The emerging role of targeting cancer metabolism for cancer therapy

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Abstract
Glucose, as the main consuming nutrient of the body, faces different destinies in cancer cells. Glycolysis, oxidative phosphorylation, and pentose phosphate pathways produce different glucose-derived metabolites and thus affect cells' bioenergetics differently. Tumor cells' dependency to aerobic glycolysis and other cancer-specific metabolism changes are known as the cancer hallmarks, distinct cancer cells from normal cells. Therefore, these tumor-specific characteristics receive the limelight as targets for cancer therapy. Glutamine, serine, and fatty acid oxidation together with 5-lipoxygenase are main pathways that have attracted lots of attention for cancer therapy. In this review, we not only discuss different tumor metabolism aspects but also discuss the metabolism roles in the promotion of cancer cells at different stages and their difference with normal cells. Besides, we dissect the inhibitors potential in blocking the main metabolic pathways to introduce the effective and non-effective inhibitors in the field.

Keywords
Cancer metabolism, glycolysis, oxidative phosphorylation, pentose phosphate pathway, cancer therapy

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Introduction
The increasing incidence in the number of cancer patients worldwide clearly calls for a more comprehensive investigation on this threatening dilemma. Accordingly, numerous studies in genetics, molecular biology, and cancer metabolism were performed. Cancer metabolism was first described by Otto Warburg in 1920s. In cancer, the main pathway for glucose consumption is the transformation to lactate, to produce adenosine triphosphate (ATP) which is a much faster process than tricarboxylic acid cycle (TCA cycle) occurring in mitochondria. However, this pathway has low output which results in more glucose consumption and several other metabolites. This cancer hallmark is an escape way for cancerous cells to bypass immune attack and thus proliferates and maintains malignancy. Furthermore, higher oxidative phosphorylation in other cancers, such as lymphoma and leukemia, generating ATP through electron transport chain (ETC) occurring in inner membrane of mitochondria, is another metabolic pathway.

Cancerous cells use pentose phosphate pathway (PPP) according to metabolic demand providing a reduced form of nicotinamide adenine dinucleotide phosphate (NADPH), electron donor in reductive reactions, and essential components for cancer cells under limited situations. Glutamine, as glutathione, carbon, and nitrogen source in cancer metabolism, is of importance in this case. Beside aforementioned pathways, we

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will discuss other metabolic pathways including 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), serine, fatty acid oxidation (FAO), 5-lipoxigenase (5-LOX), forkhead box O (FOXO), and pyruvate dehydrogenase kinase (PDK) metabolism in cancer metabolism. Hence, we aim to discuss the beneficial metabolic changes in cancers by focusing on a more selective approach as a valuable therapeutic target for treating cancers with minimal side effects for normal cells.

**Glycolysis**

Normal cells use the pyruvate derived from glucose metabolism in the TCA cycle to produce 30–32 ATP molecules per each glucose molecule. This is while cancer cells devise a faster pathway called aerobic glycolysis that occurs in the presence of plentiful oxygen molecules and converting one glucose molecule to two lactate molecules and producing only two ATP molecules. Lactate production is vital for cancer cells survival. Ascribed to low yield of ATP production in aerobic glycolysis, in a compensatory mechanism, glucose uptake in cancer cells will increase. Alteration in metabolism in cancer cell can be the result of impairment in function of mitochondria which has several mutations in related genes such as chain termination mutation in a de novo cytochrome C oxidase subunit 1 (CO1) which is under positive selection in cancer cells. Since glycolytic pathway performs as an intermediate and signaling network, its targeting can serve as a promising therapeutic candidate. Enzymes and transporters in glycolysis are attractive targets, which are the most important ones, as shown in Figure 1. Among the target enzymes in the glycolytic pathway, hexokinase with four isoforms (HK-I to HK-IV) could be the first choice. HK converts glucose to glucose-6-phosphate (G-6-P) (which is rate limiting in glycolysis) by phosphorylation. HK-II overexpression has been shown in cancer cells, in contrast to normal cells. 2-deoxyglucose (2-DG), a glucose analog, is an important inhibitor of HK-II (Table 1). 2-deoxyglucose-6-phosphate (2-DG6P) is the result of 2-DG phosphorylation by HK without being metabolized by cells to progress the glycolysis pathway, resulting in 2-DG6P accumulation and inhibition of HK-II. Loss of the intracellular glucose leads to cancer cell death, since it results in ATP depletion. The inhibitory effect of 2-DG is dose-dependent as high dose may be toxic and low dose is insufficient to work. Despite 2-DG efficiency through glycolysis inhibition in cancer cells, it has toxicity side effects to normal cells, skeletal muscles, and neuronal cells, which also apply glucose for energy. Also, it is striking that 2-DG impairs T cells’ metabolism, which results in reduced cytokines secretion and diminished antitumor function of T cell that can be critical for therapeutic achievement. According to the toxicity effect of 2-DG in metabolism of normal cells, such as T cells, which is in paradox with its anticaner properties, it has been demonstrated that combinational application of 2-DG with other treatment could be more successful specially in preclinical phase. Also, the therapeutic effect of other inhibitors of HK-II, such as 3-bromopyruvate (3BP), which works through overcoming the chemoresistance and lonidamine that induces apoptosis should attract more attentions. In order to ascertain prognostic value of HK-II, a meta-analysis investigates the suggestion that HK-II can be considered as an independent prognostic factor for patients with solid tumors. They demonstrated that there is a significant association between HK-II expression with shorter overall survival (OS) in hepatocellular carcinoma (HCC), gastric cancer, and colorectal cancer (CRC) as well as progression-free survival (PFS) in patients with solid tumor, although the correlation changes according to cancer type. In addition, to assess the prognostic significance of HK-II expression in HCC patients, the survival time of a liver cancer patient cohort from Gene Expression Omnibus (GEO) database and The Cancer Genome Atlas (TCGA) database was analyzed. The results showed a significant association between HK-II expression and OS time in HCC patients. Therefore, elevated HK-II expression in HCC is relevant to its poor clinical prognosis. In addition to the enzymes, transporters can be the other suitable potential targets for cancer therapy. Glucose transporters (GLUTs) as it is evident from
Table 1. Targets and inhibitors in cancer metabolism pathways.

| Agent                        | Target                  | Activity                                      | Tumor type                                      | Stage                                         |
|------------------------------|-------------------------|-----------------------------------------------|-------------------------------------------------|-----------------------------------------------|
| 2-deoxyglucose (2-DG)        | Hexokinase-II (HK-II)   | ATP depletion                                 | Lung, breast, and prostate cancer               | Preclinical and clinical studies             |
| 3-bromopyruvrate (3BP)       | Hexokinase-II (HK-II)   | Chemoresistance overcoming                    | Breast cancer                                   | Preclinical studies                          |
| Lonidamine                   | Glutamate              | Antitumor activity                            | Advanced solid tumor                            | Preclinical and clinical studies             |
| Silibinin                    | MCT-1 and MCT-2        | Cytosolic acidifying                          | Diffuse large B cell lymphomas                  | Phase I clinical trials                      |
| AZD3965                      | PFKFB3                 | Growth inhibition                             | Breast cancer                                   | Preclinical and clinical studies             |
| AR-C155858                   | PFK-15                 | Apoptosis induction                           | HCC                                             | Preclinical and clinical studies             |
| 3-PO                        | Silibinin              | Cytosolic acidifying                          | AML                                             |                                               |
| PFK-15                      | Cytochalasin B         | Cytosolic acidifying                          | Colon and pancreatic adenocarcinomas           | Preclinical and clinical studies             |
| PFK-158                     | Azilolicide            | Cytosolic acidifying                          | Pancreatic, endometrial, and colon cancers      |                                               |
| Metformin                    | Complex I (OXPHOS)     | Anticancer activity                            | Pancreatic, endometrial, and colon cancers      | Preclinical and clinical studies             |
| Phenformin                   | Complex I (OXPHOS)     | Tumor growth inhibition                        | CRC and NSCLC                                   |                                               |
| Lonidamine                   | Complex II (OXPHOS)    | Oxygen consumption rate alleviation            | NSCLC                                           |                                               |
| Atovaquone                   | Complex III (OXPHOS)   | Improves IR response                           | APL and NSCLC                                   | Preclinical and clinical studies             |
| Arsenic trioxide             | Complex IV (OXPHOS)    | Reducing tumor hypoxia                        | Oral cancer                                     | Phase I clinical trial                       |
| Hydrocortisone               | PDK                    | Cellular metabolism remodeling                 | Breast and NSCLC                                 |                                               |
| Nitric oxide                 | G6PD                   | Mitochondrial function reactivates            | APL and NSCLC                                   |                                               |
| Dichloroacetate              | G6PD                   | Mitochondrial defects in cancer cells          | Phase III                                       |                                               |
| Mitaplatin and cisplatin     | Dehydroepiandrosterone (DHEA) derivatives | In vivo G6PD inhibitor                          | Phase 0                                         |                                               |
| Polystein                    | 6-aminonicotinamide (6-AN) | ROS accumulation apoptosis                 | Oral cancer                                     | Phase II clinical trial                      |
| Metformin                    | Glutaminase (GLS1)     | TCA anaplerosis inhibition                     | Human colon cancer HT29-DX cell line            |                                               |
| 6-FU                         | Methotrexate            | Anticancer activity                            | Human gliomas and squamous carcinoma cell lines (in combination with 2-DG) |                                               |
| Etomoxir                     | Glutaminase (GLS1)     | Anticancer activity                            | Survival GEMM liver cancer, kidney, hematologic tumors, and solid tumors | Preclinical and clinical studies             |
| BPTES                        | Methotrexate            | Anticancer activity                            | Lymphomas and leukemias, bladder cancer, and gestational trophoblastic tumors | Clinical practice                           |
| CB-839                       | Methotrexate            | Anticancer activity                            | Gastrointestinal malignancies                   | Clinical practice                           |
| 5-FU                         | Thymidylate synthase   | Anticancer activity                            | Leukemia, breast, and prostate cancer cell lines | Retired from phase II clinical trial for diabetes and heart failures |
| Methotrexate                 | CPTI                   | Increasing ROS and decreasing NADPH production | Prostate cancer cell lines                      |                                               |
| Perhexiline                  | CPTI                   | Approved for use as an antiangina therapy     | Prostate cancer cell lines                      |                                               |

(continued)
their names are vital for cancer cells, thus interruption in their normal biological activity can decrease the source of nutrients for the cells. It has been shown that GLUT-1 inhibition induces apoptosis in breast and lung cancers and diminishes tumor growth. Also, observed GLUT-3 overexpression in some cancers makes these transporters as important targets for cancer therapy. Silibinin and Cytochalasin B are two effective GLUT inhibitors with less side effects on normal cells.

Evaluating the correlation between transcription rates of GLUT-1, GLUT-3, and GLUT-4 and prognostic clinical data in breast cancer patients from the ONCOMINE database demonstrated the elevated transcription of GLUT-1 and lower rate transcription of GLUT-3 and GLUT-4 in breast cancer patient. Besides, the transcription levels of GLUT-1 and GLUT-3 were associated with clinical cancer stage. While GLUT-3 overexpression, introduced as a potential marker of poor prognosis in oral squamous cell carcinoma and non-small cell lung cancer (NSCLC) alleviated transcription level of GLUT-3 in breast cancer associated with a worse OS and clinical cancer stage. Hence, elevated transcription of GLUT-3/4 can suggest as a potential prognostic marker (better prognosis) for breast cancer patients. In addition, meta-analysis illustrates the association between GLUT-1 overexpression and poor prognosis in breast cancer, notably these results are more reliable for Asian patients who were mostly included in the studies. As such, GLUT-1 expression is associated with poor prognosis as well as being metabolic biomarker for the Lauren classification in locally advanced gastric cancer. Monocarboxylate transporters (MCTs) including MCT-1, 2, and 4, facilitate the export of lactate, the substrate for oxygenated cancer cells, across the membrane. Increased MCT-4 expression associated with high risk of mortality as well as advanced stage and histological grade in patients with breast cancer. As such, elevated expression of MCT-4 is correlated to short OS, which may suggest poor prognosis in breast cancer consistent with data in head-and-neck squamous cell carcinoma. AR-C155858 and AZD3965 can be introduced as the lactate efflux inhibitors which make cytosol to be acidified and non-tolerable environment for proliferation. AZD3965 blocks MCT-1 and MCT-2 which inhibits solid tumor growth and large B cell lymphomas; however, its side effect on normal T cell has been shown. Lenalidomide is known as MCT inhibitor that has a role in impairing the CD147–MCT-1 ligation. Also, it has been shown that it enhances secretion of interleukin-2 (IL-2) and interferon gamma (IFN-γ) in T cells, which could repress tumor cell proliferation while supporting T cells activation.

Table 1. Continued

| Agent          | Target Type | Activity                                      | Tumor Type                                      | Stage     |
|----------------|-------------|-----------------------------------------------|-------------------------------------------------|-----------|
| ST1326 (Teglicar) | CPT1        | Growth inhibition and cytotoxicity in cell lines | Leukemia and lymphoma cell lines                | Experimental |
| NDGA           | 5-LOX       | Apoptosis induction                            | Prostate cancer, brain tumor, CNS Tumors, and Cervical intraepithelial neoplasia | II         |
| Zileuton       | 5-LOX and LT4 synthesis | Cell proliferating inhibition | Lung cancer and head and neck cancer | II         |
| Docebonone (AA861) | 5-LOX       | Diminishing metastasis                          | Human leukemia cell lines                        | Discontinued phase II (Asthma, Allergy) |
|                |             | Reducing cancer growth                          | Dihydroxyindole-induced skin tumor              |            |
|                |             | Reducing esophageal adenocarcinogenesis         | Gastric and esophageal bladder cancers          |            |

| Agent          | Target Type | Activity                                      | Tumor Type                                      | Stage     |
|----------------|-------------|-----------------------------------------------|-------------------------------------------------|-----------|
| 5-AF           | 5-LOX       | Remedy bronchial asthma                        | Chronic obstructive pulmonary disease            | II         |
|                |             | Reduce esophageal adenocarcinogenesis          | Prostate cancer, brain tumor, CNS tumors, and Cervical intraepithelial neoplasia | II         |
|                |             | Blocking proliferation                          | Lung cancer and head and neck cancer            |            |
|                |             | Diminishing metastasis                          | Oral and oesophageal cancer                     | III        |
|                |             | Reducing apoptosis                              | Oral and oesophageal cancer                     |            |
|                |             | Blocking proliferation                          | Oral and oesophageal cancer                     | III        |
|                |             | Reducing cancer growth                          | Oral and oesophageal cancer                     | III        |
|                |             | Remedy bronchial asthma                        | Chronic obstructive pulmonary disease            | II         |
|                |             | Reduce esophageal adenocarcinogenesis          | Prostate cancer, brain tumor, CNS tumors, and Cervical intraepithelial neoplasia | II         |
|                |             | Blocking proliferation                          | Lung cancer and head and neck cancer            |            |
|                |             | Diminishing metastasis                          | Oral and oesophageal cancer                     | III        |
|                |             | Reducing apoptosis                              | Oral and oesophageal cancer                     | III        |
|                |             | Blocking proliferation                          | Oral and oesophageal cancer                     | III        |
|                |             | Reducing cancer growth                          | Oral and oesophageal cancer                     | III        |

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|                |             | Reduce esophageal adenocarcinogenesis          | Prostate cancer, brain tumor, CNS tumors, and Cervical intraepithelial neoplasia | II         |
|                |             | Blocking proliferation                          | Lung cancer and head and neck cancer            |            |
|                |             | Diminishing metastasis                          | Oral and oesophageal cancer                     | III        |
|                |             | Reducing apoptosis                              | Oral and oesophageal cancer                     | III        |
|                |             | Blocking proliferation                          | Oral and oesophageal cancer                     | III        |
|                |             | Reducing cancer growth                          | Oral and oesophageal cancer                     | III        |
|                |             | Remedy bronchial asthma                        | Chronic obstructive pulmonary disease            | II         |
|                |             | Reduce esophageal adenocarcinogenesis          | Prostate cancer, brain tumor, CNS tumors, and Cervical intraepithelial neoplasia | II         |
|                |             | Blocking proliferation                          | Lung cancer and head and neck cancer            | III        |
|                |             | Diminishing metastasis                          | Oral and oesophageal cancer                     | III        |
|                |             | Reducing apoptosis                              | Oral and oesophageal cancer                     | III        |
|                |             | Blocking proliferation                          | Oral and oesophageal cancer                     | III        |
|                |             | Reducing cancer growth                          | Oral and oesophageal cancer                     | III        |

ATP: adenosine triphosphatase; GLUT: glucose transporter; MCT: monocarboxylate transporter; PFK1: glycogen phosphofructokinase; PFK2: fructose-1,6-bisphosphatase; PFK3: fructose-2,6-bisphosphatase; 5-LOX: 5-lipoxygenase; 6PGD: 6-phosphogluconate dehydrogenase; G6PD: glucose-6-phosphate dehydrogenase; 3-PO: 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one; 5-FU: 5-fluorouracil; EGF: epidermal growth factor; TGF-B: transforming growth factor beta; IL-2: interleukin-2; IFN-γ: interferon gamma; IL-12: interleukin-12; IL-15: interleukin-15; IL-18: interleukin-18; CD40: cluster of differentiation 40; CPT-1: carnitine palmitoyl transferase 1; NDGA: nordihydroguaiaretic acid; 5-LOX: 5-lipoxygenase; CNS: central nervous system; OXPHOS: oxidative phosphorylation; AML: acute myeloid leukemia; DS: DSS; AOM: azoxymethane; 3-MC: 3-methylcholanthrene; MCF7: breast cancer cells; HCT116: colorectal cancer cells; H441: squamous cell lung cancer cells; 143B: osteosarcoma cells; OVCAR-3: ovarian cancer cells; MCF-7: breast cancer cells; KB: human oral epithelial cells; AML1: acute promyelocytic leukemia; IR: ionizing radiation; APL: acute promyelocytic leukemia; PDK: pyruvate dehydrogenase kinase; G6PD: glucose-6-phosphate dehydrogenase; 3-PO: 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one; 5-LOX: 5-lipoxygenase; CNS: central nervous system; LTB4: leukotriene B4; dm/β: d-mannose/beta-pimeloyl alanine; DMBA: 7,12-dimethylbenz[a]anthracene.
**PKF FB3 in glycolysis**

A critical enzyme in the glycolysis pathway is phosphofructokinase (PFK) that makes irreversible phosphorylation in fructose-6-phosphate (F-6-P). This enzyme is divided to two types such as PFK-1 — its overexpression has been found in transformed cells and different primary cancers\(^1\) and PFK-2 — expressed in solid tumor such as breast and colon cancer.\(^2\) PFKF family with four isoforms (PFKFB 1–4) have crucial role in glycolysis regulation as they have two distinct functions of kinase-phosphatase activities. These bifunctional enzymes synthesize fructose-2,6-bisphosphate (F2,6BP) by kinase activity of 6-phosphofructo-2-kinase in N-terminal region and hydrolytically degrade the F2,6BP by the activity of fructose-2,6-bisphosphatase in C-terminal.\(^3\) Different properties, such as kinase/phosphatase ratio, have been demonstrated among four isoforms in spite of their 85% sequence homology.\(^4\) PFK-1 can draw back the deterrence effect of intracellular inhibitor such as citric acid and being activated by F2,6BP activity which itself is under control of PFKFB3 with high kinase activity causing the increase in PFK-1 activity, F1,6BP synthesizing, and finally increasing the rate of glycolysis.\(^5\) PFKFB3 gene is located on chromosome 10 at position 10p15.1, with 19 exons contains constant and variable regions finally producing six isoforms of PFKFB3.\(^6\) PFKFB3 has two distinct roles, such as tumor cell proliferation by strong kinase activity increasing the rate of glycolysis and cell cycle transition by phosphorylation of p27, G1/S suppressor, due to F2,6BP activity and decline in p27 level leading to cell cycle progression.\(^7\) PFKFB3 gene expression induction happens by some stimulants such as progestin, estrogen, hypoxia, and stress, based on their interaction by receptors which consensus respond elements exist in pfkfb3 promoter.\(^8\) Proliferation, survival, and migration, and migration of increasing activity of PFKFB3 has been shown in different cancer cell such as breast, colorectal, gastric, and leukemia.\(^9\) Critical roles of PFKFB3 in tumorigenesis make it a potential target in cancer therapy, as inhibitory effect on PFKFB3 in gynecologic cancer cells induces the apoptosis behavior.\(^10\) Analyzing PFKFB3 expression level demonstrates more frequent high expression of PFKFB3 in distant metastasis. Consistently, according to Kaplan–Meier analysis, elevated PFKFB3 expression correlated with poor OS in breast cancer patients. Therefore, since PFKFB3 showed determined characteristics of tumor cell metabolism as well as involving in poor prognosis in breast cancer patients, it can serve as a potential target in tumor therapies.\(^11\)

3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3-PO) introduced as the PFKFB3 inhibitor via diminishing F2,6BP and binding to the function site of PFKFB3.\(^12\) Breast cancer,\(^13\) HCC, and several adenocarcinomas\(^14\) took the advantage of inhibitory effects such as apoptosis induction and growth inhibition of 3-PO. However, due to low water solubility of this compound, the clinical application is not possible.\(^15\) PFK-15 derived from 3-PO has a potential role in cell cycle arrest, apoptosis induction, and a selective activity against PFKFB3.\(^16\) PFK-15 and PFK-158 are considered as two applicable compounds for cancer therapy in clinical phase.\(^17\) PFK-158 as a new inhibitor of PFKFB3 has decreasing effect on glucose uptake and energy production, and more effectiveness activity of this inhibitor was shown while accompanied with standard chemotherapies.\(^18\) Also, 5-triazolo-2-arylpirdazinone,\(^19\) 1-(3-pyridinyl)-3-(2-quinolyl)-2-propen-1-one (PQP),\(^20\) 5,6,7,8 tetrahydroxy-2-(4-hydroxyphenyl)chrome-4-one (N4A), and 7,8-dihydroxy-3-(4 hydroxyphenyl) chromen-4-one (YN1)\(^21\) can be introduced as the other PFKFB3 inhibitors.

**Oxidative phosphorylation**

Oxidative phosphorylation (OXPHOS) is a process generally observed in a downregulated manner in cancers, such as breast and gastric cancers, in which glycolysis beats the first word. Alleviation in OXPHOS activities can be ascribed to mutations in mitochondrial DNA and its DNA content reduction.\(^22\) However, recently studies showed the OXPHOS upregulation in some cancers such as lymphoma, leukemia, endometrial carcinoma, pancreatic ductal adenocarcinoma, and a subtype of melanoma.\(^23\) Thus, OXPHOS targeting seems to be attractive for cancer therapy. OXPHOS produces ATP through electron transport among protein complexes (I–IV) in the inner membrane of mitochondria called ETC where the oxygen is the final acceptor.\(^24\) Moreover, inhibition of proteins in ETC complexes, especially complex I, is considered as attractive therapeutic targets. Inhibitors that generate high amounts of reactive oxygen species (ROS) will disrupt ETC complexes.\(^25\) Metformin is one of the important tumor growth inhibitors in various types of tumors with radiation response improvement effects and hypoxia reduction.\(^26\) Metformin primarily has been reported as a selectively inhibitor of the mitochondrial respiratory-chain complex 1 which causes reducing nicotinamide adenine dinucleotide-reduced form (NADH) oxidation, diminishing proton gradient across the inner mitochondrial membrane, and decreasing oxygen consumption rate. Considering, metformin has a crucial role in antitumorigenic situations. Indeed, the complex 1 inhibition was reported in several cancer cells that may result in mitochondrial OXPHOS reduction and ATP depletion, eventually lead to adenosine monophosphate–activated protein kinase (AMPK)-mediated activation of catabolic pathways and anabolic proceeding inhibition via its regulation of mechanistic
target of rapamycin complex 1 (mTORC1). As a result of co-existing of some AMPK- and mTORC1-independent mechanisms, this metabolic reprogramming reduce growth and proliferation of cancer cells, promotion of cell cycle arrest, and apoptosis in cells that cannot stand the energetic stress.57 Metformin may express antitumor effect via alleviation of insulin-like receptor tyrosine kinases activity.58 Metformin in suitable concentration can arrest complex I in cancer cells.59 Low concentration of metformin in cancer cell will be inefficient; hence, phenformin with low dose can compensate the inefficient metformin.60,61 Besides, the outstanding result of combinational therapeutic effect of metformin and 2-DG in pancreatic cancer by depleting ATP suggests that the blocking of both glycolysis and OXPHOS pathways presents a promising cancer therapy approach.62 It is noteworthy that cancer cell’s mitochondria membranes are more negatively charged compared to the normal cells; therefore, cationic drugs showed to be more selective in targeting tumor cells. As an example, mitochondria-targeted metformin (Mitomformin), a product of metformin and triphenyl phosphonium (TPP + ) group conjunction, has been more effective than untargeted counterparts.63 Oxymatrine, myricetin, capsicain, and casticain have antitumor role by generating high level of ROS damaging mitochondrial transmembrane in cancer cells.64 Also, tamoxifen, α-tocopheryl succinate (α-TOS), and 3BP target the complexes of ETC in terms of destroying cancer cell via ROS inducing.53 Carboxyamidotriazole (CAI), ME344, and fenofibrate are the other inhibitors targeting complex I.65,66 Complex II disruption by lonidamid effect leading to delaying in growth in many tumors.67 Atovaquone acts as a complex III inhibitor in cancer cells, causing alleviation in oxygen consumption rate.68 Herein, complex IV can be the goal of action of arsenic trioxide, hydrocortisone, and nitric oxide via reducing tumor hypoxia and improving radiation sensitivity in tumors.69,70

PDK

PDKs are important enzymes in oxidative phosphorylation of mitochondria acting as the inhibitor of pyruvate dehydrogenase complex (PDC). PDC is the complex settled in the inner membrane of mitochondria with the interconnection ability of glycolysis and OXPHOS by oxidative decarboxylation of pyruvate to acetyl-CoA.1,71 Decreasing in the amount of acetyl-CoA, the prominent substrate of Krebs cycle, is the result of the inhibitory effect of these kinases which cause halting mitochondrial respiration; hence, the crucial role of PDK in cancer metabolism is obvious (Figure 2).72 PDC has two major parts such as the enzymatic part—consists of four subunits such as pyruvate dehydrogenases (E1), dihydrolipoamide transacetylase (E2), dihydrolipoamide dehydrogenase (E3), E3 binding protein (E3BP) altering pyruvate to acetyl-CoA, CO₂, and NADH73 and the regulatory part—consists of subunits such as PDKs and pyruvate dehydrogenase phosphatases (PDPs). PDK has four isoforms (PDK1–PDK4) that almost have tissue-specific functions.74 Three serine residues of E1 α 1 in pyruvate dehydrogenase have phosphorylated by the effect of PDKs in different order depending on tissue. PDK activities have been affected by acetyl-CoA, NADH, and ATP in mitochondria. Different expressions of PDK in various tissues and overexpression of PDK1 in cancer cells have been reported,75 accordingly this kinase could be an attractive target in cancer therapy. Dichloroacetate (DCA), known as the primary inhibitor of PDKs, besides its toxic effect in high dosage, has the anticancer characteristic like remodeling cellular metabolism and reactivating mitochondrial function as well.76 In addition, some agents, such as mitaplatin and cisplatin with various anticancer potentials, as the components derived from DCA, come to work.77,78

PPP

The PPP is another way for glucose consumption through G-6-P, the result of glucose phosphorylation by HK. This pathway is one of the major sources of NADPH, the molecule which is necessary to neutralize produced ROS in the ATP production process in the cells.79 The other product of PPP is ribulose-5-phosphate (Ru-5-P) which is generated in oxidative phase and can change into ribose-5-phosphate (R-5-P) as a nucleotide precursor. F-6-P and glyceraldehyde-3-phosphate (G-3-P), as two products resulting from non-oxidative branch of PPP, can be used in the glycolysis (Figure 3).80,81 Glucose-6-phosphate dehydrogenase
(G6PD) is the first and key enzyme in oxidative phase of PPP that has more expression in cancer cells compared to normal cells. Overexpression of G6PD has been observed in human cervical and esophageal carcinomas, hepatomas, and lung and colon adenocarcinomas. There are a growing body of evidences showing that inhibition of G6PD reduces proliferation and increases susceptibility to chemotherapy in cancer cells; hence, it can be a powerful target in cancer therapy. Although this pathway is a promising therapeutic target, its effective inhibitors are limited. Assessment of G6PD levels in nasopharyngeal cancer male patients showed that low rates of G6PD activity have significant correlation with tumor recurrence, although it has no association with tumor stage or lymph node or distant metastasis. According to these findings, there is an association between low activity of G6PD with poor prognosis in nasopharyngeal cancer patients. Dehydroepiandrosterone (DHEA) was introduced as the in vivo G6PD inhibitor; however, its effect is unclear because it is transformed to steroid hormones immediately. Polydatin (3,4',5-trihydroxystilbene-3-β-d-glucoside) is a natural molecule that has recently been used as the G6PD inhibitor which induces accumulation of ROS and apoptosis in carcinoma cells and limiting tumor growth. The 6-aminonicotineamide (6-AN) is the other PPP inhibitor at 6PGD level by limiting ATP production. Antitumorigenic effect of this inhibitor was reported in some experimental tumors. Also, multidrug resistance inhibition in doxorubicin-resistant human colon cancer HT29-DX cell line was reported via DHEA and 6-AN. However, combination of 2-DG and 6-AN increased radiosensitivity in human gliomas and squamous carcinoma cell lines, showing the efficiency of combinational targeting of glycolysis and PPP. Interestingly, G6PD deficiency causes disorders such as mild anemia; hence, it brings this question to our mind if G6PD deficiency help to overcome cancer development.

**Glutamine**

Glutamine is the second nutrition source for growth and proliferation of cancer cells. Glutamine is the source of nitrogen and carbon used for building purine and pyrimidine nucleotides, nonessential amino acids, and glucoseamine-6-phosphate. In addition, glutamine is considered as a fuel for TCA cycle via α-ketoglutarate (α-KG) resulting in ATP production. Besides, glutamine reduces oxidative stress by generating NADPH and biosynthesis of glutathione, and it has a key role in cellular antioxidative mechanisms. Glutamine can also regulate energy generation, redox homeostasis, and intracellular signaling. The glutamine entered into the cell has different fates as follows: (1) It can be used for nucleotide synthesis by the effect of CAD (carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase) or (2) it can be exported outside to import leucine into the cell to be used as coactivator of glutamate dehydrogenase or (3) it can be converted to glutamate and ammonium by glutaminase (GLS) effect. Then, this glutamate changes to α-KG, the TCA cycle intermediate, via glutamate dehydrogenase. Glutamine transporters, which are known as SLC1A5/ASCT2 and are involved in glutamine supplying, are upregulated in breast cancer. Indeed, “glutamine addicted” is the characteristic of some cancers that they cannot sustain in the absence of glutamine source. Therefore, glutamine and the enzymes involved in its pathway can be targeted in cancer therapies. GLS, the first enzyme in glutaminolysis, has three isoforms including GLS1, the splice variant of GLS1 and GLS2. GLS1 has a critical role in the various types of tumor cells; therefore, it is the attractive part of targeting, which has an inhibitor named Bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl) ethyl sulfide (BPTES) reducing cancer cell proliferation in vitro. In fact, BPTES can inhibit enzymatic activity of GLS by binding it. CB-839 is the other robust GLS1 inhibitor that is more effective than BPTES and nowadays applied in clinical trials in cancer patients. Acivicin, azaserine, and 6-diazo-5-oxo-l-norleucine (l-DON) are glutamine mimetic with antitumor activity through inhibitory effect on GLS.
and biosynthesis of purine; however, their toxic side effect, such as neurotoxicity, was observed in clinical trial (Figure 4).\textsuperscript{106}

Evaluating prognostic value of GLSs by systematic multiomic analysis demonstrates the association between overexpression of kidney-type glutaminase (GLS) in breast, esophagus, head-and-neck, and blood cancers with poor prognosis, as such there was a correlation between liver-type glutaminase (GLS2) overexpression with poor OS in colon, blood, ovarian, and thymoma cancers.\textsuperscript{109} It is worth to mention that depletion of asparagine and glutamine by L-asparaginase from cancer cell in acute lymphoblastic leukemia (ALL) patients shows promising result in cancer treatment.\textsuperscript{110} Also, combination of L-asparaginase by other glutamine metabolism inhibitors can increase the effect of therapeutic outcome. Overall, combinational therapy using inhibitors to target glutamine metabolism and other pathways will be more effective, such as combined inhibition of GLS and mTOR kinase causes tumor cell death in tumor-bearing mice.\textsuperscript{111}

**Serine**

Serine, a nonessential amino acid, is another most used compound by the cancer cell,\textsuperscript{112,113} which can be provided by intracellular synthesizing from glucose as the major source in cancer cells and also can be imported from extracellular environment.\textsuperscript{114} Serine, by providing carbon and nitrogen, has an important and direct or indirect role in biosynthesis of molecules, which are crucial for cell building such as sphingolipids, phospholipids, purines, and thymidine.\textsuperscript{115} Also, it maintains redox homeostasis via the folate cycle.\textsuperscript{116,117} 3-phosphoglycerate (3-PG), one of the glycolytic pathway metabolite, is the precursor of serine which is affected by the phosphoglycerate dehydrogenase (PHGDH). Increasing the role of this key enzyme, either via gene amplification or oncogenic signaling, supports the growing production of serine observed in breast cancer, lung adenocarcinoma, and melanoma.\textsuperscript{118,119} Accordingly, we can consider the inhibition of PHGDH as a strategy in cancer therapy. NCT-503 and CBR-5884 are considered as two PHGDH inhibitors.\textsuperscript{120} Serine hydroxymethyltransferases (SHMTs) are the enzymes that control converting serine to glycine and one carbon unit. Adding one carbon to tetrahydrofolate (THF) produces N\textsubscript{5},N\textsubscript{10}-methylene tetrahydrofolate (THF-CH\textsubscript{2}) that itself has also the potential of being a target in cancer therapy\textsuperscript{121} and can participate in three pathways such as (1) purine metabolisms by producing formyltetrahydrofolate (CHO-THF), (2) thymidine metabolism in cytosol via donating methyl group, and (3) S-adenosylmethionine (SAM) cycle to produce methionine.\textsuperscript{120} Methotrexate and fluorouracil (5-FU) can be introduced as the inhibitors of thymidylate synthase and dihydrofolate reductase which are involved in thymidine synthesis.\textsuperscript{122}

**FAO and CPT1A roles**

Sustainable cell energy homeostasis is somehow depending on the energy yielding and energy consuming processes named as fatty acid metabolism. Fatty acid synthesis (FAS) leads to the main processes including cell membrane integrity, energy saving, and interceding signaling.\textsuperscript{123} In return, FAO or \(\beta\)-oxidation process has a crucial role in producing energy by cyclical reaction in shortening of fatty acid by two carbons in each cycle until producing two acetyl-CoA molecules.\textsuperscript{124} Lipid accumulation, which is considered as a determined sign of cancer, occurs as a result of FAS and FAO equilibrium disturbance.\textsuperscript{125} Major part of FAO occurs in mitochondria, and the generated ATP and NADPH molecules are the result of entering the NADH and FADH\textsubscript{2}, produced in each turn of FAO, to the ETC.\textsuperscript{126} NADPH promotes cell proliferation by producing FA and cholesterol.\textsuperscript{127} FAO commences by generating long-chain acyl-CoA via the enzymatic effect of long-chain acyl-CoA synthetase (LCACS).\textsuperscript{128} Mitochondrial inner membrane impermeability to long-chain acyl-CoAs makes development of carnitine palmitoyl transferase (CPT) system by three members: CPT1, the carnitine acylearnitine translocase (CACT),
and CPT2. Altering acyl-CoAs to acylcarnitine, rate limiting stage of FAO, is catalyzed by CPT1 which has three tissue-specific isoforms (CPT1A, CPT1B, and CPT1C). Swapping acylcarnitine and carnitine between the mitochondrial membranes is done by CACT activity. CPT2, the matrix located member, is used for changing acylcarnitine to acyl-CoAs for oxidation. FAO rate is regulated by multiple mechanisms. Malonyl-CoA, a product of the first FAS step, is considered as a physiological inhibitor of CPT1A (liver form) and CPT1B (muscle form). Despite the defined similarity between these two isoforms, their resistance behavior against malonyl-CoA is different. CPT1B has been known as the more sensitive isoform; hence, CPT1A activity can be shown in high level. ATP-citrate lyase (ACLY) with high expression level reported in breast cancer, ovarian cancer, and CRC is the starter enzyme of FAS and has the ability to convert citrate to oxaloacetate and cytosolic acetyl-CoA, the building block for FAS. Acetyl-CoA carboxylase (ACC) is the other prominent lipogenic enzyme, which has two isoforms such as ACC1 located in cytoplasm producing malonyl-CoA and ACC2 in mitochondrial membrane which hinders Acyl-CoA importing to mitochondria via CPT1. ACC overexpression has been reported in gastric, lung, and breast cancers. In metabolic stress, produced ATP during FAO acts as the tumor nutrition and promotes cancer cell proliferation and metastasis.

Upregulation of lipogenic enzymes, such as fatty acid synthetase, has been observed in breast, ovarian, endometrial, and prostate cancers. Therefore, targeting these enzymes plays an important role in cancer therapy. Inhibition of CPT1A activity has been reported in several cancers. Etoposide (ETO), pharmacological inhibitor of CPT1A, will sensitize the leukemic cells to the chemotherapeutic drug, cytarabine. Also, enzalutamide can be more effective on depleted CPT1A prostate cancer. Abnormal expression of CPT1B has been seen in CRCs and bladder cancers and causes chemoresistance in breast cancer cell. While effectiveness of knock down and depletion of CPT2 were observed in triple-negative breast cancer (TNBC), high expression of CPT2 had better effect in CRC patient. CPT1C upregulation not only is observed in breast, lung, and brain cancers’ survival but also is caused by BCR-ABL positive leukemia cells resistance to imatinib or rapamycin.

Resistance to cetuximab in head-and-neck cancer and metastatic state in breast and lung cancers have been reported as a result of ACC1 phosphorylation at serine 80. FAO provides the ATP fuel for growth, survival, and proliferation of cancer cells such as prostate cancer, diffuse large B-cell lymphoma, Burkitt’s lymphoma, and human glioblastoma. Inhibition of FAO can reduce the chemoresistance property of cancer cell which can explain the overcoming of lung adenocarcinoma to its resistance to paclitaxel by FAO inhibition. Notable point is the tumor neovascularization that is promoted by the properties of CPT1 in tumor microenvironment. ETO, CPT1 inhibitor, leads to human glioblastoma cell death by increasing ROS and decreasing NADPH production. However, ST1326 (Teglicar), as the other CPT1 inhibitor derived from amino carnitine, has a defined role in preventing cancer cell growth and treatment of leukemia and lymphoma. Perhexiline, less selective inhibitor of CPT1, makes metabolic disturbance; however, it has toxic effect in long-term therapy. Trimetazidine or ranolazine is another example inhibiting 3-KAT of the trifunctional protein (TFP) (hydroxyacyl-CoA dehydrogenase/enoyl-CoA hydratase/3-KAT). Avocatin B, a natural inhibitor extracted from avocado, affects acute myeloid leukemia (AML) cell growth and survival via FAO inhibition. In general, as FAS has an important function in cancer cells relative to normal tissues, de novo targeting of this pathway is considered. Furthermore, taking up FAs through proteins in membrane can cause cell demand, thus targeting of this pathway seems to have the potential therapeutic effects in cancer therapy.

5-LOX

High-fat diets will result in overweight and potentially might result in cancers including breast and colon. Arachidonic acid, an essential C-20 fatty acid, is the indispensable element of dietary. Arachidonic acid generates bioactive lipid signaling molecules named eicosanoids through three major pathways such as cyclooxygenase (COX), LOX, and cytochrome P450. The effect of high level of eicosanoids has been reported in different phases of cancer such as promotion, progression, metastasis, and angiogenesis. Among the three mentioned enzymes, involvement of LOXs family in cancer has been reported both clinically and experimentally. This family even acts as a tumor microenvironment regulator. Importantly, there are two opposite activities for 15-LOX-1; promoting activity, reported in prostate cancer, and suppressing activity, reported in CRC and chronic myeloid leukemia (CML). These two edge situations have been reported in breast cancer as well. There are enough evidences showing high overexpression of 12-LOX in prostate and breast cancers. 5-LOX activity, which generates 5-hydroxyeicosatetraenoic acid (5-HETE) from arachidonic acid, was reported for the first time in 1976 in rabbit peritoneal neutrophils. 5-LOX gene containing 14 exons and 13 introns is located on chromosome 10q12.2. Generated products of 5-LOX activities are 5-hydroperoxyeicosatetraenoic acid (5-HPETE) which is then reduced to 5-HETE.
via glutathione peroxidase (GPx) and leukotriene A4 (LTA4), which then converted to leukotriene E4 (LTE4) under sequential reactions by participating enzymes such as hydrolase, synthase, G-glutamyl transferase, and bound membrane dipeptidase. Peroxidase also has a crucial effect on 5-LOX product generation. 5-LOX affects cancer growth and proliferation as its overexpression has been reported in several cancers such as breast, prostate, renal, and colorectal and even in atherosclerotic plaque. Oxidative stress and ROS have critical effect in expression and function of 5-LOX. However, catalytic activity of 5-LOX is owing to active site iron, which gets lost at the presence of oxygen. IL-4 leads to downregulation of 5-LOX in dendritic cells. Hence, 5-LOX expression is affected by different factors. The produced metabolites of 5-LOX pathway have major role in cell proliferation, viability, and chemoresistance. Epidermal growth factor (EGF) and neurotensin result in progression in prostate cancer through 5-LOX. Angiogenesis induction was observed in colon cancer by vascular endothelial growth factor (VEGF) expression via 5-HETE. In addition, 5-LOX overexpression is related to metastasis and invasion in several cancers. High levels of 5-LOX and leukotriene B4 (LTB4) have been observed in Kaposi sarcoma lesions and latent endothelial cells. VEGF overexpression occurs as a result of 5-LOX, 5-HETE, and LTA4 activation in human malignant mesothelioma in vitro. COX-2, the other principal eicosanoid with tumorigenesis effect, along with 5-LOX results in expression and release VEGF. Shunting mechanism of these two elements showed that inhibition of COX-2 makes 5-LOX overexpression but vice versa, 5-LOX inhibition has no redundancy effect in COX-2 expression. Hence, 5-LOX inhibition is more effective and can be a potential target in cancer therapy. According to Nottingham prognostic index, a tool for speculating the prognosis of the patients, elevated rates of 5-LOX-activating protein transcription have a significant correlation with poor prognosis, which explain the stimulator role of downstream metabolites of 5-LOX in the invasion and angiogenesis in cancer. A63162, a selective inhibitor for 5-LOX, limits DNA synthesis and PC3 prostate cancer cell growth. Apoptosis induction in prostate cancer cell and cell proliferating inhibition in lung cancer cell are caused by the effect of AA861, MK886, MK591, and nordihydroguaiaretic acid (NDGA) inhibitors. Apoptosis and growth limitation have been reported as the inhibitory effects of boswellic acids (BAs) on 5-LOX in brain tumor cell lines. BAs have been determined as active principles of the Boswellia serrata resin extracts, which has inhibitory effect on leukotriene biosynthesis in intact polymorphonuclear leukocytes. In vitro, BAs (belonging to the ursane type pentacyclic triterpene saponins) selectively blocked the leukotriene production without modifying the product formation by other dioxygenases. As such, a derivative of BAs, acetyl-11-keto-β-BA (AKBA), showed inhibition effect on 5-LOX product formation. Considering, pentacyclic triterpenes without the 11-keto-function did not express any 5-LOX inhibition, which directly states the role of AKBA on a selective site for pentacyclic triterpenes on the 5-LOX enzyme. In addition, the pentacyclic triterpene ring system is important for binding to the selective effector site, whereas functional groups are necessary for the 5-LOX inhibitory effect of BAs. Zileuton, as the other important 5-LOX inhibitor, is approved by United States Food and Drug Administration (US FDA) for remedying bronchial asthma and is able to reduce esophageal adenocarcinogenesis. Inhibitory effect of zileuton is caused by chelating iron from active site of 5-LOX. A79175 (ABT-175) and A85761 (ABT-761) have been introduced as two modified compounds of zileuton with more lasting effect in vivo as a result of the loss of glucuronidation rate. In addition, NDGA, Vigna furan, and caffeic acid have been introduced as the natural, specific, and effective inhibitors of 5-LOX. There are several interesting studies reporting the effect of Docebenone (AA861) to be useful in cancer therapy. The 5-LOX inhibitor with powerful effect in 7,12-dimethylbenz[a]anthracene (DMBA)-induced skin tumor causes blocking proliferation in human leukemia cell lines, diminishing metastasis, and inducing apoptosis in gastric cancer, also reducing cancer growth in esophageal and bladder cancers. BWA4C, another inhibitor for 5-LOX, increases apoptosis in lymphoma and reduces the growth and tumor size in pancreatic cancer cell lines. Meanwhile, esculetin (Esc), a natural compound 6,7-dihydroxycoumarin, has inhibitory effect on 5-LOX, 12-LOX, and LT synthesis in leukemia.

**Forkhead box O1 (FOXO1)**

The FOXOs are transcription factors, which have the critical regulatory functions in most important cellular processes and metabolism such as cell cycle, proliferation, development, differentiation, apoptosis, autophagy, and tumor suppressing. FOXO belongs to FOX family of transcription factors in which their forkhead domain has been conserved during evolution. There are four members of FOXO in vertebrates including FOXO1, FOXO3, FOXO4, and FOXO6, unlike invertebrates such as Drosophila melanogaster which has only one ortholog named dFOXO. Structure of FOXO1 or forkhead rhabdomysarcoma transcription factor (FKHR), the key member of FOXO family, has four parts such as a forkhead DNA-binding domain (FHD) in amino terminal, nuclear
localization signal (NLS), nuclear export sequence (NES), and a transactivation domain (TAD) in C-terminal. Phosphorylation, ubiquitination, acetylation, and deacetylation are posttranslational modifications in this structure affecting FOXO1 activities. Moreover, absence or presence of growth factor can regulate FOXO1. In this case, on one hand, FOXO1 activation is caused by insulin binding to its receptor which in turn activates phosphoinositide kinase (PI3K), Akt, and serum glucocorticoid-inducible kinase (PI3K-AKT-SGK); on the other hand, absence of insulin leads to involvement of FOXO1 in cell death. Transcriptional activity of FOXO is lost via its phosphorylation in some residues induced by AKT and SGK. It should be mentioned that nuclear export of FOXO1 and its phosphorylation manner is performed via insulin-like growth factor-1 (IGF-1)/Akt signaling and 14-3-3 proteins. FOXO1, which is mostly expressed in adipose tissue, acts as a tumor suppressor that its deletion, inactivation, or downregulation has been observed in several cancers. There are evidences demonstrating the roles of FOXO1 in the inhibition of proliferation, differentiation, angiogenesis, and enhancing apoptosis. Anticarcinogenesis characteristic of FOXO1 is amplified by PI3K, mitogen-activated protein kinase (MAPK), and IκB kinase (IKK) signaling pathways and stress signaling such as oxidative stress. Limited proliferation can be achieved by FOXO1 activities; for example, AQP9 overexpression in HCC restricts cell proliferation, which takes place via the inhibition of PI3K/Akt pathway and increase in FOXO1. FOXO1 suppression induce overexpression of hypoxia-inducible factor-1-α (HIF-1-α) and angiogenesis in gastric cancer, and also endothelial cell migration is limited following the overexpression of FOXO1 and FOXO3. Inhibition of Cyclin D1 and D2 by FOXO leads to cell cycle arrest. Restraining of PI3K/Akt pathway, which promotes FOXO1, induces apoptosis in pancreatic cancer in response to curcumin application. Also, apoptosis is induced by ROS-mediated FOXO1 activation. Extrinsic apoptosis pathway is activated by FOXO via expression of three ligands including Fas ligand, tumor necrosis factor (TNF)-related apoptosis inducing ligand, and TNF receptor-associated death domain. However, expression of Bim, BNP3, and Puma, belonging to Bel-2 family, induces intrinsic pathway through FOXO. It is well documented that FOXOs can inhibit glycolysis and suppress the Warburg effect via FOXO-mediated antagonism with Myc (one of the major oncogenes promoting the Warburg effect). As an example, FOXOs inhibit the expression of glycolysis genes in renal cancer cells through Myc inhibition. In addition, inhibiting FOXOs by acetylation via mTORC2 in glioblastoma leads to activation of Myc and Warburg effect upregulation. Also, it is demonstrated that glutamine synthetase expression can be regulated by FOXO3 and FOXO4 in the PI3K-AKT-FOXO pathway. Besides, FOXO activation leads to mTOR inhibition through glutamine synthetase as well as promoting autophagy. In addition, amino acids involve in regulating FOXO including inactivation of FOXO through mTORC2 and AKT activation in mammalian cells. It is worth to mention that, despite the unclear role of FOXO in lipid metabolism, it can cause downregulation of SREBP1c (sterol regulatory element binding proteins) through occupying the SREBP1c promoter. Notable point is the conflicting activity of FOXO that may be observed in some ways. In this regard, sustaining cancer stem cells especially in CML and AML has been reported, which arising from the increase in FOXO3, and also the expression of MDR1 protein by FOXO1 leads to drug resistance to doxorubicin and adriamycin.

Nevertheless, according to the functions reported for FOXO in cellular and physiological behaviors, it can be considered as a target in cancers. Paclitaxel, an anticancer drug applied for breast, ovarian, pancreatic, and other cancers, allows FOXO3a to be accumulated. FOXO3a nuclear translocation occurs by the effect of doxorubicin used as a drug in cancer therapy. Also, cisplatin and epirubicin are other drugs that can target this axis.

Conclusion

Common therapies, such as chemotherapy and hormone therapy, are widely used for cancer treatment; however, side effects of these approaches show the demand for alternative targeted routes. Targeting cancer metabolism with various conversion pathways, enzymes, and metabolites seems to be the way to proceed. Altered metabolic pathways in cancer cells drive cells to enhance proliferation, the event that rarely occurs in differentiated normal cells. Hence, targeting these statues can destroy tumor cells. Alteration in glycolysis, that is, producing lactate instead of delivery of pyruvate to TCA cycle, encourages the tumor cells to majorly rely on aerobic glycolysis. This is a huge finding in cancer cells relative to normal counterparts, although an increase in OXPHOS pathway has been reported in certain cancers. Key role of some enzymes in these pathways has opened a novel window to combat uncontrolled cell proliferation. So, the inhibitory effect of some drugs was examined in the preclinical or clinical phases and promising results have shown the right direction for more progress. However, finding and focusing on the approaches to improve more selective effects are still challenging. Especially focusing on handling immune cells according to their pro- or anti-tumor capacities makes the story more complex. It is worth mentioning that cancer cells have shown
varieties of altered metabolism pathways which provide sufficient fuel for their viability. Sieging multilateral using combinational blocking of these pathways is suggested as the more useful approach. Besides, when cancer cells cannot stand the inhibition effect of drugs and become sensitive, normal cells can overcome this situation using flexible characteristics.

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