Advances in Life Science for Adolescents

Review VOL 1 | Apr 2025 | doi:

Research Progress on the Role of PKM2 in the Cell Cycle of Tumor Cells and Immune Cells

Yue Lang*

Students: Capital Medical University -- *UNDERGRADULATE STUDENTS*
*Laboratory: Laboratory of Infect and Immune, Capital Medical University

Abstract:

This article comprehensively discusses the important role of pyruvate kinase M2 (PKM2) in cell cycle regulation, immune cell function, and cancer treatment. As a multifunctional protein, PKM2 plays a key role in cell metabolism, signal transduction, and transcriptional regulation, affecting biological processes such as cell proliferation, differentiation, and polarization. We conduct an in-depth analysis of the mechanisms by which PKM2 influences cell cycle checkpoints, Th17 cell differentiation, and macrophage polarization, and explore its potential value in cancer therapy. Finally, we look forward to future research directions to more fully reveal the biological functions and clinical application prospects of PKM2.

Keywords: PKM2, Cell Cycle, Tumor immunity, Cell metabolism

1. Background:

1.1 PKM2

Pyruvate kinase (PK) is one of the key enzymes in the glycolytic pathway, catalyzing the final step of glycolysis where phosphoenolpyruvate is dephosphorylated to pyruvate. There are four isoforms of pyruvate kinase: PKL, PKR, PKM1, and PKM2. PKL is expressed in the liver, PKR in red blood cells, PKM1 is highly expressed in normal tissues, and PKM2 is also expressed to some extent in normal tissues. In normal cells, M2-type pyruvate kinase (PKM2) exists in three forms: monomer, dimer, and tetramer. Tetrameric PKM2 has higher pyruvate kinase activity than dimeric PKM2 and primarily functions as a metabolic enzyme, while dimeric and monomeric PKM2 often enter the nucleus to regulate the expression of related genes. [1, 2]

1.2 Cell Cycle

Cell devision is a crucial process in cell proliferation, beginning at the end of the previous cell division and ending at the start of the next division. The eukaryotic cell cycle can be divided into interphase (including G0/G1, S, and G2 phases) and the mitotic phase (M phase). Cells that are not in the cell cycle or have temporarily exited the cycle are referred to as G0 phase cells. The G1 phase prepares necessary materials for DNA synthesis in the S phase, such as DNA polymerase and related regulatory proteins. The S phase is primarily dedicated to DNA synthesis. The G2 phase involves protein and RNA synthesis in preparation for mitosis. [3] The M phase is the mitotic phase, during which cells undergo mitosis. Additionally, the cell cycle has checkpoint mechanisms to ensure its smooth progression. The G1/S checkpoint controls the transition from G1 to S phase by monitoring cell size, extracellular environment, DNA integrity, and other factors. The G2/M checkpoint ensures genomic integrity and stability before cells enter the M phase. The spindle assembly checkpoint (SAC) monitors the connection between spindle microtubules and chromosomal kinetochores. Any issues detected at these checkpoints may cause cells to enter the G0 phase or undergo apoptosis. [4, 5]

Beyond checkpoints, the cell cycle is regulated by various proteins. Two key regulatory proteins are cyclins and cyclin-dependent kinases (CDKs). Cyclins

*Correspondence: Yue Lang
:13522857177@163.com
Received: Feb. 23, 2025.
Accepted: Apr. 09, 2025.

and CDKs have highly specific binding relationships. When they bind, cyclins activate CDKs, enabling CDKs to phosphorylate and exert their effects. The periodic formation and degradation of cyclin-CDK complexes ensure the orderly progression of the cell cycle. Additionally, cyclins are regulated by kinase inhibitors and proteins encoded by certain oncogenes or tumor suppressor genes (e.g., p53). [6]

1.3 Characteristics of PKM2 and the Cell Cycle in Cancer Cells

Currently, PKM2 upregulation has been detected in almost all known tumor cells. [7, 8] Moreover, when PKM1 replaces PKM2 expression, tumor cell growth and the Warburg effect are suppressed. [9-11] This demonstrates that PKM2, rather than PKM1, plays a critical role in tumor cells. In cancer cells, PKM2 participates in metabolic reprogramming and enters the nucleus to influence gene expression, thereby promoting tumor development. Meanwhile, cancer cells exhibit characteristics such as unlimited proliferation, prolonged stagnation, gene mutations, dysregulated control, apoptosis inhibition, and abnormal damage repair, all of which are associated with PKM2.

1.4 Immune Cells

The human immune system can be divided into the innate immune system and the adaptive immune system. At the cellular level, innate immune-related cells include phagocytes, neutrophils, macrophages, natural killer cells, mast cells, basophils, dendritic cells, and eosinophils. Adaptive immune-related cells include T cells (cell-mediated immunity) and B cells (humoral immunity). [12]

2. Impact of PKM2 on the Cell Cycle

2.1 Tumor cells

2.1.1 Metabolic Aspects

As mentioned earlier, the structural characteristics of PKM2 enable it to possess both metabolic and non-metabolic functions, each of which can influence the cell cycle. The unlimited proliferation of cancer cells means they require vast amounts of energy and materials to meet their biosynthetic needs. Experiments have shown that the pyruvate kinase activity of PKM2 plays an important role in coordinating glycolysis and deoxynucleotide synthesis. [13] The regulation of PKM2 activity by tyrosine kinase signaling is crucial for metabolic changes during tumor growth and proliferation. [9, 14] Oxidation at the C358 site of PKM2 reduces its enzymatic activity and increases the flux of the oxidative pentose phosphate pathway (PPP), helping to regulate the redox state in cells. [15] Under serine-limiting conditions,[16,17] reduced PKM2 activity can also promote serine biosynthesis and proliferation. Downregulation of pyruvate kinase activity is important for nucleotide biosynthesis in non-transformed cells. [18] Additionally, studies suggest that the ability to regulate pyruvate kinase activity according to cell state may have varying importance for cell proliferation in different cancers. [13] Furthermore, PKM2 can be activated by fructose-1,6-bisphosphate (FBP) and serine and inhibited by high concentrations of ATP and alanine. [19] PKM2 localizes to the nucleus, where it recruits HIF-1α to hypoxia response elements (HREs) and brings in p300 to acetylate H3K9, thereby promoting the transactivation of genes encoding glucose transporters and glycolytic enzymes in cancer cells. [20] These factors collectively provide the metabolic foundation for the rapid repetition of the tumor cell cycle.

2.1.2 Non-Metabolic Aspects

PKM2 also affects the cell cycle of tumor cells through various non-metabolic functions. First, dimeric and monomeric PKM2 can enter the nucleus to regulate the transcription of specific genes, thereby influencing cell cycle progression. After epidermal growth factor (EGF) receptor activation, PKM2 directly binds to histone H3 and phosphorylates the T11 site of histone H3, participating in EGF-induced Cyclin D1 and c-Myc expression, tumor cell proliferation, cell cycle progression, and tumorigenesis. [21] Studies have shown that in human glioblastoma, epidermal growth factor receptor (EGFR) activation induces PKM2 (but not PKM1) and promotes its translocation to the nucleus. At the K433 site, PKM2 binds to the c-Src-phosphorylated Y333 site of β-catenin, forming a complex that recruits to the CCND1 promoter binding element. This leads to the decoupling of histone deacetylase 3 (HDAC3) from the promoter binding element, promoting histone H3 acetylation and Cyclin D1 expression. PKM2-dependent β-catenin activation contributes to EGFR-promoted tumor cell proliferation and tumor development. [22]

At the same time, PKM2 can also bind to proteins to exert its effects. Experiments have shown that PKM2 can bind to the Cdk1-Cyclin B complex, which is critical for the G2-M phase, and in turn promote the activation of Cdk1-Cyclin B, driving cells into mitosis. [23] Studies indicate that PKM2 (but not PKM1) binds to the spindle checkpoint protein Bub3 during mitosis and phosphorylates Bub3 at the Y207 site. This phosphorylation is essential for the recruitment of the Bub3-Bub1 complex to kinetochores and its interaction with Blinkin (also known as KNL1, Spc7, Spc105, AF15q14, D40, and CASC5). This process is crucial for proper kinetochore-microtubule attachment, mitotic checkpoint function, accurate chromosome segregation, cell survival and proliferation, and EGFR-induced tumorigenesis. [24] [25] Aurora B phosphorylates PKM2 at the T45 site but does not phosphorylate PKM1. This phosphorylation is necessary for PKM2 to localize to the myosin light chain 2 (MLC2) region of the contractile ring in mitotic cells and interact with it. PKM2 phosphorylates MLC2 at the Y118 site, enabling the binding of Rho-associated coiled-coil kinase 2 (ROCK2) to MLC2 and its phosphorylation at the S15 site. PKM2-regulated MLC2 phosphorylation is significantly enhanced by EGF stimulation of EGFR

vIII, K-Ras G12V, and B-Raf V600E mutations, playing a key role in cytokinesis, cell proliferation, and tumor development. [26] [27] [28] PKM2 phosphorylates STAT3 at the Y705 site, activating downstream gene expression. [29] [30] 5-Aminoimidazole-4-carboxamide ribonucleotide (SAICAR), a metabolic intermediate in purine nucleotide biosynthesis, can directly activate the pyruvate kinase activity of PKM2. The PKM2-SAICAR complex can phosphorylate over 100 human proteins, including Erk1/2. Activated ERK/MAPK signaling increases PKM2 nuclear localization and promotes cell proliferation. [31] The p53 protein phosphorylates PKM2 at the Tyr 105 site via mTOR signaling. [32] PKM2 can be acetylated at the K433 site by the p300 acetyltransferase. Acetylation interferes with fructose-1,6-bisphosphate (FBP) binding, preventing PKM2 activation, promoting its nuclear accumulation, and enhancing its protein kinase activity, thereby driving cell proliferation and tumorigenesis. [33] Additionally, recent studies suggest that PKM2 membrane localization may be related to intercellular communication, particularly trogocytosis in immune cells, and has become a new research focus.

2.2 Immune cells

Meanwhile, the role of PKM2 in immune cells also contributes significantly to cancer research. Studies have found that checkpoint kinase 2 (Chk2) phosphorylates PKM2 at the T95 and T195 sites, promoting glycolysis and M1 macrophage polarization. [34] PKM2 is also a key mediator of Th17 cell differentiation and autoimmune inflammation. During in vitro Th17 cell differentiation experiments and the development of experimental autoimmune encephalomyelitis (EAE) models, PKM2 is highly expressed. When PKM2 is deleted in T cells, Th17 cell-mediated inflammation and demyelination are reduced, Th17 cell differentiation is inhibited, and EAE symptoms improve. Under normal conditions, PKM2 can translocate to the nucleus and interact with STAT3, enhancing its activity and promoting Th17 cell differentiation. [35] It is reasonable to speculate that the interaction between nuclear PKM2 and STAT3 in Th17 cells may also promote cell cycle progression and proliferation. PKM2 has been shown to be a key determinant of metabolic reprogramming in macrophages stimulated by lipopolysaccharide (LPS) via HIF-1α. After LPS activation, PKM2 dimers stabilize HIF-1α, regulating the expression of HIF-1α target genes such as Il1b and genes encoding glycolytic machinery, thereby playing a significant role in M1 macrophage differentiation and function. [36-37]

3. Potential Applications in Cancer Therapy

Based on the above research, we can explore PKM2 as a target for cancer therapy. First, PKM2 may serve as a potential prognostic biomarker. In lung cancer, compared to adjacent normal tissues, PKM2 expression is elevated in tumor tissues. Prognostic analysis indicates that high PKM2 expression is associated with poorer outcomes in lung adenocarcinoma (LUAD) patients. PKM2 also shows strong correlations with B cells and CD4+ T cells in LUAD, as well as with B cells, CD8+ T cells, CD4+ T cells, and macrophages in lung squamous cell carcinoma (LUSC). Moreover, PKM2 expression exhibits significant negative correlations with immune cell marker expression in LUAD and LUSC. [38] PKM2 can also serve as a biomarker for gastrointestinal cancers. [39] Additionally, researchers have designed cancer-related drugs targeting PKM2. For example, the herbal extract Shikonin can inhibit PKM2 activity by binding to it. [40] Other PKM2 inhibitors include PKM2-IN-1 and TEPP-46. [41-44]

On the other hand, research on PKM2's role in immune cells provides a foundation for cancer therapy. Immune checkpoint blockade (ICB), an immunotherapy approach including PD-1/PD-L1 inhibitors and CTLA-4 inhibitors, primarily blocks immune checkpoint proteins to activate the immune system, enabling it to attack tumor cells. However, studies show that ICB may promote hyperprogressive disease (HPD). Researchers found that CD8+ T cell-derived IFNγ targets FGF2, selectively inhibiting PKM2 and reducing NAD+ production, thereby increasing β-catenin activity in tumor cells and promoting cancer progression and tumorigenesis. [45]

4. Conclusion

As a multifunctional protein, PKM2 plays a vital role in cell cycle regulation, immune cell function, and cancer development. Its complex metabolic and signaling networks influence cell fate and disease progression. By studying PKM2's mechanisms in different physiological and pathological states, we can better understand its impact on cell biology and disease development, providing new insights for designing cancer treatments and immune disease therapies. With advancing technology, we are confident that further revelations about PKM2 will lead to breakthroughs in disease treatment.

5. References

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