

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

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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.

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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

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Abbreviations: PKM2, pyruvate kinase isoenzyme M2; PTBP1, polypyrimidine tract-binding protein 1; HIF-1 α , hypoxia inducible factor 1 alpha; CSCs, cancer stem cells; EMT, epithelial-mesenchymal transition; TGF- β 1, transforming growth factor β 1; 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

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-1 α (HIF-1 α) 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)1 α /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

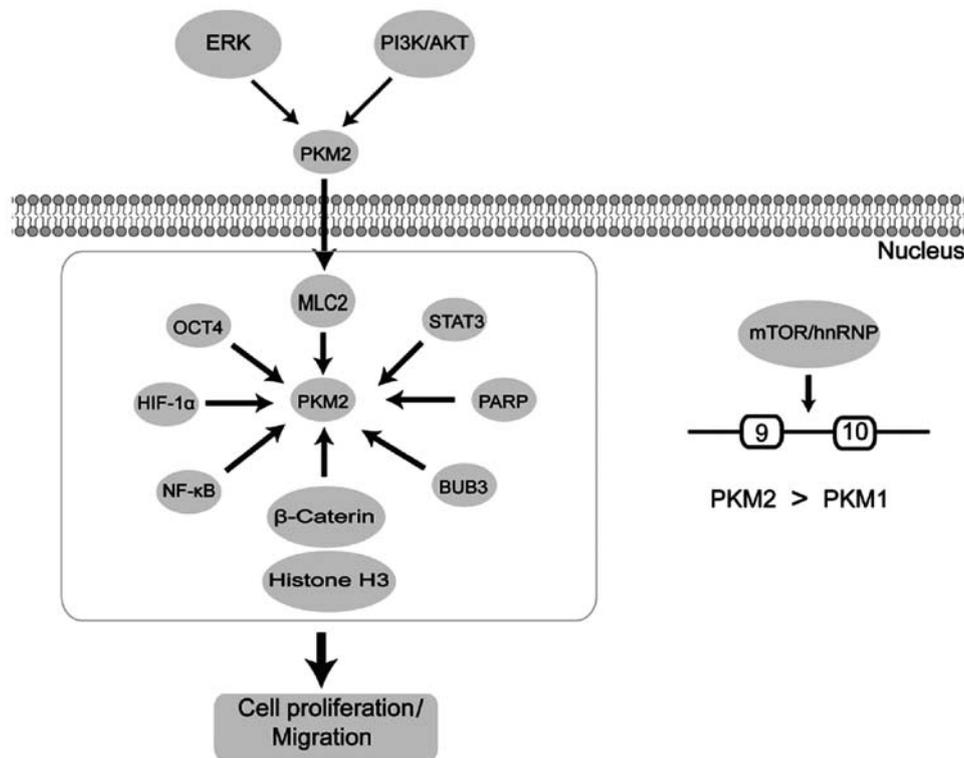


Figure 1. Pathways related to tumor growth involving PKM2. PKM2 is phosphorylated by ERK2 or PI3K/AKT resulting the nuclear translocation of PKM2. Nuclear PKM2 binds to proteins upregulating transcriptional activity, thereby promoting the Warburg effect and tumorigenesis; hnRNP induces PKM2 via alternative splicing of PKM genes to stimulate cancer cell invasion and migration. PKM2, pyruvate kinase isoenzyme M2; HIF1 α , hypoxia inducible factor 1 α ; 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 β 1 (TGF- β 1)-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.

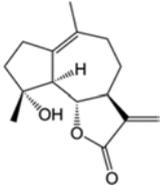
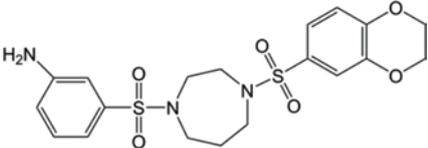
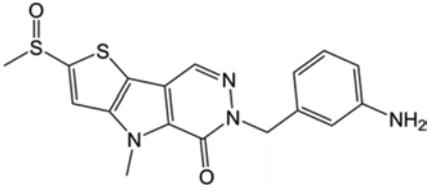
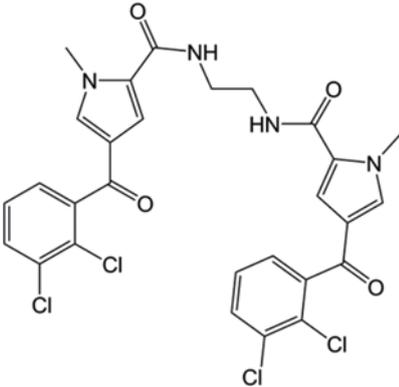
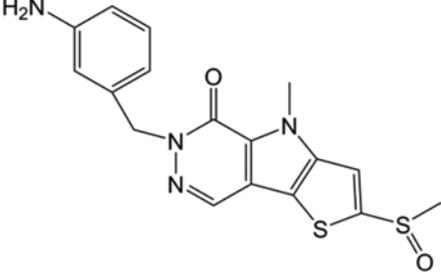
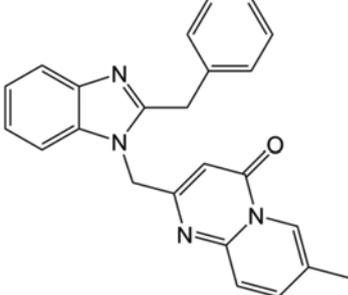
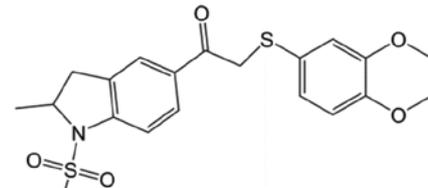
4. PKM2 activity influences chemosensitivity

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-methylpyrrole-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)

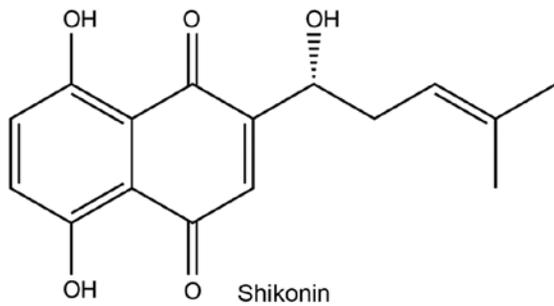


Figure 2. Chemical structure of shikonin.

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 PKM2 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

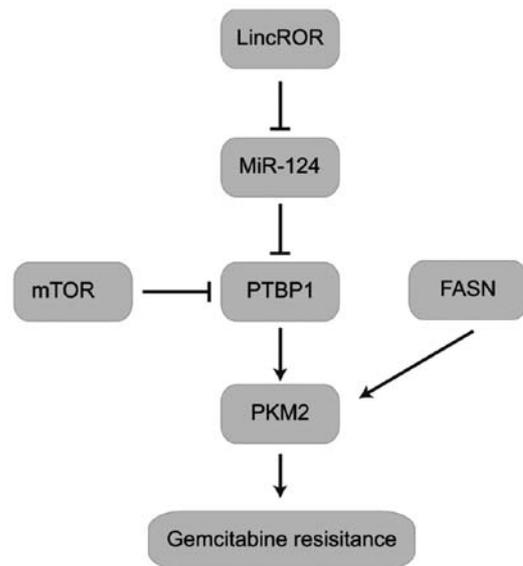


Figure 3. Major role of PKM2 in gemcitabine resistance. The lincROR/miR-124/PTBP1/PKM2 complex is involved in the regulation of gemcitabine resistance. FASN regulates PKM2 expression and is associated with gemcitabine resistance. LincROR, long intergenic non-protein coding RNA, regulator of reprogramming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

(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 HIF1 α) were then determined using immunohistochemistry. As a result, it was discovered that the mTOR/HIF-1 α /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 G₂/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 G₂/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.

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