Targeting cancer metabolism – aiming at a tumour's sweet-spot

Neil P. Jones[1] and Almut Schulze[2]

[1] Cancer Research Technology, Wolfson Institute of Biomedical Research, University College London, Gower Street, London WC1E 6BT, UK
[2] Cancer Research UK London Research Institute, Lincoln's Inn Fields Laboratories, 44 Lincoln's Inn Fields, London WC2A 3LY, UK

Targeting cancer metabolism has emerged as a hot topic for drug discovery. Most cancers have a high demand for metabolic inputs (i.e. glucose/glutamine), which aid proliferation and survival. Interest in targeting cancer metabolism has been renewed in recent years with the discovery that many cancer-related (e.g. oncogenic and tumour suppressor) pathways have a profound effect on metabolism and that many tumours become dependent on specific metabolic processes. Considering the recent increase in our understanding of cancer metabolism and the increasing knowledge of the enzymes and pathways involved, the question arises: could metabolism be cancer's Achilles heel?

During recent years, interest into the possible therapeutic benefit of targeting metabolic pathways in cancer has increased dramatically with academic and pharmaceutical groups actively pursuing this aspect of tumour physiology. Therefore, what has fuelled this revived interest in targeting cancer metabolism and what are the major advances and potential challenges faced in the race to develop new therapeutics in this area? This review will attempt to answer these questions by summarising recent developments in this field. We aim to illustrate why we, and others, believe that targeting metabolism in cancer presents such a promising therapeutic rationale.

Introduction

It has been known for over half a century that tumours exhibit an increased demand for nutrients to fuel their rapid proliferation. In the 1920s, Otto Warburg showed that tumour slices displayed increased rates of glucose uptake compared with normal tissues and that, even in the presence of oxygen, tumours metabolised glucose via oxygen-independent aerobic glycolysis rather than via the more efficient but oxygen-dependent process of oxidative phosphorylation [1–3]. This effect is known as the Warburg effect and is often considered to be the foundation for much of the research into cancer metabolism.

Processing of glucose via glycolysis only yields two ATP molecules (the main carrier of cellular energy), whereas processing via oxidative phosphorylation can yield up to 36 molecules of ATP. This suggests that tumour metabolism of glucose is energetically wasteful [4,5]. One key issue is to understand why tumour cells switch to this energetically less favourable process and how this switch is controlled in cancer cells. Considering the complex network of metabolic pathways, it becomes clear that glucose supplies many key biosynthetic intermediates that are required for the synthesis of proteins, lipids, nucleic acids and complex sugars via pathways that branch off the core glycolytic cascade (Fig. 1). The demand for these intermediates to fuel the growth and proliferation of tumour cells could explain why tumours require such a large intake of glucose.

It has also been observed that tumours have a high rate of uptake and use of glutamine. This amino acid is processed by the glutaminolysis pathway and supplies biosynthetic intermediates linked to amino acid and lipid synthesis. Furthermore, glutaminolysis can also contribute to the production of reducing equivalents (in the form of NADPH) to combat oxidative stress [6,7]. One possible theory is that, by supplementing their metabolism with glutamine, tumours could potentially avoid producing excess levels of ATP and avoid negative feedback regulation

Corresponding author:. Jones, N.P. (njones@cancertechnology.com)

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2011.12.017

GLOSSARY

ACLY ATP citrate lyase
AKT v-akt murine thymoma viral oncogene
AML acute myeloid leukemia
AMPK AMP activated protein kinase
DCA dichloroacetate
DHEA dehydroepiandrosterone
FASN fatty acid synthase
FH fumarate hydratase
G6PDH glucose-6-phospahe dehydrogenase
GLS1 glutaminase
GLUT glucose transporter
HIF hypoxia inducible factor
HK2 hexokinase-2
HSP70 heat shock 70kD protein
IDH isocitrate dehydrogenase
LDHa lactate dehydrogenase-A
LKB1 liver kinase B1
MAGL monoglyceride lipase
MCT monocarboxylic acid transporter
mIDH mutant isocitrate dehydrogenase
mTOR mechanistic target of rapamycin
Myc v-myc myelocytomatosis viral oncogne homolog
NADH nicotinamide adenine dinucleotide
NADPH nicotinamide adenine dinucleotide phosphate
NAMPT nicotinamide phosphoribosyltransferase
p53 tumour protein p53
PDH pyruvate dehydrogenase
PDK1 pyruvate dehydrogenase kinase isoenzyme 1
PFK1 6-phosphofructose-1-kinase
PFK2 6-phospho-2-kinase/fructose-2,6-bisphosphatase
PHD HIF prolyl 4-hydroxylase
PHGDH 3-phosphoglycerate dehydrogenase
PI3K phosphoinositide 3-kinase
PKM2 pyruvate kinase muscle-2
PPP pentose phosphate pathway
PTEN phosphatase and tensin homolog
RAS rat sarcoma viral homolog
ROS reactive oxygen species
SDH succinate dehydrogenase
SLC5A1 solute carrier family 1 (neutral amino acid transporter) member 5
SREBP sterol regulatory element binding protein
TIGAR TP53 induced glycolysis and apoptosis regulator
TCA tricarboxylic acid
TKT transketolase
TKTL1 transketolase like-1
VHL von Hippel-Landau tumour suppresspr

on some metabolism pathways (such as glycolysis) that are inhibited by high ATP concentrations. In this way, cancer cells can maintain the high flux rate of glucose and glutamine in the various biosynthetic pathways shown in Fig. 1.

Oncogenes and cancer metabolism

Despite evidence concluding that many tumours show increased uptake and use of glucose and glutamine, progress towards harnessing the potential therapeutic use of these observations has been relatively slow compared with areas of cancer research aimed at targeting oncogenic signalling pathways. However, increased understanding of the complex networks of oncogenic signalling pathways has revealed that altered cellular metabolism could be one of the major routes by which oncogenes promote tumour formation and progression (Fig. 1). These adaptations serve to increase the metabolic flux into multiple pathways that not only supply cellular energy (i.e. ATP) but also provide essential building blocks for macromolecule synthesis (i.e. nucleotides, lipids, proteins and complex sugars) as well as the reducing power for biosynthetic processes and redox regulation (NADPH). The complex rewiring of cellular metabolism not only fuels cell growth and proliferation but also supports cell survival under the unfavourable conditions encountered within the tumour microenvironment [2,5]. Some of the main oncogenic signalling pathways and their metabolic targets are briefly discussed below, although this is not an exhaustive treatment of the many potential links between oncogenes and metabolism that are currently under investigation.

The gene coding for the oncogenic transcription factor c-myc is found to be amplified in many tumours [8]. Myc has been shown to enhance the expression of the glutamine transporter ASCT2 (SLC5A1) directly and to increase the expression of glutaminase (GLS1) indirectly via reduction of miR23a/b, an inhibitor of GLS1 expression [9–11]. Myc also upregulates expression of pyruvate kinase (PK)M2, the isoform that is believed to be the predominant PK in cancer [12,13]. PKM2 activity is also regulated by phosphorylation via oncogenic signalling from growth factor receptors [14]. This phosphorylation switches PKM2 to a less active form, thereby slowing glycolysis and allowing the flux of glycolytic intermediates into biosynthetic pathways. Myc also regulates expression of other metabolic genes including the glucose transporter GLUT1 [15], hexokinase-2 (HK2; which retains glucose in cells by phosphorylating it to glucose-6-phosphate) [16,17] and lactate dehydrogenase (LDHA; which converts pyruvate to lactate) [16,18–20].

The PI3K/AKT pathway is one of the most commonly altered pathways in cancer [21]. It can be activated by loss or inactivating mutations in the tumour suppressor gene PTEN, activating mutations in the PI3K complex, aberrant signalling from upstream kinases and through overexpression of its components [21]. Once activated, the PI3K pathway provides strong growth- and survival-promoting signals. AKT has been shown to be a key driver of the glycolytic phenotype through the upregulation of glucose transporter expression [22,23], induction of glycolytic enzymatic activity (i.e. phosphorylation of hexokinase-2) [24,25] and the activation of the mammalian target of rapamycin (mTOR) and hypoxia inducible factor 1 (HIF1) pathways [26–28]. AKT also stimulates de novo synthesis of fatty acids by activating the SREBP transcription factor [29].

HIF1α is one of the major transcription factors responsible for gene expression changes under low oxygen conditions [14,30]. HIF1α expression can also be enhanced by oncogenic signalling pathways including Myc, Ras and PI3K/AKT [17,31,32]. Under normoxia, HIF1α is downregulated by the von Hippel-Lindau tumour suppressor, an E3 ubiquitin ligase that is absent in renal cell carcinomas [33]. HIF1α has been shown to increase the expression of many metabolic enzymes including PFKFB3 (an isoform of the glycolytic enzyme PFK2) [34,35], pyruvate dehydrogenase kinase [16,36,37], LDHA [31,38], MCT4 (a lactate transporter) [39] and GLUT1 [40].

Some of these links could still be controversial or currently only seen in rare tumour types. However, germline mutations in rare

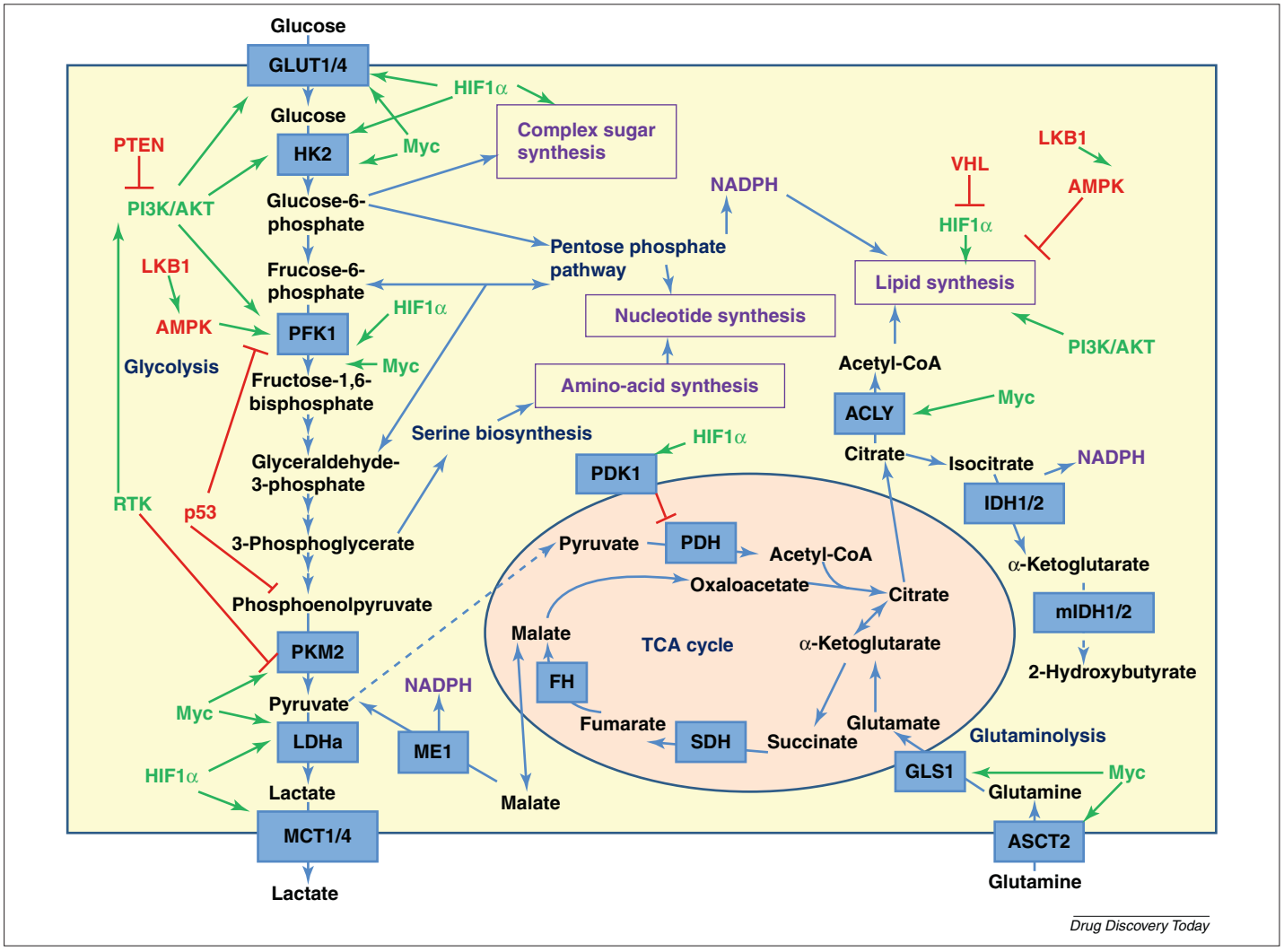


FIGURE 1

Schematic representation of the regulation of cancer metabolism pathways. Metabolic enzymes are regulated by signalling pathways involving oncogenes and tumour suppressors. Complex regulatory mechanisms, key pathway interactions and enzymes are shown along with key metabolic endpoints (shown in purple) necessary for proliferation and survival (biosynthetic intermediates and NADPH). Key oncogenic pathways are shown in green and key tumour suppressor pathways are shown in red. Mutant IDH (mIDH) pathway is listed but is only functional in cancers containing mIDH.

hereditary cancers are often indicative of a more common inactivation of a specific gene or pathway in sporadic cancers (e.g. retinoblastoma protein). With the renewed interest in cancer metabolism it is hoped this that ongoing research will further unravel the complex interplay between cancer drivers and metabolism.

Some of the most striking advances in our understanding about how cancer cells highjack metabolic pathways relate to how tumour cells adapt their metabolism to shift the flux of metabolites into pathways branching from glycolysis to yield key biosynthetic intermediates, fuelling tumour progression. Several more-recent studies have highlighted the importance of other metabolic pathways, including the TCA cycle, pentose-phosphate pathway and serine biosynthesis in certain cancer settings.

Glycolysis and cancer

Glycolysis is the process by which glucose enters the cells and is processed, via a cascade of reactions, to pyruvate which can then either enter the TCA cycle or be converted to lactate. Many proteins within the glycolytic pathway have been implicated in cancer based on overexpression, knockdown or inhibition studies. As discussed above, glycolytic enzymes are also regulated by oncogenic signalling pathways [2,28] (Fig. 1). Glycolytic targets associated with cancer include the glucose transporter proteins [41,42], hexokinase-2 [43], PFK2 isoforms [34,35] and the pyruvate kinase isoform PKM2 [44]. PKM2 is proposed to be the major PK isoform in tumours and to exist in two distinct states; a highly active tetrameric form and a low activity dimeric form [45,46]. Phosphorylation by oncogenic upstream kinases (e.g. fibroblast growth-factor receptor) promotes formation of the low activity PKM2 form and acts to slow glycolytic flux [47–49]. This has been proposed as one mechanism by which tumour cells can regulate glycolysis enabling glycolytic intermediates to be processed via alternative pathways.

TCA cycle and cancer

The TCA cycle is often seen as the link between glycolysis and oxidative phosphorylation, and in normal differentiated cells the majority of pyruvate is converted to acetyl-CoA which enters the

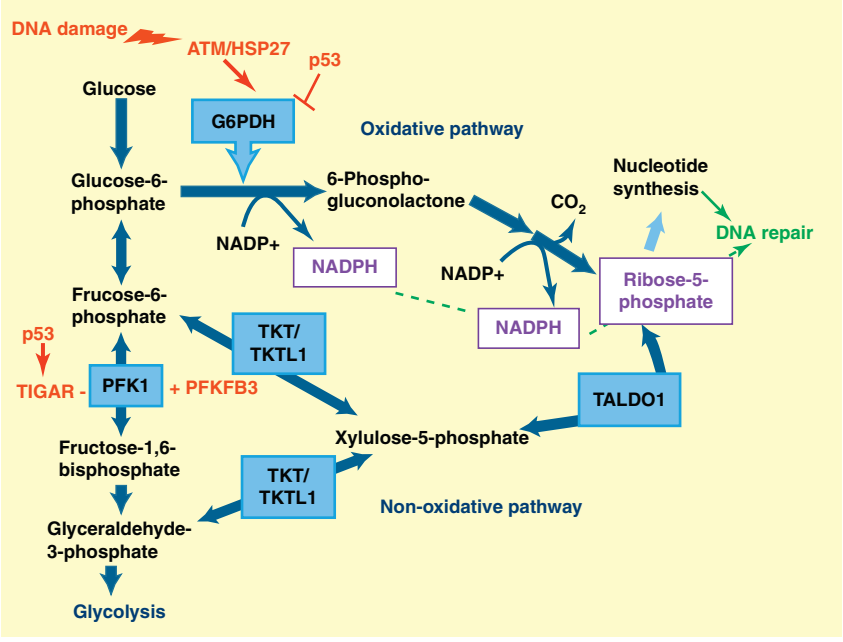
TCA cycle for processing to yield ATP (via the electron transport chain). Processing via components of the TCA cycle can also supply biosynthetic intermediates used in lipid synthesis and redox equivalents that could help cancer survival and proliferation [6,50] (Fig. 1). The first cancer-related mutations in metabolic pathways have been identified with the discovery of mutated versions of three TCA cycle proteins.

Two enzymes from the TCA cycle, succinate dehydrogenase and fumarate hydratase (FH) have been discovered to have a loss of function mutation linked to tumourigenesis and have therefore been tentatively described as tumour suppressor genes [51,52]. Heterozygous germline mutations in succinate dehydrogenase (SDH) subunits have been found in hereditary paragangliomas and in phaeochromocytomas, a rare hereditary cancer predisposition syndrome [53,54]. Carriers of SDHB (succinate dehydrogenase complex subunit B) mutations have also been reported to be more susceptible to renal cell cancers [55,56]. SDH catalyses the oxidation of succinate to fumarate. SDH mutant tumours have increased levels of succinate, are more vascularised and are associated with a hypoxic signature [51,57]. Germline mutations in FH predispose to inherited leiomyomas (generally benign), the hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome, and to certain renal carcinomas [58,59]. There are some reports of linking FH mutations to tumourigenesis in bladder, testicular and breast cancers [52,54]. FH catalyses the conversion of fumarate to malate and loss of function mutations of FH lead to increased levels of fumarate and succinate. FH-mutant tumours are also associated with a hypoxic signature and are often highly vascularised [51,52]. One mechanism by which FH and SDH mutations are believed to promote tumourigenesis is via the upregulation of HIF1α signalling. HIF1α is usually targeted for degradation via hydroxylation by the HIF prolyl 4-hydroxylases (PHDs). Increased levels of succinate or fumarate inhibit PHD activity and lead to HIF1α stabilisation resulting in pseudohypoxia, a condition in which tumour-promoting hypoxic signalling is maintained even in normoxic conditions [37,57,60].

Another component of the TCA cycle, isocitrate dehydrogenase (IDH), which catalyses the conversion of isocitrate to α-ketoglutarate (α-KG), has also recently been found to be mutated in certain cancers [61–63]. Heterozygous mutations in IDH2 have been found in ~16% of glioma patients [64], whereas IDH1 or IDH2 mutations are found in ~20% of acute myeloid leukaemia (AML) patients [61,65]. A striking discovery was the fact that the mutant IDH enzyme acquires a neomorphic catalytic activity that enables the NADPH-dependent reduction of α-KG to 2-hydroxyglutarate (2HG), an as yet poorly characterised metabolite, which was found to be significantly accumulated in the blood of AML patients and in glioma cells [66,67]. The function of 2HG, which has been termed an oncometabolite, is so far unclear although it could act by inhibiting an α-KG-dependent protein. It has also been suggested that it could have effects on the tumour microenvironment because it is excreted by malignant cells [63].

Pentose phosphate pathway and cancer

One glucose-dependent pathway that provides key biosynthetic intermediates is the pentose phosphate pathway (PPP), which consists of a non-reversible oxidative branch and reversible non-oxidative branch [25] (Fig. 2). The oxidative branch of the PPP yields ribose-5-phosphate, which is used in nucleotide synthesis, and NADPH, which is used in lipid synthesis and in combating oxidative



Drug Discovery Today

FIGURE 2

Schematic representation of key components of the pentose phosphate pathway (PPP). Key enzymes are shown in blue boxes and key intermediates in purple text/box outline. DNA damage can activate ATM which in turn activates G6PDH to upregulate nucleotide synthesis for DNA repair and NAPDH to combat reactive oxygen species. PPP is also regulated by the tumour suppressor p53. The PPP can function as two separate branches (oxidative and non-oxidative) or be coupled into a recycling pathway – the pentose phosphate shunt – for maximum NADPH production.

stress. The PPP is initiated by the conversion of the glycolytic intermediate glucose-6-phosphate to 6-phosphogluconolactone through the action of the enzyme glucose 6-phosphate dehydrogenase (G6PDH). The reversible non-oxidative branch of this pathway can either convert the glycolytic intermediates fructose-6-phosphosphate and glyceraldehyde-3-phosphate to ribose-5-phosphate without NADPH generation or can convert ribose-5-phosphate to the glycolytic intermediate glyceraldhyde-3-phosphate which can be converted back to glucose-6-phosphate and re-enter the oxidative branch. By coupling the two branches of the PPP one molecule of glucose can be used to generate six molecules of the essential reducing agent NAPDH in a highly efficient process [5,25].

Given the importance of ribose-5-phospate for nucleotide synthesis and NAPDH for biosynthetic reactions and redox balance, inhibiting components of the PPP could be an attractive way to target rapidly growing tumour cells. It has been shown that some cancer cell lines exhibit increased flux through the pentose phosphate pathway and that G6PDH is overexpressed in certain tumour types including gastric, colorectal [68] and kidney [69]. Recently, G6PDH has also been shown to be negatively regulated by wild-type, but not mutant, p53. Cancer cell lines expressing mutant p53 showed increased PPP flux, enhanced G6PDH activity and increased sensitivity to depletion of G6PDH expression by RNA interference (RNAi) or inhibition of this enzyme with the specific inhibitor DHEA [70]. Possible links between G6PDH and DNA repair have also been reported with the DNA-damage-sensing kinase ATM, shown to activate G6PDH via HSP70 [71]. Given that many chemotherapies act to induce DNA damage and also generate reactive oxygen species, inhibition of G6PDH would reduce the ability of cancer cells to counteract this damage and could represent an interesting strategy to enhance the effectiveness of these agents. A deficiency in G6PDH is found in ~400 million people worldwide, with patients suffering mild anaemia but no other serious health issues. Studies on cancer prevalence amongst this group have been inconclusive to date, although studies in the 1990s suggest no change in cancer occurrence or mortality rates associated with G6PDH deficiency [72].

Within the non-oxidative branch of the PPP, substantial interest has focused on the role of transketolase proteins. It has been reported the transketolase-like protein 1 (TKTL1) is the predominant transketolase in certain tumour types and inhibition of TKTL1 by RNAi impairs cancer cell growth [73–75]. Recently, the existence of a cancer-specific transketolase has been questioned in studies investigating TKTL1 mRNA levels that also tested several antibodies previously used for disease linkage studies [76–78]. However, the general transketolase inhibitor oxythiamine has also been reported to inhibit cancer cell growth with these effects being magnified if the G6PDH inhibitor DHEA is added [69]. Although the data support the role of the PPP at least in some types of cancer, the results also underline the importance of robust validation of potential cancer metabolism targets.

Another interesting link between the PPP and cancer is the discovery of the p53-regulated protein TIGAR [79,80]. TIGAR possesses a fructose 2,6-bisphosphatase domain that is also found in the glycolytic regulator PFK2. TIGAR negatively regulates PFK1 activity thereby slowing the glycolytic rate and promoting entry of glucose-6-phosphate into the PPP [79,81]. Although the positive regulation of TIGAR by p53 suggests that this could be an anti-tumourigenic function, TIGAR is also reported to be expressed in a p53-independent manner and is overexpressed in some tumours. It is therefore conceivable that TIGAR could have pro-tumourigenic roles at least under conditions where flux through the PPP is beneficial for tumour growth [81,82]. It is clear that understanding the balance between glycolytic flux and metabolite entry into the PPP in different tumour settings will be crucial in developing targeted strategies against this pathway.

Serine biosynthesis and cancer

Another branch diverting from glycolysis recently implicated in cancer is the serine biosynthesis pathway which converts the glycolytic intermediate 3-phosphoglycerate into serine (Fig. 3). Serine is an amino acid and an important neurotransmitter but can also provide fuel for the synthesis of other amino acids and nucleotides. The serine biosynthesis pathway also provides another key metabolic intermediate, α-KG, from glutamate breakdown via the action of phosphoserine aminotransferase (PSAT1). This pathway couples glycolysis (via 3-phosphoglycerate) with

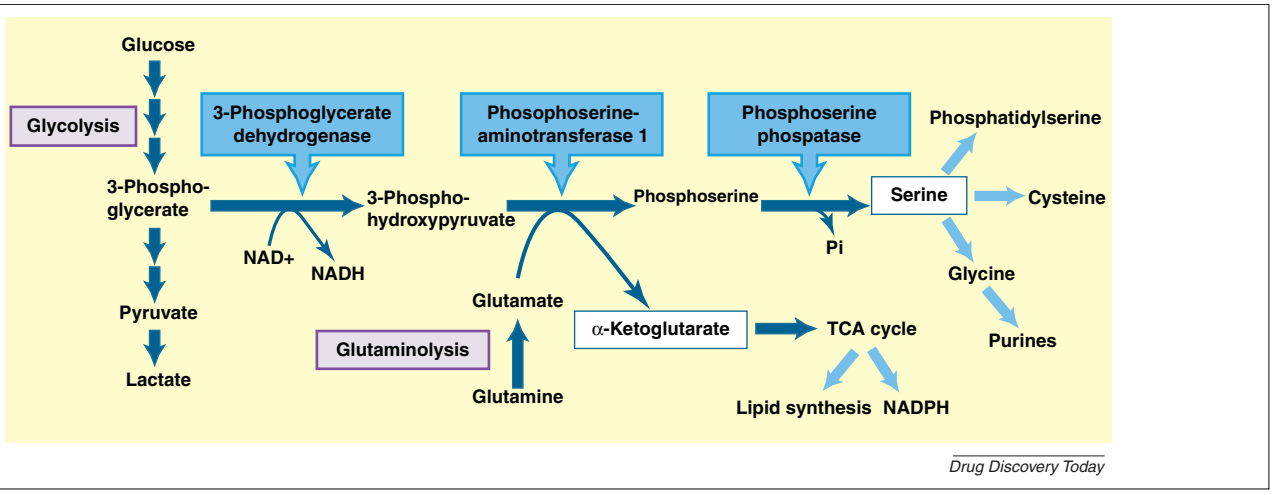


FIGURE 3

Schematic representation of the serine biosynthesis pathway. Synthesis of serine involves integration of metabolites from glycolysis and glutaminolysis pathways and generates α-ketoglutarate, a key biosynthetic intermediate, and serine. Serine has many essential uses in the cell including amino acid, phospholipid and nucleotide synthesis.

glutaminolysis (via glutamate), thereby linking two metabolic pathways known to be activated in many cancers.

All three components of the serine biosynthesis pathway have been found to be overexpressed in cancer. However, recent attention has focused mainly on the initiating enzyme 3-phosphoglycerate dehydrogenase (PHGDH) [83–86]. The PHGDH gene lies within chromosome region 1p12, a region showing copy number gain in ~16% of cancers [84,85]. Further analysis revealed that the PHGDH gene is amplified in 16% of melanomas and 6% of primary breast tumours [84]. PHGDH expression is elevated in ~70% of estrogen receptor-negative breast tumours and is associated with poor levels of five-year survival [85]. Studies showed that depletion of PHGDH expression using short-hairpin RNA (shRNA) reduces cell growth in ER-negative breast cancer or melanoma cells with amplified PHGDH [84,85]. Overexpression of PHGDH in MCF10a human breast epithelial cells is sufficient to cause morphological changes reminiscent of oncogenic transformation [84]. In vivo studies suggest that PHGDH knockdown in sensitive cell lines reduces cell growth by up to 60% [85]. Flux analysis showed that ~9% of glucose is shuttled into the PHGDH pathway in PHGDH-dependent cell lines compared with only 1% of glucose in non-sensitive cell lines. Furthermore, in cell lines with high PHGDH expression, the serine synthesis pathway is responsible for up to 50% of the net conversion of glutamate to α-KG. These studies elegantly show the importance of the serine biosynthesis pathway in regulating glycolysis and glutaminolysis in cancer [84,85].

Interestingly, clinical manifestations of deficiencies in PHGDH, PSAT1 and PSPH are known in patients presenting with neurological disorders linked to serine neuromodulator roles [87–89]. These disorders can be alleviated to some extent by treatment with exogenous serine [90]. Because these mutations are rare, no data on cancer prevalence have been available. The possibility of efficient patient stratification suggests that targeting the serine biosynthesis pathway could be of significant therapeutic value in melanoma and breast cancers with PHGDH amplifications.

Current molecular targets

The renewed interest in the potential anticancer benefit of targeting metabolism has led to numerous inhibitors being developed against key molecular targets within metabolic pathways. However, none of these potential agents has so far advanced beyond clinical trials and most are still in preclinical development or proof-of-concept stages [91–93]. A list of some of these potential agents, their targets and some of the biological data supporting them is summarised in Table 1. This illustrates the wide spectrum of metabolic pathways currently under investigation as potential anticancer intervention points including glycolysis [91] (HK-2 [39], PKM2 [13,30,44,94–97], PFKFB3 [98], LDHA [93,99], MCT [100]), TCA cycle and associated pathways {PDK1 [101], mIDH, aspartate aminotransferase (AAT) [102]}, glutaminolysis (GLS [99]), PPP (G6PDH [39], TKT/TKTL1 [73,103]), lipid synthesis (FASN [104,105], ACLY [106], MAGL [107,108]) and co-factor synthesis [17,91,93,97,111] (i.e. NAMPT [109,110]).

One of the most advanced clinical agents is 2-deoxyglucose (2DG), an analogue of glucose, which is taken up by cells using the same transporters as glucose and is phosphorylated by hexokinase to non-hydrolysable 2-deoxyglucose-phosphate [39,92]. 2DG is believed to block hexokinase-induced phosphorylation of glucose as well as the association of hexokinase with mitochondria. 2DG has been shown to inhibit glycolysis, *N*-glycosylation and to induce endoplasmic reticulum stress via accumulation of misfolded proteins. However, because the inhibition of hexokinase by 2DG is reversible, its effectiveness is reduced by high cellular glucose levels [92]. It is also interesting to note that fluorescently labelled 2DG is used in medical imaging for the visualisation of glucose uptake in tumours to aid tumour identification. In glioblastoma multiforme patients, Phase I/II trials of 2DG in combination with radiation suggested oral dosing of 2DG was tolerated without any acute toxicity. Patients showed modest survival benefits and improved quality of life [112,113]. However, progress beyond this has yet to be reported and although other trials are planned or underway results from these have not yet been forthcoming [114].

Many cancers exhibit a shift towards increased glycolysis and the processing of pyruvate to lactate suggesting that the flux through the TCA cycle is reduced. One therapeutic strategy is to try to reactivate the TCA cycle in cancer cells by inhibiting negative regulators of oxidative phosphorylation (i.e. inhibition of PDK1). Dichloroacetate (DCA) has been reported to restore pyruvate entry into the mitochondrial TCA cycle in cancer cells in vivo, thereby causing apoptosis and tumour shrinkage [115,116]. Initial small-scale clinical trials suggest that DCA is well tolerated, causes some of the expected metabolic changes and induces tumour shrinkage in three out of five tested glioblastoma patients [116]. However, more work is needed to ensure full understanding of the exact mechanism of action of this compound. Larger clinical trials will be required to investigate if this agent really has promise in targeting cancer metabolism and delivers genuine benefit to patients. Other agents that target PDK have been previously developed as possible treatments for metabolic disorders; therefore, it will be interesting to see if these also have any anticancer roles [101,117,118].

Another possible therapeutic strategy is to try to inhibit the removal of lactate from cancer cells and thereby acidify the intracellular environment killing the tumour cell [119,120]. There is also evidence for metabolic heterogeneity within a single tumour. It has been shown that cells within oxygenated regions of a tumour rely on lactate that is secreted by hypoxic tumour cells as metabolic fuel. Disrupting lactate transport could starve these cells and enhance tumour killing [121]. Lactate is usually actively removed from the cell by members of the monocarboxylate transporter (MCT) family and MCT proteins, notably MCT1 and MCT4, have been found to be overexpressed in several cancer types [100,122–126]. MCT1 inhibitors have been shown to affect cancer cell growth and invasion [100,121,127,128] and in vivo tumour growth [121]. An MCT1 inhibitor developed by AstraZeneca is about to enter Phase I clinical trials.

Metabolic disorders and cancer

Links between cancer and metabolic disorders such as diabetes have long been suspected. Metabolic disorders such as diabetes cause alterations in glucose metabolism and could be associated with increased cancer risk. This has led to much focus on studying the regulation of signalling and metabolic pathways under these disease conditions and offers the potential to use existing knowledge about

TABLE 1

Summary table of potential drugs/compounds targeting cancer metabolism. Examples listed are of published compounds or pipeline candidates that are designed to target cancer metabolism pathways and, where possible, details of molecular target, biological rationale/validation and status are given

Drug/compound (Source/reference)	Molecular or pathway target	Biological validation	Current status (if known)
Phloretin	GLUT1/4	Blocks glucose uptake	Early development
2-Deoxyglucose	Hexokinase (glycolysis)	Blocks glycolytic flux	Reported in clinical trials
3-Bromopyruvate	Hexokinase (+ other glycolytic targets?)	Blocks glycolytic flux	Preclinical development
Lonidamine	Hexokinase	Blocks glycolytic flux	Clinical trials ongoing
3PO [+ derivatives] (Advanced Cancer Therapeutics)	Phosphofructose kinase 2 [PFKFB3]	Blocks positive regulation of PFK1 and glycolysis	Preclinical development
Cap-232/TLN-232 (Thallion Pharmaceuticals)	Pyruvate kinase-M2	Blocks pyruvate formation via PK route	Trial suspended owing to licensing dispute
(Agios Pharmaceuticals)	Pyruvate kinase-M2	Blocks pyruvate formation via PK route	Preclinical
(Agios Pharmaceuticals)	Pyruvate kinase-M2 activators	Promotes glycolytic flux reducing synthesis of biosynthetic intermediates	Preclinical
Dichloroacetate	Pyruvate dehydrogenase kinase (+ metabolic targets?)	Activates PDH and promotes oxidative phosphorylation	Basic Phase I trial completed, Phase II studies proposed
FX11 (University of New Mexico/ The John Hopkins University)	Lactate dehydrogenase	Blocks metabolic flux pathways	Early development
Oxamate	Lactate dehydrogenase and aspartate aminotransferase	Blocks metabolic flux pathways	Early development
Amino oxyacetate	Aspartate aminotransferase	Blocks metabolic flux pathways	Early development
AZD-3965 (AstraZeneca)	MCT1	Blocks lactate secretion	Phase I/II trials planned with CR:UK
5-Dehydroepiandrosterone [DHEA]	Glucose-6-phosphate dehydrogenase + multiple non-metabolism targets	Blocks oxidative pentose phosphate pathway (PPP)	Early development
Oxythiamine	Transketolase	Blocks non-oxidative PPP	Early development
(Tarvagenix)	Transketolase-like 1 (TKTL1)	Could block non-oxidative PPP in cancer	Early development (no published data)
6-Diazo-5-oxo-L-norleucine	Glutaminase (glutaminolysis)	Blocks glutamine conversion to glutamate	Toxicity issue Early development
968 (Cornell University)	Glutaminase	Blocks glutamine conversion to glutamate	Early development
BPTES	Glutaminase	Blocks glutamine conversion to glutamate	Early development
GSK837149A (GSK)	Fatty acid synthase	Blocks fatty acid synthesis	Preclinical
Orlistat (Roche)	Fatty acid synthase	Blocks fatty acid synthesis	Preclinical
C75	Fatty acid synthase	Blocks fatty acid synthesis	Early development
SB-204990 (GSK)	ATP citrate ligase	Blocks fatty acid synthesis	Preclinical
(Agios Pharmaceuticals)	Mutant IDH1/2	Blocks alternative catalytic function of mIDH	Preclinical
CPI-613 (Cornerstone Pharmaceutical)	Pyruvate dehydrogenase complex/ Pyruvate dehydrogenase kinase	Mitochondrial energy metabolism	Phase I/II trials ongoing
Metformin	Energy sensing pathways (AMPK) and other targets	Blocks lipid and protein synthesis and glycolytic regulation	Used in diabetes, clinical trials in cancer ongoing
MPC-9528 (Myrexis)	Nicotinamide phosphoribosyltransferase	Blocks NAD production and reduces glycolysis	Preclinical

treatment strategies or agents used to treat metabolic disorders as potential anticancer therapies [129,130].

One striking example is the antidiabetic drug metformin, which is used in the treatment of diabetes and currently taken by 100 million people worldwide. Analysis of cancer rates amongst diabetic patients showed those prescribed metformin had a reduced risk of developing cancer compared with patients not taking this drug [131–133]. The data suggest that metformin could inhibit the tumour-initiating process. The exact molecular target of metformin is yet unknown and it is probable that it affects multiple metabolic and non-metabolic processes. One target that is modulated by metformin is the energy-sensing kinase AMPK [130]. This kinase is found to be activated by metformin resulting in inhibition of lipid and protein synthesis, rapid glycolysis and potentially increased oxidative phosphorylation. These events could serve to reduce the availability of biosynthetic intermediates and cofactors required for the growth and survival of cancer cells [129,130]. Intriguingly, one of the cellular activators of AMPK is LKB1, which is itself a tumour suppressor gene absent in some cancers. Studies are underway to understand the roles of the LKB1/AMPK pathway in tumour initiation and progression [134,135]. Given that metformin is an FDA-approved drug, clinical trials are also ongoing to investigate the effects of metformin on established tumours.

Future perspectives

The key challenge in targeting cancer metabolism will be understanding the complex nature of metabolic networks and how different cancers adapt these processes to fulfil their metabolic requirements. Only a detailed understanding will enable the identification of the targets that can be of therapeutic benefit. Understanding how oncogenes control metabolism will be essential in the development of stratified treatments against cancer metabolism targets. It will also be important to understand potential redundancies or by-pass mechanisms within complex metabolic processes to predict whether it might be necessary to block multiple points within the network. The potential of using novel agents targeting metabolic enzymes in combination with conventional or existing therapies could offer increased therapeutic benefits and reduced risks of developing resistance. Many current chemotherapies increase cellular ROS levels, damage DNA or impact other metabolic processes. It is probable that blocking the biosynthetic supply routes used by cancer cells could act synergistically to enhance the therapeutic effect of these drugs. However, targeting metabolic enzymes also offers novel challenges within the drug discovery process because metabolic targets can be structurally more complex than protein kinases, which are the main target class for conventional targeted therapies. Alternative assay formats and novel screening and chemical strategies will need to be considered.

Many of these tools are already in place in industry from either established oncology work or from drug discovery efforts in metabolic disorders. Transfer of this expertise to the cancer metabolism area will assist in drug development of anticancer metabolism agents. Many pharmaceutical companies are also looking to academia to assist with this process. Academic laboratories have been the driving force behind many of the recent developments. Academic groups are also crucial for the ongoing cancer metabolism work within the industry. For example, Agios Pharmaceuticals and Cornerstone Pharmaceuticals were both founded on the basis of the work of academic experts in cancer metabolism and both companies still actively collaborate with academic groups to progress targets of interest. Advanced Cancer Therapeutics also works closely with academic groups to pursue their cancer metabolism interest. AstraZeneca and Cancer Research Technology (CRT) have entered into a three-year alliance to explore metabolism targets in cancer linked to CRUK-funded academic research. CRUK, CRT and AstraZeneca are also in partnership to progress a clinical trial using AstraZeneca's inhibitor of the lactate transporter MCT1. It is through these academic and commercial partnerships that biological knowledge and drug discovery expertise can be brought together to tackle the complex field of cancer metabolism. It will be interesting to follow how the revived research and drug discovery efforts in cancer metabolism will progress over the next few years to lead to new therapeutic strategies and patient benefit in the fight against cancer.

Conflicts of interest

Dr Neil P. Jones is a Principal Target Validation Scientist at Cancer Research Technology and is involved in the drug discovery alliance between Cancer Research Technology and AstraZeneca to identify new cancer therapies targeting cancer metabolism. He has previously worked on lipid signalling pathways and cancer at the Institute of Cancer Research, London, and on signalling pathways and diabetes at the University of Southampton.

Dr Almut Schulze is a Group Leader at the CRUK London Research Institute heading the Gene Expression Analysis Group. Her research is focused on the regulation of cell metabolism by the PI3K/AKT signalling pathway and its role in cell growth and transformation. She has published several high-impact papers in this area. She was awarded a prestigious EMBO Young Investigator Fellowship in 2008 and is one of the CRUK Principal Investigators associated with the CRUK/CRT Cancer Metabolism Alliance with AstraZeneca.

References

1 Warburg, O. *et al.* (1927) The metabolism of tumors in the body. *J. Gen. Physiol.* 8, 519–530

2 Vander Heiden, M.G. *et al.* (2009) Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 324, 1029–1033

3 Koppenol, W.H. *et al.* (2011) Otto Warburg's contributions to current concepts of cancer metabolism. *Nat. Rev. Cancer* 11, 325–337

4 Racker, E. (1972) Bioenergetics and the problem of tumor growth. *Am. Sci.* 60, 56–63

5 Cairns, R.A. *et al.* (2011) Regulation of cancer cell metabolism. *Nat. Rev. Cancer* 11, 85–95

6 Dang, C.V. (2010) Glutaminolysis: supplying carbon or nitrogen or both for cancer cells? *Cell Cycle* 9, 3884–3886

7 Wise, D.R. and Thompson, C.B. (2010) Glutamine addiction: a new therapeutic target in cancer. *Trends Biochem. Sci.* 35, 427–433

8 Dang, C.V. *et al.* (2009) MYC-induced cancer cell energy metabolism and therapeutic opportunities. *Clin. Cancer Res.* 15, 6479–6483

9 Gao, P. *et al.* (2009) c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. *Nature* 458, 762–765

10 Dang, C.V. (2010) Rethinking the Warburg effect with Myc micromanaging glutamine metabolism. *Cancer Res.* 70, 859–862

11 Wise, D.R. *et al.* (2008) Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction. *Proc. Natl. Acad. Sci. U.S.A.* 105, 18782–18787

12 Collier, J.J. *et al.* (2003) c-Myc is required for the glucose-mediated induction of metabolic enzyme genes. *J. Biol. Chem.* 278, 6588–6595
13 Sun, Q. *et al.* (2011) Mammalian target of rapamycin up-regulation of pyruvate kinase isoenzyme type M2 is critical for aerobic glycolysis and tumor growth. *Proc Natl Acad. Sci. U.S.A.* 108, 4129–4134
14 Semenza, G.L. (2010) HIF-1: upstream and downstream of cancer metabolism. *Curr. Opin. Genet. Dev.* 20, 51–56
15 Osthus, R.C. *et al.* (2000) Deregulation of glucose transporter 1 and glycolytic gene expression by c-Myc. *J. Biol. Chem.* 275, 21797–21800
16 Kim, J.W. *et al.* (2007) Hypoxia-inducible factor 1 and dysregulated c-Myc cooperatively induce vascular endothelial growth factor and metabolic switches hexokinase 2 and pyruvate dehydrogenase kinase 1. *Mol. Cell Biol.* 27, 7381–7393
17 Podar, K. and Anderson, K.C. (2010) A therapeutic role for targeting c-Myc/Hif-1-dependent signaling pathways. *Cell Cycle* 9, 1722–1728
18 Lewis, B.C. *et al.* (2000) Tumor induction by the c-Myc target genes rcl and lactate dehydrogenase A. *Cancer Res.* 60, 6178–6183
19 Shim, H. *et al.* (1997) c-Myc transactivation of LDH-A: implications for tumor metabolism and growth. *Proc. Natl. Acad. Sci. U.S.A.* 94, 6658–6663
20 Fantin, V.R. *et al.* (2006) Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. *Cancer Cell* 9, 425–434
21 Yuan, T.L. and Cantley, L.C. (2008) PI3K pathway alterations in cancer: variations on a theme. *Oncogene* 27, 5497–5510
22 Elstrom, R.L. *et al.* (2004) Akt stimulates aerobic glycolysis in cancer cells. *Cancer Res.* 64, 3892–3899
23 Robey, R.B. and Hay, N. (2009) Is Akt the Warburg kinase''?-Akt-energy metabolism interactions and oncogenesis. *Semin. Cancer Biol.* 19, 25–31
24 Majewski, N. *et al.* (2004) Hexokinase-mitochondria interaction mediated by Akt is required to inhibit apoptosis in the presence or absence of Bax and Bak. *Mol. Cell* 16, 819–830
25 Tong, X. *et al.* (2009) The molecular determinants of de novo nucleotide biosynthesis in cancer cells. *Curr. Opin. Genet. Dev.* 19, 32–37
26 Zoncu, R. *et al.* (2011) mTOR: from growth signal integration to cancer, diabetes and ageing. *Nat. Rev. Mol. Cell Biol.* 12, 21–35
27 Fan, Y. *et al.* (2010) Akt and c-Myc differentially activate cellular metabolic programs and prime cells to bioenergetic inhibition. *J. Biol. Chem.* 285, 7324–7333
28 DeBerardinis, R.J. *et al.* (2008) The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. *Cell Metab.* 7, 11–20
29 Porstmann, T. *et al.* (2005) PKB/Akt induces transcription of enzymes involved in cholesterol and fatty acid biosynthesis via activation of SREBP. *Oncogene* 24, 6465–6481
30 Semenza, G.L. (2011) Regulation of metabolism by hypoxia-inducible factor 1. Cold Spring Harb Symp. Quant. Biol. Published in Advance 2011, doi:10.1101/sqb.2011.76.010678.
31 Dang, C.V. (2007) The interplay between MYC and HIF in the Warburg effect. *Ernst Schering Found. Symp. Proc.* 4, 35–53
32 Gordan, J.D. *et al.* (2007) HIF and c-Myc: sibling rivals for control of cancer cell metabolism and proliferation. *Cancer Cell* 12, 108–113
33 Kaelin, W.G., Jr (2008) The von Hippel-Lindau tumour suppressor protein: O2 sensing and cancer. *Nat. Rev. Cancer* 8, 865–873
34 Obach, M. *et al.* (2004) 6-Phosphofructo-2-kinase (pfkfb3) gene promoter contains hypoxia-inducible factor-1 binding sites necessary for transactivation in response to hypoxia. *J. Biol. Chem.* 279, 53562–53570
35 Bobarykina, A.Y. *et al.* (2006) Hypoxic regulation of PFKFB-3 and PFKFB-4 gene expression in gastric and pancreatic cancer cell lines and expression of PFKFB genes in gastric cancers. *Acta Biochim. Pol.* 53, 789–799
36 Koukourakis, M.I. *et al.* (2005) Pyruvate dehydrogenase and pyruvate dehydrogenase kinase expression in non small cell lung cancer and tumor-associated stroma. *Neoplasia* 7, 1–6
37 Boulahbel, H. *et al.* (2009) Prolyl hydroxylases as regulators of cell metabolism. *Biochem. Soc. Trans.* 37, 291–294
38 Firth, J.D. *et al.* (1995) Hypoxic regulation of lactate dehydrogenase A. Interaction between hypoxia-inducible factor 1 and cAMP response elements. *J. Biol. Chem.* 270, 21021–21027
39 Maher, J.C. *et al.* (2007) Hypoxia-inducible factor-1 confers resistance to the glycolytic inhibitor 2-deoxy-D-glucose. *Mol. Cancer Ther.* 6, 732–741
40 Pollard, P.J. *et al.* (2007) Targeted inactivation of fh1 causes proliferative renal cyst development and activation of the hypoxia pathway. *Cancer Cell* 11, 311–319
41 Macheda, M.L. *et al.* (2005) Molecular and cellular regulation of glucose transporter (GLUT) proteins in cancer. *J. Cell Physiol.* 202, 654–662
42 Furuta, E. *et al.* (2010) Metabolic genes in cancer: their roles in tumor progression and clinical implications. *Biochim Biophys. Acta* 1805, 141–152
43 Pedersen, P.L. (2007) Warburg, me and Hexokinase 2: multiple discoveries of key molecular events underlying one of cancers' most common phenotypes, the ''Warburg Effect'', i.e., elevated glycolysis in the presence of oxygen. *J. Bioenerg. Biomembr.* 39, 211–222
44 Mazurek, S. (2007) Pyruvate kinase type M2: a key regulator within the tumour metabolome and a tool for metabolic profiling of tumours. *Ernst Schering Found. Symp. Proc.* 4, 99–124
45 Gupta, V. and Bamezai, R.N. (2010) Human pyruvate kinase M2: a multifunctional protein. *Protein Sci.* 19, 2031–2044
46 Dang, C.V. (2009) PKM2 tyrosine phosphorylation and glutamine metabolism signal a different view of the Warburg effect. *Sci. Signal.* 2, 75
47 Christofk, H.R. *et al.* (2008) The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. *Nature* 452, 230–233
48 Christofk, H.R. *et al.* (2008) Pyruvate kinase M2 is a phosphotyrosine-binding protein. *Nature* 452, 181–186
49 Hitosugi, T. *et al.* (2009) Tyrosine phosphorylation inhibits PKM2 to promote the Warburg effect and tumor growth. *Sci. Signal.* 2, 73
50 DeBerardinis, R.J. *et al.* (2007) Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. *Proc. Natl. Acad. Sci. U.S.A.* 104, 19345–19350
51 Pollard, P.J. *et al.* (2003) The TCA cycle and tumorigenesis: the examples of fumarate hydratase and succinate dehydrogenase. *Ann. Med.* 35, 632–639
52 Frezza, C. *et al.* (2011) Inborn and acquired metabolic defects in cancer. *J. Mol. Med. (Berl.)* 89, 213–220
53 Bardella, C. *et al.* (2011) SDH mutations in cancer. *Biochim. Biophys. Acta* 1807, 432–443
54 Pollard, P.J. *et al.* (2005) Accumulation of Krebs cycle intermediates and over-expression of HIF1alpha in tumours which result from germline FH and SDH mutations. *Hum. Mol. Genet.* 14, 2231–2239
55 Srirangalingam, U. *et al.* (2008) Clinical manifestations of familial paraganglioma and phaeochromocytomas in succinate dehydrogenase B (SDH-B) gene mutation carriers. *Clin. Endocrinol. (Oxf.)* 69, 587–596
56 Srirangalingam, U. *et al.* (2009) Contrasting clinical manifestations of SDHB and VHL associated chromaffin tumours. *Endocr. Relat. Cancer* 16, 515–525
57 Selak, M.A. *et al.* (2005) Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-alpha prolyl hydroxylase. *Cancer Cell* 7, 77–85
58 Ahvenainen, T. *et al.* (2008) Mutation screening of fumarate hydratase by multiplex ligation-dependent probe amplification: detection of exonic deletion in a patient with leiomyomatosis and renal cell cancer. *Cancer Genet. Cytogenet.* 183, 83–88
59 Alam, N.A. *et al.* (2003) Genetic and functional analyses of FH mutations in multiple cutaneous and uterine leiomyomatosis, hereditary leiomyomatosis and renal cancer, and fumarate hydratase deficiency. *Hum. Mol. Genet.* 12, 1241–1252
60 Tennant, D.A. *et al.* (2009) Reactivating HIF prolyl hydroxylases under hypoxia results in metabolic catastrophe and cell death. *Oncogene* 28, 4009–4021
61 Figueroa, M.E. *et al.* (2010) Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. *Cancer Cell* 18, 553–567
62 Frezza, C. *et al.* (2010) IDH1 mutations in gliomas: when an enzyme loses its grip. *Cancer Cell* 17, 7–9
63 Yen, K.E. *et al.* (2010) Cancer-associated IDH mutations: biomarker and therapeutic opportunities. *Oncogene* 29, 6409–6417
64 Yan, H. *et al.* (2009) IDH1 and IDH2 mutations in gliomas. *N. Engl. J. Med.* 360, 765–773
65 Gross, S. *et al.* (2010) Cancer-associated metabolite 2-hydroxyglutarate accumulates in acute myelogenous leukemia with isocitrate dehydrogenase 1 and 2 mutations. *J. Exp. Med.* 207, 339–344
66 Dang, L. *et al.* (2009) Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature* 462, 739–744
67 Ward, P.S. *et al.* (2010) The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. *Cancer Cell* 17, 225–234
68 Kekec, Y. *et al.* (2009) Antioxidant enzyme levels in cases with gastrointesinal cancer. *Eur. J. Intern. Med.* 20, 403–406
69 Langbein, S. *et al.* (2008) Metastasis is promoted by a bioenergetic switch: new targets for progressive renal cell cancer. *Int. J. Cancer* 122, 2422–2428
70 Jiang, P. *et al.* (2011) p53 regulates biosynthesis through direct inactivation of glucose-6-phosphate dehydrogenase. *Nat. Cell Biol.* 13, 310–316
71 Cosentino, C. *et al.* (2011) ATM activates the pentose phosphate pathway promoting anti-oxidant defence and DNA repair. *EMBO J.* 30, 546–555
72 Pisano, M. *et al.* (1991) Glucose-6-phosphate dehydrogenase deficiency and lung cancer: a hospital based case-control study. *Tumorigenesis* 77, 12–15

73 Coy, J.F. *et al.* (2005) Mutations in the transketolase-like gene TKTL1: clinical implications for neurodegenerative diseases, diabetes and cancer. *Clin. Lab.* 51, 257–273
74 Foldi, M. *et al.* (2007) Transketolase protein TKTL1 overexpression: a potential biomarker and therapeutic target in breast cancer. *Oncol. Rep.* 17, 841–845
75 Xu, X. *et al.* (2009) Transketolase-like protein 1 (TKTL1) is required for rapid cell growth and full viability of human tumor cells. *Int. J. Cancer* 124, 1330–1337
76 Mayer, A. *et al.* (2011) Evidence against a major role for TKTL-1 in hypoxic and normoxic cancer cells. *Adv. Exp. Med. Biol.* 701, 123–128
77 Mayer, A. *et al.* (2010) Glucose metabolism of malignant cells is not regulated by transketolase-like (TKTL)-1. *Int. J. Oncol.* 37, 265–271
78 Mitschke, L. *et al.* (2010) The crystal structure of human transketolase and new insights into its mode of action. *J. Biol. Chem.* 285, 31559–31570
79 Bensaad, K. *et al.* (2006) TIGAR, a p53-inducible regulator of glycolysis and apoptosis. *Cell* 126, 107–120
80 Gottlieb, E. and Vousden, K.H. (2009) p53 regulation of metabolic pathways. *Cold Spring Harb. Perspect. Biol.* 2, Abstr. 001040
81 Bensaad, K. *et al.* (2009) Modulation of intracellular ROS levels by TIGAR controls autophagy. *EMBO J.* 28, 3015–3026
82 Vousden, K.H. and Ryan, K.M. (2009) p53 and metabolism. *Nat. Rev. Cancer* 9, 691–700
83 Snell, K. *et al.* (1988) Enzymic imbalance in serine metabolism in human colon carcinoma and rat sarcoma. *Br. J. Cancer* 57, 87–90
84 Locasale, J.W. *et al.* (2011) Phosphoglycerate dehydrogenase diverts glycolytic flux and contributes to oncogenesis. *Nat. Genet.* 43, 869–874
85 Possemato, R. *et al.* (2011) Functional genomics reveal that the serine synthesis pathway is essential in breast cancer. *Nature* 476, 346–350
86 Pollari, S. *et al.* (2011) Enhanced serine production by bone metastatic breast cancer cells stimulates osteoclastogenesis. *Breast Cancer Res. Treat.* 125, 421–430
87 de Koning, T.J. and Klomp, L.W. (2004) Serine-deficiency syndromes. *Curr. Opin. Neurol.* 17, 197–204
88 Hart, C.E. *et al.* (2007) Phosphoserine aminotransferase deficiency: a novel disorder of the serine biosynthesis pathway. *Am. J. Hum. Genet.* 80, 931–937
89 Klomp, L.W. *et al.* (2000) Molecular characterization of 3-phosphoglycerate dehydrogenase deficiency – a neurometabolic disorder associated with reduced L-serine biosynthesis. *Am. J. Hum. Genet.* 67, 1389–1399
90 de Koning, T.J. (2006) Treatment with amino acids in serine deficiency disorders. *J. Inherit. Metab. Dis.* 29, 347–351
91 Tennant, D.A. *et al.* (2010) Targeting metabolic transformation for cancer therapy. *Nat. Rev. Cancer* 10, 267–277
92 Pelicano, H. *et al.* (2006) Glycolysis inhibition for anticancer treatment. *Oncogene* 25, 4633–4646
93 Hammoudi, N. *et al.* (2011) Metabolic alterations in cancer cells and therapeutic implications. *Chin. J. Cancer* 30, 508–525
94 Jiang, J.K. *et al.* (2010) Evaluation of thieno[3,2-b]pyrrole[3,2-d]pyridazinones as activators of the tumor cell specific M2 isoform of pyruvate kinase. *Bioorg. Med. Chem. Lett.* 20, 3387–3393
95 Luo, W. and Semenza, G.L. (2011) Pyruvate kinase M2 regulates glucose metabolism by functioning as a coactivator for hypoxia-inducible factor 1 in cancer cells. *Oncotarget* 2, 551–556
96 Lv, L. *et al.* (2011) Acetylation targets the M2 isoform of pyruvate kinase for degradation through chaperone-mediated autophagy and promotes tumor growth. *Mol. Cell* 42, 719–730
97 Vander Heiden, M.G. *et al.* (2010) Identification of small molecule inhibitors of pyruvate kinase M2. *Biochem. Pharmacol.* 79, 1118–1124
98 Clem, B. *et al.* (2008) Small-molecule inhibition of 6-phosphofructo-2-kinase activity suppresses glycolytic flux and tumor growth. *Mol. Cancer Ther.* 7, 110–120
99 Seltzer, M.J. *et al.* (2010) Inhibition of glutaminase preferentially slows growth of glioma cells with mutant IDH1. *Cancer Res.* 70, 8981–8987
100 Fang, J. *et al.* (2006) The H+-linked monocarboxylate transporter (MCT1/SLC16A1): a potential therapeutic target for high-risk neuroblastoma. *Mol. Pharmacol.* 70, 2108–2115
101 Mann, W.R. *et al.* (2000) Diverse mechanisms of inhibition of pyruvate dehydrogenase kinase by structurally distinct inhibitors. *Biochim. Biophys. Acta* 1480, 283–292
102 Thornburg, J.M. *et al.* (2008) Targeting aspartate aminotransferase in breast cancer. *Breast Cancer Res.* 10, 84
103 Liu, H. *et al.* (2010) Fructose induces transketolase flux to promote pancreatic cancer growth. *Cancer Res.* 70, 6368–6376
104 Kuhajda, F.P. (2006) Fatty acid synthase and cancer: new application of an old pathway. *Cancer Res.* 66, 5977–5980
105 Zhan, Y. *et al.* (2008) Control of cell growth and survival by enzymes of the fatty acid synthesis pathway in HCT-116 colon cancer cells. *Clin. Cancer Res.* 14, 5735–5742
106 Hatzivassiliou, G. *et al.* (2005) ATP citrate lyase inhibition can suppress tumor cell growth. *Cancer Cell* 8, 311–321
107 Nomura, D.K. *et al.* (2010) Monoacylglycerol lipase regulates a fatty acid network that promotes cancer pathogenesis. *Cell* 140, 49–61
108 Ye, L. *et al.* (2011) Monoacylglycerol lipase (MAGL) knockdown inhibits tumor cells growth in colorectal cancer. *Cancer Lett.* 307, 6–17
109 Watson, M. *et al.* (2009) The small molecule GMX1778 is a potent inhibitor of NAD+ biosynthesis: strategy for enhanced therapy in nicotinic acid phosphoribosyltransferase 1-deficient tumors. *Mol. Cell Biol.* 29, 5872–5888
110 Zoppoli, G. *et al.* (2010) Potent synergistic interaction between the Nampt inhibitor APO866 and the apoptosis activator TRAIL in human leukemia cells. *Exp. Hematol.* 38, 979–988
111 Gottlieb, E. (2009) Cancer: the fat and the furious. *Nature* 461, 44–45
112 Singh, D. *et al.* (2005) Optimizing cancer radiotherapy with 2-deoxy-d-glucose dose escalation studies in patients with glioblastoma multiforme. *Strahlenther. Onkol.* 181, 507–514
113 Prasanna, V.K. *et al.* (2009) Differential responses of tumors and normal brain to the combined treatment of 2-DG and radiation in glioablastoma. *J Cancer Res. Ther.* 5 (Suppl. 1), 44–47
114 Dwarakanath, B.S. *et al.* (2009) Clinical studies for improving radiotherapy with 2-deoxy-D-glucose: present status and future prospects. *J Cancer Res. Ther.* 5 (Suppl. 1), 21–26
115 Bonnet, S. *et al.* (2007) A mitochondria-K+ channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth. *Cancer Cell* 11, 37–51
116 Papandreou, I. *et al.* (2011) Anticancer drugs that target metabolism: is dichloroacetate the new paradigm? *Int. J. Cancer* 128, 1001–1008
117 Mayers, R.M. *et al.* (2003) AZD7545, a novel inhibitor of pyruvate dehydrogenase kinase 2 (PDHK2), activates pyruvate dehydrogenase in vivo and improves blood glucose control in obese (fa/fa) Zucker rats. *Biochem. Soc. Trans.* 31, 1165–1167
118 Morrell, J.A. *et al.* (2003) AZD7545 is a selective inhibitor of pyruvate dehydrogenase kinase 2. *Biochem. Soc. Trans.* 31, 1168–1170
119 Semenza, G.L. (2008) Tumor metabolism: cancer cells give and take lactate. *J. Clin. Invest.* 118, 3835–3837
120 Kennedy, K.M. and Dewhirst, M.W. (2010) Tumor metabolism of lactate: the influence and therapeutic potential for MCT and CD147 regulation. *Future Oncol.* 6, 127–148
121 Sonveaux, P. *et al.* (2008) Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice. *J. Clin. Invest.* 118, 3930–3942
122 Pertega-Gomes, N. *et al.* (2011) Monocarboxylate transporter 4 (MCT4) and CD147 overexpression is associated with poor prognosis in prostate cancer. *BMC Cancer* 11, 312
123 Pinheiro, C. *et al.* (2010) Monocarboxylate transporter 1 is up-regulated in basal-like breast carcinoma. *Histopathology* 56, 860–867
124 Pinheiro, C. *et al.* (2008) Increasing expression of monocarboxylate transporters 1 and 4 along progression to invasive cervical carcinoma. *Int. J. Gynecol. Pathol.* 27, 568–574
125 Pinheiro, C. *et al.* (2008) Increased expression of monocarboxylate transporters 1, 2, and 4 in colorectal carcinomas. *Virchows. Arch.* 452, 139–146
126 Pinheiro, C. *et al.* (2010) Expression of monocarboxylate transporters 1, 2, and 4 in human tumours and their association with CD147 and CD44. *J. Biomed. Biotechnol.* 2010, 427694
127 Fischer, K. *et al.* (2007) Inhibitory effect of tumor cell-derived lactic acid on human T cells. *Blood* 109, 3812–3819
128 Izumi, H. *et al.* (2011) Monocarboxylate transporters 1 and 4 are involved in the invasion activity of human lung cancer cells. *Cancer Sci.* 102, 1007–1013
129 Birnbaum, M.J. and Shaw, R.J. (2011) Genomics: drugs, diabetes and cancer. *Nature* 470, 338–339
130 Hardie, D.G. (2011) AMP-activated protein kinase: a cellular energy sensor with a key role in metabolic disorders and in cancer. *Biochem. Soc. Trans.* 39, 1–13
131 Bo, S. *et al.* (2012) Cancer mortality reduction and metformin. A retrospective cohort study in type 2 diabetic patients. *Diabetes Obes. Metab.* 14, 23–29
132 Bowker, S.L. *et al.* (2006) Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. *Diabetes Care* 29, 254–258
133 Evans, J.M. *et al.* (2005) Metformin and reduced risk of cancer in diabetic patients. *BMJ* 330, 1304–1305
134 Shaw, R.J. *et al.* (2004) The LKB1 tumor suppressor negatively regulates mTOR signaling. *Cancer Cell* 6, 91–99
135 Shaw, R.J. *et al.* (2004) The tumor suppressor LKB1 kinase directly activates AMP-activated kinase and regulates apoptosis in response to energy stress. *Proc. Natl. Acad. Sci. U.S.A.* 101, 3329–3335