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Review Article

Cancer metabolism meets systems biology: Pyruvate kinase isoform PKM2 is a metabolic master regulator

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Abstract

Pyruvate kinase activity is controlled by a tightly woven regulatory network.The oncofetal isoform of pyruvate kinase (PKM2) is a master regulator of cancer metabolism. PKM2 engages in parallel, feed-forward, positive and negative feedback control contributing to cancer progression. Besides its metabolic role, non-metabolic functions of PKM2 as protein kinase and transcriptional coactivator for c-MYC and hypoxia-inducible factor 1-alpha are essential for epidermal growth factor receptor activation-induced tumorigenesis. These biochemical activities are controlled by a shift in the oligomeric state of PKM2 that includes acetylation, oxidation, phosphorylation, prolyl hydroxylation and sumoylation. Metabolically active PKM2 tetramer is allosterically regulated and responds to nutritional and stress signals. Metabolically inactive PKM2 dimer is imported into the nucleus and can function as protein kinase stimulating transcription. A systems biology approach to PKM2 at the genome, transcriptome, proteome, metabolome and fluxome level reveals how differences in biomolecular structure translate into a global rewiring of cancer metabolism. Cancer systems biology takes us beyond the Warburg effect, opening unprecedented therapeutic opportunities.

Keywords: Cancer metabolism, catenin, control, epidermal growth factor receptor, feed-forward, feedback, fructose-1,6-bisphosphate, fructose-1,6-bisphosphatase, glutamic-oxalacetic transaminase, glutaminase, hypoxia-inducible factor 1-alpha, isoform, metabolomics, MYC, NMR, omics, pyruvate dehydrogenase, pyruvate dehydrogenase kinase, PKM1, PKM2, pyruvate kinase M2, pyruvate kinase, succinylaminoimidazolecarboxamide ribose-5-phosphate, seven in absentia homolog 2, serine, serine/arginine-rich splicing factor 3, signal transducer and activator of transcription 3, systems biology, Warburg

CANCER SYSTEMS BIOLOGY — ARRIVING AT A SYSTEMS UNDERSTANDING OF CANCER METABOLISM

Pyruvate kinase has been recognized as an attractive target for cancer therapy. In its metabolic role as terminal enzyme of glycolysis, its activity determines cellular energy level, redox homeostasis and ability to proliferate. The oncofetal isoform of pyruvate kinase (PKM2) differs at only 22 of 531 amino acids from its normal isoform (PKM1). If we understand the mechanistic implications of how atomic differences translate into global rewiring of cancer metabolism, unique therapeutic opportunities will open up. Until recently, there has been a conceptual disconnect between available pictograms of cellular events and tangible proof of direct molecular interaction. Today, the field of PKM2 offers high-resolution data at all levels of the omics hierarchy to unravel how basic genetic events can impact metabolism at a systems level[1,2] [Figure 1].

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FROM GENE TO PROTEIN TO FUNCTION

Cancer is a genetic disease. One approach to the enigma of the pyruvate kinase reaction is by strictly translating genetic information into protein encoded enzymatic function observed in cancer cells.[3] The fate of pyruvate kinase is governed by splicing, transcriptional regulation, post-translational modification, allosteric modulation, cellular localization, metabolic pathway concertation, and biomass balancing [Figure 1]. Taken together these well-defined physiochemical events determine pyruvate kinase activity and result in up-regulated glycolysis decoupled from glutamine-fueled tricarboxylic acid (TCA) cycle enabling uncontrollable growth of cancer. Two genes, *PKLR* and *PKM*, encode four isoforms of pyruvate kinase protein in red blood cells (PKR), liver (PKL), normal muscle (PKM1), and proliferating tissue (PKM2), and their expression is regulated by tissue-specific promoters.[4] However, independent of their tissue of origin most cancer cells are PKM2 positive. Recent work showed how a mutually exclusive splicing event determines whether PKM2 is expressed and able to promote the Warburg effect.[5,6] Exon-blockage by heterogeneous nuclear ribonucleoproteins (hnRNPs) (PKM1-specific exon) in combination with serine/arginine-rich splicing factor 3 (SRSF3) binding to an exonic splicing enhancer (PKM2-specific exon), activates PKM1-specific exon exclusion and favors PKM2 production,[5-7] [Figure 1]. Intriguingly, mutually exclusive splicing is a rare event (<4%),[8] and presents a potential therapeutic target. In spite of the fact that PKM2-specific exonic splicing enhancer differs from its PKM1 counterpart by only two nucleotides, PKM2 action takes more than just its genetic code.

MULTI-LEVEL NETWORK CONTROL

Pyruvate kinase activity is tightly controlled at the transcriptomic, proteomic and metabolomic level [Figure 2]. Nuclear localization of PKM2 has been a first indicator that the enzyme brings more to the table than its exonic sequence.[9] Studies of transcriptional regulation at individual promoters have led to the general model that structurally coordinated binding of protein factors achieves gene-specific transcription. Global omics analyses extend this model and let sequential or combinatorial networks of regulatory motifs emerge, such as feed-forward loops, regulatory cascades and feedback stabilization [Figure 2].

Recent results connected epidermal growth factor receptor (EGFR) signaling — commonly observed in early cancer progression — to PKM2.[10-12] Early on, a phosphoproteomic screen for cancer signaling peptides identified PKM2 activity to be modulated by phosphotyrosine-binding.[13,14] However, linear growth factor dependent activation of *PKM* would be too simple: PKM2 itself is involved in the signaling [Figure 2a]. PKM2 has two non-metabolic functions in the direct control of cell cycle progression, one as transcriptional coactivator and one as protein kinase. PKM2 binds β-catenin and coactivates *c-MYC* transcription by phosphorylating histone H3.[10-12] PKM2 also participates in an alternative mechanism where EGFR stimulates hypoxia-inducible factor 1-alpha *(HIF1a)* transcription.[15-17] In this case, PKM2 interaction with prolyl hydroxylase 3 (PHD3) enhances PKM2 coactivator function and *HIF1a* transcription. This nuclear function of PKM2 is shared with other transcription factors and highlights the non-metabolic role of PKM2 in cancer systems biology during tumorigenesis. Since *PKM* itself is under the direct

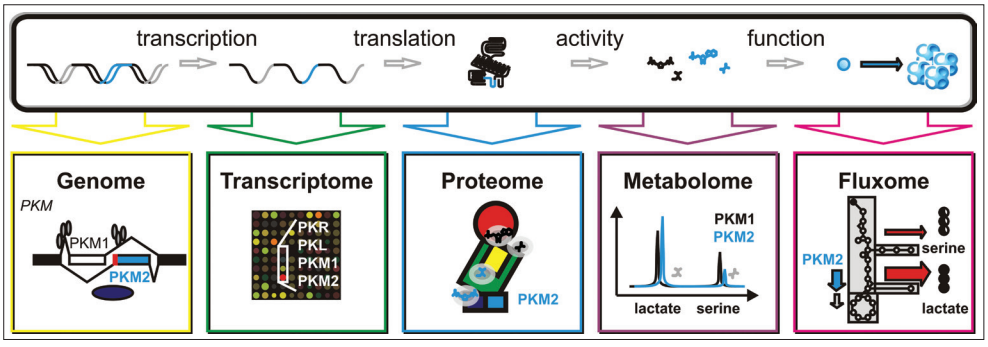

Figure 1: PKM2 controls cancer metabolism at a systems-level. Genome, transcriptome, proteome, metabolome and fluxome data provide detailed mechanistic understanding how the tumor form of pyruvate kinase promotes cancer growth. The genomic sequence of PKM1 and PKM2 differs at only 22 out of 531 amino acids. Exon binding of splicing factor (blue circle bound to red splicing enhancer) in combination with exon blockage mediates alternative splicing. PKM2 is the predominantly transcribed isoform of pyruvate kinase in tumors. Binding of activators facilitate the formation of its active tetrameric state. Pyruvate kinase is the rate-limiting glycolytic enzyme converting phosphoenol pyruvate and adp to pyruvate and atp, thereby contributing to aerobic glycolysis, biomass production and lactate fermentation. The control of PKM2 at the genome, transcriptome, proteome, metabolome and fluxome level ensures optimal growth by balancing energy generation and flux into biosynthetic precursors.

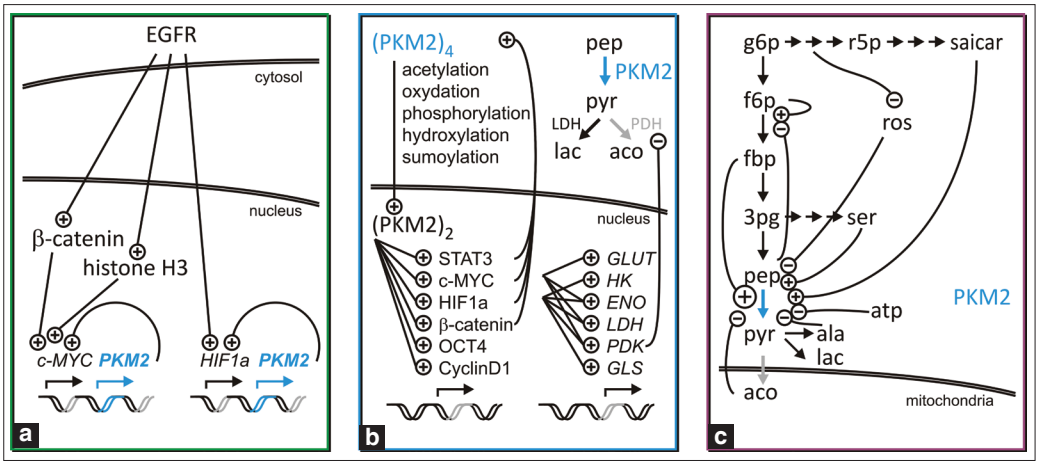

Figure 2: PKM2 activity is controlled by a tight regulatory network at the transcriptional, proteomic and metabolic level. (a) Upon EGFR activation parallel signaling pathways initiate transcription of *c-MYC* and *HIF1a*. Since PKM2 is both, transcriptional target and transcriptional coactivator, parallel in combination with forward control initiates and amplifies the signal. (b) Post-translational modifications control the equilibrium between metabolically active tetramer $(PKM2)_4$ and transcriptional active dimer $(PKM2)_2$ with protein kinase activity. In the nucleus PKM2 serves as coactivator of glycolytic genes including itself. This further amplifies the signal. (c) A network of feedback mechanisms provides a metabolic phenotype that is robust against perturbations. The combination of positive and negative feedback control guarantees stable flux through the glycolytic pathway with PKM2 as terminal master regulator. PKM2 transcript, protein tetramer, and metabolic activity are highlighted in blue. The gate keeping pyruvate dehydrogenase (PDH) reaction between cytosol and mitochondria is negatively regulated by pyruvate dehydrogenase kinase (PDK) and labeled in grey. Genes are displayed in *Italic*. Enzymes are abbreviated in uppercase as enolase (ENO), glucose transporter (GLUT), hexokinase (HK), lactate dehydrogenase (LDH), glutaminase (GLS), PDH, PDK, PKM2. Metabolites are abbreviated in lowercase as acetyl-CoA (aco), alanine (ala), adenosine triphosphate (atp), fructose-1,6-bisphosphatase (fbp), fructose-6-phosphatase (f6p), glucose-6-phosphate (g6p), lactate (lac), phosphoenol pyruvate (pep), 3-phosphoglycerate (3pg), pyruvate (pyr), reactive oxygen species (ros), ribose-5-phosphate (r5p), succinylaminoimidazolecarboxamide ribose-5-phosphate (saicar), serine (ser).

control of both transcription factors, c-MYC and HIF1a, an enhancing feed-forward loop is present that promotes *c-MYC* and *HIF1a* transactivation to reprogram glucose metabolism in cancer cells.

The transcriptional cascade of PKM2 reveals multiple incidences of forward control. Signal transducer and activator of transcription 3 (STAT3) and β-catenin follow the pattern of c-MYC and HIF1a and positively regulate PKM2 [Figure 2b]. The common program of these transcription factors seems redundant. Parallel activation of glucose transporter, glycolytic genes, lactate dehydrogenase and pyruvate dehydrogenase kinase ensures that the glycolytic pathway is strongly up-regulated in a concerted fashion. Inclusion of pyruvate dehydrogenase kinase and glutamine synthase in this transcriptional program is critical, since it allows for decoupling of glycolysis from glutamine-fueled TCA cycle.[18] Taken together, the concerted transcriptional activation of PKM2 and associated cancer metabolism genes yields a phenotype referred to as "Warburg effect and beyond."[19]

METABOLIC NETWORK CONTROL — ALLOSTERIC FEEDBACK REGULATION OPENS GLYCOLYTIC FLUX

Metabolic activity of PKM2 is controlled by allosteric regulation and post-translational modifications that include acetylation, oxidation, phosphorylation, hydroxylation and sumoylation. Structure-function relationship reveals how PKM2 related metabolism is embedded into a tightly woven web of feedback control [Figure 2c].

PKM2 structures in complex with serine or small organic molecules revealed the mechanistic link between the serine-biosynthetic pathway and glycolytic flux.[20-22] Inactive PKM2 monomer causes a build-up of glycolytic intermediates and channels the branch point metabolite 3-phosphoglycerate into serine biosynthesis. If PKM2 is switched into its catalytically active tetramer, glycolytic flux is supported as long as pool sizes of upstream metabolites support their activator role.[23-25] A similar feedback mechanism has been observed by the purine biosynthesis intermediate succinylaminoimidazolecarboxamide ribose-5-phosphate (saicar) showing how PKM2 senses and synchronizes supply of distant pathways.[25] In contrast, multiple downstream metabolites like alanine or adenosine triphosphate follow a negative feedback mechanism and deactivate the PKM2 tetramer.[27]

Similarly to metabolite binding, post-translational modification can shift the equilibrium between active tetramer and inactive monomer or dimer forms of PKM2.[22,28,29] Acetylation targets

PKM2 for degradation through chaperone-mediated autophagy and promotes tumor growth.[30] Reactive oxygen species cause inhibition of PKM2 through oxidation of a cysteine residue.[31,32] This inhibition diverts carbon into the pentose phosphate pathway and generates reducing potential to withstand oxidative stress for detoxification of reactive oxygen species. Using the mechanism of cysteine oxidation, PKM2 contributes to chemoresistance of cancer cells. Death-associated protein kinase directly binds, phosphorylates and activates PKM2.[33] EGFR-activated extracellular signal-regulated kinase 2 (ERK2) binds PKM2 and phosphorylates PKM2.[10] While both phosphorylation events up-regulate glycolysis, the mechanism of regulation is different. The interaction with death-associated protein kinase stabilized cytosolically active PKM2 tetramer.[33] In contrast, ERK2 phosphorylation mediated nuclear import of PKM2 dimer. Nuclear PKM2 acted as protein kinase itself to phosphorylate STAT3 using phosphoenolpyruvate as a phosphate donor, transactivating transcription and promoting tumour growth.[10,34] Similarly, metabolically inactive, nuclear PKM2 dimer bound phosphorylated β-catenin, phosphorylates histone and promoted its transcriptional activity; in particular, cyclin D1 expression.[11,12] PHD3 was found to amplify ubiquitin-E3 ligase seven in absentia homolog 2 (SIAH2) and HIF1a signaling through hydroxylation of two proline residues.[16,35] While nuclear localization of PKM2 has been reported in many instances,[9-12,16,28] the mechanism of translocation is much less understood.[36] Peculiarly, PIAS, the protein inhibitor of activated STAT3, is the sumo-E3 ligase targeting PKM2. While other players of the PKM2 specific sumoylation still have to be identified, this reveals yet another regulatory mechanism where PIAS balances nuclear targeting of PKM2, PKM2 mediated STAT3 transactivation and STAT3 inhibition.

Taken together, PKM2 wears different hats: Metabolically active PKM2 tetramer is tightly regulated and responds to nutritional and stress signals. Metabolically inactive PKM2 dimer is imported into the nucleus to function as protein kinase stimulating transcription. Pyruvate kinase, protein kinase and transcriptional coactivator activity of PKM2 are controlled by allosteric regulators, oligomeric state, post-translational modifications and intracellular localization. Given the pleiotropic effects of PKM2 on cancer biology, PKM2 represents an attractive target for basic science discoveries yet poses challenges for cancer therapy.

TOTAL CONTROL — FROM IGNITING GROWTH FACTOR SIGNALING TOWARDS THE WARBURG EFFECT AND BEYOND

Within the biological hierarchy – from *PKM* gene to PKM2 protein tetramer toward glycolytic flux – executed control matches stages in progressing cancer [Figures 1 and 3]. At the initiation stage, *PKM* activation comprises redundancy by

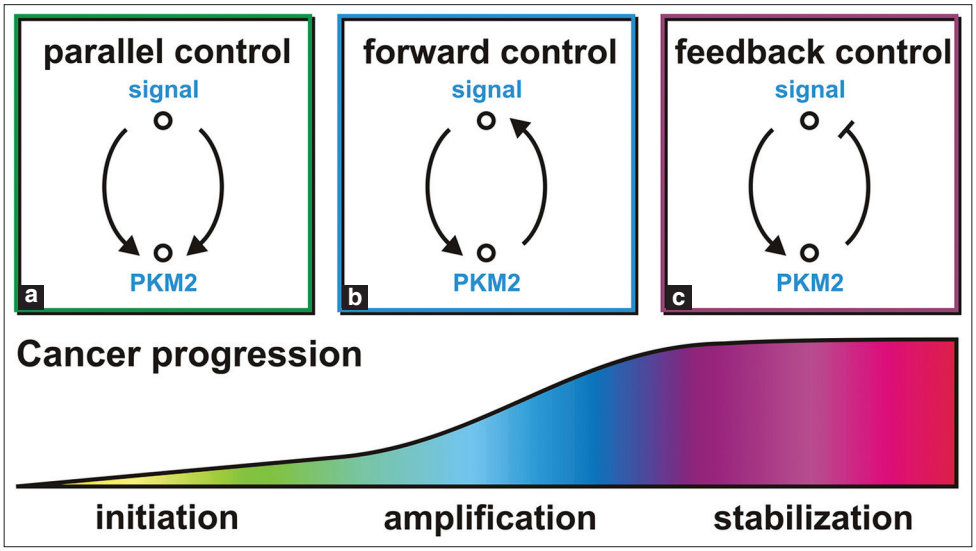

Figure 3: Control mechanisms in cancer progression. Parallel control circuits allow transmission of signals with logical connectives such as conjunction (and), disjunction (or), exclusive disjunction (either or). Forward control (or feed-forward control) is an open control circuit to enhance a signal and reach a threshold value. Feedback control can be used in positive or negative feedback mode to make a system self-regulating. An example for conjunctive parallel control is A and B lead to C. An example for disjunctive parallel control is A or B lead to C. An example for conjunctive forward control is A and B lead to A. An example for negative feedback control A leads to B and B suppresses A. An example for positive feedback control is A leads to B, A and B lead to C, C suppresses A. For system stability closed circuitry as well as feedback control is essential. In cancer biology, signaling pathways respond to mutations or growth factor activation resulting in the commonly known metabolic phenotype called Warburg effect. The progression can be divided into three steps. (a) Initiation of responds of master regulators like PKM2 is achieved by triggering parallel controlled signaling pathways. (b) Amplification of the signal is achieved by feed-forward control. (c) Stabilization of phenotype is achieved by feedback control.

parallel signaling pathways and allows for conjunction (activation of A and B lead to C) or disjunction (activation of A or B lead to C) of responses [Figure 3a]. Corresponding to β-catenin mediated *c-MYC* transcription and an alternative EGFR response through *HIF1a* transcription, both pathways lead to hnRNP-dependent *PKM* expression. At the propagation stage, feed-forward activation amplifies the signal [Figure 3b]. Transcriptional response of PKM2 is governed by signal enhancement (for example A activates B, A and B activate C). This feed-forward theme is commonly observed in cellular differentiation, where irreversible commitments are made. In the context of cancer, the feed-forward themes allow for signal enhancement and rapid responds to extracellular matrix. At the stabilization stage, multiple feedback loops create a robust phenotypic outcome [Figure 3c]. A closed positive feedback circuit includes enhancement and repression elements (for example synthesis of A leads to B, A and B lead to C, C suppresses A). Strikingly, the metabolic master regulator PKM2 engages in positive and negative feedback control. Positive feedback control of PKM2 occurs by allosteric activators fructose-1,6-bisphosphate, serine, or saicar. Activators communicate an abundance of biosynthetic intermediates and open glycolytic flux. Negative feedback control or inhibition of PKM2 activity, occurs by production metabolites atp, acetyl-CoA, or alanine. PKM2 inhibitors indicate sufficient building blocks and cause glycolytic flux to back up until further production metabolites are required. In this picture, exhibited control reflects shifting requirements during different stages of tumor progression. Once PKM2 action is initiated and ramped up, the overall result is strong, perturbation-robust glycolytic flux in cancer cells.

By tracing PKM2 from its source growth factor signal through coactivator and allosteric activator functions, today, we are in a position to interpret the Warburg effect in cancer cells at a molecular level. Multilevel control of pyruvate kinase activity provides proliferating cells with a perturbation-resistant growth phenotype. This has important consequences for future therapeutic directions. The dual roles of metabolic control as active tetramer and transcriptional control as inactive dimer are directed toward tumor metabolic rewiring and favor tumor cell proliferation. Systemic targeting of PKM2 activity is further challenged by the fact that PKM2 expression is not restricted to oncofetal tissue like initially anticipated, but detected in many adult tissues.[37] From a systems perspective, the common theme of feedback loops is an essential tumor growth element and has to be disrupted for successful therapeutic intervention, otherwise the master regulator PKM2 will counter strike. A current opportunity for cancer biology is to merge two approaches, promoter-specific molecular biology and systems network biology, to reveal the molecular events that shape multistage gene expression programs during cancer progression.

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