

# Dysregulated Metabolism in Cancer

Asmida Isa <sup>\*</sup> 



Use your smartphone to scan this QR code and download this article

## ABSTRACT

Metabolism describes the cellular bioenergetic pathways that provide energy and macromolecules for protein, lipid, and nucleic acid syntheses. In cancer, malignant cells alter the metabolic pathways to acquire nutrients needed for proliferation and survival. The various metabolic modifications exhibited by cancer cells include aerobic glycolysis, decreased oxidative phosphorylation, and elevated production of biosynthetic intermediates. To support the increasing need for these metabolic modifications, cancer cells increase the expressions of plasma membrane transporters and enzymes involved in the metabolic pathways. Additionally, some cancer cells escape chemotherapy treatment by reprogramming their metabolic activities. This chemotherapy-induced resistance mechanism allows malignant cells to promote their survival as well as to provide defense against cell damage by engaging various metabolic shunt pathways. Therefore, understanding metabolic reprogramming in cancer may provide useful information that can further be exploited to strategize potential treatment interventions and subsequently foster better outcomes among patients with cancer.

**Key words:** Cancer metabolic pathway, glycolysis, OXPHOS, TCA cycle, tumour bioenergetics, Warburg effect

## INTRODUCTION

Some of the characteristics that distinguish cancer cells from normal cells are high proliferation activity, self-renewal property, and cell death evasion<sup>1,2</sup>. As cells evolve toward neoplastic characteristics, they modify nutrient acquisition mechanisms as well as rewire bioenergetic pathways and undergo metabolic changes.

Dysregulated metabolism is one of the seven hallmarks of cancer and is rooted back to the study by Otto Warburg in 1956<sup>1-3</sup>. In the study, he observed an abnormal metabolic phenomenon exhibited by cancer cells, in which tumors utilized glycolysis to produce energy in the presence of oxygen<sup>1</sup>. This observation opposes the normal energy production in normal cells whereby the cells prefer to employ oxidative phosphorylation (OXPHOS) over glycolysis when oxygen is available. Since then, research on cancer metabolism has been growing steadily with less emphasis given on the area. However, in the last decade, the field has emerged as an area of interest among scientists and clinicians to unravel the link between dysregulated metabolic activity and cancer<sup>2</sup>. For instance, studies have found that during transformation, cancer cells require continuous bioenergetic reactions and copious amounts of ATPs to guarantee a sufficient supply of energy<sup>4-6</sup>. Accordingly, cancer cells adopt numerous metabolic strategies to

support the need for energy, such as higher uptake of nutrients, execution of different shunt pathways, and overexpression of several metabolic enzymes and proteins<sup>7-10</sup>.

More recently, the roles of dysregulated metabolism in cancer have also been speculated to underlie the disease resistance to therapy. Emerging evidence has pointed toward metabolic reprogramming in resistant cancer cells when they are exposed to selective pharmacological or molecular inhibitions<sup>11-13</sup>. For example, a portion of surviving cancer cells treated with a standard chemotherapy agent shunted their metabolic activities toward building of membrane skeletons and nucleotide blocks and remained dormant for a certain period<sup>12,14,15</sup>. This phase of dormancy prepares the cells to emerge as resistant clones and cause relapse in the future<sup>14</sup>. Therefore, this review aimed to discuss the fundamental role of metabolism in cancer and present recent findings on the rewiring of metabolic activity when tumor cells evolve toward resistancy. Targeting metabolism by inhibiting known metabolic pathways and issues surrounding this approach are also outlined in this review.

## Glycolysis

Glycolysis is the main catabolic pathway that breaks down glucose molecules into pyruvate following a series of enzymatic reactions. A complete glycolysis reaction processes 1 mole of glucose into 2 moles of ATP

Advanced Medical and Dental Institute,  
Universiti Sains Malaysia 13200 Bertam  
Kepala Batas, Penang Malaysia

### Correspondence

Asmida Isa, Advanced Medical and  
Dental Institute, Universiti Sains  
Malaysia 13200 Bertam Kepala Batas,  
Penang Malaysia

Email: asmida.isa@usm.my

### History

- Received: Jun 22, 2022
- Accepted: Aug 07, 2022
- Published: Aug 31, 2022

DOI : 10.15419/bmrat.v9i8.757

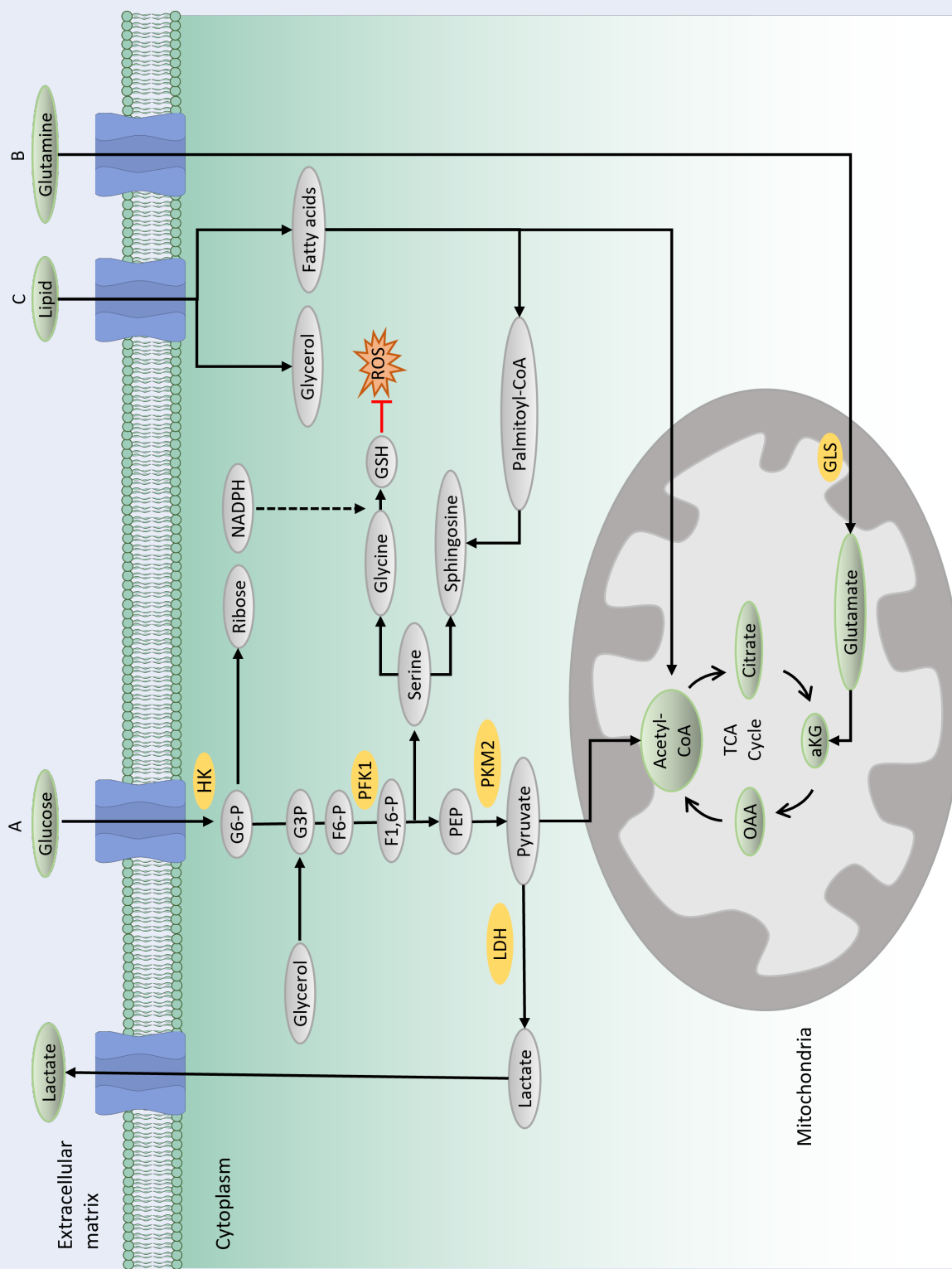


### Copyright

© Biomedpress. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International license.



Cite this article : Isa A. Dysregulated Metabolism in Cancer. *Biomed. Res. Ther.*, 2022; 9(8):5201-5208.



**Figure 1: Overview of the metabolic pathways. The substrates for metabolism include glucose, glutamine and lipid.** The substrates for metabolism include glucose, glutamine and lipid. A) Glucose is the substrate for glycolysis and is transported into the cells through glucose transporter. It is phosphorylated by HK to produce G6P that prevents diffusion of the molecule to the outer membrane. G6P can enter pentose phosphate pathway to produce backbone for nucleotide synthesis and reducing agent, NADPH. PFK1 catalyses the conversion of F6P to F1,6P. Glycolysis intermediate can also execute SSP. Serine is the precursor for the synthesis of GSH as well as sphingosine. GSH protects cells from oxidative damage by ROS. The final product of glycolysis is pyruvate that enters mitochondria for TCA cycle and complete oxidation for energy generation. Pyruvate can also be converted into lactate by LDH which later is transported to the extracellular matrix. B) Glutamine is transported into the cells by glutamine transporter and is converted into glutamate by GLS in the mitochondria. Glutamate is transformed into aKG which feeds into the TCA cycle. C) Lipid is broken down into fatty acids and glycerol in the cytoplasm. In mitochondria, beta-oxidation of fatty acids produces acetyl-CoA which feeds the TCA cycle. Fatty acids can also be transformed into palmitoyl-CoA that provides backbone for sphingosine. Sphingosine is used for the synthesis of membrane lipids. HK: hexokinase; G6P: glucose 6-phosphate; PFK1: phosphofructokinase; F6P: fructose 6-phosphate; F1,6P: fructose 1,6-bisphosphate; SSP: serine synthesis pathway; GSH: glutathione; ROS: reactive oxygen species; TCA: tricarboxylic cycle; LDH: lactate dehydrogenase; GLS: glutaminase; aKG: alpha-ketoglutarate.

and 2 moles of NADH. In the first step of glycolysis, glucose is transported into the cytoplasm by a glucose transporter (GLUT) and is then phosphorylated by hexokinase, producing a negatively charged glucose 6-phosphate (**Figure 1 A**). The negative charge prevents diffusion of the molecule through the cell membrane, thus trapping the molecule within the cytoplasm. Along the glycolysis pathway, phosphofructokinase 1 (PFK1), a rate-limiting enzyme, catalyzes the conversion of fructose 6-phosphate to fructose-1,6-bisphosphate. In this process, ATP is consumed, making this reaction a crucial and irreversible step in the glycolysis pathway. The final product of glycolysis is pyruvate, a three-carbon molecule that serves as a carbon precursor for subsequent bioenergetic processes. Depending on the physiological condition, pyruvate has two fates: either to enter the mitochondria for the tricarboxylic acid (TCA) cycle and subsequent OXPHOS reaction or to be converted into lactate by lactate dehydrogenase<sup>16</sup>.

When the oxygen is less favorable, cells opt to convert pyruvate into lactate, which is then transported out to the extracellular matrix by a lactate transporter<sup>16</sup>. This process is termed aerobic glycolysis, which generates 2 ATPs per glucose molecule.

### TCA and OXPHOS

In the presence of oxygen, pyruvate enters the mitochondria for complete catabolic and anabolic reactions in the TCA cycle. In the mitochondrial matrix, pyruvate is oxidized by coenzyme A (CoA) to produce acetyl-CoA. Acetyl-CoA then reacts with oxaloacetate to produce citrate, which later undergoes eight enzymatic reactions in the TCA cycle. The final product of the TCA cycle is oxaloacetate, which consequently feeds back into the cycle (**Figure 1A**). A complete TCA cycle produces a number of TCA cycle intermediates that serve as precursors for biosynthetic processes. The TCA cycle also produces reducing agents, NADH and FADH<sub>2</sub>, which are needed for electron transfer in the mitochondrial respiratory chain. In the presence of oxygen, this electron transport chain funnels electrons through the four complexes (I to IV) in the inner mitochondrial membrane to generate 32–34 ATPs per glucose molecule, making it an efficient energy production process (i.e., OXPHOS)<sup>17</sup>.

The TCA cycle is also fueled by glutamine-derived metabolites (**Figure 1 B**). Glutamine provides both carbon and nitrogen precursors for cellular bioenergetics and biosynthesis. It is transported into the cells by glutamine transporters and transformed into glutamate by glutaminase (GLS), which is later converted to alpha-ketoglutarate and feeds back into the

TCA cycle. Glutamine metabolism has been shown to maintain TCA cycle activity in cells with impaired mitochondria, thus providing crucial support for cell survival<sup>18</sup>.

### Pentose Phosphate Pathway (PPP) and Serine Synthesis Pathway (SSP)

The PPP and SSP are two metabolic pathways parallel to glycolysis (**Figure 1 A**). The PPP (also known as the phosphogluconate or hexose pathway) produces the sugar-phosphate backbone for nucleic acid synthesis and NADPH for fatty acid synthesis and maintenance of reduction-oxidation under stress conditions<sup>19</sup>. Meanwhile, the SSP produces serine, which is the source for biosynthesis of nonessential amino acids, glycine and cysteine. Glycine acts as a precursor for the production of glutathione (GSH), an antioxidant that provides defense from oxidative stress damage<sup>20</sup>. Serine provides a backbone for sphingosine in the synthesis of membrane lipids. Notably, PPP and SSP dysregulations have been reported to be involved in several types of cancer, such as breast and blood cancers<sup>8,21</sup>.

### Lipid Metabolism

Lipid metabolism is the process of synthesizing, storing, and degrading lipids (triglycerides, cholesterol, fatty acids, and phospholipids) to produce energy or structural components of cell membranes. In lipid catabolism, triglycerides are broken down into fatty acids and glycerol (**Figure 1C**). In the cytosol, glycerol is transformed to glyceraldehyde 3-phosphate, an intermediate in the glycolysis pathway that can further be oxidized to generate energy. In the mitochondria, beta-oxidation of fatty acid produces acetyl-CoA that feeds into the TCA cycle. Membrane lipid biosynthesis involves the synthesis of the membrane backbones, sphingosine or glycerol, followed by the addition of fatty acids to generate phosphatidic acid. Phosphatidic acid is modified by the addition of hydrophilic head groups to the membrane skeleton, making a complete structure of membrane lipids. Recently, lipid reprogramming has been shown to be responsible for the resistance mechanism seen in blood and solid tumors that have been treated with chemotherapeutic agents<sup>14,22</sup>.

## DYSREGULATED METABOLISM IN CANCER

In cancer, the transformed cells undergo a complex metabolic reprogramming activity to promote their increased need for energy. This alteration is manifested by an increased uptake of nutrients, such as

glucose and glutamine, a high rate of glycolysis resulting in increased extracellular acidification, and a higher expression of metabolic enzymes and proteins<sup>5,15,23,24</sup>.

An increased uptake of glucose is one of the characteristics of dysregulated metabolism in cancer<sup>7,9,23</sup>. In a study of breast cancer cells, upregulated glucose intake and increased production of both pyruvate and lactate were observed in an aggressive tumor model<sup>23</sup>. Furthermore, inhibition of the glycolytic function with glycolytic inhibitor 2-deoxyglucose diminished cell growth, whereas inhibition of the mitochondrial function with 3-nitropropionic acid, an inhibitor of the TCA cycle, did not reduce the invasiveness; these findings indicate the reliance of invasive characteristics on glycolysis but not on the mitochondrial energetic pathway<sup>23</sup>.

A high intake of glucose is supported by an increased expression of GLUTs and is linked to the oncogenic role of the transcription factor, NF-KB<sup>25-27</sup>. Among the 14 homologous families of GLUT proteins, GLUT1 and GLUT3 have been predominantly reported to be implicated in many types of cancer, such as breast cancer, colorectal carcinoma, leukemia, and glioblastoma<sup>7,9,26-28</sup>. High expressions of GLUT1 and GLUT3 are also associated with poor clinical outcomes in patients with colorectal carcinoma and glioblastoma<sup>7,9</sup>.

The rate of glycolysis is increased in many types of cancer owing to overexpression of PFK1<sup>29-32</sup>. PFK1 has three isoforms: PFK1 platelet (PFKP), PFK1 muscle, and PFK1 liver, which are differentially expressed in different organs and tissues<sup>33,34</sup>. However, PFKP is predominantly dysregulated in many types of cancer, including lung, breast, liver, and kidney cancers<sup>21,30-32,35</sup>. In a PTEN loss brain tumor model, AKT phosphorylated and stabilized PFKP and subsequently promoted glycolysis and tumor progression<sup>36</sup>. Furthermore, PFKP was reported to be involved in epithelial–mesenchymal transition in breast cancer cells, and its overexpression is a poor prognostic factor for patients with breast cancer with BRCA1 deficiency<sup>21,37</sup>.

PKM2 is another glycolytic enzyme that functions at the end of the glycolytic pathway and is overexpressed in many types of cancer that exhibit a high glycolytic activity<sup>10,38</sup>. It converts phosphoenolpyruvate to produce pyruvate and ATP, which gives advantage to tumor cells that have a higher expression of this enzyme, such as pancreatic cancer cells<sup>10</sup>. Intriguingly, PKM2 is translocated to the plasma membrane and provides exclusive ATP supply for ATP-dependent calcium pump, thus preventing cytoplasmic calcium overload and subsequent cell death<sup>10</sup>.

Dysregulated PKM2 is also reported in cells with a compromised mitochondrial function, which hinders the glycolytic flux from entering the TCA cycle<sup>39</sup>.

Consequently, a high rate of glycolysis results in the accumulation of extracellular lactate, making the tumor microenvironment acidic and optimal for metastasis, vascularization, and resistance<sup>40</sup>. For example, an acidic microenvironment poses a growth advantage for aggressive colon and breast tumors in both *in vitro* and *in vivo* studies<sup>17,40</sup>. A low-pH environment is also associated with drug resistance and poor drug efficacy as exhibited by acid-adapted colon carcinoma cells<sup>13</sup>. Correspondingly, cancer cells require adaptation to maintain a low extracellular pH. Thus, cancer cells increase the expression of various membrane transporters, including sodium–hydrogen exchanger-1 and monocarboxylate transporters (MCTs), which are directly linked to tumors with high metabolic rates, such as cervix squamous cell carcinoma and B-cell lymphoma<sup>40-42</sup>.

Cancer cells also rely on the PPP and SSP as alternatives for glycolysis and OXPHOS. For example, T-cell acute lymphoblastic leukemia cells suppress glycolysis and shift the glycolysis intermediates toward the PPP and SSP, both of which are important for providing skeletons for tumor growth as well as for protecting against oxidative damage<sup>8</sup>. Interestingly, glycolysis is suppressed owing to the phosphorylation of PFKP and PKM2 by cyclin D3–CDK6 kinase, a core complex in the cell cycle machinery<sup>8</sup>. The inhibition of these glycolytic enzymes results in an increased production of NADPH and GSH<sup>8</sup>.

Additionally, an increased glutamine uptake has been observed in many types of cancer<sup>4,43-45</sup>. In the study by Yoo *et al.* (2020), an increased uptake of glutamine through glutamine-supported OXPHOS supplied the ATP demand of the highly proliferative pancreatic cancer cells<sup>43</sup>. A high glutamine level also increases the cellular GSH level, which suppresses the production of reactive oxygen species (ROS) and protects cells from chemotherapy damage<sup>11,21,43</sup>. Dysregulated glutamine metabolism is associated with an increased expression of oncogenes, such as c-Myc<sup>4</sup>. c-Myc induces the overexpression of several genes in the glutamine metabolism pathway, including GLS I and phosphoribosyl pyrophosphate amidotransferase, and consequently mediates the malignant progression of small-cell lung cancer<sup>4,29</sup>. A high level of glutamine also increases the cellular GSH level, which minimizes the damage caused by ROS and leads to chemotherapy drug resistance in both cancer cell lines and patient samples<sup>11,21,43</sup>.

### Metabolic Rewiring Under Selective Pressure

Many anti-cancer agents target cells in the proliferating stage that are dependent on glycolysis<sup>11,12,46</sup>; however, recent evidence shows that surviving cancer cells escape treatment by shifting their metabolic activities toward other shunt pathways, such as OXPHOS, the PPP, and the SSP<sup>11,12,14,47</sup>. These cells remain dormant for a certain period and potentially rise and cause relapse in the future<sup>12,14,47</sup>.

Notably, in their studies on acute myeloid leukemia (AML), Jones and colleagues have identified glycolytic-dependent treatment-sensitive and OXPHOS-dependent treatment-resistant leukemia cells<sup>11</sup>. Interestingly, the OXPHOS-dependent cells did not rely on glucose as the source of nutrients; instead, they were dependent on amino acid metabolism<sup>11</sup>. Treatment-resistant cells can also dysregulate metabolism toward lipid biosynthesis<sup>14,22</sup>. For example, a multi-omics analysis revealed an upregulation of fatty acid biosynthesis accompanied with a downregulation of TCA and amino acid in EZH2 inhibitor-treated cells<sup>22</sup>. Additionally, invasive breast cancer cells can also shift toward the PPP and SSP when glycolysis is suppressed<sup>8,21</sup>.

The mechanism of how cancer cells reprogram their metabolic activity to acquire resistance is thus far poorly understood. Some studies have suggested a compensatory energy acquisition associated with dysregulated expressions of oncogenes in resistant subclones, such as RAS and MAPK<sup>12,14,44,48</sup>. For example, an RNA-seq analysis on samples from relapsed or resistant AML cases revealed an enrichment of the intrinsic RAS expression in resistant subclones<sup>12,14</sup>. RAS can induce mitochondrial fusion that further elevates OXPHOS activity<sup>39,49</sup>. Furthermore, when the glycolysis pathway is inhibited, cancer cells direct the glycolytic flux toward the PPP, thereby increasing the NADPH level<sup>21</sup>. NADPH is essential not only for macromolecule synthesis in the growing phase of the cell but also for protecting cells from oxidative damage. In the presence of NADPH, GSH reductase converts oxidized GSH to reduce the GSH level, which protects cancer cells from oxidative damage caused by ROS. Notably, low levels of ROS have been linked to the stemness properties of resistant cancer cells, explaining the protective mechanism executed by resistant cells<sup>11,21</sup>.

Furthermore, the metabolic shift from glycolysis toward lipid metabolism under anti-cancer therapy is linked to cell cycle reprogramming as well as global methylation status modification<sup>14,22,50</sup>. For example,

FLT3-mutated AML cells with an altered metabolism escaped the initial chemotherapy-induced G0G1 cell cycle arrest<sup>14</sup>. In the evolution toward resistancy, sphingolipid or phospholipid metabolism was enriched in surviving cells accompanied by an expansion of NRAS mutation and a more prominent AU-RKB signaling that drove the cells out from dormancy to become highly proliferative<sup>14</sup>. Another study crosslinked transcriptomic and metabolomic data of solid tumor samples that have been treated with GSK126, a selective inhibitor of EZH2 methyltransferase<sup>22</sup>. The analysis revealed that epigenetic modifications were implicated in the treatment-insensitive samples, in which a global reduction of the H3K27me3 level was observed; this thereby increased the expression of target genes in lipid biosynthesis, such as SCD1 and ELOVL2<sup>22</sup>.

### TARGETING METABOLISM

The class of drugs resembling the structure of nucleotide metabolites but differing enough to inhibit the metabolic activity is termed antimetabolites. The development of antimetabolites originated from the success of aminopterin used in clinical trials to treat childhood leukemia<sup>51,52</sup>. The discovery of aminopterin led to the development of methotrexate and pemetrexed, two folate analogs that inhibit the *de novo* synthesis of nucleotide<sup>53</sup>. Methotrexate is used in childhood acute lymphoblastic leukemia chemotherapy treatment, which has been reported to yield a cure rate significantly higher than 80% in a phase III clinical study<sup>54</sup>. Another synthetic nucleotide used in the treatment of gastrointestinal cancer is 5-fluorouracil (5-FU), an analog of pyrimidine<sup>53</sup>. 5-FU inhibits the formation of thymidine nucleotides during DNA synthesis. Conversely, purine analogs, 6-mercaptopurine and 6-thioguanine, obstruct the synthesis of purine<sup>53</sup>. Gemcitabine and cytarabine are nucleoside analogs competitively incorporated into replicating DNA internucleoside, thus inhibiting nucleotide chain elongation; they have been used extensively in treating leukemia<sup>55,56</sup>.

Recently, efforts have been made to target the metabolic enzymes or proteins that are differentially expressed in cancer. For example, STF-31 was developed to inhibit GLUT1 activity; however, this compound also inhibits nicotinamide phosphoribosyltransferase, an enzyme involved in NADH biosynthesis<sup>57</sup>. Another inhibitor of GLUT is Glutor, which targets GLUT1, GLUT2, and GLUT3<sup>58</sup>. However, Glutor alone is not enough to completely eradicate cancer cells. The combination of Glutor and GLS inhibitor at low concentrations synergistically inhibited

HCT116 cell growth, which may offer a promising approach for dual inhibition<sup>58</sup>. Furthermore, a potent MCT1 inhibitor, AZD3965, has undergone phase 1 clinical study in patients with advanced-stage solid tumors<sup>59</sup>. The results indicate a promising therapeutic value in patients with a high MCT1 expression, and further clinical trials for this compound are ongoing<sup>59</sup>. A glutamine transport antagonist was also developed to inhibit the uptake of glutamine through the specific glutamine transporter, ASCT2<sup>60,61</sup>. The compound known as V-9302 mimics glutamine and is able to hamper cell proliferation and induce apoptosis *in vitro* in more than half of various cell lines used in the study<sup>60</sup>. However, an *in vivo* study showed a non-target effect of V-9302 on other transporters, which impedes further exploration of this compound as a potential therapeutic agent<sup>61</sup>. A comprehensive review of the drugs used to target metabolism in cancer can be found in this study<sup>53</sup>.

Nevertheless, specificity remains one of the issues in targeting dysregulated metabolism in cancer. Furthermore, single-drug treatment is usually associated with high toxicity, as high concentrations of drug used during chemotherapy induction further increase the risks of long-term side effects in children and worse clinical outcomes in adult patients<sup>12</sup>. Single-drug treatment can also cause residual disease, indicating resistance and potential relapse<sup>14,50</sup>. Thus, combinations of standard chemotherapy agents with novel compound or drug repurposing approaches may help beneficial therapeutic strategies to overcome these issues, as indicated in many studies<sup>10-12,14</sup>.

## CONCLUSION

The global landscape of cancer metabolism has evolved from a simple model of the Warburg effect to more complex models of tumor metabolism. Currently, researchers are exploring metabolic targets and pathways used by cancer cells during tumor evolution, invasion, and resistance that can be exploited as biomarkers for diagnostic purposes. More importantly, the discovery can be manipulated to develop novel inhibitors for targeted therapy that may have the potential to synergize with chemotherapy agents currently used in clinics. Not only will this approach eradicate the metabolic flexible- and resistant-cancer cells but also address the toxicity issue of single-drug treatment in cancer therapy. Consequently, this strategy is hoped to foster a better clinical outcome among patients diagnosed with cancer and further improve the quality of life among survivors.

## ABBREVIATIONS

**ATP:** Adenosine triphosphate, **CDK6:** Cyclin-dependent kinase 6, **ETC:** Electron transport chain,

**FADH2:** Flavin adenine dinucleotide, **GLS:** Glutaminase, **GLUT:** Glucose transporter, **GSH:** Glutathione, **HK:** Hexokinase, **LDH:** Lactate dehydrogenase, **MCT:** Monocarboxylate transporter, **NADH:** Nicotinamide adenine dinucleotide, **NADPH:** Nicotinamide adenine dinucleotide phosphate, **NHE-1:** Sodium-hydrogen exchanger, **OXPHOS:** Oxidative phosphorylation, **PFK1:** Phosphofructokinase 1, **PPAT:** Phosphoribosyl pyrophosphate amidotransferase, **PPP:** Pentose phosphate pathway, **ROS:** Reactive oxygen species, **SSP:** Serine synthesis, **TCA:** Tricarboxylic acid

## ACKNOWLEDGMENTS

None.

## AUTHOR'S CONTRIBUTIONS

Not applicable.

## FUNDING

None.

## AVAILABILITY OF DATA AND MATERIALS

Not applicable.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## CONSENT FOR PUBLICATION

Not applicable.

## COMPETING INTERESTS

The authors declare that they have no competing interests.

## REFERENCES

1. Warburg O. On the origin of cancer cells. *Science*. 1956;123(3191):309–14. PMID: [13298683](#). Available from: [10.1126/science.123.3191.309](#).
2. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000;100(1):57–70. PMID: [10647931](#). Available from: [10.1016/S0092-8674\(00\)81683-9](#).
3. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646–74. PMID: [21376230](#). Available from: [10.1016/j.cell.2011.02.013](#).
4. Kodama M, Oshikawa K, Shimizu H, Yoshioka S, Takahashi M, Izumi Y. A shift in glutamine nitrogen metabolism contributes to the malignant progression of cancer. *Nature Communications*. 2020;11(1):1320. PMID: [32184390](#). Available from: [10.1038/s41467-020-15136-9](#).
5. Liu YC, Lin P, Zhao YJ, Wu LY, Wu YQ, Peng JB. Pan-cancer analysis of clinical significance and associated molecular features of glycolysis. *Bioengineered*. 2021;12(1):4233–46. PMID: [34304708](#). Available from: [10.1080/21655979.2021.1955510](#).

6. Harami-Papp H, Pongor LS, Munkácsy G, Horváth G, Nagy AM, Ambrus A. TP53 mutation hits energy metabolism and increases glycolysis in breast cancer. *Oncotarget*. 2016;7(41):67183–95. PMID: 27582538. Available from: [10.18632/oncotarget.11594](https://doi.org/10.18632/oncotarget.11594).
7. Cosset E, Ilmjärv S, Dutoit V, Elliott K, von Schalscha T, Caramo MF. Glut3 Addiction Is a Druggable Vulnerability for a Molecularly Defined Subpopulation of Glioblastoma. *Cancer Cell*. 2017;32(6). PMID: 29198914. Available from: [10.1016/j.ccell.2017.10.016](https://doi.org/10.1016/j.ccell.2017.10.016).
8. Wang H, Nicolay BN, Chick JM, Gao X, Geng Y, Ren H. The metabolic function of cyclin D3-CDK6 kinase in cancer cell survival. *Nature*. 2017;546(7658):426–30. PMID: 28607489. Available from: [10.1038/nature22797](https://doi.org/10.1038/nature22797).
9. Dai W, Xu Y, Mo S, Li Q, Yu J, Wang R. GLUT3 induced by AMPK/CREB1 axis is key for withstanding energy stress and augments the efficacy of current colorectal cancer therapies. *Signal Transduction and Targeted Therapy*. 2020;5(1):177. PMID: 32873793. Available from: [10.1038/s41392-020-00220-9](https://doi.org/10.1038/s41392-020-00220-9).
10. James AD, Richardson DA, Oh IW, Sritangos P, Attard T, Barrett L. Cutting off the fuel supply to calcium pumps in pancreatic cancer cells: role of pyruvate kinase-M2 (PKM2). *British Journal of Cancer*. 2020;122(2):266–78. PMID: 31819190. Available from: [10.1038/s41416-019-0675-3](https://doi.org/10.1038/s41416-019-0675-3).
11. Jones CL, Stevens BM, D'Alessandro A, Reisz JA, Culp-Hill R, Nemkov T. Inhibition of Amino Acid Metabolism Selectively Targets Human Leukemia Stem Cells. *Cancer Cell*. 2018;34(5). PMID: 30423294. Available from: [10.1016/j.ccell.2018.10.005](https://doi.org/10.1016/j.ccell.2018.10.005).
12. Pei S, Pollyea DA, Gustafson A, Stevens BM, Minhajuddin M, Fu R. Monocytic subclones confer resistance to venetoclax-based therapy in patients with acute myeloid leukemia. *Cancer Discovery*. 2020;10(4):536–51. PMID: 31974170. Available from: [10.1158/2159-8290.CD-19-0710](https://doi.org/10.1158/2159-8290.CD-19-0710).
13. Pellegrini P, Serviss JT, Lundbäck T, Bancaro N, Mazurkiewicz M, Kolosenko I. A drug screening assay on cancer cells chronically adapted to acidosis. *Cancer Cell International*. 2018;18(1):147. PMID: 30263014. Available from: [10.1186/s12935-018-0645-5](https://doi.org/10.1186/s12935-018-0645-5).
14. Joshi SK, Nechiporuk T, Bottomly D, Piehowski PD, Reisz JA, Pittsenbarger J. The AML microenvironment catalyzes a stepwise evolution to gilteritinib resistance. *Cancer Cell*. 2021;39(7). PMID: 34171263. Available from: [10.1016/j.ccell.2021.06.003](https://doi.org/10.1016/j.ccell.2021.06.003).
15. Wei J, Huang K, Chen Z, Hu M, Bai Y, Lin S. Characterization of glycolysis-associated molecules in the tumor microenvironment revealed by pan-cancer tissues and lung cancer single cell data. *Cancers (Basel)*. 2020;12(7):1–23. PMID: 32635458. Available from: [10.3390/cancers12071788](https://doi.org/10.3390/cancers12071788).
16. Prochownik EV, Wang H. Review the metabolic fates of pyruvate in normal and neoplastic cells. *Cells*. 2021;10(4):1–36. PMID: 33808495. Available from: [10.3390/cells10040762](https://doi.org/10.3390/cells10040762).
17. de la Cruz-López KG, Castro-Muñoz LJ, Reyes-Hernández DO, García-Carrancá A, Manzo-Merino J. Lactate in the Regulation of Tumor Microenvironment and Therapeutic Approaches. *Frontiers in Oncology*. 2019;9(1143):1143. PMID: 31737570. Available from: [10.3389/fonc.2019.01143](https://doi.org/10.3389/fonc.2019.01143).
18. Yang C, Ko B, Hensley CT, Jiang L, Wasti AT, Kim J. Glutamine oxidation maintains the TCA cycle and cell survival during impaired mitochondrial pyruvate transport. *Molecular Cell*. 2014;56(3):414–24. PMID: 25458842. Available from: [10.1016/j.molcel.2014.09.025](https://doi.org/10.1016/j.molcel.2014.09.025).
19. Jin L, Zhou Y. Crucial role of the pentose phosphate pathway in malignant tumors. *Oncology Letters*. 2019;17(5):4213–21. PMID: 30944616. Available from: [10.3892/ol.2019.10112](https://doi.org/10.3892/ol.2019.10112).
20. Mattaini KR, Sullivan MR, Heiden MG. The importance of serine metabolism in cancer. *The Journal of Cell Biology*. 2016;214(3):249–57. PMID: 27458133. Available from: [10.1083/jcb.201604085](https://doi.org/10.1083/jcb.201604085).
21. Kim NH, Cha YH, Lee J, Lee SH, Yang JH, Yun JS. Snail reprograms glucose metabolism by repressing phosphofructokinase PFKP allowing cancer cell survival under metabolic stress. *Nature Communications*. 2016;2017(8):1–12. PMID: 28176759. Available from: [10.1038/ncomms14374](https://doi.org/10.1038/ncomms14374).
22. Zhang T, Guo Z, Huo X, Gong Y, Li C, Huang J. Dysregulated lipid metabolism blunts the sensitivity of cancer cells to EZH2 inhibitor. *EBioMedicine*. 2022;77(103872):103872. PMID: 35158113. Available from: [10.1016/j.ebiom.2022.103872](https://doi.org/10.1016/j.ebiom.2022.103872).
23. Fujita M, Imadome K, Somasundaram V, Kawanishi M, Karasawa K, Wink DA. Metabolic characterization of aggressive breast cancer cells exhibiting invasive phenotype: impact of non-cytotoxic doses of 2-DG on diminishing invasiveness. *BMC Cancer*. 2020;20(1):929. PMID: 32993545. Available from: [10.1186/s12885-020-07414-y](https://doi.org/10.1186/s12885-020-07414-y).
24. Warburg O. On respiratory impairment in cancer cells. *Science (80-)*. 1956;10:269–70; 1956. Available from: [10.1126/science.124.3215.269](https://doi.org/10.1126/science.124.3215.269).
25. Xia Y, Shen S, Verma IM. NF- $\kappa$ B, an active player in human cancers. *Cancer Immunology Research*. 2014;2(9):823–30. PMID: 25187272. Available from: [10.1158/2326-6066.CIR-14-0112](https://doi.org/10.1158/2326-6066.CIR-14-0112).
26. Wang X, Liu R, Qu X, Yu H, Chu H, Zhang Y.  $\alpha$ -Ketoglutarate-Activated NF- $\kappa$ B Signaling Promotes Compensatory Glucose Uptake and Brain Tumor Development. *Molecular Cell*. 2019;76(1). PMID: 31447391. Available from: [10.1016/j.molcel.2019.07.007](https://doi.org/10.1016/j.molcel.2019.07.007).
27. Sommermann TG, O'Neill K, Plas DR, Cahir-McFarland E. IKK $\beta$  and NF- $\kappa$ B transcription govern lymphoma cell survival through AKT-induced plasma membrane trafficking of GLUT1. *Cancer Research*. 2011;71(23):7291–300. PMID: 21987722. Available from: [10.1158/0008-5472.CAN-11-1715](https://doi.org/10.1158/0008-5472.CAN-11-1715).
28. Isa A, Martinez-Soria N, McKenzie L, Blair H, Issa H, Luli S. Identification of glycolytic pathway as RUNX1/ETO-dependent for propagation and survival. *Klinische Padiatrie*. 2018;230(03):3.
29. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. *Nature Reviews Cancer*. 2017;17(12):725–37. PMID: 29077690. Available from: [10.1038/nrc.2017.87](https://doi.org/10.1038/nrc.2017.87).
30. Sha X, Wang K, Wang F, Zhang C, Yang L, Zhu X. Silencing PFKP restrains the stemness of hepatocellular carcinoma cells. *Experimental Cell Research*. 2021;407(1):112789. PMID: 34418458. Available from: [10.1016/j.yexcr.2021.112789](https://doi.org/10.1016/j.yexcr.2021.112789).
31. Inaishi T, Shibata M, Ichikawa T, Kanda M, Hayashi M, Soeda I. Platelet isoform of phosphofructokinase accelerates malignant features in breast cancer. *Oncology Reports*. 2022;47(1):9. PMID: 34751415. Available from: [10.3892/or.2021.8220](https://doi.org/10.3892/or.2021.8220).
32. Umar SM, Kashyap A, Kahol S, Mathur SR, Gogia A, Deo SV. Prognostic and therapeutic relevance of phosphofructokinase platelet-type (PFKP) in breast cancer. *Experimental Cell Research*. 2020;396(1):112282. PMID: 32919954. Available from: [10.1016/j.yexcr.2020.112282](https://doi.org/10.1016/j.yexcr.2020.112282).
33. Keildson S, Fadista J, Ladenvall C, Hedman AK, Elgzyri T, Small KS, et al. Expression of phosphofructokinase in skeletal muscle is influenced by genetic variation and associated with insulin sensitivity. *Diabetes*. 2014;63(3):1154–65. PMID: 24306210. Available from: [10.2337/db13-1301](https://doi.org/10.2337/db13-1301).
34. Lee JH, Liu R, Li J, Zhang C, Wang Y, Cai Q. Stabilization of phosphofructokinase 1 platelet isoform by AKT promotes tumorigenesis. *Nature Communications*. 2017;8(1):949. PMID: 29038421. Available from: [10.1038/s41467-017-00906-9](https://doi.org/10.1038/s41467-017-00906-9).
35. Wang J, Zhang P, Zhong J, Tan M, Ge J, Tao L. The platelet isoform of phosphofructokinase contributes to metabolic reprogramming and maintains cell proliferation in clear cell renal cell carcinoma. *Oncotarget*. 2016;7(19):27142–57. PMID: 27049827. Available from: [10.18632/oncotarget.8382](https://doi.org/10.18632/oncotarget.8382).
36. Lee JH, Shao F, Ling J, Lu S, Liu R, Du L. Phosphofructokinase 1 Platelet Isoform Promotes  $\beta$ -Catenin Transactivation for Tumor Development. *Frontiers in Oncology*. 2020;10(March):211. PMID: 32195176. Available from: [10.3389/fonc.2020.00211](https://doi.org/10.3389/fonc.2020.00211).
37. Yeerken D, Hong R, Wang Y, Gong Y, Liu R, Yang D. PFKP is transcriptionally repressed by BRCA1/ZBRK1 and predicts prognosis in breast cancer. *PLoS One*. 2020;15(5):e0233750. PMID: 32333750.

32470015. Available from: [10.1371/journal.pone.0233750](https://doi.org/10.1371/journal.pone.0233750).
38. Zahra K, Dey T, Ashish, Mishra SP, Pandey U. Pyruvate Kinase M2 and Cancer: The Role of PKM2 in Promoting Tumorigenesis. *Frontiers in Oncology*. 2020;10(159):1–9. Available from: [10.3389/fonc.2020.00159](https://doi.org/10.3389/fonc.2020.00159).
  39. Li T, Han J, Jia L, Hu X, Chen L, Wang Y. PKM2 coordinates glycolysis with mitochondrial fusion and oxidative phosphorylation. *Protein & Cell*. 2019;10(8):583–94. PMID: 30887444. Available from: [10.1007/s13238-019-0618-z](https://doi.org/10.1007/s13238-019-0618-z).
  40. Estrella V, Chen T, Lloyd M, Wojtkowiak J, Cornell HH, Ibrahim-Hashim A. Acidity generated by the tumor microenvironment drives local invasion. *Cancer Research*. 2013;73(5):1524–35. PMID: 23288510. Available from: [10.1158/0008-5472.CAN-12-2796](https://doi.org/10.1158/0008-5472.CAN-12-2796).
  41. Pinheiro C, Garcia EA, Morais-Santos F, Scapulatempo-Neto C, Mafra A, Steenberg RD. Lactate transporters and vascular factors in HPV-induced squamous cell carcinoma of the uterine cervix. *BMC Cancer*. 2014;14(1):751. PMID: 25296855. Available from: [10.1186/1471-2407-14-751](https://doi.org/10.1186/1471-2407-14-751).
  42. Noble RA, Bell N, Blair H, Sikka A, Thomas H, Phillips N. Inhibition of monocarboxylate transporter 1 by AZD3965 as a novel therapeutic approach for diffuse large B-cell lymphoma and Burkitt lymphoma. *Haematologica*. 2017;102(7):1247–57. PMID: 28385782. Available from: [10.3324/haematol.2016.163030](https://doi.org/10.3324/haematol.2016.163030).
  43. Yoo HC, Park SJ, Nam M, Kang J, Kim K, Yeo JH. A Variant of SLC1A5 Is a Mitochondrial Glutamine Transporter for Metabolic Reprogramming in Cancer Cells. *Cell Metabolism*. 2020;31(2). PMID: 31866442. Available from: [10.1016/j.cmet.2019.11.020](https://doi.org/10.1016/j.cmet.2019.11.020).
  44. Son J, Lyssiotis CA, Ying H, Wang X, Hua S, Ligorio M. Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. *Nature*. 2013;496(7443):101–5. PMID: 23535601. Available from: [10.1038/nature12040](https://doi.org/10.1038/nature12040).
  45. Yang L, Achreja A, Yeung TL, Mangala LS, Jiang D, Han C. Targeting Stromal Glutamine Synthetase in Tumors Disrupts Tumor Microenvironment-Regulated Cancer Cell Growth. *Cell Metabolism*. 2016;24(5):685–700. PMID: 27829138. Available from: [10.1016/j.cmet.2016.10.011](https://doi.org/10.1016/j.cmet.2016.10.011).
  46. Martinez-Soria N, McKenzie L, Draper J, Ptasinska A, Issa H, Potluri S. The Oncogenic Transcription Factor RUNX1/ETO Corrupts Cell Cycle Regulation to Drive Leukemic Transformation. *Cancer Cell*. 2018;34(4). PMID: 30300583. Available from: [10.1016/j.ccell.2018.08.015](https://doi.org/10.1016/j.ccell.2018.08.015).
  47. Shiratori R, Furuichi K, Yamaguchi M, Miyazaki N, Aoki H, Chibana H. Glycolytic suppression dramatically changes the intracellular metabolic profile of multiple cancer cell lines in a mitochondrial metabolism-dependent manner. *Scientific Reports*. 2019;9(1):18699. PMID: 31822748. Available from: [10.1038/s41598-019-55296-3](https://doi.org/10.1038/s41598-019-55296-3).
  48. Wang X, Wu W, Zheng Z, Chi P. Exploring Better Strategies for RAS Mutation-Associated EGFR-Targeted Resistance in Colorectal Cancer: From the Perspective of Cancer Community Ecology. *Frontiers in Oncology*. 2021;11(October):754220. PMID: 34745987. Available from: [10.3389/fonc.2021.754220](https://doi.org/10.3389/fonc.2021.754220).
  49. Yao CH, Wang R, Wang Y, Kung CP, Weber JD, Patti GJ. Mitochondrial fusion supports increased oxidative phosphorylation during cell proliferation. *eLife*. 2019;8:1–19. PMID: 30694178. Available from: [10.7554/eLife.41351](https://doi.org/10.7554/eLife.41351).
  50. Lee HJ, Jedrychowski MP, Vinayagam A, Wu N, Shyh-Chang N, Hu Y. Proteomic and Metabolomic Characterization of a Mammalian Cellular Transition from Quiescence to Proliferation. *Cell Reports*. 2017;20(3):721–36. PMID: 28723573. Available from: [10.1016/j.celrep.2017.06.074](https://doi.org/10.1016/j.celrep.2017.06.074).
  51. Farber S, Diamond LK, Mercer RD, Sylvester RF, Wolff JA. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid. *The New England Journal of Medicine*. 1948;238(23):787–93. PMID: 18860765. Available from: [10.1056/NEJM194806032382301](https://doi.org/10.1056/NEJM194806032382301).
  52. Luengo A, Gui DY, Heiden MG. Targeting Metabolism for Cancer Therapy. *Cell Chemical Biology*. 2017;24(9):1161–80. PMID: 28938091. Available from: [10.1016/j.chembiol.2017.08.028](https://doi.org/10.1016/j.chembiol.2017.08.028).
  53. Stine ZE, Schug ZT, Salvino JM, Dang CV. Targeting cancer metabolism in the era of precision oncology. *Nature Reviews Drug Discovery*. 2022;21(2):141–62. PMID: 34862480. Available from: [10.1038/s41573-021-00339-6](https://doi.org/10.1038/s41573-021-00339-6).
  54. Sakura T, Hayakawa F, Sugiura I, Murayama T, Imai K, Usui N. High-dose methotrexate therapy significantly improved survival of adult acute lymphoblastic leukemia: a phase III study by JALSG. *Leukemia*. 2018;32(3):626–32. PMID: 28914260. Available from: [10.1038/leu.2017.283](https://doi.org/10.1038/leu.2017.283).
  55. Wang E, Gulbis A, Hart JW, Nieto Y. The emerging role of gemcitabine in conditioning regimens for hematopoietic stem cell transplantation. *Biology of Blood and Marrow Transplantation*. 2014;20(9):1382–9. PMID: 24816580. Available from: [10.1016/j.bbmt.2014.04.025](https://doi.org/10.1016/j.bbmt.2014.04.025).
  56. Lv S, Li A, Wu H, Wang X. Observation of clinical efficacy and toxic and side effects of pirarubicin combined with cytarabine on acute myeloid leukemia. *Oncology Letters*. 2019;17(3):3411–7. PMID: 30867778. Available from: [10.3892/ol.2019.9966](https://doi.org/10.3892/ol.2019.9966).
  57. Adams DJ, Ito D, Rees MG, Seashore-Ludlow B, Puyang X, Ramos AH. NAMPT is the cellular target of STF-31-like small-molecule probes. *ACS Chemical Biology*. 2014;9(10):2247–54. PMID: 25058389. Available from: [10.1021/cb500347p](https://doi.org/10.1021/cb500347p).
  58. Reckzeh ES, Karageorgis G, Schwalfenberg M, Ceballos J, Nowacki J, Stroet MC. Inhibition of Glucose Transporters and Glutaminase Synergistically Impairs Tumor Cell Growth. *Cell Chemical Biology*. 2019;26(9). PMID: 31303578. Available from: [10.1016/j.chembiol.2019.06.005](https://doi.org/10.1016/j.chembiol.2019.06.005).
  59. Halford SE, Jones P, Wedge S, Hirschberg S, Katugampola S, Veal G. A first-in-human first-in-class (FIC) trial of the monocarboxylate transporter 1 (MCT1) inhibitor AZD3965 in patients with advanced solid tumours. *Journal of Clinical Oncology*. 2017;35:2516. Available from: [10.1200/JCO.2017.35.15\\_suppl.2516](https://doi.org/10.1200/JCO.2017.35.15_suppl.2516).
  60. Schulte ML, Fu A, Zhao P, Li J, Geng L, Smith ST. Pharmacological blockade of ASCT2-dependent glutamine transport leads to antitumor efficacy in preclinical models. *Nature Medicine*. 2018;24(2):194–202. PMID: 29334372. Available from: [10.1038/nm.4464](https://doi.org/10.1038/nm.4464).
  61. Bröer A, Fairweather S, Bröer S. Disruption of amino acid homeostasis by novel ASCT2 inhibitors involves multiple targets. *Frontiers in Pharmacology*. 2018;9(785):785. PMID: 30072900. Available from: [10.3389/fphar.2018.00785](https://doi.org/10.3389/fphar.2018.00785).