

# [Isoenzymes-therapeutic targets in cancer](https://assignbuster.com/isoenzymes-therapeutic-targets-in-cancer/)

The technological advances that have occurred over the past decade and the increasing number of evidences that have emerged from previous studies, show a wide array of metabolic rewiring in cancer cells compared to normal cells. Many metabolic enzymes which are specific to important metabolic pathways and which are altered in cancer cells have been identified. These enzymes help in mediating the aberrant metabolic pathway of cancer cells and could serve as a promising source of novel drug targets [1, 2]. Isoforms of many of these metabolic enzymes are found to be specifically expressed in tumor cells, the current research is being refocused on interventions to specially target these isoforms of various important metabolic pathway.

### Targeting glycolytic isoenzymes

Glycolytic pathway serves as the principal energetic source for the cell. The higher dependency of cancer cells upon glycolytic metabolism for the production of ATP [3] provides a loftier motive to target glycolytic enzymes. Many isoforms of these enzymes have been found to be specifically expressed in tumor cells and are being exploited as a potential candidates to be used as drug targets. The transport of glucose across the plasma membrane is regulated by various isoforms of glucose transporters (GLUT1-14 or SLC2A1-14). GLUT1, GLUT3 and GLUT4 are found to be expressed at higher levels in cancer cells compared to normal cells [4]. GLUT3 and other transporters could be targeted by the use of specific antibodies or drugs like Phloretin or Ritonavir causing the cells to starve by blocking their nutrient uptake through these transporters.

Another important metabolic enzyme of the glycolytic pathway is hexokinase (HK), which regulates the first rate limiting step of glucose metabolism. Cancer cells have been found to be heavily dependent on hexokinases isoforms, like the hexokinase 2 (HK2) [5]. The specific expression of HK2 in adipose tissue and skeletal muscles provides an opportunity to target HK2 without having the risk of affecting other tissues. Compounds like Methyl Jasmonate isolated from plants have shown to disrupt the association between mitochondria and hexokinases (HKI & HKII) involved in regulating apoptosis [6] and have shown to be lethal to cancer cells in vitro [7].

Recent evidence in literature suggests the a key role of pyruvate kinase (PK) isoenzyme- pyruvate kinase M2 (PKM2) in mediating the Warburg effect in cancer cells [8] signifies its prospective as an enzymatic target against cancer cells. The enzyme activity of PKM2 is inhibited after its binding to proteins phosphorylated by tyrosine downstream of cellular growth signals [9]. Cell proliferation and aerobic glycolysis in tumors are greatly dependent on this ability to inhibit the activity of PKM2 enzyme. Many approaches using small molecule inhibitors of PKM2 and small hairpin RNA based inhibition of PKM2 have shown to cause cell death and slow down cell proliferation in vitro [8, 10]

Other metabolic targets from the glycolytic pathway include the Phosphofructokinase/fructose-bisphosphatase 3 (PFKFB3) isoform. PFKFB3 is shown to be important in RAS mediated tumors [11] and inhibition of PFKFB3 by small molecule inhibitors have shown to have cytostatic effect on the growth of cancer [12]. Inhibition of Lactate Dehydrogenase (LDH) isoform, like the LDHA using FX11 or oxamate have shown to induce oxidative stress and cause cell death in cancer cells [13, 14]. Targeting LDHA combined with nicotinamide phosphoribosyltransferase (NAMPT) inhibitors have shown to slow down tumor regression and thus making it a potential candidate for drug targets [15]

### Targeting TCA isoenzymes/mitochondrial Complex

Pyruvate dehydrogenase kinase (PDK) phosphorylates pyruvate dehydrogenase (PDH) and inhibits the conversion of pyruvate to acetyl-CoA, thus preventing acetyl-CoA from entering the tricarboxylic acid (TCA) cycle. Isotype PDK3 is induced by upregulation of HIF-1α under hypoxic conditions and results in cells to undergo glycolysis instead of TCA for energy production. Inhibition of PDK3 increases the susceptibility of tumor cells towards anti-cancer drugs and causes inhibition of hypoxia induced glycolysis [16]. Thus PDK3 could be used as a drug target to overcome drug resistance and improving chemotherapy.

Isoforms of isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) are found to be mutated in almost 70% of glioma’s and in 10% of acute myeloid leukemia [17, 18]. Mutation in IDH1 and IDH2 results overexpression of both of these enzymes and production of 2-hydroxyglutarate (2-HG) which competitively inhibit α-ketoglutarate dependent dioxygenase enzymes. Association between high levels of 2-HG and tumorigenicity is yet to be established but interestingly the levels of several TCA metabolites remain unaltered suggesting an alternate pathway which could be acting in normalizing the metabolite levels in cells with IDH1 mutations.

### Targeting Isoenzymes of Pentose Phosphate Pathway (PPP)

Cancer cells are in a constant demand for more amounts of purines and pyrimidines to maintain their highly proliferative nature. The key enzyme for the ox-PPP, G6PDH, enzyme is over expressed in certain types of cancers and it has shown to transform fibroblast and help in tumor cell proliferation [19]. On the other hand, TKTL1 (an isoform of TKT) is found to be over expressed in many forms of cancer. [20, 21]. It has been hypothesized that overexpression of TKTL1 could increase the concentration of glyceraldehyde-3-phosphate (G-3-P) and help in mediating the Warburg effect in cancer cells [21, 22]. Combinatorial approach of targeting G6PDH and TKTL1 can help overcoming drug resistance and may cause cell death [23]

### Targeting Isoenzymes of glutamine metabolism

The discovery of utilization of glutamine as a carbon source for TCA cycle [24] in cancer cells strived the researchers to consider enzymes of glutamine metabolism as potential therapeutic target. Glutaminase (GLS) and glutamate dehydrogenase (GDH) play a key role in catalyzing the glutamine metabolism. GLS exists as GLS1 and GLS2, the kidney and liver isoforms respectively. 6-diazo-5-oxo-L-norleucine (DON) or bis-2-(5-phenylacetamido-1, 2, 4-thiadiazol-2-yl)ethyl sulphide BPTES mediated inhibition of GLS or siRNA induced silencing of GLS and GDH have shown to inhibit the activation of mTORC1 [25]. Thus a combinatorial targeting of GLS and GDH along with chemotherapy may prove to be more efficacious in treatment of cancers.

Many important metabolic targets from various other metabolic pathways have been identified which can be potential therapeutic target against cancer. But one of the major challenges towards targeting any of these metabolites is the lack of clear understanding of how the metabolic profile of a cancer cell varies from a normal proliferating cell and the potential toxicity risk associated with targeting metabolism. A better understanding of how the metabolism differs in a specific type of cancer beyond just the analysis of expression levels of various metabolites, may help us predict and identify better targets without having the risk of affecting normal cells. Lack of a proper model depicting the complete human metabolism makes selecting the best possible target combinations difficult. Thus a more efforts need to be made in developing new methods to study tumor metabolism and have a better understanding of pathway biochemistry in cancer cells.