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Alternative Fuels for Cancer Cells

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Abstract

Tumor metabolism is significantly altered to support the various metabolic needs of tumor cells. The most prominent change is the increased tumor glycolysis that leads to increased glucose uptake and utilization. However, it has become obvious that many non-glucose nutrients, such as amino acids, lactate, acetate and macromolecules, can serve as alternative fuels for cancer cells. This knowledge reveals an unexpected flexibility and evolutionarily-conserved model in which cancer cells uptake nutrients from their external environment to fulfill their necessary energetic needs. It is possible that tumor cells have evolved the ability to utilize different carbon sources due to the limited supply of nutrient that can be driven by oncogenic mutations and tumor microenvironmental stresses. In certain cases, these factors permanently alter the tumor cells' metabolism, causing certain nutrients to become indispensable and thus creating opportunities for therapeutic intervention to eradicate tumors by their metabolic vulnerabilities.

1. Altered metabolic needs and alternative fuels of tumor cells

Compared to normal cells, transformed cells possess the capacity to continuously proliferate and avoid cellular senescence, which allows them to continuously expand to become tumors. Tumor metabolism is significantly altered to accommodate for the increased metabolic needs for energy generation (bioenergetic) and macromolecule synthesis (biosynthetic) necessary for oncogenic transformation. The Warburg Effect remains a central concept of tumor metabolism that describes the preferential use of glucose and glycolysis for energy generation[1,2]. This preferential use of the anaerobic mode of glycolysis produces lactate and contributes to the prominent lactic acidosis in most solid tumors. The causes and functional consequences of this increased glucose uptake and utilization are the subject of intense investigation. However, glucose deprivation is a common feature in solid tumors. Furthermore, the extracellular acidosis further restricts the glucose uptake and glycolysis [3-5]. Therefore, recent research efforts have found that, beside glucose, tumor cells also rely on a wide variety of "alternative fuels" to provide various metabolic needs. The consumption and utilization of these alternative fuels are affected by various oncogenic signaling events

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and/or tumor microenvironmental stresses and can restrict certain metabolic flexibilities. Tumor cells' reliance on alternative fuels may present tumor-specific metabolic vulnerabilities, and thus, meaningful therapeutic windows to eradicate tumor cells. Targeting essential tumor metabolism may be of particular interest for the tumors that have developed resistance to chemotherapeutics or targeting agents. In this article, we hope to outline some of the alternative fuels that are known to become indispensable for certain tumor cells, with the hope that improved understanding of these nutrient addictions will allow us to better target these metabolic dependencies.

2. Adaptive mechanisms to cope with nutrient deprivation and metabolic stresses

It is important to note that most mammalian cells have efficient ways to cope with, and therefore survive, nutrient deprivation in their external environments that occurs during pathological adaptations or therapeutic intervention. The success of these mechanisms allows cells to survive nutrient deprivation and preserve the capacity to resume proliferation after the resolution of the metabolic stresses. Therefore, addiction to alternative nutrients, as measured by cell death upon deprivation, will only manifest when these adaptive mechanisms fail or are inadequate. During nutrient starvation, cells can resort to autophagy (self-eating) to generate amino acids, lipids and other nutrients by degrading existing macromolecules. Multiple components of the autophagy pathway are necessary for tumor development in mouse tumor models [6]. In addition, mammalian cells can trigger at least three highly conserved signaling mechanisms in response to nutrient deprivation and other metabolic stresses to control protein translation and transcriptional responses. The first mechanism is via mammalian target of rapamycin (mTOR), a conserved Ser/Thr kinase (a part of the mTOR complexes), to regulate cell growth and autophagy. Another sensing mechanism is the GCN2 kinase that, by detecting levels of uncharged free tRNAs during amino acid deprivation, regulates protein translation initiation through the phosphorylation of eukaryotic translation initiation factor (eIF) 2a. Phosphorylated eIF2α suppresses general protein synthesis, but promotes the translation of select mRNA species, such as the activating transcription factor 4 (ATF4) [7], that facilitate cell survival under stress. Third, the AMP-activated protein kinase (AMPK) is a central regulator of cellular metabolism and energy homeostasis that adjusts cell growth and survival in response to an increased AMP/ATP ratio during energy depletion. The importance of these nutrient sensing and adaptive pathways in cancer biology is manifested by the number of the tumor suppressors and oncogenes in these pathways that are oncogenic drivers. Employing these nutrient sensing pathways allows many cells to adapt to and survive nutrient limitations in their environments. However, these adaptive mechanisms are not adequate for certain cancer cells to survive the deprivation of specific nutrients.

3. Alternative fuels and nutrient addiction associated with oncogenic events

Generally, there are several underlying mechanism by which an alternative fuels become indispensable for tumor-specific nutrient addictions. First, as mentioned, the increased

proliferation of tumor cells imposes greater demands on the quantity of building blocks necessary to synthesize the macromolecules required for proliferation. In addition, tumor cells may also need nutrients to maintain pro-growth gene expression programs and redox homeostasis. Second, many mechanisms of oncogenic transformation alter the expression or activities of enzymes critical for the metabolism of essential nutrients. Third, the expression of rate-limiting enzymes themselves may be transcriptionally regulated or affected by the DNA amplifications or deletions that become selected for during tumor development since they provide survival advantage. However, these changes in metabolism may also restrict metabolic flexibility. Fourth, tumor cells are often exposed to various tumor microenvironmental stresses, including hypoxia, lactic acidosis and glucose deprivation, which further restrict the nutrients and fuels available to the tumor cells. Fifth, tumor cells have different cellular origins and may retain some of the metabolic properties of the original cells that are associated with a particular differentiation program or environmental milieu. All of these different factors may contribute to the particular nutrient addictions and metabolic vulnerabilities that different tumor cells develop. We will discuss several example alternative fuels of cancers to illustrate their regulation by oncogenic mutations and stresses, as well as discuss their contribution to the metabolic needs of cancer cells. The figure will illustrate the relative metabolic pathways of these alternative fuels and their intersection with their biological functions.

5. Glutamine

Glutamine is the most abundant amino acid in plasma and has long been recognized to play a unique role in the metabolism of proliferating cells. While first reported in 1970s[8], the essential role of glutamine in cancer metabolism was not well understood until recent studies employed modern biochemical and genetic tools. It is now clear that glutamine plays several important metabolic roles, including as a carbon source for energy production, a nitrogen source for biosynthetic reactions, a regulator of lipid generation and a maintainer of redox homeostasis. Glutamine availability and metabolism also tightly intersect with oncogenic mutations and transduction pathways involved in oncogenesis. Glutamine is essential for the survival of cancer cells harboring specific oncogenic events, including c-myc activation[9-11], inhibition of Akt-mediated glycolysis[12] and IDH1 mutation[13]. In addition, basal-type breast cancer cells required exogenous glutamine maintain its survival because of its lack of expression of glutamine synthetase[14]. Interestingly, when co-cultured with glutamine-independent luminal breast cancer cells, the luminal cells may provide the essential glutamine to maintain survival of glutamine-addicted basal-type cells. Therefore, there may exist a metabolic symbiosis has between glutamine-addicted basal-type breast epithelial cells and glutamine-independent luminal-like breast epithelial cells within breast cancers[14]. Other reports have also revealed that exogenous glutamine is essential under hypoxia for lipid biogenesis or in the presence of an IDH1 mutation[15,16]. Therefore, glutamine metabolism may be a particularly attractive therapeutic target for the significant number of tumors that appear to be addicted to this nutrient[17,18].

Glutamine as a carbon source

One of the most important metabolic needs of proliferating tumor cells is the biosynthesis of macromolecules for cell division. To support lipid biosynthesis from acetyl-CoA, citrate is exported out of the mitochondria to generate acetyl-CoA in the cytoplasm (Figure 1). As this depletes TCA cycle intermediate metabolites, an additional carbon source is required to replenish the TCA cycle, and this occurs in the process of “anapleurosis”. In most proliferating cells, glutamine serves as an important anaplerotic substrate to generate oxaloacetate that will combine with acetyl-CoA to replenish citrate. Consequently, for many of the cancer cells that are glutamine-addicted, it serves a critical role as a carbon source to feed anaplerotic reactions. Additionally, under hypoxia or with mitochondrial dysfunction, glutamine can directly supply the acetyl-CoA needed for lipogenesis by being converting into pyruvate that re-enters the TCA cycle as acetyl-CoA. The α-ketoglutarate can undergo reductive carboxylation to generate isocitrate, which is then converted into citrate by a process termed “reductive carboxylation”[15,16]. Therefore, the direction of metabolic flow and utilization of glutamine can vary among different tumors with distinct somatic mutations and degrees of hypoxia.

Glutamine as a nitrogen source

The amido and amino groups of glutamine contribute to the nucleotide synthesis, especially during proliferation. For example, the cell cycle arrest of K-ras transformed fibroblasts caused by glutamine deprivation could be rescued by addition of deoxyribonucleotides[19]. Interestingly, the expression of glutaminase 1 (GLS1), that encodes the critical enzyme for glutaminolysis into glutamat, is tightly regulated within the cell cycle[20]. GLS1 is a target of APC/C (anaphase-promoting complex/cyclosome)-Cdh1, the ubiquitin ligase that controls the G1- to S-phase transition. A decrease in the activity of APC/C-Cdh1 in mid-to-late G1 releases GLS1 and simultaneously increases glutamine utilization during cell proliferation. Thus, the degree of glutaminolysis is tightly coupled with DNA synthesis, which probably contributes to its role in supporting DNA synthesis and cell proliferation.

Glutamine maintains redox homeostasis

Glutamine can also modulate cellular signaling pathways, including redox homeostasis[21]. Glutamine metabolism is a critical substrate in the synthesis of glutathione (GSH), an endogenous antioxidant comprised of glutamate, cysteine, and glycine. High endogenous levels of glutathione make it the predominant cellular anti-oxidant that neutralizes reactive oxygen species by donating electrons and becoming oxidized (GSSG). The regeneration of GSH from GSSG requires NADPH, which can also be produced by glutamine metabolism through malic enzyme[22,23]. In addition, glutamine also increases the NADPH/NADP+ ratio and maintains the GSH levels and cellular redox state by being converted to pyruvate [24]. Therefore, glutamine metabolism is essential to maintain the GSH level and redox homeostasis. Furthermore, the pathological acidosis in the tumors or kidney nephrons also increases glutaminolysis to maintain the redox homeostasis[25-27]. Therefore, glutamine may be indispensable for many tumor cells because its critical role in maintaining the redox homeostasis.

6. Non-Glutamine Amino Acids

In addition to glutamine, a wide variety of studies and systems have indicated that amino acid addiction is a common phenomenon of cancer cells that varies significantly among different normal and cancerous cells. Asparagine is known to maintain the viability of ALL cells that lack functional asparaginase, providing the rationale to use asparaginase to treat the disease[28]. Leucine deprivation also causes the apoptotic death of melanoma cells due the lack of appropriate autophagic response[29]. Other studies have highlighted the essentiality of arginine [30], methionine[31] and valine[32]. Exogenous cysteine is also essential for several cancer types (glioma[33], prostate[34] and pancreatic[35]), as blocking uptake through the cystine/glutamate antiporter (system X_{c-}) reduces viability due to the cell death caused by uncontrolled oxidative stresses[36,37].

While there are many differences between stem cell and cancer cell biology, the metabolism and downstream consequences of methionine-related metabolites suggest some potential commonalities of nutrient-usage between these two systems. Several papers describe the essential role of amino acids in the regulation and maintenance of epigenetic landscape of stem cells. For example, threonine and methionine are both essential for maintaining levels of S-Adenosyl methionine (SAM). SAM is critical for subsequent histone methylation, especially tri-methylation of histone H3 lysine-4 (H3K4me3), an active mark that is crucial for maintaining the stem cell fate[38,39]. Given the potential involvement of HeK4me3 and H3K4 demethylase JARID1B upregulation in prostate cancer[40], methionine restriction may affect the epigenetic landscape and oncogenesis of tumors cell driven by these epigenetic features. Given the association of methionine-related metabolites and putative therapeutic potential of methionine restriction for tumors[41,42]. While these studies focus on mouse and human stem cells, similar regulatory mechanisms are likely to be relevant in cancer cells.

7. Lactate

Lactate is a high energy metabolic intermediate that is the product of anaerobic glycolysis by lactate dehydrogenase (LDH). Therefore, the degree of lactate production and accumulation indicate the degree of anaerobic glycolysis, either under hypoxia or a “Warburg”-type of metabolism. An accumulation of extracellular lactate and low pH, often called lactic acidosis (LA), is one prominent microenvironmental stress found in most solid cancer tumors[43]. Many studies have shown that LA triggers transcriptional responses, somatic alterations and phenotypic alterations[3,4,44,45]. In addition, lactate can serve as a signaling molecule to trigger HIF-1α [46], NF-κB [47] and stemness [48] pathways to alter the signaling events and oncogenic properties of cancer cells. High levels of lactate in tumors are associated with severe tumor progression, more metastasis and poor clinical outcomes[49,50]. While such correlation was initially thought to reflect a high degree of tumor glycolysis and hypoxia, lactate is now also appreciated as an alternative fuel to be fed back into metabolism via pyruvate in tumor cells with limited access to glucose[51,52]. Importantly, since lactate is continuously produced in the hypoxic regions of tumors, the exported lactate may allow the survival in regions of the tumors that do not have access to glucose, as a form of metabolic symbiosis between tumor cells in different regions[52].

The export and uptake of lactate is mediated by a family of monocarboxylate transporters. MCT1 (SLC16A1) and/or MCT4 (SLC16A3) are upregulated in tumors and most likely contribute to the lactate movement across membranes. In particular, overexpression of MCT1 is induced by MYC, p53 loss and glucose deprivation[53,54]. The overexpression of MCT4 is induced by HIF-1α[55]. Cell surface expression of active MCT1 and MCT4 transporters also requires CD147, a transmembrane chaperone protein[56]. These modulations of lactate import and export by various oncogenic events highlight the important role of lactate export and import for tumors' survival. Therefore, targeting lactate transport by blocking MCT1, MCT4 and/or CD147 may be an attractive therapeutic strategy to eradicate tumor cells by starving them of this critical alternative fuel[52]. For more detail on lactate metabolism, please see the review by Poporato et. al in this same issue.

4. Acetate

Another only recently appreciated alternative fuel for cancer cells is acetate. Precedence for acetate as a fuel source resides in bacterial metabolism; under stress an "acetate switch" is triggered and bacteria begin to use acetate as an alternative fuel [57]. In tumor cells, acetate is "activated" to form acetyl coenzyme A (acetyl-CoA), which supplies the crucial central metabolite for TCA cycle, fatty acid synthesis and various acetylation modifications of tumor cells. Therefore, the level of acetyl-CoA is highly dynamic and vital to maintaining proper cell function. Acetyl-CoA is found in both the mitochondria and the cytosol with distinct metabolism and utilization in each compartment. Mitochondrial acetyl-CoA drives the TCA cycle to generate cellular ATP. An excess of mitochondrial acetyl-CoA leads to excessive citrate production, which can be exported into the cytosol to give rise to cytosolic acetyl-CoA. Cytosolic acetyl-CoA can also be synthesized in the cytosol by ATP citrate lyase (ACLY) from glycolysis [58], which contributes to the synthesis of long-chain fatty acids and the acetylation of proteins. It is also the source of acetyl groups used for DNA acetylation modifications in the nucleus. Therefore, the level of acetyl-CoA can regulate the histone acetylation and gene expression program.

Recently, exogenous acetate has been identified as an important alternative fuel for cancer cells using functional genomic screens and metabolic flux in culture cells, xenograft models and patients [59-61]. The studies show that exogenous acetate is used to generate cytosolic acetyl-CoA for epigenetic modifications and lipogenesis under metabolic stresses and for primary or metastatic brain tumors [59-61]. These studies also find that the incorporation of acetate is mediated by the cytosolic acetyl-Coenzyme A synthetase 2 (ACSS2) that is amplified or over-expressed in many tumors. Furthermore, the knockdown of cytosolic ACSS2, but not mitochondria-enriched ACSS1, dramatically reduced the utilization of exogenously supplied acetate and reduced tumor growth. Importantly, mice with genetic deletion of ACSS2 do not have overt phenotypes. However, the deletion of ACSS2 delayed tumor development in multiple models of spontaneous tumor development. These results strongly indicate that exogenous acetate contributes significantly to the cellular pool of acetyl-CoA, especially in brain tumors, as well as under hypoxia or starvation in other tumors types. This suggests that there might be a significant therapeutic window of blocking ACSS2 in cancer cells that rely on acetate as an alternative fuel.

5. Scavenging macromolecules

In addition to individual nutrients, it is becoming clear that cancer cells also use several vesicle-driven pathways to uptake, or "scavenge", proteins and lipids directly from their environment for their metabolic needs[62]. For example, macropinocytosis is a unique mode of endocytosis in which extracellular content is internalized in a clathrin- and caveolin-independent manner[63]. The endocytosed vesicles filled with these engulfed macromolecules fuse with lysosomes for their break down to supply the metabolic substrates are required for energy and macromolecule synthesis. In one sense, this is similar to the autophagy pathway that digests existing cellular macromolecules to provide essential nutrients. However, instead of digesting existing intracellular macromolecules, the scavenger pathways uptake and digest macromolecules from the outside environment. Multiple oncogenic mutations, such as Ras and Src, increase vesicle transport and macropinocytosis by regulating the proteins involved in these processes[64,65]. Consistent with the association of macropinocytosis with Kras mutations, patients with pancreatic cancers, most of whom have Kras mutations, have elevated plasma levels of branched-chain amino acids (BCAAs) that may indicate a prominent role of protein breakdown[66]. Direct protein uptake by cancer cells can be therapeutically targeted by various drug-albumin conjugates, such as Nanoparticle albumin-bound (Nab)-Paclitaxel, which is showing promising efficacy for several tumor types[67-69]. It is likely that tumor cells use macropinocytosis to uptake the albumin, thus facilitating the intracellular delivery of Paclitaxel. Other protein-drugs conjugates are likely to be of therapeutic values for the tumors with prominent macropinocytosis.

Diverse functions for alternative fuels

These recent studies reveal at least two novel aspects of tumor biology. First, collectively, these studies have shown that tumor cells are extremely versatile in obtaining nutrients from their outside environments to fulfill their metabolic needs. With the limited availability and metabolism of glucose, tumor cells resort to using various amino acids, lactate, acetate, and scavenged proteins and lipids as alternative fuels to support their continuous survival and proliferation. There is extensive cross-talk and reciprocal metabolite flow between these alternative fuels and the sensing and metabolic pathways of glucose metabolism. The importance of these pathways can be demonstrated by the DNA amplifications or significant up-regulation of many genes involved in the metabolic adaptations under stresses[44,45]. It is important to note that while lactate and acetate are well-appreciated fuels for yeast and bacteria, they were not considered viable metabolic fuels for human cells until recently. The enormous flexibility in the nutrients that tumor cells are able to successfully metabolize likely reflects both the metabolic demands necessary to support oncogenesis and the survival advantage for cells that have developed the abilities to utilize these nutrients.

Second, these alternative fuels supply many aspects of tumor biology beyond the bioenergetic and biosynthetic needs. For example, acetate feeds into acetyl-CoA that supplies both the lipid (biosynthesis) and histone (epigenetic regulation and gene expression). Methionine may be important for the levels of SAM and the proper pattern of histone and DNA methylation. Both glutamine and cysteine are essential for the generation of GSH and maintenance of redox homeostasis. These results indicate an extensive and

intricate involvement of metabolic flux into many aspects of tumor biology, which were not previously thought to be fueled by metabolic needs.

It is interesting to note that a nutrient addiction screen was used by Beadle and Tatum in 1941 to establish the one gene-one enzyme hypothesis [70]. By evaluating the nutrient addictions of different Neurospora mutants, Beadle and Tatum were able to identify genetic mutations that created nutrient addiction phenotypes that can be rescued by the supplementation of essential nutrients that mutants cannot synthesize due to mutations in the essential enzymes. Their results suggested that products of genes encode a required enzyme that is required for the synthesis of an essential metabolite in the dispensable biochemical pathway. It is likely similar nutri-genetic screens, by removing one nutrient at a time, may be applied to a large number of cancer cells with genetic information to uncover, on a systemic level, the linkage of particular oncogenic events with nutrient addictions.

Metabolic phenotypes of human tumors

Most of the studies of alternative fuels were performed using either established cancer cell lines or early passaged tumor cells. It is becoming clear that some of these metabolic phenotypes, obtained in vitro, cannot be readily replicated in vivo. These discrepancies highlight the importance of evaluating the metabolic phenotypes of more in vivo relevant models. At least two approaches are being used to determine the metabolic phenotypes and heterogeneity of human tumors. First, it is possible to analyze the global metabolomes of primary human and murine model tumor tissues via mass spectrometry or NMR to integrate with transcriptional profiling and genetic analyses of human cancers[71-75]. Such integrative analyses in breast cancers has further classified breast cancer subtypes and found higher levels of Warburg-associated metabolites in more aggressive cancer types[71-75]. Other studies profiling the metabolomics of TCGA breast tumors found that in ER- breast tumors have a higher glutathione pathway component, 2-hydroxyglutarate (2-HG) and the immunomodulatory tryptophan metabolite, kynurenine. Additionally, BRCA1 mRNA levels were positively associated with CoA, acetyl-CoA, and GSH and negatively associated with multiple lipid species, supporting the known regulation of ACC1 and NRF2 by BRCA1[76]. Therefore, integrative analyses of tumor metabolomes with associated genetic alterations or dysregulated gene expression may provide an important new tool for discovery and hypothesis testing of the genetic regulation of tumor metabolism.

Another important tool to study cancer metabolism in humans is to inject labeled metabolites that can be monitored non-invasively to evaluate the degree of uptake and utilization the injected metabolite by cancer cells. While a parallel idea forms the basis of monitoring glucose consumption in PET scans, it can also be applied to achieve a better understanding of the use of alternative carbon fuels. For example, while several studies showed avid consumption of glutamine by brain tumor cells in vitro[18,77], very little uptake of glutamine by brain tumors was actually observed [78]. This discrepancy prompted the investigator to identify acetate consumption as an important alternative fuel in vivo? [59-61]. It is therefore important to evaluate the relevance of an identified “alternative fuel” with more in vivo relevant models in order to best guide our understanding of tumor metabolic phenotypes and potential targeting strategies.

Conclusion

The recent surge of interest in understanding cancer metabolism has identified several alternative fuels that tumor cells can utilize to support their metabolic needs. The dependence of tumors on these fuels reveals their unexpected metabolic flexibility to utilize a wide variety of alternative fuels. By understanding how oncogenic mutations regulate the uptake and metabolisms of these alternative fuels, we may be able to identify therapeutic targets to eradicate tumors via their metabolic vulnerabilities. These novel arsenals against tumors may be particularly effective against the tumors that have developed resistance to chemotherapeutics or targeting agents.

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Glossary

2-HG	2-hydroxyglutarate
ACC1 (ACACA)	Acetyl-CoA carboxylase
acetyl-CoA	Acetyl-Coenzyme A
ACSS2	Acetyl-Coenzyme A synthetase 2
ACSS1	Acetyl-Coenzyme A synthetase 1
Akt	v-akt murine thymoma viral oncogene homolog
ALL	Acute lymphoblastic leukemia
AMP	Adenosine monophosphate
AMPK	AMP-activated protein kinase
APC/C-Cdh1	Anaphase-promoting complex/cyclosome- cadherin 1, type 1, E-cadherin
ATP	Adenosine triphosphate
BCAAs	Branched-chain amino acids
BRCA1	Breast cancer 1, early onset
CD147 (BSG)	Basigin (Ok Blood Group)
c-Myc	c- V-Myc Avian Myelocytomatosis Viral Oncogene Homolog
DNA	Deoxyribonucleic acid
eIF2α	Eukaryotic translation initiation factor 2a
ER-	Estrogen Receptor negative
GLS1	Glutaminase 1
GSH	Glutathione
GSSG	Oxidized form of glutathione
H3K4	Histone 3 lysine 4
H3K4me3	tri-methylation of histone H3 lysine 4
HIF-1α	Hypoxia-inducible factor 1 alpha
JARID1B (KDM5B)	Lysine (K)-specific demethylase 5B

LDH	Lactate dehydrogenase
LA	Lactic acidosis
GCN2 (EIF1AK4)	General control derepressible 2 (Eukaryotic Translation Initiation Factor 2 Alpha Kinase 4)
IDH1	Isocitrate dehydrogenase
K-ras	Kirsten rat sarcoma viral oncogene homolog
MCT1 (SLC16A1)	Solute carrier family 16 (monocarboxylate transporter), member 1
MCT4 (SLC16A3)	Solute carrier family 16 (monocarboxylate transporter), member 3
mRNA	Messenger RNA
mTOR	Mammalian target of rapamycin
NADPH/NADP+	Nicotinamide adenine dinucleotide phosphate
NF-κB	Nuclear Factor of kappa light polypeptide gene enhancer In B-cells
Nab	Nanoparticle albumin-bound
NMR	Nuclear magnetic resonance
NRF2 (NFE2L2)	Nuclear factor, erythroid 2-like 2
p53 (TP53)	Tumor protein 53
PET	Positron emission tomography
Ras	any of the RAS Viral (V-Ras) oncogene homolog family members
system X_c^-(SLC7A11)	Cystine/glutamate antiporter (solute carrier family 7 (anionic amino acid transporter light chain, xc- system), member 11)
SAM	S-Adenosyl methionine
Src	v-src avian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog
TCA cycle	The Citric Acid cycle
TCGA	The Cancer Genome Atlas
tRNAs	transfer RNAs

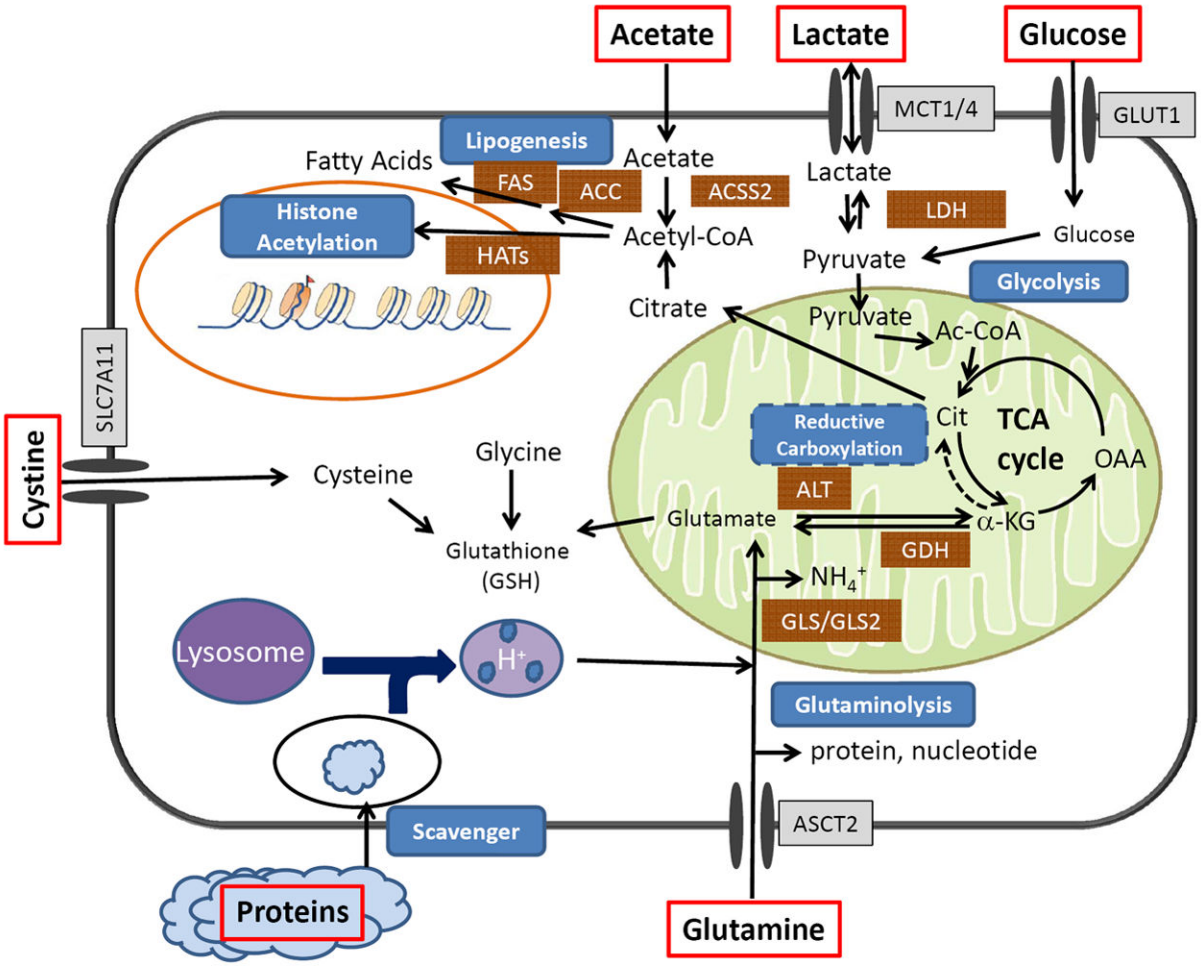

Figure 1. Alternative fuels for cancer cells

The figure shows how various alternative fuels (boxed in red) are transported and utilized by cancer cells. Metabolomic processes are indicated by blue boxes. Enzymes are indicated by brown squares. Transporters are indicated by gray boxes. Directions of metabolite flow within the cell are indicated by arrows.