Review Article

The Role of PKM2 in the Regulation of Mitochondrial Function: Focus on Mitochondrial Metabolism, Oxidative Stress, Dynamic, and Apoptosis. PKM2 in Mitochondrial Function

Jing Gao, 1 Yuwei Zhao, 1 Tao Li, 2 Xueqi Gan, 1 and Haiyang Yu 1

1 State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China
2 Laboratory of Mitochondrial and Metabolism, Department of Anesthesiology, National Clinical Research Center for Geriatrics, West China Hospital of Sichuan University, Chengdu 610041, China

Correspondence should be addressed to Xueqi Gan; xueqigan@scu.edu.cn and Haiyang Yu; yhyang6812@scu.edu.cn

Received 30 April 2021; Accepted 16 March 2022; Published 6 May 2022

Academic Editor: Daniel Lopez Malo

Copyright © 2022 Jing Gao et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The M2 isoform of pyruvate kinase (PKM2) is one isoform of pyruvate kinase (PK). PKM2 is expressed at high levels during embryonic development and tumor progression and is subject to complex allosteric regulation. PKM2 is a special glycolytic enzyme that regulates the final step of glycolysis; the role of PKM2 in the metabolism, survival, and apoptosis of cancer cells has received increasing attention. Mitochondria are directly or indirectly involved in the regulation of energy metabolism, susceptibility to oxidative stress, and cell death; however, the role of PKM2 in mitochondrial functions remains unclear. Herein, we review the related mechanisms of the role of PKM2 in the regulation of mitochondrial functions from the aspects of metabolism, reactive oxygen species (ROS), dynamic, and apoptosis, which can be highlighted as a target for the clinical management of cardiovascular and metabolic diseases.

1. Introduction

Pyruvate kinase (PK) is one of the key enzymes of glycolysis. PK can catalyze the transphosphorylation from phosphoenolpyruvate (PEP) to ADP as the last step of glycolysis to generate ATP [1]. The M2 isoform of pyruvate kinase (PKM2) is distributed in tissues such as the brain, liver, and tumor tissues [2, 3]. PKM2 has two different forms: a dimeric form and a tetrameric form [4]. The tetrameric form of PKM2 has a higher PK enzymatic activity to catalyze the production of pyruvate [2]. The dimer form of PKM2 has a low PK activity and is closely related to biosyntheses such as energy metabolism and material synthesis [5]. PKM2 expression is associated with several biological activities, including regulation of tumor growth [6], embryogenesis [7], tissue regeneration [8], and inflammatory regulation [9]. Some scholars have suggested that PKM2 can attach to the mitochondrial outer membrane to maintain mitochondrial function; the involvement of PKM2 in the regulation of mitochondrial functions has received increasing attention [10–12].

Mitochondria are important organelles that play a pivotal role in cell life and cell death. Mitochondria are dynamic organelles that consistently migrate, fuse, and divide to modulate their number, size, and shape [13]. In addition, mitochondria play a crucial role in different physiological processes, especially in energy production, the generation of reactive oxygen species, and calcium signaling [14]. Thus, mitochondrial dysfunction leads to various diseases, such as metabolic diseases and cancer [15]. Accumulating evidence suggests that PKM2 may participate in the regulation of the mitochondrial physiological process [10–12]. Therefore, this review focuses on the role of PKM2 in mitochondrial physiological function with respect to metabolism, oxidative stress, dynamic, and apoptosis.
2. PKM2 Expression and Its Biological Functions

There are four tissue-specific isoforms of PK in mammals, including PKM1, PKM2, PKL, and PKR [16]. PKL and PKR are predominantly expressed in the liver and erythrocytes, respectively. PKM1 is abundantly expressed in high-energy demanding organs such as the heart, brain, and muscle, while PKM2 is highly expressed in various proliferating cells, especially embryonic and tumor tissues [3]. PKM1 and PKM2 are produced through alternative splicing under the regulation of several splicing factors, such as heterogeneous nuclear ribonucleoproteins (hnRNPs) and polypyrimidine-tract binding (PTB) [17]. PTBP1 leads to the expression of PKM2 through blocking the inclusion of exon 9 and inducing the inclusion of exon 10 [18].

PKM2, existing as tetrameric and dimeric forms, has been found in the nucleus, mitochondria, and extracellular secretion [19]. The dimeric PKM2 can enter the nucleus, and PKM2 in the nucleus functions as a co-activator of the transcription factor to activate the transcription of target genes that are involved in mitochondrial biogenesis [20]. The subcellular PKM2 can be regulated by multiple signaling pathways, including the phosphorylation of PKM2 at tyrosine, serine, and threonine residues [21], acetylation of PKM2 at K305 [3] succinylation [11], and O-Glucosylation [22].

PKM2 exerts several biological functions [20]. PKM2 is highly expressed and shifts the glucose metabolism from mitochondrial respiration to lactate production in tumor cells; therefore, PKM2 may serve as a potential diagnostic marker in cancer [23]. The inhibitors and activators of PKM2 can be promising anti-cancer drugs. Exerting a similar role, PKM2 may also act as a key protein kinase in other diseases [9, 17, 24]. PKM2 is a requisite for Th1 and Th17 differentiation and may be a therapeutic target for T cell-dependent autoimmune diseases [25]. PKM2 is also involved in renal inflammation in type 2 diabetic nephropathy by promoting the phosphorylation of STAT3 and NF-κB [24].

3. Mitochondrial Function

Mitochondria are essential components of eukaryotic life [26]. Mitochondria are comprised of two separate and functionally distinct outer membranes (OMs) and inner membranes (IMs), that encapsulate the intermembrane space (IMS) and matrix compartments [27]. Mitochondria contain a circular genome, mitochondrial DNA (mtDNA), which qualify mitochondria for the function of semi-conservative replication, transcription, and translation [28].

Mitochondria are the energy-producing organelles of the cell; they can generate the majority of a cell’s ATP via oxidative phosphorylation (OXPHOS) [29]. Glucose is metabolized to ATP for energy supply via two types of reactions, OXPHOS in mitochondria and aerobic glycolysis in the cytosol [30, 31]. Mitochondria are the major intracellular source of reactive oxygen species (ROS); mitochondrial ROS originates from respiratory chain complexes, particularly at the level of complex III and complex I [32]. ROS can cause cumulative damage to mitochondria and mtDNA, leading to mitochondrial dysfunction, which further causes ROS production and mtDNA damage [33].

Mitochondria are dynamic organelles that undergo a dynamic cycle of transport, fission, and fusion. The mitochondrial dynamics maintain the shape, distribution, and size of mitochondria [34]. In mammals, mitochondrial fusion is mediated by mitofusion (Mfn1 and Mfn2, located in the OMs) and optic atrophy gene 1 (Opa1, located in the IMs) [35]. Meanwhile, mitochondrial fission is mediated by fission 1 protein (Fis1, located in the OMs) and dynamin-related protein 1 (Drp1, which is mostly cytosolic and translocates to the OMs during fission) [36]. Imbalanced mitochondrial dynamics lead to mitochondrial dysfunction.

Mitochondria exert multiple functions in the life process, including the control of stress responses, cell signal regulation, and cell apoptosis [37]. The molecular mechanisms underlying function regulation of mitochondria remain elusive, but numerous investigations have documented that PKM2 may be involved in the regulation of the mitochondrial functions.

4. The Effect of PKM2 on Mitochondrial Function

4.1. PKM2 and the Regulation of Mitochondrial Metabolism

PKM2 favors aerobic glycolysis, where glucose is primarily catabolized to lactate, rather than fully metabolized to carbon dioxide using mitochondrial OXPHOS [38]. This phenomenon is termed as the Warburg effect [39, 40].

The function of PKM2 as a metabolic switch can be regulated via three pathways. First, the expression of PKM2 is closely associated with cell metabolism [41, 42]; increased PKM2/PKM1 ratio has been reported to promote aerobic glycolysis. Several factors, such as never in mitosis (NIMA)-related kinase 2 (NEK2) [43], Sam68 [44], Fenobrate [45], and SNHG6 [46], have been proven to affect glycolysis pathway by regulating the proportion of PKM2/PKM1. Second, the forms of PKM2 can also affect cell metabolism. Tetrameric PKM2 exhibits high catalytic activity to catalyze the production of pyruvate by PEP, promoting the flux of glucose-derived carbons to OXPHOS [19], while dimeric PKM2 is the less active state of PKM2 that facilitates the glycolytic intermediates for aerobic glycolysis pathways [47]. Third, some factors can also affect the glycolysis pathway by regulating the transport of PKM2 mRNA. T cells upregulate PKM2 expression through the mTOR1-HIF1 signaling [48], and the nuclear translocation of dimeric PKM2 is improved to increase the STAT3 phosphorylation in T cells [49], which further enhances Th1 and Th17 differentiation by promoting the glycolysis metabolism, representing as a therapeutic target for T cell-dependent autoimmune diseases [25].

With insights into the mechanisms underlying the effect of PKM2 on mitochondrial metabolism, several signaling pathways are involved [50]. First, PKM2 leads to a reduction of TCA intermediates. PKM2 can activate the transcriptions of HIF-1 and subsequently pyruvate dehydrogenase kinase 1 (PDK1) [51], and Bcl2-interacting protein 3 (BNIP3) [52].
PDK1 inhibits the mitochondrial PDH to inhibit the conversion of pyruvate to acetyl-CoA [53]. BNIP3 reduces the levels of mitochondrial-encoded proteins involved in OXPHOS [52]. Second, PKM2 reduces mitochondrial activity without damaging the mitochondria. PKM2 induces the phosphorylation of AMP-activated protein kinase (AMPK), a known inducer of mitochondrial activity [54]. Collectively, PKM2 shifts the glucose metabolism from mitochondrial OXPHOS to aerobic glycolysis, thereby acting as a potential diagnostic marker for tumors (Figure 1).

4.2. PKM2 and the Regulation of Mitochondrial ROS Signaling. PKM2 expression and the PKM2/PKM1 ratio are associated with the production of ROS [38–40]. However, no agreement has been reached about the positive or negative effect of PKM2 on ROS production. Some studies have reported that higher PKM2 expression leads to the decreased ROS production. PKM2 activation by TEPP-46 can decrease ROS production induced by either high-glucose [41] or inflammasome activation [42]. Another activator of PKM2, DASA-58, has also been proven to maintain ROS at a low level [43]. Besides, inhibition of the expression level of PKM2 by the PKM2-siRNA interference significantly stimulated ROS overproduction [44]. In contrast, some other studies came to the opposite conclusions [45–48]. Shuvalov et al. [46] have reported that the overexpression of PKM2 causes elevation of the membrane mitochondrial potential (MMP), subsequently leading to an increase in ROS production. Song et al. [47] have also proven that PCB126-increased ROS production is associated with activation of PKM2/STAT3/Snail1 cascades. It has been reported that PKM2 knockdown effectively relieved the increased ROS level in pancreatic cancer [48].

While PKM2 is involved in ROS regulation, several studies have proven that ROS exerts a negative effect on PKM2 [49–53]. The ROS inhibition of PKM2 may be involved in several signaling. ROS can oxidize PKM2 Cys358, further decrease the active tetramer and promote the phosphorylation of PKM2, thereby causing the inhibition of PKM2 activity [44, 54]. Xiangyun et al. [55] have also reported that high concentrations of ROS can decrease both the succinylation and activity of PKM2 by increasing its binding to SIRT5. Furthermore, ROS can not only affect the expression level and localization of PKM2 but also mediate the crosstalk between PKM2 and other enzymes, including apurinic/apyrimidinic endonuclease (APE1) and ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2) [56, 57]. While another study has shown that the PKM2 mRNA is not inhibited by ROS, the decrease of PKM2 expression is caused by PKM2 degradation. The interaction of PKM2 and ROS can also increase the cell sensitivity to ROS [58]. The increased level of ROS induces mitochondrial translocation of PKM2, and mitochondrial PKM2 interacts with and phosphorylates Bcl2, which inhibits ROS-induced apoptosis [10]. Besides, ROS-dependent inhibition of PKM2 may promote glucose influx into the pentose phosphate pathway (PPP), which contributes to a metabolic response that can deplete ROS [59].

4.3. PKM2 and Mitochondrial Dynamic. Overexpression of PKM2 can regulate mitochondrial dynamics, including decreasing the numbers and increasing the sizes of mitochondria [41] (Figure 2). PKM2 can translocate to mitochondria and inhibit mitochondria fission by downregulating the expression of Drp1 [60]. Drp1 activity relates to its binding partners on the OMs, including mitochondrial dynamics factor (MFF), Fis1, and mitochondrial dynamics proteins of 49 and 51 kDa (MiD49 and MiD51). PKM2 can inhibit the expression of Fis1 [43], and future studies can be conducted to explore the relationship of PKM2 with MFF, MiD51, and MiD49.

PKM2 promotes mitochondrial fusion by triggering the Mfn2 expression [61, 62]. The interaction of PKM2 and Mfn2 can be increased by mammalian target of rapamycin (mTOR)-mediated phosphorylation of Mfn2 at Ser200 [12]. Several microRNAs are involved in this process; smiR-106b is associated with the down-regulation of Mfn2 expression and the PKM2 mediation of mitochondrial fusion [63]. Besides, miR-214 targets Mfn2 by impairing its binding with PKM2 [64]. Others like mitochondrial MiD51 [65] and mitochondrial calcium unipporter complex (MCUC) [66] may be the potential mechanism linking PKM2 and mitochondrial dynamics.

The effect of PKM2 on mitochondrial autophagy still requires validation with additional experiments. On the one hand, PKM2 contributes to mitochondrial autophagy via the HIF-1/BNI3 pathway in hypoxic and some cancer cells [67, 68]. PKM2 activates the transcription of BNI3 by inducing HIF-1α; BNI3 can induce mitochondrial membrane permeabilization by Bax/Bak1 or via the opening of the mPTP, which leads to release of mitochondrial pro-death proteins and activation of cell death [67, 69]. On the other hand, PKM2 inhibits autophagy by activating the mTOR [70, 71]. PKM2 activates mTORC1 via the PI3K-Akt signaling pathways to inhibit autophagy in Hela, HEK293T, and HCT116 cells [71]. PKM2 overexpression may phosphorylate S202/203 of AKT1S1 and their phosphorylation activates mTORC1 [72]. Besides, PKM2 may reduce the ratio of AMP/ATP and the inhibition of AMP to mTORC1 kinase activity and autophagy in A549 cells [73].

4.4. PKM2 and Mitochondrial Apoptosis Pathway. PKM2 plays a crucial role in cell apoptosis progression [74, 75] (Figure 3). The silencing of PKM2 expression with shRNA or microRNA promotes cell apoptosis in multiple cancer cells [76–79]; the phosphorylation of PKM2 by the dysregulation of microRNAs (miR) has also been reported to regulate cell apoptosis [80–82].

A possible mechanism underlying the effect of PKM2 on mitochondrial apoptosis is that the metabolic function of PKM2 is involved in modulating mitochondrial apoptosis of cancer cells [66, 83, 84]; the enhanced glycolysis by PKM2 can attenuate cell apoptosis in cancer cells [85–87]. Several studies have proven that HIF-1α/PKM2 pathway-associated metabolic changes may facilitate apoptosis resistance in cancer cells [88, 89]. The use of metabolic regulation by PKM2 to interfere with cell apoptosis is a new strategy for
cancer treatment [90]. PKM2 can also regulate apoptosis via modulation of mitochondrial dynamics. Wu et al. [60] have reported that PKM2-mediated mitochondrial dynamic disorders participate in cell apoptosis. Mitochondrial metabolic and dynamics work together to promote the apoptosis resistance in several cells [66, 81].

On the other hand, PKM2 regulates mitochondrial proteins that are involved in cell apoptosis. PKM2 translocates to the outer membrane of mitochondria under oxidative stress [10]. In the mitochondria, tetrameric PKM2 suppresses the p53 transcriptional activity and p53-related apoptotic pathway in a high oxidation state [78, 91, 92]. Except for the p53-related apoptotic pathway, mitochondrial PKM2 can interact with Bcl2 and phosphorylates Bcl2 at T69, thus sustaining Bcl2 protein stability and controlling mitochondrial membrane permeability [89, 93, 94]. Besides, PKM2 can also enhance the stability of NF-κB p65 subunit, promoting the binding of NF-κB p65 subunit to Bcl-xL promoter, thereby up-regulating the expression of Bcl-xL protein (an anti-apoptotic member of Bcl-2 protein family).
Some studies have reported that PKM2 exerts its effects on apoptosis via the caspase-dependent pathway, including the expression of cleaved caspase 3, caspase 7, and caspase 9 [96–101]. Meanwhile, some other studies have reported that the nuclear translocation of PKM2 is responsible for regulating cell apoptosis, which is caspase-independent, isoform-specific, and independent of its enzymatic activity [102–104].

In summary, this review concerns the related mechanisms of the role of PKM2 in the regulation of mitochondrial functions from the aspects of metabolism, reactive oxygen species (ROS), dynamic, and apoptosis (Figure 4). They may be potentially used in diagnosis and as indicators of disease progression. These findings have increased our understanding of the signaling pathways of PKM2-related mitochondrial functions and indicated that PKM2 may serve as a potential therapeutic intervention for cardiovascular and metabolic diseases [9, 105, 106]. Therefore, the role of PKM2 in mitochondrial functions can be highlighted as a target for the clinical management of cardiovascular and metabolic diseases [17, 20, 107].

5. Conclusions

PKM2, known as a key rate-limiting enzyme in glycolysis, is widely involved in the regulation of mitochondrial function, including mitochondrial respiration, reducing ROS damage to mitochondria, mitochondrial morphology, and...
mitochondrial-dependent apoptosis (Figure 4). Mitochondrial dysfunction plays an important role in the progress of several diseases, especially in cancers. PKM2 can be a potential target for therapeutic intervention in these diseases. However, the current research on the relationship between PKM2 and mitochondrial function is not enough; the specific mechanism of the relationship remains unclear. Further deciphering the functions of PKM2 on mitochondrial function might lead to successful mitochondria-related disease prevention and therapy.

Data Availability
The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest
The authors declare no conflicts of interest.

Authors’ Contributions
Jing Gao and Yuwei Zhao contributed equally to this study.

Acknowledgments
There are many excellent studies that are relevant to this topic that we were unable to cover due to space constraints. We sincerely apologize to those authors whose work we have overlooked. The present work was supported by the National Natural Science Foundation of China (No. 81771113) and the National Natural Science Foundation of China (81870802), Sichuan Science and Technology Program (2019YFS0356).

References
[1] J. Zhang and Y. Lu, “Biocomputing for portable, resettable, and quantitative point-of-care diagnostics: making the glucose meter a logic-gate responsive device for measuring many clinically relevant targets,” Angewandte Chemie (International Ed. in English), vol. 57, no. 31, pp. 9702–9706, 2018.
[2] Z. Zhang, X. Deng, Y. Liu, Y. Liu, L. Sun, and F. Chen, “Pkm2, function and expression and regulation,” Cell & Bioscience, vol. 9, no. 1, 2019.
[3] K. Zahra, T. Dey, S. P. Ashish, and U. Pandey, “Pyruvate kinase M2 and cancer: the role of Pkm2 in promoting tumorigenesis,” Frontiers in Oncology, vol. 10, 2020.
[4] A. Munoz-Colmenero, A. Fernandez-Suarez, D. Fatela-Cantillo, E. Ocana-Perez, J. L. Dominguez-Jimenez, and J. M. Diaz-Iglesias, “Plasma tumor M2-pyruvate kinase levels in different cancer types,” Anticancer Research, vol. 35, no. 7, pp. 4271–4276, 2015.
[5] W. J. Israelson and M. G. Vander Heiden, “Pyruvate kinase: function, regulation and role in cancer,” Seminars in Cell & Developmental Biology, vol. 43, p. 43, 2015.
[6] Y. H. Li, X. F. Li, J. T. Liu et al., “Pkm2, a potential target for regulating cancer,” Gene, vol. 668, p. 48, 2018.
[7] W. Yang and Z. Lu, “Pyruvate kinase M2 at a glance,” Journal of Cell Science, vol. 128, no. 9, pp. 1655–1660, 2015.
[8] T. L. Dayton, V. Goecheva, K. M. Miller et al., “Isoform-specific deletion of Pkm2 constrains tumor initiation in a mouse model of soft tissue sarcoma,” Cancer & Metabolism, vol. 6, no. 1, 2018.
[9] E. M. Palsson-McDermott and L. A. O’Neill, “The Warburg effect then and now: from cancer to inflammatory diseases,” BioEssays, vol. 35, no. 11, pp. 965–973, 2013.
[10] J. Liang, R. Cao, X. Wang et al., “Mitochondrial Pkm2 regulates oxidative stress-induced apoptosis by stabilizing Bcl2,” Cell Research, vol. 27, no. 3, pp. 329–351, 2017.
[11] H. Qi, X. Ning, C. Yu et al., “Succinylation-dependent mitochondrial translocation of Pkm2 promotes cell survival in response to nutritional stress,” Cell Death & Disease, vol. 10, no. 3, p. 170, 2019.
[12] T. Li, J. Han, L. Jia, X. Hu, L. Chen, and Y. Wang, “Pkm2 coordinates glycolysis with mitochondrial fusion and oxidative phosphorylation,” Protein & Cell, vol. 10, no. 8, pp. 583–594, 2019.
[13] S. Kausar, F. Wang, and H. Cui, “The role of mitochondria in reactive oxygen species generation and its implications for neurodegenerative diseases,” Cells, vol. 7, no. 12, p. 274, 2018.
[14] H. Vakifahmetoglu-Norberg, A. T. Ouchida, and E. Norberg, “The role of mitochondria in metabolism and cell death,” Biochemical and Biophysical Research Communications, vol. 482, no. 3, pp. 426–431, 2017.
[15] P. Theurey and J. Rieusset, “Mitochondria-associated membranes response to nutrient availability and role in metabolic diseases,” Trends in Endocrinology & Metabolism, vol. 28, no. 1, pp. 32–45, 2017.
[16] G. Dong, Q. Mao, W. Xia et al., “Pkm2 and cancer: the function of Pkm2 beyond glycolysis,” Oncology Letters, vol. 11, no. 3, pp. 1980–1986, 2016.
[17] J. C. Alves-Filho and E. M. Palsson-McDermott, “Pyruvate kinase M2: a potential target for regulating inflammation,” Frontiers in Immunology, vol. 7, 2016.
[18] K. Taniguchi, K. Uchiyama, and Y. Akao, “Ptpb1-targeting micrornas regulate cancer-specific energy metabolism through the modulation of Pkm1/M2 splicing,” Cancer Science, vol. 112, no. 1, pp. 41–50, 2020.
[19] N. Wong, J. De Melo, and D. Tang, “Pkm2, a central point of regulation in cancer metabolism,” International Journal of Cell Biology, vol. 2013, Article ID 242513, 11 pages, 2013.
[20] T. L. Dayton, T. Jacks, and M. G. Vander Heiden, “Pkm2, cancer metabolism, and the road ahead,” EMBO Reports, vol. 17, no. 12, pp. 1721–1730, 2016.
[21] E. K. Wiese and T. Hitsug, “Tyrosine kinase signaling in cancer metabolism: Pkm2 paradox in the Warburg effect,” Frontiers in Cell and Developmental Biology, vol. 6, 2018.
[22] X. Yang and K. Qian, “Protein _O_ -GlcNAcylation: emerging mechanisms and functions,” Nature Reviews. Molecular Cell Biology, vol. 18, no. 7, pp. 452–465, 2017.
[23] N. Wong, D. Ojo, J. Yan, and D. Tang, “Pkm2 contributes to cancer metabolism,” Cancer Letters, vol. 356, no. 2 Part A, pp. 184–191, 2015.
[24] L. Li, L. Tang, X. Yang et al., “Gene regulatory effect of pyruvate kinase M2 is involved in renal inflammation in type 2 diabetic nephropathy,” Experimental and Clinical Endocrinology & Diabetes, vol. 128, no. 9, pp. 599–606, 2020.
[25] M. Kono, K. Maeda, I. Stockton-Gavancescu et al., “Pyruvate kinase M2 is requisite for Th1 and Th17 differentiation,” JCI Insight, vol. 4, no. 12, 2019.
Oxidative Medicine and Cellular Longevity

[26] S. J. Annesley and P. R. Fisher, "Mitochondria in health and disease," Cells, vol. 8, no. 7, p. 680, 2019.

[27] Y. Tamura, S. Kawano, and T. Endo, "Lipid homeostasis in mitochondria," Biological Chemistry, vol. 401, no. 6-7, pp. 821–833, 2020.

[28] F. Guerra, A. A. Arbini, and L. Moro, "Mitochondria and cancer chemoresistance," Biochimica et Biophysica Acta - Bioenergetics, vol. 1858, no. 8, pp. 686–699, 2017.

[29] T. Bender and J. C. Martinou, "The mitochondrial pyruvate carrier in health and disease: to carry or not to carry?," Biochimica et Biophysica Acta, vol. 1863, no. 10, pp. 2436–2442, 2016.

[30] A. Vallee, Y. Lecarpentier, R. Guillemin, and J. N. Vallee, "Aerobic glycolysis hypothesis through Wnt/Beta-catenin pathway in exudative age-related macular degeneration," Journal of Molecular Neuroscience, vol. 62, no. 3-4, pp. 368–379, 2017.

[31] E. M. Rueda, J. E. Johnson Jr., A. Giddabasappa et al., "The cellular and compartmental profile of mouse retinal glycolysis, tricarboxylic acid cycle, oxidative phosphorylation, and γP transferring kinases," Molecular Vision, vol. 22, pp. 847–855, 2016.

[32] M. L. Circu and T. Y. Aw, "Reactive oxygen species, cellular redox systems, and apoptosis," Free Radical Biology & Medicine, vol. 48, no. 6, pp. 749–762, 2010.

[33] Y. Yang, S. Karakhanova, W. Hartwig et al., "Mitochondria and mitochondrial Ros in cancer: novel targets for anticancer therapy," Journal of Cellular Physiology, vol. 231, no. 12, pp. 2570–2581, 2016.

[34] L. Tilokani, S. Nagashima, V. Paupe, and J. Prudent, "Mitochondrial dynamics: overview of molecular mechanisms," Essays in Biochemistry, vol. 62, no. 3, pp. 341–360, 2018.

[35] S. Revora-Llopis, C. Bañuls, N. Diaz-Morales, A. Hernandez-Mijares, M. Rocha, and V. M. Victor, "Mitochondrial dynamics in type 2 diabetes: pathophysiological implications," Redox Biology, vol. 11, pp. 637–645, 2017.

[36] A. Pena-Blanco and A. J. García-Saez, "Bax, Bak and beyond-mitochondrial performance in apoptosis," The FEBS Journal, vol. 285, no. 3, pp. 416–431, 2018.

[37] J. H. Lee, A. Park, K. J. Oh, Lee, Kim, and Bae, "The role of adipose tissue mitochondria: regulation of mitochondrial function for the treatment of metabolic diseases," International Journal of Molecular Sciences, vol. 20, no. 19, pp. 4924, 2019.

[38] Q. Li, X. Qi, and W. Jia, "3,3′,5-triiodothyroxine inhibits apoptosis and oxidative stress by the PKM2/PKM1 ratio during oxygen-glucose deprivation/reperfusion AC16 and HCM-a cells; T3 inhibits apoptosis and oxidative stress by PKM2/PKM1 ratio," Biochemical and Biophysical Research Communications, vol. 475, no. 1, pp. 51–56, 2016.

[39] K. Taniguchi, M. Sakai, N. Sugito et al., "Ptpb1-associated microrna-1 and -133b suppress the Warburg effect in colorectal tumors," Oncotarget, vol. 7, no. 14, pp. 18940–18952, 2016.

[40] M. Kurihara-Shimomura, T. Sasahira, C. Nakashima, H. Kuniyasu, H. Shimomura, and T. Kiriti, "The multifarious functions of pyruvate kinase M2 in oral cancer cells," International Journal of Molecular Sciences, vol. 19, no. 10, p. 2907, 2018.

[41] W. Qi, H. A. Keenan, Q. Li et al., "Pyruvate kinase M2 activation may protect against the progression of diabetic glomerular pathology and mitochondrial dysfunction," Nature Medicine, vol. 23, no. 6, pp. 753–762, 2017.

[42] S. Le, H. Zhang, X. Huang et al., "Pkm2 activator Tepp-46 attenuates thoracic aortic aneurysm and dissection by inhibiting Nlrp3 inflammasome-mediated IL-1β secretion," Journal of Cardiovascular Pharmacology and Therapeutics, vol. 25, no. 4, pp. 364–376, 2020.

[43] R. Ren, J. Guo, J. Shi, Y. Tian, M. Li, and H. Kang, "Pkm2 regulates angiogenesis of Vr-Epcs through modulating glycolysis, mitochondrial fission, and fusion," Journal of Cellular Physiology, vol. 235, no. 9, pp. 6204–6217, 2020.

[44] C. Yin, W. Lu, M. Ma et al., "Efficacy and mechanism of combination of oxaliplatin with Pkm2 knockdown in colorectal cancer," Oncology Letters, vol. 20, no. 6, p. 1, 2020.

[45] C. Wang, Y. Chao, W. Xu, Z. Liu, H. Wang, and K. Huang, "Myeloid Fbw7 deficiency disrupts redox homeostasis and aggravates dietary-induced insulin resistance," Redox Biology, vol. 37, article 101688, 2020.

[46] O. Shuvalov, A. Kizenko, A. Petukhov et al., "Semp1/2 augments energy metabolism of tumor cells," Cell Death & Disease, vol. 11, no. 12, p. 1047, 2020.

[47] L. Song, L. Guo, and Z. Li, "Molecular mechanisms of 3′,4′,5′-pentachlorobiphenyl-induced epithelial-mesenchymal transition in human hepatocellular carcinoma cells," Toxicology and Applied Pharmacology, vol. 322, p. 75, 2017.

[48] X. Li, S. Deng, M. Liu et al., "The responsively decreased Pkm2 facilitates the survival of pancreatic cancer cells in hypoglucone," Cell Death & Disease, vol. 9, no. 2, p. 133, 2018.

[49] J. Brandi, D. Cecconi, M. Cordani et al., "The antioxidant uncoupling protein 2 stimulates Hnmp2/P1, Glut1 and Pkm2 expression and sensitizes pancreas cancer cells to glycolysis inhibition," Free Radical Biology & Medicine, vol. 101, p. 305, 2016.

[50] W. Liang, Y. Zhang, L. Song, and Z. Li, "2,3,4,4′-Penta-chlorobiphenyl induces hepatocellular carcinoma cell proliferation through pyruvate kinase M2-dependent glycolysis," Toxicology Letters, vol. 313, p. 108, 2019.

[51] Y. Zhang, L. Song, and Z. Li, "Polychlorinated biphenyls promote cell survival through pyruvate kinase M2-dependent glycolysis in Hela cells," Toxicology Mechanisms and Methods, vol. 29, no. 6, pp. 428–437, 2019.

[52] W. Yu, Z. Yang, R. Huang, Z. Min, and M. Ye, "Sirt6 promotes the Warburg effect of papillary thyroid cancer cell Bcpap through reactive oxygen species," Oncotargets and Therapy, vol. 12, pp. 2861–2868, 2019.

[53] Z. Wang, J. Yin, M. Li et al., "Combination of shikonin with paclitaxel overcomes multidrug resistance in human ovarian carcinoma cells in a P-gp-independent manner through enhanced Ros generation," Chinese Medicine, vol. 14, no. 1, 2019.

[54] E. Mullarky, L. C. Cantley, Nakao K, Minato N, and Uemoto S, "Diverting glycolysis to combat oxidative stress," in Innovative Medicine: Basic Research and Development, K. Nakao, N. Minato, and S. Uemoto, Eds., pp. 3–23, Springer, Tokyo, 2015.

[55] Y. Xiangyun, N. Xiaomin, G. Linping et al., "Desucinylation of pyruvate kinase M2 by Sirt5 contributes to antioxidant response and tumor growth," Oncotarget, vol. 8, no. 4, pp. 6984–6993, 2017.

[56] R. P. Cholia, M. Dhiman, R. Kumar, and A. K. Mantha, "Oxidative stress stimulates invasive potential in rat C6 and
human U-87 mg glioblastoma cells via activation and crosstalk between Pkm2, Ernpp2 and Ape1 enzymes,” Metabolic Brain Disease, vol. 33, no. 4, pp. 1307–1326, 2018.

[57] L. Song, N. Dong, and Z. Li, “P,P'-dichlorodiphenyltrichloroethane promotes aerobic glycolysis via reactive oxygen species-mediated extracellular signal-regulated kinase/M2 isoform of pyruvate kinase (Pkm2) signaling in colorectal cancer cells,” Environmental Toxicology, vol. 35, no. 3, pp. 333–345, 2020.

[58] N. Duraipandy, G. Dharunya, R. Lakra, P. S. Korapatti, and M. Syamala Kiran, “Fabrication of plumbagin on silver nano-framework for tunable redox modulation: implications for therapeutic angiogenesis,” Journal of Cellular Physiology, vol. 234, no. 8, pp. 13110–13127, 2019.

[59] S. Fukuda, H. Miyata, Y. Miyazaki et al., “Pyruvate kinase M2 modulates esophageal squamous cell carcinoma chemotherapy response by regulating the pentose phosphate pathway,” Annals of Surgical Oncology, vol. 22, no. S3, p. 1461, 2015.

[60] H. Wu, Y. Wang, C. Wu, P. Yang, H. Li, and Z. Li, “Resveratrol induces cancer cell apoptosis through MiR-326/Pkm2-mediated Er stress and mitochondrial fission,” Journal of Agricultural and Food Chemistry, vol. 64, no. 49, pp. 9356–9367, 2016.

[61] H. Wu, P. Yang, W. Hu et al., “Overexpression of Pkm2 promotes mitochondrial fusion through attenuated P53 stability,” Oncotarget, vol. 7, no. 47, pp. 78069–78082, 2016.

[62] J. Guo, R. Ren, X. Yao et al., “Pkm2 suppresses osteogenesis and facilitates adipogenesis by regulating β-catenin signaling and mitochondrial fusion and fission,” Aging (Albany NY), vol. 12, no. 4, pp. 3976–3992, 2020.

[63] H. Wu, Z. Li, Y. Wang et al., “MiR-106b-mediated Mfn2 suppression is critical for Pkm2 induced mitochondrial fusion,” American Journal of Cancer Research, vol. 6, no. 10, pp. 2221–2234, 2016.

[64] T. Liu, B. Wang, G. Li et al., “Disruption of mircoRNA-214 during general anaesthesia prevents brain injury and maintains mitochondrial fusion by promoting Mfn2 interaction with Pkm2,” Journal of Cellular and Molecular Medicine, vol. 24, no. 23, pp. 13589–13599, 2020.

[65] P. Y. Xiong, L. Tian, K. J. Dunham-Snyr et al., “Biventricular increases in mitochondrial fission mediator (Mid51) and pro-glycolytic pyruvate kinase (Pkm2) isoform in experimental group 2 pulmonary hypertension-novel mitochondrial abnormalities,” Frontiers in Cardiovascular Medicine, vol. 5, 2019.

[66] A. Dasgupta, D. Wu, L. Tian et al., “Mitochondria in the pulmonary vasculature in health and disease: oxygen- sensing, metabolism, and dynamics,” Comprehensive Physiology, vol. 10, no. 2, pp. 713–765, 2020.

[67] G. L. Semenza, “Hif-1 mediates metabolic responses to intratumoral hypoxia and oncogenic mutations,” The Journal of Clinical Investigation, vol. 123, no. 9, pp. 3664–3671, 2013.

[68] Y. Xu, L. Chu, S. Yuan et al., “Rgd-modified oncolytic adenovirus-harboring Shpkm2 exhibits a potent cytotoxic effect in pancreatic cancer via autophagy inhibition and apoptosis promotion,” Cell Death & Disease, vol. 8, no. 6, article e2835, 2017.

[69] A. Nagao, M. Kobayashi, S. Koyasu, C. C. T. Chow, and H. Harada, “Hif-1-dependent reprogramming of glucose metabolic pathway of cancer cells and its therapeutic significance,” International Journal of Molecular Sciences, vol. 20, no. 2, p. 238, 2019.

[70] Y. Wang, H. Zhao, M. Guo, D. Fei, L. Zhang, and M. Xing, “Targeting the Mir-122/Pkm2 autophagy axis relieves arsenic stress,” Journal of Hazardous Materials, vol. 383, article 121217, 2020.

[71] C. Wang, J. Jiang, J. Ji et al., “Pkm2 promotes cell migration and inhibits autophagy by mediating Pi3k/Akt activation and contributes to the malignant development of gastric cancer,” Scientific Reports, vol. 7, no. 1, p. 2886, 2017.

[72] Z. Yu, D. Wang, and Y. Tang, “Pkm2 promotes cell metastasis and inhibits autophagy via the Jak/Stat3 pathway in hepatocellular carcinoma,” Molecular and Cellular Biochemistry, vol. 476, no. 5, pp. 2001–2010, 2021.

[73] B. Chu, J. Wang, Y. Wang, and G. Yang, “Knockdown of Pkm2 induces apoptosis and autophagy in human A549 alveolar adenocarcinoma cells,” Molecular Medicine Reports, vol. 12, no. 3, pp. 4358–4363, 2015.

[74] J. Feng, T. Ma, Z. Ge et al., “Pkm2 gene regulates the behavior of pancreatic cancer cells via mitogen-activated protein kinase pathways,” Molecular Medicine Reports, vol. 11, no. 3, pp. 2111–2117, 2015.

[75] H. Li, H. Xu, R. Xing et al., “Pyruvate kinase M2 contributes to cell growth in gastric cancer via aerobic glycolysis,” Pathology, Research and Practice, vol. 215, no. 6, article 152409, 2019.

[76] X. L. Yan, X. B. Zhang, R. Ao, and L. Guan, “Reracted: Effects of shRNA-mediated silencing of Pkm2 gene on aerobic glycolysis, cell migration, cell invasion, and apoptosis in colorectal cancer cells,” Journal of Cellular Biochemistry, vol. 118, no. 12, pp. 4792–4803, 2017.

[77] Y. Miao, M. Lu, Q. Yan, S. Li, and Y. Feng, “Inhibition of proliferation, migration, and invasion by knockdown of pyruvate kinase-M2 (Pkm2) in ovarian cancer Skov3 and Ovar3 cells,” Oncology Research, vol. 24, no. 6, pp. 463–475, 2016.

[78] R. Ao, L. Guan, Y. Wang, and J. N. Wang, “Effects of Pkm2 gene silencing on the proliferation and apoptosis of colorectal cancer LS-147T and SW620 cells,” Cellular Physiology and Biochemistry, vol. 42, no. 5, pp. 1769–1778, 2017.

[79] W. Q. Lu, Y. Y. Hu, X. F. Lin, and W. Fan, “Knockdown of Pkm2 and Gls1 expression can significantly reverse oxaliplatin-resistance in colorectal cancer cells,” Experimental and Therapeutic Medicine, vol. 8, no. 27, pp. 44171–44185, 2017.

[80] L. Song, W. Zhang, Z. Chang et al., “Mir-4417 targets tripartite motif-containing 35 (Trim35) and regulates pyruvate kinase muscle 2 (Pkm2) phosphorylation to promote proliferation and suppress apoptosis in hepatocellular carcinoma cells,” Medical Science Monitor, vol. 23, pp. 1741–1750, 2017.

[81] D. Wu, A. Dasgupta, A. D. Read et al., “Oxygen sensing, mitochondrial biology and experimental therapeutics for pulmonary hypertension and cancer,” Free Radical Biology and Medicine, vol. 170, pp. 150–178, 2021.

[82] Z. Zhu, G. Tang, and J. Yan, “Microrna-122 regulates doce-taxel resistance of prostate cancer cells by regulating <b>Pkm2</b>,” Experimental and Therapeutic Medicine, vol. 20, no. 6, p. 247, 2020.

[83] V. Iansante, P. M. Choy, S. W. Fung et al., “Parp14 promotes the Warburg effect in hepatocellular carcinoma by inhibiting Ink1-dependent Pkm2 phosphorylation and activation,” Nature Communications, vol. 6, no. 1, p. 7882, 2015.

[84] S. Papa and C. Bucibi, “Linking apoptosis to cancer metabolism: another missing piece of junk,” Molecular & Cellular Oncology, vol. 3, no. 2, article e1103398, 2016.
[85] J. Yan, D. Zhang, Y. Han, Z. Wang, and C. Ma, “Antitumor activity of SR splicing-factor 5 knockdown by downregulating pyruvate kinase M2 in non–small cell lung cancer cells,” *Journal of Cellular Biochemistry*, vol. 120, no. 10, pp. 17303–17311, 2019.

[86] Q. Tang, Q. Ji, W. Xia et al., “Pyruvate kinase M2 regulates apoptosis of intestinal epithelial cells in Crohn’s disease,” *Digestive Diseases and Sciences*, vol. 60, no. 2, pp. 393–405, 2015.

[87] J. Feng, L. Wu, J. Ji et al., “PKM2 is the target of proanthocyanidin B2 during the inhibition of hepatocellular carcinoma,” *Journal of Experimental & Clinical Cancer Research*, vol. 38, no. 1, p. 204, 2019.

[88] Q. Wang, D. Lu, L. Fan et al., “Cox-2 induces apoptosis resistance in hepatocellular carcinoma cells via the HIF-1α/PKM2 pathway,” *International Journal of Molecular Medicine*, vol. 43, no. 1, pp. 475–488, 2019.

[89] J. Feng, W. Dai, Y. Mao et al., “Simvastatin re-sensitizes hepatocellular carcinoma cells to sorafenib by inhibiting HIF-1α/PPAR-γ/PKM2-mediated glycolysis,” *Journal of Experimental & Clinical Cancer Research*, vol. 39, no. 1, p. 24, 2020.

[90] D. Dong, Y. Dong, J. Fu et al., “Bcl2 inhibitor ABT737 reverses the Warburg effect via the Sirt3-HIF1α axis to promote oxidative stress-induced apoptosis in ovarian cancer cells,” *Life Sciences*, vol. 255, article 117846, 2020.

[91] B. Saleme, V. Gurtu, Y. Zhang et al., “Tissue-specific regulation of P53 by Pkm2 is redox dependent and provides a therapeutic target for anthracycline-induced cardiotoxicity,” *Science Translational Medicine*, vol. 11, no. 478, 2019.

[92] D. J. Kim, Y. S. Park, M. G. Kang et al., “Pyruvate kinase isoenzyme M2 is a therapeutic target of gemcitabine-resistant pancreatic cancer cells,” *Experimental Cell Research*, vol. 336, no. 1, pp. 119–125, 2015.

[93] Z. Lu and T. Hunter, “Metabolic kinases moonlighting as protein kinases,” *Trends in Biochemical Sciences*, vol. 43, no. 4, pp. 301–310, 2018.

[94] W. Hu, S. X. Lu, M. Li et al., “Pyruvate kinase M2 prevents apoptosis via modulating Bim stability and associates with poor outcome in hepatocellular carcinoma,” *Oncotarget*, vol. 6, no. 9, pp. 6570–6583, 2015.

[95] X. He, S. Du, T. Lei et al., “Pkm2 in carcinogenesis and oncotherapy,” *Oncotarget*, vol. 8, no. 66, pp. 110656–110670, 2017.

[96] J. Yang, T. Guo, X. Liang et al., “Cadmium inhibits apoptosis of human esophageal epithelial cells by upregulating Cdk6,” *Ecotoxicology and Environmental Safety*, vol. 205, article 111146, 2020.

[97] J. C. Tang, R. An, Y. Q. Jiang, and J. Yang, “Effects and mechanisms of metformin on the proliferation of esophageal cancer cells in vitro and in vivo,” *Cancer Research and Treatment*, vol. 49, no. 3, pp. 778–789, 2017.

[98] Y. Lin, H. Zhai, Y. Ouyang et al., “Knockdown of Pkm2 enhances radiosensitivity of cervical cancer cells,” *Cancer Cell International*, vol. 19, no. 1, p. 129, 2019.

[99] Q. Yuan, H. Yu, J. Chen, X. Song, and L. Sun, “Knockdown of pyruvate kinase type M2 suppresses tumor survival and invasion in osteosarcoma cells both in vitro and in vivo,” *Experimental Cell Research*, vol. 362, no. 1, pp. 209–216, 2018.

[100] Z. Z. Li, F. Wang, S. Liu, H. Li, and Y. Wang, “Ablation of PKM2 ameliorated ER stress-induced apoptosis and associated inflammation response in IL-1β-treated chondrocytes via blocking Rspo2-mediated Wnt/β-catenin signaling,” *Journal of Cellular Biochemistry*, vol. 121, no. 10, pp. 4204–4213, 2020.