Int J Clin Exp Med 2016;9(6):9744-9751
www.ijcem.com /ISSN:1940-5901/IJCEM0022849

Review Article

PKM2 affects the development of hepatocellular carcinoma

Rui Zhao[1], Lei Li[2], Jinbo Yang[3]

[1]Department of Hepatology, Lanzhou University Second Hospital, Lanzhou 730030, China; [2]Department of Interventional Radiology, Lanzhou University First Hospital, Lanzhou 730000, China; [3]School of Life Sciences, Lanzhou University, Lanzhou 730000, China

Received December 28, 2015; Accepted March 22, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: Hepatocellular carcinoma (HCC) is the fifth common malignant tumor worldwide and has the characteristics of insidious onset, high malignancy, invasive fast-growth, high recurrence and poor prognosis. Currently, besides the alpha-fetoprotein (AFP), there are still no other markers for the accurate HCC diagnosis. Emerging evidence shows that pyruvate kinase isozyme splice variant 2 (PKM2) is highly expressed in various tumors, and is a master regulator of cancer cell metabolism. In the occurrence and development of HCC, PKM2 is involved in a variety of signal pathways, such as Hedgehog, STAT3, PI3K/AKT and EGFR. Whether PKM2 may serve as a target for HCC diagnosis and prognosis is still unclear. Herein, we reviewed the emerging evidence about the effect of PKM2 on the HCC, aiming to push forward clinical application of PKM2 in the early diagnosis and prognosis evaluation of HCC.

Keywords: PKM2, hepatocellular carcinoma, marker

Introduction

Hepatocellular carcinoma (HCC) is the fifth common malignancy and the third leading cause of cancer related death world wide. Due to the difficulty in its early diagnosis and its poor response to available treatments, its 5-year mortality remains at a high level [1]. Up to present, alpha-fetoprotein (AFP) has been the only one marker widely used in the diagnosis of HCC. Unfortunately, the positive rate is only 70%-90% in patients with early HCC, and other diseases or conditions such as pregnancy, active hepatitis, severe hepatitis disease, etc should be excluded. Therefore, it's imperative to develop some effective and specific markers for the early diagnosis and prognosis evaluation of HCC [2]. The therapies of HCC include surgery (including surgical resection and liver transplantation), ablation, interventional therapy, molecular targeted therapy and others. Surgical treatment of HCC is established as a potentially curative treatment modality, but the mortality is high in some patients. Local ablation is considered the first line treatment option for patients at early stages not suitable for surgical therapies, but HCC tumors in a subcapsular location or adjacent to the gallbladder have a higher risk of incomplete ablation, leading to its recurrence. In recent years, increasing attention has been paid to the molecular targeted therapy which has changed the landscape of cancer management [3]. Around 20 molecular targeted therapies have been approved during recent years for patients with breast, colorectal, non-small cell lung, renal cancer and HCC, among other malignancies [3]. Recently a multikinase inhibitor, sorafenib, has shown survival benefits in patients with advanced HCC. This advancement represents a breakthrough in the treatment of this complex disease, and proves that molecular therapies can be effective in this cancer. A better understanding of the molecular hepatocarcinogenesis is critical for identifying novel targets and oncogenic addition loops.

Currently, many studies have been conducted to investigate the molecular pathogenesis of HCC, but metabolic mechanism is rarely investigated in HCC cells. In 1926, Warburg found that pyruvate produced by glycolysis in tumor cells is

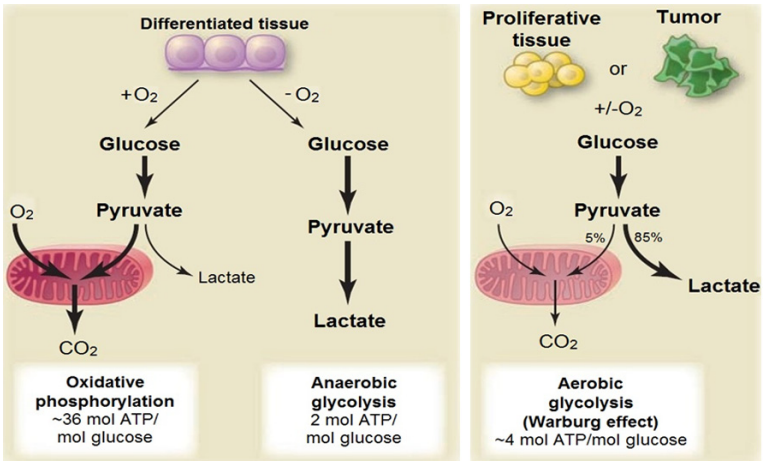

Figure 1. Different energy metabolism in normal cells and cancer cells (Warburg effect). Left: In the case of sufficient oxygen, Glucose within the normal tissue cells produces 36 mol ATP, carbon dioxide and oxygen mainly through oxidative phosphorylation. In the condition of lack of oxygen, Glucose produces lactic acid mainly through glycolytic pathway; Right: In proliferative tissue cells or cancer cells, no matter in aerobic or lack of oxygen, glucose produces lactic acid and 4 mol ATP mainly through glycolytic pathway.

mainly converted to lactic acid and discharged outside, while in normal cells, it mainly enters the mitochondrial oxidative respiratory chain, which is also known as the Warburg effect (aerobic glycolysis) (**Figure 1**) [4]. In 2008, Christofk et al found that the M2 splice isoform of pyruvate kinase (PKM2) was required for the Warburg effect and tumor development [5]. Since 2011, numerous studies have been conducted to investigate the roles of PKM2 in the pathogenesis of tumors. Available studies have shown that the expression and low enzymatic activity of PKM2 confer on cancer cells the glycolytic phenotype, which promotes rapid energy production and flow of glycolytic intermediates into collateral pathways to synthesize nucleic acids, amino acids, and lipids without the accumulation of reactive oxygen species. More recently, the nonglycolytic functions of PKM2 are of particular interest in cancer cells. PKM2 is induced translocation into the nucleus, where it activates transcription of various genes by interacting with and phosphorylating specific nuclear proteins, endowing cancer cells with a survival and growth advantage. Therefore, inhibitors and activators of PKM2 are well underway to evaluate their anticancer effects and suitability for use as novel therapeutic strategies [6, 7]. Although a variety of studies have been conducted to investigate PKM2, PKM2 is less studied in HCC. Herein, we summarized the roles of PKM2 in HCC.

PKM2 and its characteristic in cancer

Normal cells rely on two kinds of oxidative phosphorylation and glycolysis metabolic pathways for metabolic energy. Nevertheless, even with sufficient oxygen, tumor cells can produce large amounts of lactic acid mainly by glycolysis metabolic pathway, which is also known as Warburg Effect. Originally, researchers surmised that Warburg effect is caused by mitochondrial dysfunction of tumor cells, but later found that the case is not universal. Mitochondrial function is normal in many cancer cells [8]. In aerobic glycolysis, pyruvate kinase (PKs) functions at the final step and is an important rate-limiting enzyme [9]. The existence of different PK isoforms reflects the importance of the last step of glycolysis to cope with the differential metabolic requirements of cells. The mammalian pyruvate kinase (PK) family is comprised of two genes that encode four isoforms (L, R, M1 and M2). L and R isoforms, present in liver and erythrocytes, respectively [10], are encoded by PKLR gene using different promoters. M1 and M2 isoforms are alternative splicing products of the PKM gene. M1 is mainly found in adult skeletal muscle and brain, while M2 is the dominant isoform in proliferating cells [11]. The presence of PKM2 in embryonic tissues is a first sign of its importance for proliferating cells. The PKM locus encodes for the mutually exclusive M1 and M2 isoforms of pyruvate kinase [11]. These isoforms result from alternative splicing of the PKM pre mRNA into the M1 (with exon 9) and M2 (with exon 10) isoforms. Both isoforms differ only in 22 out of 531 amino acids and the exon that is exchanged encodes for 56 amino acids [11]. This region forms the inter-subunit contact domain (ISCD) of PKM2, which is involved in the association of dimers into tetramers [12].

The distribution of the PK isoforms is tissue specific depending on the metabolic necessities of the tissues. Constitutively active M1 isoform is expressed in muscle and brain tissues

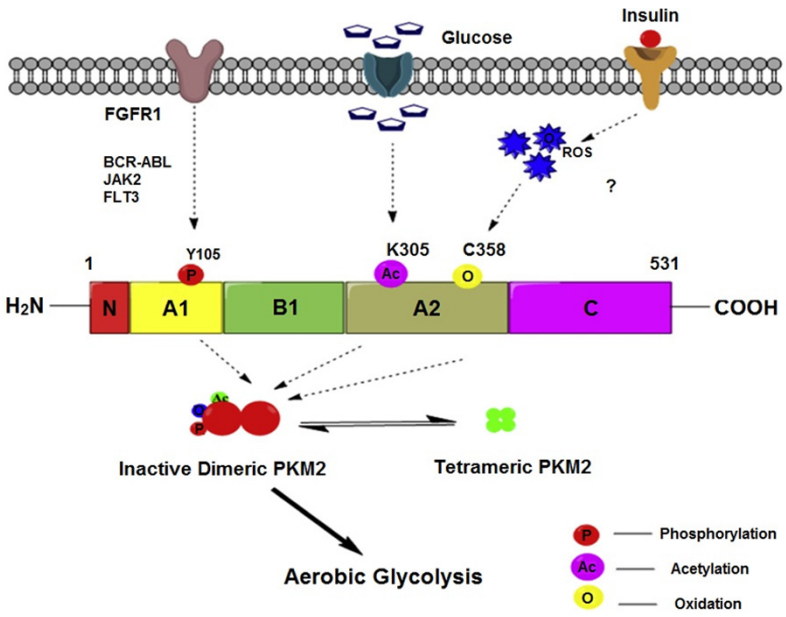

Figure 2. The structural properties of PKM2. Four domains of human PKM2 include A-, B-, C-domains, and N-terminal domain. PK activity is regulated through the level of expression and allosteric regulation. PKM2 has two structural forms, Dimeric PKM2 (inactive) and Tetrameric PKM2 (active). FGFR-dependent phosphorylation of PKM2 at Y105, Glose-dependent acetylation of PKM2 at K503, and Insulin-dependent oxidation of PKM2 at C358 cause PKM2 dimerization.

that need a large supply of ATP. Cells and tissues with a high rate of nucleogenesis are characterized by the expression of the isoform M2. PKM2 is the prototypic isoform of pyruvate kinase and is gradually replaced by other tissue specific isoforms during differentiation [13]. The replacement of PKM2 by other isoforms during tissue differentiation is indicative of a mechanism that ensures the strict regulation of PKM2 expression during development. Several studies have reported an isoform shift back to PKM2 during tumor formation.

In addition, the structural properties and catalytic activity of PKM2 are associated with tumorigenesis. PKM2 may exist in both tetrameric and dimeric forms. Kinetic analysis has revealed that the tetrameric form has high affinity (km, 0.03 mM) to its substrate PEP, whereas the dimeric form has low affinity to PEP (km, 0.46) [13-15]. It is proposed that the inter-conversion between dimeric and tetrameric PKM2 is dynamic. Increased levels of dimeric PKM2 that is less active than tetrameric lower the rate of glycolysis and increase the accumulation of fructose-1, 6-biphosphate (FBP) (a glycolysis intermediate product upstream of PKM2 and an allosteric activator of PKM2), and the latter promotes the tetramerization of PKM2. Tetrameric PKM2 in turn increases the rate of glycolysis and decreases FBP concentration, leading to dimerization of PKM2. The ratio between the tetrameric and dimeric form of PKM2 decides the overall activity of PKM2 in cellular milieu [16] and thus the glycolytic flux towards catabolism or anabolism. The tetramer: dimer ratio is also regulated by post-translational modifications as well as interactions with oncoproteins which favor the inactive dimeric form of the enzyme [13]. As thus, its characteristics are closely related to many oncogenes and tumor related transcriptional factors [16] (**Figure 2**) and it is a bridge between cancer metabolism and tumorigenesis mechanism.

PKM2 expression in HCC

Studies have confirmed that PKM2 is highly expressed in HCC tissue. Immunohistochemical analysis shows that PKM2 is mainly expressed in the cytoplasm and nucleus, and PKM2 expression is higher in cancer tissues than in paracancerous tissues [17]. Same results are also observed by mass spectrometry of serum PKM2 [18]. Even more, the levels of nuclear PKM2 can predict a poor prognosis in patients with various differentiated esophageal squamous cell carcinoma [19]. However, whether the PKM2 expression can predict a poor prognosis in HCC patients is still unclear and whether combined use of AFP and PKM2 can improve the early diagnosis of HCC is needed to be further resolved.

PKM2-related signaling pathways in HCC

Nuclear PKM2 acts as a transcriptional coactivator and non-glycolytic functions, it functions in HCC via some important signaling pathways, including Hedghog, AKT, STAT, microRNAs, etc.

Effect of PKM2 on the hedgehog (Hh) signaling pathway in HCC: Hh signaling pathway plays an important role in the process of embryonic development, which can regulate cell proliferation and differentiation. In recent years, studies have shown that Hh is not expressed in normal hepatocytes, but is related to the occurrence and development of liver cancer although the specific mechanism is still under further investigation. In HCC, when the Hh signaling pathway is activated, it can activate the expressions of *Shh*, *Ptch, Gil-1 and Smo* and other target genes or molecules (such as *P21*, *cyclin D*, etc) to participate in the proliferation and development of tumor cells. Studies also show that silencing of PKM2 can induce the down-regulation of *Gli1* expression. In contrast, PKM2 overexpression can induce up-regulation of *Gli1* expression. Some studies have revealed that PKM2 plays a regulatory role in the Hh signaling pathway [20]. However, evidence on the role of PKM2 in the Hh signaling pathway is still limited. In HCC, what are the upstream and downstream molecules of PKM2 in the Hh signaling pathway, whether PKM2 selectively regulates Gil1 expression, and whether PKM2 is able to regulate other molecules are needed to be further studied.

Effect of PKM2 on AKT signaling pathway in HCC: Many studies have demonstrated that PI-3K, AKT, and mTOR signaling pathways are regulated by dual regulation. When PI-3K and AKT are activated or PTEN and Spry2Y55F are mutated or inactivated, mTOR will be abnormally activated. Among down-regulated factors of Myc, the mTOR family and HIFs are often activated, which is related to tumor cell proliferation and nutrition supply. At present, studies have shown that *HIF-1* can increase the expression of PKM, c-Myc can regulate the variable splicing of PKM mRNA, and combined HIF-1 and c-Myc can cause a high expression of PKM2, but the specific mechanism is poorly understood [21]. In PKM2 silencing H1299 and A549 cells, the p-AKT expression significantly increased, and the changes in glucose metabolism related proteins as compared to wild strains could inhibit cell proliferation [22]. Therefore, it is necessary to compare the changes in related factors of the pathway in liver cancer cell lines with those in wild strains, PKM2 silencing cells and PKM2 over expressing cells, and to investigate the consequences of PKM2 silencing and whether PI3K, AKT and mTOR inhibitors have a synergistic effect.

Effect of PKM2 on the JAK-STAT signaling pathway in HCC: JAK-STAT signaling pathway is involved in tumor cell proliferation, differentiation, apoptosis and immune regulation [23]. It is mainly composed of three components: tyrosine kinase related receptors, tyrosine kinase JAK and transcription factor STAT. JAK has four family members, JAK1-3 and Tyk2. STAT is known as “signal transducer and activator of transcription”. STAT plays a key role in the signal transduction and transcriptional activation. To date, a total of six members have been identified for STAT, and the biological effect of STAT3 is the most important. STAT3 phosphorylation (p-STAT3) can form homodimer or heterodimer, and enter the nucleus to regulate gene transcription. Larner et al. found that STAT3 was present in the mitochondria of cells, which affected the function of mitochondrial oxidative respiratory chain complexes I and II and STAT3 in mitochondria was important for the Ras-induced tumorigenesis [24]. In 2010, Demaria et al found that the sustained activation of STAT3 caused aerobic glycolysis and reduced the mitochondrial activity of cells [25]. Recent studies have indicated that PKM2 can regulate the development of tumor through the STAT3 signaling pathway. As in colon cancer cells, PKM2 can be used as a kinase and may phosphorylate STAT3. The p-STAT3 then activates downstream factors, such as *Snail-1, Snail-2, MMP-2, MMP-9*, etc. In addition, clinical findings show that PKM2 is highly expressed and STAT3 is highly activated in colon cancer [26]. However, more studies are required to verify the relationship between PKM2 and JAK-STAT pathway in HCC.

Effect of PKM2 on β-catenin signaling pathway in cancer: As is known to all, beta catenin (β-catenin) is a key molecule in the Wnt signaling pathway. In the study on brain tumors, epidermal growth factor receptor (EGFR) activation can induce the translocation of PKM2 into the nucleus where the PKM2 binds to K433 and phosphorylates β-catenin Y333. The resultant protein complex binds to the Cyclin D1 (CCND1) promoter region, to regulate CCND1 expression [27]. Thus, it can accelerate cell proliferation and tumor formation. In colon cancer, PKM2 may be secreted from cancer cells after activation of Wnt/β-catenin signaling

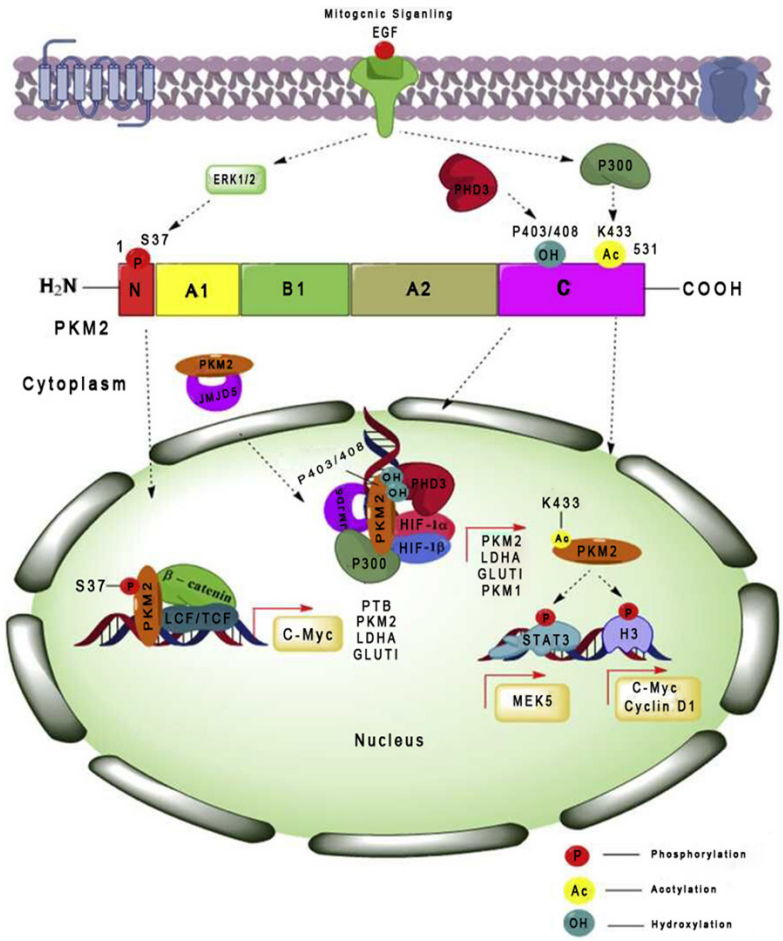

Figure 3. Functions and regulation of PKM2 in tumor cells.

pathway to induce colon cancer cell migration [28]. However, in the development of liver cancer, the activation of PKM2 and β-catenin is related to EGFR and WNT, which needs further investigation.

Effect of PKM2 on NF-κB signaling pathway in cancer: NF-kappa B (NF-κB) signaling pathway can regulate the expression of many genes [29]. PKM2 will not only affect NF-κB subunit p52 activation and stability, but lead to PLCγ-1 dependent PKCε ubiquitination through EGFR activation. After the fall down of IKKβ, NF-κB is activated [30]. By binding activation of NF-κB subunit p65 (Rela) and the promoter of PKM2, HIF-1α is further activated [31]. Thus, PKM2 may be a bridge between EGFR and NF-κB. In HCC, whether interventions of PKM2 may affect the NF-κB signaling pathway need to be further clarified.

Studies have revealed that, different from vascular endothelial growth factor (VEGF), PKM2 has a dual role: it not only plays an important role in the energy metabolism of tumor cells, but participates in the regulation of many cell signaling pathways and regulates the expressions of key genes or molecules in the tumor development. Thus, PKM2 may become a potential target in the tumor therapy (**Figure 3**). Although the function and regulation of PKM2 in tumor cells have been studied since 2011, information on the role of PKM2 in HCC is still limited, whether PKM2 functions through multiple or single signaling pathway needs further studies.

Effect of PKM2 on the microRNAs in cancer: MicroRNAs (miRs) are non-coding RNAs with specific regulatory role in gene expression. Recent reports suggest miRs have been associated with carcinogenesis and cell energy metabolism.

a. In colon cancer, miR-124, miR-137 and miR-340 can switch PKM gene expression from PKM2 to PKM1 through the feedback mechanism, which enhances oxidative stress and counteracts the Warburg effect [32].

b. In prostate cancer, results showed the miR-128-mediated ribosomal protein S6 kinase 1 (RPS6KB1)/HIF-1α/PKM2 signaling pathway can regulate the ectopic expression of SNAIL. Moreover, PKM2 can regulate cell growth, energy metabolism and play a key role in the reprogramming of cancer metabolism [33].

c. PKM2 is another target of miRNA-326. In glioma and glioma stem cells, studies found that the abnormal expression of miRNA-326 may induce cell apoptosis and impact metabolic activity by Notch pathways; PKM2 may internally adjust the expression of miRNA-326 and has the potential and trends to inhibit its expression [34].

d. Findings shown that miR-133a and miR-133b are target transcripts of PKM2, and over-

expressed PKM2 is able to inhibit the expressions of miR-133a and miR-133b in HCC [35].

On the basis of above findings, PKM2 is associated with miRNAs and multiple signaling pathways, but their relationships need to be further studied in HCC.

PKM2-induced Warburg effect and HCC

Studies have shown that HCC cell proliferation is associated with Warburg effect instead of relying on blood vessels [36]. In the proliferation of HCC cells and nodular regeneration, anaerobic glycolysis plays an important pole in the cell energy metabolism. A large number of studies have demonstrated that PKM2 is an important adjustment point. *In vitro*, PKM2 knockdown is able to decrease some lactic acid, which can further reduce HCC cell proliferation. In addition, Warburg effect is regulated by two transcription factors, hypoxia-inducible factor (*Hif*s) and *C-Myc* [37]. PKM2 and *Hif*s or PKM2 and *C-Myc* can cause a vicious cycle of Warburg effect. On the other hand, tripartite motif-containing protein 35 (TRIM35) can suppress the Warburg effect and tumorigenicity by blocking PKM2 Y105 phosphorylation [38], prolyl Hydroxylase3 (PHD3) can enhance the Warburg effect and promote HCC cells proliferation by hydroxylating PKM2 403/408 proline, and PKM2 K433 acetylation can phosphorylate β-catenin and promote the expression of c-Myc and Cyclin D1, indirectly leading to the recurrence of liver cancer [39].

Conclusion

Up to now, it is still difficult for diagnosis of early HCC. Clinically, besides AFP, no any another marker has been used for the accurate diagnosis and prognosis evaluation of HCC. Robust evidence shows PKM2 may become a factor used in this field: (1) PKM2 detection in the feces and plasma due to its sensitivity and specificity plays an important role in early diagnosis of colon cancer [28]; (2) PKM2 expression increases significantly in the endometrial cancer high-risk group of colon cancer patients [28]; (3) Clinical characteristics and tissue microarray assays prompted that PKM2 can predict an adverse outcome in patients with esophageal squamous cell carcinoma [19]. However, more direct evidence on the role of PKM2 in the early diagnosis and prognosis evaluation of HCC is needed.

Acknowledgements

This study was supported by Natural Science Youth Fund of Gansu Province (No. 1506RJYA-225) and National Natural Science Foundation of China (No. 31571439).

Disclosure of conflict of interest

None.

Address correspondence to: Jinbo Yang, School of Life Sciences, Lanzhou University, Lanzhou 730000, China. E-mail: yangjb@lzu.edu.cn

References

[1] Gluer AM, Cocco N, Laurence JM, Johnston ES, Hollands MJ, Pleass HC, Richardson AJ and Lam VW. Systematic review of actual 10-year survival following resection for hepatocellular carcinoma. HPB (Oxford) 2012; 14: 285-290.

[2] Qin LX and Tang ZY. Recent progress in predictive biomarkers for metastatic recurrence of human hepatocellular carcinoma: a review of the literature. J Cancer Res Clin Oncol 2004; 130: 497-513.

[3] Llovet JM and Bruix J. Molecular targeted therapies in hepatocellular carcinoma. Hepatology 2008; 48: 1312-1327.

[4] Warburg O. On the origin of cancer cells. Science 1956; 123: 309-314.

[5] Christofk HR, Vander Heiden MG, Harris MH, Ramanathan A, Gerszten RE, Wei R, Fleming MD, Schreiber SL and Cantley LC. The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. Nature 2008; 452: 230-233.

[6] Liu VM and Vander Heiden MG. The Role of Pyruvate Kinase M2 in Cancer Metabolism. Brain Pathol 2015; 25: 781-783.

[7] Tamada M, Suematsu M and Saya H. Pyruvate kinase M2: multiple faces for conferring benefits on cancer cells. Clin Cancer Res 2012; 18: 5554-5561.

[8] Fantin VR, St-Pierre J and Leder P. Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. Cancer Cell 2006; 9: 425-434.

[9] Anastasiou D, Poulogiannis G, Asara JM, Boxer MB, Jiang JK, Shen M, Bellinger G, Sasaki AT, Locasale JW, Auld DS, Thomas CJ, Vander Heiden MG and Cantley LC. Inhibition of pyruvate kinase M2 by reactive oxygen species contributes to cellular antioxidant responses. Science 2011; 334: 1278-1283.

[10] Noguchi T, Yamada K, Inoue H, Matsuda T and Tanaka T. The L- and R-type isozymes of rat pyruvate kinase are produced from a single gene

by use of different promoters. J Biol Chem 1987; 262: 14366-14371.
[11] Noguchi T, Inoue H and Tanaka T. The M1- and M2-type isozymes of rat pyruvate kinase are produced from the same gene by alternative RNA splicing. J Biol Chem 1986; 261: 13807-13812.
[12] Dombrauckas JD, Santarsiero BD and Mesecar AD. Structural basis for tumor pyruvate kinase M2 allosteric regulation and catalysis. Biochemistry 2005; 44: 9417-9429.
[13] Mazurek S, Boschek CB, Hugo F and Eigenbrodt E. Pyruvate kinase type M2 and its role in tumor growth and spreading. Semin Cancer Biol 2005; 15: 300-308.
[14] Mazurek S. Pyruvate kinase type M2: a key regulator within the tumour metabolome and a tool for metabolic profiling of tumours. Ernst Schering Found Symp Proc 2007; 99-124.
[15] Eigenbrodt E, Reinacher M, Scheefers-Borchel U, Scheefers H and Friis R. Double role for pyruvate kinase type M2 in the expansion of phosphometabolite pools found in tumor cells. Crit Rev Oncog 1992; 3: 91-115.
[16] Gupta V and Bamezai RN. Human pyruvate kinase M2: a multifunctional protein. Protein Sci 2010; 19: 2031-2044.
[17] Yamashita T, Honda M, Takatori H, Nishino R, Minato H, Takamura H, Ohta T and Kaneko S. Activation of lipogenic pathway correlates with cell proliferation and poor prognosis in hepatocellular carcinoma. J Hepatol 2009; 50: 100-110.
[18] Jia D, Wei L, Guo W, Zha R, Bao M, Chen Z, Zhao Y, Ge C, Zhao F, Chen T, Yao M, Li J, Wang H, Gu J and He X. Genome-wide copy number analyses identified novel cancer genes in hepatocellular carcinoma. Hepatology 2011; 54: 1227-1236.
[19] Zhang X, He C, He C, Chen B, Liu Y, Kong M, Wang C, Lin L, Dong Y and Sheng H. Nuclear PKM2 expression predicts poor prognosis in patients with esophageal squamous cell carcinoma. Pathol Res Pract 2013; 209: 510-515.
[20] Xu Q, Liu X, Zheng X, Yao Y and Liu Q. PKM2 regulates Gli1 expression in hepatocellular carcinoma. Oncol Lett 2014; 8: 1973-1979.
[21] Nemazanyy I, Espeillac C, Pende M and Panasyuk G. Role of PI3K, mTOR and Akt2 signalling in hepatic tumorigenesis via the control of PKM2 expression. Biochem Soc Trans 2013; 41: 917-922.
[22] Qin X, Du Y, Chen X, Li W, Zhang J and Yang J. Activation of Akt protects cancer cells from growth inhibition induced by PKM2 knockdown. Cell Biosci 2014; 4: 20.
[23] Murray PJ. The JAK-STAT signaling pathway: input and output integration. J Immunol 2007; 178: 2623-2629.
[24] Demaria M and Poli V. PKM2, STAT3 and HIF-1alpha: The Warburg's vicious circle. Jakstat 2012; 1: 194-196.
[25] Demaria M, Giorgi C, Lebiedzinska M, Esposito G, D'Angeli L, Bartoli A, Gough DJ, Turkson J, Levy DE, Watson CJ, Wieckowski MR, Provero P, Pinton P and Poli V. A STAT3-mediated metabolic switch is involved in tumour transformation and STAT3 addiction. Aging (Albany NY) 2010; 2: 823-842.
[26] Papadaki C, Sfakianaki M, Lagoudaki E, Giagkas G, Ioannidis G, Trypaki M, Tsakalaki E, Voutsina A, Koutsopoulos A, Mavroudis D, Georgoulias V and Souglakos J. PKM2 as a biomarker for chemosensitivity to front-line platinum-based chemotherapy in patients with metastatic non-small-cell lung cancer. Br J Cancer 2014; 111: 1757-1764.
[27] Yang W, Xia Y, Ji H, Zheng Y, Liang J, Huang W, Gao X, Aldape K and Lu Z. Nuclear PKM2 regulates beta-catenin transactivation upon EGFR activation. Nature 2011; 480: 118-122.
[28] Yang P, Li Z, Wang Y, Zhang L, Wu H and Li Z. Secreted pyruvate kinase M2 facilitates cell migration via PI3K/Akt and Wnt/beta-catenin pathway in colon cancer cells. Biochem Biophys Res Commun 2015; 459: 327-332.
[29] Senftleben U, Cao Y, Xiao G, Greten FR, Krahn G, Bonizzi G, Chen Y, Hu Y, Fong A, Sun SC and Karin M. Activation by IKKalpha of a second, evolutionary conserved, NF-kappa B signaling pathway. Science 2001; 293: 1495-1499.
[30] Cui Y, Nadiminty N, Liu C, Lou W, Schwartz CT and Gao AC. Upregulation of glucose metabolism by NF-kappaB2/p52 mediates enzalutamide resistance in castration-resistant prostate cancer cells. Endocr Relat Cancer 2014; 21: 435-442.
[31] Xu Q, Liu LZ, Yin Y, He J, Li Q, Qian X, You Y, Lu Z, Peiper SC, Shu Y and Jiang BH. Regulatory circuit of PKM2/NF-kappaB/miR-148a/152-modulated tumor angiogenesis and cancer progression. Oncogene 2015; 34: 5482-5493.
[32] Sun Y, Zhao X, Zhou Y and Hu Y. miR-124, miR-137 and miR-340 regulate colorectal cancer growth via inhibition of the Warburg effect. Oncol Rep 2012; 28: 1346-1352.
[33] Tao T, Li G, Dong Q, Liu D, Liu C, Han D, Huang Y, Chen S, Xu B and Chen M. Loss of SNAIL inhibits cellular growth and metabolism through the miR-128-mediated RPS6KB1/HIF-1alpha/PKM2 signaling pathway in prostate cancer cells. Tumour Biol 2014; 35: 8543-8550.
[34] Kefas B, Comeau L, Erdle N, Montgomery E, Amos S and Purow B. Pyruvate kinase M2 is a target of the tumor-suppressive microRNA-326 and regulates the survival of glioma cells. Neuro Oncol 2010; 12: 1102-1112.
[35] Wong TS, Liu XB, Chung-Wai Ho A, Po-Wing Yuen A, Wai-Man Ng R and Ignace Wei W.

Identification of pyruvate kinase type M2 as potential oncoprotein in squamous cell carcinoma of tongue through microRNA profiling. Int J Cancer 2008; 123: 251-257.

[36] Kitamura K, Hatano E, Higashi T, Narita M, Seo S, Nakamoto Y, Yamanaka K, Nagata H, Taura K, Yasuchika K, Nitta T and Uemoto S. Proliferative activity in hepatocellular carcinoma is closely correlated with glucose metabolism but not angiogenesis. J Hepatol 2011; 55: 846-857.

[37] Gordan JD, Thompson CB and Simon MC. HIF and c-Myc: sibling rivals for control of cancer cell metabolism and proliferation. Cancer Cell 2007; 12: 108-113.

[38] Chen Z, Wang Z, Guo W, Zhang Z, Zhao F, Zhao Y, Jia D, Ding J, Wang H, Yao M and He X. TRIM35 Interacts with pyruvate kinase isoform M2 to suppress the Warburg effect and tumorigenicity in hepatocellular carcinoma. Oncogene 2015; 34: 3946-3956.

[39] Luo W, Hu H, Chang R, Zhong J, Knabel M, O'Meally R, Cole RN, Pandey A and Semenza GL. Pyruvate kinase M2 is a PHD3-stimulated coactivator for hypoxia-inducible factor 1. Cell 2011; 145: 732-744.