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Research Progress on the Role of PKM2 in Perioperative Neurocognitive Disorders in Elderly Patients

Qianyu Li[1], Jie Liang[2]*

[1]Department of Anesthesiology, Affiliated Hospital of Hebei University, Baoding 071000, Hebei, China
[2]Department of Gastroenterology, Affiliated Hospital of Hebei University, Baoding 071000, Hebei, China

Author to whom correspondence should be addressed.

Abstract: Perioperative Neurocognitive Disorders (PND) are common postoperative complications affecting cognitive and behavioral function in elderly patients, significantly impacting recovery quality. Its pathogenesis is closely linked to an imbalance in cerebral metabolic-immune homeostasis. Recent studies have identified the key metabolic and immune enzyme, Pyruvate Kinase M2 (PKM2), as a participant in the initiation and progression of PND. Surgical trauma and anesthesia can upregulate PKM2 via signaling pathways such as HMGB1, TLR4, and HIF-1α, promoting its acetylation, dimerization, and nuclear translocation. Subsequently, activated PKM2 enhances oxidative stress and recruits NLRPs to drive neuroinflammation and synaptic plasticity decline, leading to postoperative cognitive dysfunction. These cascading changes, to a certain extent, affect postoperative neurological recovery. Mouse model studies have revealed therapeutic strategies targeting PKM2. This review summarizes the mechanisms by which PKM2 influences cognitive and behavioral function through the regulation of neuroinflammation and energy metabolism disorders, and discusses precise brain protection strategies targeting PKM2, offering new insights for the prevention and treatment of PND.

Keywords: Perioperative neurocognitive disorders; Elderly; Pyruvate kinase M2; Metabolic reprogramming; Targeted therapy

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1. Introduction

Perioperative neurocognitive disorder (PND) is a common complication in elderly surgical patients. The prevention and treatment of PND has become a major challenge affecting the postoperative survival and recovery of the elderly [1]. Aging reduces brain reserve capacity and systemic chronic inflammation (inflammaging) [2], increasing susceptibility to PND. Surgical and anesthetic stress acts as a "second hit", activating the HMGB1-TLR4 pathway and exacerbating the PKM2-induced neuroinflammatory cascade

[4,12]. This indicates that PKM2 connects the physiological characteristics of aging with perioperative neuroinflammatory responses. Currently, neuroinflammation and metabolic reprogramming are widely recognized as key processes in PND [3]. Accumulating evidence suggests that PKM2, possessing unique "metabolic-immune" features, plays a pivotal role in PND. Notably, anesthetics themselves can modulate PKM2: inhalational anesthetics like sevoflurane induce PKM2 activation and nuclear migration, while intravenous anesthetics like propofol help maintain its metabolic enzyme activity and suppress inflammation. This review aims to summarize recent basic research advances on the role of PKM2 in PND, focusing on its clinical translation pathways and precision intervention strategies, to provide new perspectives for perioperative brain protection.

2. Molecular properties of PKM2 and its functional hub role in the nervous system

PKM2 is a rate-limiting enzyme in the glycolytic pathway, catalyzing pyruvate metabolism. Its conformational plasticity and functional changes associated with different forms render it a critical nodal molecule integrating cellular energy and inflammatory responses [5]. Thus, PKM2 possesses both metabolic and immune functions, playing a significant role in PND development by transducing signals such as surgical trauma and anesthetic stress into downstream neuroinflammation and metabolic disorders, thereby triggering disease onset and progression.

2.1. Conformational plasticity of PKM2: Functional switching between tetramer and dimer

Under oxidative stress, inflammation, and other signaling stimuli, PKM2 undergoes various important post-translational modifications (including Ser37 phosphorylation, Tyr105 phosphorylation, and Lys433 acetylation) [6], promoting its dissociation from tetramers to dimers. The dimeric form can act as a co-activator, directly recruiting and stimulating transcription factors such as NF-κB and STAT3, thereby amplifying inflammatory responses [5].

2.2. Cell-specific functions of PKM2 in the central nervous system

The expression and function of PKM2 in neural cells exhibit high specificity, constituting the cellular basis for its complex role in PND.

(1) Microglia: Microglia highly express PKM2, which is a major determinant of their metabolic reprogramming and functional transformation. Polarization of microglia towards a pro-inflammatory M1 phenotype requires PKM2 activation, leading to the release of disease-promoting inflammatory molecules such as IL-1β and TNF-α, which contribute to neuronal death and ignite a burst of microglia-mediated dynamic pro-inflammatory damage [8]. In experimental studies, knocking out PKM2 in microglia almost eliminated or prevented the production of other types of pro-inflammatory factors, significantly attenuating neuroinflammation by approximately 62%. [9]

(2) Neurons: Under stress, neurons activate intracellular PKM2 dimers to carry out aerobic respiration, disrupting their reliance on glucose for energy supply and leading to the accumulation of large amounts of lactate, which contributes to cognitive deficits. This can result in reduced or even phagocytosed lactate at synapses and swelling (up to 55%) of postsynaptic densities due to lactate accumulation and disrupted synaptic calcium influx [10].

(3) Blood-Brain Barrier (BBB): PKM2 dysregulation-mediated lactate accumulation can activate matrix metalloproteinase-9 (MMP-9), degrading tight junction proteins and compromising BBB integrity. Clinical studies show a significant positive correlation (r=0.81) between cerebrospinal fluid lactate levels and the BBB damage marker S100β in PND patients^1111^, highlighting the central role of the "PKM2-lactate-MMP-9" axis in PND-associated BBB disruption.

3. Core mechanisms of perioperative stress regulating PKM2 to drive PND

Surgical trauma and anesthetic drugs, as the core perioperative stressors, converge on the key node PKM2 via different upstream signaling pathways, regulating its expression, conformation, and subcellular localization, thereby initiating the pathological cascade of PND.

3.1. Specific regulatory pathways of surgical trauma and anesthetics

3.1.1 Surgical trauma: The HMGB1-TLR4-NF-κB axis upregulates PKM2 expression

Tissue injury releases high-mobility group box 1 (HMGB1), which promotes PKM2 transcription via the TLR4/MyD88/NF-κB axis. Studies show that serum HMGB1 increases 3.3-fold, and hippocampal PKM2 mRNA and protein increase 2.1-fold and 1.8-fold, respectively, at 24 hours post-surgery, correlating with the timing of delirium onset (r=0.73, $P < 0.01$) [13].

3.1.2. Inhalational anesthetic (Sevoflurane): The ROS-HIF-1α axis promotes PKM2 nuclear translocation

Sevoflurane inhibits mitochondrial complex I (IC50=0.34 mM), inducing a mitochondrial ROS burst (2.8-fold increase in DCF fluorescence intensity) [14]. ROS inhibits PHD activity, stabilizing HIF-1α, which in turn enhances PKM2 transcription and recruits p300 for acetylation at the K433 site, promoting nuclear translocation (approximately 3.5-fold increase in nuclear PKM2, $P < 0.001$) [15].

3.1.3. Intravenous anesthetic (Propofol): Antioxidant effects maintain PKM2 metabolic homeostasis

Compared to sevoflurane, propofol, possessing more phenolic hydroxyl groups, significantly reduces ROS (78%±6% 2-OH clearance level), inhibiting the initiation of the ROS-HIF-1 axis at its source. [16] Concurrently, propofol inhibits the Raf-1/ERK signaling pathway, reducing Ser37 phosphorylation of PKM2 by 59% [17]. The combined effect promotes the retention of PKM2 in its fully active, soluble tetrameric form, ensuring normal glycolysis and thereby reducing hippocampal lactate accumulation by 55%, mitigating hippocampal neuronal death or neuroinflammation-associated brain edema, and exerting neuroprotective effects [18]. This may partially explain why sevoflurane anesthesia is more likely to induce postoperative delirium (POD) compared to propofol (34.5% vs. 19.2% incidence, P=0.003) [13].

3.2. Spatiotemporal-specific regulation of PKM2 and PND subtype evolution

PKM2's role in the PND process exhibits a clear temporal sequence, driving the progression of different clinical subtypes. In the early postoperative period (0-6 hours), NF-κB binds to the PKM2 promoter, rapidly upregulating its expression and initiating inflammatory pathways like TLR4/MyD88, marking the inflammatory initiation phase^1313^. Subsequently (6-24 hours), PKM2 undergoes nuclear translocation,

acting as a co-activator for STAT3 and NF-κB, forming a positive feedback loop that significantly promotes the release of pro-inflammatory cytokines like IL-1β and M1 polarization of microglia. This phase is closely associated with the development of postoperative delirium (POD)[8, 26]. From 24 to 72 hours post-surgery, cytosolic PKM2 dimers dominate, leading to aberrant glycolytic flux and lactate accumulation, which activates MMP-9, disrupts the BBB, and causes cognitive fluctuations, corresponding to delayed neurocognitive recovery (DNCR) [11,21]. If metabolic disturbances persist (>72 hours), severe lactic acidosis and mitochondrial damage ensue, leading to a sharp decline in ATP synthesis and ultimately impairing synaptic plasticity, potentially progressing to postoperative neurocognitive disorder (PNCD) [7,18].

4. Specific mechanisms of PKM2 in PND: In-depth differentiation from AD and therapeutic implications

Although both PND and Alzheimer's disease (AD) involve cognitive impairment, the roles of PKM2 differ fundamentally, offering unique insights for targeted PND therapy. First, the triggers differ: PND is acutely induced by perioperative stress (surgery/anesthesia), whereas AD is driven by chronic Aβ/tau accumulation. Second, the kinetics of PKM2 activation differ markedly: PKM2 activation in PND is transient and self-limiting (peaking within 72 hours post-surgery), while in AD, it is persistent and progressive [9]. Third, the core molecular modifications and cellular targets differ: PND is characterized by transient phosphorylation/acetylation primarily driving acute neuroinflammation via M1 polarization of microglia [8, 20]; AD favors sustained Aβ-induced K433 acetylation, affecting both neurons (e.g., tau phosphorylation) and microglia. Finally, and most importantly, is the "reversibility" of the condition: the pathological state in PND, especially PKM2-mediated synaptic damage and inflammation, is essentially reversible, with functional recovery possible after drug withdrawal or intervention; AD pathology is largely irreversible [9, 22]. These fundamental differences dictate distinct therapeutic strategies: PND focuses on "corrective" intervention during the acute window to break the PKM2-driven pathological cascade, whereas AD requires long-term "maintenance" therapy. Therefore, targeting PKM2 represents a more promising and time-sensitive strategy for PND.

4.1. Core pathway of neuronal injury: PKM2-mediated metabolic-synaptic axis dysregulation

In PND, neuronal injury does not arise from protein aggregation akin to AD but from acute functional disruption of the "metabolic-synaptic axis" due to PKM2 dysregulation.

(1) Metabolic Initiation: Perioperative stress promotes PKM2 dimerization, disrupting glycolytic homeostasis in hippocampal neurons and leading to abnormal lactate accumulation.

(2) Cascade Amplification: Accumulated lactate activates MMP-9, disrupting the BBB (forming a "metabolic-barrier disruption" positive feedback) and causing intracellular acidosis, inhibiting mitochondrial respiratory chain complex function and severely reducing ATP synthesis (by 72%) [18, 21].

(3) Functional Impairment: ATP depletion impairs synaptic structure and function, reducing PSD-95 protein cluster density and the success rate of LTP induction [7].

4.2. Theoretical innovation and clinical implications: Why PKM2 is a more promising target for PND

Based on the aforementioned mechanistic differences between PND and AD, PKM2 emerges as a more

promising intervention target for PND due to three key advantages:

(1) Its acute, transient activation provides a clear intervention window (e.g., the 72-hour postoperative golden period), more amenable to short-term, potent intervention to break the acute pathological cascade compared to the chronic, persistent, and difficult-to-target processes in AD.

(2) The synaptic damage and inflammation in PND are inherently reversible, meaning that interventions targeting PKM2 can potentially "reset" the system and restore metabolic and synaptic function, whereas AD's pathological accumulation and epigenetic changes are largely irreversible, limiting treatment efficacy.

(3) These characteristics underscore the fundamental difference in therapeutic strategies: PND focuses on "corrective" treatment to break the acute cascade, while AD necessitates long-term, safe "maintenance" therapy, making the drug development path for targeting PKM2 clearer and more feasible. Leveraging these advantages, utilizing biomarkers of PKM2 activation status (such as lactate, HMGB1, imaging markers) as entry points for precision medicine holds promise for accurate diagnosis, stratification, and individualized intervention in high-risk PND patients.

5. PKM2-targeted intervention strategies: From molecular mechanisms to clinical translation prospects

Currently, intervention strategies targeting PKM2 are primarily categorized as follows. They show promise in preclinical studies but face distinct challenges.

(1) Small Molecule Inhibitors (e.g., Shikonin and its derivative SK-102): These covalently bind to the Cys424 site of PKM2, effectively inhibiting its dimerization and nuclear translocation. Studies show these strategies can significantly improve cognitive function, increasing the Neurological Recovery Index (NRI) by 35% and reducing escape latency in the Morris water maze by 31-38% [23]. They offer potent, rapid action but face challenges such as hepatotoxicity (e.g., a 200% increase in ALT) and low brain penetration (only 0.28). Recent research focuses on prodrug modifications (e.g., CPP-ACP) to reduce systemic toxicity [24].

(2) Allosteric Activators (e.g., TEPP-46): These adopt a different approach by stabilizing the tetrameric form of PKM2 to maintain metabolic homeostasis. This strategy effectively restores hippocampal synaptic plasticity (75%±8% LTP recovery) and reduces the microglial activation marker Iba-1 by 55% [22]. These agents exhibit a better safety profile but are limited by ineffectiveness in AD models and limited efficacy against already nuclear-translocated PKM2. Combination strategies with anti-inflammatory drugs are currently being explored.

(3) Gene Silencing Techniques (e.g., LNP-based siRNA Delivery Systems): These aim to address the root cause by specifically degrading PKM2 mRNA to reduce protein expression. Preclinical models show a silencing efficiency of up to 80% in the hippocampus [25]. Advantages include high target specificity and durable effect, but delivery efficiency and long-term safety remain unknown. Future strategies involve antibody-modified LNPs to enhance targeting towards microglia [25].

(4) Natural Products and Derivatives (e.g., Shikonin derivatives): These are also attracting interest due to their multi-target effects and wide availability, improving neuroinflammation and oxidative stress. However, their precise mechanisms of action are often unclear, and their pharmacokinetics are complex, necessitating structural optimization for enhanced selectivity and bioavailability.

5.1. Clinical translation pathways and precision treatment

Translating the above strategies from bench to bedside requires addressing three key issues:

(1) Biomarker-Guided Patient Stratification: Utilizing genetic markers (ApoE ε4), other fluid biomarkers (PKM2 dimer, HMGB1, lactate) [19], or imaging markers (PET) for screening and stratifying high-risk groups.

(2) Clinical Endpoints and Efficacy Evaluation: Phase II clinical trials could employ composite endpoints, including changes in 30-day postoperative MoCA scores, 90-day dementia conversion rate, 7-day delirium incidence, and changes in imaging biomarkers.

(3) Combination Therapeutic Strategies: Combining PKM2 inhibitors with anti-inflammatory agents (e.g., IL-1 receptor antagonists), or PKM2 activators with neurotrophic agents (e.g., BDNF enhancers), presents potential for synergy.

5.2. Challenges and perspectives of PKM2-targeted intervention in the elderly

Due to age-related declines in liver and kidney function in elderly patients, adverse effects related to drug metabolism and tolerance are expected to increase. For instance, compounds with known hepatotoxicity (e.g., shikonin) require significant attention; developing novel prodrugs or delivery vector systems to reduce systemic exposure will be a major focus. Furthermore, comorbidities like diabetes can directly impact PKM2-targeted therapy. Hyperglycemia can directly modify PKM2 (e.g., O-GlcNAcylation) and may render patients less sensitive to certain inhibitors, necessitating patient stratification strategies [28]. Finally, the high heterogeneity among the elderly underscores the importance of utilizing key clinical biomarkers (e.g., preoperative HMGB1, lactate, ApoE ε4 genotype) for individualized intervention. In the future, integrating PKM2-related biomarkers into comprehensive geriatric assessment frameworks may facilitate preoperative identification of high-risk PND patients and synergize with other perioperative geriatric management strategies (e.g., prehabilitation, multimodal analgesia) to achieve personalized brain protection.

6. Future research challenges and directions: Towards precision perioperative brain protection

6.1. Intelligent delivery systems

Utilizing engineered exosomes (e.g., CD47 ligand-modified) [19] or bacterial vectors for microglia-targeted delivery

6.2. Real-time intraoperative dynamic monitoring: From biomarkers to precision anesthesia management

Developing PKM2 activity monitoring methods based on Surface-Enhanced Raman Scattering (SERS) technology, offering pM-level sensitivity and conformational discrimination capabilities [26]. This requires advancing SERS probe clinical translation, developing portable devices, and establishing real-time warning-intervention closed-loop systems. Preliminary studies suggest this strategy could reduce delirium risk by 40% [27].

6.3. Precision medicine: Building risk prediction models and individualized dosing

Individual genetic backgrounds and underlying diseases significantly influence the efficacy and safety of PKM2-targeted interventions.

(1) Integrating Multi-Omics: Integrating multi-omics data (e.g., genomics, proteomics, inflammatory cytokine profiles) with clinical parameters (e.g., age, medical history, blood glucose) using machine learning algorithms to build PND risk prediction models.

(2) "Modification-Insensitive" Drug Development: Hyperglycemia in diabetic patients may induce O-GlcNAc modification of PKM2, leading to insensitivity to inhibitors [12]. Novel PKM2 modulators that can overcome or are unaffected by common pathological modifications need to be developed to suit complex clinical metabolic environments.

7. Conclusions and perspectives

This review explored the role of PKM2 in PND in the elderly, elucidated the "surgical trauma-anesthetic stress-PKM2-neuroinflammation" axis, and analyzed the similarities and differences between PND in the elderly and AD. As a metabolic-immune hub, PKM2 offers a potential precision strategy for perioperative brain protection in elderly surgical patients. Future research can leverage new-generation medical technologies, utilizing detection methods such as exosomes and SERS probes, to establish intraoperative monitoring-treatment optimization closed-loop feedback cycles. This will propel the precision development of perioperative medicine for elderly patients, ultimately achieving precise perioperative brain protection and improving postoperative cognitive and behavioral outcomes.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Evered L, Silbert B, Knopman DS, et al., 2018, Recommendations for the Nomenclature of Cognitive Change Associated With Anaesthesia and Surgery-2018. Anesthesiology, 129(5): 872–879.

[2] Liu XH, Kang L, Zhu ML, 2023, Guidelines for Frailty Assessment and Management in Elderly Patients. Chinese Journal of Geriatrics, 42(1): 13–19.

[3] Li J, Yang L, Qin W, et al., 2022, Pyruvate Kinase M2 in Neurodegeneration and Neuroinflammation. Nature Reviews Neuroscience, 23(12): 857–873.

[4] Zhou HY, Wang FR, Luo WF, 2023, Research Progress on Neuroinflammatory Mechanisms of Perioperative Neurocognitive Disorders. Chinese Journal of Behavioral Medicine and Brain Science, 32(4): 375–380.

[5] Yang W, Lu Z, 2023, Regulation and Function of Pyruvate Kinase M2 in Cancer and Inflammation. Trends in Biochemical Sciences, 48(7): 625–638.

[6] Dayton TL, Jacks T, Vander Heiden MG, 2023, PKM2 Isoform-Specific Functions in Cellular Metabolism. EMBO Journal, 42(10): e113456.

[7] Wang Y, Liu T, Yang N, et al., 2023, PKM2-Dependent Synaptic Plasticity Regulation. Neuron, 111(7): 1123–1135.

[8] Li J, Chen Y, Wang X, et al., 2023, Propofol Attenuates Neuroinflammation via ROS Scavenging. Metabolism, 148: 155689.

[9] Zhang Y, Liu X, Wang Z, et al., 2023, PKM2-MMP9 Axis in BBB Regulation. Nature Neuroscience, 26(11):

1583–1596.

[10] Zhang Z, Qin P, Li J, et al., 2023, PKM2 in Neuronal Energy Homeostasis. Journal of Clinical Investigation, 133(9): e167892.

[11] Wang Y, Liu Y, Zhang X, et al., 2023, CSF Biomarkers in POCD Patients. Annals of Neurology, 93(4): 789–801.

[12] Wang Y, Liu T, Yang N, et al., 2023, Surgical Stress and PKM2 Expression in Hippocampal Microglia: Role of HMGB1-TLR4-NF-κB Signaling. Annals of Surgery, 277(5): e1024–e1031.

[13] Zhang Q, Li R, Chen S, et al., 2021, Systemic HMGB1 Neutralization Prevents Postoperative Neurocognitive Dysfunction in Aged Mice. Molecular Medicine, 27: 102.

[14] Sadasivan S, et al., 2023, Sevoflurane-Induced Mitochondrial Dysfunction Promotes PKM2 Nuclear Translocation. Anesthesiology, 139(5): 634–648.

[15] Shen Y, Jiang Y, Zhang Y, et al., 2023, Surgical Stress Induces Lactate-Mediated Microglial Activation and Cognitive Decline Through NLRP3 Inflammasome. Aging Cell, 22(5): e13822.

[16] Li J, Chen Y, Zhang X, et al., 2023, PKM2-Mediated Microglial Activation. Nature Neuroscience, 26(5): 678–690.

[17] Lin D, Wang S, Liu F, et al., 2022, Propofol Attenuates Neuroinflammation by Inhibiting the ROS/HIF-1α Pathway in Microglia. Journal of Neuroinflammation, 19(1): 148.

[18] Li Y, Zhang Y, Wang X, et al., 2023, Propofol Maintains Pyruvate Kinase M2 Activity by Inhibiting Reactive Oxygen Species-Mediated Degradation. British Journal of Anaesthesia, 131(1): e45–e54.

[19] Li Y, Chen J, Xu Y, 2022, Current Status and Prospects of Biomarkers for Postoperative Delirium. Chinese Journal of Neuromedicine, 21(8): 843–849.

[20] Zhang Q, Liu R, Wang Y, et al., 2024, PKM2 S-Palmitoylation Mediates Microglial Metabolic Reprogramming in Neurodegenerative Disorders. Cell Metabolism, 36(1): 156–170.

[21] Zhou Y, et al., 2023, Lactate Accumulation Impairs Synaptic Plasticity via MMP-9 Activation. Nature Communications, 14: 5123.

[22] Jiang Y, et al., 2023, TEPP-46 Stabilizes PKM2 Tetramers to Suppress Neuroinflammation. Cell Reports, 42(5): 112456.

[23] Zhang H, Liu R, Yang W, et al., 2023, Nose-to-Brain Delivery of PKM2 Inhibitors. ACS Nano, 17: 3785–3798.

[24] Wang D, Chen Y, Liu R, et al., 2020, Mitochondrial Dysfunction Mediates Hepatotoxicity of PKM2 Modulators. Toxicological Sciences, 177(2): 347–359.

[25] Kulkarni JA, et al., 2023, Brain-Targeted Lipid Nanoparticles for RNA Delivery to Microglia. Advanced Drug Delivery Reviews, 192: 114644.

[26] Zhang Y, Wang H, Li J, et al., 2023, Real-Time Intraoperative Monitoring of Metabolic Biomarkers Using SERS Nanoprobes. Nature Biomedical Engineering, 7: 456–468.

[27] Qin Z, et al., 2023, Surface-Enhanced Raman Spectroscopy (SERS) for In Vivo Biosensing: Towards Intraoperative Monitoring. Nature Reviews Bioengineering, 1(2): 1–15.

[28] Zhao Y, Zhou X, Wu W, 2022, Current Research Status of the Impact of Comorbidities on Postoperative Cognitive Function in Elderly Surgical Patients. International Journal of Anesthesiology and Resuscitation, 43(6): 456–461.