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Clemens A. Schmitt *Editors*

Metabolism in Cancer

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Metabolism in Cancer

Springer

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Description and Purpose of the Work

The notion that tumor cells display characteristic alterations of metabolic pathways has significantly changed our understanding of cancer. While the first description of tumor-specific changes in cellular energetics was published over 90 years ago, the causal significance of this observation for the pathogenesis of cancer was only discovered in the post-genome era. The first 10 years of the twenty-first century were characterized by a rapid gain in knowledge on the functional role of cancer-specific metabolism as well as the underlying molecular pathways. Various unanticipated interrelations of metabolic alterations with cancer-driving pathways were identified and are awaiting translation into diagnosis and therapy of cancer. Velocity, quantity, and complexity of these new discoveries render it difficult for researchers to keep up-to-date with the latest developments. This textbook provides concise chapters of internationally renowned experts on various important aspects of cancer-associated metabolism and hence a comprehensive platform for an overview of the central features of this exciting research field.

The Role of Glucose and Lipid Metabolism in Growth and Survival of Cancer Cells

Charlene Brault and Almut Schulze

Abstract

One of the prerequisites for cell growth and proliferation is the synthesis of macromolecules, including proteins, nucleic acids and lipids. Cells have to alter their metabolism to allow the production of metabolic intermediates that are the precursors for biomass production. It is now evident that oncogenic signalling pathways target metabolic processes on several levels and metabolic reprogramming has emerged as a hallmark of cancer. The increased metabolic demand of cancer cells also produces selective dependencies that could be targeted for therapeutic intervention. Understanding the role of glucose and lipid metabolism in supporting cancer cell growth and survival is crucial to identify essential processes that could provide therapeutic windows for cancer therapy.

Keywords

Glucose metabolism · Lipid metabolism · Cancer · Fatty acids · Lipid peroxidation · Oncogenic signalling pathways

1 Glucose Metabolism in Cancer Cells

The german biochemist Otto Warburg already established in the first half of the last century that cancer tissue consumes large amounts of glucose irrespective of the availability of oxygen (Warburg et al. 1924). This observation led to the definition

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of aerobic glycolysis in cancer cells, meaning that the relative use of oxidative and non-oxidative glucose metabolism is uncoupled from oxygen levels, which is now better known as the 'Warburg effect'. It was initially thought that increased glycolytic ATP production in cancer cells is the consequence of reduced mitochondrial function, potentially caused by the mutation of the mitochondrial genome. However, it is now clear that the increased glucose uptake and glycolytic activity in cancer cells allow the redirection of glucose-derived metabolites into biosynthetic pathways (Fig. 1).

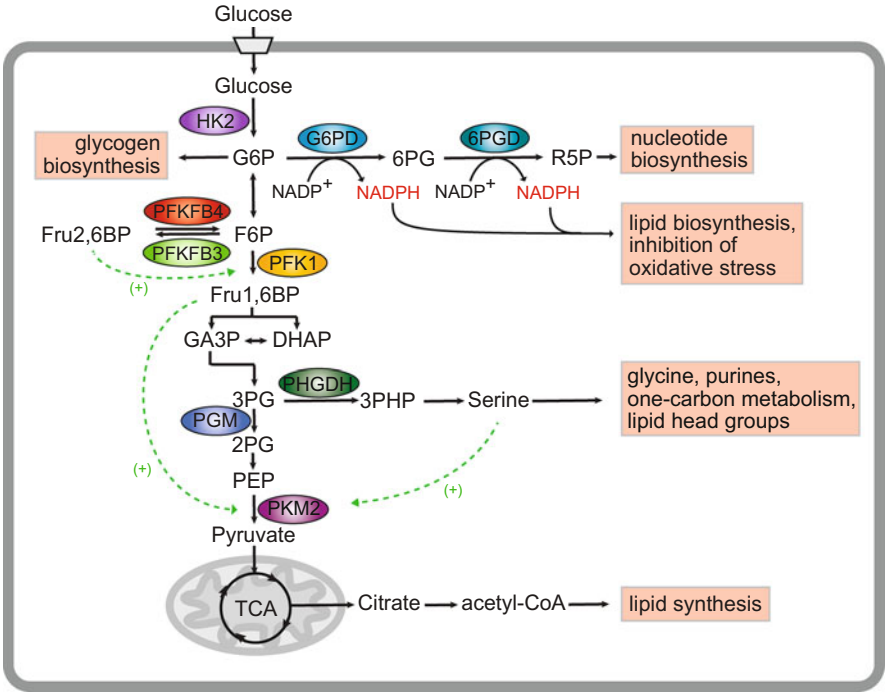

Fig. 1 Glucose metabolism in cancer cells. Overview of the major biosynthetic pathways fuelled by glucose in cancer cells. Phosphorylation of glucose by hexokinase 2 (HK2) retains glucose within the cell. Glucose-6-phosphate (G6P) can enter glycolysis, pentose phosphate pathway or glycogen biosynthesis. Regulation of the levels of the allosteric activator fructose-2,6-bisphosphate (FR2,6BP) by phosphofructokinase-2/fructose-2,6-bisphosphatase (PFKFB3 and PFKFB4) controls the activity of phosphofructokinase 1 (PFK1). Redirection of 3-phosphoglycerate (3PG) into serine biosynthesis by phosphoglycerate dehydrogenase (PHGDH) fuels the production of glycine, purines and lipid head groups as well as the one-carbon metabolism. The low activity of the M2 isoform of pyruvate kinase (PKM2) controls the last step of the glycolytic cascade, thereby allowing the use of glycolytic intermediates into biosynthetic reactions. Production of NADPH from NADP + by glucose-6-phosphate dehydrogenase (G6PDH) and 6-phosphogluconate dehydrogenase (6PGD), two enzymes within the oxidative arm of the pentose phosphate pathway, provides reducing equivalents for lipid biosynthesis and antioxidant production

Many oncogenic signalling pathways affect glycolytic activity in cancer cells. The expression of many glycolytic enzymes is induced by the oncogenic transcription factor c-Myc and the hypoxia-inducible factor (HIF) (Cairns et al. 2011). One of the best-studied pathways is the phosphatidylinositol 3-phosphate kinase (PI3K) pathway, which is frequently activated in human cancer. In normal cells, PI3K is activated in response to growth factor binding to receptor tyrosine kinases at the cell surface. This stimulates the lipid kinase activity of PI3K and leads to the generation of phosphatidylinositol 3,4,5-trisphosphate (PIP3), a lipid second messenger (Vanhaesebroeck et al. 2012). This activates several downstream effectors including the serine/threonine kinase Akt (c-Akt/PKB). Akt is one of the major mediators of insulin signalling and has a number of important metabolic target proteins in different tissues, thereby controlling the removal of glucose from the bloodstream (Manning and Cantley 2007). In cancer cells, Akt increases glucose uptake by enhancing the localisation of the glucose transporters 1 and 4 (GLUT1 and GLUT4) to the plasma membrane. Akt also leads to the phosphorylation of hexokinase 2 (HK2), the enzyme that catalyses the first and irreversible step of the glycolytic cascade, and enhances its localisation to the mitochondrial membrane (Gottlob et al. 2001; Majewski et al. 2004). This couples the conversion of glucose to glucose-6-phosphate to mitochondrial ATP production and protects cancer cells from apoptosis. Increased hexokinase activity in cancer cells is also exploited for diagnostic purposes as it causes the retention of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) for positron emission tomography (PET) imaging. Targeting hexokinase activity to inhibit glycolysis in cancer cells has been discussed for some time. But it has only been shown quite recently that deletion of HK2 efficiently blocks tumour development in several genetically engineered mouse models of human cancer (Patra et al. 2013). Importantly, the same study showed that systemic deletion of HK2 in adult mice has no detrimental effects, making the inhibition of this enzyme a valid strategy for drug development.

Akt also modulates glycolytic activity by phosphorylating the heart isoform of phosphofructokinase-2/fructose-2,6-bisphosphatase (PFK-2/Fru-2,6BPase). This family of bifunctional enzymes regulates the interconversion of fructose 6-phosphate (F6-P) and fructose-2,6-bisphosphate (F2,6-BP), which is an allosteric activator of the enzyme that catalyses the second irreversible step of glycolysis, phosphofructokinase 1 (PFK1). The mammalian genome encodes several PFKFB isoforms (PFKFB1-4), which show differences in their tissue-specific expression and relative activity of their kinase and bisphosphatase domains (Rider et al. 2004). The high kinase activity of the brain isoform (PFKFB3) can promote glycolysis in tumour cells (Yalcin et al. 2009), and PFKFB3 has been shown to be required for Ras-dependent transformation (Telang et al. 2006). However, PFKFB3 inhibition also stimulates autophagy, thereby providing a survival mechanism in tumour cells (Klarer et al. 2014). Interestingly, PFKFB3 activity promotes glycolysis in endothelial cells and supports the induction of vessel sprouting during developmental angiogenesis (De Bock et al. 2013). This observation exemplifies that metabolic processes in both tumour and stromal cells could be targeted therapeutically.

Another PFKFB isoform, PFKFB4, was identified as an important gene for prostate cancer cell survival in a functional screen (Ros et al. 2012). This isoform seems to function mainly as a fructose-2,6-bisphosphatase, at least in prostate cancer cells, as depletion of PFKFB4 increased the levels of F2,6-BP leading to enhanced glycolytic flux and depletion of metabolites from the pentose phosphate pathway. This reduces the production of NADPH and, consequently, the reduced form of glutathione, an important antioxidant, leading to oxidative stress and cell death (Ros et al. 2012). Another screen, this time in glioma stemlike cells, also demonstrated a role for PFKFB4 in cancer cell survival (Goidts et al. 2012). While normal brain expresses high levels of PFKFB3, PFKFB4 expression was increased in primary high-grade glioma and was predictive of poor survival outcome (Goidts et al. 2012).

The regulation of glycolytic activity by PFKFB proteins is also tightly associated with the function of the AMP-activated protein kinase (AMPK). Several PFKFB isoforms, including PFKFB3, can be phosphorylated by AMPK on a conserved serine in the C-terminal regulatory domain. AMPK-dependent phosphorylation increases the activity of the kinase domain of PFKFB (Barford et al. 1991). As AMPK is activated in response to low ATP levels, phosphorylation of PFKFB by AMPK increases glycolytic ATP generation under conditions of energy deprivation. While the AMPK pathway is generally considered to have tumour suppressor functions, experimental evidence also suggests that AMPK could be important to limit biosynthetic processes in cancer cells when nutrients are scarce, thereby preserving NADPH for the regeneration of antioxidant molecules (Jeon et al. 2012). Interestingly, the regulatory domain, which contains the AMPK phosphorylation site in PFKFB3, is missing in PFKFB4, suggesting that the regulation of PFKFB4 is quite different from that of the other isoforms. As isoform-specific inhibitors of PFKFB3 have been developed and their efficacy is currently tested in different cancer cells (Clem et al. 2013), a more detailed understanding of the differential roles of PFKFB3 and PFKFB4 in cancer will emerge.

Two of the enzymes of the oxidative pentose phosphate pathway (PPP) have also been associated with metabolic reprogramming in cancer cells. Glucose-6-phosphate dehydrogenase (G6PD) is part of the metabolic transcriptional signature downstream of the mammalian target of rapamycin complex 1 (mTORC1) (Duvel et al. 2010). The activity of G6PD is inhibited by the p53 tumour suppressor through direct binding (Jiang et al. 2011). Moreover, knockdown of 6-phosphogluconate dehydrogenase (6PGD), the second NADPH-producing enzyme of the PPP, induces senescence in lung cancer cells (Sukhatme and Chan 2012). 6PGD is also inhibited by the accumulation of 3-phosphoglycerate (3PG) in response to the inhibition of phosphoglycerate mutase (PGM) by p53 (Hitosugi et al. 2012). TP53 also regulates the activity of PFK1 by inducing the expression of the TP53-induced glycolysis and apoptosis regulator (TIGAR), which has structural similarities to the fructose-2,6-bisphosphatase domain of PFKFB proteins. TIGAR reduces the amounts of F2,6-BP, resulting in the inhibition of glycolysis and redirection of metabolites into the PPP in response to DNA damage (Bensaad et al.

2006). Together, the modulation of glycolytic activity by TP53 allows cells to increase the production of nucleotides for DNA repair. However, loss of TP53 through deletion results in increased NADPH production to support biosynthetic reactions.

Another glycolytic enzyme that has been shown to be important for cancer cell survival is phosphoglycerate dehydrogenase (PHGDH) (Locasale et al. 2011; Possemato et al. 2011). PHGDH promotes the redirection of 3-phosphoglycerate into the biosynthesis of serine and glycine, two non-essential amino acids. As glycine is required for the production of glutathione, enhanced flux through the serine biosynthesis pathway could ensure sufficient production of this important antioxidant. Moreover, serine and glycine are closely linked to the one-carbon metabolism (also known as folate-mediated one-carbon metabolism or folate and methionine cycles), which provides intermediates for purine biosynthesis, head groups for lipid synthesis and methyl groups for the modification of DNA and histones (Locasale 2013). Several enzymes in the metabolism of glycine have been shown to be upregulated in non-small-cell lung cancer (NSCLC) stem cells, and overexpression of glycine decarboxylase, which converts glycine into CO_2, ammonia and methyl tetrahydrofolate (methyl-THF), is required for lung cancer development (Zhang et al. 2012). Glycine uptake has also been linked to the proliferation of cancer cells (Zhang et al. 2012), while serine is essential for the survival of p53 null cancer cells in vitro and in vivo (Maddocks et al. 2013). Moreover, a systems biology approach identified one-carbon metabolism as part of the unique metabolic phenotype of clear cell renal carcinoma (ccRCC) (Gatto et al. 2014). As one-carbon metabolism occupies such a central position and connects to many important metabolic processes, it will be challenging to unravel the exact contribution of this important metabolic node to cancer cell growth and tumour development.

Probably, the best-studied glycolytic enzyme in cancer cells is pyruvate kinase. The muscle isoform of this enzyme (PKM) comes in two splice variants, M1 and M2, which differ in a single exon. Exon 9 is specific to the M2 isoform (also known as the embryonic isoform, PKM2), while the M1 isoform (PKM1) contains exon 10. Most proliferating cells, including cancer cells, express mainly PKM2 (Christofk et al. 2008a). In contrast to PKM1, PKM2 can switch between a tetrameric state with high activity and a dimeric state with low activity (Mazurek et al. 2005). This allows cancer cells to fine-tune the flux of metabolites through the last glycolytic reaction, thereby allowing the use of glycolytic intermediates for biosynthetic reactions. The alternative splicing of exons 9 and 10 is controlled by heterogeneous nuclear ribonucleoproteins (hnRNPs), which are, in turn, regulated downstream of the oncogenic transcription factor c-Myc (David et al. 2010). The activity of PKM2 is also controlled by allosteric regulation. F1,6-BP, the product of PFK1, binds to and stabilises the high-activity tetrameric form of PKM2, providing a coupling between pyruvate production and metabolite levels of upper glycolysis. The association of F2,6-BP with the PKM2 tetramer is prevented by tyrosine-phosphorylated peptides (Christofk et al. 2008b) or ROS-dependent cysteine oxidation (Anastasiou et al. 2011). In addition, PKM2 activity is also