Pyruvate kinase M2 in cancer progression, tumor microenvironment remodeling and therapeutic resistance (Review)

FEI PAN[1,2*], XIELIN YAN[1,2*], JUAN LING[3*], JIAN SHEN[1], QICHEN CUI[1], HAO NIE[4], XIAOYING WANG[2], JUNJIE WU[4] and YONG ZHAO[1,2,4]

[1]Department of Thoracic Surgery I, Affiliated Hospital of Jiangnan University, Wuxi, Jiangsu 214122, P.R. China; [2]Wuxi School of Medicine, Jiangnan University, Wuxi, Jiangsu 214122, P.R. China; [3]Department of Oncology, The Affiliated Shunde Hospital of Jinan University, Foshan, Guangdong 528303, P.R. China; [4]Institute of Integrated Chinese and Western Medicine, Affiliated Hospital of Jiangnan University, Wuxi, Jiangsu 214122, P.R. China

Received July 6, 2026; Accepted November 6, 2026

DOI: 10.3892/or.2026.9226

Abstract. Pyruvate kinase M2 (PKM2) is increasingly recognized as a multifunctional regulator in cancer rather than merely a glycolytic enzyme. Its biological functions are influenced not only by expression level but also by oligomeric state, post-translational regulation and subcellular or extracellular localization. In the present review, the current evidence on the role of PKM2 in cancer progression, metabolic adaptation, tumor microenvironment remodeling and therapeutic resistance is summarized. In defined cancer models, reduced cytosolic PKM2 activity redirects glycolytic intermediates toward biosynthetic or antioxidant pathways during nutrient deprivation or oxidative stress. Nuclear PKM2 participates in transcription-associated programs related to hypoxia adaptation, inflammatory signaling, programmed death ligand 1 regulation and therapy tolerance, although the precise catalytic and non-catalytic mechanisms of nuclear PKM2 remain incompletely defined. Extracellular PKM2 is implicated in tumor-stromal communication, including effects on monocytes, macrophages and fibroblasts; its interpretation depends on its cellular source, extracellular form and recipient cell. In the present review, unresolved issues, including the context-dependent requirement for PKM2 in tumor maintenance and the limitations of total PKM2 abundance as a biomarker are also examined. Overall, PKM2 should be evaluated according to its molecular state, cellular localization and tumor context when considering biomarker development and therapeutic strategies in cancer.

Correspondence to: Dr Yong Zhao, Wuxi School of Medicine, Jiangnan University, 1800 Lihu Avenue, Binhu, Wuxi, Jiangsu 214122, P.R. China
E-mail: yongzhaojnu@126.com

Dr Junjie Wu, Institute of Integrated Chinese and Western Medicine, Affiliated Hospital of Jiangnan University, 1000 Hefeng Road, Binhu, Wuxi, Jiangsu 214122, P.R. China
E-mail: 18119652961@163.com

*Contributed equally

Abbreviations: ATP, adenosine triphosphate; EGFR, epidermal growth factor receptor; EV, extracellular vesicle; HIF, hypoxia-inducible factor; NADPH, nicotinamide adenine dinucleotide phosphate; PD-L1, programmed death ligand 1; PET, positron emission tomography; PKM, pyruvate kinase muscle isozyme; PKM1, pyruvate kinase M1; PKM2, pyruvate kinase M2; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; tM2-PK, tumor M2-pyruvate kinase

Key words: pyruvate kinase M2, cancer progression, cancer metabolism, tumor microenvironment, macrophage polarization, extracellular vesicles, therapeutic resistance, biomarkers

Contents

1. Introduction
2. Review scope, literature identification and evidence interpretation
3. Structural regulation and functional plasticity of pyruvate kinase M2
4. Pyruvate kinase M2-mediated metabolic adaptation and therapeutic resistance in cancer cells
5. Nuclear and extracellular pyruvate kinase M2 in tumor microenvironment remodeling
6. Therapeutic targeting of pyruvate kinase M2 in cancer
7. Pyruvate kinase M2-related biomarkers and imaging approaches
8. Conclusions and perspectives

1. Introduction

Pyruvate kinase M2 (PKM2) catalyzes the final reaction of glycolysis, converting phosphoenolpyruvate into pyruvate with concomitant adenosine triphosphate (ATP) generation (1,2). In

cancer, PKM2 has also been linked to metabolic adaptation, transcriptional regulation, immune signaling and treatment response (3,4). These findings raise several questions: Why PKM2 is required for tumor maintenance in some models but not others, why pharmacological activation suppresses tumor growth in selected settings, and how cytosolic, nuclear and extracellular PKM2 contribute to these outcomes.

A structure-state-localization framework can help organize PKM2 biology, provided that its regulatory dimensions are distinguished. Alternative splicing determines PKM1 vs. PKM2 expression (5), whereas allosteric regulation and post-translational modifications influence the activity and oligomeric properties of the expressed PKM2 protein (6,7). Nuclear localization and extracellular-vesicle-associated release involve additional trafficking mechanisms (8,9). These processes may interact in defined experimental settings, but they do not constitute a universal sequence in which low-order PKM2 necessarily undergoes nuclear translocation or extracellular release. Their biological consequences should therefore be interpreted according to the regulatory mechanism, cellular compartment and tumor context examined.

Susceptibility to cell death provides one way to relate PKM2 biology to therapeutic research. Studies of cancer metabolism have identified context-specific metabolic dependencies (10,11). Nuclear and extracellular PKM2 have also been implicated in transcriptional regulation and tumor-microenvironment interactions in defined models (12-14). Tetramer-stabilizing compounds, circulating PKM2 assays and PKM2-targeted imaging offer approaches for investigating these processes, but their value for therapeutic selection requires further validation.

The present review examines how PKM2 isoform selection, oligomerization, allosteric regulation, post-translational modification and localization relate to cancer progression, tumor microenvironment remodeling and therapeutic resistance. The regulatory axes and compartment-specific functions considered are summarized in Fig. 1. Experimental evidence for metabolic adaptation, transcriptional regulation and extracellular communication are examined, and its implications for biomarkers and therapeutic strategies are then assessed.

2. Review scope, literature identification and evidence interpretation

The present narrative review examines PKM2 regulation and its roles in cancer metabolism, cell-death susceptibility, tumor microenvironment remodeling and treatment response. Literature searches were conducted in PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/) and Google Scholar (https://scholar.google.com/), without restrictions on publication year or language. The last search was performed on October 5, 2026. Searches combined PKM2-related terms ('PKM2', 'pyruvate kinase M2' and 'M2 pyruvate kinase') with cancer-related terms ('cancer', 'tumor', 'tumour', 'neoplasm' and 'malignancy') and topic-specific terms in separate searches. These topics included alternative splicing, oligomerization, phosphorylation, acetylation, oxidation, nuclear translocation, glycolysis, the pentose phosphate pathway, redox regulation, apoptosis, ferroptosis, anoikis, drug-tolerant persisters, macrophages, fibroblasts, extracellular vesicles, immune checkpoints, therapeutic targeting and diagnostic imaging. Additional searches used specific molecular or agent names, including HIF-1α, STAT3, STAT1, β-catenin, MYC, PD-L1, CD274, TEPP-46, DASA-58, TP-1454, mitapivat and DASA-23. Foundational mechanism-focused searches did not require cancer-related terms. Complete database-specific search strings were not retained; the terms reported herein summarize the search approach. The present review is a narrative synthesis rather than a systematic review or meta-analysis.

Studies were selected for their relevance to PKM2 regulation, biological function or clinical application. Eligible primary research included biochemical experiments, cell-based studies, animal investigations and studies involving human samples or clinical interventions. Foundational studies in non-cancer systems were included where relevant, with their experimental context distinguished from cancer-specific evidence. Reviews were used for background and identification of primary sources, while mechanistic conclusions prioritized original research. Clinical trial registry records were considered separately to establish study design and development stage, rather than to demonstrate clinical benefit or target engagement. Unrelated publications and duplicate records were excluded, and retracted studies were not used to support scientific claims. Negative and conflicting findings were considered alongside supportive evidence. General cancer metabolism studies provided biological context but were not treated as direct demonstrations of PKM2-specific mechanisms.

Evidence was evaluated according to the experimental model, cellular source of PKM2, type and specificity of perturbation, and endpoint measured. Notably conflicting findings were interpreted in relation to cancer lineage, oncogenic background, cell type, experimental conditions, the timing of PKM2 perturbation and potential compensation by PKM1. Tumor initiation, tumor maintenance, proliferation, cell death and treatment response were considered distinct outcomes. PKM2-specific perturbations, rescue experiments and complementary experimental approaches strengthened mechanistic interpretations but were not mandatory inclusion criteria. Changes in metabolic activity or cell viability alone were not considered sufficient to establish a specific cell-death mechanism, and associations in human samples were not interpreted as demonstrating causality.

Representative studies by cancer type, experimental model, PKM2 perturbation, principal outcome and evidential limitations are summarized in Table I, which provides a qualitative comparison rather than an exhaustive evidence inventory or a formal risk-of-bias assessment. Throughout the review, direct experimental evidence is distinguished from biological inference, and diagnostic or imaging findings are evaluated separately from therapeutic intervention studies.

3. Structural regulation and functional plasticity of pyruvate kinase M2

PKM isoform selection and PKM2 oligomeric regulation. PKM1 and PKM2 arise from mutually exclusive alternative splicing of PKM pre-mRNA: Exon 9 inclusion generates PKM1, whereas exon 10 inclusion generates PKM2 (15). This

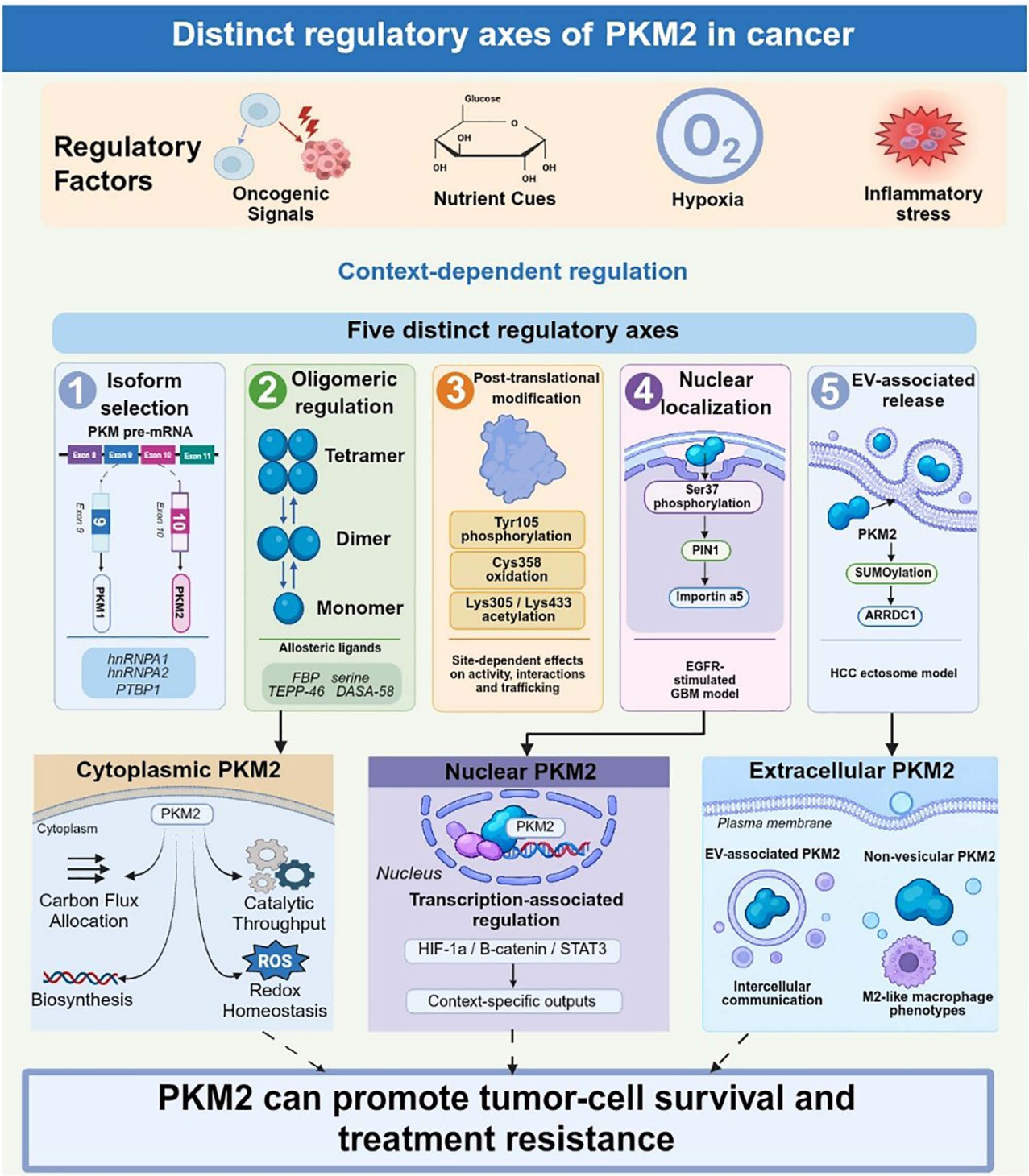

Figure 1. Distinct regulatory axes of PKM2 in cancer. Schematic overview of five interacting regulatory axes: Isoform selection, oligomerization, post-translational modification, nuclear localization and extracellular vesicle-associated release. These axes connect oncogenic, nutrient, hypoxic and inflammatory cues to cytoplasmic metabolism, nuclear transcription-associated regulation and extracellular communication. Nuclear import is illustrated by the Ser37-PIN1-importin α5 pathway in EGFR-stimulated glioblastoma models, and vesicular export by SUMOylation and ARRDC1 in a hepatocellular carcinoma ectosome model. Splicing does not directly determine oligomerization; low-order assembly does not obligatorily induce nuclear import or extracellular release. Solid arrows indicate regulatory relationships; dashed arrows indicate potential contributions to survival and treatment resistance. Depicted mechanisms and M2-like macrophage phenotypes are context-dependent. PKM2, pyruvate kinase M2; EGFR, epidermal growth factor receptor; PIN1, peptidyl-prolyl cis-trans isomerase NIMA-interacting 1; ARRDC1, arrestin domain-containing protein 1.

choice is regulated by heterogeneous nuclear ribonucleoprotein (hnRNP)A1, hnRNPA2 and polypyrimidine tract-binding protein 1 (PTBP1; also termed PTB or hnRNPI). PTBP1 binds the polypyrimidine tract in intron 8 upstream of exon 9, whereas hnRNPA1/A2 bind an inhibitory sequence immediately downstream of the exon 9 5' splice site. Together, these factors repress exon 9 inclusion and favor exon 10-containing PKM2 transcripts (5).

Table I. Representative studies of PKM2 in cancer: Experimental models, perturbations, outcomes and evidential limitations.

Cancer type/context	Experimental model and cell type	PKM2 perturbation or measurement	Principal outcome	Evidence strength and limitations	(Refs.)
Non-small-cell lung cancer; FGFR1-associated cancer models	H1299 cells with PKM2 replacement; biochemical assays and mouse xenografts.	Endogenous PKM2 knockdown with WT or Y105F rescue; FGFR1 manipulation.	Tyr105 phosphorylation inhibited PKM2 activity. Y105F reduced lactate production and xenograft growth.	Direct site-specific mechanistic evidence with rescue and *in vivo* support; not evidence of universal PKM2 dependence or clinical efficacy.	(7)
Lung cancer	A549/H1299 cells under oxidative stress; metabolic and survival assays.	PKM2 knockdown and WT/C358S replacement; oxidative challenge.	Cys358 oxidation inhibited PKM2 and supported antioxidant metabolism; oxidation-resistant PKM2 impaired adaptation to oxidative stress.	Direct redox-site evidence with genetic replacement; antioxidant adaptation does not by itself establish ferroptosis regulation.	(22)
Non-small-cell lung cancer	H1299 cells, purified PKM2 and immunodeficient-mouse xenografts.	TEPP-46/DASA-58 activation studies; TEPP-46 treatment in mice.	Activators stabilized active tetramers. TEPP-46 delayed xenograft emergence and reduced tumor size.	Biochemical target engagement and preclinical tumor evidence; xenograft formation is not equivalent to regression of established tumors or human benefit.	(6)
GBM	EGFR-stimulated U87 cells; mouse brain-tumor models; human GBM specimens.	WT vs. nuclear-translocation-deficient PKM2 S37A; analysis of ERK/PIN1/importin α5.	Ser37 phosphorylation enabled PIN1-dependent nuclear import. S37A attenuated EGFR-driven metabolic changes and brain-tumor development.	Direct site-specific mechanistic and preclinical evidence; human phosphorylation associations do not establish clinical treatment response.	(8)
Transformed-cell apoptosis model; not a cancer-specific *in vivo* model	293T cells; PKM2-deficient and Mfn1-deficient cellular systems; isolated mitochondria.	PKM2-binding intrabody IB5, PKM2 deletion and tetrameric mutant K422R; Mfn1-deficiency tests.	IB5-mediated protection from BimS-induced apoptosis required PKM2 and Mfn1. K422R reconstitution supported clonogenic survival with IB5 at early passages and without IB5 after extended passaging to passage 7.	Genetic dependency tests support an IB5-associated mechanism; the artificial intrabody/BimS system and passaging-dependent effects limit generalization.	(57)
GBM	Human GBM gliomaspheres and *in vivo* human GBM models under irradiation.	PKM2 activators combined with radiation; metabolic and enzymatic analyses.	Radiation increased PPP-associated antioxidant adaptation; PKM2 activation antagonized this rewiring and radiosensitized models *in vitro* and *in vivo*.	Direct preclinical combination evidence with metabolic validation; does not establish clinical radiosensitization or a drug-tolerant persister mechanism.	(69)

Table I. Continued.

Cancer type/context	Experimental model and cell type	PKM2 perturbation or measurement	Principal outcome	Evidence strength and limitations	(Refs.)
Intrahepatic cholangiocarcinoma	HCCC-9810 and RBE cells; erastin challenge; tumor experiments focused on upstream ETV4/ALYREF regulation.	ETV4/ALYREF knockdown with PKM2 overexpression rescue.	PKM2 overexpression reversed increases in lipid ROS, MDA and $Fe2^{+}$ following upstream knockdown under erastin treatment.	Functional rescue evidence for a ferroptosis-related phenotype in defined cell models; not proof of a universal PKM2 effect or a low-activity-PKM2 mechanism.	(58)
Colon carcinoma and activated immune-cell models	LPS-stimulated mouse macrophages; CT26 syngeneic tumors with immune/stromal-cell analyses.	PKM2 RNA silencing and TEPP-46; promoter-binding assays.	PKM2/HIF-1α associated with PD-L1 promoter regions in macrophages. TEPP-46 reduced PD-L1 in multiple tumor-associated cell populations.	Direct promoter and perturbation evidence plus mouse validation; tumor growth was not significantly altered in the reported setting. PD-L1 reduction is not clinical checkpoint efficacy.	(89)
HCC	HCC-derived ectosomes and recipient monocytes; patient-plasma ectosomal PKM2 measurements.	Ectosome-transfer experiments and analysis of PKM2-dependent release involving SUMO modification/ARRDC1.	Ectosomal PKM2 supported monocyte metabolic reprogramming and macrophage differentiation; ectosomal PKM2 was detected in patient plasma.	Experimental evidence for a defined ectosomal pathway with human detection; does not equate ectosomes with all exosomes or soluble PKM2, or validate clinical utility.	(9)
Breast cancer, melanoma and NSCLC mouse models	RAW264.7/bone-marrow macrophages; 4T1 tumors, B16 melanoma and genetically engineered NSCLC models.	Recombinant PKM2; integrin β3 knockdown; extracellular PKM2-blocking antibody PKAb, including combination with anti-PD-1.	Extracellular PKM2 promoted M2-like features through integrin αvβ3/FAK/PI3K and PTEN/Arg1 regulation. PKAb plus anti-PD-1 improved outcomes in B16 mice.	Direct receptor/pathway perturbation and preclinical combination evidence; recombinant exposure and murine models limit extrapolation, and binary macrophage labels are incomplete.	(14)
BRCA1-loss-driven breast cancer	Genetically engineered mammary-tumor model with tumor-cell PKM1 analysis.	Conditional isoform-specific Pkm2 deletion preserving the Pkm1 coding capacity.	Pkm2 deletion accelerated mammary-tumor formation; PKM1 expression was heterogeneous within PKM2-null tumors.	Direct genetic evidence of context-dependent dispensability/paradoxical effects; deletion during tumor development is not equivalent to acute drug treatment of established tumors.	(76)
APC-loss-driven colon cancer	Conditional Apc/Pkm2 mouse colon-tumor model.	Conditional isoform-specific Pkm2 deletion during tumor induction.	Deletion did not significantly alter tumor penetrance, multiplicity or survival; PKM1 increased in PKM2-deficient tumors.	Direct *in vivo* genetic evidence for dispensability in this model; concurrent deletion does not resolve dependencies of established tumors or other oncogenic backgrounds.	(77)

Table I. Continued.

Cancer type/context	Experimental model and cell type	PKM2 perturbation or measurement	Principal outcome	Evidence strength and limitations	(Refs.)
Pancreatic ductal adenocarcinoma	Kras-G12D/Trp53-null/Pdx1-Cre genetically engineered pancreatic-cancer model.	Conditional Pkm2 deletion in the pancreatic lineage.	No statistically significant differences in overall survival, tumor weight or proliferation measures were observed; PKM1 expression increased.	Direct *in vivo* genetic evidence of model-specific dispensability; does not exclude responses to acute inhibition, other drivers or different treatment stresses.	(80)
HRAS-driven urothelial carcinoma	Genetically engineered HRAS-driven urothelial tumors; inducible isoform expression; human bladder samples.	Pkm2 ablation, chemical inhibition and timed PKM2/PKM1 overexpression.	PKM2 ablation spared initiation but impaired tumor growth/maintenance. PKM2 overexpression promoted progression in nodular, not simple, hyperplasia.	Complementary genetic/pharmacological preclinical evidence with human expression support; dependence is stage/model specific, and clinical efficacy remains untested.	(78)

These qualitative, claim-specific assessments do not constitute a formally validated scoring system. Genetic rescue, orthogonal validation, model specificity and experimental scope are considered separately. Human associations do not establish causality, and preclinical activity does not establish clinical efficacy. This is a representative, not exhaustive, evidence table. PKM2, pyruvate kinase M2; WT, wild-type; FGFR1, fibroblast growth factor receptor 1; GBM, glioblastoma multiforme; EGFR, epidermal growth factor receptorERK, extracellular signal-regulated kinase; PIN1, peptidyl-prolyl cis-trans isomerase NIMA-interacting 1; Mfn1, mitofusin 1; IB5, intrabody 5; PPP, pentose phosphate pathway; ETV4, ETS variant transcription factor 4; ALYREF, Aly/REF export factor; ROS, reactive oxygen species; MDA, malondialdehyde; LPS, lipopolysaccharide; HIF-1α, hypoxia-inducible factor 1α; PD-L1, programmed death-ligand 1; HCC, hepatocellular carcinoma; ARRDC1, arrestin domain-containing protein 1; NSCLC, non-small-cell lung cancer; FAK, focal adhesion kinase; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; Arg1, arginase 1; PKAb, anti-PKM2 antibody; PD-1, programmed cell death protein 1; BRCA1, breast cancer type 1 susceptibility gene; PKM1, pyruvate kinase M1; APC, adenomatous polyposis coli; Trp53, transformation-related protein 53; Pdx1-Cre, pancreatic and duodenal homeobox 1 promoter-driven Cre recombinase; HRAS, Harvey rat sarcoma viral oncogene homolog.

Functional depletion experiments further support a role for these repressors in PKM isoform selection. In A172 cells, combined depletion of hnRNPA1 and hnRNPA2, or depletion of PTB, increased PKM1 expression (16). PKM1 generally exhibits high constitutive pyruvate kinase activity, whereas PKM2 is more responsive to allosteric and post-translational regulation (2).

Isoform selection and oligomeric regulation represent distinct regulatory processes. Alternative splicing determines which PKM isoform is expressed; it does not directly specify whether the resulting PKM2 protein adopts a tetrameric, dimeric or monomeric assembly. The oligomeric properties of expressed PKM2 are subsequently influenced by allosteric ligands, post-translational modifications and experimental conditions (5,6,17,18).

At the biochemical level, PKM2 can adopt tetrameric, dimeric and monomeric assemblies, with their relative abundance influenced by allosteric ligands and experimental conditions. Catalytic activity depends on both oligomeric assembly and conformation (19): PKM2 tetramers can adopt an active R-state or a less active T-state, whereas dissociated forms generally exhibit lower pyruvate kinase activity (20,21). In defined cancer-cell models, reduced PKM2 activity can favor the retention and diversion of upstream glycolytic intermediates into selected biosynthetic and redox-supporting pathways. Examples include enhanced *de novo* serine synthesis during serine deprivation and increased pentose phosphate pathway (PPP) flux following oxidative inhibition of PKM2 (22-24). These findings support a context-dependent role for PKM2 in metabolic adaptation, rather than a universal relationship in which lower-order assembly or reduced catalytic activity necessarily promotes cancer-cell proliferation.

PKM2 activity does not have a uniform relationship with tumor growth (25). Pharmacological stabilization of catalytically active tetramers suppressed tumor growth in the experimental systems examined by Anastasiou *et al* (6) and Parnell *et al* (26). These results are consistent with a context-dependent role for reduced PKM2 activity in metabolic adaptation (27), rather than a universal requirement for low-activity PKM2. Interpretation also requires separating PKM2 abundance and catalytic state from the non-canonical functions discussed in the broader literature (28-30).

Post-translational and allosteric regulation of PKM2. PKM2 is regulated by allosteric ligands and site-specific

post-translational modifications that affect distinct properties of the protein (31,32). Fructose-1,6-bisphosphate (FBP) and synthetic activators such as TEPP-46 and DASA-58 can stabilize catalytically active PKM2 assemblies (6). However, modifications affecting catalytic activity, protein stability and nuclear trafficking should be described separately rather than treated as equivalent mechanisms.

Tyr105 phosphorylation provides a mechanistic link between oncogenic tyrosine kinase signaling and reduced PKM2 activity. Hitosugi *et al* (7) demonstrated that fibroblast growth factor receptor 1 (FGFR1) directly phosphorylates PKM2 at Tyr105, promoting FBP release and reducing formation of the active tetramer. In NSCLC models, effective inhibition of epidermal growth factor receptor (EGFR) signaling also reduced PKM2 Tyr105 phosphorylation (33). This supports regulation within an EGFR-dependent signaling context, but should be distinguished from evidence identifying the kinase that directly phosphorylates this residue.

Ser37 phosphorylation primarily illustrates regulation of nuclear trafficking. In EGFR-stimulated glioblastoma models, activated ERK1/2 phosphorylates PKM2 at Ser37. This phosphorylation recruits the prolyl isomerase peptidyl-prolyl cis/trans isomerase, NIMA-interacting 1 (PIN1), whose isomerization activity facilitates PKM2 binding to importin α5 and subsequent nuclear import (8). This experimentally defined pathway should not be generalized into a requirement that all low-activity PKM2 enters the nucleus.

Lys305 and Lys433 acetylation have different functional consequences. Under high-glucose conditions, p300/CBP-associated factor (PCAF)-mediated Lys305 acetylation reduces PKM2 catalytic activity and enhances its interaction with heat shock cognate protein 70 (HSC70), promoting lysosomal degradation through chaperone-mediated autophagy (34). By contrast, p300-mediated Lys433 acetylation interferes with FBP binding and activation, favors dimer accumulation and promotes nuclear accumulation in the models examined (35). Lys305 acetylation therefore links nutrient availability to enzyme activity and protein turnover, whereas Lys433 acetylation connects allosteric regulation with compartmental redistribution.

PKM2 also responds to oxidative stress through Cys358 oxidation, linking reduced catalytic activity to antioxidant metabolic adaptation (22). The PPP-dependent redox consequences are discussed in greater detail later in the present review. These modification-specific mechanisms establish effects on PKM2 regulation, but their consequences for a particular cell-death pathway require corresponding functional evidence.

These regulatory mechanisms have been established in defined experimental settings. Their contribution to tumor growth or treatment response should be evaluated in relation to lineage, oncogenic background, nutrient availability, redox conditions and PKM1 expression, rather than assumed to operate uniformly across cancers.

Compartment-specific functions of PKM2. Subcellular localization and extracellular-vesicle-associated release require consideration beyond PKM2 oligomerization. In EGFR-stimulated glioblastoma models, ERK1/2-mediated phosphorylation of PKM2 at Ser37 promotes PIN1-dependent isomerization and importin α5 binding, thereby enabling nuclear translocation (8). By contrast, in hepatocellular carcinoma, PKM2 SUMOylation promotes plasma-membrane targeting and arrestin domain-containing protein 1 (ARRDC1)-associated release through ectosomes (9). These examples demonstrate specific regulatory mechanisms for nuclear import and vesicular release rather than a universal trafficking consequence of a low-order PKM2 state.

Cytosolic PKM2 regulates glycolytic carbon allocation. Its catalytic activity can influence the availability of upstream intermediates for biosynthetic and redox-supporting pathways (36-40). The consequences for cell survival are considered later in the present review.

Nuclear PKM2 has been linked to transcription-associated programs involving hypoxia adaptation (41,42), stem-like phenotypes, checkpoint regulation and treatment response in defined tumor-cell models (43-46). Its proposed direct protein kinase activity remains disputed (47-49). Nuclear localization, transcriptional association and direct catalytic activity should therefore be evaluated separately.

Extracellular PKM2 comprises distinct pools that should be interpreted according to their cellular source, vesicular association and recipient cell. For example, hepatocellular carcinoma cells release PKM2 through ectosomes that influence monocyte differentiation (9), whereas extracellular recombinant PKM2 can activate receptor-associated signaling in macrophages (14). These mechanisms should be distinguished from the functions of endogenous PKM2 within tumor cells or immune cells. The relevant source-recipient relationships and experimental evidence are discussed later in this review.

Integration of distinct regulatory axes in PKM2 biology. PKM2 biology can be organized around five distinct regulatory axes: Isoform selection, oligomerization, post-translational modification, nuclear localization and extracellular-vesicle-associated release. Isoform selection controls the relative expression of PKM1 and PKM2. Oligomerization contributes to the catalytic properties of PKM2, while site-specific modifications can influence activity, protein interactions, stability or trafficking (50,51). Nuclear localization depends on import and retention mechanisms, whereas vesicular release involves cargo targeting (52) and vesicle formation or release (53).

These axes are distinct but may interact. For example, a specific modification may influence both protein interactions and localization (54,55), and an allosteric intervention may affect nuclear functions in a particular model. Such coupling should be established experimentally rather than inferred from PKM2 abundance or oligomeric state alone. The framework therefore does not assume a fixed sequence from low-order assembly to nuclear translocation or extracellular release.

Subsequently, PKM2-associated metabolic adaptation, transcriptional regulation and intercellular communication are considered according to the regulatory axis and cellular compartment directly examined. Their relationships with cell survival and therapeutic response are interpreted as context-dependent findings, with direct experimental evidence distinguished from biological inference. Representative mechanisms linking cytosolic, nuclear and extracellular PKM2 to cell-death susceptibility and treatment response across distinct experimental models are summarized in Fig. 2,

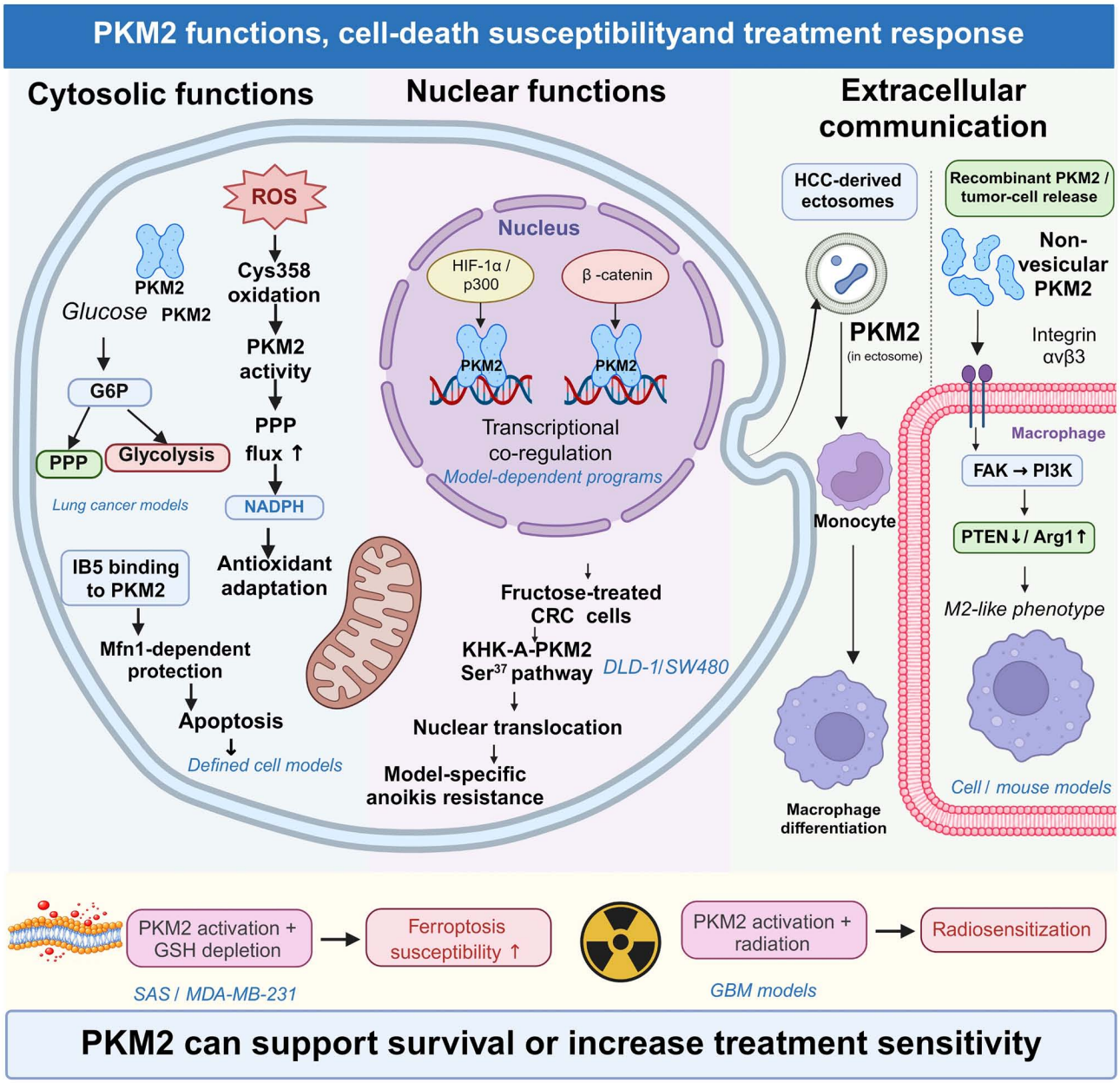

Figure 2. Context-dependent roles of PKM2 in cell-death susceptibility and treatment response. This schematic integrates distinct experimental models; the depicted pathways need not coexist in one cell or tumor. Cytoplasmic panels show antioxidant adaptation and IB5-associated, mitofusin 1-dependent protection in defined cell models. Nuclear panels show model-dependent transcriptional co-regulation and, in LPS-stimulated murine bone-marrow-derived macrophages, PKM2/HIF-1α co-occupancy at the *Cd274* promoter and PD-L1 regulation. Co-occupancy does not establish sequence-specific DNA binding by PKM2 alone. In fructose-treated DLD-1 and SW480 cells, KHK-A-PKM2 Ser37 signaling and nuclear accumulation were linked to reduced detachment-induced apoptosis. Extracellular panels distinguish PKM2-containing ectosomes from hepatocellular carcinoma cells promoting monocyte-to-macrophage differentiation from non-vesicular PKM2-integrin αvβ3 signaling in macrophages studied with recombinant protein and tumor-cell release models. Lower panels show increased ferroptosis susceptibility with PKM2 activation combined with erastin in SAS and MDA-MB-231 cells, and radiosensitization with PKM2 activation plus radiation in glioblastoma models. Arrows represent model-specific relationships; M2-like denotes a context-dependent phenotype, and protein icons do not specify oligomeric states. PKM2, pyruvate kinase M2; IB5, integrin β5; LPS, lipopolysaccharide; HIF-1α, hypoxia-inducible factor-1α; PD-L1, programmed death-ligand 1; KHK-A, ketohexokinase-A.

which illustrates that PKM2 can support survival or increase treatment sensitivity depending on the biological context and intervention.

4. Pyruvate kinase M2-mediated metabolic adaptation and therapeutic resistance in cancer cells

PKM2-associated modulation of apoptosis. PKM2-related changes in metabolism may influence cellular stress responses (56), but metabolic adaptation alone does not establish an anti-apoptotic mechanism. Reduced proliferation, altered ATP production and increased reactive oxygen species (ROS) should therefore be distinguished from experimentally measured apoptosis.

Liu *et al* (57) identified intrabody 5 (IB5), which binds PKM2 and protects cells from short isoform of Bim (BimS)-induced apoptosis. Separate loss-of-function experiments showed that IB5-mediated clonogenic protection

required PKM2 and mitofusin 1 (Mfn1). In PKM2-deficient fibroblasts reconstituted with tetrameric K422R, IB5 enhanced clonogenic survival at early passages; IB5-independent protection emerged after extended passaging to passage 7. Neither TEPP-46 alone nor PKM1 expression reproduced the protection (57). These results identify a PKM2-associated anti-apoptotic function in an engineered model, rather than a general protective effect of increased pyruvate kinase activity or tetramer stabilization.

Oxidative stress control and ferroptosis susceptibility. PKM2 participates in a redox-responsive feedback mechanism. In human lung cancer cells, oxidative stress induces Cys358 oxidation and inhibits PKM2 activity. Oxidant treatment also weakens PKM2 subunit association, consistent with destabilization of active assemblies. Reduced PKM2 activity permits diversion of glucose-derived carbon into the oxidative PPP, which generates nicotinamide adenine dinucleotide phosphate (NADPH) to support glutathione reduction and ROS detoxification (22). NADPH is therefore produced through the PPP rather than by PKM2 itself. This mechanism establishes antioxidant adaptation, but does not independently demonstrate ferroptosis resistance; that interpretation requires lipid-peroxidation measurements and ferroptosis-specific rescue experiments.

More direct ferroptosis-related evidence has emerged in defined cancer models. In intrahepatic cholangiocarcinoma cells, PKM2 overexpression reversed increases in lipid ROS, malondialdehyde and $Fe2^{+}$ following ETS variant transcription factor 4 (ETV4) or Aly/REF export factor (ALYREF) depletion under erastin treatment (58). These rescue experiments support a functional contribution to the reported ferroptosis-related phenotype, without establishing a universal effect of PKM2 oligomeric state.

Conversely, Chen *et al* (59) found that the PKM2 activator DASA-58 enhanced erastin-induced death in SAS and MDA-MB-231 cells. The combination increased lipid peroxidation, and ferrostatin-1 rescued viability (59). These studies differ in model and intervention and do not establish a common directional effect of PKM2 on ferroptosis.

PKM2 should therefore be described as a context-dependent modulator of ferroptosis susceptibility. Changes in general ROS, glutathione or cell viability alone are insufficient to assign ferroptosis without supporting lipid-peroxidation and death-rescue evidence (60).

Detachment-associated survival and model-specific evidence for anoikis resistance. Anoikis is apoptosis triggered by loss of appropriate extracellular-matrix attachment. Migration, epithelial-mesenchymal transition, metastatic burden and anchorage-independent growth are relevant but do not, by themselves, demonstrate resistance to detachment-induced apoptosis.

In fructose-treated DLD-1 and SW480 colorectal cancer cells, Peng *et al* (61) reported ketohexokinase A (KHK-A)-dependent PKM2 Ser37 phosphorylation and nuclear accumulation, together with reduced detachment-induced apoptosis after KHK-A expression in ultra-low-attachment cultures. These observations support a link between the KHK-A-PKM2 pathway and anoikis resistance in this setting. They do not establish that nuclear PKM2 is independently required for the detachment-survival phenotype.

General studies showing that antioxidant metabolism supports detached-cell survival provide a biological rationale for investigating PKM2, rather than direct proof of a PKM2-dependent anoikis mechanism (62-64). The available findings do not establish that low-order or nuclear PKM2 universally prevents anoikis across cancers.

Treatment response and the distinction from drug-tolerant persistence. Direct PKM2 studies support effects on treatment response in selected models (65-68). Bailleul *et al* (69) demonstrated that irradiation induced antioxidant metabolic adaptation in glioblastoma models and that PKM2 activators antagonized this response and enhanced radiosensitivity *in vitro* and *in vivo*. These findings support a preclinical treatment-sensitization strategy, but do not establish a drug-tolerant persister mechanism.

Drug-tolerant persistence is a distinct experimental phenotype involving survival during treatment and reversible tolerance, as demonstrated in foundational studies of cancer-cell subpopulations (70,71). Residual viability after treatment, altered drug sensitivity or resistance in an established cell line should not automatically be labeled as drug-tolerant persistence.

The aforementioned PKM2 treatment-response studies discussed do not, by themselves, establish that PKM2 controls the formation or maintenance of drug-tolerant persister cells. Such a role remains a hypothesis requiring direct PKM2 perturbation in experimentally characterized persister populations, together with drug-withdrawal and rechallenge analyses. PKM2-associated treatment resistance and potential persister biology should therefore be discussed separately.

Why model dependence matters. PKM2 dependency varies across experimental contexts (72-75). The mammary-tumor, adenomatous polyposis coli (APC)-loss-driven colon-cancer and Harvey rat sacroma viral oncogene homolog (HRAS)-driven urothelial-tumor studies summarized in Table I illustrate different outcomes following PKM2 perturbation (76-78). These findings should be compared according to tumor lineage, experimental model, the timing and nature of PKM2 perturbation, and the outcome measured. Tumor initiation, growth and maintenance are distinct endpoints; effects on these endpoints do not, by themselves, establish altered susceptibility to cell death.

Several dimensions provide a framework for comparing model-dependent PKM2 findings: Tumor lineage, oncogenic driver, PKM1 expression and potential compensation, the timing of PKM2 perturbation, and experimental conditions such as oxygen (79), nutrient supply and immune context. These are dimensions for interpretation rather than established determinants in every model. Increased PKM1 expression after PKM2 loss does not, by itself, demonstrate functional compensation. These context variables alongside the reported outcomes of specific tumor models are summarized in Fig. 3 (76,78,80,81).

The preceding studies address tumor-cell-intrinsic PKM2 functions. Nuclear and extracellular PKM2 also participate in

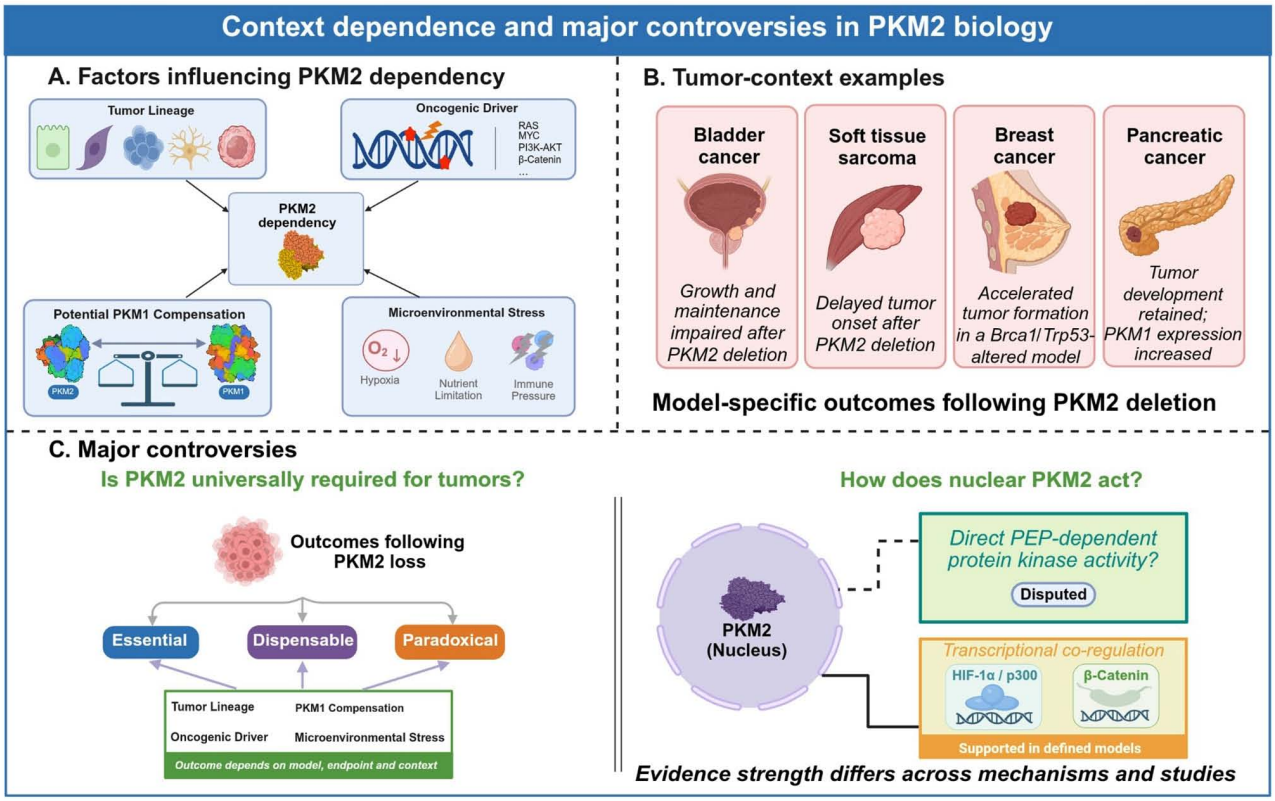

Figure 3. Context dependence and major controversies in PKM2 biology. (A) Variables for comparing model-specific PKM2 dependency include tumor lineage, oncogenic drivers, PKM1 expression, microenvironmental conditions and perturbation timing. (B) PKM2 deletion impairs growth and maintenance in a bladder cancer model, delays onset in a soft tissue sarcoma model, accelerates formation in a *Brca1*/*Trp53*-altered breast cancer model, and does not prevent tumor development in a pancreatic cancer model with increased PKM1 expression. These distinct endpoints do not rank dependency across cancer types; increased PKM1 alone does not establish functional compensation. (C) PKM2 is not universally required for tumor development or maintenance. The dashed connection denotes disputed phosphoenolpyruvate-dependent protein kinase activity; the solid connection denotes transcriptional co-regulation supported in defined models. This controversy does not concern the glycolytic pyruvate kinase activity of PKM2. PKM2, pyruvate kinase M2; PKM1, pyruvate kinase M1; *Brca1*, breast cancer type 1 susceptibility gene; *Trp53*, transformation-related protein 53.

tumor-microenvironment interactions, which require attention to both the producing and responding cell types.

5. Nuclear and extracellular pyruvate kinase M2 in tumor microenvironment remodeling

Cell-type-specific functions of nuclear PKM2. Nuclear PKM2 participates in transcription-associated regulation through mechanisms that depend on its interacting partner and cellular context (82-85). Luo *et al* (43) demonstrated that PKM2 interacts with hypoxia inducible factor (HIF)-1α and enhances HIF-1-dependent transcription by promoting HIF-1 occupancy and p300 recruitment at hypoxia-response elements. This coactivator function was stimulated by prolyl hydroxylase domain-containing protein 3 (PHD3) and did not require PKM2 pyruvate kinase activity (43).

In EGFR-stimulated glioblastoma models, PKM2 binds β-catenin phosphorylated at Tyr333 by c-Src. Recruitment of this complex to the cyclin D1 (CCND1) promoter was associated with histone deacetylase 3 (HDAC3) removal, histone acetylation and increased cyclin D1 expression (86). Related experiments showed that PKM2-dependent β-catenin transactivation induced MYC expression, followed by increased glucose transporter 1 (GLUT1), lactate dehydrogenase A (LDHA) and polypyrimidine tract-binding protein 1 (PTBP1) expression (8). In this pathway, c-Myc is principally a downstream transcriptional output rather than an interchangeable member of a PKM2 coactivator complex.

Signal transducer and activator of transcription (STAT)3-associated regulation represents another reported mechanism. Gao *et al* (87) described PKM2-dependent STAT3 Tyr705 phosphorylation and increased mitogen-activated protein kinase kinase 5 (MEK5) transcription. However, the proposed intrinsic protein kinase activity of PKM2 has been challenged by subsequent biochemical work (47). STAT3-associated effects should therefore be distinguished from established coactivator interactions and interpreted according to the assays and models examined.

This distinction is particularly important when discussing inflammatory signaling and immune checkpoints. PKM2-associated regulation of programmed death-ligand 1 (PD-L1) has been investigated in both macrophages and tumor cells, using different stimuli and experimental systems (88,89). Similarly, nuclear PKM2-associated inflammatory signaling in fibroblasts represents a stromal mechanism rather than a tumor-cell-intrinsic pathway. These examples are considered separately below.

Transcriptional regulation, altered checkpoint expression and resistance to immune-mediated killing are also distinct endpoints. A study demonstrating changes in nuclear PKM2

or inflammatory gene expression does not, by itself, establish reduced cytotoxic lymphocyte function. Such conclusions require functional immune assays in the relevant model.

PD-L1 and checkpoint-linked immune resistance. PKM2-associated regulation of CD274, the gene encoding PD-L1, has been examined directly at the promoter level. In lipopolysaccharide (LPS)-stimulated primary murine bone-marrow-derived macrophages, PKM2 silencing or TEPP-46 treatment reduced PD-L1 expression. Promoter oligonucleotide pull-down and ChIP assays detected PKM2 and HIF-1α at CD274 hypoxia-response elements, while sequential ChIP supported their concurrent occupancy of the same promoter regions. These findings support PKM2-HIF-1α-associated transcriptional regulation in this macrophage model; they should not be interpreted as demonstrating sequence-specific DNA recognition by PKM2 alone. In CT26 tumor-bearing mice, TEPP-46 reduced PD-L1 expression on several immune-cell populations and the CD45-negative tumor/stromal compartment, without significantly altering tumor growth under the conditions examined (89).

A different source-recipient relationship was reported in pancreatic ductal adenocarcinoma. Tumor-associated macrophage (TAM)-derived TGF-β1 induced PKM2 nuclear accumulation in cancer cells, where PKM2-STAT1-associated promoter regulation increased PD-L1 expression. Thus, macrophages supplied the extracellular cytokine, whereas the relevant PKM2 pool was located within the responding tumor cells. The study included cell-based mechanistic and natural killer (NK)-cell cytotoxicity assays, mouse xenograft experiments and analyses of human tumor specimens. The human findings provided clinical associations, while mechanistic and treatment effects were investigated experimentally (90).

A separate bladder cancer study reported that macrophage-derived TGF-β promoted nuclear accumulation of a PKM2-phosphorylated STAT3 complex and increased PD-L1 expression (91). This example of STAT3-associated checkpoint regulation should be distinguished from the PKM2-HIF-1α promoter co-occupancy demonstrated in macrophages and the PKM2-STAT1 mechanism reported in pancreatic cancer. These findings do not establish a universal PKM2-HIF-1α-STAT3 complex at the CD274 promoter.

These studies support model-specific links between PKM2 and checkpoint regulation, rather than a single pathway shared by all tumor and immune cells.

Extracellular PKM2 communication defined by cellular source, extracellular form and recipient cell. Extracellular PKM2 should be discussed according to its producing cell, extracellular form, recipient cell and experimental setting. Vesicle-associated PKM2 and non-vesicular extracellular PKM2 are distinct experimental entities. Detection of PKM2 in an extracellular vesicle (EV)-preparation does not, by itself, establish vesicle biogenesis or identify the cellular origin of circulating PKM2. Accordingly, EV is used as the general term here, while study-specific terminology is identified where relevant (92).

In hepatocellular carcinoma, Hou *et al* (9) identified tumor-cell-derived ectosomes carrying PKM2. PKM2 SUMOylation promoted membrane targeting and ARRDC1-associated ectosomal release. The recipient monocytes underwent metabolic reprogramming and differentiation-associated STAT3 signaling. These findings concern tumor-to-monocyte communication and should not be presented simply as a universal M1-to-M2 switch. Ectosomal PKM2 was also detected in patient plasma; this human observation supports its circulating presence, but does not independently establish the proposed signaling mechanism in patients (9).

Peng *et al* (14) examined extracellular recombinant PKM2 in RAW264.7 cells and mouse bone-marrow-derived macrophages. PKM2 engaged integrin αvβ3 and activated focal adhesion kinase (FAK)- phosphoinositide 3-kinase (PI3K) signaling, accompanied by reduced PTEN and increased arginase 1 (Arg1) expression and activity. Receptor-blocking antibodies, integrin β3 knockdown and pathway inhibition supported this mechanism. Mouse tumor experiments identified changes in CD206-positive macrophage populations consistent with M2-like features. These findings support a model-specific macrophage response rather than a fixed macrophage identity. The study discussed downstream Akt-mTOR activation as a possibility requiring investigation; it was not established as part of the PKM2-induced cascade. The receptor mechanism should also be distinguished from EV-mediated PKM2 delivery (14).

In gastric cancer, Yuan *et al* (93) studied PKM2-containing EV preparations, termed exosomes in the original study, released by AGS and MKN28 cells. Recipient THP-1-derived macrophages showed sterol regulatory element-binding protein 1 (SREBP1)-associated lipid metabolic changes and M2-like features. The study combined cell-culture experiments, patient-derived xenografts and a retrospective plasma analysis of 144 patients and 72 healthy donors. The plasma findings concerned biomarker associations and did not establish that every circulating PKM2-positive vesicle originated from malignant cells (93).

Fibroblast responses represent a separate route. Gu *et al* (13) reported that gastric cancer-cell-derived exosomes transferred PKM2 to mesenchymal stem cells undergoing cancer-associated fibroblast (CAF) differentiation. Increased nuclear PKM2 reflected both transferred protein and endogenous expression and was associated with p300/NF-κB p65 signaling and inflammatory cytokine production. Mechanistic evidence was principally obtained in culture; the accompanying xenograft intervention targeted p300 rather than selectively targeting PKM2 in CAFs (13).

Throughout the present review, M1-like and M2-like are used as descriptive shorthand for activation-associated features observed in specific experimental settings, rather than as fixed, mutually exclusive macrophage identities. Interpretation should account for species, cellular origin, stimulation conditions, multiple markers and functional measurements; individual markers should not be treated as definitive evidence of an activation state (94). In human tumors, macrophage states can extend beyond this binary framework, as demonstrated by single-cell profiling of breast cancer (95). Accordingly, changes in CD206 or Arg1 expression are described here as marker-associated phenotypic changes rather than sufficient evidence of a discrete, functionally defined M2-like TAM population.

From immune escape to immune-mediated killing. Nuclear and extracellular PKM2 provide distinct routes through which metabolism may be linked to tumor-microenvironment interactions (89,96). Nuclear transcription-associated regulation, non-vesicular receptor signaling (97,98) and EV-mediated transfer are supported by different experimental systems and should be interpreted according to the cell types and endpoints examined (9,14,89). Their combined contribution within a given tumor remains a model-specific question rather than a universal sequence of events.

Evidence should also be distinguished by endpoint. Changes in PKM2 localization, transcription or PD-L1 expression do not, by themselves, establish reduced immune-cell cytotoxicity. In the CT26 model, TEPP-46 reduced PD-L1 expression in several cell populations without significantly altering tumor growth under the reported conditions (89). By contrast, extracellular PKM2 blockade combined with anti-PD-1 improved treatment outcomes in the B16 model (14). These findings concern different interventions and models and should not be combined into a single universal mechanism of immune escape.

These findings support further investigation of model-specific PKM2 interventions, including combinations with immune checkpoint blockade (99-101). Nuclear or EV-associated PKM2 measurements and macrophage-associated features may serve as exploratory variables in such studies, but they are not established treatment-selection criteria. The effects of an intervention on target engagement, cell-specific signaling and antitumor immune function should be evaluated separately before drawing conclusions about patient benefit.

Translation requires two distinct questions: Whether a PKM2-related measurement identifies a clinically relevant tumor phenotype, and whether perturbing the implicated PKM2 pool changes treatment response. A biomarker association alone does not establish a therapeutic dependency.

6. Therapeutic targeting of pyruvate kinase M2 in cancer

State-locking strategies targeting cytosolic PKM2 signaling. Therapeutic evaluation of PKM2 requires specifying the molecular state, compartment and biological context targeted by an intervention (102). For the present review, proposed approaches are organized into three groups: Stabilization of catalytically active PKM2 assemblies, interference with nuclear trafficking or transcription-associated functions, and blockade of extracellular PKM2 signaling (6,14,48). These approaches may overlap in particular models and differ in their experimental support and stage of development. Their mechanisms, evidence stages and potential combination strategies are summarized in Fig. 4.

TEPP-46 and DASA-58 established the preclinical rationale for pharmacological PKM2 activation. TEPP-46 is also designated NCGC00186528 or ML265, whereas DASA-58 is designated NCGC00185916 or ML203; these identifiers should not be counted as separate compounds. Both agents stabilize active PKM2 assemblies and showed selectivity over recombinant PKM1 in the reported assays. Their antitumor effects provide proof of concept in experimental models, rather than evidence of clinical efficacy (6).

PKM2 activators may affect non-catalytic outputs in particular models (103,104), but tetramer stabilization should not be assumed to inhibit nuclear localization or extracellular release universally. In LPS-stimulated primary macrophages, TEPP-46 reduced PD-L1 expression; in CT26 tumor-bearing mice, it reduced PD-L1 in several cell populations without significantly altering tumor growth under the reported conditions (89). These observations do not establish clinical immune sensitization or predict the response of TAMs in other settings. Localization, cell identity and functional treatment endpoints therefore require direct assessment in each model.

The broader pyruvate kinase activator field also includes compounds developed primarily for hematological indications. Mitapivat (AG-348) is an oral allosteric activator with activity against protein kinase R (PKR), pyruvate kinase, liver isoform (PKL) and PKM2, rather than a PKM2-selective oncology agent (105). Studies in healthy volunteers demonstrated systemic exposure and erythrocyte pharmacodynamic effects, while clinical studies in pyruvate kinase deficiency provided disease-specific safety and hematologic-response data (106,107). These findings demonstrate the feasibility of systemic pyruvate kinase activation, but do not establish tumor PKM2 engagement, antitumor efficacy or an oncology therapeutic window.

AG-946, subsequently named tebapivat, illustrates further medicinal chemistry optimization. Structure-based development improved PKR activation potency and the persistence of enzyme activation, while addressing off-target liabilities identified in the starting scaffold (108). A 2024 American Society of Hemotology (ASH) conference abstract described its clinical development in anemia associated with lower-risk myelodysplastic syndromes and reported activation of PKR and PKM2 (109). These findings do not establish a clinically validated PKM2-directed anticancer treatment.

Clinical development of PKM2 activation should be described at the level of individual compounds. The investigational oral PKM2 activator TP-1454 was evaluated in a phase I study in patients with advanced solid tumors and anal cancer (NCT04328740). The registry lists the study as completed, with 31 participants, but does not provide posted results. Its objectives included safety, dose determination, pharmacokinetics and exploratory antitumor activity. Trial registration and completion therefore establish human evaluation, but the registry record does not demonstrate PKM2 target engagement, tetramer stabilization in patient tumors or clinical antitumor efficacy. TP-1454 should consequently be described as having undergone early clinical evaluation, whereas TEPP-46 and DASA-58 are discussed here on the basis of preclinical evidence (6).

Isoform selectivity provides only part of the safety assessment. Lack of PKM1 activation in an enzyme assay does not establish safety in PKM1-expressing tissues, and selectivity for PKM2 does not confer tumor specificity because PKM2 also functions in nonmalignant cells (110-112). In the original H1299 xenograft study, TEPP-46 at 50 mg/kg twice daily produced no apparent toxicity during >7 weeks of exposure, based on blood counts, serum chemistry and tissue histology (6). This supports tolerability under that regimen, rather than a defined human therapeutic index.

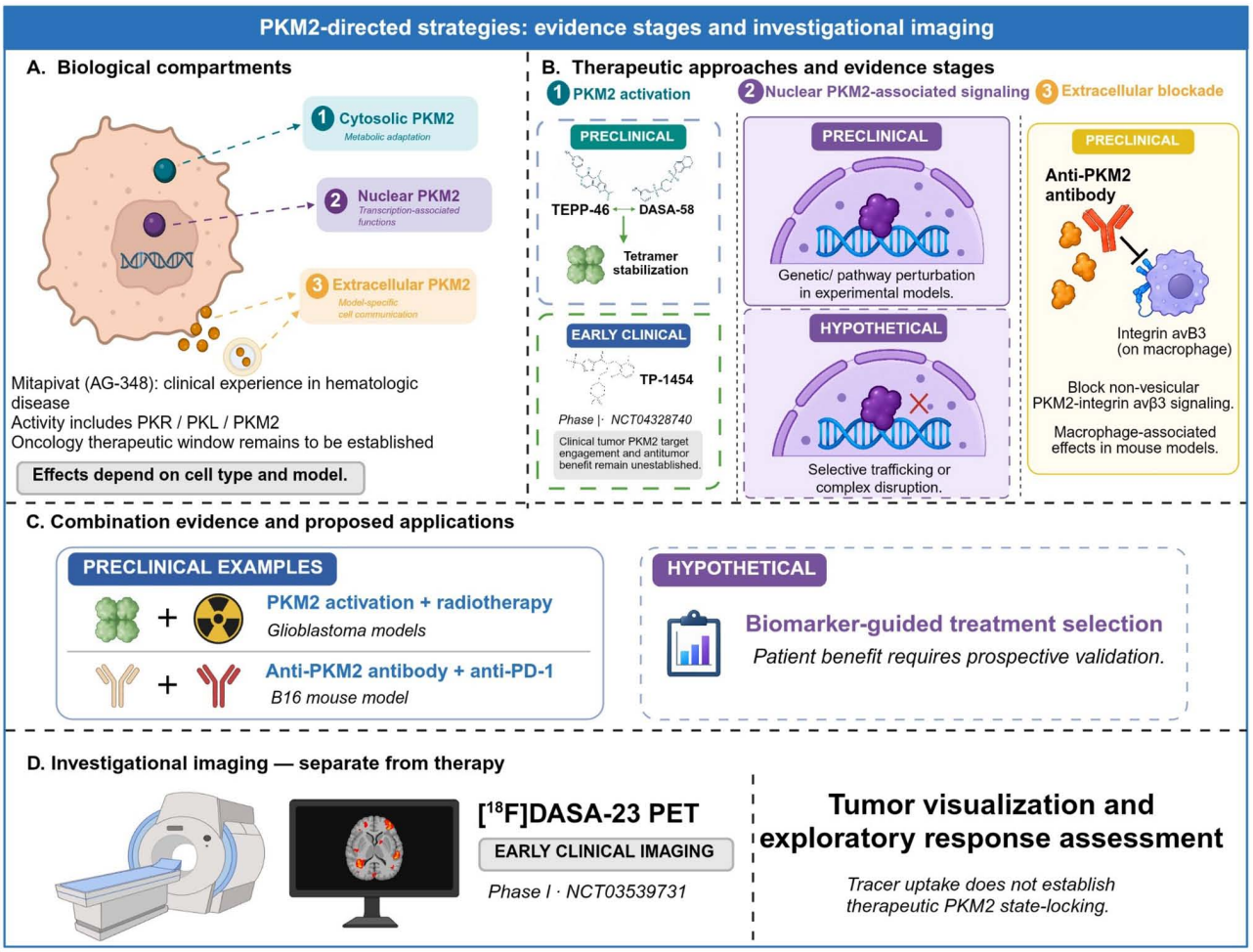

Figure 4. PKM2-directed strategies. Evidence stages and investigational imaging. (A) Cytosolic, nuclear and extracellular PKM2 define model-dependent intervention contexts. Mitapivat experience in hematologic disease does not establish an oncology therapeutic window or tumor-selective PKM2 modulation. (B) Evidence stages distinguish preclinical tetramer-stabilizing activators (TEPP-46 and DASA-58), phase I investigation of TP-1454, preclinical nuclear signaling studies and extracellular antibody blockade, and proposed selective disruption of nuclear trafficking or transcription-associated complexes. Clinical investigation does not establish tumor PKM2 target engagement or antitumor benefit. (C) Preclinical combinations include PKM2 activation with radiotherapy in glioblastoma models and anti-PKM2 plus anti-PD-1 antibodies in the B16 mouse model. Biomarker-guided treatment selection remains hypothetical and requires prospective validation of patient benefit. (D) (^{18}F)DASA-23 PET is an investigational imaging approach evaluated in early clinical studies for tumor visualization and exploratory response assessment. Uptake does not demonstrate therapeutic state-locking, and imaging feasibility does not establish predictive utility for treatment selection. Evidence-stage labels do not imply regulatory approval, ongoing recruitment or established efficacy. PKM2, pyruvate kinase M2; PD-1, programmed cell death protein 1; PET, positron emission tomography.

For mitapivat, clinical experience documents both erythrocyte pharmacology and safety limitations. Headache and nausea were reported in a healthy-volunteer study (106). Prescribing information identifies acute hemolysis after abrupt treatment interruption or discontinuation, and hepatocellular injury in patients treated for another condition at doses higher than those recommended for pyruvate kinase deficiency. These observations do not establish isoform-specific mechanisms of toxicity or a class effect of PKM2 activators. Defining an oncology therapeutic window requires comparing tumor target engagement and antitumor activity with normal-tissue toxicity at relevant exposures.

Targeting nuclear PKM2-associated transcriptional signaling. Localization-directed intervention is a proposed therapeutic approach that may overlap with oligomeric regulation in particular models. Its rationale should rest on experimentally demonstrated trafficking mechanisms and nuclear PKM2 functions rather than an assumed link between low catalytic activity and nuclear accumulation. For example, ERK1/2-dependent Ser37 phosphorylation, PIN1-dependent conformational regulation and importin α5 binding provide a defined pathway for nuclear import in EGFR-stimulated glioblastoma models (8). Interfering with such trafficking or with nuclear PKM2-associated complexes warrants investigation, but therapeutic effects and specificity must be established in the relevant model.

The evidence for targeting nuclear PKM2-associated signaling remains preclinical and model specific (113). A change in nuclear localization or transcription does not, by itself, demonstrate increased apoptosis, treatment sensitivity or immune-cell killing. Each proposed effect requires corresponding functional measurements in the relevant model. Selective interference with trafficking or nuclear interactions therefore remains a strategy to test, rather than an established means of reversing multiple forms of cell-death resistance.

Evaluation of catalytic inhibitors and activators requires evidence of target engagement and specificity, together with measurements of the PKM2 functions relevant to the model. Changes in viability alone cannot distinguish altered glycolytic activity from effects on nuclear signaling, extracellular communication or other targets. Strategy selection should therefore follow the demonstrated mechanism and treatment endpoint in each setting.

Blocking extracellular PKM2-mediated intercellular communication. Extracellular PKM2 blockade has been investigated preclinically using an antibody that disrupts the PKM2-integrin αvβ3 interaction. In mouse tumor models, this approach altered macrophage-associated phenotypes, and combination with anti-PD-1 improved treatment outcomes in the B16 model (14). These findings support further investigation of extracellular receptor signaling as a therapeutic target. They do not establish clinical efficacy or demonstrate equivalent inhibition of EV-associated PKM2 transfer. Blocking receptor engagement, preventing vesicle release and limiting vesicle uptake should therefore be considered distinct intervention strategies.

Biomarker-guided combinations and patient selection. Biomarker-guided selection for PKM2-directed therapy remains investigational. Nuclear PKM2 enrichment (114), extracellular PKM2-associated signaling and treatment-induced metabolic adaptation provide hypotheses for identifying responsive tumors, but have not been established as companion-diagnostic criteria. The three therapeutic approaches discussed above should therefore be evaluated within defined models and clinical development programs rather than assumed to benefit corresponding patient subgroups.

Future trials should distinguish drug exposure, target engagement, downstream pharmacodynamic changes and clinical outcomes. For a proposed state-locking agent, evidence of systemic exposure or altered tumor metabolism alone would not establish PKM2 tetramer stabilization. Where feasible, paired tumor samples and validated assays of PKM2 activity or oligomeric state could help assess the intended mechanism. Imaging and circulating biomarkers may provide complementary information, but require validation for the specific treatment and clinical decision being studied.

7. Pyruvate kinase M2-related biomarkers and imaging approaches

Tissue, circulating and exosomal markers of PKM2 signaling states. PKM2-related readouts represent different biological compartments and measurements (115,116). Total tissue PKM2, nuclear PKM2, tumor M2-pyruvate kinase (tM2-PK), EV-associated PKM2 and PKM2-targeted positron emission tomography (PET) should therefore be evaluated separately and against a defined clinical question. Elevated signal alone does not establish a PKM2-dependent survival mechanism or identify patients likely to benefit from PKM2-directed treatment. These readouts, their limitations and proposed research applications are summarized in Table II. Any use for therapeutic selection requires prospective validation.

Tissue assessment should resolve both cell identity and subcellular localization. As a proposed validation approach, multiplex immunofluorescence could combine PKM2, a nuclear counterstain, tumor-lineage markers and macrophage markers. In epithelial tumors, a panel incorporating pan-cytokeratin, CD68 and CD163 or CD206 could help distinguish nuclear PKM2 within malignant cells from nuclear PKM2 within macrophages. CD163 and CD206 should be interpreted as phenotype-associated markers rather than definitive identifiers of a fixed M2 state.

Image analysis should distinguish marker expression within the same segmented cell from spatial proximity between different cells. Relevant measurements could include the proportion of tumor cells with nuclear PKM2, nuclear PKM2 within macrophages, and distances between nuclear-PKM2-positive tumor cells and defined TAM populations. Antibody specificity, single-marker validation, autofluorescence correction, segmentation and analysis thresholds require validation (117). Spatial association would support a tissue-level relationship, but would not by itself demonstrate PKM2 transfer, receptor signaling or immune suppression.

tM2-PK is commonly measured using immunoassays designed to preferentially detect the dimeric form. Such conformational selectivity does not identify the producing cell or its original intracellular compartment. A positive plasma result cannot distinguish tumor-derived PKM2 from contributions associated with nonmalignant inflammation, nor determine whether the relevant protein previously resided in the cytoplasm or nucleus.

Inflammatory disease also limits diagnostic specificity. In one plasma enzyme-linked immunosorbent assay (ELISA) study using a cutoff of 15 U/ml, elevated values occurred in 44% of patients with nonmalignant diseases and in 67% of those with an acute inflammatory reaction (118). These percentages are specific to that cohort and threshold, rather than universal false-positive rates. Increased plasma tM2-PK has also been associated with rheumatoid arthritis activity (119). Sample matrix and preanalytical interference, including hemolysis, require consideration (120). Plasma and fecal assays should therefore be evaluated separately, using specimen-specific thresholds and appropriate nonmalignant inflammatory controls (121).

Plasma EV-associated PKM2 is an investigational biomarker. In gastric cancer, Yuan *et al* (93) reported elevated plasma exosomal PKM2 and diagnostic associations in a retrospective cohort. These observations should be distinguished from the cell-culture and animal experiments of the study addressing macrophage responses. A plasma measurement alone does not identify the producing cell, demonstrate delivery to macrophages or establish immune suppression in an individual patient. Clinical application requires standardized EV characterization, independent validation and evidence that the assay informs a defined clinical decision.

EV-associated PKM2 assays require standardized sample handling and separation, together with complementary measurements of particle properties, EV-associated proteins and non-vesicular co-isolates. CD63/CD81 co-detection can characterize a defined particle population, but neither marker is universal or specific for endosome-derived exosomes, and bulk detection does not establish that PKM2 is present on the same

Table II. PKM2-related biomarker and imaging readouts: Investigated uses, proposed applications and limitations.

Readout	Compartment/ state reflected	Specimen/ platform	Interpretation and evidence limits	Investigated or proposed use	Main limitation
Total tissue PKM2	Bulk intratumoral PKM2 abundance; limited state specificity	FFPE tissue; IHC, IF, or bulk proteomics	PKM2 abundance; functional interpretation requires additional measurements of activity, localization and cell identity	Exploratory associations with clinicopathological features or outcomes	Poor specificity for oligomeric state, subcellular localization, and cell type; difficult to separate tumor-cell from stromal signal
nPKM2	nPKM2 abundance and localization within identified cell types	Tissue sections with compartment-aware IHC/IF scoring	Indicates nuclear localization; links to transcriptional programs or treatment response require model- and assay-specific evidence	Exploratory correlative assessment in trials; proposed treatment-selection use requires prospective validation	Assay-specific scoring and validation; preanalytical variability; functional interpretation depends on cell type and mechanism
Fecal tM2-PK	Immunoreactive tM2-PK in stool; cellular origin and intracellular compartment unresolved	Stool; ELISA or lateral-flow assay	Protein signal investigated for association with colorectal neoplasia; not a measurement of PKM2-dependent cell-death resistance	Investigated for colorectal neoplasia detection; screening or triage utility requires validation in the intended population	In one comparative study, the fecal M2-PK test showed higher sensitivity but lower specificity than guaiac fecal occult blood testing for colorectal cancer detection (127). Performance depends on the population, assay and threshold; the signal does not identify cellular origin or intracellular localization.
Circulating tM2-PK	Circulating tM2-PK immunoreactivity; cellular source and intracellular compartment unresolved	Plasma or serum; immunoassay	Blood measurement affected by nonmalignant inflammation; does not directly measure tumor metabolic activity	Investigated as a blood-based biomarker; clinical utility requires indication- and specimen-specific validation	Nonmalignant inflammatory confounding; specimen-specific thresholds and preanalytical interference, including hemolysis; limited compartment and cell-source resolution
Plasma or serum EV-associated PKM2	PKM2 detected in EV preparations; producing cell, particle association and membrane topology require characterization	Plasma or serum EV separation and characterization plus ELISA, immunoblot or particle-based PKM2 measurement	Investigational circulating measurement; does not by itself identify the producing cell or establish macrophage delivery or immune suppression	Retrospective diagnostic associations in gastric cancer; proposed treatment-selection and monitoring uses require validation	Variable separation and quantification; uncertain cell of origin and co-isolated contaminants; PKM2-EV association and topology require validation; limited independent clinical validation

Table II. Continued.

Readout	Compartment/ state reflected	Specimen/ platform	Interpretation and evidence limits	Investigated or proposed use	Main limitation
PKM2-targeted PET [(^{18F})DASA-23]	Lesion-level uptake of an investigational PKM2-targeted tracer	PET imaging	Investigational tumor visualization and exploratory associations with treatment outcome; not a validated measure of PKM2 oligomeric state or death resistance	Research use for tumor visualization and exploratory response assessment; treatment selection requires prospective validation	Small early clinical cohorts; limited availability; thresholds, predictive performance and clinical utility require validation

PKM2-related assays are organized by the biological compartment or measurement represented, specimen or platform, interpretation, investigated or proposed use, and principal limitations. Tissue expression, nuclear localization, circulating tM2-PK, EV-associated PKM2 and PKM2-targeted PET are distinct readouts. Their diagnostic, monitoring or treatment-selection value requires validation for the specific specimen, population and clinical question. PKM2, pyruvate kinase M2; FFPE, formalin-fixed paraffin-embedded; IHC, immunohistochemistry; IF, immunofluorescence; nPKM2, nuclear pyruvate kinase M2; tM2-PK, tumor M2-pyruvate kinase; ELISA, enzyme-linked immunosorbent assay; M2-PK, M2-pyruvate kinase; EV, extracellular vesicle; PET, positron emission tomography.

particles. Controlled single-particle co-detection can support particle association. Separately, protease treatment with and without membrane permeabilization can assess surface accessibility and membrane protection. Surface-associated PKM2 may itself be EV-associated; protection assays alone do not establish EV identity or luminal localization. These analyses require complementary controls and reporting consistent with MISEV2023 (92).

Early clinical evaluation of (^{18}F)DASA-23 PET imaging. (^{18}F)DASA-23 is an investigational PET radiotracer studied for imaging PKM2-associated tumor biology, rather than a therapeutic intervention intended to stabilize PKM2 tetramers (122). Its phase I clinical evaluation (NCT03539731) included healthy volunteers and patients with intracranial tumors. Published studies reported human biodistribution and radiation dosimetry, followed by initial visualization of gliomas (123,124).

A subsequent pilot study included four healthy controls and 9 patients with high-grade gliomas, with follow-up imaging available in 5 patients. Exploratory associations between post-treatment uptake and progression-free survival supported further investigation, but the small and heterogeneous cohort limits clinical interpretation (125).

These findings support early clinical feasibility of PKM2-directed imaging. They do not establish therapeutic PKM2 activation, drug-induced tetramer stabilization or clinical benefit from a PKM2-directed treatment. Tracer uptake should also not be treated as a validated measurement of PKM2 oligomeric state or tumor dependence on PKM2. Its potential use for treatment-response assessment or patient selection requires further prospective validation (126).

Matching biomarkers to signaling-defined clinical questions. PKM2-related assays should be evaluated against a defined clinical question and an appropriate reference standard (127). Tissue staining can resolve cell identity and localization when analytically validated; circulating tM2-PK requires attention to inflammatory confounding and specimen-specific performance; EV-associated PKM2 requires standardized separation and characterization; and (^{18}F)DASA-23 PET remains an investigational imaging approach. None should be assumed to identify a PKM2-dependent therapeutic vulnerability solely because the measured signal is elevated. Clinical translation requires independent validation, predefined thresholds and evidence that the result improves a specific diagnostic, monitoring or treatment decision.

8. Conclusions and perspectives

PKM2 contributes to cancer biology through metabolic, nuclear and extracellular functions that vary with molecular regulation, cell type and tumor model. Isoform selection, oligomerization, post-translational modification, localization and vesicular release are distinct variables; measurements of one do not establish the others. This distinction helps reconcile the model-dependent effects of genetic deletion and pharmacological activation without assigning all PKM2-associated phenotypes to a single mechanism.

Several questions remain. Studies of PKM2 deletion show that tumor initiation and maintenance can respond differently across models. Comparisons should account for lineage, oncogenic driver, perturbation timing, PKM1 expression and experimental conditions; increased PKM1 expression should not be equated with proven functional compensation. Nuclear PKM2-associated effects may involve transcriptional co-regulation, chromatin-associated interactions or other mechanisms, whereas its proposed direct protein kinase activity remains disputed. Resolving these questions requires models that distinguish PKM2 expression, oligomerization, localization and extracellular release.

Future studies can test localization-directed interventions in models with demonstrated nuclear PKM2 functions, and extracellular blockade in models with defined PKM2-dependent source-recipient signaling. Such studies should separate tumor-cell effects from stromal or immune-cell responses and assess combinations with checkpoint blockade where supported by the model. Tissue, circulating and imaging measurements may complement these experiments, but their predictive value requires prospective validation. Integrating PKM2 molecular state, cellular compartment and tumor context into biomarker-guided stratification could enable rational combinations with immunotherapy, provided that target engagement, predictive value and clinical benefit are prospectively demonstrated.

Acknowledgements

Not applicable.

Funding

The present review was supported by the Major Scientific Research Project of Wuxi Municipal Health Commission (grant no. Z200202), the Wuxi City 'Double Hundred' Young and Middle-aged Top-notch Medical and Health Talent Training Program (grant no. HB2023049), the Wuxi Taihu Lake Talent Plan: Supports for Leading Talents in Medical and Health Profession (grant no. SKJY2021076), the Wuxi Municipal Health Commission Research Project (grant no. Q202437), the Wuxi Young Scientific and Technological Talent Support Project (grant no. TJXD-2025-233); and the 2024 Internal Research Cultivation Fund Project of Shunde Hospital Affiliated to Jinan University (grant no. 202402012). The funders had no role in the conception of this review, literature interpretation, manuscript preparation or the decision to submit the article for publication.

Availability of data and materials

Not applicable.

Authors' contributions

FP designed the scope and structure of the review and drafted major sections of the manuscript. XY and JL contributed to drafting and revising major sections of the manuscript. JS, QC and HN critically reviewed and revised major sections of the manuscript. JW and XW provided critical intellectual input and revised major sections of the manuscript. YZ guided the development of the review and critically revised major sections of the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. Alquraishi M, Puckett DL, Alani DS, Humidat AS, Frankel VD, Donohoe DR, Whelan J and Bettaieb A: Pyruvate kinase M2: A simple molecule with complex functions. Free Radic Biol Med 143: 176-192, 2019.
2. Israelsen WJ and Vander Heiden MG: Pyruvate kinase: Function, regulation and role in cancer. Semin Cell Dev Biol 43: 43-51, 2015.
3. Zhu S, Guo Y, Zhang X, Liu H, Yin M, Chen X and Peng C: Pyruvate kinase M2 (PKM2) in cancer and cancer therapeutics. Cancer Lett 503: 240-248, 2021.
4. Zulfareen, Taiyab A, Hasan GM and Hassan MI: A review on the role of pyruvate kinase M2 in cancer: From metabolic switch to transcriptional regulation. Int J Biol Macromol 330 (Pt 2): 148067, 2025.
5. David CJ, Chen M, Assanah M, Canoll P and Manley JL: HnRNP proteins controlled by c-Myc deregulate pyruvate kinase mRNA splicing in cancer. Nature 463: 364-368, 2010.
6. Anastasiou D, Yu Y, Israelsen WJ, Jiang JK, Boxer MB, Hong BS, Tempel W, Dimov S, Shen M, Jha A, *et al*: Pyruvate kinase M2 activators promote tetramer formation and suppress tumorigenesis. Nat Chem Biol 8: 839-847, 2012.
7. Hitosugi T, Kang S, Vander Heiden MG, Chung TW, Elf S, Lythgoe K, Dong S, Lonial S, Wang X, Chen GZ, *et al*: Tyrosine phosphorylation inhibits PKM2 to promote the Warburg effect and tumor growth. Sci Signal 2: ra73, 2009.
8. Yang W, Zheng Y, Xia Y, Ji H, Chen X, Guo F, Lyssiotis CA, Aldape K, Cantley LC and Lu Z: ERK1/2-dependent phosphorylation and nuclear translocation of PKM2 promotes the Warburg effect. Nat Cell Biol 14: 1295-1304, 2012.
9. Hou PP, Luo LJ, Chen HZ, Chen QT, Bian XL, Wu SF, Zhou JX, Zhao WX, Liu JM, Wang XM, *et al*: Ectosomal PKM2 Promotes HCC by inducing macrophage differentiation and remodeling the tumor microenvironment. Mol Cell 78: 1192-1206.e10, 2020.
10. Finley LWS: What is cancer metabolism. Cell 186: 1670-1688, 2023.
11. Abecunas C, Kidd AD, Jiang Y, Zong H and Fallahi-Sichani M: Multivariate analysis of metabolic state vulnerabilities across diverse cancer contexts reveals synthetically lethal associations. Cell Rep 43: 114775, 2024.
12. Hsu MC and Hung WC: Pyruvate kinase M2 fuels multiple aspects of cancer cells: From cellular metabolism, transcriptional regulation to extracellular signaling. Mol Cancer 17: 35, 2018.
13. Gu J, Li X, Zhao L, Yang Y, Xue C, Gao Y, Li J, Han Q, Sun Z, Bai C and Zhao RC: The role of PKM2 nuclear translocation in the constant activation of the NF-κB signaling pathway in cancer-associated fibroblasts. Cell Death Dis 12: 291, 2021.
14. Peng G, Li B, Han H, Yuan Y, Mishra F, Huang Y and Liu ZR: Extracellular PKM2 modulates cancer immunity by regulating macrophage polarity. Cancer Immunol Immunother 74: 195, 2025.
15. Wang Z, Chatterjee D, Jeon HY, Akerman M, Vander Heiden MG, Cantley LC and Krainer AR: Exon-centric regulation of pyruvate kinase M alternative splicing via mutually exclusive exons. J Mol Cell Biol 4: 79-87, 2012.
16. Clower CV, Chatterjee D, Wang Z, Cantley LC, Vander Heiden MG and Krainer AR: The alternative splicing repressors hnRNP A1/A2 and PTB influence pyruvate kinase isoform expression and cell metabolism. Proc Natl Acad Sci USA 107: 1894-1899, 2010.

17. Mitchell AR, Yuan M, Morgan HP, McNae IW, Blackburn EA, Le Bihan T, Homem RA, Yu M, Loake GJ, Michels PA, *et al*: Redox regulation of pyruvate kinase M2 by cysteine oxidation and S-nitrosation. Biochem J 475: 3275-3291, 2018.
18. Wang RH, Chen PR, Chen YT, Chen YC, Chu YH, Chien CC, Chien PC, Lo SY, Wang ZL, Tsou MC, *et al*: Hydrogen sulfide coordinates glucose metabolism switch through destabilizing tetrameric pyruvate kinase M2. Nat Commun 15: 7463, 2024.
19. Macpherson JA, Theisen A, Masino L, Fets L, Driscoll PC, Encheva V, Snijders AP, Martin SR, Kleinjung J, Barran PE, *et al*: Functional cross-talk between allosteric effects of activating and inhibiting ligands underlies PKM2 regulation. Elife 8: e45068, 2019.
20. Morgan HP, O'Reilly FJ, Wear MA, O'Neill JR, Fothergill-Gilmore LA, Hupp T and Walkinshaw MD: M2 pyruvate kinase provides a mechanism for nutrient sensing and regulation of cell proliferation. Proc Natl Acad Sci USA 110: 5881-5886, 2013.
21. Wang P, Sun C, Zhu T and Xu Y: Structural insight into mechanisms for dynamic regulation of PKM2. Protein Cell 6: 275-287, 2015.
22. Anastasiou D, Poulogiannis G, Asara JM, Boxer MB, Jiang JK, Shen M, Bellinger G, Sasaki AT, Locasale JW, Auld DS, *et al*: Inhibition of pyruvate kinase M2 by reactive oxygen species contributes to cellular antioxidant responses. Science 334: 1278-1283, 2011.
23. Ye J, Mancuso A, Tong X, Ward PS, Fan J, Rabinowitz JD and Thompson CB: Pyruvate kinase M2 promotes de novo serine synthesis to sustain mTORC1 activity and cell proliferation. Proc Natl Acad Sci USA 109: 6904-6909, 2012.
24. Chaneton B, Hillmann P, Zheng L, Martin ACL, Maddocks ODK, Chokkathukalam A, Coyle JE, Jankevics A, Holding FP, Vousden KH, *et al*: Serine is a natural ligand and allosteric activator of pyruvate kinase M2. Nature 491: 458-462, 2012.
25. Cortés-Cros M, Hemmerlin C, Ferretti S, Zhang J, Gounarides JS, Yin H, Muller A, Haberkorn A, Chene P, Sellers WR and Hofmann F: M2 isoform of pyruvate kinase is dispensable for tumor maintenance and growth. Proc Natl Acad Sci USA 110: 489-494, 2013.
26. Parnell KM, Foulks JM, Nix RN, Clifford A, Bullough J, Luo B, Senina A, Vollmer D, Liu J, McCarthy V, *et al*: Pharmacologic activation of PKM2 slows lung tumor xenograft growth. Mol Cancer Ther 12: 1453-1460, 2013.
27. Wiese EK and Hitosugi T: Tyrosine kinase signaling in cancer metabolism: PKM2 paradox in the warburg effect. Front Cell Dev Biol 6: 79, 2018.
28. Zhang Z, Deng X, Liu Y, Liu Y, Sun L and Chen F: PKM2, function and expression and regulation. Cell Biosci 9: 52, 2019.
29. Chen X, Chen S and Yu D: Protein kinase function of pyruvate kinase M2 and cancer. Cancer Cell Int 20: 523, 2020.
30. Liang J, Cao R, Wang X, Zhang Y, Wang P, Gao H, Li C, Yang F, Zeng R, Wei P, *et al*: Mitochondrial PKM2 regulates oxidative stress-induced apoptosis by stabilizing Bcl2. Cell Res 27: 329-351, 2017.
31. Christofk HR, Vander Heiden MG, Wu N, Asara JM and Cantley LC: Pyruvate kinase M2 is a phosphotyrosine-binding protein. Nature 452: 181-186, 2008.
32. Miao C, Wang Z, Li K, Lin J, Wu X, Zhu Z, Zhang X, Zhou X, Zou J, Zhu Y, *et al*: Auto-S-fatty acylation of PKM2 regulates its tetramerization and glycolytic metabolism in cancer cells. J Mol Biol 438: 170041, 2026.
33. De Rosa V, Iommelli F, Monti M, Fonti R, Votta G, Stoppelli MP and Del Vecchio S: Reversal of warburg effect and reactivation of oxidative phosphorylation by differential inhibition of EGFR signaling pathways in non-small cell lung cancer. Clin Cancer Res 21: 5110-5120, 2015.
34. Lv L, Li D, Zhao D, Lin R, Chu Y, Zhang H, Zha Z, Liu Y, Li Z, Xu Y, *et al*: Acetylation targets the M2 isoform of pyruvate kinase for degradation through chaperone-mediated autophagy and promotes tumor growth. Mol Cell 42: 719-730, 2011.
35. Lv L, Xu YP, Zhao D, Li FL, Wang W, Sasaki N, Jiang Y, Zhou X, Li TT, Guan KL, *et al*: Mitogenic and oncogenic stimulation of K433 acetylation promotes PKM2 protein kinase activity and nuclear localization. Mol Cell 52: 340-352, 2013.
36. Mazurek S: Pyruvate kinase type M2: A key regulator of the metabolic budget system in tumor cells. Int J Biochem Cell Biol 43: 969-980, 2011.
37. Mazurek S: Pyruvate kinase type M2: A key regulator within the tumour metabolome and a tool for metabolic profiling of tumours. Ernst Schering Found Symp Proc: 99-124, 2007.
38. Wu S and Le H: Dual roles of PKM2 in cancer metabolism. Acta Biochim Biophys Sin (Shanghai) 45: 27-35, 2013.
39. Benzarti M, Neises L, Oudin A, Krötz C, Viry E, Gargiulo E, Pulido C, Schmoetten M, Pozdeev V, Lorenz NI, *et al*: PKM2 diverts glycolytic flux in dependence on mitochondrial one-carbon cycle. Cell Rep 43: 113868, 2024.
40. Xiangyun Y, Xiaomin N, Linping G, Yunhua X, Ziming L, Yongfeng Y, Zhiwei C and Shun L: Desuccinylation of pyruvate kinase M2 by SIRT5 contributes to antioxidant response and tumor growth. Oncotarget 8: 6984-6993, 2017.
41. Wang HJ, Hsieh YJ, Cheng WC, Lin CP, Lin YS, Yang SF, Chen CC, Izumiya Y, Yu JS, Kung HJ, *et al*: JMJD5 regulates PKM2 nuclear translocation and reprograms HIF-1alpha-mediated glucose metabolism. Proc Natl Acad Sci USA 111: 279-284, 2014.
42. Pandkar MR, Raveendran A, Biswas K, Mutnuru SA, Mishra J, Samaiya A, Malys T, Mitrophanov AY, Sharan SK and Shukla S: PKM2 dictates the poised chromatin state of PFKFB3 promoter to enhance breast cancer progression. NAR Cancer 5: zcad032, 2023.
43. Luo W, Hu H, Chang R, Zhong J, Knabel M, O'Meally R, Cole RN, Pandey A and Semenza GL: Pyruvate kinase M2 is a PHD3-stimulated coactivator for hypoxia-inducible factor 1. Cell 145: 732-744, 2011.
44. Shi Y, Liu N, Lai W, Yan B, Chen L, Liu S, Liu S, Wang X, Xiao D, Liu X, *et al*: Nuclear EGFR-PKM2 axis induces cancer stem cell-like characteristics in irradiation-resistant cells. Cancer Lett 422: 81-93, 2018.
45. Wang X, Liang C, Yao X, Yang RH, Zhang ZS, Liu FY, Li WQ, Pei SH, Ma J, Xie SQ and Fang D: PKM2-Induced the phosphorylation of histone H3 contributes to EGF-Mediated PD-L1 transcription in HCC. Front Pharmacol 11: 577108, 2020.
46. Yang YC, Chien MH, Liu HY, Chang YC, Chen CK, Lee WJ, Kuo TC, Hsiao M, Hua KT and Cheng TY: Nuclear translocation of PKM2/AMPK complex sustains cancer stem cell populations under glucose restriction stress. Cancer Lett 421: 28-40, 2018.
47. Hosios AM, Fiske BP, Gui DY and Vander Heiden MG: Lack of evidence for PKM2 protein kinase activity. Mol Cell 59: 850-857, 2015.
48. Chen TJ, Wu CH, Hung MC, Wang WC and Kung HJ: Nuclear PKM2: A signal receiver, a gene programmer, and a metabolic modulator. J Biomed Sci 32: 75, 2025.
49. Wang Y, Shu H, Qu Y, Jin X, Liu J, Peng W, Wang L, Hao M, Xia M, Zhao Z, *et al*: PKM2 functions as a histidine kinase to phosphorylate PGAM1 and increase glycolysis shunts in cancer. EMBO J 43: 2368-2396, 2024.
50. Yu Z, Huang L, Qiao P, Jiang A, Wang L, Yang T, Tang S, Zhang W and Ren C: PKM2 Thr454 phosphorylation increases its nuclear translocation and promotes xenograft tumor growth in A549 human lung cancer cells. Biochem Biophys Res Commun 473: 953-958, 2016.
51. Guo Z, Jiang H, Wang X, Xuan K, Zhong H, Liu C, Zhang M, Li Z, Huang W and Sun Y: FUT8 reprograms glycolytic metabolism to promote PKM2 lactylation and drive clear cell renal cell carcinoma progression. Cell Death Discov 12: 146, 2026.
52. Wang J, Liu L, Gao X, Liu X, Dai Y, Mao Z, Huang S, Li J, Wang D, Qi Y, *et al*: A novel pathway for stemness propagation and chemoresistance in non-small cell lung cancer via phosphorylated PKM2-loaded small extracellular vesicles. Theranostics 15: 3439-3461, 2025.
53. Wei Y, Wang D, Jin F, Bian Z, Li L, Liang H, Li M, Shi L, Pan C, Zhu D, *et al*: Pyruvate kinase type M2 promotes tumour cell exosome release via phosphorylating synaptosome-associated protein 23. Nat Commun 8: 14041, 2017.
54. Bhardwaj A and Das S: SIRT6 deacetylates PKM2 to suppress its nuclear localization and oncogenic functions. Proc Natl Acad Sci USA 113: E538-E547, 2016.
55. Li W, Peng J, He J, Liao L, Kang D, Zhang W, Wang W, Wang R, Wang S, Liao Y, *et al*: PKM2 lactylation promotes colorectal cancer vasculogenic mimicry and bevacizumab resistance by facilitating FOSL1 Super-enhancer Formation. Cancer Res 86: 2759-2776, 2026.
56. Qi H, Ning X, Yu C, Ji X, Jin Y, McNutt MA and Yin Y: Succinylation-dependent mitochondrial translocation of PKM2 promotes cell survival in response to nutritional stress. Cell Death Dis 10: 170, 2019.
57. Liu T, Kuwana T, Zhang H, Vander Heiden MG, Lerner RA and Newmeyer DD: Phenotypic selection with an intrabody library reveals an anti-apoptotic function of PKM2 requiring Mitofusin-1. PLoS Biol 17: e2004413, 2019.

58. Wang X, Duan W, Ma Z, Wen H, Mao X and Liu C: ETV4/ALYREF-mediated glycolytic metabolism through PKM2 enhances resistance to ferroptosis and promotes the development of intrahepatic cholangiocarcinoma. Cancer Metab 13: 19, 2025.
59. Chen TJ, Lo CJ, Wu MJ, Sit WY, Hsu HY, Huang YC, Lu CH, Chen YL, Fang WK, Yang SM, *et al*: GSH as an A-A type allosteric activator of PKM2: modulating cancer cell homeostasis and ferroptosis susceptibility. Adv Sci (Weinh) 13: e19368, 2026.
60. Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS, Cheah JH, Clemons PA, Shamji AF, Clish CB, *et al*: Regulation of ferroptotic cancer cell death by GPX4. Cell 156: 317-331, 2014.
61. Peng C, Yang P, Zhang D, Jin C, Peng W, Wang T, Sun Q, Chen Z, Feng Y and Sun Y: KHK-A promotes fructose-dependent colorectal cancer liver metastasis by facilitating the phosphorylation and translocation of PKM2. Acta Pharm Sin B 14: 2959-2976, 2024.
62. Kamarajugadda S, Stemboroski L, Cai Q, Simpson NE, Nayak S, Tan M and Lu J: Glucose oxidation modulates anoikis and tumor metastasis. Mol Cell Biol 32: 1893-1907, 2012.
63. Schafer ZT, Grassian AR, Song L, Jiang Z, Gerhart-Hines Z, Irie HY, Gao S, Puigserver P and Brugge JS: Antioxidant and oncogene rescue of metabolic defects caused by loss of matrix attachment. Nature 461: 109-113, 2009.
64. Davison CA, Durbin SM, Thau MR, Zellmer VR, Chapman SE, Diener J, Wathen C, Leevy WM and Schafer ZT: Antioxidant enzymes mediate survival of breast cancer cells deprived of extracellular matrix. Cancer Res 73: 3704-3715, 2013.
65. Martin SP, Fako V, Dang H, Dominguez DA, Khatib S, Ma L, Wang H, Zheng W and Wang XW: PKM2 inhibition may reverse therapeutic resistance to transarterial chemoembolization in hepatocellular carcinoma. J Exp Clin Cancer Res 39: 99, 2020.
66. Wang Y, Zhao H, Zhao P and Wang X: Targeting PKM2 promotes chemosensitivity of breast cancer cells in vitro and in vivo. Cancer Biomark 32: 221-230, 2021.
67. Tee SS, Park JM, Hurd RE, Brimacombe KR, Boxer MB, Massoud TF, Rutt BK and Spielman DM: PKM2 activation sensitizes cancer cells to growth inhibition by 2-deoxy-D-glucose. Oncotarget 8: 90959-90968, 2017.
68. Ginés A, Bystrup S, Ruiz de Porras V, Guardia C, Musulén E, Martínez-Cardús A, Manzano JL, Layos L, Abad A and Martínez-Balibrea E: PKM2 subcellular localization is involved in oxaliplatin resistance acquisition in HT29 human colorectal cancer cell lines. PLoS One 10: e0123830, 2015.
69. Bailleul J, Ruan Y, Abdulrahman L, Scott AJ, Yazal T, Sung D, Park K, Hoang H, Nathaniel J, Chu FI, *et al*: M2 isoform of pyruvate kinase rewires glucose metabolism during radiation therapy to promote an antioxidant response and glioblastoma radioresistance. Neuro Oncol 25: 1989-2000, 2023.
70. Sharma SV, Lee DY, Li B, Quinlan MP, Takahashi F, Maheswaran S, McDermott U, Azizian N, Zou L, Fischbach MA, *et al*: A chromatin-mediated reversible drug-tolerant state in cancer cell subpopulations. Cell 141: 69-80, 2010.
71. Rehman SK, Haynes J, Collignon E, Brown KR, Wang Y, Nixon AML, Bruce JP, Wintersinger JA, Singh Mer A, Lo EBL, *et al*: Colorectal Cancer Cells Enter a Diapause-like DTP State to Survive Chemotherapy. Cell 184: 226-242.e21, 2021.
72. Zhou Z, Li M, Zhang L, Zhao H, Şahin Ö, Chen J, Zhao JJ, Songyang Z and Yu D: Oncogenic kinase-induced PKM2 tyrosine 105 phosphorylation converts nononcogenic PKM2 to a tumor promoter and induces cancer stem-like cells. Cancer Res 78: 2248-2261, 2018.
73. Li X, Deng S, Liu M, Jin Y, Zhu S, Deng S, Chen J, He C, Qin Q, Wang C and Zhao G: The responsively decreased PKM2 facilitates the survival of pancreatic cancer cells in hypoglucose. Cell Death Dis 9: 133, 2018.
74. Luo J, Zhang L, Guo L and Yang S: PKM2 regulates proliferation and apoptosis through the Hippo pathway in oral tongue squamous cell carcinoma. Oncol Lett 21: 461, 2021.
75. Li C, Zhao Z, Zhou Z and Liu R: PKM2 promotes cell survival and invasion under metabolic stress by enhancing warburg effect in pancreatic ductal adenocarcinoma. Dig Dis Sci 61: 767-773, 2016.
76. Israelsen WJ, Dayton TL, Davidson SM, Fiske BP, Hosios AM, Bellinger G, Li J, Yu Y, Sasaki M, Horner JW, *et al*: PKM2 isoform-specific deletion reveals a differential requirement for pyruvate kinase in tumor cells. Cell 155: 397-409, 2013.
77. Lau AN, Israelsen WJ, Roper J, Sinnamon MJ, Georgeon L, Dayton TL, Hillis AL, Yilmaz OH, Di Vizio D, Hung KE and Vander Heiden MG: PKM2 is not required for colon cancer initiated by APC loss. Cancer Metab 5: 10, 2017.
78. Xia Y, Wang X, Liu Y, Shapiro E, Lepor H, Tang MS, Sun TT and Wu XR: PKM2 is essential for bladder cancer growth and maintenance. Cancer Res 82: 571-585, 2022.
79. Koo H, Byun S, Seo J, Jung Y, Lee DC, Cho JH, Park YS, Yeom YI and Park KC: PKM2 regulates HSP90-mediated stability of the IGF-1R precursor protein and promotes cancer cell survival during hypoxia. Cancers (Basel) 13: 3850, 2021.
80. Hillis AL, Lau AN, Devoe CX, Dayton TL, Danai LV, Di Vizio D and Vander Heiden MG: PKM2 is not required for pancreatic ductal adenocarcinoma. Cancer Metab 6: 17, 2018.
81. Dayton TL, Gocheva V, Miller KM, Bhutkar A, Lewis CA, Bronson RT, Vander Heiden MG and Jacks T: Isoform-specific deletion of PKM2 constrains tumor initiation in a mouse model of soft tissue sarcoma. Cancer Metab 6: 6, 2018.
82. Zhang R, Shen M, Wu C, Chen Y, Lu J, Li J, Zhao L, Meng H, Zhou X, Huang G, *et al*: HDAC8-dependent deacetylation of PKM2 directs nuclear localization and glycolysis to promote proliferation in hepatocellular carcinoma. Cell Death Dis 11: 1036, 2020.
83. Hamabe A, Konno M, Tanuma N, Shima H, Tsunekuni K, Kawamoto K, Nishida N, Koseki J, Mimori K, Gotoh N, *et al*: Role of pyruvate kinase M2 in transcriptional regulation leading to epithelial-mesenchymal transition. Proc Natl Acad Sci USA 111: 15526-15531, 2014.
84. Qian J, Huang C, Wang M, Liu Y, Zhao Y, Li M, Zhang X, Gao X, Zhang Y, Wang Y, *et al*: Nuclear translocation of metabolic enzyme PKM2 participates in high glucose-promoted HCC metastasis by strengthening immunosuppressive environment. Redox Biol 71: 103103, 2024.
85. Chen S, Youhong T, Tan Y, He Y, Ban Y, Cai J, Li X, Xiong W, Zeng Z, Li G, *et al*: EGFR-PKM2 signaling promotes the metastatic potential of nasopharyngeal carcinoma through induction of FOSL1 and ANTXR2. Carcinogenesis 41: 723-733, 2020.
86. Yang W, Xia Y, Ji H, Zheng Y, Liang J, Huang W, Gao X, Aldape K and Lu Z: Nuclear PKM2 regulates β-catenin transactivation upon EGFR activation. Nature 480: 118-122, 2011.
87. Gao X, Wang H, Yang JJ, Liu X and Liu ZR: Pyruvate kinase M2 regulates gene transcription by acting as a protein kinase. Mol Cell 45: 598-609, 2012.
88. Guo CY, Zhu Q, Tou FF, Wen XM, Kuang YK and Hu H: The prognostic value of PKM2 and its correlation with tumour cell PD-L1 in lung adenocarcinoma. BMC Cancer 19: 289, 2019.
89. Palsson-McDermott EM, Dyck L, Zasłona Z, Menon D, McGettrick AF, Mills KHG and O'Neill LA: Pyruvate kinase M2 is required for the expression of the immune checkpoint PD-L1 in immune cells and tumors. Front Immunol 8: 1300, 2017.
90. Xia Q, Jia J, Hu C, Lu J, Li J, Xu H, Fang J, Feng D, Wang L and Chen Y: Tumor-associated macrophages promote PD-L1 expression in tumor cells by regulating PKM2 nuclear translocation in pancreatic ductal adenocarcinoma. Oncogene 41: 865-877, 2022.
91. Yu Y, Liang Y, Xie F, Zhang Z, Zhang P, Zhao X, Zhang Z, Liang Z, Li D, Wang L, *et al*: Tumor-associated macrophage enhances PD-L1-mediated immune escape of bladder cancer through PKM2 dimer-STAT3 complex nuclear translocation. Cancer Lett 593: 216964, 2024.
92. Welsh JA, Goberdhan DCI, O'Driscoll L, Buzas EI, Blenkiron C, Bussolati B, Cai H, Di Vizio D, Driedonks TAP, Erdbrügger U, *et al*: Minimal information for studies of extracellular vesicles (MISEV2023): From basic to advanced approaches. J Extracell Vesicles 13: e12404, 2024.
93. Yuan M, Zheng X, Zheng S, Li H, Zhang X, Chen Y, Zhang X, Han B, Wei W, Wu J and Sun Q: Exosomal PKM2: A noninvasive diagnostic marker linking macrophage metabolic reprogramming to gastric cancer pathogenesis. Cancer Sci 116: 1537-1549, 2025.
94. Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, Gordon S, Hamilton JA, Ivashkiv LB, Lawrence T, *et al*: Macrophage activation and polarization: nomenclature and experimental guidelines. Immunity 41: 14-20, 2014.
95. Azizi E, Carr AJ, Plitas G, Cornish AE, Konopacki C, Prabhakaran S, Nainys J, Wu K, Kiseliovas V, Setty M, *et al*: Single-cell map of diverse immune phenotypes in the breast tumor microenvironment. Cell 174: 1293-1308.e36, 2018.
96. Li L, Zhang Y, Qiao J, Yang JJ and Liu ZR: Pyruvate kinase M2 in blood circulation facilitates tumor growth by promoting angiogenesis. J Biol Chem 289: 25812-25821, 2014.

97. Hamza A, Cho JY, Cap KC, Hossain AJ, Kim JG and Park JB: Extracellular pyruvate kinase M2 induces cell migration through p-Tyr42 RhoA-mediated superoxide generation and epithelial-mesenchymal transition. Free Radic Biol Med 208: 614-629, 2023.
98. Wang C, Zhang S, Liu J, Tian Y, Ma B, Xu S, Fu Y and Luo Y: Secreted pyruvate kinase M2 promotes lung cancer metastasis through activating the integrin Beta1/FAK signaling pathway. Cell Rep 30: 1780-1797.e6, 2020.
99. Markowitz GJ, Ban Y, Tavarez DA, Yoffe L, Podaza E, He Y, Martin MT, Crowley MJP, Sandoval TA, Gao D, *et al*: Deficiency of metabolic regulator PKM2 activates the pentose phosphate pathway and generates TCF1+ progenitor CD8+ T cells to improve immunotherapy. Nat Immunol 25: 1884-1899, 2024.
100. Mortazavi Farsani SS, Soni J, Jin L, Yadav AK, Bansal S, Mi T, Hilakivi-Clarke L, Clarke R, Youngblood B, Cheema A and Verma V: Pyruvate kinase M2 activation reprograms mitochondria in CD8 T cells, enhancing effector functions and efficacy of anti-PD1 therapy. Cell Metab 37: 1294-1310.e7, 2025.
101. Han L, Gan L, Schäfer B, Voss DM, Danielsen M, Kostov O, Liu J, Wang T, Caruthers MH, Chen H and Krainer AR: ASO-based PKM splice-switching therapy increases anti-CTLA-4 antibody efficacy in pancreatic ductal adenocarcinoma. Cell Discov 12: 28, 2026.
102. Chen M, Liu H, Li Z, Ming AL and Chen H: Mechanism of PKM2 affecting cancer immunity and metabolism in tumor microenvironment. J Cancer 12: 3566-3574, 2021.
103. Apostolidi M, Vathiotis IA, Muthusamy V, Gaule P, Gassaway BM, Rimm DL and Rinehart J: Targeting pyruvate kinase M2 phosphorylation reverses aggressive cancer phenotypes. Cancer Res 81: 4346-4359, 2021.
104. Palsson-McDermott EM, Curtis AM, Goel G, Lauterbach MA, Sheedy FJ, Gleeson LE, van den Bosch MW, Quinn SR, Domingo-Fernandez R, Johnston DG, *et al*: Pyruvate kinase M2 Regulates Hif-1alpha Activity and IL-1beta induction and is a critical determinant of the warburg effect in LPS-Activated macrophages. Cell Metab 21: 65-80, 2015.
105. Kung C, Hixon J, Kosinski PA, Cianchetta G, Histen G, Chen Y, Hill C, Gross S, Si Y, Johnson K, *et al*: AG-348 enhances pyruvate kinase activity in red blood cells from patients with pyruvate kinase deficiency. Blood 130: 1347-1356, 2017.
106. Yang H, Merica E, Chen Y, Cohen M, Goldwater R, Kosinski PA, Kung C, Yuan ZJ, Silverman L, Goldwasser M, *et al*: Phase 1 single- and multiple-ascending-dose randomized studies of the safety, pharmacokinetics, and pharmacodynamics of AG-348, a first-in-class allosteric activator of pyruvate kinase R, in healthy volunteers. Clin Pharmacol Drug Dev 8: 246-259, 2019.
107. Grace RF, Rose C, Layton DM, Galactéros F, Barcellini W, Morton DH, van Beers EJ, Yaish H, Ravindranath Y, Kuo KHM, *et al*: Safety and efficacy of mitapivat in pyruvate kinase deficiency. N Engl J Med 381: 933-944, 2019.
108. Liu T, Padyana AK, Judd ET, Jin L, Hammoudeh D, Kung C and Dang L: Structure-based design of AG-946, a pyruvate kinase activator. ChemMedChem 19: e202300559, 2024.
109. Zeidan AM, Sekeres MA, Al-Samkari H, Carraway HE, DeZern AE, Mittelman M, Little M, Beynon V, Dai X, Sommakia S, *et al*: A phase 2B, open-label multicenter study of tebapivat (AG-946), a potent pyruvate kinase activator, in patients with anemia due to lower-risk myelodysplastic syndromes. Blood 144 (Suppl 1): 6708, 2024.
110. Shirai T, Nazarewicz RR, Wallis BB, Yanes RE, Watanabe R, Hilhorst M, Tian L, Harrison DG, Giacomini JC, Assimes TL, *et al*: The glycolytic enzyme PKM2 bridges metabolic and inflammatory dysfunction in coronary artery disease. J Exp Med 213: 337-354, 2016.
111. Holling GA, Chavel CA, Sharda AP, Lieberman MM, James CM, Lightman SM, Tong JH, Qiao G, Emmons TR, Giridharan T, *et al*: CD8+ T cell metabolic flexibility elicited by CD28-ARS2 axis-driven alternative splicing of PKM supports antitumor immunity. Cell Mol Immunol 21: 260-274, 2024.
112. Zhang J, Wu S, Yin Q, Liu Y, Zheng S and Yang P: Targeting PKM2 enhances the anti-tumor function of CD8+ T cells through metabolic reprogramming. Int J Mol Sci 27: 7664, 2026.
113. Li Q, Zhang D, Chen X, He L, Li T, Xu X and Li M: Nuclear PKM2 contributes to gefitinib resistance via upregulation of STAT3 activation in colorectal cancer. Sci Rep 5: 16082, 2015.
114. Suzuki A, Puri S, Leland P, Puri A, Moudgil T, Fox BA, Puri RK and Joshi BH: Subcellular compartmentalization of PKM2 identifies anti-PKM2 therapy response in vitro and in vivo mouse model of human non-small-cell lung cancer. PLoS One 14: e0217131, 2019.
115. Zhang X, He C, He C, Chen B, Liu Y, Kong M, Wang C, Lin L, Dong Y and Sheng H: Nuclear PKM2 expression predicts poor prognosis in patients with esophageal squamous cell carcinoma. Pathol Res Pract 209: 510-515, 2013.
116. Aalami AH, Shahriari A, Mazaheri M, Aalami F, Amirabadi A and Sahebkar A: Diagnostic accuracy of tumor M2-pyruvate kinase (tM2-PK) as a non-invasive biomarker in colorectal cancer: A systematic review and meta-analysis. Clin Biochem 120: 110652, 2023.
117. Taube JM, Akturk G, Angelo M, Engle EL, Gnjatic S, Greenbaum S, Greenwald NF, Hedvat CV, Hollmann TJ, Juco J, *et al*: The society for immunotherapy of cancer statement on best practices for multiplex immunohistochemistry (IHC) and immunofluorescence (IF) staining and validation. J Immunother Cancer 8: e000155, 2020.
118. Staib P, Hoffmann M and Schinköthe T: Plasma levels of tumor M2-pyruvate kinase should not be used as a tumor marker for hematological malignancies and solid tumors. Clin Chem Lab Med 44: 28-31, 2006.
119. Ahn SS, Kim HM and Park Y: Assessment of disease activity in patients with rheumatoid arthritis using plasma tumour M2-pyruvate kinase test. Front Immunol 13: 901555, 2022.
120. Oremek GM, Gerstmeier F, Sauer-Eppel H, Sapoutzis N and Wechsel HW: Pre-analytical problems in the measurement of tumor type pyruvate kinase (tumor M2-PK). Anticancer Res 23 (2A): 1127-1130, 2003.
121. Sithambaram S, Hilmi I and Goh KL: The diagnostic accuracy of the M2 pyruvate kinase quick stool test-A rapid office based assay test for the detection of colorectal cancer. PLoS One 10: e0131616, 2015.
122. Beinat C, Alam IS, James ML, Srinivasan A and Gambhir SS: Development of (18F)DASA-23 for imaging tumor glycolysis through noninvasive measurement of pyruvate kinase M2. Mol Imaging Biol 19: 665-672, 2017.
123. Beinat C, Patel CB, Haywood T, Shen B, Naya L, Gandhi H, Holley D, Khalighi M, Iagaru A, Davidzon G and Gambhir SS: Human biodistribution and radiation dosimetry of (18F) DASA-23, a PET probe targeting pyruvate kinase M2. Eur J Nucl Med Mol Imaging 47: 2123-2130, 2020.
124. Beinat C, Patel CB, Haywood T, Murty S, Naya L, Castillo JB, Reyes ST, Phillips M, Buccino P, Shen B, *et al*: A clinical PET imaging tracer ((18F)DASA-23) to monitor pyruvate kinase M2-Induced glycolytic reprogramming in glioblastoma. Clin Cancer Res 27: 6467-6478, 2021.
125. Khalaf A, Naya L, Flynt L, Surasi DS, Lu Y, Nagpal S, Thomas RP, Recht LD, Beckham TH, Liu HL, *et al*: (18F) DASA-23 PET/MRI evaluation in newly-diagnosed and recurrent high-grade glioma. Neuroradiology 68: 1687-1698, 2026.
126. Beinat C, Patel CB, Xie Y and Gambhir SS: Evaluation of glycolytic response to multiple classes of anti-glioblastoma drugs by noninvasive measurement of pyruvate kinase M2 using (18F) DASA-23. Mol Imaging Biol 22: 124-133, 2020.
127. Che Alhadi S, Wan Zain WZ, Zahari Z, Md Hashim MN, Syed Abd Aziz SH, Zakaria Z, Wong MP and Zakaria AD: The use of M2-Pyruvate kinase as a stool biomarker for detection of colorectal cancer in tertiary teaching hospital: A comparative study. Ann Coloproctol. 2020. 36: 409-414, 2020.

Copyright © 2026 Pan et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.