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MicroRNAs and oncogenic transcriptional regulatory networks controlling metabolic reprogramming in cancers

Pannapa Pinweha [a,1], Khanti Rattanapornsompong [a,1], Varodom Charoensawan [a,b], Sarawut Jitrapakdee [a,*]

[a] Department of Biochemistry, Faculty of Science, Mahidol University, Bangkok 10400, Thailand
[b] Integrative Computational BioScience (ICBS) Center, Mahidol University, Nakhon Pathom 73170, Thailand

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ABSTRACT

Altered cellular metabolism is a fundamental adaptation of cancer during rapid proliferation as a result of growth factor overstimulation. We review different pathways involving metabolic alterations in cancers including aerobic glycolysis, pentose phosphate pathway, *de novo* fatty acid synthesis, and serine and glycine metabolism. Although oncoproteins, c-MYC, HIF1α and p53 are the major drivers of this metabolic reprogramming, post-transcriptional regulation by microRNAs (miR) also plays an important role in finely adjusting the requirement of the key metabolic enzymes underlying this metabolic reprogramming. We also combine the literature data on the miRNAs that potentially regulate 40 metabolic enzymes responsible for metabolic reprogramming in cancers, with additional miRs from computational prediction. Our analyses show that: (1) a metabolic enzyme is frequently regulated by multiple miRs, (2) confidence scores from prediction algorithms might be useful to help narrow down functional miR-mRNA interaction, which might be worth further experimental validation. By combining known and predicted interactions of oncogenic transcription factors (TFs) (c-MYC, HIF1α and p53), sterol regulatory element binding protein 1 (SREBP1), 40 metabolic enzymes, and regulatory miRs we have established one of the first reference maps for miRs and oncogenic TFs that regulate metabolic reprogramming in cancers. The combined network shows that glycolytic enzymes are linked to miRs via p53, c-MYC, HIF1α, whereas the genes in serine, glycine and one carbon metabolism are regulated via the c-MYC, as well as other regulatory organization that cannot be observed by investigating individual miRs, TFs, and target genes.

1. Overall metabolic reprograming in cancers

In response to overstimulation of growth factor signaling, cancer cells reprogram their metabolism in order to accommodate a high demand for macromolecules during rapid proliferation [1–4]. The hallmark of the above metabolic reprograming is the shift from oxidative phosphorylation to aerobic glycolysis, known as the "Warburg effect" [5]. This phenomenon provides some advantages to the tumors because aerobic glycolysis allows them to survive under hypoxic conditions, while an acidic environment selects a highly aggressive population of cancers to survive and metastasize to distal tissues or organs [3,6]. Cancers are also highly anabolic because they require lipids, protein and nucleic acids as constituents of the structural components of the newly divided cells [2]. This highly anabolic phenotype is partly attributed to the Warburg effect because inhibition of pyruvate entering into the mitochondria results in the redirection of glycolytic intermediates to the pentose phosphate pathway (PPP), which provides biosynthetic precursors for nucleotides and lipids [4]. Furthermore, mitochondrial metabolism of cancers is also reprogrammed toward cataplerosis where substantial amounts of tricarboxylic acid (TCA) cycle intermediates are used as the biosynthetic precursors of lipids and amino acids [2]. Therefore, it is not surprising to see up-regulate expression of key enzymes that catalyze the above biosynthetic pathways in several types of cancers. Fig. 1 shows the overall metabolic reprogramming pathways in cancers together with the key regulatory enzymes.

Abbreviations: ACC, acetyl-CoA carboxylase; ACL, ATP-citrate lyase; BRCA1, breast cancer type 1 susceptibility protein; c-MYC, V-myc avian myelocytomatosis viral oncogene homolog; FAS, fatty acid synthase; FH, fumarate hydratase; G6PD, glucose-6-phosphate dehydrogenase; GDH, glutamate dehydrogenase; GLS, glutaminase; GLUT, glucose transporter; HK, hexokinase; 2-HG, 2-hydroxyglutarate; HIF1α, hypoxia inducible factor 1α; IDH, isocitrate dehydrogenase; miR/miRNA, LDH, lactate dehydrogenase micro RNA; p53, tumor protein p53; PEP, phosphoenolpyruvate; MCT, monocarboxylic acid transporter; ME, malic enzyme; PEPCK, phosphoenolpyruvate carboxykinase; PFK, phosphofructokinase; PHGDH, phosphoglycerate dehydrogenase; PGK, phosphoglycerate kinase (PGK); PSAT, phosphoserine aminotransferase; PSPH, phosphoserine phosphatase; PKM, muscle-pyruvate kinase; PDH, pyruvate dehydrogenase; PC, pyruvate carboxylase; PDK, pyruvate dehydrogenase kinase; PPP, pentose phosphate pathway; SDH, succinate dehydrogenase; SHMT, serine hydroxymethyl transferase; SREBP1, sterol regulatory element binding protein 1; TCA, tricarboxylic acid; TFs, transcription factors.

* Corresponding author at: Department of Biochemistry, Faculty of Science, Mahidol University, Rama 6 Rd, Rajathewee, Bangkok 10400, Thailand. Tel.: +66 2 201 5458; fax: +66 2 354 7174.
E-mail address: sarawut.jit@mahidol.ac.th (S. Jitrapakdee).

[1] Equal authorship.

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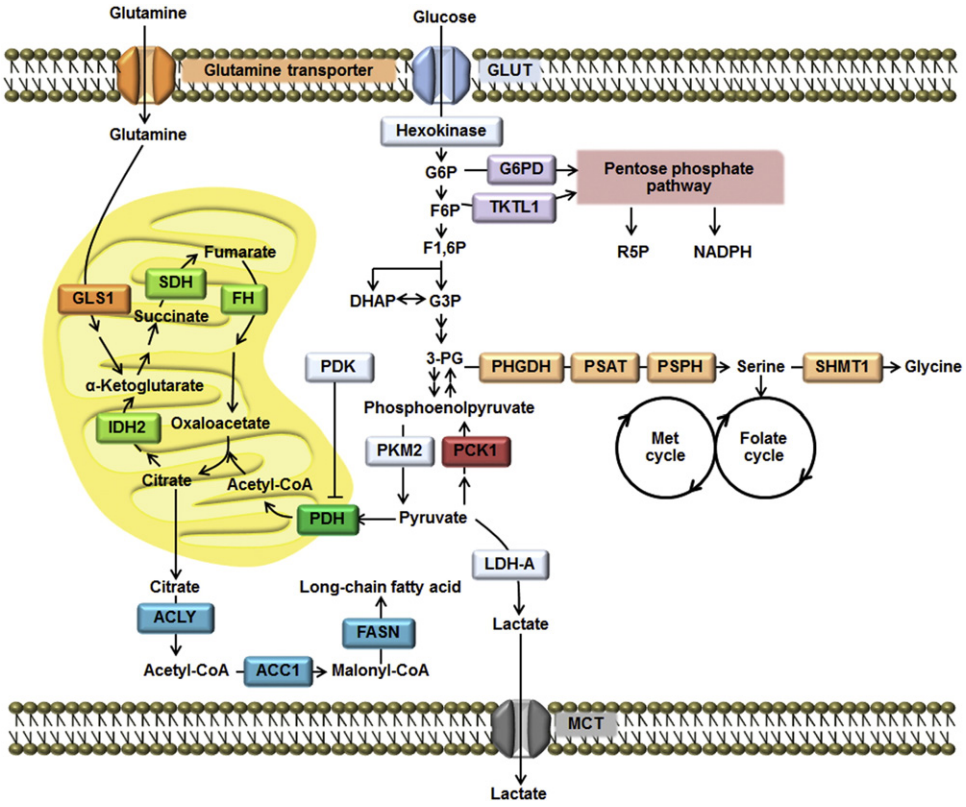

Fig. 1. Metabolic pathways in cancers. Glucose and glutamine are two major carbon sources that are metabolized through these biochemical pathways.

Here we review the altered metabolic pathways and the relevant enzymes in cancers inferred from experimental and computational based data [7–9]. We also review the oncogenic transcription factors (TFs) and miRNAs that regulate those metabolic pathways. In addition, using known and predicted miRNA-target gene interaction, we establish and analyze the network of oncogenic miRNA-metabolic target gene networks that interplay and regulate metabolic reprograming in cancers.

1.1. miRNAs regulate metabolic pathways

Post-transcriptional regulation by microRNAs (miRNAs) has long been known as a mechanism to silence gene expression. miRNAs are short double stranded RNAs, comprising 15–25 nucleotides. They are first transcribed in the nucleus as the primary miRNAs, consisting of multiple stem loop structures, which are then subsequently digested to precursor miRNAs (pre-miRNAs) by Drosha, an RNase III family enzyme [10]. Pre-miRNAs are then transported to the cytoplasm where the hairpin structure is further removed by a dicer enzyme, yielding approximately 21 base pairs miRNA duplex. The miRNA duplex is subsequently incorporated in the Argonaute protein which digests one strand of the duplex miRNA, generating a single stranded miRNA. This single stranded miRNA is further brought to their target mRNAs by an RNA-induced silencing (RISC) complex. Binding of single stranded miRNAs to their targets is mediated by hybridization of 7–8 nucleotides of the miRNAs (known as seed match) to their complementary nucleotides in the 3′-untranslated regions of their targets. Such hybridization results in translational inhibition or degradation of target mRNAs, thus providing a means to inhibit gene expression. Furthermore, one miRNA can bind to more than one species of mRNA targets due to a non-stringent hybridization of the seed match region, allowing simultaneous down-regulation of multiple target mRNAs. In the same way, multiple species of miRNAs can bind to the same mRNA targets and enhance translational inhibition [11]. It is estimated that 45,000 miRNA target sites are found in the human genome, and these miRNAs control expression of up to 60% of human genes [12].

miRNAs are implicated in the regulation of various biological processes. Biochemically, miRNAs also regulate cellular metabolism either directly by targeting key enzymes of metabolic pathways or indirectly by modulating the expression of important transcription factors. Multiple studies have revealed that the altered metabolic pathways in cancers are tightly regulated by miRNAs [13]. In the first half of the review, we describe the metabolic pathways and key enzymes that are altered in various cancers and regulated by miRNAs. This will be followed by the second half on the regulatory networks between metabolic enzymes, regulatory miRNAs and oncogenic transcription factors.

1.2. Glycolytic and pentose phosphate pathways

The Warburg effect is a primary event of metabolic reprogramming during tumorigenesis. This effect includes induced expression of enzymes such as GLUT1, hexokinase 2 (HK2), phosphofructokinase 2 (PFK2) and pyruvate dehydrogenase kinase 1 (PDK1) [3]. Up-regulation of the expression of the first three targets results in a rapid uptake of glucose and increased glycolytic rate, while increased expression of PDK1 inactivates pyruvate dehydrogenase, restricting the conversion of pyruvate to acetyl-CoA in the mitochondria and thus uncoupling glycolysis from subsequent mitochondrial oxidation. Increased expression of lactate dehydrogenase and monocarboxylic acid transporter 4 (MCT4) further sequesters pyruvate toward lactate production, lowering the pH of the extracellular environment [14]. The muscle-specific pyruvate kinase M (PKM) isoform has also been implicated in metabolic reprogramming in certain cancers [15]. PKM exists in two isoforms, PKM1 and PKM2 that have arisen from alternative splicing of exons 9 and 10 [16]. The activities of these two enzymes are determined by their conformers. PKM1 has a tendency to form tetramers that possess high enzymatic activity while PKM2 shows relatively low activity due to its main conformer being dimers. PKM1 is the