



The Role of PKM2 in Multiple Signaling Pathways Related to Neurological Diseases

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Abstract

Pyruvate kinase M2 (PKM2) is a key rate-limiting enzyme in glycolysis. It is well known that PKM2 plays a vital role in the proliferation of tumor cells. However, PKM2 can also exert its biological functions by mediating multiple signaling pathways in neurological diseases, such as Alzheimer's disease (AD), cognitive dysfunction, ischemic stroke, post-stroke depression, cerebral small-vessel disease, hypoxic-ischemic encephalopathy, traumatic brain injury, spinal cord injury, Parkinson's disease (PD), epilepsy, neuropathic pain, and autoimmune diseases. In these diseases, PKM2 can exert various biological functions, including regulation of glycolysis, inflammatory responses, apoptosis, proliferation of cells, oxidative stress, mitochondrial dysfunction, or pathological autoimmune responses. Moreover, the complexity of PKM2's biological characteristics determines the diversity of its biological functions. However, the role of PKM2 is not entirely the same in different diseases or cells, which is related to its oligomerization, subcellular localization, and post-translational modifications. This article will focus on the biological characteristics of PKM2, the regulation of PKM2 expression, and the biological role of PKM2 in neurological diseases. With this review, we hope to have a better understanding of the molecular mechanisms of PKM2, which may help researchers develop therapeutic strategies in clinic.

Keywords PKM2 · Neurological diseases · Glycolysis · Inflammatory reaction · Apoptosis · Cell proliferation · Oxidative stress

Abbreviations

PKM2	Pyruvate kinase M2	NF-κB	Nuclear factor kappa enhancer binding protein
AD	Alzheimer's disease	PPAR-γ	Peroxisome proliferator-activated receptor γ
PD	Parkinson's disease	mTORC2	Mammalian target of rapamycin complex 2
PK	Pyruvate kinase	AKT	Protein kinase B
PEP	Phosphoenolpyruvate	APJ	Angiotensin II receptor-like 1
ADP	Adenosine diphosphate	SRSF3	Arginine rich splicing factor 3
ATP	Adenosine triphosphate	PTBP1	Polypyrimidine tract binding protein 1
HIF-1α	Hypoxia-inducible factor 1α	hnRNPA1/A2	Heterogeneous nuclear ribonucleoprotein A1/A2
HRE	Hypoxia response element	circRNA	Circular RNAs
PI3K	Phosphoinositide 3-kinase	circSRRM4	CircRNA serine/arginine repetitive matrix 4
mTOR	Mammalian target of rapamycin	miRNAs	MicroRNAs
AMPK	AMP-activated protein kinase	miR-124	MicroRNA-124
PTEN	Phosphatase and tensin homolog	RBM4	RNA-binding motif 4
EGFR	Epidermal growth factor receptor	PHB2	Prohibitin 2
PKC	Protein kinase C	lncRNAs	Long non-coding RNAs
		LINC00689	LncRNA long intergenic non-protein coding RNA 689

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ceRNA	Competing endogenous RNA	C1q	Complement component 1q
circMAT2B	Circular RNA MAT2B	TNF	Tumor necrosis factor
Mbd2	Methyl-CpG binding domain protein 2	IL	Interleukin
PPP	Pentose phosphate pathway	C3	Complement component 3
FBP	Fructose-1,6-bisphosphate	C3aR	C3a receptors
PHD3	Prolyl hydroxylase 3	RA	Rheumatoid arthritis
GLUT1	Glucose transporter 1	Th17	Helper T cells 17
LDHA	Lactate dehydrogenase A	DCs	Dendritic cells
PDK1	Pyruvate dehydrogenase kinase 1	JNK	C-Jun N-terminal kinase
iNs	Induced neurons	mDCs	Myeloid dendritic cells
LDH5	Lactate dehydrogenase isoform 5	RNS	Reactive nitrogen species
MCTs	Monocarboxylate transporters	NADPH	Nicotinamide adenine dinucleotide phosphate hydride
NMDA	N-methyl-D-aspartate	GSH	Reduced glutathione
NMDAR	NMDA receptor	Nrf2	Nuclear factor-erythroid-2-related factor 2
ERK1/2	Extracellular signal-regulated protein kinases 1 and 2	GPX4	Glutathione peroxidase 4
Bcl-2	B-cell lymphoma 2	Gclc	The catalyzing subunit of glutamate-cysteine ligase
Bax	Bcl2-associated X	Gclm	The modifying subunit of glutamate-cysteine ligase
CDKs	Cyclin-dependent kinases	NQO1	NADPH quinone oxidoreductase 1
STAT3	Signal transducers and activators of transcription 3	TrxR1	Thioredoxin reductase 1
6-OHDA	6-Hydroxydopamine	Trx	Thioredoxin
LPS	Lipopolysaccharide	NAD ⁺	Nicotinamide adenine dinucleotide
Wnt	Wingless/integrated	NADH	Reduced nicotinamide adenine dinucleotide
GCI	Global cerebral ischemia	UPR	Unfolded protein response
5' Tyr-tRF	5' TRNA fragments derived from tyrosine pre-tRNA	ARE	Antioxidant response element
CCND1	Cyclin D1	Drp1	Dynammin-related protein 1
HDACs	Histone deacetylases	Mfn2	Mitochondrial fusion protein 2
MAPK	Mitogen-activated protein kinase	MMP	Mitochondrial membrane potential
SCI	Spinal cord injury	OPA1	Optic atrophy 1
TCF4	T-cell factor 4	PP1	Protein phosphatase 1
FAK	Focal adhesion kinase	FUNDC1	FUN14 domain-containing 1
VEGF	Vascular epithelial growth factor	A β	Amyloid β -peptide
VCP	Valosin-containing protein	APH1	Aph-1 homolog
TLRs	Toll-like receptors	NCT	Nicastrin
Pyk2	Proline-rich tyrosine kinase 2	IFITM3	Interferon-induced transmembrane protein 3
PGC-1 α	Peroxisome proliferator-activated receptor- γ co-activator 1- α	NPSLE	Neuropsychiatric systemic lupus erythematosus
HMGB1	High-mobility group box 1	MCI	Mild cognitive impairment
NLRP3	NLR family, pyrin domain containing 3	BDNF	Brain-derived neurotrophic factor
AIM2	Absent in melanoma 2	PSD	Post-stroke depression
EIF2AK2 or PKR	Eukaryotic translation initiation factor 2 alpha kinase 2		
iNOS	Inducible nitric oxide synthase		
COX-2	Cyclooxygenase-2		
MyD88	Myeloid differentiation factor 88		
TRAF6	TNF receptor-associated factor 6		
NOX4	NADPH oxidase 4		
IFN- γ	Interferon- γ		
ROS	Reactive oxygen species		
ATF2	Activation transcription factor 2		
H3	Histone 3		

Introduction

Pyruvate kinase (PK), as the key enzymes in regulating the final rate-limiting step of glycolysis, catalyzes the transfer of phosphate groups from phosphoenolpyruvate (PEP) to adenosine diphosphate (ADP) to produce pyruvate and

adenosine triphosphate (ATP) [1, 2]. PK is composed of four isoenzymes encoded by two different genes (*PKLR* and *PKM*) in mammals [3], namely PKM1, PKM2, PKL, and PKR [4]. Among them, PKM2 is a key rate-limiting enzyme of glycolysis and a key regulator of tumor metabolism [1]. It has been shown to be overexpressed in various cancers and promote the proliferation and metastasis of tumor cells [1]. However, the capabilities of PKM2 are not limited to this. There is growing evidence that PKM2 also plays important roles in neurological diseases [5, 6]. Furthermore, PKM2 has multiple biological roles in addition to its abilities to regulate glycolysis and cell proliferation. And the enzymatic activity of PKM2 is complexly regulated by multiple signaling pathways, allowing cells to adapt to different physiological states [7].

In this review, we will introduce the biological characteristics of PKM2 and the regulation of PKM2 expression in non-neoplastic diseases, as well as its biological roles by mediating multiple signaling pathways, and focuses on the role of PKM2 in multiple signaling pathways related to neurological diseases. A better understanding of these contents has important implications for the treatment of neurological diseases in which PKM2 is involved.

The Biological Characteristics of PKM2

Studies have shown that the *PKM* gene produces a pre-mRNA product that is alternatively spliced to produce two different subtypes, PKM1 mRNA and PKM2 mRNA [8, 9]. The difference between the mRNA encoding PKM1 and PKM2 lies only in exon 9 containing PKM1 information or exon 10 containing PKM2 information [10, 11]. PKM1 is expressed in most adult tissues with high catabolic needs, such as muscles and brain [12]. However, PKM2 is present in all tissues of the embryonic stage and is gradually replaced by other isoenzyme forms in specific tissues during development [13]. Studies have shown that PKM2 is also expressed in other cells or tissues in addition to embryonic tissue, such as cancerous tissue, myocardium, liver, brain, stem cells, endothelial cells, monocytes, macrophages, T cells, and platelets [12, 14–19]. Notably, PKM1 is the most abundantly expressed subtype in nerve cells under normal conditions, while PKM2 is less expressed, mainly in proliferating cells, especially embryonic cells and neural progenitor cells of the hippocampus, cerebellum, and subventricular region [9, 20]. Studies have also shown that PKM1 is specifically expressed in neurons, while PKM2 is expressed in astrocytes and other glial cells in the nervous system [5, 6].

Functions of PKM2 are heavily regulated by multiple mechanisms, such as endogenous allosteric effectors

and intracellular signaling pathways [21], and are largely dependent on its oligomerization, subcellular localization, and post-translational modifications [2, 22–24]. Post-translational modifications include phosphorylation, methylation, acetylation, oxidation, hydroxylation, lactylation, succinylation, and glycation [24, 25]. Oligomers of PKM2 mainly exist in high activity tetramer and low activity dimer/monomer forms [26, 27]. The increase in lactylation of PKM2 at K62 inhibits its tetramer-to-dimer transition, which promotes its pyruvate kinase activity and reduces nuclear distribution [24]. However, the phosphorylation, acetylation, sulfinylation, succinylation, and oxidation of PKM2 promote its conformational transformation from tetramers to dimers [28–31]. The oligomers of PKM2 are present in the cytoplasm in the tetramer forms and exhibit pyruvate kinase activity (metabolic enzyme activity) [32, 33]. PKM2 is localized in the nucleus and induced by various mechanisms to exert protein kinase activity [34]. PKM2 can also translocate to the nucleus through its dimer forms, regulating the transcription and expression of downstream genes [1, 27]. Furthermore, PKM2 nuclear translocation is thought to depend on various complex protein–protein interactions [22]. PKM2 dimers dominate in cancer cells and play an integral role in cancer metabolism [22]. Therefore, the diversity of PKM2's biological roles is determined by the complexity of its biological characteristics.

Common Signaling Pathways that Regulate PKM2 Expression

The gene for the PKM2 protein is *PKM* [8, 9]. The synergistic effect of *PKM* transcription and the alternative splicing of the pre-mRNA lead to PKM2 protein expression [35]. The transcription of *PKM* and the alternative splicing of its pre-mRNA are regulated by multiple signaling pathways.

Hypoxia-inducible factor 1 α (HIF-1 α) is a common transcription factor that regulates *PKM* gene transcription. One study has shown that HIF-1 α expression is upregulated in microglia after cerebral ischemia [32]. Moreover, under hypoxic conditions, prolyl hydroxylation of HIF-1 α being inhibited, which leads to proteasome degradation of HIF-1 α being inhibited, thereby stabilizing and activating HIF-1 α protein [36]. HIF-1 α dimerizes with HIF-1 β and recruits the hypoxia response element (HRE) site of the *PKM* gene in the nucleus, thereby activating the transcription of the *PKM* gene [32, 34]. And the resulting HIF-1 α -PKM2 complex can enhance PKM2 nuclear translocation in the dimer form [32]. In turn, PKM2 can interact directly with the HIF-1 α subunit and promote transactivation of HIF-1 target genes [34]. The interaction between HIF-1 α and PKM2 forms a positive feedback loop [34]. In addition, activation of the phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin

(mTOR) signaling pathway upregulates HIF-1 α -mediated *PKM* gene transcription [37, 38]. The AMP-activated protein kinase (AMPK)/mTOR signaling pathway can also promote HIF-1 α protein expression, thereby upregulating PKM2 protein levels [39]. This signaling pathway links the regulation of PKM2 to hypoxia-ischemic conditions [40]. However, increased expression of phosphatase and tensin homolog (PTEN) can inhibit mTOR activation, thereby reducing the expression of PKM2 [41] (Fig. 1).

Furthermore, activation of the epidermal growth factor receptor (EGFR) mediates upregulation of protein kinase C (PKC) and nuclear factor kappa enhancer binding protein (NF- κ B)-dependent PKM2 expression [35]. Among

them, the activation of NF- κ B can bind to GCGACTTTC in the *PKM* gene promoter and activate its transcription [35]. NF- κ B activation can also increase the expression of PKM2 by inducing HIF-1 α expression [42]. In addition, the nucleus pluripotent factor Oct4 binds to the region of the *PKM* gene and directly controls the expression of PKM2 in embryonic stem cells [43]. Peroxisome proliferator-activated receptor γ (PPAR- γ) is a nuclear hormone receptor that specifically transcribes and regulates the expression of PKM2 [40, 44, 45]. Research has shown that the Sin1 (the basic component of mTORC2)/mammalian target of rapamycin complex 2 (mTORC2)/protein kinase B (AKT)-dependent PPAR- γ nuclear translocation

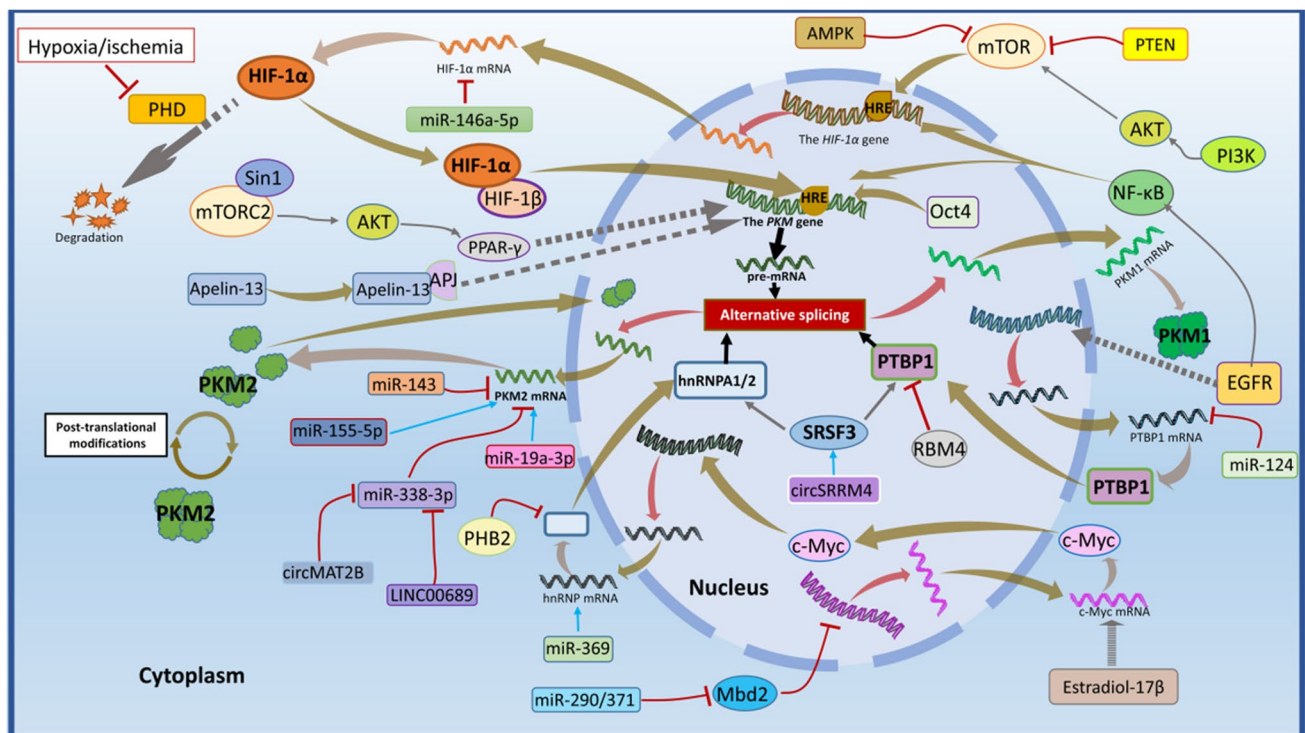


Fig. 1 PKM2 expression and common signaling pathways for regulation of PKM2 expression. The pre-mRNA transcribed by the *PKM* gene is spliced by alternative splicing factors, such as PTBP1, hnRNPA1/A2, or SRSF3, to produce PKM2 mRNA. Due to the presence of post-translational modifications, oligomers of PKM2 mainly exist in tetramer and dimer/monomer forms. Signaling pathways, such as PI3K/AKT/mTOR/HIF-1 α , AMPK/mTOR/HIF-1 α , PTEN/mTOR/HIF-1 α , EGFR/NF- κ B/HIF-1 α , EGFR/NF- κ B, Sin1/mTORC2/AKT/PPAR- γ , Apelin-13/APJ, or Oct4, can regulate expression of the *PKM* gene. MiR-146a-5p interferes with translation of HIF-1 α mRNA. CircSRRM4 can bind SRSF3 and inhibit its ubiquitination. The Mbd2/c-Myc and estradiol-17 β /c-Myc pathways regulate the expression of hnRNPA1/A2. MiR-290/371 blocks the inhibition of c-Myc transcription by Mbd2. MiR-369 facilitates the translation of hnRNP mRNA. However, PHB2 directly inhibits the splicing effect of hnRNPA1/A2. MiR-124 interferes with translation of PTBP1 mRNA. RBM4 inhibits the splicing effect of PTBP1. MiR-143 and miR-338-3p interfere with translation of PKM2 mRNA.

CircMAT2B and LINC00689 block the interference effect of miR-338-3p. However, miR-155-5p and miR-19a-3p can facilitate the translation of PKM2 mRNA. HIF-1 α , hypoxia-inducible factor 1 α ; HRE, hypoxia response element; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; AMPK, AMP-activated protein kinase; PTEN, phosphatase and tensin homolog; EGFR, epidermal growth factor receptor; NF- κ B, nuclear factor kappa enhancer binding protein; PPAR- γ , peroxisome proliferator-activated receptor γ ; mTORC2, mammalian target of rapamycin complex 2; AKT, protein kinase B; APJ, angiotensin II receptor-like 1; SRSF3, arginine rich splicing factor 3; PTBP1, polypyrimidine tract binding protein 1; hnRNPA1/A2, heterogeneous nuclear ribonucleoprotein A1/A2; circSRRM4, circRNA serine/arginine repetitive matrix 4; miR-124, microRNA-124; RBM4, RNA-binding motif 4; PHB2, prohibitin 2; LINC00689, lncRNA long intergenic non-protein coding RNA 689; circMAT2B, circular RNA MAT2B; Mbd2, methyl-CpG binding domain protein 2

can mediate the expression of PKM2 in thymic cells [46]. In addition, apelin is an endogenous ligand of angiotensin II receptor-like 1 (APJ), a G protein-coupled receptor, and both apelin and APJ receptors are distributed in vascular smooth muscle cells [47]. Apelin-13 promotes PKM2 expression in human aortic vascular smooth muscle cells in a dose- and time-dependent manner [47] (Fig. 1).

After the *PKM* gene transcription into the pre-mRNA, the alternative splicing of the pre-mRNA is regulated by several alternative splicing factors. Studies have shown that overexpression of alternative splicing factors, such as serine and arginine rich splicing factor 3 (SRSF3), polypyrimidine tract binding protein 1 (PTBP1), and heterogeneous nuclear ribonucleoprotein A1/A2 (hnRNPA1/A2), can reduce the ratio of PKM1 to PKM2, which contributes to glycolysis-dominated metabolism [8, 48–52]. Among them, SRSF3 collaborates with PTBP1 or hnRNPA1 to participate in the splicing of PKM mRNA [48] (Fig. 1).

One study found that the circular RNA (circRNA) serine/arginine repetitive matrix 4 (circSRRM4) can bind SRSF3 and inhibit its ubiquitination in epilepsy models, improving SRSF3-mediated the alternative splicing of PKM, thereby stimulating glycolysis in cells [51]. In addition, microRNAs (miRNAs) are small non-coding RNAs that regulate genes expression by targeting mRNAs [53]. MicroRNA-124 (miR-124) controls alternative splicing of PKM1 and PKM2 by regulating the expression of PTBP1 in pulmonary hypertension [52]. Moreover, the downregulation of miR-124 is responsible for the increase in PTBP1 expression, resulting in an increase in the ratio of PKM2 to PKM1, which can promote glycolysis and cell proliferation even under aerobic environment [52, 54]. In addition, EGFR activation can also stimulate the expression of PTBP1 [35]. However, the splicing regulator RNA-binding motif 4 (RBM4) antagonizes the function of PTB and induces the expression of PTB isoforms with reduced splicing activity in mesenchymal stem cells [55]. Furthermore, the overexpression of miR-369 can stimulate PKM2 splicing by stabilizing the translation of hnRNPA2B1 and enhance the induction of cell reprogramming by inducing pluripotent stem cell factors in embryonic stem cells [56]. Research has also shown that the estradiol-17 β can enhance PKM splicing into the PKM2 subtype by activating the c-Myc/hnRNP axis in human embryonic stem cells [57]. Prohibitin 2 (PHB2) can also inhibit the alternative splicing function of hnRNPA1 by its C-terminus interacting directly with hnRNPA1 [50] (Fig. 1).

In addition, the long non-coding RNA (lncRNA) long intergenic non-protein coding RNA 689 (LINC00689) promotes the expression of PKM2 by interacting directly with miR-338-3p, thereby playing the role of competing endogenous RNA (ceRNA) [58]. Circular RNA MAT2B (circ-MAT2B) upregulates the expression levels of miR-338-3p target gene PKM2 by “sponging” miR-338-3p [59]. Studies

have shown that the gene for the PKM2 protein is one of the target genes of miR-122 in the liver [53, 60]. Moreover, in polycystic ovary syndrome, the expression of exosome miR-143-3p in follicular fluid was upregulated, which inhibited PKM2 expression and glycolysis in cells, while the overexpression of miR-155-5p can significantly promote PKM2 expression and glycolysis in cells [61]. Similarly, miR-143 is significantly induced by ischemic injury in primary neurons, thereby inhibiting PKM2 expression [62]. Moreover, miR-19a-3p is also significantly induced by ischemic injury, which aggravates ischemic stroke by mediating glycometabolism [63]. Furthermore, the miR-290/371-methyl-CpG binding domain protein 2 (Mbd2)-Myc circuit facilitates glycolysis and reprogramming in human fibroblasts, and PKM2 is essential for miR-290-mediated reprogramming [64]. Among them, the miR-371 cluster is a human congener of the miR-290 cluster [64]. The miR-290 cluster reverses inhibition of the transcriptional activator Myc transcription by Mbd2 through targeting the transcriptional inhibitor Mbd2, a reader of methylated CpGs, and inhibiting its function, thereby regulating glycolysis and metabolic reprogramming [64]. In addition, miR-146a-5p in microglia is reduced in acute spinal cord injury, resulting in increased expression of HIF-1 α [65] (Fig. 1).

To sum up, multiple signaling factors or signaling pathways can directly or indirectly affect PKM2 protein expression. Moreover, different diseases and types of stimulation/injury, as well as different cells, result in the signaling molecules that affect PKM2 expression are not completely the same.

PKM2 Exerts Its Biological Roles by Various Signaling Pathways and Modalities

PKM2 and Glycometabolism

PKM2 and Glycolysis

Glycometabolism is precisely regulated by several glycolytic enzymes, including PK, hexokinase, and pyruvate dehydrogenase [66]. Among the isoenzymes of PK, PKM1 is a tetrameric protein with enzymatic activity that efficiently converts PEP to pyruvate, contributing to pyruvate flow to support mitochondrial oxidative phosphorylation [16, 24]; however, PKM2 directs its pyruvate kinase activity through its own complex allosteric regulation, and the oligomers of PKM2 exist mainly in monomer or dimer forms, resulting in its enzymatic activity being lower than PKM1 [25]. The low catalytic activity of PKM2 dimers prevents pyruvate production at normal rates, leading to the accumulation of upstream glycolysis intermediates [34]. These intermediates are then transferred to other pathways,

such as the pentose phosphate pathway (PPP), which supports biosynthesis in cells [34, 67]. PPP is an alternative metabolic pathway parallel to glycolysis in the nervous system, not only providing key intermediates for biosynthesis, but also controlling the fate of nerve stem/progenitor cells [68]. Thus, PKM2 is highly dimerized in cells or tissues with high nucleic acid synthesis [34]. When most PKM2 molecules are in highly active tetrameric conformations, they have a high affinity for PEP and bind to other glycolytic enzymes in the glycolytic enzyme complex, such as hexokinase, glyceraldehyde 3-phosphate dehydrogenase, phosphoglycerol transferase, and enolase, resulting in the degradation of glucose mainly to pyruvate and lactic acid and regenerating energy [2, 69, 70]. Notably, PKM2 has a low affinity for PEP even as a tetramer in the absence of fructose-1,6-bisphosphate (FBP) [21]. FBP binds to PKM2 at a site different from the active PEP binding site, which will promote and stabilize the tetramerization of PKM2 and increase the binding affinity between PEP and PKM2, so that the kinetic parameters of PKM2 are almost the same as those of PKM1 [21, 71, 72]. In addition, a study showed that PKM2 contains an inducible nuclear transposition signal that allows cells to regulate their glycolysis flow based on local energy states [5]. However, PKM1 is not regulated by allosteric and locks neurons into a steady state of glycolysis [5] (Fig. 2).

Warburg pointed out in 1920 that tumor cells, unlike their normally differentiated counterparts, have an increased rate of glucose uptake and lactate production in the presence of oxygen [73, 74]. This phenomenon is known as aerobic glycolysis or the Warburg effect [73, 74]. Aerobic glycolysis is capable of transferring glucose metabolites from ATP production to the synthesis of cellular building blocks (nucleotides, amino acids, and lipids) to meet proliferation needs [33]. Studies have shown that activated immune cells, such as macrophages, dendritic cells, and T cells, also have the ability to switch from oxidative phosphorylation to aerobic glycolysis in a manner similar to tumor cells [75–78]. FBP and serine have a synergistic allosteric effect on PKM2 [79]. And bound PKM2 has higher information transfer efficiency than the FBP/PKM2 or the serine/PKM2 [79]. Moreover, FBP-K433-T459-R461-A109-V71-R73-MG2-OXL and Ser-I47-C49-R73-MG2-OXL are two possible collaborative allosteric pathways [79]. Other amino acids, such as Asn, Asp, Val, and Cys, have also been shown to bind to the amino acid-binding pockets of PKM2 and modulate its oligomerization, substrate binding affinity, and activity [80]. However, when cells are stimulated by certain growth factors, the binding of phosphotyrosine peptides with PKM2 leads to the release of the allosteric activator FBP, thereby inhibiting the enzymatic activity of PKM2 and transferring glucose metabolites from energy production to anabolic processes [81]. In addition, as mentioned earlier, several post-translational modifications, such

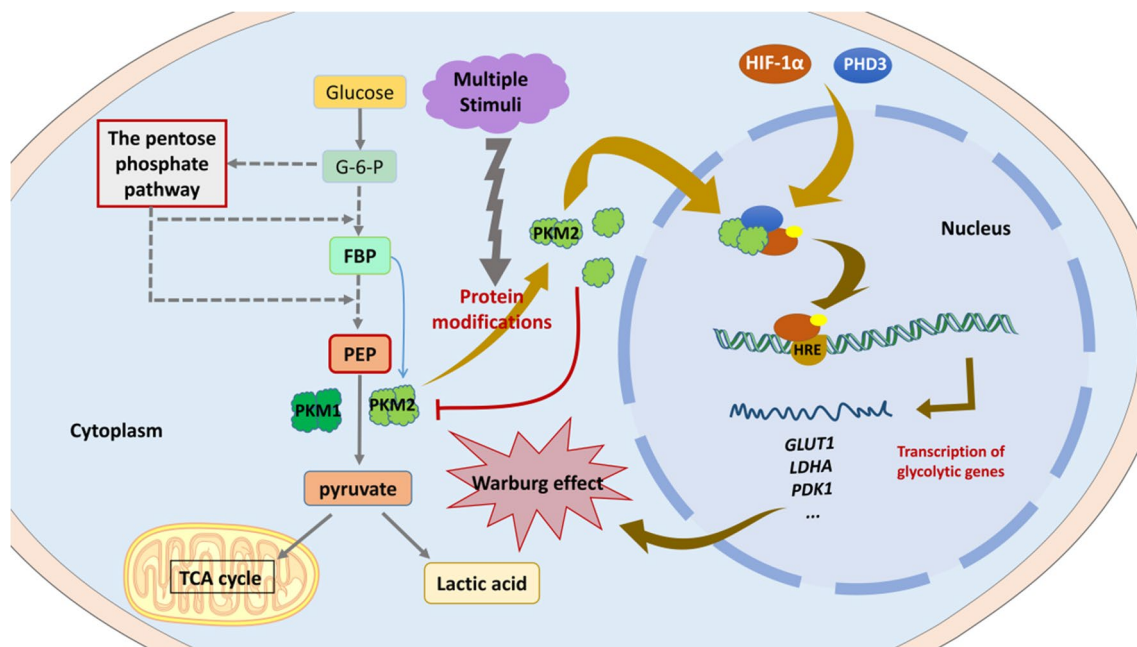


Fig. 2 PKM2 is involved in the glycolytic process. The tetramer PKM2 catalyzes the production of pyruvate from PEP and is more stable in the presence of FBP. Multiple stimuli promote the tetramer-to-dimer transition of PKM2 by protein modifications. The dimer PKM2 leads to the transfer of glycolysis intermediates to the pentose phosphate pathway. The dimer PKM2 nuclear translocation

interacts with HIF-1 α and PHD3 to promote the transcription of glycolytic genes, ultimately leading to the Warburg effect. PEP, phosphoenolpyruvate; HIF-1 α , hypoxia-inducible factor 1 α ; FBP, fructose-1,6-bisphosphate; PHD3, prolyl hydroxylase 3; GLUT1, glucose transporter 1; LDHA, lactate dehydrogenase A; PDK1, pyruvate dehydrogenase kinase 1; HRE, hypoxia response element

as phosphorylation, acetylation, sulfinylation, succinylation, and oxidation, facilitate the conversion of PKM2 to its dimer. The dimer PKM2 is a key regulator of aerobic glycolysis, promoting metabolic reprogramming and lactic acid production [12]. With a decrease in PKM2 activity, the monomer/dimer PKM2 can transfer to the nucleus and form a complex with HIF-1 α and prolyl hydroxylase 3 (PHD3) on the promoter of HIF-1 α , which then regulates the expression of many glycolysis-related genes, such as glucose transporter 1 (*GLUT1*), lactate dehydrogenase A (*LDHA*), and pyruvate dehydrogenase kinase 1 (*PDK1*) [76, 78, 82]. Nuclear PKM2 dimers can also induce c-Myc expression by their histone kinase action, promoting the expression of glycolytic proenzymes that induce the Warburg effect [73]. An imbalance in favor of PKM2 leads to the accumulation of glycolytic metabolites and an increase in lactic acid production [16, 78]. And the PKM2-driven change is a major component of the Warburg effect [16, 78]. In addition to playing a significant role in many cancers [22, 83], this effect is also evident in induced neurons (iNs) and postmortem prefrontal cortex tissue in patients with AD [16]. One study showed that PKM2 promotes Warburg effect-like glycolytic reprogramming in older neurons, and the expression of several genes induced by the PKM2/HIF1 α signaling pathway is involved in the production of precursor metabolites and energy and the metabolism of carbohydrates [16]. In addition, boosting pyruvate kinase activity of PKM2 can lead to a decrease in lactic acid production, which is known as the PKM2 paradox in the Warburg effect [24] (Fig. 2).

Potential Effects of Glycolytic Metabolites on the Nervous System

Neuronal activity is a high-energy-demanding process that recruits all nerve cells adapted to their metabolism to maintain neuronal energy and normal physiological functions [84]. PKM2-mediated aerobic glycolysis plays a critical role in energy metabolism and proliferation of tumor cells, but it may not be suitable for normal metabolism of neurons. One study showed that chemical inhibition of PKM2 nuclear translocation can reduce PKM2 load in the nucleus and restore metabolic patterns in mature neurons [16]. Moreover, the inhibition of PKM2 can slow down the rate of glycolysis to prevent the toxic effect of glycolytic products on neurons [16, 83, 85]. This phenomenon may be related to the fact that neurons compensate for their energy shortages mainly rely on oxidative phosphorylation and cannot use aerobic glycolysis or mitochondrial biogenesis [85]. Similar conclusions have been reached in studies of other diseases. For example, one study found that the activation (tetramerization) of PKM2 can increase glucose metabolic flux by activating the glycolytic pathway, which inhibits the accumulation of highly glucose-induced toxic glucose-derived end products in podocytes [29].

However, lactic acid produced by the glycolysis pathway appears to be essential for regulating neuronal functions. Lactic acid in the brain is mainly formed from glucose or glycogen in astrocytes under normal physiological conditions [51, 86]. Glucose is transferred from cerebral vessels to astrocyte via glucose transporters and then converted to pyruvate and lactic acid by catalysis by PKM2 and lactate dehydrogenase isoform 5 (LDH5) [87, 88]. Lactic acid is transferred from astrocytes to nearby neurons via monocarboxylate transporters (MCTs) to meet the energy needs of neurons and provide signals that regulate neuronal functions, including plasticity, excitability, and memory consolidation [6, 86, 87, 89]. The LDH1 converts lactic acid back to pyruvate in neurons, which is then transferred to mitochondria via the tricarboxylic acid cycle for aerobic energy production [88]. The study showed that L-lactate in neurons can stimulate the expression of synaptic plasticity-related genes, such as *Arc*, *c-Fos*, and *Zif268*, by the N-methyl-D-aspartate (NMDA) receptor (NMDAR)/extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) signaling pathway [90]. Failure to utilize lactic acid can lead to increased neuronal death due to glutamate [91]. In addition, PKM2 deletion mediates impaired lactate homeostasis and mitochondrial ATP production in myelinating Schwann cells of the sciatic nerve, resulting in slowed mitochondrial transport of the axon, the axon terminal retraction of the muscle, and cellular stress of motor neurons [89]. This suggests that aerobic glycolysis is necessary to maintain transport of peripheral nerve axons and neuromuscular junctions [89].

Therefore, the role of PKM2-mediated aerobic glycolysis on the nervous system cannot be generalized. The biological activity of neurons mainly depends on the energy provided by oxidative phosphorylation, and the right amount of lactic acid is also essential for maintaining neuronal energy requirements and physiological functions. However, excessive accumulation of glycolytic metabolites has a toxic effect on neurons.

PKM2 and Apoptosis

Apoptosis is a tightly regulated cell death program involving the caspase cascade and the B-cell lymphoma 2 (Bcl-2) family, such as the anti-apoptosis members Bcl-2 and Bcl-xl, as well as pro-apoptosis members Bcl2-associated X (Bax) and Bak [92, 93]. PKM2 can regulate apoptosis by various signaling pathways.

The Change in Enzymatic Activity (the Dimer-to-Tetramer Transition) of PKM2 Can Antagonize Apoptosis

Vallée et al. [94] suggest that inactivation of PKM2 may lead to the death of neurons in AD. A study also showed that nuclear PKM2 combines with the signal transducers and activators of transcription 3 (STAT3) and HIF1 α to induce

relevant genes expression, promoting damage signaling, cytokine activity, and apoptosis of elderly neurons in AD iNs [16]. Conversely, inhibition of non-metabolic nuclear effect of PKM2 in neurons not only leads to a decrease in toxic glycolytic metabolites but also reverses the loss of fate, thereby restoring neuronal braking to prevent apoptosis [16]. This seems to suggest the difference between human elderly neurons and tumor cells that promote their proliferation by the PKM2/STAT3 signaling pathway [95]. In addition, PKM2 is also able to regulate apoptosis in other non-neoplastic diseases. Zhou et al. [96] found that pharmacological activation (tetramerization) of PKM2 alleviated the death process of photoreceptor in the rd10 mouse model. Zhao et al. [97] found that PKM2 accumulates in mitochondria and is highly acetylated during lung ischemia/reperfusion injury. In contrast, the K433 deacetylation of PKM2 leads to a change in its enzymatic activity, which reverses Bcl-2 degradation and significantly reduces apoptosis [97] (Fig. 3).

Decreased Expression of PKM2 Can Regulate Apoptosis

Zhao et al. [98] found that silencing PKM2 promoted Bcl-2 expression and reduced the level of Bax and the ratio of Bax to Bcl-2 in the nerve growth factor-PC12 cells treated with

hyperglycemia and 6-hydroxydopamine (6-OHDA). Several studies have also shown that PKM2 mediates the inactivation of phosphorylated PI3K/AKT to participate in neuronal apoptosis in hypoxic-ischemic encephalopathy and traumatic brain injury, as well as anesthesia-induced apoptosis of hippocampal neurons [99–101]. Conversely, silencing PKM2 can improve neuronal apoptosis in these diseases [99–101]. This appears to be different from PKM2 promoting tumor cells proliferation by mediating phosphorylation of the PI3K/AKT signaling pathway [102] (Fig. 3).

In summary, the change in enzymatic activity (the dimer-to-tetramer transition) or silencing of PKM2 can antagonize apoptosis. Moreover, the way PKM2 regulates apoptosis in different cells is not entirely the same. For example, PKM2 leads to apoptosis by mediating dephosphorylation of PI3K/AKT and phosphorylation of STAT3 in the nervous system [16, 99–101]. However, PKM2 promotes the proliferation of various tumors by mediating phosphorylation of PI3K/AKT or STAT3 [95, 102]. Therefore, further research and exploration of the similarities and differences in metabolic switches between neurons or other non-tumor cells and different types of cancer are needed (Fig. 3).

Interestingly, the above research results still have some controversy, and there are even completely opposite research

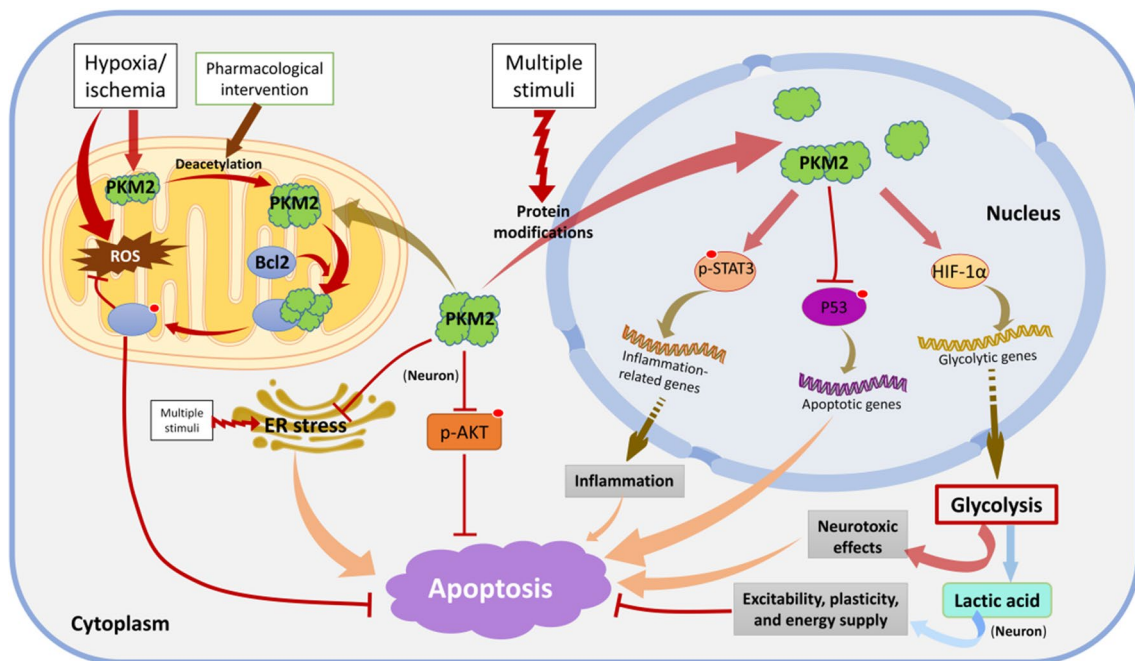


Fig. 3 PKM2 is involved in the regulation of apoptosis. The deacetylation of mitochondrial PKM2 gives it the effect of inhibiting Bcl2 degradation, which then inhibits oxidative stress-induced apoptosis. PKM2 inhibits ER stress but promotes the inactivation of p-AKT in nerve cells, which then regulates apoptosis. Nuclear PKM2 can activate HIF-1 α , STAT3, or block P53, which then regulates the transcription of glycolytic genes, inflammatory genes, or apoptotic genes.

Excess glycolytic metabolites are neurotoxic. However, lactic acid regulates neuronal excitability and synaptic plasticity and provides a source of energy. Bcl-2, B-cell lymphoma 2; STAT3, signal transducers and activators of transcription 3; HIF-1 α , hypoxia-inducible factor 1 α ; AKT, protein kinase B; ROS, reactive oxygen species; ER, endoplasmic reticulum

results. Gu et al. [103] found that MiR-326 reduced PKM2 expression in SH-SY5Y cells treated with A β 25–35, leading to persistent endoplasmic reticulum stress and subsequent apoptosis. Kang et al. [87] found that the loss of PKM2 increased the degree of hippocampal neuronal damage and lactic acid metabolism disorders after global cerebral ischemia (GCI). Conversely, the neuronal death was significantly reduced, and the neuronal survival was saved after lactate supplementation, which may be related to the ability of lactic acid to maintain energy metabolism in neurons [87]. Inoue et al. [104] found that overexpression of PKM2 improved neuronal apoptosis and defects in zebrafish induced by the 5' tRNA fragments derived from tyrosine pre-tRNA (5' Tyr-tRF). 5'Tyr-tRF binds directly to PKM2, and it may enhance the phosphorylation of p53 at serine 15 by inhibiting the interference of nuclear PKM2 on the phosphorylation of classical apoptosis-associated protein p53 [104]. These findings suggest that overexpression of PKM2 appears to be beneficial for the anti-apoptotic effects of cells. However, which oligomerized form of PKM2 exerts an anti-apoptotic effect has not been clearly identified in these studies (Fig. 3).

Thus, PKM2 regulates apoptosis by several not complete same signaling pathways in different diseases or cells. Moreover, there is some controversy among some studies. This phenomenon may be related to the oligomerization, subcellular localization, and post-translational modification of PKM2 in different diseases or cells.

PKM2 Is Associated with Cell Proliferation, Differentiation, or Migration

Cell proliferation is an important life characteristic of an organism and the basis for its growth, development, reproduction and heredity. It is precisely controlled by genetically programmed regulatory pathways. In normally developing tissues, these pathways are able to specify when and where cells can increase or subtract. Both cancer and normal cells utilize the same “universal molecular toolbox” to coordinate cell proliferation. However, compared to normal cells, cancer cells have the abilities to proliferate independently of exogenous growth-promoting or growth-inhibitory signals, to invade surrounding tissues and metastasize to distant sites, to elicit angiogenesis responses, and to evade mechanisms that limit cell proliferation, such as apoptosis and replicative senescence [105]. This allows cancer cells to survive and multiply while normal cells cannot survive and proliferate. The cell cycle, as a complex process, is a core event that regulates cell proliferation [106, 107]. It consists of DNA synthesis (S) and mitosis (M), which are separated by two intervals (G1 and G2); these phases are carried out in the order of G1-S-G2-M [107, 108]. Cell cycle switching is primarily driven by cyclin-dependent kinases (CDKs)

and cyclins [108]. It is well known that metabolic regulation plays a key role in cell proliferation, differentiation, or migration [109].

One study showed that the deletion of PKM2 led to PKM1 expression and proliferation arrest in primary cells [109]. PKM1 expression impairs nucleotide production and the ability to synthesize DNA, as well as progression of the cell cycle; however, the expression of PKM2 supports influx into metabolic pathways to support DNA synthesis [109]. Qiao et al. [110] found that α -synuclein regulates glucose metabolism by the PKM2-dependent signaling pathways in microglia, thereby promoting the cell migration. In traumatic spinal cord injury (SCI), PKM2 nuclear translocation further interacts with β -catenin and p27, and they are recruited into the cyclin D1 gene (*CCND1*) promoter, regulating the expression of the gene *CCND1*, thereby promoting astrocytes proliferation [111]. Lu et al. [112] found that the inhibition of PKM2 can lead to significant downregulation of protein levels of β -catenin, c-Myc, and *CCND1*, as well as a decrease in the number of hippocampal microglia. Similarly, Wu et al. [30] demonstrated that PKM2 located in the nucleus rescues cell survival by mediating the β -catenin/T-cell factor 4 (TCF4) signaling cascade under the conditions of ischemic injury. β -catenin and its induced TCF4 are combined with upregulating gene induction of *Myc*, *CCND1*, and *Sgk1*, thereby regulating cell proliferation and anti-apoptotic effects [30, 113–115] (Fig. 4).

In addition, STAT3 is a transcription factor that regulates proliferation, growth, and apoptosis [116]. Chen et al. [40] found that PKM2 accelerates cell migration by regulating key adhesion/migration factors, such as the focal adhesion kinase (FAK), and nuclear PKM2 dimers can directly phosphorylate STAT3, resulting in STAT3 activation and downstream associated gene transcription. Activation of FAK and STAT3 can increase angiogenesis, neurogenesis, and functional recovery in adult mice with ischemic stroke [40]. PKM2 can also mediate the activity of the MAPK/ERK pathway by activating the vascular epithelial growth factor (VEGF), thereby upregulating oligodendrocytes proliferation [117]. VEGF can promote the proliferation and differentiation of neural precursor cells, neural stem cells, and even glial cells, playing a vital role in brain injury repair and neuronutrition [117, 118]. ERK1/2, as a member of the mitogen-activated protein kinase (MAPK) signaling pathway, has been shown to regulate cell proliferation, differentiation, and motility, as well as cytoskeletal construction [117, 119]. In addition, one study showed that extracellular PKM2 can enhance the proliferation of skeletal muscle cells and the axon growth of cultured neurons [120]. Extracellular PKM2/the valosin-containing protein (VCP) signaling molecules in neurons drive ATPase activity in chronic SCI, mediating axon increase and motor function recovery [121] (Fig. 4).

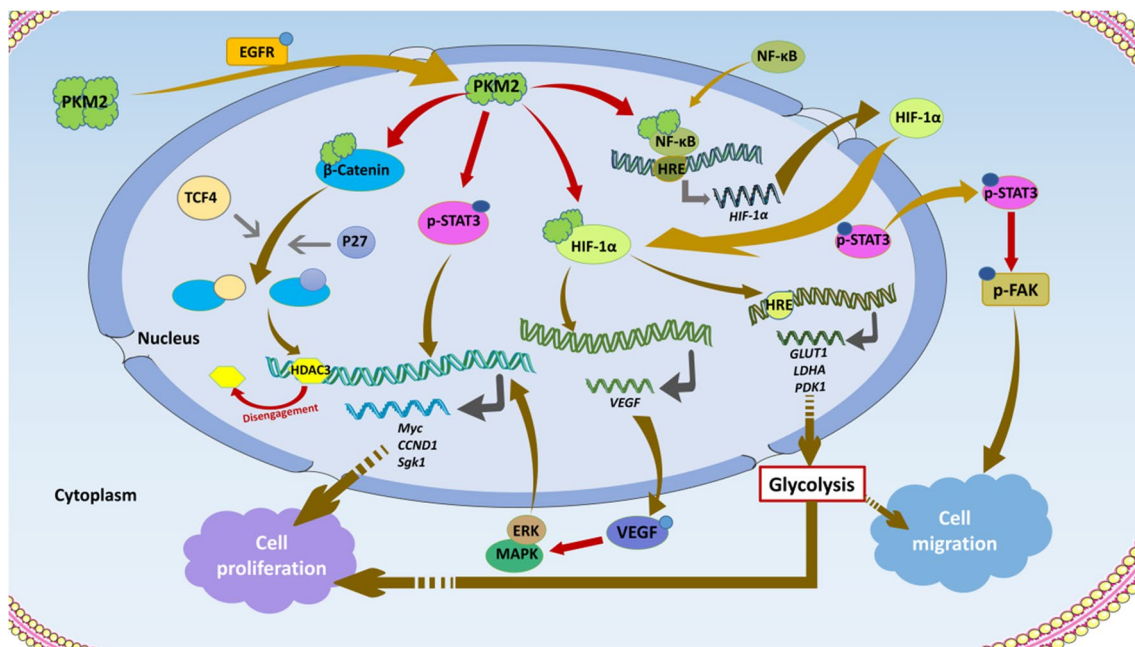


Fig. 4 PKM2 is involved in the proliferation, differentiation, and migration of cells. Nuclear PKM2 participates in the proliferation, differentiation, and migration of cells via activating signaling pathways, such as β -catenin/TCF4, β -catenin/P27, STAT3, STAT3/FAK, HIF-1 α , or NF- κ B/HIF-1 α . HIF-1 α -mediated glycolysis provides an energy source for the proliferation, differentiation, and migration of cells. HIF-1 α -mediated VEGF can participate in the expression of

cell proliferative genes via the MAPK/ERK pathway. CCND1, cyclin D1; MAPK, mitogen-activated protein kinase; TCF4, T-cell factor 4; FAK, focal adhesion kinase; VEGF, vascular epithelial growth factor; HIF-1 α , hypoxia-inducible factor 1 α ; HRE, hypoxia response element; NF- κ B, nuclear factor kappa enhancer binding protein; STAT3, signal transducers and activators of transcription 3

In summary, PKM2 regulates gene expression of cell proliferation by multiple signaling pathways, especially gene expression of proteins related to driving cell cycle transition, thereby promoting cell proliferation.

PKM2 and Inflammatory Response

Inflammation is a well-controlled process triggered by signals from damaged tissues or infections, aimed at re-establishing tissue homeostasis [21]. The inflammatory reaction involves metabolic reprogramming, directing nutrients to the efficient production of ATP, and the synthesis of macromolecules in order to adapt to a highly active metabolic state [6, 21]. These macromolecules are required for the production of pro-inflammatory mediators, cytoskeletal rearrangements, and proliferation of immune cells [21]. Compared with the oxidative phosphorylation of mitochondria, the glycolytic pathway, although less efficient in the utilization of glucose, can produce more energy per unit time during immune cell hypermetabolism to accommodate the rapidly increasing ATP requirement [6, 122]. Therefore, the metabolic conversion from oxidative phosphorylation to glycolysis is the way to adapt to this high metabolic demand. PKM2 regulates aerobic glycolysis and is an important regulator of metabolism and function of inflammatory cells, implying

its potential role in inflammation [19]. At the same time, the dimer PKM2 can also be used as a transcription factor for the expression of target genes in inflammation to promote inflammatory responses [9, 123]. Moreover, HIF-1 α , which interacts with PKM2, can also play an important role in the metabolic reprogramming of inflammatory cells by promoting the expression of target genes in inflammation [124].

PKM2 Is Involved in the Activation of Macrophages and Their Mediated Local or Systemic Inflammatory Responses

Toll-like receptors (TLRs) play a key role in regulating inflammation and abnormal activation of immune cells [125, 126]. Activation of TLR2 can induce PKM2 nuclear transposition [127]. Zhang et al. [125] found that PKM2 can enhance the activation of TLR4, TLR7, and TLR9 by activating proline-rich tyrosine kinase 2 (Pyk2). And they speculate that PKM2 may promote Pyk2 activation by promoting glycolysis and ATP production [125]. Histone deacetylases (HDACs) can drive inflammation mediated by innate immune cells [128, 129]. One study showed that class IIa HDACs (HDAC4, 5, 7, and 9), specifically HDAC7, are key molecules that link TLR-induced aerobic glycolysis and inflammatory responses in macrophages [128]. Moreover,

the HDAC7-PKM2 complex, acting as an immune metabolic signaling center, mediates the deacetylation of PKM2 at lysine 433 and enhances its pro-inflammatory function [128]. In addition, Wang et al. [24] demonstrated that the lactation of PKM2 inhibits its tetramer-to-dimer transition, promotes its pyruvate kinase activity, and reduces its nuclear distribution, thereby promoting the transition of pro-inflammatory macrophages to repair phenotypes and limiting the inflammatory response. Li et al. [130] also found that the downregulation of the intracellular ratio of dimer/monomer-to-tetramer of PKM2 led to the inhibition of nuclear translocation of functional PKM2 in macrophages, which then increased the percentage of infiltrated M2 macrophages in the brain after stroke. In addition, Palsson-McDermott et al. [82] found that PKM2 upregulates and phosphorylates in lipopolysaccharides (LPS)-treated macrophages and forms a complex with HIF-1 α , which can bind directly to the promoter of interleukin (IL)-1 β . They believe that PKM2 is a key determinant of LPS activating macrophages and promoting the inflammatory response. Wang et al. [31] came to a similar conclusion, and they believe that succinylation of

PKM2 promotes the conversion of PKM2 from tetramer to dimer. Moreover, the PKM2/HIF-1 α /peroxisome proliferator-activated receptor- γ co-activator 1- α (PGC-1 α) signaling pathway can also regulate polarization of macrophages and inflammatory responses [131] (Fig. 5).

In addition, Rao et al. [132] and Yang et al. [78] confirmed that PKM2-mediated aerobic glycolysis contributes to the activation of macrophages and the resulting inflammatory response. Moreover, the PKM2/HIF1 α glycolytic pathway plays a key role in regulating the release of high-mobility group box 1 (HMGB1) by activated macrophages [78, 133]. In this signaling pathway, lactic acid produced by glycolysis can increase hyperacetylation of HMGB1 by inhibiting HDAC activity [78, 134]. Activated macrophages/monocytes acetylate HMGB1 in their nuclear localization sequences, leading to chelation of HMGB1 within cytoplasmic vesicles and subsequent release into the extracellular environment [78]. HMGB1 is a late mediator of fatal systemic inflammation [133]. One study showed that PKM2-mediated glycolysis promotes the activation of NLRP3, also known as NLR family, pyrin domain containing 3, and

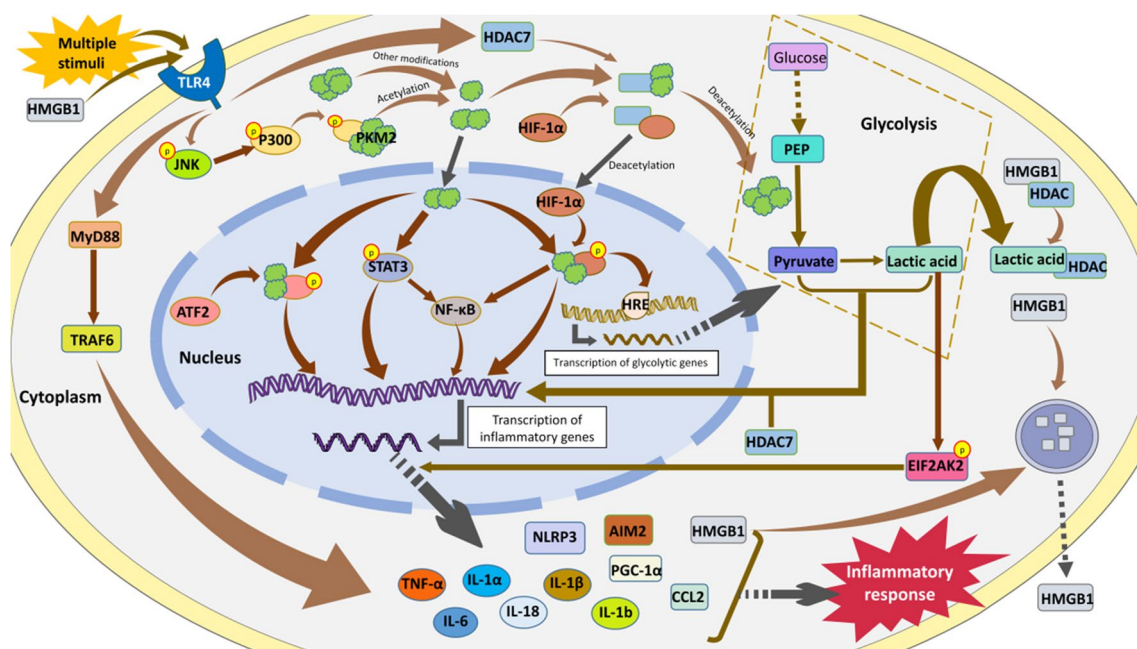


Fig. 5 PKM2 is involved in inflammatory responses. Multiple stimuli promote PKM2 nuclear translocation via TLR4-mediated signaling pathways. Nuclear PKM2 mediates the expression of inflammatory genes via signaling pathways, such as ATF2, STAT3, STAT3/NF- κ B, HIF-1 α /NF- κ B, or HIF-1 α , ultimately leading to inflammation. Lactic acid produced by the glycolytic pathway is involved in the transcription of inflammatory genes and can regulate the expression of inflammatory genes by activating EIF2AK2. In addition, lactic acid can interact with HDAC to block the deacetylation of HMGB1. Acetylated HMGB1 chelates it within the cytoplasmic vesicle and subsequently releases it into the extracellular environment. The HMGB1-mediated TLR4/MyD88/TRAF6 signaling pathway promotes

neuroinflammatory responses and damage of cells. HDAC7, histone deacetylase 7; TLR4, toll-like receptor 4; PGC-1 α , peroxisome proliferator-activated receptor- γ co-activator 1- α ; HMGB1, high-mobility group box 1; NLRP3, NLR family, pyrin domain containing 3; AIM2, absent in melanoma 2; EIF2AK2 or PKR, eukaryotic translation initiation factor 2 alpha kinase 2; MyD88, myeloid differentiation factor 88; TRAF6, TNF receptor-associated factor 6; ATF2, activation transcription factor 2; TNF, tumor necrosis factor; IL, interleukin; JNK, c-Jun N-terminal kinase; NF- κ B, nuclear factor kappa enhancer binding protein; STAT3, signal transducers and activators of transcription 3; PEP, phosphoenolpyruvate

absent in melanoma 2 (AIM2) inflammasomes by regulating phosphorylation of eukaryotic translation initiation factor 2 alpha kinase 2 (EIF2AK2, also known as PKR) in macrophages, thereby promoting the release of IL-1 β , IL-18, and HMGB1 by macrophages [135]. In this signaling pathway, lactic acid-mediated phosphorylation of EIF2AK2 is the main event that controls the activation of inflammasomes in macrophages [135]. In addition, nuclear PKM2-mediated signaling pathways related to inflammatory responses also include JAK1-STAT1/3, NF- κ B, MAPK, p65, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) in macrophages, which are activated by PKM2 to further promote the release of pro-inflammatory cytokines [136] (Fig. 5).

PKM2 Is Involved in the Activation of Glial Cells and Their Mediated Neuroinflammatory Responses

There is evidence that PKM2 plays a key role in neuroinflammation and central nervous system disorders [23, 137]. Zhang et al. [137] found that PKM2 aggravates oxygen–glucose deprivation and reoxygenation induced neuroinflammatory responses and damage of cells by activating the HMGB1-mediated TLR4/myeloid differentiation factor 88 (MyD88)/tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) signaling pathway. TLR4 belongs to the type 1 transmembrane proteins family with an extracellular leucine-rich repeat domain and an intracellular domain homologous to Toll and the IL-1 receptor in mammals [138]. MyD88 is a transfer factor of TLR4 and mainly promotes signal transduction of TLR4 [138]. Furthermore, PKM2 can mediate activation of glycolysis and NLRP3 inflammasomes in mouse models of LPS-induced neuroinflammation [139] (Fig. 5).

Activation of glial cells and production of inflammatory mediators are the main events of neuroinflammation [140]. Microglia, as tissue-resident macrophages of the central nervous system, are key nervous system-specific immune cells [141, 142]. PKM2 plays a potential role in microglia-mediated neuroinflammation [23]. One study showed an increase in PKM2 expression in LPS-treated microglia cultures [9]. PKM2 can be recruited as a transcription factor and localized in the nucleus under inflammatory conditions [9]. Moreover, microglia polarize into M1-type cells with pro-inflammatory activity in inflammatory diseases, which are activated along with the TLR4 signaling [143]. Inhibition of PKM2 can inhibit polarization of BV2 cells and activation of the TLR4 signaling [143]. Similarly, Zhai et al. [144] found that NADPH oxidase 4 (NOX4) promotes PKM2 expression in microglia treated with LPS and interferon- γ (IFN- γ) by increasing the expression of reactive oxygen species (ROS), thereby accelerating polarization of M1-type cells and production

of inflammatory factors. Furthermore, Li et al. [23] found that the dimer PKM2 directly interacts with the pro-inflammatory transcription factor activation transcription factor 2 (ATF2) and regulates ATF2 phosphorylation and nuclear accumulation to bridge glycolysis and pyroptosis in microglia, which may be a key crosstalk between metabolic reprogramming and neuroinflammation in central nervous system. In addition, lactic acid can also further promote the release of pro-inflammatory cytokines by glial cells under pathological conditions [145] (Fig. 5).

In addition, p300 acetyltransferase can catalyze PKM2 acetylation to enter the nucleus and bind to histone 3 (H3) and STAT3 [146]. Moreover, Gao et al. [32] found that stroke-mediated translocation of PKM2 into the nucleus in a dimer forms in microglia, followed by phosphorylation and activation of the transcription factor STAT3, thereby promoting transcription of pro-inflammatory genes and subsequent production of pro-inflammatory factors TNF- α and IL-1 β . Dhanesha et al. [17] also found that nuclear PKM2 regulates excessive activation of neutrophils after cerebral ischemia by promoting STAT3 phosphorylation, driving the thrombo-mediated inflammatory response, thereby aggravating the severity of stroke, and it is likely that the PKM2/STAT3/NF- κ B axis plays a role in it. The PKM2/STAT3 signaling pathway also plays an important role in the activation of astrocytes. Wei et al. [6] found that activated astrocytes after LPS treatment take up more glucose to increase aerobic glycolysis and promote sustained activation of active astrocytes and HMGB1 secretion by the PKM2/STAT3 signaling pathway. In addition, knocking out PKM2 in epilepsy inhibits microglial activation and secretion of inflammatory factors, such as complement component 1q (C1q), TNF- α , and IL-1 α , by inhibiting the activation of NF- κ B, resulting in decreased expression of complement component 3 (C3) in astrocytes and subsequent neuronal damage caused by the interaction of C3 with neuronal C3a receptors (C3aR) [147] (Fig. 5).

Thus, the non-enzymatic nucleogenesis of PKM2, as well as PKM2-mediated metabolic reprogramming and glycolytic products, play important roles in various inflammatory diseases by regulating multiple signaling pathways.

PKM2 and Pathological Autoimmune Responses

Autoimmunity is the phenomenon in which the body's immune system responds to autoantigens and produces autoantibodies and/or self-sensitized lymphocytes [148]. Autoimmune diseases are diseases in which the body reacts to autoantigens and causes damage to its own tissues [148]. The emerging field of immunometabolism focuses on the functional link between metabolic reprogramming and the immune system, which provides an additional

dimension to understanding immunity in health and disease [149].

Elevated PKM2 levels have been reported in several autoimmune diseases, such as autoimmune encephalomyelitis, rheumatoid arthritis (RA), inflammatory bowel disease, idiopathic inflammatory myopathy, and dermatomyositis/polymyositis [150–153]. A study showed that CD4+ T cells are a population of immune cells that play a key role in the immune response [34]. They induce B cells to produce antibodies; induce microbicidal activity of macrophages; recruit neutrophils, eosinophils, and basophils to the site of infection; and produce cytokines and chemokines to induce the immune response [154]. Among them, helper T cells 17 (Th17) and Th1 cells play important roles in the pathogenesis of autoimmune diseases, and their energy source relies on glycolysis [155, 156]. A study has shown that PKM2 is necessary for the development and differentiation of Th1 and Th17 cells [155]. Angiari et al. [153] found that inducing PKM2 tetramerization and inhibiting its nuclear translocation can limit the development of Th17 and Th1 cells and improve the immune response in experimental autoimmune encephalomyelitis. Similarly, PKM2 was expressed in T cells infiltrating the central nervous system in a mouse model of multiple sclerosis, and the regulation of PKM2 may provide a new avenue for the treatment of multiple sclerosis [157]. In addition, dendritic cells (DCs) play a central role in innate and adaptive immunity [158, 159]. One study showed that the c-Jun N-terminal kinase (JNK) signaling pathway stimulates the binding of p300 and PKM2 when DCs are activated by LPS, resulting in PKM2 acetylation and nuclear translocation [158]. Subsequently, nuclear PKM2 binds to c-Rel to enhance IL12p35 expression, which then regulates differentiation of Th1 cells [158]. Moreover, PKM2 with low enzyme activity promotes glycolysis and fatty acid synthesis, helping DCs meet the demand for biological macromolecules [158].

These findings suggest that PKM2-mediated metabolic and non-metabolic pathways can modulate pathological autoimmune responses by promoting differentiation and activation of several immune cells. Therefore, it plays a crucial role in autoimmune diseases.

Antioxidant Damaging Effects of PKM2

The body produces excess ROS and reactive nitrogen species (RNS) in response to various harmful stimuli [160]. They accumulate in tissues or cells and cause an imbalance between high ROS/RNS and low antioxidant defenses, which will lead to a state of oxidative stress and cause cytotoxic reactions and tissue damage [160–162]. Therefore, the body's antioxidant capacity is essential for maintaining the function of cells or tissues. PKM2 is an important signaling

molecule in the body to regulate antioxidant capacity and plays a crucial role in oxidative damage.

Zhu et al. [163] found that light-induced oxidative stress levels of retinal cone cells in mouse were significantly reduced after treatment with PKM2 inhibitors, which might be related to upregulation of PPP. The S-nitrosation (decreased enzyme activity) or inhibition of PKM2 can increase substrate flow through PPP to produce reducing equivalents, such as nicotinamide adenine dinucleotide phosphate hydride (NADPH) and reduced glutathione (GSH), and protect cells from oxidative stress [163–166]. This is because PKM2 is slower than PKM1 in enzymatic activity, and the decrease in its pyruvate kinase activity promotes an anabolic pathway that replaces the glycolytic pathway, i.e., PPP, resulting in generation of reducing equivalents to prevent oxidative stress [2, 67, 167] (Fig. 6).

In addition, nuclear factor-erythroid-2-related factor 2 (Nrf2) is the main regulator of cytoprotective responses in response to oxidative stress [168]. Ren et al. [169] found that nuclear PKM2 can bind to Nrf2 and form a complex that activates and facilitates cytoplasmic Nrf2 entry into the nucleus in hippocampal HT-22 neurons. The PKM2-Nrf2 complex further regulates the transcription of mitochondrial glutathione peroxidase 4 (GPX4) [169]. One study showed that levels of PKM2 expression in the blood were inversely correlated with the PD comprehensive score scale [170]. Nrf2, trans-activated by the PKM2 dimer in astrocytes, can upregulate expression of the catalyzing subunit (Gclc) and modifying subunit (Gclm) of glutamate-cysteine ligase (GSH-synthesized rate-limiting enzyme) by binding to promoters of their genes, thereby improving oxidative stress of PD [171]. Moreover, dimerized PKM2 binds to Nrf2 and activates the Nrf2/antioxidant response element (ARE) pathway in PC12 cells, triggering upregulation of Nrf2-driven antioxidant molecules, such as NADPH quinone oxidoreductase 1 (NQO1), thioredoxin reductase 1 (TrxR1), thioredoxin (Trx), and GSH, thereby improving antioxidant capacity and exerting neuroprotective effects [14].

In addition, lactic acid, as a crucial bioenergetic metabolite, is formed under anaerobic or aerobic glycolytic conditions and can also be used by cells as an oxidation substrate [86, 90, 172]. One study showed that L-lactate is transported into cells through MCTs, and L-lactate dehydrogenase converts it to L-pyruvate with the help of the cofactor nicotinamide adenine dinucleotide (NAD⁺), resulting in elevated levels of intracellular reduced nicotinamide adenine dinucleotide (NADH), thereby regulating the redox state of neurons [90]. L-lactic acid can also upregulate cellular defense mechanisms by promoting outbreaks of mild ROS, including the unfolded protein response (UPR) and Nrf2 activation [172] (Fig. 6).

These studies suggest that the PKM2-mediated Nrf2 signaling pathway and PPP, as well as lactic acid produced

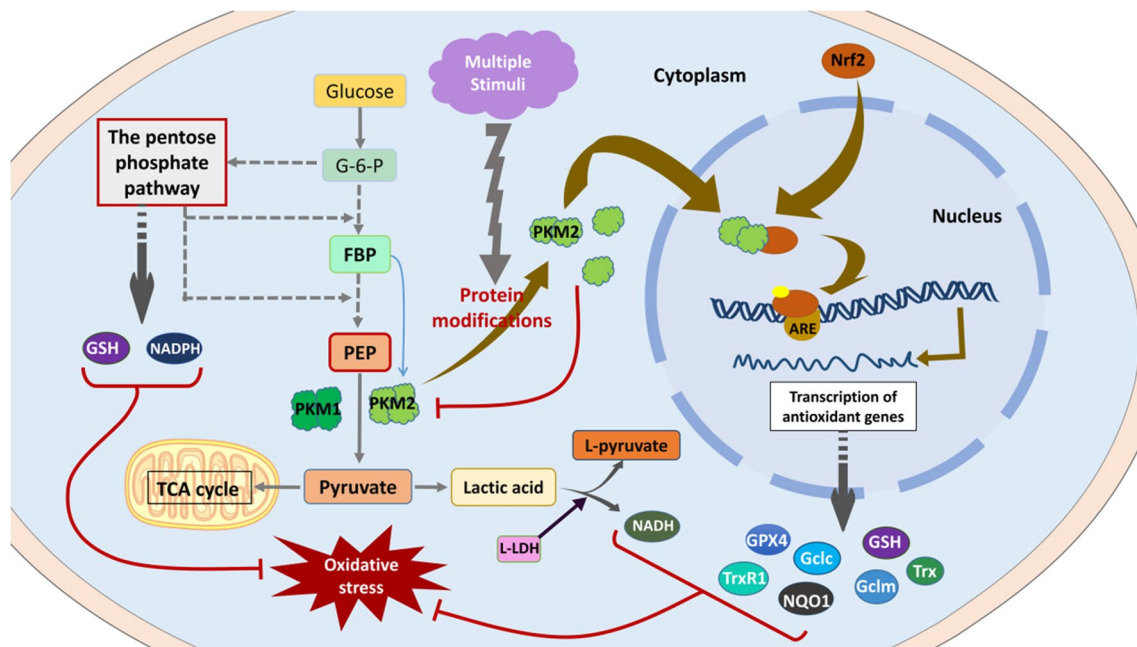


Fig. 6 PKM2 is involved in the regulation of oxidative stress. The dimer PKM2 leads to the transfer of glycolysis intermediates to the pentose phosphate pathway, which then produces reducing equivalents, such as GSH and NADPH. Nuclear PKM2 interacts with Nrf2 to promote the expression of antioxidant genes, resulting in the production of antioxidant molecules. The lactic acid produced by the glycolysis process produces L-pyruvate and NADH under the action of L-LDH. These antioxidant molecules can antagonize oxidative stress. NADPH, nicotinamide adenine dinucleotide phosphate hydride;

GSH, reduced glutathione; Nrf2, nuclear factor-erythroid-2-related factor 2; GPX4, glutathione peroxidase 4; Gclc, the catalyzing subunit of glutamate-cysteine ligase; Gclm, the modifying subunit of glutamate-cysteine ligase; NQO1, NADPH quinone oxidoreductase 1; TrxR1, thioredoxin reductase 1; Trx, thioredoxin; NADH, reduced nicotinamide adenine dinucleotide; L-LDH, L-lactate dehydrogenase; PEP, phosphoenolpyruvate; FBP, fructose-1,6-bisphosphate; ARE, antioxidant response element

by glycolysis, play a crucial role in improving oxidative damage.

PKM2 and Mitochondrial Dysfunction

Mitochondria are organelles coated by two layers of membranes and are crucial structures in cells for producing energy [173]. In addition to oxidative phosphorylation to produce ATP, mitochondria are capable of fission and fusion, mitophagy, and mitochondrial biogenesis [174]. Mitochondrial dysfunction is associated with apoptosis, aging, cancer, and many neurodegenerative and muscle diseases [175, 176]. PKM2 plays an important role in regulating mitochondrial functions.

Mitochondria are constantly dividing and fusing to repair damaged components of mitochondria, with the division process separating damaged mitochondria and the fusion process enabling material exchange between healthy mitochondria [177]. Lack of fission or fusion reduces mitochondrial transport, leading to abnormal mitochondrial distribution and functional defects in cells [178]. A study has shown that elevated PKM2 can lead to abnormal mitochondrial

division/fusion events and mitochondrial dysfunction by weakening the stability of P53 targeting dynamin-related protein 1 (Drp1) [178]. Furthermore, Zhao et al. [98] found that diabetes-mediated PKM2 overexpression leads to increased vulnerability of dopaminergic neurons to 6-OHDA by promoting high glycolysis and abnormal mitochondrial fusion (upregulation of mitochondrial fusion protein 2 (Mfn2) expression) in neurons. Conversely, silencing PKM2 can increase the number of mitochondria and improve the metabolic homeostasis of mitochondria [98]. However, a study showed that weakened interaction between Mfn2 and PKM2 and mitochondrial defects were found in rat hippocampal tissues after exposure to 2% sevoflurane [179]. Conversely, promoting Mfn2-PKM2 interaction can prevent brain damage and maintain mitochondrial fusion [179]. In addition, Qi et al. [29] found that hyperglycemia or diabetes reduced the tetramerization and activity of PKM2 by its sulfenylation and oxidation. Conversely, PKM2 activation could improve or even reverse diabetes or hyperglycemia-induced mitochondrial dysfunction by increasing levels of PGC-1 α protein, mitochondrial membrane potential (MMP), and mitochondrial quality [29]. This phenomenon may be related to PKM2-mediated enhancement of the optic atrophy

1 (OPA1) protein [29, 180]. The activation or tetramerization of PKM2 can also promote PGC-1 α -mediated mitochondrial biogenesis by inhibiting the phosphorylated PI3K/Akt signaling pathway [181]. Furthermore, the PKM2/AMPK signaling pathway mediates the activation of mitophagy [182]. In addition, Li et al. [19] found that PKM2 can upregulate the PINK1/Parkin signaling pathway-mediated mitophagy. Shen et al. [183] suggested that the interaction of PKM2 with protein phosphatase 1 (PP1) mediates the binding of PP1 to FUN14 domain-containing 1 (FUNDC1), resulting in FUNDC1 dephosphorylation and occurrence of FUNDC1-dependent mitophagy.

These findings suggest that PKM2 can modulate mitochondrial fission and fusion, mitophagy, or mitochondrial biogenesis by mediating multiple signaling pathways. However, some of these studies do not point to how different forms of PKM2 oligomerization regulate mitochondrial functions. Therefore, how PKM2 regulates mitochondrial functions in different diseases or cells needs further research and exploration.

In summary, PKM2 has diverse biological functions. In addition to the classical regulation of glycolysis and metabolic reprogramming, it also has the effects of regulating apoptosis and proliferation of cells, inflammatory responses, pathological autoimmune responses, oxidative stress, and mitochondrial dysfunction. However, the pathophysiological mechanisms of PKM2 in different tissues/cells or diseases need to be further studied.

Potential Link of PKM2 to Neurological Diseases

PKM2 and Cognitive Dysfunction

PKM2 and Amyloid β -Peptide (A β) Production

It is known that β -amyloid plaques are the main pathological feature of AD, the main component of which is fibrillar aggregates formed by A β aggregation [184]. PKM2 expression was increased in brain samples of patients with AD and in the cerebral cortex of mice with AD [185]. Moreover, upregulation of PKM2 was concentrated in microglia near A β plaques in mice with AD [186]. One study found that hypoxia induced upregulation of PKM2 expression in the nucleus of neurons with AD, the PKM2 dimer modulated the aph-1 homolog (APH1)-nicastrin (NCT) subcomplex to regulate gamma-secretase by transcriptional control of *Aph-1a*, and activation of gamma-secretase could promote A β production [185]. In addition, elevated PKM2 promotes abnormal activation of aerobic glycolysis in microglia with AD, leading to excessive production of lactic acid [186]. Lactic acid-mediated histone lactification, especially when

elevated H4K12la markers are detected, can modify genes of multiple transcription factors that activate genes of glycolytic enzymes, such as *HIF-1 α* , *PKM*, and *LDHA* [186]. Lactic acid can also directly promote the release of microglial pro-inflammatory factors, such as TNF- α , IL-6, and IL-1 β , to mediate neuroinflammation [145]. Subsequently, inflammatory cytokines induce interferon-induced transmembrane protein 3 (IFITM3) expression in neurons and astrocytes, which then binds to and activates γ -secretase, increasing A β production [187]. Therefore, the positive feedback loop of glycolysis/H4K12la/PKM2 aggravates the glucose metabolism disorder and microglial dysfunction of the cortex and hippocampus in patients with AD, thereby promoting the formation of A β plaques [186] (Fig. 7).

Thus, both non-enzymatic nuclear action of PKM2 and glycolytic metabolites mediated by PKM2 can regulate A β production by relevant signaling pathways.

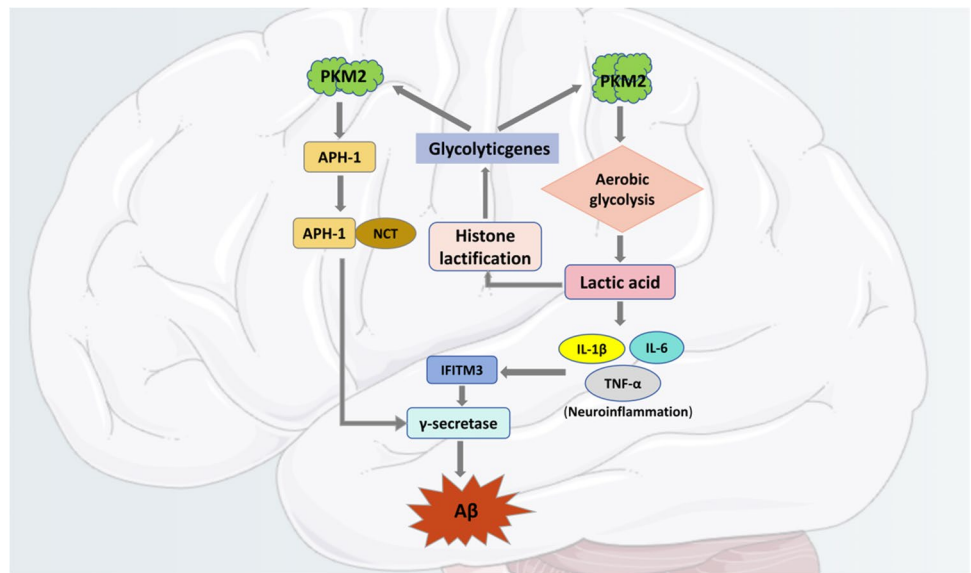
PKM2 Is Involved in the Regulation of Cognitive Dysfunction Associated with Various Diseases

Cognitive function belongs to the advanced functions of the brain, including memory, language expression, visuospatial ability, executive ability, calculation ability, and ability to understand and judge [188]. Impaired one or more of the above can manifest cognitive dysfunction [188]. Several diseases, including AD, cerebral small vessel disease, neuropsychiatric systemic lupus erythematosus (NPSLE), and AIDS, can cause cognitive dysfunction, and PKM2 has been shown to be involved in the regulation of cognitive dysfunction via related signaling pathways in these diseases [112, 123, 186, 189].

The Downregulation of PKM2 Can Improve Cognitive Dysfunction

As mentioned earlier, nuclear PKM2 regulates the relevant gene expression and assists A β production by some signaling pathways. Conversely, PKM2-specific deletion in microglia can improve spatial learning and memory in mice with AD by reducing the burden of A β [186]. Lu et al. [112] found that the PKM2-mediated β -catenin signaling pathway promoted microglial activation and phagocytosis of over-activated microglia, aggravated the loss of neuronal synapses, and then promoted cognitive dysfunction in mice with NPSLE. Conversely, inhibiting the expression of PKM2 in microglia could alleviate the above symptoms [112]. In addition, Bian et al. [123] found that serum PKM2 levels in patients with cerebral small vessel disease were positively correlated with the white matter hyperintensity and increased perivascular space and negatively correlated with cognitive function. Moreover, higher levels of serum PKM2

Fig. 7 PKM2 is involved in the production of A β . PKM2 modulated APH1-NCT sub-complex to regulate γ -secretase by transcriptional control of *Aph-1a*. In addition, PKM2 promotes aerobic glycolysis-mediated the overproduction of lactic acid. Lactic acid promotes the release of pro-inflammatory factors to mediate neuroinflammation. Subsequently, inflammatory cytokines induce IFITM3 expression to bind to and activate γ -secretase. Activation of γ secretase promotes the production of A β . A β , amyloid β -peptide; APH1, aph-1 homolog; NCT, nicastrin; IFITM3, interferon-induced transmembrane protein 3



may lead to chronic inflammation, decreased cerebral blood flow, and cognitive dysfunction [123]. Conversely, inhibiting PKM2 expression may help suppress inflammation, restore cerebral blood flow, and reduce cerebral infarction area, as well as reduce cognitive impairment after stroke [190] (Fig. 8).

Inactivation of PKM2 Can Worsen Cognitive Dysfunction

Impaired activity of PKM2 is exhibited in methamphetamine-induced deficits in neurocognitive function [191]. One study found that protein oxidation played an important role

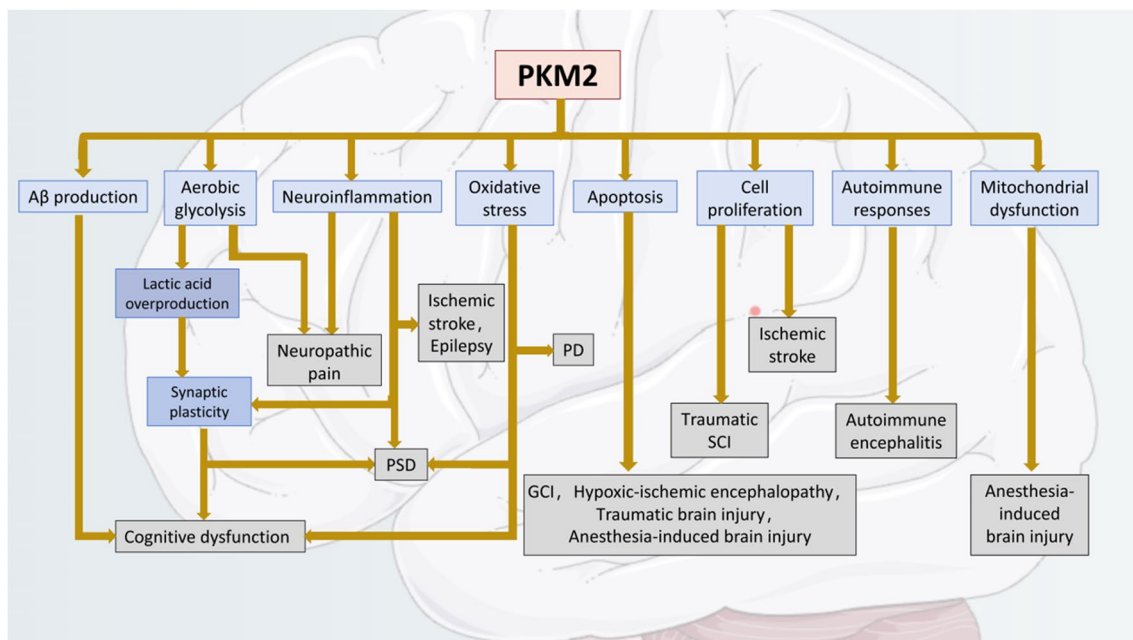


Fig. 8 Potential link of PKM2 to neurological diseases. PKM2 can exert various biological functions, including regulation of A β production, glycolysis, inflammatory responses, apoptosis, proliferation of cells, oxidative stress, mitochondrial dysfunction, or pathological autoimmune responses. In addition, PKM2 is involved in the occurrence and development of neurological diseases, such as cognitive

dysfunction, ischemic stroke, PSD, cerebral small vessel disease, hypoxic-ischemic encephalopathy, traumatic brain injury, traumatic SCI, PD, epilepsy, neuropathic pain, GCI, and autoimmune encephalitis by different biological roles. A β , amyloid β -peptide; PSD, post-stroke depression; PD, Parkinson's disease; SCI, spinal cord injury; GCI, global cerebral ischemia

in the progression of mild cognitive impairment (MCI) to AD [192]. PKM2, functionally involved in the regulation of energy metabolism and synaptic plasticity, was also found to be significantly oxidized in the hippocampus of subjects with MCI [192]. In HIV-related neurocognitive dysfunction, the HIV-1 protein gp120 alters the expression of PKM1 and PKM2 by promoting the expression of PTBP1, leading to the accumulation of advanced glycation end products and preventing the cleavage of the pro-brain-derived neurotrophic factor (pro-BDNF) protein into mature brain-derived neurotrophic factor (BDNF), which ultimately alters normal synaptic plasticity [189]. Instead, these events can be reversed by stabilizing the tetrameric form of PKM2 [189] (Fig. 8).

PKM2-Mediated Aerobic Glycolysis or Antioxidant Damaging Effects Can Improve Cognitive Dysfunction

PKM2 is thought to also improve cognitive dysfunction. Some studies have shown that electroacupuncture can improve cognitive function of AD by boosting glucose metabolism in the brain [193–195]. Li et al. [195] believe that aerobic glycolysis decreases significantly in AD. In contrast, electroacupuncture can promote the expression of aerobic glycolysis-related proteins in the hippocampus, including PKM2, thereby improving the learning and memory ability of APP/PS1 mice [195]. Similarly, Kang et al. [87] found that lactic acid supplementation after GCI restored exacerbation of neuronal damage and cognitive dysfunction due to PKM2 gene deletion. In addition, Ren et al. [169] suggested that nuclear PKM2 in hippocampal HT-22 neurons can inhibit iron death by mediating the PKM2/NRF2/GPX4 signaling pathway, thereby mitigating radiation-induced damage of hippocampal neurons and improving cognitive and memory consolidation decline (Fig. 8).

In summary, regulatory effects of PKM2 on cognitive dysfunction cannot be generalized. The oligomerized form of PKM2 and the biological role it plays differently in different cognitive-related diseases will lead to different ways in which it regulates cognitive dysfunction. Therefore, disease-specific analysis should be carried out. However, the link between PKM2 and cognitive dysfunction needs to be verified by a large number of experimental studies.

PKM2 and Neuropathic Pain

Neuropathic pain is usually a chronic disease caused by lesions or pathological changes within the nervous system [66, 140]. Peripheral and central sensitization can lead to highly sensitive pain behaviors and are considered crucial mechanisms of neuropathic pain [196]. Inflammatory

processes and metabolic disorders are two aspects of central sensitization [66, 197, 198]. Neurons and glial cells, such as microglia and astrocytes, as well as bloodborne macrophages, play a key role in inducing and maintaining neuropathic pain by releasing powerful neuromodulators, such as pro-inflammatory cytokines and chemokines, to enhance neuronal excitability [66, 140, 199]. Studies have shown that glial cells can synthesize and secrete many inflammatory factors and cytokines by PKM2-mediated aerobic glycolysis, which can bind to the corresponding receptors of neurons to enhance the excitability of neurons, thus playing a key role in chronic pain [6, 200]. Activated astrocytes exacerbate inflammatory pain via PKM2-mediated aerobic glycolysis and the STAT3 signaling pathway [6]. In contrast, Wang et al. [66] found that inhibition of PKM2 effectively attenuated the neuropathic pain and inflammatory responses in rats induced by chronic compressive injury, which might be achieved by modulating the ERK and STAT3 signaling pathways. In addition, the accumulation of lactic acid can cause a decrease in intracellular pH and acidification of tissues under pathological conditions, which can also lead to painful behavior [6] (Fig. 8).

Thus, both PKM2-mediated aerobic glycolysis and inflammatory responses can worsen neuropathic pain.

PKM2 and Post-stroke Depression (PSD)

PSD is a common psychiatric disorder after cerebrovascular injury [201]. Depression is characterized by low mood, lack of energy, sadness, insomnia, and an inability to enjoy life [202]. Pathological mechanisms of PSD may involve an increase in inflammatory factors, dysregulation of the hypothalamic–pituitary–adrenal axis, decreased levels of monoamines, glutamate-mediated neuronal excitotoxicity, and abnormal neurotrophic responses [203, 204]. However, disruption of hippocampal synaptic plasticity may be a significant pathological mechanism in depression [205]. Yang et al. [206] found that hydrogen sulfide can inhibit β 2-microglobulin-induced depression-like behavior, which may be associated with improving hippocampal synaptic plasticity by enhancing the hippocampal Warburg effect. Feng et al. [117] found that PKM2 improves PSD by activating the VEGF-mediated MAPK/ERK signaling pathway, which may be associated with improving of inflammatory responses and oxidative stress and proliferation of oligodendrocytes. In addition, some studies on PKM2 in stroke may indirectly suggest a potential link between PKM2 and PSD. For example, PKM2 plays a vital role in the inflammatory response after stroke [32]; PKM2-mediated lactate production plays an important role in maintaining neuronal excitability and synaptic plasticity [90]. As mentioned earlier, inflammatory responses, neuronal excitatory toxicity,

and impaired synaptic plasticity may be pathological mechanisms of PSD [203–205] (Fig. 8).

Therefore, there is a certain connection between PKM2 and PSD. However, the mechanism of the link between the two needs to be further studied.

PKM2 and Other Neurological Diseases

In addition to the above neurological diseases, PKM2 is also involved in pathological changes in other neurological diseases. For example, PKM2 is involved in neuronal apoptosis in GCI, hypoxic-ischemic encephalopathy, and traumatic brain injury, as well as anesthetic-induced apoptosis of hippocampal neurons [87, 99–101], proliferation of astrocytes in traumatic SCI [111], angiogenesis, neurogenesis, and functional recovery after ischemic stroke [40], as well as activation of neutrophils and infiltrating macrophages in the brain after stroke [17, 130], activation of glial cells in epilepsy [147], immune responses in autoimmune encephalitis [153], regulating oxidative stress of dopaminergic neurons in PD [171], and regulating mitochondrial dysfunction in anesthesia-induced brain injury [179]. Therefore, PKM2 has a crucial role in neurological diseases (Fig. 8).

Conclusion

This article focuses on the key role of PKM2 in neurological diseases, expanding the understanding of the typical and atypical biological role of PKM2. Moreover, PKM2 does not work exactly the same in different diseases or cells, which is related to its oligomerization, subcellular localization, and post-translational modifications. Multiple signaling pathways intricately regulate the biological activity of PKM2, allowing cells to adapt to different physiological states. Therefore, PKM2 may have potential links with neurological diseases and may be used as a research direction for the treatment of these diseases and become a potential new target for clinical treatment of these diseases.

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Declarations

Ethics Approval Not applicable.

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