SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 18: 5663-5672, 2019

The role of pyruvate kinase M2 in anticancer therapeutic treatments (Review)

QIONGLI SU[1], SHENGPING LUO[1], QIUHONG TAN[1], JUN DENG[2], SICHUN ZHOU[2], MEI PENG[3], TING TAO[4] and XIAOPING YANG[2]

[1]Department of Pharmacy, Zhuzhou Central Hospital, Zhuzhou, Hunan 412000; [2]Key Laboratory of Study and Discovery of Small Targeted Molecules of Hunan Province, School of Medicine, Hunan Normal University, Changsha, Hunan 410013; [3]Department of Pharmacy, Xiangya Hospital, Central South University, Changsha, Hunan 410008; [4]Department of Pharmacy, Yueyang Maternal-Child Medicine Health Hospital, Yueyang, Hunan 414000, P.R. China

Received January 28, 2019; Accepted September 6, 2019

DOI: 10.3892/ol.2019.10948

Abstract. Cancer cells are characterized by a high glycolytic rate, which leads to energy regeneration and anabolic metabolism; a consequence of this is the abnormal expression of pyruvate kinase isoenzyme M2 (PKM2). Multiple studies have demonstrated that the expression levels of PKM2 are upregulated in numerous cancer types. Consequently, the mechanism of action of certain anticancer drugs is to downregulate PKM2 expression, indicating the significance of PKM2 in a chemotherapeutic setting. Furthermore, it has previously been highlighted that the downregulation of PKM2 expression, using either inhibitors or short interfering RNA, enhances the anticancer effect exerted by THP treatment on bladder cancer cells, both *in vitro* and *in vivo*. The present review summarizes the detailed mechanisms and therapeutic relevance of anticancer drugs that inhibit PKM2 expression. In addition, the relationship between PKM2 expression levels and drug resistance were explored. Finally, future directions, such as the targeting of PKM2 as a strategy to explore novel anticancer agents, were suggested. The current review explored and highlighted the important role of PKM2 in anticancer treatments.

Correspondence to: Ms. Qiongli Su, Department of Pharmacy, Zhuzhou Central Hospital, 116 Changjiang South Road, Tianyuan, Zhuzhou, Hunan 412000, P.R. China
E-mail: suqiongli151@163.com

Dr Xiaoping Yang, Key Laboratory of Study and Discovery of Small Targeted Molecules of Hunan Province, School of Medicine, Hunan Normal University, 371 Tongzipo Road, Changsha, Hunan 410013, P.R. China
E-mail: xiaoping.yang@hunnu.edu.cn

Abbreviations: PKM2, pyruvate kinase isoenzyme M2; PTBP1, polypyrimidine tract-binding protein 1; HIF-1α, hypoxia inducible factor 1 alpha; CSCs, cancer stem cells; EMT, epithelial-mesenchymal transition; TGF-β1, transforming growth factor β1; P53, tumor protein 53; mTOR, mammalian target of rapamycin; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; CRC, colorectal cancer; NSCLC, non-small-cell lung carcinoma

Key words: PKM2, cancer, chemotherapeutic drugs, resistance, target

Contents

1. Introduction

Cancer is a disease with a high prevalence and mortality rate, and its treatment represents a considerable clinical challenge. The benefits of current chemotherapeutics are limited due to their propensity to cause DNA damage in normal cells (1). Therefore, research has been directed towards finding safer and more sustainable cancer treatments. Notably, it has been demonstrated that targeting the regulation of tumor cell metabolism, without causing toxicity in normal cells, is a potential strategy for the treatment or adjuvant therapy of cancer (2).

The metabolic mechanism is one of a multitude of differential characteristics separating cancer cells from normal cells. Tumor cells are primarily dependent on aerobic glycolysis to obtain energy and produce lactate, even in the presence of oxygen (3). Recently, the targeting of cancer cell metabolism has gained traction as an effective strategy for the development of new cancer treatments (4,5). In 2017, the Food and Drug Administration approved Enasidenib (AG-221), an inhibitor of the mutant isocitrate dehydrogenase 2 (IDH2) protein, for the treatment of relapsed or refractory acute myeloid leukemia (6). In addition to IDH2, pyruvate kinase isoenzyme M2 (PKM2) has also emerged as a critical regulator of cancer cell metabolism. PK is an enzyme that plays a critical function in the glycolytic pathway, catalyzing the final, rate-limiting step of glycolysis by converting phosphoenolpyruvate and ADP to

pyruvate and ATP, respectively (7,8). Alternate splicing of PKM pre-mRNA by heterogeneous nuclear ribonucleoprotein A1/2 and polypyrimidine-tract binding protein (PTBP1), results in PKM2 generation (9). There is mounting evidence that unlike other PK isoforms, PKM2 is upregulated in multiple carcinomas, including colorectal (10), lung (11), liver (12), breast cancer (13) and pancreatic ductal adenocarcinoma (14). The general molecular mechanisms involved in tumor growth are briefly summarized in Fig. 1.

The upregulation of PKM2 expression enhances chemosensitivity in breast (15), gastric (16) and colorectal cancer (17). High expression levels of PKM2 have been shown to be associated with increased chemosensitivity to 5-fluorouracil (5-FU) and epirubicin in breast and cervical cancer (15,18). By contrast, PKM2 contributes to gefitinib resistance via the upregulation of STAT3 in colorectal cancer (19). Moreover, the downregulation of PKM2 leads to cell apoptosis and increases the sensitivity of tumor cells to chemotherapy (20). This highlights the ability of PKM2 to alter cell sensitivity to chemotherapy.

The present review summarizes the advancements in targeting PKM2 expression as a novel therapeutic strategy. The underlying mechanisms, and the potential for future clinical translation, were also analyzed. An informative overview of PKM2 is detailed, establishing a precedent for the development of clinical therapeutics that target PKM2, for the treatment of cancer.

2. Biochemical role of PKM2 in physiological processes

PKM2 can function as: i) A metabolic enzyme; ii) a protein kinase; or iii) a transcriptional coactivator of genes that influence cell proliferation, migration and apoptosis. It has been demonstrated that the inhibition of PKM2 slows tumor growth or causes tumor cell death (21). Following PKM2 inhibition, a reduction in cancer cell proliferation and survival have both been observed (21,22). RNA interference and peptide aptamers that ablate PKM2 have been reported to elicit anticancer effects, such as the impairment of tumor growth, the induction of apoptotic cell death and increasing sensitivity to chemotherapy (20,23-26). Conversely, a PKM2 activator was proven to effectively induce apoptosis in lung cancer cells via the inhibition of AKT phosphorylation (27). The aforementioned findings support the hypothesis that PKM2 represents a promising therapeutic target.

Activators of PKM2 exert their effects by stabilizing the molecular in its tetramer form, subsequently affecting cancer cell metabolism and indicating a novel anti-cancer therapeutic strategy (28). To date, several PKM2 activators have been reported, including N,N'-diarylsulfonamide (29) and 2-((1H-benzo[d]imidazol-1-yl)methyl)-4H-pyrido[1,2-a] pyrimidin-4-ones (30). The structures of certain PKM2 activators are detailed in Table I (29-35). Conversely, PKM2 inhibitors (such as shikonin; Fig. 2) have been studied and will be explored in the following sections.

3. PKM2-inhibitory compounds

Shikonin. Shikonin is an active chemical component extracted from *Lithospermum erythrorhizon*, which has been found to exert multiple pharmacological effects. Notably, it exhibits antitumor properties in numerous human cancer types (36,37). Shikonin has been identified as a PKM2 inhibitor and is able to reduce the rate of cancer cell glycolysis (38). Additionally, one study determined that shikonin improved the therapeutic efficacy of Taxol, and reduced chemoresistance to cisplatin in advanced bladder cancer (BC) via the inhibition of PKM2 (38). In summary, shikonin is able to inhibit tumor growth by suppressing aerobic glycolysis, which is mediated by PKM2 *in vivo* (39).

Li *et al* (40) demonstrated that PKM2 expression levels were higher in skin tumor tissues than normal tissues. Moreover, it was also observed that shikonin inhibited cancer-cell transformation and PKM2 activation, which was induced by the tumor promoter 12-O-tetradecanoylphorbol 13-acetate in the early stages of carcinogenesis. Furthermore, another study indicated that shikonin reduced epidermal growth factor receptor, PI3K, p-AKT, Hypoxia inducible factor-1α (HIF-1α) and PKM2 expression levels. Moreover, the viability of esophageal cancer cells was decreased and cell apoptosis was induced in the presence of shikonin (41). Additionally, increased expression levels of PKM2 increase the resistance of esophageal cancer cells to shikonin. It was observed that shikonin exerted its chemotherapeutic effects via the induction of cell apoptosis *in vivo*. To summarize, shikonin was determined to inhibit esophageal and bladder cancer progression via the inhibition of PKM2 expression (41,42).

However, because the clinical use of shikonin as an anticancer agent is still limited by its toxicity and poor solubility (43), it is problematic to incorporate directly into cancer therapy regimes. The study of PKM2 inhibitors is ongoing and the discovery of novel inhibitors with low toxicity would confer great benefit to patients with cancer (44).

Metformin. Metformin (a commonly prescribed drug used for the treatment of type II diabetes) has been extensively investigated as a metabolic modulator, but also exhibits anticancer properties. Epidemiological evidence has demonstrated that metformin exhibits high potential efficacy as an antitumor agent (45). Data gathered from multiple xenograft cancer models suggest that metformin may inhibit the progression and recrudescence of cancer (46).

Moreover, metformin induces tumor cell death and increases sensitivity to chemotherapeutic drugs via the inhibition of PKM2. For instance, Shang *et al* (47) demonstrated that metformin enhanced the sensitivity of osteosarcoma stem cells to cisplatin, by reducing the expression level of PKM2. Mechanistically, it was confirmed that upregulated expression levels of PKM2 were responsible for resistance to cisplatin in osteosarcoma stem cells. Additionally, PKM2 downregulation by metformin has been shown to result in the inhibition of glucose uptake, lactate production and ATP production in human osteosarcoma cancer stem cells (CSCs). Metformin was also found to exert a significant antitumor effect on gastric cancer cells via inhibition of the hypoxia-inducible factor (HIF)1α/PKM2 signaling pathway (48). Moreover, it was determined that the upregulation of PKM2 induced epithelial-mesenchymal transition (EMT), which in turn increased the invasion and metastatic potential of carcinoma cells (49). Cheng *et al* (50) discovered that metformin inhibits

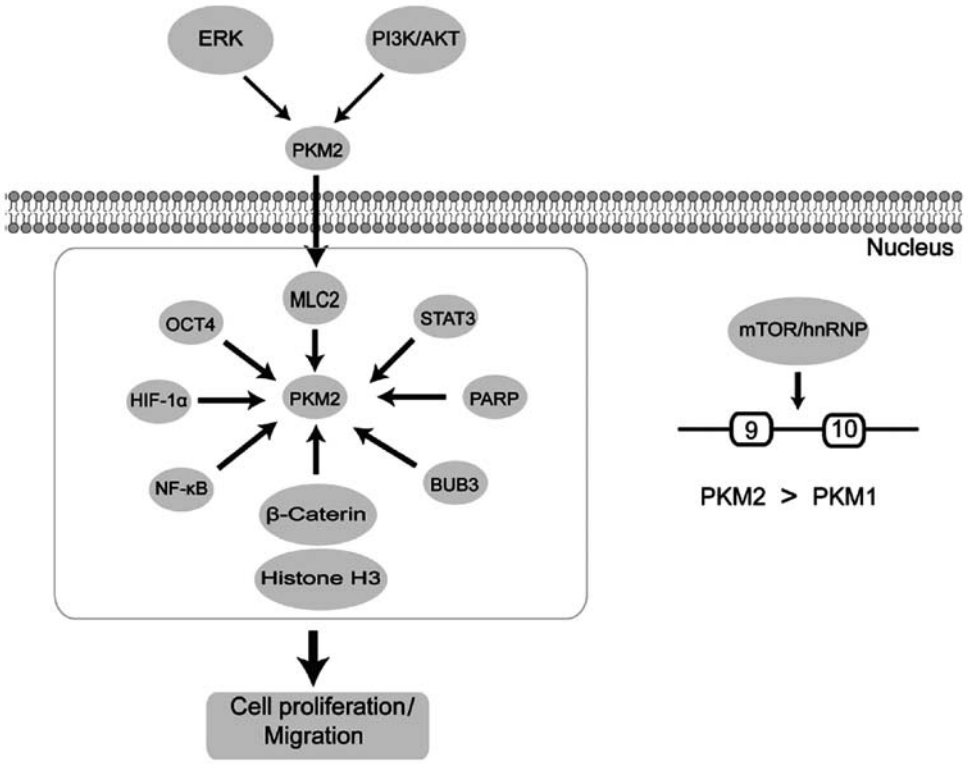


Figure 1. Pathways related to tumor growth involving PKM2. PKM2 is phosphorylated by ERK2 or PI3K/AKT resulting the nuclear translocation of PKM2. Nuclear PKM2 binds to proteins upregulating transcriptional activity, thereby promoting the Warburg effect and tumorigenesis; hnRNP induces PKM2 via alternative splicing of PKM genes to stimulate cancer cell invasion and migration. PKM2, pyruvate kinase isoenzyme M2; HIF1α, hypoxia inducible factor 1α; hnRNP, heterogeneous nuclear ribonucleoproteins; MLC2, myosin light chain 2; PARP, poly(ADP-ribose) polymerase 1; BUB3, BUB3 mitotic checkpoint protein; OCT4, octamer-binding transcription factor 4.

transforming growth factor β1 (TGF-β1)-induced EMT in cervical cancer cells, and also investigated the mechanisms involved in tumorigenesis (which reduced PKM2 expression levels). Furthermore, the present authors demonstrated that decreased PKM2 expression levels, induced by metformin, enhanced the efficiency of THP (Docetaxel, Trastuzumab and Pertuzumab) for BC treatment (51).

Vitamin K (VK)3 and 5. VK family members are essential and fat-soluble naphthoquinones that serve vital physiological roles (52). Numerous studies have suggested that VK3 and 5 are promising anticancer adjuvants, both *in vitro* and *in vivo* (53-57). It has been demonstrated that combination therapy with VK3 and vitamin C exerts a synergistic anticancer effect in Jurkat and K562 cells (58,59). VK3 also improves the efficacy of anticancer drugs such as doxorubicin (DOX) (58,60). Moreover, a clinical trial suggested that VK3 improves cell sensitivity to Inopera: Chen *et al* (61) discovered that VK3 and 5 inhibit PKM2 significantly more than PKM1 and pyruvate kinase isoenzyme L, while other isoforms of PK are predominantly expressed in most adult tissues and the liver. This study further demonstrated that VK3 and 5 have the potential to exert a therapeutic effect on cancer cells via the suppression of PKM2 expression.

Temozolomide (TMZ). TMZ is an antitumor drug that damages DNA, and is used to treat glioblastoma (GBM). It also inhibits the rate of pyruvate-to-lactate transformation (62-64). Park *et al* (65) demonstrated that TMZ alters PKM2 expression, leading to changes in pyruvate metabolism, and highlighting that PKM2 plays a key role in the DNA-damage response.

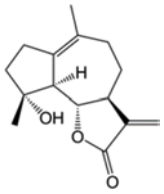
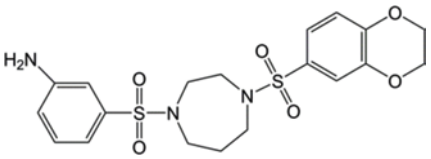
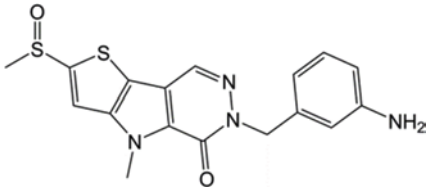
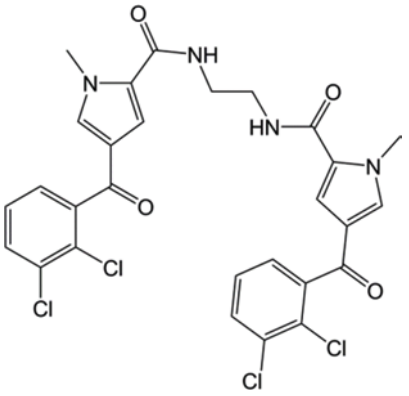
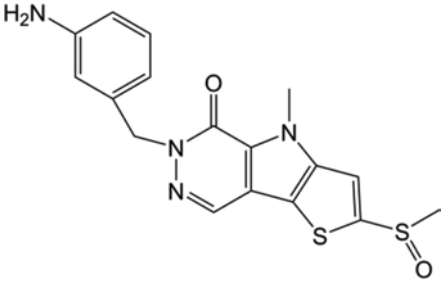
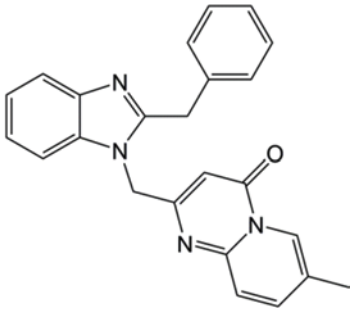
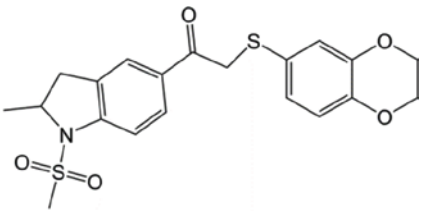
4. PKM2 activity influences chemosensitivity

Resistance to chemotherapy is a major challenge concerning cancer treatment; therefore, overcoming the development of resistance in cancer cells remains a primary focus (66). Drug-resistant cancer cells exhibit an increased glycolytic rate, meaning that targeting glycolysis may represent a novel strategy to reduce the adverse effects of drug resistance (67). Therefore, the role of PKM2 in the development of chemoresistance in cancer cells, and the targeting of PKM2 expression, are important factors that could help to increase the sensitivity of cancer cells to chemotherapy.

Gemcitabine (GEM). GEM is a targeted drug metabolite with two fluorine atoms that has been suggested by the National Comprehensive Cancer Network guidelines as a first-line chemotherapeutic agent for the treatment of pancreatic cancer (68); however, only a small proportion of patients respond positively to GEM. Despite a meta-analysis showing that the combination of GEM with other therapeutics results in significantly higher disease response rates, and longer progression-free and overall survival, after several typical chemotherapy treatment cycles, the emergence of drug resistance often leads to therapeutic failure (69).

The resistance of pancreatic cancer cells to GEM involves PKM2 expression and its nonmetabolic function.

Table I. Structures of representative PKM2 activators.

PKM2 activators	Structures	(Refs.)
Micheliolide		(31)
Diarylsulfonamides		(29)
Thieno[3,2-b]pyrrole[3,2-d]pyridazinones		(32)
4-(2,3-dichlorobenzoyl)-1-methyl-pyrrole-2-carboxamide		(33)
TEPP-46		(34)
2-((1H-benzo[d]imidazol-1-yl)methyl)-4H-pyrido[1,2-a]pyrimidin-4-ones		(30)
1-(sulfonyl)-5-(arylsulfonyl)indoline		(35)

PKM2, pyruvate kinase isoenzyme M2.

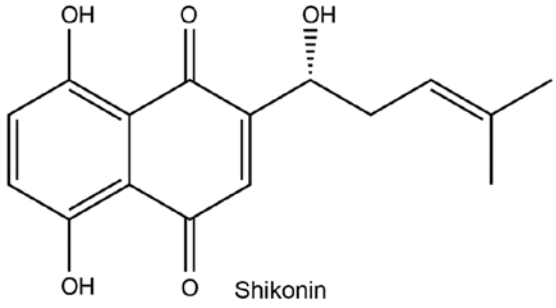


Figure 2. Chemical structure of shikonin.

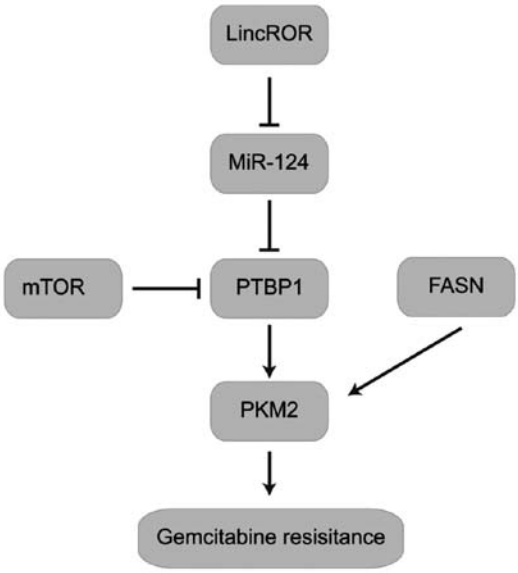


Figure 3. Major role of PKM2 in gemcitabine resistance. The lincROR/miR-124/PTBP1/PKM2 complex is involved in the regulation of gemcitabine resistance. FASN regulates PKM2 expression and is associated with gemcitabine resistance. LincROR, long intergenic non-protein coding RNA, regulator of reprogramming PKM2, pyruvate kinase isoenzyme M2; PTBP1, polypyrimidine tract binding protein; FASN, Fatty acid synthase; miR, micro RNA.

Thus, PKM2 should be considered a therapeutic target in GEM-resistant pancreatic cancer cells (70,71). The role of PKM2 in GEM resistance is demonstrated in Fig. 3. Kim *et al* (72) discovered that PKM2-knockdown induced tumor protein 53 activation via the p38 mitogen-activated protein kinase signaling pathway, following treatment with GEM. Subsequent apoptosis was then induced through the activation of caspase 3/7 and poly ADP-ribose polymerase cleavage. These findings further indicate PKM2 as a novel target for the treatment of GEM resistance, and also support the combination of GEM with a PKM2 inhibitor for treating pancreatic cancer.

Calabretta *et al* (73) mechanistically characterized a novel PTBP1/PKM2 pro-survival pathway, triggered by chronic treatment of pancreatic ductal adenocarcinoma (PDAC) cells with GEM. It was observed that alternative splicing of PKM was found to be differently regulated in DR-PDAC cells, leading to an increase in the cancer-associated PKM2 isoform. Moreover, upregulation of PKM2 expression was also associated with shorter recurrence-free survival times in patients with PDAC. These findings indicate that PKM2 is a novel potential therapeutic target that may improve the response of PDAC to chemotherapy, and reduce the resistance of cancer cells to current treatments (73). Li *et al* (71) also determined that GEM resistance to pancreatic cancer cells is associated with a long intergenic non-protein coding RNA, regulator of reprogramming /PTBP1/PKM2 axis (71).

Platinum. Cisplatin, carboplatin and oxaliplatin (OXA) are typically used to treat human cancers. However, their clinical success is limited by severe side effects and intrinsic or acquired resistance (74).

Cisplatin. Cisplatin, the first discovered platinum anticancer drug, is active against a wide spectrum of solid neoplasms, including ovarian, bladder, colorectal and lung cancer (75-77). However, treatment with cisplatin often results in drug resistance and several adverse side effects (78).

Wang *et al* (76) determined that shikonin inhibited PKM2 and reduced BC cell survival time in a dose-dependent, but also a PK activity-independent manner. PKM2 upregulation is strongly associated with cisplatin resistance; however, cisplatin-resistant cells respond sensitively to shikonin when PKM2 is upregulated. In mice, the combination of shikonin and cisplatin significantly reduced BC growth and metastasis (in contrast to monotherapy with either drug). Thus, PKM2 is indicated as a key factor in the development of resistance to cisplatin treatment in advanced BC. Suppression of PKM2 via RNAi or specific inhibitors may be an effective approach to reducing resistance and improving the outcomes of patients with advanced BC (76). Furthermore, a study conducted by Shang *et al* (47) confirmed that osteosarcoma stem cells exhibit significantly higher levels of cisplatin resistance compared with osteosarcoma non-CSCs. The aforementioned results indicated that PKM2 upregulation caused resistance to cisplatin in osteosarcoma stem cells.

Zhu *et al* (18) collected tumor tissues from 36 patients with cervical cancer (pre- and post-chemotherapy). The expression levels of multiple tumor-associated proteins (including PKM2 and HIF1α) were then determined using immunohistochemistry. As a result, it was discovered that the mTOR/HIF-1α/c-Myc/PKM2 signaling pathway was significantly downregulated in patients with cervical cancer, following chemotherapy. It was then demonstrated that PKM2 inhibited the proliferation of cervical cancer cells, and enhanced their sensitivity to cisplatin *in vitro*. Additionally, PKM2 was inextricably associated with the mTOR pathway. PKM2 and mTOR expression in cervical cancer tissues may serve as predictive biomarkers for the use of cisplatin-based chemotherapy. Consequently, it was concluded that PKM2 increased the sensitivity of cervical cancer cells to cisplatin, by interacting with the mTOR signaling pathway.

It has been demonstrated that PKM2 is closely associated with the sensitivity of certain cancer cells to cisplatin. However, PKM2 may exert an opposing effect by either increasing or decreasing the antitumor activity of cisplatin. Table II summarizes the effect of PKM2 on the sensitivity of multiple tumors to cisplatin treatment (18,47,76,79,80).

Table II. Effect of pyruvate kinase isoenzyme M2 on cisplatin sensitivity in different cancers.

Cancer type	Effect	Treatment	(Refs.)
Bladder cancer	Overcomes resistance	Shikonin	(76,79)
Hepatocellular carcinoma	Chemosensitivity	MicroRNA-199a	(80)
Osteosarcoma	Chemosensitivity	Metformin	(47)
Cervical cancer	Chemosensitivity	PKM2	(18)

PKM2, pyruvate kinase isoenzyme M2.

Carboplatin. Carboplatin is also a platinum-based chemotherapeutic drug. It is an effective treatment for various solid tumor types, particularly non-small cell lung cancer (NSCLC) (81). However, NSCLC cells commonly develop resistance following carboplatin treatment (82). Liu *et al* (83) investigated carboplatin-resistant NSCLC models using the A549 and PC9 lung cancer cell lines, termed A549/R and PC9/R, respectively. It was discovered that as well as the low sensitivity of A549/R and PC9/R cells to carboplatin treatment, resistant cells exhibited higher glucose metabolism than wild type cells. Mechanistically, it was confirmed that a high expression level of PKM2 in A549/R and PC9/R cells was dependent on both a high rate of glucose metabolism, and carboplatin resistance (83).

OXA. OXA is a third-generation platinum-based compound (84) and is the first platinum-based therapy to categorically exhibit clinical activity against CRCs (85). However, an increasing number of research reports have detailed the development of OXA resistance in CRC therapy, and this has become problematic for its clinical application (86,87). Despite this, it has been elucidated that PKM2 is associated with OXA resistance *in vitro* (88,89). In conclusion, PKM2 may play an important role in the development of OXA resistance in cancer cells.

5-FU. 5-FU is an anticancer drug, commonly used in the treatment of colon cancer. Acquired resistance is becoming a key challenge for the treatment of patients in the advanced stages of colon cancer (90). He *et al* (91) discovered that aerobic glycolysis was significantly upregulated in 5-FU-resistant cells (91). It was also reported that PKM2 is targeted by miR-122 in colon cancer cells. High expression levels of miR-122 in 5-FU-resistant cells has been shown to reduce resistance to 5-FU through the inhibition of PKM2, both *in vitro* and *in vivo*. In summary, research indicates that enhanced glucose metabolism reduces 5-FU resistance to cancer cells, and that the inhibition of glycolysis may be a possible therapeutic method to overcome 5-FU resistance (91,92).

DOX. DOX is an anticancer drug used to treat hepatocellular carcinoma. Acquired drug resistance following treatment represents a major challenge for both DOX and other chemotherapeutic agents. Pan *et al* (93) determined that the expression levels of miR-122 were lower in DOX-resistant Huh7/R cells compared with wild type cells, demonstrating that miR-122 is associated with chemoresistance to DOX. This was supported by the results of a luciferase reporter assay. High expression levels of miR-122 in Huh7/R cells were shown to reverse doxorubicin resistance via the inhibition of PKM2, leading to DOX-resistant cancer cell apoptosis. Therefore, it was demonstrated that the upregulation of glucose metabolism increases resistance to DOX, thus, inhibition of glycolysis by miR-122 may represent a potential therapeutic strategy to reduce DOX resistance in liver cancer (93).

Docetaxel. Docetaxel, a derivative of taxane, is an antineoplastic drug that is effective for the treatment of multiple malignant tumor types. It inhibits microtubule disassembly, consequently interfering with mitotic progress by blocking cells at the G_2/M checkpoint, and promoting apoptosis (94). Docetaxel is widely used to treat breast cancer (95-97), NSCLC (98,99) and other solid tumors (100), exhibiting significant therapeutic efficacy.

Shi *et al* (11) determined that combining plasmid short hairpin (sh)RNA-PKM2 with standard docetaxel treatment significantly improved its efficacy (11). Moreover, a significant reduction in the expression level of PKM2 markedly suppressed A549 cell proliferation (11). Yuan *et al* (66) investigated the effect of PKM2 silencing combined with docetaxel treatment, on cell viability, cell cycle distribution and apoptosis of the A549 and H460 NSCLC cell lines. shRNA-PKM2 could serve as a combination therapy with docetaxel in patients with NSCLC by reducing PKM2 expression, resulting in decreased cell viability, an increase in cell cycle arrest at the G_2/M checkpoint, and apoptosis. These results further suggest that targeting PKM2 has the potential to improve the treatment outcomes of patients with NSCLC, by increasing the chemotherapeutic efficacy of docetaxel (66).

5. Conclusions

Cancer is a fatal and prevalent disease with a high mortality rate worldwide, and it is predicted that the number of new cancer cases will increase to 19.3 million per year by 2025 (101). The reprogramming of cell metabolism is essential for tumorigenesis and is regulated by a complex network, in which PKM2 plays a critical role (102). PKM2 is typically upregulated in rapidly proliferating cells, such as cancerous and embryonic cells. It has been suggested that PKM2 plays an important role in cancer progression through the regulation of both metabolic and nonmetabolic pathways. Intermediate products of glycolysis, such as amino acids, nucleotides and lipids are required to sustain the rapid growth of cancer cells (103). Furthermore,

high patient mRNA expression levels of PKM2 are associated with reduced median overall survival time (104). Interestingly, PKM2 can also serve as a biomarker, indicating patient sensitivity to chemotherapy. It has been demonstrated that downregulation of PKM2 expression improved the anticancer efficacy of THP treatment (51), thus, the clinical application of PKM2 activators and inhibitors in cancer therapy warrants further investigation.

In the present review, the antitumor effects of various PKM2 inhibitors were summarized. A multitude of *in vitro* and *in vivo* studies have determined the role of PKM2 in tumorigenesis and progression. Moreover, the effect of PKM2 on the sensitivity of cancer cells to certain clinically-available chemotherapeutic drugs was investigated. Numerous studies have confirmed that the inhibition of PKM2 increased tumor cell sensitivity to chemotherapy. However, PKM2 increased the sensitivity of cervical cancer cells to cisplatin by interacting with the mTOR pathway (18). The association between PKM2 expression and the development of resistance has been investigated in several types of cancer, albeit with conflicting results. A potential explanation for these discrepancies is that PKM2 has been proposed to fluctuate between different forms in order to regulate glucose metabolism. The low activity dimeric form supports cell growth by increasing the levels of glycolytic intermediates necessary for biosynthetic processes. However, when energy levels decrease, the enzyme can switch to the high activity tetrameric form and facilitate oxidative phosphorylation (20). Therefore, the resulting mechanisms may be quite different. Another explanation for the conflicting results may be that cancer cells possess the ability to alter their metabolism and regulate sensitivity to chemotherapeutics (80). Although PKM2 has become a focus of research in recent years, the development of specific inhibitors and activators of PKM2 remains to be achieved. Moreover, limited research has been conducted on results from clinical trials. It is suggested that the intervention of cancer cell metabolism via the precise regulation of PKM2 expression and activity may represent a promising translational application that warrants further investigation.

Acknowledgements

Not applicable.

Funding

The present review was supported by grants from the National Natural Science Foundation of China (grant no. 81874212), the Hunan Natural Science Foundation (grant no. 2016JJ2187), the Key Project of Hunan Province 2016 (grant no. 2016JC2036) and start-up funds of the Key Laboratory of Study and Discovery of Targeted Small Molecules of Hunan Province (grant no. 2017TP020) to XY, and from the National Natural Science Foundation of China (grant no. 81703008) and the Institutional Fund of Xiangya Hospital Central South University (grant no. 2016Q02) to MP.

Availability of data and materials

Not applicable.

Authors' contributions

QS wrote the manuscript draft. QS, QT, JD, SZ, MP and TT contributed to the preparation of the manuscript. XY and SL revised the manuscript. QS, DJ and XY conceived the design of the figures. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Li Y, Wang Y, Zhou Y, Li J, Chen K, Zhang L, Deng M, Deng S, Li P and Xu B: Cooperative effect of chidamide and chemotherapeutic drugs induce apoptosis by DNA damage accumulation and repair defects in acute myeloid leukemia stem and progenitor cells. Clin Epigenetics 9: 83, 2017.
2. Ward PS and Thompson CB: Metabolic reprogramming: A cancer hallmark even warburg did not anticipate. Cancer Cell 21: 297-308, 2012.
3. Vander Heiden MG, Cantley LC and Thompson CB: Understanding the Warburg effect: The metabolic requirements of cell proliferation. Science 324: 1029-1033, 2009.
4. Kang YP, Ward NP and DeNicola GM: Recent advances in cancer metabolism: A technological perspective. Exp Mol Med 50: 31, 2018.
5. Martinez-Outschoorn UE, Peiris-Pagés M, Pestell RG, Sotgia F and Lisanti MP: Cancer metabolism: A therapeutic perspective. Nat Rev Clin Oncol 14: 11-31, 2017.
6. Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, Stone RM, DeAngelo DJ, Levine RL, Flinn IW, *et al*: Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood 130: 722-731, 2017.
7. Bayley JP and Devilee P: The Warburg effect in 2012. Curr Opin Oncol 24: 62-67, 2012.
8. Mazurek S: Pyruvate kinase type M2: A key regulator of the metabolic budget system in tumor cells. Int J Biochem Cell Biol 43: 969-980, 2011.
9. Shinohara H, Taniguchi K, Kumazaki M, Yamada N, Ito Y, Otsuki Y, Uno B, Hayakawa F, Minami Y, Naoe T and Akao Y: Anti-cancer fatty-acid derivative induces autophagic cell death through modulation of PKM isoform expression profile mediated by bcr-abl in chronic myeloid leukemia. Cancer Lett 360: 28-38, 2015.
10. Taniguchi K, Sugito N, Kumazaki M, Shinohara H, Yamada N, Nakagawa Y, Ito Y, Otsuki Y, Uno B, Uchiyama K and Akao Y: MicroRNA-124 inhibits cancer cell growth through PTB1/PKM1/PKM2 feedback cascade in colorectal cancer. Cancer Lett 363: 17-27, 2015.
11. Shi HS, Li D, Zhang J, Wang YS, Yang L, Zhang HL, Wang XH, Mu B, Wang W, Ma Y, *et al*: Silencing of pkm2 increases the efficacy of docetaxel in human lung cancer xenografts in mice. Cancer Sci 101: 1447-1453, 2010.
12. Zheng Q, Lin Z, Xu J, Lu Y, Meng Q, Wang C, Yang Y, Xin X, Li X, Pu H, *et al*: Long noncoding RNA MEG3 suppresses liver cancer cells growth through inhibiting β-catenin by activating PKM2 and inactivating PTEN. Cell Death Dis 9: 253, 2018.
13. Benesch C, Schneider C, Voelker HU, Kapp M, Caffier H, Krockenberger M, Dietl J, Kammerer U and Schmidt M: The clinicopathological and prognostic relevance of pyruvate kinase M2 and pAkt expression in breast cancer. Anticancer Res 30: 1689-1694, 2010.

14. Lockney NA, Zhang M, Lu Y, Sopha SC, Washington MK, Merchant N, Zhao Z, Shyr Y, Chakravarthy AB and Xia F: Pyruvate kinase muscle isoenzyme 2 (PKM2) expression is associated with overall survival in pancreatic ductal adenocarcinoma. J Gastrointest Cancer 46: 390-398, 2015.
15. Lin Y, Lv F, Liu F, Guo X, Fan Y, Gu F, Gu J and Fu L: High expression of pyruvate kinase M2 is associated with chemosensitivity to epirubicin and 5-fluorouracil in breast cancer. J Cancer 6: 1130-1139, 2015.
16. Yoo BC, Ku JL, Hong SH, Shin YK, Park SY, Kim HK and Park JG: Decreased pyruvate kinase M2 activity linked to cisplatin resistance in human gastric carcinoma cell lines. Int J Cancer 108: 532-539, 2004.
17. Martinez-Balibrea E, Plasencia C, Ginés A, Martinez-Cardús A, Musulén E, Aguilera R, Manzano JL, Neamati N and Abad A: A proteomic approach links decreased pyruvate kinase M2 expression to oxaliplatin resistance in patients with colorectal cancer and in human cell lines. Mol Cancer Ther 8: 771-778, 2009.
18. Zhu H, Wu J, Zhang W, Luo H, Shen Z, Cheng H and Zhu X: PKM2 enhances chemosensitivity to cisplatin through interaction with the mTOR pathway in cervical cancer. Sci Rep 6: 30788, 2016.
19. Li Q, Zhang D, Chen X, He L, Li T, Xu X and Li M: Nuclear PKM2 contributes to gefitinib resistance via upregulation of STAT3 activation in colorectal cancer. Sci Rep 5: 16082, 2015.
20. 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 452: 230-233, 2008.
21. Prakasam G, Singh RK, Iqbal MA, Saini SK, Tiku AB and Bamezai RNK: Pyruvate kinase M knockdown-induced signaling via AMP-activated protein kinase promotes mitochondrial biogenesis, autophagy, and cancer cell survival. J Biol Chem 292: 15561-15576, 2017.
22. Zheng B, Liu F, Zeng L, Geng L, Ouyang X, Wang K and Huang Q: Overexpression of pyruvate kinase type M2 (PKM2) promotes ovarian cancer cell growth and survival via regulation of cell cycle progression related with upregulated CCND1 and downregulated CDKN1A expression. Med Sci Monit 24: 3103-3112, 2018.
23. Goldberg MS and Sharp PA: Pyruvate kinase M2-specific siRNA induces apoptosis and tumor regression. J Exp Med 209: 217-224, 2012.
24. Spoden GA, Mazurek S, Morandell D, Bacher N, Ausserlechner MJ, Jansen-Dürr P, Eigenbrodt E and Zwerschke W: Isotype-specific inhibitors of the glycolytic key regulator pyruvate kinase subtype M2 moderately decelerate tumor cell proliferation. Int J Cancer 123: 312-321, 2008.
25. Spoden GA, Rostek U, Lechner S, Mitterberger M, Mazurek S and Zwerschke W: Pyruvate kinase isoenzyme M2 is a glycolytic sensor differentially regulating cell proliferation, cell size and apoptotic cell death dependent on glucose supply. Exp Cell Res 315: 2765-2774, 2009.
26. Guo W, Zhang Y, Chen T, Wang Y, Xue J, Zhang Y, Xiao W, Mo X and Lu Y: Efficacy of RNAi targeting of pyruvate kinase M2 combined with cisplatin in a lung cancer model. J Cancer Res Clin Oncol 137: 65-72, 2011.
27. Li RZ, Fan XX, Shi DF, Zhu GY, Wang YW, Luo LX, Pan HD, Yao XJ, Leung EL and Liu L: Identification of a new pyruvate kinase M2 isoform (PKM2) activator for the treatment of non-small-cell lung cancer (NSCLC). Chem Biol Drug Des 92: 1851-1858, 2018.
28. Liu B, Yuan X, Xu B, Zhang H, Li R, Wang X, Ge Z and Li R: Synthesis of novel 7-azaindole derivatives containing pyridin-3-ylmethyl dithiocarbamate moiety as potent PKM2 activators and PKM2 nucleus translocation inhibitors. Eur J Med Chem 170: 1-15, 2019.
29. Boxer MB, Jiang JK, Vander Heiden MG, Shen M, Skoumbourdis AP, Southall N, Veith H, Leister W, Austin CP, Park HW, *et al*: Evaluation of substituted N,N'-diarylsulfonamides as activators of the tumor cell specific M2 isoform of pyruvate kinase. J Med Chem 53: 1048-1055, 2010.
30. Guo C, Linton A, Jalaie M, Kephart S, Ornelas M, Pairish M, Greasley S, Richardson P, Maegley K, Hickey M, *et al*: Discovery of 2-((1H-benzo[d]imidazol-1-yl)methyl)-4H-pyrido[1,2-a] pyrimidin-4-ones as novel PKM2 activators. Bioorg Med Chem Lett 23: 3358-3363, 2013.
31. Li J, Li S, Guo J, Li Q, Long J, Ma C, Ding Y, Yan C, Li L, Wu Z, *et al*: Natural product micheliolide (MCL) irreversibly activates pyruvate kinase M2 and suppresses leukemia. J Med Chem 61: 4155-4164, 2018.
32. Jiang JK, Boxer MB, Vander Heiden MG, Shen M, Skoumbourdis AP, Southall N, Veith H, Leister W, Austin CP, Park HW, *et al*: 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, 2010.
33. Matsui Y, Yasumatsu I, Asahi T, Kitamura T, Kanai K, Ubukata O, Hayasaka H, Takaishi S, Hanzawa H and Katakura S: Discovery and structure-guided fragment-linking of 4-(2,3-dichlorobenz oyl)-1-methyl-pyrrole-2-carboxamide as a pyruvate kinase M2 activator. Bioorg Med Chem 25: 3540-3546, 2017.
34. Qi W, Keenan HA, Li Q, Ishikado A, Kannt A, Sadowski T, Yorek MA, Wu IH, Lockhart S, Coppey LJ, *et al*: Pyruvate kinase M2 activation may protect against the progression of diabetic glomerular pathology and mitochondrial dysfunction. Nat Med 23: 753-762, 2017.
35. Yacovan A, Ozeri R, Kehat T, Mirilashvili S, Sherman D, Aizikovich A, Shitrit A, Ben-Zeev E, Schutz N, Bohana-Kashtan O, *et al*: 1-(sulfonyl)-5-(arylsulfonyl)indoline as activators of the tumor cell specific M2 isoform of pyruvate kinase. Bioorg Med Chem Lett 22: 6460-6468, 2012.
36. Chen C, Xiao W, Huang L, Yu G, Ni J, Yang L, Wan R and Hu G: Shikonin induces apoptosis and necroptosis in pancreatic cancer via regulating the expression of RIP1/RIP3 and synergizes the activity of gemcitabine. Am J Transl Res 9: 5507-5517, 2017.
37. Lin TJ, Lin HT, Chang WT, Mitapalli SP, Hsiao PW, Yin SY and Yang NS: Shikonin-enhanced cell immunogenicity of tumor vaccine is mediated by the differential effects of DAMP components. Mol Cancer 14: 174, 2015.
38. Chen J, Xie J, Jiang Z, Wang B, Wang Y and Hu X: Shikonin and its analogs inhibit cancer cell glycolysis by targeting tumor pyruvate kinase-M2. Oncogene 30: 4297-4306, 2011.
39. Zhao X, Zhu Y, Hu J, Jiang L, Li L, Jia S and Zen K: Shikonin inhibits tumor growth in mice by suppressing pyruvate kinase M2-mediated aerobic glycolysis. Sci Rep 8: 14517, 2018.
40. Li W, Liu J and Zhao Y: PKM2 inhibitor shikonin suppresses TPA-induced mitochondrial malfunction and proliferation of skin epidermal JB6 cells. Mol Carcinog 53: 403-412, 2014.
41. Tang JC, Zhao J, Long F, Chen JY, Mu B, Jiang Z, Ren Y and Yang J: Efficacy of Shikonin against esophageal cancer cells and its possible mechanisms in vitro and in vivo. J Cancer 9: 32-40, 2018.
42. Tao T, Su Q, Xu S, Deng J, Zhou S, Zhuang Y, Huang Y, He C, He S, Peng M, *et al*: Downr-egulation of PKM2 decreases FASN expression in bladder cancer cells through AKT/mTOR/SREBP-1c axis. J Cell Physiol 234: 3088-3104, 2019.
43. Boulos JC, Rahama M, Hegazy MF and Efferth T: Shikonin derivatives for cancer prevention and therapy. Cancer Lett 459: 248-267, 2019.
44. Ning X, Qi H, Li R, Jin Y, McNutt MA and Yin Y: Synthesis and antitumor activity of novel 2, 3-didithiocarbamate substituted naphthoquinones as inhibitors of pyruvate kinase M2 isoform. J Enzyme Inhib Med Chem 33: 126-129, 2018.
45. Ruiter R, Visser LE, van Herk-Sukel MP, Coebergh JW, Haak HR, Geelhoed-Duijvestijn PH, Straus SM, Herings RM and Stricker BH: Lower risk of cancer in patients on metformin in comparison with those on sulfonylurea derivatives: Results from a large population-based follow-up study. Diabetes Care 35: 119-124, 2012.
46. Dalva-Aydemir S, Bajpai R, Martinez M, Adekola KU, Kandela I, Wei C, Singhal S, Koblinski JE, Raje NS, Rosen ST and Shanmugam M: Targeting the metabolic plasticity of multiple myeloma with FDA-approved ritonavir and metformin. Clin Cancer Res 21: 1161-1171, 2015.
47. Shang D, Wu J, Guo L, Xu Y, Liu L and Lu J: Metformin increases sensitivity of osteosarcoma stem cells to cisplatin by inhibiting expression of PKM2. Int J Oncol 50: 1848-1856, 2017.
48. Silvestri A, Palumbo F, Rasi I, Posca D, Pavlidou T, Paoluzi S, Castagnoli L and Cesareni G: Metformin induces apoptosis and downregulates pyruvate kinase M2 in breast cancer cells only when grown in nutrient-poor conditions. PLoS One 10: e0136250, 2015.
49. Hamabe A, Konno M, Tanuma N, Shima H, Tsunekuni K, Kawamoto K, Nishida N, Koseki J, Mimori K, Gotoh N, *et al*: Role of pyruvate kinase M2 in transcriptional regulation leading to epithelial-mesenchymal transition. Proc Natl Acad Sci USA 111: 15526-15531, 2014.
50. Cheng K and Hao M: Metformin inhibits TGF-β1-induced Epithelial-to-Mesenchymal transition via PKM2 relative-mTOR/p70s6k signaling pathway in cervical carcinoma cells. Int J Mol Sci 17: pii: E2000, 2016.

51. Su Q, Tao T, Tang L, Deng J, Darko KO, Zhou S, Peng M, He S, Zeng Q, Chen AF and Yang X: Down-regulation of PKM2 enhances anticancer efficiency of THP on bladder cancer. J Cell Mol Med 22: 2774-2790, 2018.
52. Hey E: Vitamin K-what, why, and when. Arch Dis Child Fetal Neonatal Ed 88: F80-F83, 2003.
53. Ogawa M, Nakai S, Deguchi A, Nonomura T, Masaki T, Uchida N, Yoshiji H and Kuriyama S: Vitamins K2, K3 and K5 exert antitumor effects on established colorectal cancer in mice by inducing apoptotic death of tumor cells. Int J Oncol 31: 323-331, 2007.
54. Ivanova D, Zhelev Z, Getsov P, Nikolova B, Aoki I, Higashi T and Bakalova R: Vitamin K: Redox-modulation, prevention of mitochondrial dysfunction and anticancer effect. Redox Biol 16: 352-358, 2018.
55. Hitomi M, Nonomura T, Yokoyama F, Yoshiji H, Ogawa M, Nakai S, Deguchi A, Masaki T, Inoue H, Kimura Y, *et al*: *In vitro* and *in vivo* antitumor effects of vitamin K5 on hepatocellular carcinoma. Int J Oncol 26: 1337-1344, 2005.
56. Yamada A, Osada S, Tanahashi T, Matsui S, Sasaki Y, Tanaka Y, Okumura N, Matsuhashi N, Takahashi T, Yamaguchi K and Yoshida K: Novel therapy for locally advanced triple-negative breast cancer. Int J Oncol 47: 1266-1272, 2015.
57. Osada S, Saji S and Osada K: Critical role of extracellular signal-regulated kinase phosphorylation on menadione (vitamin K3) induced growth inhibition. Cancer 91: 1156-1165, 2001.
58. Lamson DW and Plaza SM: The anticancer effects of vitamin K. Altern Med Rev 8: 303-318, 2003.
59. Bonilla-Porras AR, Jimenez-Del-Rio M and Velez-Pardo C: Vitamin K3 and vitamin C alone or in combination induced apoptosis in leukemia cells by a similar oxidative stress signalling mechanism. Cancer Cell Int 11: 19, 2011.
60. Parekh HK, Mansuri-Torshizi H, Srivastava TS and Chitnis MP: Circumvention of adriamycin resistance: Effect of 2-methyl-1,4-naphthoquinone (vitamin K3) on drug cytotoxicity in sensitive and MDR P388 leukemia cells. Cancer Lett 61: 147-156, 1992.
61. Chen J, Jiang Z, Wang B, Wang Y and Hu X: Vitamin K(3) and K(5) are inhibitors of tumor pyruvate kinase M2. Cancer Lett 316: 204-210, 2012.
62. Scicchitano BM, Sorrentino S, Proietti G, Lama G, Dobrowolny G, Catizone A, Binda E, Larocca LM and Sica G: Levetiracetam enhances the temozolomide effect on glioblastoma stem cell proliferation and apoptosis. Cancer Cell Int 18: 136, 2018.
63. Johnson DR and O'Neill BP: Glioblastoma survival in the United States before and during the temozolomide era. J Neurooncol 107: 359-364, 2012.
64. Chu L, Wang A, Ni L, Yan X, Song Y, Zhao M, Sun K, Mu H, Liu S, Wu Z and Zhang C: Nose-to-brain delivery of temozolomide-loaded PLGA nanoparticles functionalized with anti-EPHA3 for glioblastoma targeting. Drug Deliv 25: 1634-1641, 2018.
65. Park I, Mukherjee J, Ito M, Chaumeil MM, Jalbert LE, Gaensler K, Ronen SM, Nelson SJ and Pieper RO: Changes in pyruvate metabolism detected by magnetic resonance imaging are linked to DNA damage and serve as a sensor of temozolomide response in glioblastoma cells. Cancer Res 74: 7115-7124, 2014.
66. Yuan S, Qiao T, Zhuang X, Chen W, Xing N and Zhang Q: Knockdown of the M2 isoform of pyruvate kinase (PKM2) with shRNA enhances the effect of docetaxel in human NSCLC cell lines in vitro. Yonsei Med J 57: 1312-1323, 2016.
67. Cheng C, Xie Z, Li Y, Wang J, Qin C and Zhang Y: PTBP1 knockdown overcomes the resistance to vincristine and oxaliplatin in drug-resistant colon cancer cells through regulation of glycolysis. Biomed Pharmacother 108: 194-200, 2018.
68. Taieb J, Pointet AL, Van Laethem JL, Laquente B, Pernot S, Lordick F and Reni M: What treatment in 2017 for inoperable pancreatic cancers? Ann Oncol 28: 1473-1483, 2017.
69. Sun C, Ansari D, Andersson R and Wu DQ: Does gemcitabine-based combination therapy improve the prognosis of unresectable pancreatic cancer? World J Gastroenterol 18: 4944-4958, 2012.
70. Tian S, Li P, Sheng S and Jin X: Upregulation of pyruvate kinase M2 expression by fatty acid synthase contributes to gemcitabine resistance in pancreatic cancer. Oncol Lett 15: 2211-2217, 2018.
71. Li C, Zhao Z, Zhou Z and Liu R: Linc-ROR confers gemcitabine resistance to pancreatic cancer cells via inducing autophagy and modulating the miR-124/PTBP1/PKM2 axis. Cancer Chemother Pharmacol 78: 1199-1207, 2016.
72. Kim DJ, Park YS, Kang MG, You YM, Jung Y, Koo H, Kim JA, Kim MJ, Hong SM, Lee KB, *et al*: Pyruvate kinase isoenzyme M2 is a therapeutic target of gemcitabine-resistant pancreatic cancer cells. Exp Cell Res 336: 119-129, 2015.
73. Calabretta S, Bielli P, Passacantilli I, Pilozzi E, Fendrich V, Capurso G, Fave GD and Sette C: Modulation of PKM alternative splicing by PTBP1 promotes gemcitabine resistance in pancreatic cancer cells. Oncogene 35: 2031-2039, 2016.
74. Dilruba S and Kalayda GV: Platinum-based drugs: Past, present and future. Cancer Chemother Pharmacol 77: 1103-1124, 2016.
75. Belanger F, Fortier E, Dubé M, Lemay JF, Buisson R, Masson JY, Elsherbiny A, Costantino S, Carmona E, Mes-Masson AM, *et al*: Replication protein A availability during DNA replication stress is a major determinant of cisplatin resistance in ovarian cancer cells. Cancer Res 78: 5561-5573, 2018.
76. Wang X, Zhang F and Wu XR: Inhibition of pyruvate kinase M2 markedly reduces chemoresistance of advanced bladder cancer to cisplatin. Sci Rep 7: 45983, 2017.
77. Galanski M: Recent developments in the field of anticancer platinum complexes. Recent Pat Anticancer Drug Discov 1: 285-295, 2006.
78. Galluzzi L, Senovilla L, Vitale I, Michels J, Martins I, Kepp O, Castedo M and Kroemer G: Molecular mechanisms of cisplatin resistance. Oncogene 31: 1869-1883, 2012.
79. Wang Y, Hao F, Nan Y, Qu L, Na W, Jia C and Chen X: PKM2 inhibitor shikonin overcomes the cisplatin resistance in bladder cancer by inducing necroptosis. Int J Biol Sci 14: 1883-1891, 2018.
80. Li W, Qiu Y, Hao J, Zhao C, Deng X and Shu G: Dauricine upregulates the chemosensitivity of hepatocellular carcinoma cells: Role of repressing glycolysis via miR-199a: HK2/PKM2 modulation. Food Chem Toxicol 121: 156-165, 2018.
81. Miya T, Kobayashi K, Hino M, Ando M, Takeuchi S, Seike M, Kubota K and Gemma A; East Japan Chesters Group: Efficacy of triple antiemetic therapy (palonosetron, dexamethasone, aprepitant) for chemotherapy-induced nausea and vomiting in patients receiving carboplatin-based, moderately emetogenic chemotherapy. Springerplus 5: 2080, 2016.
82. Sève P and Dumontet C: Chemoresistance in non-small cell lung cancer. Curr Med Chem Anticancer Agents 5: 73-88, 2005.
83. Liu Y, He C and Huang X: Metformin partially reverses the carboplatin-resistance in NSCLC by inhibiting glucose metabolism. Oncotarget 8: 75206-75216, 2017.
84. Kelland L: The resurgence of platinum-based cancer chemotherapy. Nat Rev Cancer 7: 573-584, 2007.
85. Graham J, Mushin M and Kirkpatrick P: Oxaliplatin. Nat Rev Drug Discov 3: 11-12, 2004.
86. Hsu HH, Chen MC, Baskaran R, Lin YM, Day CH, Lin YJ, Tu CC, Vijaya Padma V, Kuo WW and Huang CY: Oxaliplatin resistance in colorectal cancer cells is mediated via activation of ABCG2 to alleviate ER stress induced apoptosis. J Cell Physiol 233: 5458-5467, 2018.
87. Fang Z, Gong C, Yu S, Zhou W, Hassan W, Li H, Wang X, Hu Y, Gu K, Chen X, *et al*: NFYB-induced high expression of E2F1 contributes to oxaliplatin resistance in colorectal cancer via the enhancement of CHK1 signaling. Cancer Lett 415: 58-72, 2018.
88. Lu WQ, Hu YY, Lin XP and Fan W: Knockdown of PKM2 and GLS1 expression can significantly reverse oxaliplatin-resistance in colorectal cancer cells. Oncotarget 8: 44171-44185, 2017.
89. Ginés A, Bystrup S, Ruiz de Porras V, Guardia C, Musulén E, Martínez-Cardús A, Manzano JL, Layos L, Abad A and Martínez-Balibrea E: PKM2 subcellular localization is involved in oxaliplatin resistance acquisition in HT29 human colorectal cancer cell lines. PLoS One 10: e0123830, 2015.
90. Russo A, Maiolino S, Pagliara V, Ungaro F, Tatangelo F, Leone A, Scalia G, Budillon A, Quaglia F and Russo G: Enhancement of 5-FU sensitivity by the proapoptotic rpL3 gene in p53 null colon cancer cells through combined polymer nanoparticles. Oncotarget 7: 79670-79687, 2016.
91. He J, Xie G, Tong J, Peng Y, Huang H, Li J, Wang N and Liang H: Overexpression of microRNA-122 re-sensitizes 5-FU-resistant colon cancer cells to 5-FU through the inhibition of PKM2 in vitro and in vivo. Cell Biochem Biophys 70: 1343-1350, 2014.
92. Hjerpe E, Egyhazi Brage S, Carlson J, Frostvik Stolt M, Schedvins K, Johansson H, Shoshan M and Avall-Lundqvist E: Metabolic markers GAPDH, PKM2, ATP5B and BEC-index in advanced serous ovarian cancer. BMC Clin Pathol 13: 30, 2013.
93. Pan C, Wang X, Shi K, Zheng Y, Li J, Chen Y, Jin L and Pan Z: MiR-122 reverses the doxorubicin-resistance in hepatocellular carcinoma cells through regulating the tumor metabolism. PLoS One 11: e0152090, 2016.
94. Han TD, Shang DH and Tian Y: Docetaxel enhances apoptosis and G2/M cell cycle arrest by suppressing mitogen-activated protein kinase signaling in human renal clear cell carcinoma. Genet Mol Res: 15, 2016 doi: 10.4238/gmr.15017321.

95. Sim S, Bergh J, Hellström M, Hatschek T and Xie H: Pharmacogenetic impact of docetaxel on neoadjuvant treatment of breast cancer patients. Pharmacogenomics 19: 1259-1268, 2018.
96. van Rossum AGJ, Kok M, van Werkhoven E, Opdam M, Mandjes IAM, van Leeuwen-Stok AE, van Tinteren H, Imholz ALT, Portielje JEA, Bos MMEM, *et al*: Adjuvant dose-dense doxorubicin-cyclophosphamide versus docetaxel-doxorubicin-cyclophosphamide for high-risk breast cancer: First results of the randomised MATADOR trial (BOOG 2004-04). Eur J Cancer 102: 40-48, 2018.
97. Sharma P, López-Tarruella S, García-Saenz JA, Khan QJ, Gómez HL, Prat A, Moreno F, Jerez-Gilarranz Y, Barnadas A, Picornell AC, *et al*: Pathological response and survival in triple-negative breast cancer following neoadjuvant carboplatin plus docetaxel. Clin Cancer Res 24: 5820-5829, 2018.
98. Hata A, Katakami N, Shimokawa M, Mitsudomi T, Yamamoto N and Nakagawa K: Docetaxel Plus RAmucirumab with primary prophylactic pegylated Granulocyte-ColONy stimulating factor support for elderly patients with advanced Non-small-cell lung cancer: A multicenter prospective single arm phase II Trial: DRAGON study (WJOG9416L). Clin Lung Cancer 19: e865-e869, 2018.
99. Tanimura K, Uchino J, Tamiya N, Kaneko Y, Yamada T1, Yoshimura K and Takayama K: Treatment rationale and design of the RAMNITA study: A phase II study of the efficacy of docetaxel + ramucirumab for non-small cell lung cancer with brain metastasis. Medicine (Baltimore) 97: e11084, 2018.
100. Milbar N, Kates M, Chappidi MR, Pederzoli F, Yoshida T, Sankin A, Pierorazio PM, Schoenberg MP and Bivalacqua TJ: Oncological outcomes of sequential intravesical gemcitabine and docetaxel in patients with Non-muscle invasive bladder cancer. Bladder Cancer 3: 293-303, 2017.
101. Mortimer J, Zonder HB and Pal SK: Lessons learned from the bevacizumab experience. Cancer Control 19: 309-316, 2012.
102. Wong N, Ojo D, Yan J and Tang D: PKM2 contributes to cancer metabolism. Cancer Lett 356: 184-191, 2015.
103. Hsu MC and Hung WC: Pyruvate kinase M2 fuels multiple aspects of cancer cells: From cellular metabolism, transcriptional regulation to extracellular signaling. Mol Cancer 17: 35, 2018.
104. Papadaki C, Sfakianaki M, Lagoudaki E, Giagkas G, Ioannidis G, Trypaki M, Tsakalaki E, Voutsina A, Koutsopoulos A, Mavroudis D, *et al*: PKM2 as a biomarker for chemosensitivity to front-line platinum-based chemotherapy in patients with metastatic non-small-cell lung cancer. Br J Cancer 111: 1757-1764, 2014.