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Non-metabolic functions of pyruvate kinase M2: PKM2 in tumorigenesis and therapy resistance

Minireview

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Cancer is the disease of uncontrollably dividing cells in the body. As cancer cells proliferate at higher rates, they need more energy in a short time necessitating deregulation of energy-generating pathways for their benefit. Although oxidative phosphorylation generates more energy from a glucose molecule, cancer cells have a tendency to enhance aerobic glycolysis by consuming more glucose and producing lactate as a by-product even if oxygen is present. In addition to the generation of rapid energy to fulfill their increasing demands, this strategy also provides the use of glucose metabolites such as lactate as a source for the synthesis of anabolic molecules, such as nucleotides, amino acids, and lipids during the rapid phase of the proliferation. Pyruvate kinase M2 (PKM2) is an isoform of pyruvate kinase, which mediates the balancing of energy generation mechanisms during the anabolic and catabolic events. Due to its vital role in glycolysis, PKM2 has been investigated to target cancer cell metabolism for several years. However, recent studies demonstrate that PKM2 may also promote cancer progression by regulating core steps in metastasis such as migration, angiogenesis, and stemness. Of note, it is estimated that 90% of cancer-related deaths are due to metastasis. This review is intended to summarize the recent advances in the non-metabolic roles of PKM2 in cancer progression and to indicate its potential uses for the development of new treatment strategies.

Key words: PKM2, metastasis, stemness, drug resistance

Tumorigenesis starts with uncontrolled proliferation of abnormal cells in the tissue of origin, which in turn, usually ends up with a mass of undifferentiated cells, called a tumor [1]. Along with the increased energy demands, cancer cells reorganize their means of energy production. Instead of regular oxidative phosphorylation, they produce energy through aerobic glycolysis irrespective of the presence of oxygen named as Warburg effect [2]. This strategy not only provides a rapid energy supply in a short time but by-products of energy production act as a source for the synthesis of anabolic molecules (Figure 1), namely, the synthesis of nucleotides, amino acids, and lipids during rapid proliferation [3]. Activation of certain survival signaling cascades such as PI3K-Akt and mTOR pathways and upregulation of some genes with oncogenic effects, such as c-Myc and HIF1 are frequently seen events during metabolic deregulation [4]. Pyruvate kinase M2 (PKM2) has an important role in the enhancement of aerobic glycolysis. Apart from its role in energy metabolism, it was shown that PKM2 interacts with HIF1 in hypoxic conditions. However, its interaction is not limited to HIF1 and PKM2 interacts with other oncogenic pathways to regulate the progression of different types of malignancies through its non-metabolic effects [5–9].

Here, it is intended to summarize the recent findings regarding PKM2 role in different stages of cancer progression.

PKM2 in hypoxia and angiogenesis

Capillaries are able to provide enough oxygen and nutrients in the early stages of tumor formation, however, proportional to an increased cell number, more oxygen and nutrients are required which necessitates the formation of additional capillaries around the tumor core region by a process called

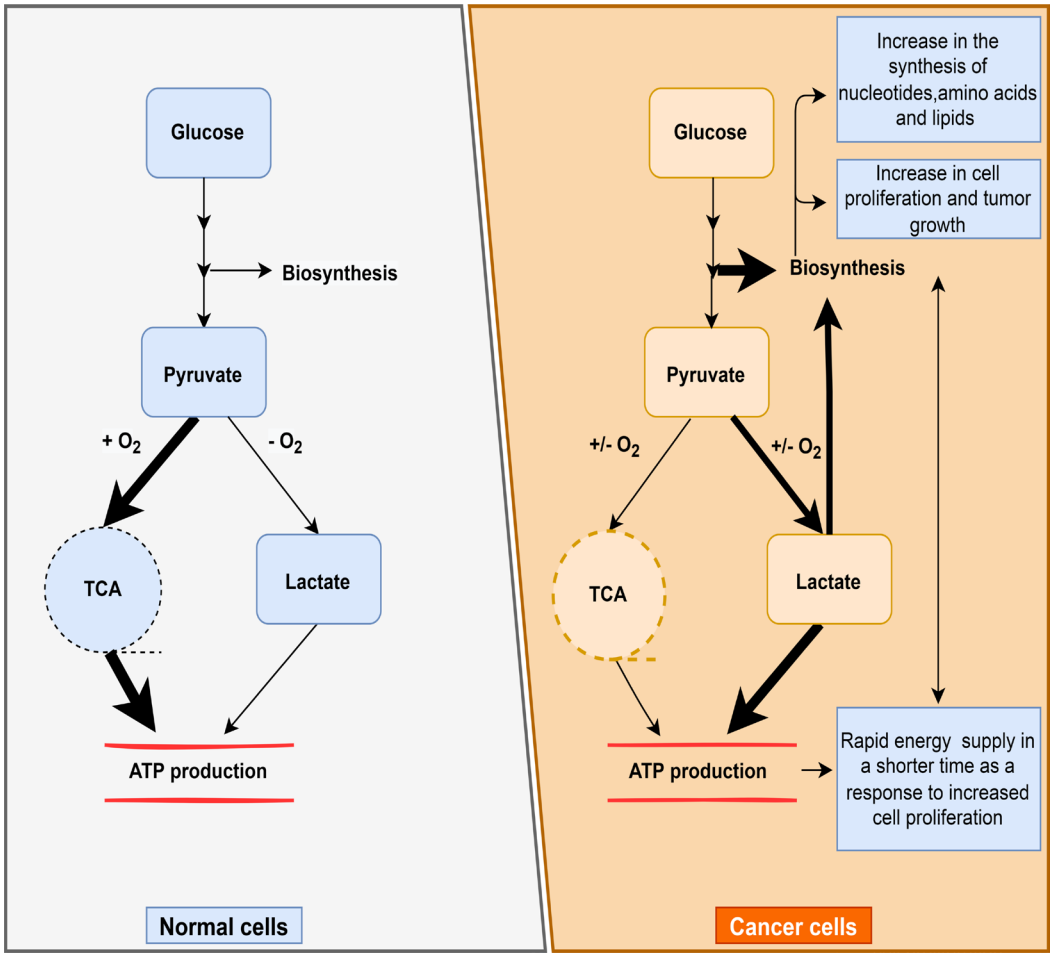

Figure 1. Simplified illustration of aerobic glycolysis in normal and cancer cell metabolism. Schematic illustration shows the aerobic respiration and glycolysis in the presence/absence of oxygen. While normal cells dominantly use oxidative phosphorylation through the Krebs cycle (TCA) for the generation of ATP, cancer cells generate ATP mainly through aerobic glycolysis irrespective of the oxygen availability. Bold arrows indicate the dominant fate of a glucose molecule during the ATP production in normal and cancer cells.

angiogenesis [10]. In addition to its fundamental role in glucose metabolism, PKM2 modulates the formation of capillaries through its interaction with different mediators (Figure 2). PKM2 interacts with the transactivation domain of HIF-1α and stimulates its transcriptional activity in both normal and cancer cell lines. In this study, Luo et al. showed that hypoxic conditions induce PKM2 expression via direct control through hypoxia response element (HRE) on PKM2 promoter [11]. Similarly, Azoitei et al. showed that PKM2 translocation to the nucleus increases when cells are incubated in hypoxic conditions in pancreatic adenocarcinoma cells, and silencing of PKM2 decreases blood vessel formation *in vivo* through decreased VEGF expression and its secretion in pancreatic cancer cells [7]. Furthermore, inhibition of PKM2 in lung adenocarcinoma cell line, A549, decreased the expression level of VEGF [12]. Of note, Li et al. found that PKM2 is secreted to the blood circulation by cancer cells, and inhibition of PKM2 impairs blood vessel formation. However, impaired vessel formation was rescued by the injection of recombinant PKM2 (rPKM2) [13].

In addition to cancer cell-derived effects of PKM2 on endothelial cells, PKM2 expression in endothelial cells mediates angiogenesis by regulating ATP-dependent trafficking of VE-cadherin and mitochondrial membrane potential in endothelial cells [8, 14]. Boeckel et al. reported that silencing of PKM2 decreases the sprout formation ability of endothelial cells [15]. Interestingly, Kim et al. suggested that PKM2 has a dual role in the endothelial cell context and they demonstrated that PKM2 suppresses the p53 tumor suppressor gene in proliferating endothelial cells triggering angiogenesis, whereas, PKM2 maintains vascular integrity via the NF-kB pathway in quiescent endothelial cells [16]. Similarly, Xu et al. showed that PKM2 interacts with the NF-κB p65 subunit, and a conditioned medium of PKM2-overexpressing human breast cancer cell lines promotes tube formation ability of HUVEC *in vitro* [17].

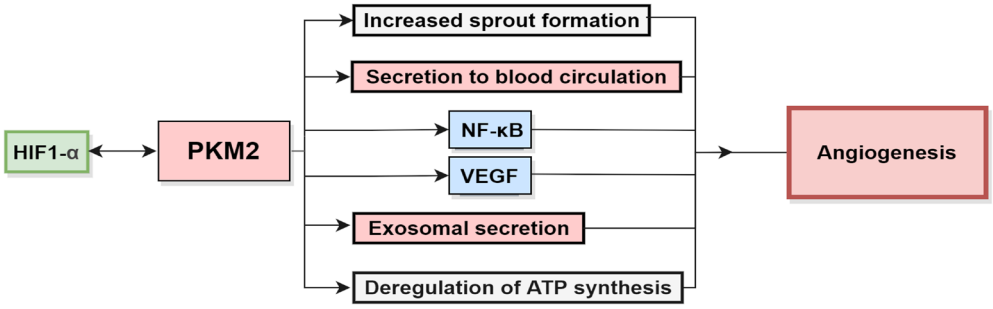

Figure 2. Overview of events regulated by PKM2 during angiogenesis. A simplified schematic illustration summarizes the known interacting partners of PKM2 and its downstream effects in angiogenesis.

However, inhibition of both the p65 subunit and PKM2 decreased the number of tube formation [17]. Cancer-associated fibroblasts (CAFs) are important players in establishing and/or remodeling of the tumor microenvironment. The findings of Gu et al. further support the interaction between PKM2 and NF-kB pathway. They showed that gastric cancer cell lines secrete PKM2 via exosomes to activate NF-kB expression in CAFs through increased acetylation [18].

PKM2 in cancer progression and metastasis

Although cancer cells form a tumor mass in the tissue of origin, their growth is, yet, restricted to the boundaries of the original tissue due to separation from neighboring tissues with a basement (basal) membrane. However, in parallel with an increase in tumor size, cancer cells expand further and start to invade surrounding tissue by penetrating the basal membrane [19, 20]. Therefore, invasion is a critical step in the progression of cancer. During the early stages of invasion, cells lose epithelial character and gain more mesenchymal characteristics by a process called epithelial-to-mesenchymal transition (EMT), enhancing their ability for migration and invasion. Then, cells with increased migration ability enter blood or lymph circulation through intravasation and travel in the circulation until they reach a point where there are appropriate stimulatory factors in the microenvironment [21]. If the conditions are available for their growth, they exit the circulation by extravasation and settle down in distant sites. Then, disseminated cells adapt to the new microenvironment and increase in number to form secondary tumors. The sum of complex processes ending with the formation of a secondary tumor in a distant site is called "metastasis" [22]. Remarkably, most cancer cases are curable if it is detected in the early stages of cancer development, however, metastatic tumors are usually difficult to cure completely and they are responsible for relapses and majority of the cancer-related deaths [23, 24]. Therefore, understanding the mechanism of metastasis and targeting cancer cells prior to metastatic spread is crucial for efficient cancer treatment strategies.

Similar to the roles of PKM2 in angiogenesis, studies by different groups suggest that PKM2 drives EMT in cancer progression (Figure 3). Wang et al. showed that in addition to the anti-proliferative role of PKM2 via cell cycle arrest at the G1 phase in gastric cancer cell lines and PKM2 overexpression increases migratory behaviors of cancer cells *in vitro* through the PI3K/Akt- axis [25]. Inhibition of PKM2 impaired migration of breast cancer cell lines *in vitro* through downregulation of mesenchymal marker genes N-cadherin and Vimentin [26, 27]. Similarly, Ma et al. showed that PKM2 is involved in the TGF-β1-mediated EMT process by modulating EMT markers through increased STAT3 phosphorylation, which was further supported by enhanced migration and invasion ability of esophageal squamous cell carcinoma cell lines *in vitro* [28]. Different groups also reported that PKM2 translocation to the nucleus might directly regulate the expression of core epithelial marker E-cadherin during EMT induction. PKM2 mediates suppression of E-cadherin transcription by changing its promoter accessibility through degradation of TGF-β Induced Factor Homeobox 2 (TGIF2) in colon cancer [29] and oral squamous cell carcinoma *in vitro* [30]. Additionally, Zhang et al. demonstrated that PKM2 acts downstream of heat shock protein 27 (HSP27) and is required for HSP27-mediated changes in EMT marker expression of esophageal squamous cell carcinoma (ESCC) *in vitro* [31].

Along with its effect on EMT regulation, PKM2 regulates the invasion of cancer cells (Figure 3). Sun et al. demonstrated that PKM2 increases the protein level of matrix metalloproteinases (MMPs), which are critical for the degradation of extracellular matrix (ECM) during the invasion, in human lung cancer cell lines, and PKM2 inhibition decreased the number of invading cells *in vitro* [12]. Similarly, inhibition of PKM2 decreases the expression of MMPs in human hilar cholangiocarcinoma [32], ovarian cancer [33], and oral squamous cell carcinoma [34] *in vitro*. Cheng et al. showed that PKM2 protects PAK2 from proteasomal degradation via increased phosphorylation and uses PAK2 as a mediator for the invasion of pancreatic ductal adenocarcinoma cell lines *in vitro* [35]. On the other hand,

Gupta et al. showed that c-Myc increases the expression of PKM2 via direct binding to the PKM2 promoter [36]. They suggested that PKM2 might regulate the invasion of head and neck cancer cells downstream of c-Myc *in vitro* [36]. Furthermore, Yu et al. demonstrated that inhibition of PKM2 increases the activity of the JAK/STAT3 pathway and inhibits migration of hepatocellular carcinoma cells *in vitro* and chemical inhibition of STAT3 reversed the effect of PKM2 on cell migration suggesting PKM2-induced migration is mediated through STAT3 [37]. Besides, they also demonstrated that the inhibition of PKM2 increases apoptosis by suppressing STAT3 in hepatocellular carcinoma *in vitro* [37]. Similarly, the silencing of PKM2 causes cell cycle arrest and triggers apoptosis through increased expression of Hippo pathway-related genes in oral tongue squamous cell carcinoma [38].

Recent studies also suggest that PKM2 might be involved in cancer progression downstream of the canonical Wnt signaling pathway (Figure 3). Jiang et al. showed that PKM2-mediated cell cycle arrest is controlled via cyclin D1 (CCND1) to control chromosome segregation during mitosis of brain cancer cells [39]. Additionally, PKM2 expression increases upon loss of Adenomatous Polyposis Coli (APC) tumor suppressor gene, which is the core protein for β-catenin degradation [40]. Of note, blocking of PKM2 with monoclonal antibody treatment reversed tumor growth in PKM2-overexpressing xenograft of human colon cancer [13]. In addition to the tumor inhibitory effect of blocking PKM2, knockdown, and/or chemical inhibition of PKM2 decreased metastasis of human lung cancer xenografts [41]. Similarly, Zhao et al. showed that metastatic breast cancer samples had higher PKM2 expression than non-metastatic ones, which further supports the possible role and clinical relevance of PKM2 in metastasis [42].

PKM2 in stemness and drug resistance

During the metastasis of a primary tumor to a distant region, some tumor cells turn into stem cell-like phenotype called cancer stem cells (CSCs) and have the ability to migrate and enter circulation [43]. They also have critical roles in remodeling the tumor microenvironment and supporting tumor growth [44–46]. Due to their tumor-initiating potential, CSCs are also attributed to drug resistance and relapses in cancer patients after tumor dormancy [47, 48]. Studies by different groups suggest that PKM2 plays a role in the regulation of stemness and drug resistance in cancer therapies (Figure 4). Zhao et al. reported that β-catenin is upregulated upon PKM2 overexpression and inhibition of β-catenin impaired the increase in the PKM2-mediated CSC population in breast cancer cells [42]. Similarly, Yang et al. demonstrated that PKM2 translocates to the nucleus and binds to β-catenin, and then, they activate β-catenin target gene CCND1 in the Epidermal growth factor receptor (EGFR)-activated brain tumor cells [49]. EGFR triggers nuclear translocation of PKM2 and they make a complex to induce the expression of stem cell markers in irradiation-resistant lung cancer cell lines [50].

In addition to the role of PKM2 downstream of the canonical Wnt pathway, findings of Yang et al. showed that PKM2 and AMP-activated protein kinase (AMPK) co-translocate to the nucleus and form a complex with octamer-binding transcription factor-4 (Oct-4) [51]. Then, they upregulate the expression of stem cell markers in human pancreatic adenocarcinoma (HPAC) under low glucose conditions [51]. However, Morfouace et al. demonstrated that PKM2 triggers the differentiation of glioma cells by interacting with Oct-4 and represses its function [52]. It was also reported that CD44, a stem cell marker, interacts with PKM2 and facilitates

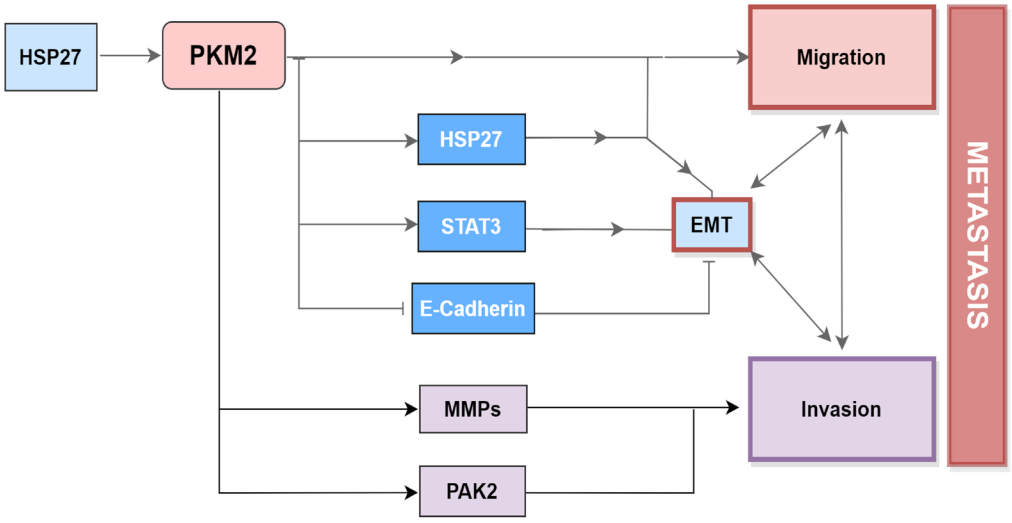

Figure 3. Overview of events regulated by PKM2 during EMT, migration, and invasion. The schematic illustration summarizes the role of PKM2 in different steps of metastasis. PI3K/Akt signaling is upregulated by PKM2 and increases the migration of cancer cells. PKM2 also suppresses E-cadherin to inhibit EMT and through upregulation of MMPs, PKM2 enhances the invasion ability of cancer cells.

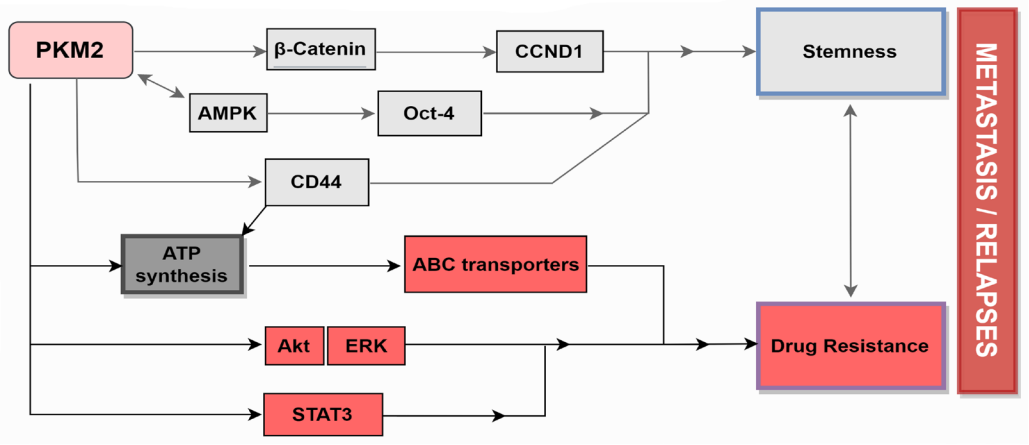

Figure 4. Schematic illustration of events regulated by PKM2 during stemness and drug resistance. PKM2 induces stemness through upregulation of stemness marker genes. In addition to deregulation of energy metabolism, PKM2 also affects the availability of ATP for ABC transporters, which are important for multidrug resistance.

enhanced glycolysis of colorectal cancer cells in the hypoxic environment [53]. This suggests that the stemness-promoting effect of PKM2 is cell type and context-dependent.

Besides, PKM2 is found as an important player involved in resistance to cisplatin, gefitinib, and EGFR inhibitors by regulating cell cycle and several signaling cascades such as STAT3 in different contexts [53–55]. Yu et al. demonstrated that the anti-apoptotic molecule, Survivin, is regulated by PKM2 through c-Myc phosphorylation and is responsible for tamoxifen resistance in breast cancer *in vitro* [26]. Furthermore, He et al. suggest that PKM2 might contribute to cell adhesion mediated drug resistance of multiple myeloma cells via increased phosphorylation of Akt and ERK [56]. Remarkably, the inhibition of PKM2 limits the energy source of ATP-binding cassette (ABC) transporters. Thus, PKM2 decreases drug resistance and enhances doxorubicin-mediated apoptosis in human lung cancer cell line, A549 [9] and inhibition of PKM2 enhanced the drug sensitivity of oxaliplatin-resistant colorectal cancer cell lines *in vitro* [57]. Similarly, cisplatin-resistant cancer cells have a higher level of PKM2 expression and chemical inhibition of PKM2 improved the response of bladder cancer cells to cisplatin through increased necroptosis [58]. On the other hand, Wang et al. showed that exosomal secretion of PKM2 increases with hypoxia and improves drug response in non-small-cell lung carcinoma (NSCLC) cells [59]. The findings of Zhu et al. also demonstrated that PKM2 expression increases upon cisplatin-based chemotherapy in cancer patient samples and silencing of PKM2 in cervical cancer cell lines causes resistance to cisplatin, potentially through the involvement of the mTOR pathway [60].

Conclusion

Cancer cells proliferate in an uncontrolled manner and form a mass of undifferentiated cells in the tissue of origin. In parallel to the increased proliferation rate, their energy demand increases, and cancer cells have to reorganize their means of energy production. Instead of regular oxidative phosphorylation, they produce energy through aerobic glycolysis. Irrespective of their origin and the availability of oxygen, tumor cells dominantly use aerobic glycolysis for glucose metabolism [61]. PKM2 is one of the core enzymes playing a role in aerobic glycolysis. Since cancer cells use dominantly glycolysis for ATP synthesis, PKM2 has been attracting the attention of researchers for many years. However, recent studies also showed that in addition to its role in the deregulation of cancer cells' metabolism, PKM2 has a pivotal role during the progression of the disease by affecting different steps of metastasis. Of note, metastasis is the cause of almost 90% of cancer-related deaths and due to its complex mechanism, it is important to understand the underlying mechanism and to reveal potential mediators of metastasis in cancer cells. Here, it was aimed to summarize the recent advances in cancer research with a focus on PKM2 during the progression of malignancies. From the findings above-mentioned here, one could conclude that the PKM2 expression is proportional to the progression of cancer, and it involves different stages of disease during metastasis such as angiogenesis and stemness by interacting with some other proteins. PKM2 itself or in combination with interactor proteins orchestrates several signaling cascades such as PI3K/Akt and JAK/STAT pathways to regulate core steps of metastasis. HIF1α is a key mediator of cancer progression in parallel to the increased hypoxic environment in the tumor core [62], and it was shown as an important partner of PKM2 through direct interaction with PKM2. In addition to its role downstream of HIF1α, PKM2 interacts with NF-kB and it has an impact, in particular, on the regulation of vascular integrity as well as direct control of capillary formation. Intriguingly, PKM2 was shown as a secreted protein and is found in blood circulation, which suggest nominating PKM2 as an early tumor detection marker during the diagnosis.

Although PKM2 seems to be a good candidate and holds the promise for more effective treatment strategies from different aspects, there are yet still some points that need to be further answered. For instance, it remains unclear whether PKM2 circulates also in the bloodstream of healthy individuals or is only secreted and/or has elevated levels in cancer patients. If its secretion correlates with the disease progression or is unique to cancer patients, PKM2 could be considered a marker for the cancer patient diagnosis. Besides, the role of PKM2 in angiogenesis is evident with the above-mentioned findings and PKM2 could be targeted to prevent angiogenesis, which is vital for tumor growth, however, further studies should also address the role of PKM2 in the formation and maintenance of blood vessels in healthy tissues. For instance, PKM2 also has a role in fetal development and it is expressed in the placenta during pregnancy [63].

Most of the drug resistance genes are ATP-dependent transporters [64]. Of note, PKM2 is a critical player in ATP synthesis of cancer cells, and findings of different studies already suggest that PKM2 could mediate drug resistance of cancer cells by changing the availability of ATP for ABC transporters. However, some tissues in our body also mainly use glycolysis such as T lymphocytes. T cells use dominantly aerobic glycolysis during the activation stage [65] and T-cells and their activation are crucial for effective immune response. Endothelial cells also mostly depend on aerobic glycolysis during the sprout formation [66] and aerobic glycolysis is also dominant in energy generation in some other cell types reviewed in [61]. Therefore, another open question is whether systemic treatment with PKM2 inhibitors would have adverse effects on other tissues or would adversely affect the immune response of the patients. Thus, further studies should also investigate the impact of PKM2 inhibition on immune response and systemic effects in animal models. Lastly, according to current literature, it is still unclear if PKM2 inhibition triggers upregulation of other pyruvate kinase isoforms to balance the manipulation. It would be also useful to understand the effect of PKM2 inhibition on the expression of other isoforms.

In summary, PKM2 holds the promise to develop more efficient treatment strategies. For instance, a combination of HIF1 and PKM2 inhibitors could be considered for targeting angiogenesis. PKM2 could be considered an early predictive marker for the development of malignancies in near future. Further studies would shed light to answer if PKM2 is a good candidate to reverse drug resistance and would be able to help to prevent relapses. However, first, the above-mentioned questions need to be answered.

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