabolic challenges to disseminating cancer cells. However, little is known regarding how changes in cellular metabolism, both within the cancer cell and the metastatic microenvironment, alter the ability of tumor cells to colonize and grow in distinct secondary sites. This review examines the concept of metabolic heterogeneity within the primary tumor, and how cancer cells are metabolically coupled with other cancer cells that comprise the tumor and cells within the tumor stroma. We examine how metabolic strategies, which are engaged by cancer cells in the primary site, change during the metastatic process. Finally, we discuss the metabolic adaptations that occur as cancer cells colonize foreign metastatic microenvironments and how cancer cells influence the metabolism of stromal cells at sites of metastasis. Through a discussion of these topics, it is clear that plasticity in tumor metabolic programs, which allows cancer cells to adapt and grow in hostile microenvironments, is emerging as an important variable that may change clinical approaches to managing metastatic disease. *Cancer Res; 76(18); 5201–8. ©2016 AACR.*

Introduction

A growing tumor consists of heterogeneous cancer and stromal cell populations, both of which contribute significantly to disease progression. Tumor heterogeneity arises due to unique combinations of genetic and epigenetic alterations within distinct cancer cell subpopulations. In addition to this genetic heterogeneity, alterations in tumor metabolism coupled with the ability of cancer cells to engage different metabolic strategies based on the environmental context, greatly contributes to tumor heterogeneity. Cellular energetics or "oncometabolism" is now considered one of the defining hallmarks of cancer (1). Metabolic heterogeneity arises and is maintained through coupled metabolic interactions that occur between distinct tumor cell populations within the tumor, as well as between the tumor and the stroma (2).

During tumor growth, cancer cells are faced with heightened bioenergetic and biosynthetic demands to maintain tumor cell proliferation. In addition to increased requirements for ATP generation, tumor cells also need to increase the biosynthesis of macromolecules (lipids, amino acids), reducing equivalents (NADH, NADPH, $FADH_2$), and other cofactors for metabolic reactions (3). Cancer cells must balance energy-producing and energy-consuming processes to fuel tumor growth, while adapting their metabolism to the dynamic changes in nutrient and oxygen availability that occur during tumor progression, including the emergence of hypoxic regions within a rapidly growing tumor. While we now understand many of the metabolic strategies used by cancer cells to fuel primary tumor growth, how cancer metabolism changes during the metastatic process is less well known. Emerging data suggest that cancer cells, once they leave the primary tumor, must engage different metabolic strategies, distinct from the primary tumor, to successfully metastasize. This review examines the metabolic flexibility that occurs during the metastatic process and how metabolic adaptation is influenced by unique microenvironments to control tumor metastasis.

Metabolic Strategies Engaged during Tumorigenesis

Although normal cells can use different substrates for energy production, glucose is a key fuel source. Nontransformed cells generate much of their ATP via mitochondrial-dependent oxidative phosphorylation (OXPHOS), which allows for maximal production of ATP from glucose. When molecular oxygen, which is required for ATP production during OXPHOS, is limiting, such as under hypoxia, differentiated cells instead use anaerobic glycolysis to convert glucose into lactate, yielding a much smaller amount of ATP from glucose (2 molecules of ATP per molecule of glucose).

Glycolysis

In contrast to untransformed cells, most cancer cells display high rates of glucose uptake but divert glucose-derived pyruvate away from the mitochondria and toward lactate production, even under conditions where oxygen is not limiting. This metabolic strategy, known as "aerobic glycolysis" or the Warburg effect (4, 5), is one of the most commonly observed examples of

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doi: 10.1158/0008-5472.CAN-16-0266

Table 1. Metabolic strategies that are prioritized by different solid cancers.

Cancer type	Metabolic strategy	References
Breast cancer	ER^+: Glycolysis < **OXPHOS** - Metabolic coupling with CAFs (Reverse Warburg effect) - ↑ MCT1, ↑ LDH-A/B - ↑ Glutamine secretion, ↑ glutamine synthesis (high GS) TNBC: **Glycolysis** > OXPHOS - ↑ Glucose uptake, ↑ GLUT1, ↑ MCT4, ↑ LDH-A/B - ↑ Glutamine uptake, ↓ glutamine synthesis (low GS) ↑ Glutaminolysis	(13, 37–42)
Prostate cancer	Early-stage: Glycolysis < **OXPHOS** - Low glucose uptake - Metabolic coupling with CAFs (Reverse Warburg effect) - ↑ FFAs synthesis (↑ FAS) Late-stage: **Glycolysis** = **OXPHOS** - ↑ MCT1, ↑ LDH-A - ↑ Glucose uptake - Metabolic coupling with CAFs (Reverse Warburg effect) - ↑ FFAs synthesis (↑ FAS)	(13, 49, 51–54)
Hepatocellular carcinoma	**Glycolysis** > OXPHOS - ↑ Glycolysis, ↓ neoglucogenesis, ↓ glycogenesis - ↑ Glycolytic enzymes (HK2, G6PD, PKM2) - ↑ GLUT1 - ↑ Glutamine synthesis (↑ GS) - ↑ FFAs synthesis (↑ FAS)	(13, 28–31)
Colorectal cancer	**Glycolysis** > OXPHOS - ↑ GLUT1, LDH-A, HK1, PKM2 - ↑↑ LDH-A for CRC tumors with liver metastases (trend for the other enzymes) - ↑ Glutaminolysis (↑ GLS1) - ↑ FFAs synthesis (↑ FAS)	(32–36)

Abbreviations: CRC, colorectal cancer; FAS, fatty acid synthase; FFA, free fatty acid; G6PD, glucose-6-phosphate dehydrogenase; GLS, glutaminase; GLUT, glucose transporter; GS, glutamine synthetase; HK, hexokinase; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; PKM2, pyruvate kinase M2 isoform; TNBC, triple-negative breast cancer.

metabolic reprogramming in cancer cells. Increased glycolysis is associated with highly proliferative tumors and positively correlates with a poor prognosis in many types of cancer (6). The metabolic switch to aerobic glycolysis may confer several advantages to proliferating tumor cells including rapid ATP production from glycolysis and the synthesis of glucose-derived macromolecules necessary for cell division (3, 4).

Targeting glycolytic metabolism may represent an attractive strategy for the treatment of some cancers (7–9). Inhibiting glycolysis by 2-deoxy-D-glucose (2-DG) induces a metabolic shift toward OXPHOS, decreases lactate production, and consequently inhibits cancer metastasis (10). In fact, several key glycolytic enzymes and glucose transporters are currently in preclinical or clinical development, either alone or in combination with other anticancer drugs. These include inhibitors of GLUT1 (WZB117), hexokinase II (2-DG, Lonidamine), phosphofructokinase (3PO), glyceraldehyde 3-phosphate dehydrogenase (3-BP), and lactate dehydrogenase A (FX11, Oxamate; refs. 8–10).

Oxidative phosphorylation

In addition to the Warburg effect, tumor cells engage other metabolic pathways to support cell growth. The importance of OXPHOS in cancer metabolism has been underappreciated despite evidence that mitochondria contribute to efficient ATP production in a variety of cancer cell lines (11, 12). On the basis of the observation that breast cancer cells produce 80% of their ATP via mitochondrial-dependent metabolism, the concept of "oxidative tumors" has been introduced to describe ATP production by OXPHOS from glucose, fatty acids, or glutamine oxidation (13–15). In addition, maintenance of mitochondrial membrane potential by the electron transport chain is required to support the proliferation of cancer cells (16). Tumor cells can also adopt intermediate metabolic phenotypes. For example, tumor cells can perform a truncated TCA cycle, exporting the TCA cycle intermediate citrate to the cytosol to produce acetyl-coA, to prioritize lipid and protein synthesis (6, 17).

Targeting mitochondrial-dependent metabolism is also an area of intense interest (18). This has been fueled by the prospect of repurposing an effective anti-type II diabetes drug, metformin, for oncology applications (19, 20). Numerous studies have demonstrated that metformin impairs cancer cell proliferation and growth of diverse tumor types (21–24). The precise mechanism of metformin action has been debated; however, recent studies demonstrate that mitochondrial complex I is the key target for this drug (25, 26). Interestingly, complex I mutations, which are frequently observed in many cancers such as the breast, may serve as biomarkers for increased metformin sensitivity (27). In addition to drugs that directly impair the electron transport chain, strategies that target the biosynthetic and redox functions of mitochondria may emerge as viable therapeutic paths for impairing tumor growth (18).

Metabolic heterogeneity between tumor types

Cancer cells can display distinct metabolic features that are characteristic of the tissue of origin (13). Indeed, lung, liver, colorectal cancers, and leukemias rely heavily on glycolysis; whereas, lymphomas, melanomas, and glioblastomas are characterized as oxidative tumors (Table 1; refs. 13, 15, 28–36).

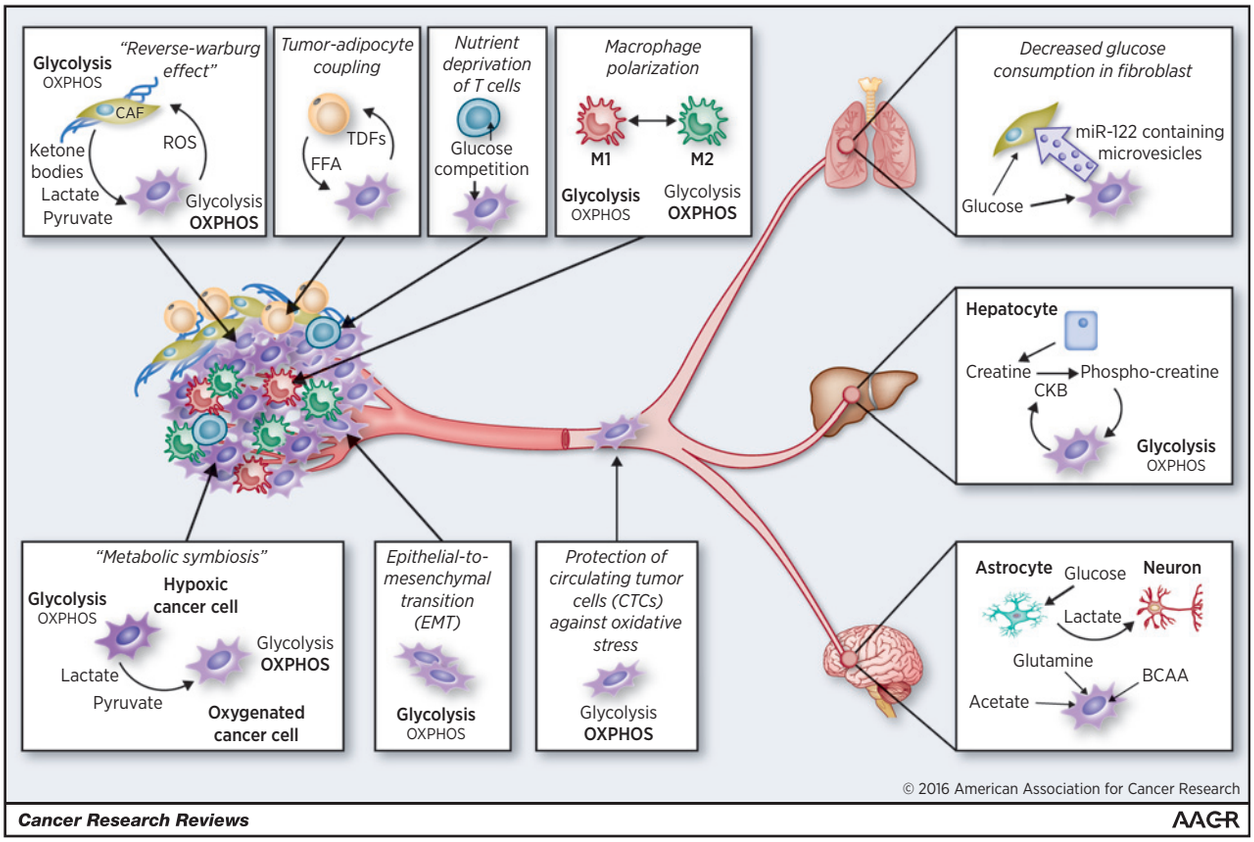

Figure 1.

Tumor growth and progression to metastatic disease requires complex metabolic interactions with a variety of different cell types that comprise the primary tumor and metastatic microenvironments. Breast cancer cells must engage distinct modes of cellular metabolism depending on the cellular and environmental influences that they experience at each stage of disease progression, which contributes to a high degree of metabolic heterogeneity. Metabolic flexibility and adaptation exhibited by cancer cells is critical for their ability to seed and colonize distinct metastatic microenvironments. ROS, reactive oxygen species; TDF, tumor-derived factors; FFA, free fatty acids; CKB, creatinine kinase brain-type; BCAA, branched chain amino acids.

Interestingly, recent evidence indicates that tumor cell subtypes within a particular type of cancer can also adopt distinct metabolic strategies. For example, triple-negative breast cancers (TNBC) typically exhibit a classical Warburg-like phenotype, while estrogen receptor–positive breast cancers may rely on OXPHOS (Table 1; refs. 13, 37–42). Accumulating evidence reveals that high glycolytic rates are associated with increased proliferation index in TNBCs (43), and that activation of oxidative metabolism in TNBCs can reduce both primary tumor growth and the formation of metastases (44). Recent work has demonstrated that tumor cell metabolic profiles can differ depending on their metastatic potential. By analyzing the metabolic profiles of various breast cancer cell lines that possess different metastatic abilities, we and others have shown that both glycolysis and OXPHOS are increasingly engaged as metastatic ability is acquired (45, 46).

In contrast to most tissues, normal prostatic epithelial cells are highly dependent on glycolysis. During transformation to early lesions, prostate cancer cells progressively switch toward OXPHOS-dependent metabolism (47). Interestingly, prostate cancer cells prioritize glycolytic metabolism during late stages of cancer progression, rendering them sensitive to 2-DG (13, 48–54). Thus, prostate cancer cells exhibit a mixed phenotype, where both glycolysis and OXPHOS are required for energy metabolism at different stage of disease progression (Table 1; ref. 13). Glycolysis and OXPHOS may be considered complementary strategies that afford cancer cells maximum metabolic flexibility to deal with changes in nutrient supply, the biosynthetic/energy demands of the cell, and the immediate tumor microenvironment.

Metabolic heterogeneity within tumors

In the context of the primary tumor, spatiotemporal influences such as oxygenation, pH, and the concentrations of glucose and other metabolites can strongly reinforce metabolic heterogeneity. Depending on their location within a growing tumor, cancer cell subpopulations may adopt different metabolic profiles to maintain bioenergetics. Hypoxia represents a major factor that determines the metabolic status of tumor cells, and oxygen gradients within tissues adjacent to blood vessels have been demonstrated. Hypoxia promotes glycolysis through the stabilization of hypoxia-inducible factor-1α (HIF-1α), leading to the upregulation of glucose transporters and a variety of glycolytic enzymes (4). A model of "two compartment" metabolism has been postulated, in which a symbiotic relationship exists between cancer cells present in an oxygenated microenvironment with those that exist in an

adjacent hypoxic zone. In this model, a "glycolytic subpopulation" of cancer cells exposed to hypoxia can release lactate as a by-product, which serves as fuel for OXPHOS-dependent metabolism within an "oxidative" cancer cell population (Fig. 1; refs. 12, 55). This metabolic symbiosis may be controlled by the differential expression of distinct lactate transporters such as the monocarboxylate transporters, MCT1 and MCT4 (56). Hypoxic/glycolytic cancer cells express high level of MCT4 that functions as a major lactate exporter, whereas oxygenated/aerobic cells express MCT1, which promotes lactate uptake (2).

On the basis of the importance of MCT transporters as mediators of metabolic symbiosis, inhibition of MCT1 has been proposed as an anticancer treatment. Inhibition of MCT1 by CHC (alpha-cyano-4-hydroxycinnamate) or depletion by siRNA-mediated approaches reduces lactate uptake, induces a switch from lactate-fueled respiration to glycolysis, and consequently blocks metabolic symbiosis and tumor progression (55). The MCT1 inhibitor, AZD3965, is currently under clinical evaluation for various advanced cancers (ClinicalTrials.gov, NCT01791595). Interestingly, recent work has shown that MCT1 inhibition, in cells that coexpress MCT1 and MCT4, decreases pyruvate export in glycolytic breast cancer cells, promotes oxidative metabolism, and decreases the proliferation of tumor cells *in vitro* and *in vivo*, suggesting an alternative lactate transport–independent role for MCT1 as a pyruvate exporter (57). Thus, MCT1 inhibitors may interfere with "two-compartment" metabolism by disrupting metabolic symbiosis in heterogeneous tumors or impair tumor growth of uniformly glycolytic tumors by forcing a shift towards oxidative phosphorylation.

In addition, metabolic reprogramming is a key determinant allowing cancer stem cells (CSC) to survive drastic changes in the tumor microenvironment and maintain their unique self-renewal abilities (2, 58, 59).

Metabolic coupling between cancer cells and the tumor stroma

Metabolic symbiosis is not restricted to interactions between distinct cancer cell populations, but also extends to metabolic crosstalk between the tumor and stroma. The stromal component is mainly composed of cancer-associated fibroblasts (CAF), adaptive and innate immune cells, mesenchymal progenitor cells, adipocytes, and endothelial cells that are situated within an extracellular matrix, although this varies between tumor types (60). A bidirectional interaction between cancer and stromal cells supports tumor growth, metastasis, and therapeutic response (e.g., chemoresistance, radioresistance) through the secretion of a diverse repertoire of soluble and vesicle-associated factors (60).

The Reverse Warburg Effect

In 2009, Lisanti and colleagues proposed that tumor cells promote the Warburg effect in neighboring CAFs, a process referred to as the "Reverse Warburg effect" (61). Subsequently, CAFs secrete energy-rich metabolites, such as ketone bodies, lactate, and pyruvate, which in turn can be taken up by cancer cells and oxidized in the mitochondria for energy production (62). Accumulating evidence suggests that glycolytic CAFs promote tumor progression (63). Given the major role of CAFs in tumor progression, the Reverse Warburg effect may represent an important metabolic hallmark of CAFs.

In contrast to tumor cells, the increase in glycolysis within CAFs is not associated with elevated proliferation of CAFs themselves, but strongly promotes tumor growth and metastasis (64). Lactate secretion from CAFs induces a local acidic microenvironment, which can enhance extracellular proteolysis and promotes the acquisition of drug resistance by tumor cells (65). As with metabolic interactions between distinct tumor subpopulations, metabolic coupling between CAFs and cancer cells relies upon unique MCT expression patterns within these compartments. Epithelial cancer cells typically express high level of MCT1, thus promoting the uptake of lactate from the MCT4-expressing CAFs (63, 66). Interestingly, metabolic coupling between cancer cells and stromal cells may occur in an opposite fashion. For example, in a colorectal cancer model, metabolic symbiosis has been described between oxidative stromal fibroblasts and glycolytic cancer cells (67).

Cancer Cells Interact Metabolically with Multiple Stromal Cell Types

While the paradigm of metabolic coupling between tumor and stroma has been the most extensively studied with CAFs, other stromal cells types may engage in a similar fashion with the growing tumor. In response to tumor-derived factors, adipocytes release free fatty acids through lipolysis, which can be directly taken up by cancer cells to sustain tumor growth via β-oxidation (68). Metabolic reprogramming in cancer cells can also modulate the functions of infiltrating immune cells, thereby leading to tumor progression (69). Recent studies suggest that altered energy metabolism in tumor-associated macrophages (TAM) can lead to distinct polarization states of these inflammatory cells. M1 (antitumor) macrophages preferentially engage glycolysis, whereas M2 macrophages (protumor) predominantly rely on OXPHOS (70). Cancer cells can also blunt antitumor T-cell responses by outcompeting cytotoxic tumor-infiltrating lymphocytes (TIL) for available glucose, effectively creating an immunosuppressive environment through starvation of TILs, which favors tumor growth (71, 72). Thus, metabolic reprogramming in stromal cells can support a symbiotic relationship between cancer and the microenvironment that fuels tumor growth and metastasis (Fig. 1).

Metabolic Plasticity during Metastasis

The majority of cancer-related deaths result from the spread of cancer cells from the primary tumor to a distant site of metastasis. The metastatic cascade is divided into distinct steps that include: (i) the acquisition of migratory and invasive abilities in the primary tumor, (ii) intravasation of cancer cells into the bloodstream, (iii) extravasation of cancer cells into the parenchyma of a distant organ or tissue, and (iv) cancer cell survival and proliferation to form macrometastases (73). This traditional view of the metastatic process is known as the "linear progression model" of metastasis. In contrast, an alternate hypothesis, referred to as the "parallel progression model," has been proposed that argues metastatic dissemination is an early event during tumor progression (74, 75). In accordance with this model, recent genomic studies of matched primary tumors and metastases suggest independent evolution (76, 77). Interestingly, the study of chemically induced skin tumors and metastases suggest that common mutations have an A-to-T signature indicative of the carcinogen while nonshared mutations are G-to-T transitions that signify exposure to oxidative stress (76). Accumulating evidence suggests that

disseminating cancer cells undergo profound metabolic reprogramming during the discrete steps to successfully metastasize. It is conceivable that these metabolic changes are selected by the pressures exerted on tumor cells by the metastatic microenvironment, which enables the emergence of distinct subpopulations that appear genomically distinct from the primary tumor. Alternatively, it is also possible that these metabolic stresses may shape the genomic evolution of disseminated cancer cells, resulting in parallel progression that is divergent from the primary tumor.

Transient metabolic changes during metastasis

A reversible epithelial-to-mesenchymal transition (EMT) is one mechanism that enhances the migratory and metastatic phenotypes of cancer cells (78). Recent work has demonstrated that breast cancer cells undergoing EMT exhibit enhanced glycolytic metabolism associated with suppression of anabolic metabolic pathways (Fig. 1; ref. 79). Another group identified a specific metabolic signature associated with the EMT process in breast cancer cells, which was associated with poor overall survival in breast cancer patients (80). In contrast, invasive breast cancer cells exhibit a shift toward OXPHOS metabolism, via a pathway dependent on the transcriptional coactivator, PGC-1α (peroxisome proliferator-activated receptor gamma coactivator-1α), which is a key regulator of mitochondrial biogenesis and metabolism. Clinical data have also correlated PGC-1α expression with invasive breast cancers and formation of distant metastases (81). PGC-1α confers cellular protection from oxidative stress (82), and its engagement may protect circulating cancer cells from apoptosis. Consistent with these findings, metastatic melanoma cells have been shown to undergo reversible metabolic changes, marked by elevated expression of key enzymes within the folate pathway. Engagement of the folate pathway manages oxidative stress through the production of NADPH, which enhances the ability of melanoma cells to withstand oxidative stress and colonize distinct metastatic sites (83). Circulating cancer cells isolated from the bloodstream preferentially engage OXPHOS-dependent metabolism when compared with the primary tumor or lung metastases, reinforcing the concept of metabolic plasticity of the cancer cells during discrete steps of the metastatic process (Fig. 1; ref. 81).

Distinct metastatic microenvironments select for specific modes of cancer cell metabolism

Metabolic characterization of breast cancer cells has revealed distinct metabolic profiles as cells gain metastatic potential. A shift toward aerobic glycolysis is observed in tumorigenic but non-metastatic breast cancer cells compared with normal mammary epithelial cells, and the acquisition of metastatic phenotypes is associated with further changes in both glycolytic and OXPHOS metabolites (84). OXPHOS and increased mitochondrial metabolism have also been shown to be required for the metastatic phenotype (81, 85). We recently demonstrated that highly metastatic breast cancer cells enhance their metastatic fitness by engaging both OXPHOS and glycolysis as metabolic strategies, and that distinct metabolic profiles may dictate metastatic fitness to distinct organ sites. Using organ-selective breast cancer variants obtained by *in vivo* selection, we have demonstrated that metastatic breast tumor cells differentially engage distinct metabolic strategies depending on their metastatic site. Breast cancer cells isolated from bone or lung metastases preferentially engage OXPHOS, compared with liver-metastatic breast cancer cells that prioritize glycolysis (45). The unique metabolic profile of liver-metastatic breast cancer cells was associated with engagement of HIF-1α- and pyruvate dehydrogenase kinase1 (PDK1)-dependent pathways. PDK1, which inhibits PDH (pyruvate dehydrogenase) to prevent the conversion of pyruvate to acetyl-coA, is specifically required to efficiently promote the formation of liver metastases, and is highly expressed in liver metastases from human breast cancer patients. Finally, in contrast to the primary tumor, silencing PDK1 in liver-metastatic breast cancer cells induces a dramatic reduction in liver metastatic burden (45). These results raise the idea that particular metabolic programs may better equip metastatic breast cancer cells to survive and colonize distinct metastatic microenvironments (Fig. 1).

These data highlight PDK1 as a therapeutic target for metastatic breast cancer. Dichloroacetate (DCA), a structural analogue of pyruvate, represents the most-studied agent capable of inhibiting PDK activity (86). DCA-mediated PDK inhibition allows entry of pyruvate into the TCA cycle, restoration of oxidative phosphorylation in cancer cells, and diminishes metastasis (87–89). The efficacy of DCA as a cancer therapy is under clinical evaluation in various models, including treatment-refractory metastatic breast cancer (90). However, DCA suffers from some drawbacks as a therapeutic agent, such as low potency/selectivity and poor pharmacokinetics (91). The potential of PDK family members as therapeutic targets has prompted considerable interest in developing specific inhibitors against these enzymes (91–93).

Metabolic Adaptations of Tumor and Stroma within Unique Metastatic Microenvironments

On the basis of the tenets of the "seed and soil" hypothesis first proposed by Stephen Paget, once metastatic tumor cells extravasate into a foreign tissue, their ability to successfully colonize and grow depends on their ability to influence and respond to their new microenvironment. Thus, the efficient formation of metastases is largely determined by the compatibility between tumor cells and the metastatic microenvironment in which they seed (94). Emerging studies support the idea that specific metastatic microenvironments are associated with unique metabolic characteristics of the metastatic cancer cells.

Metabolic adaptation of disseminated cancer cells to unique metastatic microenvironments

Metabolic adaptation by cancer cells to specific metastatic sites is best exemplified by the recent studies of brain metastases. The brain possesses unique metabolic characteristics with respect to glucose availability, such as metabolic coupling between astrocytes and neurons, commonly referred to as the "lactate shuttle." In this scenario, lactate secreted by astrocytes is taken up by neurons to fuel OXPHOS-dependent metabolism (2). Thus, as a consequence of the lactate shuttle, available glucose concentrations are variable and may be growth limiting for brain metastases. However, the brain interstitial space contains high levels of glutamine and branched chain amino acids, which can serve as alternate energy substrates to fuel the growth of metastatic breast cancer cells seeding the brain (95). Brain metastases may also adapt to limiting glucose levels by oxidizing acetate in the TCA cycle (96).

Recently, it was demonstrated that metastatic colorectal cancer cells reprogram hepatocyte-derived metabolites to enable the

successful colonization and formation of liver metastases (97). miR-551 and miR-483 were identified as suppressors of efficient colorectal cancer liver metastasis through their ability to inhibit the expression of creatinine kinase brain-type. This enzyme, when released by metastatic cells, phosphorylates liver-derived creatine to produce phosphocreatine, which is subsequently imported into the metastatic colorectal cancer cells to generate ATP (97). Thus, disseminated cancer cells can adopt strategies to utilize metabolites present within the microenvironment to survive the metabolic stresses encountered during seeding and successful colonization of a foreign metastatic site (Fig. 1).

Cancer cells influence the metabolism of stromal cells within different metastatic sites

Cancer cells not only respond to the foreign microenvironment in which they seed, but they can also influence the metabolism of stromal cells. Tumor-derived exosomes, which are derived from the endocytic pathway, represent emerging effectors of intercellular communication between cancer cells and their microenvironment (98). Recent work demonstrated that breast cancer–derived vesicles can suppress glucose uptake by niche cells in common metastatic sites, including lung fibroblasts and astrocytes, to allow preferential glucose uptake by metastatic breast cancer cells (99). These vesicles were found to contain high miR-122 levels, which suppresses glucose uptake by stromal cells by downregulating glycolytic enzymes such as pyruvate kinase (99). These observations suggest that reprogramming the metabolism of stromal cells in the tumor microenvironment is an active process initiated by cancer cells to favor their own growth (Fig. 1).

Conclusions

Accumulating evidence has highlighted the diversity of metabolic strategies adopted by cancer cells, and the metabolic interplay between distinct cancer cell populations within the tumor and between the tumor and stroma. In addition to aerobic glycolysis, metastatic tumor cells can engage complementary metabolic strategies such as OXPHOS for maximum metabolic flexibility, which allows cancer cells to respond to rapidly changing metabolic demands and/or conditions. Emerging data suggest that metabolic reprogramming is required during metastatic dissemination and is critical for efficient colonization of distant sites. Depending on the specific site of metastasis, metastatic cancer cells differentially engage distinct metabolic programs to ensure their survival. One future challenge is to better understand how tumor cells maximize available resources by remodeling the tumor microenvironment (e.g. CAFs, macrophages, adipocytes) to sustain their survival and proliferation. Understanding the mechanisms underlying critical metabolic adaptations made by metastatic cancer cells and defining key metabolic codependencies between cancer cells and the surrounding stroma may afford new approaches to clinically manage metastatic disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors thank members of the Jones and Siegel laboratories for their thoughtful comments on the manuscript.

Grant Support

The research conducted in the authors' laboratories was supported by grants from the CIHR (MOP-93799 to R.G. Jones; MOP-136907 to P.M. Siegel) and TFRI (TFRI-239585 to R.G. Jones and P.M. Siegel).

Received January 26, 2016; revised April 12, 2016; accepted April 21, 2016; published OnlineFirst September 1, 2016.

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