Mitochondrial and Metabolic Pathways Regulate Nuclear Gene Expression to Control Differentiation, Stem Cell Function, and Immune Response in Leukemia

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Abstract

Mitochondria are involved in many biological processes including cellular homoeostasis, energy generation, and apoptosis. Moreover, mitochondrial and metabolic pathways are interconnected with gene expression to regulate cellular functions such as cell growth, survival, differentiation, and immune recognition. Metabolites and mitochondrial enzymes regulate chromatin-modifying enzymes, chromatin remodeling, and transcription regulators. Deregulation of mitochondrial pathways and metabolism leads to alterations in gene expression that promote cancer development, progression, and evasion of the immune system. This review highlights how mitochondrial and metabolic pathways function as a central mediator to control gene expression, specifically on stem cell functions, differentiation, and immune response in leukemia.

Significance: Emerging evidence demonstrates that mitochondrial and metabolic pathways influence gene expression to promote tumor development, progression, and immune evasion. These data highlight new areas of cancer biology and potential new therapeutic strategies.

Introduction

Mitochondria are well known for their role in energy production, cofactor synthesis, and apoptosis. However, emerging data indicate that mitochondrial pathways and metabolites also regulate gene expression and thereby control cellular functions such as differentiation and immune recognition. This review will discuss this emerging role for mitochondria and metabolism in controlling gene expression in the nucleus with a focus on stem cell function, differentiation, and immune response in the setting of cancer.

Mitochondrial Structure and Function

Mitochondria originated 2 billion years ago from the engulfment of an α-proteobacterium by a nucleus-containing eukaryotic cell. In keeping with this origin, mitochondria contain an outer and inner mitochondrial membrane separated by an intermembrane space. Mitochondria are the main site of energy production within the cell. Catabolism of carbohydrates, fatty acids, and amino acids produces the metabolite acetyl-CoA, which is transported into the mitochondrial matrix. In the matrix, acetyl-CoA is oxidized in a series of chemical reactions called the tricarboxylic acid (TCA) cycle that produces energy and the redox cofactor NADH. NADH feeds electrons into the mitochondrial respiratory chain, which consists of a series of protein complexes embedded in the inner mitochondrial membrane. These electrons are transferred from respiratory chain complexes I, II, III, and IV to oxygen while generating an electrochemical gradient across the inner mitochondrial membrane. The energy stored in this gradient is used by complex V to produce ATP. This process is termed oxidative phosphorylation.

Cancer cells adapt to their increasing energetic and biosynthetic demands by reprogramming their metabolic pathways. For example, normal hematopoietic stem cells primarily rely on energy produced from anaerobic glycolysis as evidenced by high levels of glycolytic intermediates and pyruvate (1). These normal cells are also metabolically flexible. Inhibiting
one source of energy production, such as fatty acid oxidation, leads to a compensatory increase in glycolysis to meet their metabolic needs. Conversely, leukemic cells and stem cells have greater reliance on oxidative phosphorylation for energy and are limited in their ability to upregulate glycolysis when other metabolic pathways are inhibited (2, 3). As such, leukemic cells are highly sensitive to strategies that target oxidative phosphorylation.

Recent studies show that respiratory chain complexes assemble into large quaternary structures called respiratory chain supercomplexes (RCS), and mitochondrial function is closely linked to RCS formation (4). RCS consist of complexes I, III, and IV in defined stoichiometries. RCS are increased in a subset of patients with acute myeloid leukemia (AML) compared with normal hematopoietic cells. The primary function of RCS is debated, but studies suggest that RCS reduce reactive oxygen species levels, promote electron transfer, and improve the stability of individual complexes. RCS are formed through a complex assembly pathway, but the mechanisms that promote the assembly of RCS are not yet fully understood (5). In breast, endometrial, and pancreatic cancers, overexpression of the RCS stabilizing factor COX7A2L promotes cancer growth and hypoxia tolerance (6, 7). The mitochondrial protease neurolysin (NLN) also regulates the formation of RCS by stabilizing the LETM1 complex. Inhibiting NLN or LETM1 impairs RCS formation, leading to decreased oxidative phosphorylation and death in AML cells and stem cells (8). Thus, targeting RCS formation may be a strategy to target respiratory chain complexes and provide a therapeutic window that is greater than targeting the enzymatic activity of the complexes directly. Already, small-molecule inhibitors of NLN have been developed and used as proof-of-concept tools to demonstrate the potential efficacy of targeting NLN and RCS. In the future, more potent and specific NLN inhibitors could be developed and serve as leads for novel anticancer agents.

Beyond their role in respiration and energy production, mitochondria are the site of several anabolic pathways, such as amino acid, nucleotide, and lipid synthesis. Mitochondria produce glutamine and aspartate, which are important for pyrimidine ring production. Pyrimidine synthesis also relies on the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), which has been identified as a potential therapeutic target in several preclinical cancer models (9–11). DHODH is a metabolic regulator of differentiation in AML and inhibits transcriptional elongation in melanoma (10, 11). Mitochondria also play a key role in lipogenesis. Citrate produced by the mitochondria is exported to the cytosol, where it is converted to acetyl-CoA and then to fatty acids. In addition, mitochondrial lipid remodeling affects downstream signaling pathways. For example, knockdown of the cardiolipin remodeling enzyme tafazzin activates Toll-like receptor (TLR) signaling and reduces AML stemness (12). Thus, targeting mitochondrial pathways not only affects oxidative phosphorylation, but also affects pathways beyond energy production.

The integrity of the mitochondrial network is maintained by several quality-control pathways, such as mitophagy. Leukemia stem cells (LSC) rely on mitophagy to sequester and destroy defective mitochondria, and mitophagy is necessary for their self-renewal (13). Likewise, mitophagy is required to maintain hepatic cancer stem cells (14). In addition to mitophagy, cancer cells rely on a network of mitochondrial chaperones and proteases to remove defective mitochondrial proteins. The mitochondrial protease caseinolytic protease P (CLPP) forms a complex with the AAA ATPase chaperone CLPX (caseinolytic mitochondrial matrix peptidase chaperone subunit X; ref. 15). CLPP degrades defective respiratory chain proteins and proteins important for mitochondrial translation (16, 17). Inhibiting CLPP leads to accumulation of misfolded and damaged respiratory chain proteins that impair oxidative phosphorylation. Genetic and chemical inhibition of CLPP also kills AML cells with high CLPP expression (16). Cancer cells also show increased sensitivity to hyperactivating this protease. Chemical compounds, such as the imidazones ONC201 and ONC212, bind CLPP at its interface with CLPX and lock CLPP in an active conformation (18). When locked into its active conformation, CLPP is hyperactivated and shows increased degradation of respiratory chain complex substrates, resulting in impaired oxidative phosphorylation. ONC201 is currently being studied in phase I and II clinical trials in both solid and hematologic malignancies (NCT03034200, NCT03932643, NCT03099499, NCT03295396, and NCT03394027; ref. 19).

Collectively, these data highlight mitochondrial proteases as novel therapeutic targets for a subset of aggressive malignancies. In addition, these data illustrate that mitochondrial proteases must be tightly regulated in cancer and join a small subset of enzymes where both activation and inhibition of the target are cytotoxic to malignant cells.

Subsets of Malignancies Have Increased Reliance on Mitochondrial Metabolism and Oxidative Phosphorylation

Several cancer subtypes including AML show an increased reliance on mitochondrial metabolism and oxidative phosphorylation with high rates of oxygen consumption, enhanced expression of TCA cycle enzymes, and increased flux of metabolites into the TCA cycle (20–25). In part related to the increased flux of metabolites into the TCA cycle, these malignant cells have reduced spare reserve capacity and an inability to tolerate reductions in respiratory chain complex activity (26). Of note, this increased reliance on oxidative phosphorylation is not correlated with known cytogenetic or molecular mutations, suggesting that this vulnerability is a downstream effect of genetic transformation or related to the cell’s microenvironment (2). In particular, aspartate synthesis is important for tumor growth, and cells with high levels of aspartate are resistant to inhibitors of oxidative phosphorylation (27, 28). In addition to being a hallmark of some cancers at diagnosis, increased reliance on mitochondrial metabolism and oxidative phosphorylation is also a feature of chemoresistance and relapse. For example, at relapse of B-cell acute lymphoblastic leukemia (B-ALL), there is enrichment of genes involved in amino acid metabolism, the TCA cycle, oxidative phosphorylation, mitochondrial translation and transport, and lipid metabolism. Compared with diagnostic samples, these relapsed B-ALL samples show greater sensitivity to strategies that target mitochondrial pathways and oxidative phosphorylation (29).
Contributing to their increased reliance on oxidative phosphorylation, this subset of cancer cells is also metabolically inflexible and does not upregulate glycolysis as a compensatory mechanism in response to blocks in oxidative phosphorylation. For example, PDAC stem cells and AML stem cells have high rates of oxidative phosphorylation, but are metabolically inflexible as they cannot upregulate glycolysis to meet their energetic demands (2, 3, 25). As a result, inhibiting oxidative phosphorylation is cytotoxic to these cells. In contrast, their normal counterparts remain viable after inhibiting oxidative phosphorylation as they have greater reserves in their respiratory chain enzymes and upregulate glycolysis to compensate for the decreased energy production. A recent study by Sharon and colleagues revealed a mechanism for why some malignant cells are metabolically inflexible (30). In response to stresses within their microenvironment including nutrient deprivation and oxidative stress, some malignant cells upregulate the integrated stress response (ISR; ref. 31). Moreover, the ISR is further upregulated upon inhibition of oxidative phosphorylation. Although designed to protect cells from external stressors, overactivation of ISR suppresses cells’ glycolytic capacity and makes these cells metabolically inflexible (30).

The unique mitochondrial and metabolic biology of these cancer cells highlights vulnerabilities for potential therapeutic strategies. For example, inhibiting mitochondrial pathways such as mitochondrial protein translation, mitochondrial DNA replication, mitochondrial protein degradation, or respiratory chain complexes can preferentially kill the subset of malignant cells and stem cells that have high rates of flux of metabolites into the TCA cycle, low spare reserve capacity, and an inability to compensate for inhibition of oxidative phosphorylation by upregulating glycolysis (Fig. 1). Importantly, these therapeutic strategies are not cytotoxic to their normal counterparts, which rely on energy produced from glycolysis and are metabolically flexible (1, 23).

Although most studies on mitochondrial biology and function focus on its role in energy production and metabolism, emerging evidence indicates that mitochondria and metabolism regulate additional cell functions, including nuclear gene expression. These additional roles are particularly relevant in cancer as mitochondrial and metabolic pathways
Mitochondrial Metabolites Regulate Cancer Gene Expression

Mitochondrial pathways can control gene expression, stemness, and differentiation by altering levels of specific metabolites that serve as cofactors/substrates in epigenetic modifications. Changes in the level of metabolites required for processes, including DNA/histone methylation and histone acetylation, contribute to oncogenesis in a number of malignancies (Fig. 2).

Mitochondrial Metabolites Influence Nuclear DNA Expression to Regulate Growth and Differentiation of Malignant Cells

Beyond their role in acting as cofactors for energy production and biomass formation, mitochondrial metabolites control DNA and histone methylation, important epigenetic marks that control nuclear gene transcription. Disregulation of these metabolites alters these epigenetic marks, leading to alterations in gene expression that block differentiation and promote malignancy.

For example, the TCA metabolite alpha-ketoglutarate (α-KG) and the oncometabolite R-2-hydroxyglutarate (R-2-HG) are important regulators of DNA and histone methylation. α-KG and Fe (II) are necessary for the activity of ten–eleven translocation (TET) methylcytosine dioxygenases (32) and JmC-domain–containing histone demethylases (33). α-KG is produced through the oxidative decarboxylation of isocitrate by isocitrate dehydrogenase (IDH). Mutations in IDH1 and IDH2 are unique among the spectrum of cancer mutations and result in loss of the normal catalytic activity of the enzyme and an accumulation of R-2-HG. Of note, the TCA cycle continues to function, and the abnormalities in patients with IDH mutations are not related to impaired energy production. Rather, R-2-HG functions as an oncometabolite and competitively inhibits α-KG–dependent dioxygenases, including TET2. In AML, IDH mutations lead to increased DNA and histone methylation, which result in blocking of myeloid differentiation (34). As such, IDH mutations highlight the intersection of metabolism and epigenetics. Ivosidenib and enasidenib selectively inhibit the mutant IDH1 and IDH2 proteins, respectively, reduce levels of R-2-HG, and restore DNA and histone methylation. As clinical agents, these drugs induce myeloid differentiation, recover trilineage hematopoiesis, and produce objective responses in 40% of patients with these mutations (35, 36). These agents have been approved for use in patients with relapsed/refractory IDH-mutated AML. However, it remains unclear which subset of patients with IDH mutations will respond to this therapy, as suppression of R-2-HG production is not sufficient to predict response. Nonetheless, the success of IDH inhibitors exemplifies the efficacy of targeting specific mitochondrial metabolites in hematologic malignancies.
Mitochondria and Metabolism Regulate Gene Expression

Similar to R-2-HG, fumarate and succinate also act as α-KG antagonists, inhibiting dioxygenases including the JmjC-domain-containing histone demethylases and TET methylcytosine dioxygenases (37). Germline mutations in fumarate hydratase lead to increased cellular fumarate (38) and are associated with cutaneous leiomyomas, uterine leiomyomas, and papillary renal cell cancer (39), whereas somatic mutations are associated with progression of chronic myeloid leukemia (40). Likewise, germline mutations in succinate dehydrogenase lead to increased cellular levels of succinate (38) and are associated with the development of paragangliomas and pheochromocytomas (41, 42). Through their effects on DNA and histone demethylases, increased cellular levels of fumarate and succinate lead to increased H3K4 monomethylation, H3K27 and H3K79 dimethylation, and H3K4 trimethylation (37). Increased H3K79 dimethylation is strongly linked to active gene transcription and has been associated with upregulation of HOXA genes, which leads to expansion of stem cell populations, coupled with a differentiation block (37, 43, 44). Increasing concentrations of succinyl-CoA and succinate through succinate dehydrogenase defects also directly influence gene expression through the posttranslational modification of succinylation. Lysine succinylation occurs in the mitochondria where it affects respiratory chain complex and TCA cycle activity (45). In addition, increased succinate results in hypersuccinylation of histones, leading to increased chromatin openness and gene expression (46) that can promote cancer stem cell function and viability. Thus, increased and dysregulated levels of fumarate and succinate lead to alterations in DNA and histone, which blocks differentiation and promotes cancer progression.

Potentially, dietary or pharmacologic interventions to restore normal levels of fumarate and succinate in patients with germline or somatic defects could be an effective therapeutic approach for treatment of these malignancies and may even be a successful preventative strategy in patients at risk of these hereditary cancers.

**Metabolites Serve as Cofactors for Epigenetic Enzymes**

Metabolites also serve as important cofactors for epigenetic enzymes. For example, the redox cofactor flavin adenine dinucleotide (FAD) is necessary for oxidative phosphorylation in the mitochondria, where it acts as an electron carrier and cofactor for the respiratory chain complex II enzyme succinate dehydrogenase. FAD is also found in the nucleus where it acts as a cofactor for the H3K4/K9 lysine-specific histone demethylase 1A (LSD1) by binding to the C-terminal amino oxidase--like domain of the enzyme (47). By demethylating histones, LSD1 is both a transcriptional repressor and activator. High LSD1 expression is seen in many solid tumors including prostate cancer (48), neuroblastoma (49), non–small cell lung cancer (50), and breast cancer (51). In prostate and breast cancers, LSD1 demethylates the repressive H3K9 to facilitate androgen- and estrogen-dependent transcription (48, 52). In hematologic malignancies, LSD1 is overexpressed in AML, myeloproliferative neoplasms, chronic myelomonocytic leukemia, and myelodysplastic syndromes (53). In MLL-AF9 leukemia, LSD1 promotes the oncogenic gene program by demethylating H3K4 at the promoter sites of oncogenes (54). LSD1 also demethylates H3K4me2 and H3K4me3 on the promoters of CD11b and CD86. Knocking down LSD1 promotes the expression of these differentiation markers and reduces clonogenicity in AML (55). Alterations of the FAD cofactor increase or decrease LSD1 activity. As such, targeting FAD and its binding to LSD1 is an emerging anticancer strategy that has advanced into early-phase clinical trials. For example, transthyretin and related analogues form a covalent bond with FAD in LSD1, which leads to inhibiting LSD1 activity, increasing H3K4me2, and promoting myeloid differentiation in AML (56). A phase I trial of transthyretin with ATRA in patients with relapsed/refractory AML and high-grade myelodysplastic syndrome (MDS) demonstrated that this combination was tolerable with some evidence of clinical activity (57). However, transthyretin likely lacks the potency and specificity to produce significant benefit, and second-generation inhibitors will be required. In that regard, CC-90011 is a more selective LSD1 inhibitor with antitumor activity in solid tumors and relapsed/refractory non-Hodgkin lymphoma (58). In summary, metabolites serve as important cofactors for epigenetic enzymes and may offer therapeutic options. However, it may be challenging to develop drugs that block cofactor binding to epigenetic enzymes without disrupting the metabolic functions of the cofactor.

**Mitochondrial and Metabolic Pathways Regulate the Production of the Methyl Donor SAM**

Mitochondrial pathways and metabolism also directly regulate the production of the methyl donor S-adenosylmethionine (SAM) that is required for DNA and histone methylation. Mitochondrial 10-formyl-THF generates cytosolic one-carbon which flows into the folate and methionine cycle, resulting in the production of SAM from methionine and ATP. SAM donates a methyl group to DNA methyltransferase for DNA methylation, and to lysine and arginine methyltransferases for histone methylation. After SAM donates a methyl group, it forms S-adenosylhomocysteine (SAH), which is converted to homocysteine by SAH hydrolase (SAHH).

The mitochondrial one-carbon pathway is consistently overexpressed in cancer (59), contributing to increased SAM levels and subsequently increased DNA and histone methylation. Conversely, depleting SAM decreases DNA and histone methylation, reduces expression of specific oncogenes, and promotes the differentiation of cancer stem cells. Thus, targeting SAM production is a potential anticancer strategy.

One potential method to target SAM is to restrict methionine intake. In cancer cells, methionine depletion decreases histone methylation at gene promoter sites associated with proliferation and oncogenesis (60, 61). For example, in MLL-rearranged leukemia that is associated with an increased reliance on the histone-modifying enzyme DOT1, disrupting methionine/SAM metabolism by methionine deprivation or by using SAHH inhibitors profoundly decreases H3K79, leading to decreased cell viability and increased apoptosis (62). In breast cancer models, depleting exogenous methionine decreases the viability and proliferation of taxane-resistant breast cancer cells, which have altered rates of methionine-derived carbon uptake and SAM synthesis, compared with taxane-sensitive breast cancer cells (63). Although effective in cell culture models, this approach might not be a successful therapeutic approach in treating patients with cancer due to the lack of specificity of methionine depletion and the systemic toxicity it would produce.
Recently, a novel method to modify SAM levels in AML was discovered. Redistribution of mitochondrial copper by inhibition of the copper chaperone COX17 negatively affects SAHH levels, which reduces SAM levels. This reduction in SAM ultimately decreases DNA methylation in regions associated with differentiation, disrupting LSC function and promoting myeloid differentiation (64).

**Mitochondrial Metabolites Alter Histone Acetylation**

Mitochondrial and metabolic pathways are necessary for histone acetylation. Histone acetylation is performed by histone acetyltransferases that catalyze the transfer of acetyl groups from acetyl-CoA to lysine residues within the N-terminal extensions of core histones. Acetylation of histones neutralizes the charge on histones, decreases histone interaction with DNA, opens chromatin, and increases gene transcription. Thus, cellular levels of acetyl-CoA are an important determinant of the amount of histone acetylation and thus chromatin accessibility and gene transcription.

Acetyl-CoA is produced in the nucleus, cytoplasm, and mitochondria. When produced in the mitochondria, it cannot diffuse across the mitochondrial membrane. Instead, citrate, which is produced from the condensation of acetyl-CoA and oxaloacetate by citrate synthase, is transported out of the mitochondria into the cytoplasm by the mitochondrial tri-carboxylate transporter SLC25A1. Citrate can diffuse freely through the nuclear pore complex where it is converted back to acetyl-CoA by ATP-citrate lyase and can be conjugated to histones. Acetyl-CoA can also be synthesized in the nucleus by the acetyl-CoA synthetase short-chain family member 2 (ACSS2). ACSS2 uses exogenous acetate, as well as recycled acetate produced inside the cell by histone deacetylase (HDAC) reactions, to catalyze the ATP-dependent ligation of acetate and CoA to produce acetyl-CoA. Targeting histone acetylation is a well-described anticancer strategy. HDACs remove acetyl groups from histones, thereby compacting heterochromatin and silencing gene transcription. Overexpression of HDACs is frequent in cancer, resulting in decreased expression of tumor-suppressor genes. HDAC inhibitors restore gene expression and kill malignant cells. HDAC inhibitors, such as vorinostat, produce clinical responses in 30% of patients with refractory cutaneous T-cell lymphoma (65). Likewise, 27% of patients with relapsed/refractory Hodgkin lymphoma respond to another HDAC inhibitor, panobinostat (66).

**Mitochondrial Enzymes Localize to the Nucleus and Regulate Gene Expression through Their Metabolic Functions**

As noted above, mutations in fumarase lead to increased levels of fumarate that compete with α-KG to inhibit TET2, resulting in increased DNA methylation, gene silencing, and blocked differentiation. In addition, fumarase also directly localizes to the nucleus where it affects histone methylation. In the nucleus, the bidirectional enzyme fumarase converts malate to fumarate, leading to increased levels of nuclear fumarate (67) that compete with α-KG to inhibit the lysine-specific demethylase 2A (KDM2A), resulting in stabilization and higher levels of histone H3K36me2. By increasing H3K36me2, nuclear fumarase promotes the expression of ATF2 target genes responsible for cell growth arrest, such as C-JUN and ATF3. In pancreatic cancer cells, fumarase is highly O-GlcNAcylated, which inhibits the expression of downstream targets such as ATF2 genes, leading to the formation of pancreatic cancer (68).

Likewise, mitochondrial enzymes also act in the nucleus to regulate histone acetylation and thereby control gene expression and cell fate. For example, the mitochondrial enzyme complex pyruvate dehydrogenase (PDH) translocates to the nucleus to control histone acetylation, gene expression, and cellular differentiation. PDH is a multiprotein enzyme complex localized in the mitochondrial matrix where it converts pyruvate to acetyl-CoA that feeds into the TCA cycle. Under conditions of mitochondrial stress, including respiratory chain complex inhibitors or depletion of the mitochondrial outer membrane protein MTCH2, the mature PDH complex translocates from the mitochondria to the nucleus (69, 70). Of note, the mechanisms by which full-length functional mitochondrial proteins exit the mitochondria and translocate to the nucleus have not been fully elucidated. However, in the case of PDH, its nuclear translocation is dependent on the heat shock protein HSP70 (69). In the nucleus, PDH catalyzes the conversion of pyruvate to acetyl-CoA. As such, nuclear PDH bypasses the canonical route of acetyl-CoA production in the cytoplasm to produce local levels of the metabolite. The increased acetyl-CoA in the nucleus leads to greater histone acetylation, which in turn results in more open chromatin and increased gene expression. In the context of AML, increased nuclear PDH, in response to knockdown of MTCH2, increases nuclear acetyl-coA and subsequently H3K27 acetylation at enhancer/promoter regions of genes associated with myeloid differentiation (70). As a result, mitochondrial stressors that increase nuclear PDH induce changes in gene expression, which promote AML differentiation and loss of stem cell function. Thus, the anticancer effects of some mitochondrial stressors may result from these nuclear effects.
### Table 1. Mitochondrial and metabolic enzymes moonlighting in the nucleus

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<th>Enzyme</th>
<th>Mitochondrial/metabolic function</th>
<th>Nuclear function</th>
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| **ACSS2**                       | Catalyzes acetate to acetyl-CoA                                       | • Forms a complex with TFEB and induces the expression of TFB-regulated lysosomal and autophagy genes by locally producing acetyl-CoA for histone H3 acetylation in the promoter regions of these genes  
• Provides acetyl-CoA for CBP-mediated HIF2α acetylation |
| **ATP-citrate lyase (ACYL)**    | Converts citrate to oxaloacetate and acetyl-CoA                       | By producing acetyl-CoA, increases histone acetylation and gene expression        |
| **α-KG dehydrogenase (α-KGDH)** | Catalyzes the conversion of α-KG to succinyl-CoA                      | Forms a complex with KAT2A to succinylate histone H3 to regulate gene expression  |
| **AMPK**                        | Cellular energy sensor. Upon changes in ATP-to-AMP ratio, it is activated and restores energy homeostasis by increasing catabolic pathways and decreasing anabolism | • Regulates nuclear gene expression by phosphorylating EZH2, leading to decreased histone H3 methylation  
• Controls DNA demethylation by phosphorylating and destabilizing TET2 |
| **Carnitine acetyltransferase (CRAT)** | Generates acetyl-CoA                                              | Produces acetyl-CoA to increase histone acetylation and transcriptional regulation |
| **Enolase (ENO1)**              | Converts 2-phosphoglycerate to PEP                                    | Alternative splicing product of ENO1, MBP1, binds to C-MYC promoter and represses the expression of the gene |
| **Fumarase**                    | Catalyzes fumarate to malate                                          | Locally produced fumarate inhibits the demethylase KDM2A and increases H3 methylation, thereby promoting the expression of ATF2 target genes |
| **6-Phosphofructose-2-kinase/ fructose-2,6-bisphosphatase (PFKFB3 and PFKFB4)** | Converts fructose 6-phosphate to fructose 2,6-bisphosphate (F2,6BP) | • PFKB3: Promotes cell-cycle progression by increasing the expression of cell-cycle regulators CDK1, CDC25C, and cyclin D3 and inhibiting cell-cycle inhibitor p27  
• PFKFB4: Phosphorylates SRC3 and stabilizes its binding to ATF4 at target gene promoters to regulate their expression |
| **Fructose 1, 6 bisphosphatase 1 (FBP1)** | Catalyzes hydrolysis of fructose-1,6-bisphosphate to fructose-6-phosphate | Interacts with HIF to inhibit its transcriptional activity, leading to decreased expression of glycolysis genes, angiogenesis, and cell proliferation |
| **GAPDH**                       | Converts glyceraldehyde 3-phosphate to 1,3-bisphosphoglycerate        | Recruited to the H2B promoter in S-phase where it binds OCT1 and NPAR, a substrate of G1–S-specific cyclin E–CDK2 complex, to regulate histone H2B expression |
| **Guanosine 5-monophosphate synthase (GMPS)** | Catalyzes the amination of xanthosine monophosphate (XMP) to GMP | Interacts with nuclear ubiquitin–specific processing protease 7 (USP7). The GMPS–USP7 complex acts as a transcriptional corepressor to deubiquitylate p53 and histone H2B |
| **Inosine 5′-monophosphate dehydrogenase (IMPDH)** | Catalyzes the first rate-limiting step in de novo guanine nucleotide biosynthesis pathway, the NAD⁺-dependent oxidation of IMP to XMP | Functions as a transcription factor and represses the expression of histone genes and E2F genes |
| **Lactate dehydrogenase (LDH)** | Converts lactate to pyruvate                                            | • Interacts with SIRT1 and increases its activity by locally producing NAD⁺, and subsequently controls histone deacetylation and gene expression  
• Produces α-hydroxybutyrate and induces DOT1L-mediated histone H3K79 hypermethylation, and activates antioxidant genes and WNT target genes |
| **Methionine adenosyl transferase (MATII)** | Produces SAM from methionine                                         | Recruited to the MAFK recognition element at HO1 and represses its expression by increasing histone methylation and interacting with chromatin corepressor complexes |

(continued)
required. However, we anticipate that a role for mitochondrial enzymes regulating gene expression unrelated to their usual enzymatic function will become more established in the next few years. Although data continue to emerge, one early reported example is the glycolytic enzyme pyruvate kinase isoform 2 (PKM2) that normally functions in the cytoplasm to convert phosphoenolpyruvate (PEP) to pyruvate by transferring a phosphate from PEP to ADP at the final step of the glycolytic pathway. Although it is normally located in the cytoplasm, some reports indicate that PKM2 translocates to the nucleus in response to growth factors, hypoxia, and the cytoplasm, some reports indicate that PKM2 translocates to the nucleus in response to growth factors, hypoxia, and mitogenic, oncogenic, and lipopolysaccharide stimulation (71–73). Of note, although mechanisms that facilitate its translocation still need to be fully defined, its nuclear import is mediated by importin α5, a member of the importin family that shuttles proteins into the nucleus. Nuclear PKM2 binds and phosphorylates histone H3, which facilitates the dissociation of HDAC3 from cyclin D and C-MYC gene promoters, leading to H3K9ac and activation of these genes, promoting tumorigenesis (74). PKM2 also phosphorylates STAT3 directly at the Y405 residue independent of JAK2 and c-SRC pathways and promotes the transcriptional activation of MEK5, leading to gene transcription (72). These studies suggest that PKM2 can function as a protein kinase. However, it is important to note that other studies challenge this concept by using recombinant PKM2 and in vitro systems with PKM2 knockout cells (75). The authors were not able to detect any PKM2-catalyzed phosphorylation event in vitro using either radiolabeled PEP or ATP as a phosphate donor. Rather, all PKM2-dependent phototransfer events detected were due to the regeneration of ATP from ADP and PEP, the known glycolytic function of PKM2. This study argues against a role for PKM2 as a protein kinase. The discrepancy of these studies is currently unresolved. However, the ATP generated by PKM2 through its canonical pyruvate kinase activity can be subsequently used by other kinases. This may provide an explanation for the reported PKM2 protein kinase activity. Thus, the function of PKM2 as a protein kinase remains controversial and requires further investigations.

Likewise, AMP-activated protein kinase (AMPK) phosphorylates epigenetic modifiers to regulate gene expression. AMPK is a heterotrimeric serine/threonine metabolic checkpoint kinase and acts as a major cellular energy sensor and modulator of metabolic pathways. Upon changes in energy availability, AMPK is activated by an allosteric mechanism that stimulates its kinase activity. Once activated, AMPK restores cellular energy balance by inhibiting anabolic processes such as mTORC1-dependent protein synthesis, gluconeogenesis, and lipid biosynthesis, while switching on catabolic processes including glucose uptake and glycolysis, amino acid oxidation, fatty acid oxidation, glycolgen catabolism, and mitochondrial biogenesis (76, 77). The increased catabolic processes by AMPK increase the TCA cycle intermediates such as α-KG by regulating IDH2. AMPK is located in both the cytoplasm and nucleus, and the nucleocytoplasmic shuttling depends on cellular and signaling contexts. For example, in response to oxidative stress, energy depletion, or heat shock, AMPK accumulates in the nucleus (78). Nuclear AMPK regulates gene expression by phosphorylating EZH2, leading to decreased histone H3 methylation (79). It also controls DNA demethylation by phosphorylating and destabilizing TET2 (80). As such, it regulates TET2 activity both through direct phosphorylation of the target and through increasing/decreasing levels of α-KG.

The glycolytic metabolic enzyme GAPDH, which converts glyceraldehyde 3-phosphate to 1,3-bisphosphoglycerate, can also be found in the nucleus. This “housekeeping” protein is involved in several biological processes beyond glycolysis, such as microtubule assembly, nuclear RNA export, DNA repair, and regulation of gene expression. In the nucleus, GAPDH functions as a transcriptional coactivator to enhance cell-cycle progression by coupling histone gene expression to DNA replication. In S-phase, GAPDH is selectively recruited to the H2B promoter where it binds OCT1 and NPAT, a substate of the G1–S-specific cyclin E–CDK2 complex, to activate the transcription machinery to regulate histone H2B expression. Interestingly, the interaction of OCT1 and GAPDH is regulated by levels of NADH, highlighting a potential link between the cellular redox state and histone expression. Upregulation of GAPDH-associated cell-cycle genes is correlated to advanced stage and poor prognosis of patients with non–small cell lung cancer (81).

**Mitochondrial Enzymes Act as Scaffolds in the Nucleus to Regulate Gene Expression Independent of Their Enzymatic Functions**

By acting as scaffolds, mitochondrial and metabolic enzymes also regulate gene expression through mechanisms...
unrelated to their enzymatic functions. For example, as noted above, PKM2 localizes to the nucleus where it may control gene expression through its controversial kinase function. However, emerging data demonstrate that PKM2 also has nuclear functions distinct from its reported kinase activity. Specifically, PKM2 binds transcription factors including hypoxia-inducible factor 1α (HIF1α) to increase its transcriptional activity and promote the expression of HIF-target genes including GLUT1, LDHA, and PDK1 (82). In particular, PKM2 binds to the HIF1 transactivation domain through its alternatively spliced domain when it is prolyl hydroxylated by PHD3 on Pro-403 and Pro-408 residues. This binding enhances the recruitment of p300 acetyltransferase to the hypoxia response elements of HIF target genes and promotes H3K9 acetylation, leading to increased expression of the genes. PKM2 thus acts as a HIF coactivator. PKM2 also binds OCT4 through its C-terminal domain, a key transcription factor involved in maintenance of the pluripotent state of embryonic stem cells, to regulate its transcriptional activity (83). In glioma spheroids, the interaction of PKM2 with OCT4 inhibits the expression of OCT4-dependent genes and promotes the differentiation of glioma cells (84). As such, PKM2 maintains stem cell function through effects in the nucleus that are not associated with and distant from its primary role as a glycolytic enzyme.

Finally, isoforms of metabolic enzymes localize to the nucleus and regulate gene expression through mechanisms unrelated to their enzymatic and metabolic function. For example, the metabolic enzyme enolase catalyzes the conversion of 2-phosphoglycerate to PEP in the glycolytic pathway. A truncated form of α-enolase (ENO1) is present in the nucleus. This short isoform [also termed C-MYC promoter-binding protein 1 (MBP1)] lacks the first 96 amino acid residues and enzymatic activity of ENO1 (85). This protein binds to the major C-MYC promoter, P2, and prevents the formation of a transcription initiation complex, thereby functioning as a transcriptional repressor to inhibit MYC expression (86). The decreased expression of MBP1 is commonly detected in invasive ductal breast carcinoma with a concomitant increase in C-MYC activity, supporting the tumor-suppressor role of MBP1 (87). The expression of MBP1 is also inversely correlated with ERBB2 and Ki-67 expression and tumor grade. Thus, the loss of MBP1 expression can be a predictor of local recurrence of breast cancer, as it reduced the recurrence-free survival of patients from 92% to 54%.

**ROLE OF MITOCHONDRIA IN IMMUNOCETY OF CANCER CELLS**

Mitochondrial and metabolic pathways drive oxidative phosphorylation and energy production. However, emerging data demonstrate an additional role for these pathways in regulating gene expression that influences the immunogenicity of cancer cells and their susceptibility to detection and killing by immune cells.

**Mitochondrial Pathways Trigger Viral Mimicry Response**

Hypomethylating agents such as azacitidine and decitabine are nucleoside analogues that inhibit the activity of DNA methyltransferases, leading to global hypomethylation. Initially, it was thought that the anticancer effects of these drugs were due to this global decrease in DNA methylation and increased expression of tumor suppressors. However, more recent data indicate that these drugs also act by enhancing the responsiveness of cancer cells to immune-mediated killing through mechanisms related to the mitochondria. In fact, the immune-mediated mechanism of these drugs may be their primary mechanism of action. In studies originally conducted in colon and ovarian cancer cells, hypomethylating agents, such as azacitidine and decitabine, demethylated endogenous retroviral (ERV) genes, and DNA sequences of viral origin integrated into the human genome (88, 89). As a result, azacitidine and decitabine increase expression of double-stranded (ds) ERV transcripts in malignant cells. dsRNA are formed during viral replication and are recognized by the host innate immune system through pattern recognition receptors such as RIG-1 and MDA5. MDA5 and RIG-I complexed with dsRNA interact with a downstream molecule, mitochondria antiviral signaling protein (MAVS; Fig. 3). MAVS is an adaptor protein located on the outer membrane of mitochondria that drives the immune response against RNA virus infection. MAVS is comprised of three functional domains, a caspase activation and recruitment domain (CARD) at the N-terminus, a proline-rich domain, and a membrane-targeting transmembrane domain at the C-terminus. RIG-I/MDA5 complexes with dsRNA interacts with MAVS through the CARD domain. This interaction results in the formation of aggregates on the surface of mitochondria that recruit the downstream effectors TRAF2, TRAF3, TRAF5, and TRAF6 to form a signaling supercomplex termed “MAVS signalosome.” Recruited TRAFs then phosphorylate the transcription factors IRF3, IRF7, and NFκB. Phosphorylated IRF3 and IRF7 upregulate type I/III IFNs, and phosphorylated NFκB induces expression of genes involved in inflammation including cytokines, chemokines, adhesion molecules, and survival factors. Type I IFNs include IFNα and IFNβ, and type III IFNs include IFNαs. Both type I and III IFNs signal through the JAK–STAT pathway and induce expression of IFN-stimulated genes (ISG) which can suppress cancer cell division and modulate the immunogenicity of cancer cells. As a result, azacitidine- or decitabine-treated cancer cells showed increased expression of type I/III IFNs and ISGs in a MAVS-dependent manner. Although initially reported in ovarian and colon cancer cells, recent reports also indicate that evasion of viral mimicry response allows growth of taxane-resistant breast cancer (63) and that the effects of hypomethylating agents on cancer cell immunogenicity may also extend to hematologic malignancies such as AML and MDS where these drugs are frequently used (90, 91).

Cytosolic DNA is another stimulant that can trigger a viral mimicry response in malignant cells. Oxidative stress and mitochondrial dysfunction in cancer cells result in aberrant accumulation of mitochondrial DNA in the cytoplasm. Like dsRNA, cells recognize cytosolic dsDNA as a danger-associated molecule through a cytosolic DNA sensor, cyclic GMP–AMP synthase (cGAS), that interacts with cytosolic dsDNA regardless of its sequence (Fig. 3). This interaction promotes a conformational change of cGAS, and the active form of cGAS converts ATP and GTP into 2’, 3’-cyclic GMP–AMP (cGAMP).
Subsequently, cGAMP activates an adaptor protein, stimulator of interferon genes (STING), localized at the endoplasmic reticulum. Activated STING oligomerizes and translocates to the Golgi where it recruits a downstream kinase, TBK1. TBK1 phosphorylates STING to recruit and activate a transcription factor, IRF3. As described above, activated IRF3, which activates the ISGs, can render cancer cells more immunogenic.

The importance of the cGAS–STING pathway in cancer immunity has been demonstrated in prostate cancer and melanoma models, where increased cytosolic DNA levels enhance T cell or natural killer (NK) cell–mediated clearance of the disease in a STING-dependent manner (92, 93). Also, Curran and colleagues showed that treating mice bearing systemic AML with STING agonists improved survival of the mice in a T cell–dependent manner (94). Notably, ongoing clinical trials investigating the effect of the STING agonists ADU-S100 and MK-1454 in combination with PD-1/PD-L1 blockade show preliminary but encouraging outcomes in patients with solid tumors and lymphomas (95, 96). However, it should be noted that in the context of triple-negative breast cancer, activation of the DTX3L–LIPG–ISG15 signaling axis promotes the growth and viability of breast cancer cells and cancer stem cells (97). Given this report, further studies are necessary to determine which tumors respond positively and negatively to ISG stimulation, as these findings will influence the clinical development of STING agonists as anticancer agents.

**Mitochondrial and Metabolic Pathways Regulate Immunogenicity by Affecting Cancer Cell Differentiation**

Through their effects on controlling the fate, stemness, and differentiation of cancer cells, mitochondrial and metabolic pathways also regulate the recognition of malignant cells by the immune system. Cancer stem cells, including LSCs, are often responsible for disease relapse and are less immunogenic than bulk leukemic cells. Cancer stem cells show higher expression of immune checkpoint molecules such as TIM3, with lower expression of MHC class I and II (98–101). MHC class I and II form a complex with antigenic peptides including cancer-associated antigens and present to CD8+ T cells and CD4+ T cells, respectively, which is critical for initiating a T cell–mediated anticancer immune response. Downregulation of MHC molecules is a common mechanism employed by different cancer types to evade antitumoral immunity. Therefore, inherently lower expression of MHC molecules makes cancer stem cells less susceptible to T cell–mediated killing. Also, higher expression of coinhibitory molecules, such as TIM3, protects cancer stem cells from immune cells (102). Recently, Paczulla and Egan et al. 

![Diagram of the cGAS–STING pathway](image-url)
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the conversion of isocitrate to also influence immune recognition through a similar path-
tion of LSCs may result in loss of TIM3. Collectively, these
by TIM3 reported (108), and leukemia initiation selectively mediated
expression of AML differentiation (12). Notably, TLR4 induces expres-
mediators, IL6 and IFN
expression of TLR4 and TLR8 and their downstream cytokine
Mechanistically, the alterations in phospholipids increased
ence differentiation. For example, decreasing the generation
bolic pathways control the expression of genes that influ-
expression of nutrient transporters, such as GLUT1
increased expression of nutrient transporters, such as GLUT1
trast, activated T cells are more dependent on glycolysis with
on oxidative phosphorylation as their energy source. In con-
ontocytotoxic lym-
phocytes including NK cells, CD8+ T cells, and γδ-T cells (103). Blocking the NKG2D pathway reduces immune-mediated cytotoxicity against leukemic cells (104–106). As such, absence of NKG2DL expression contributes to resistance of LSCs to NK cell– and other immune cell–mediated lysis. Collectively, these inherent characteristics of cancer stem cells contribute to their resistance to immune surveillance.

One of the frequently reported features of cancer cell differ-
etiation is the upregulation of immune response pathways
that makes these cells more responsive to immune-mediated
killing. Recent work discovered that mitochondrial and meta-
abolic pathways control the expression of genes that influence
derdifferentiation. For example, decreasing the generation
of the mitochondrial phospholipid cardiolipin or increasing
this phospholipid and cytoplasmic phospholipid phospho-
phatidylserine induced the differentiation of AML cells (12).
Mechanistically, the alterations in phospholipids increased
expression of TLR4 and TLR8 and their downstream cytokine
mediators, IL6 and IFNβ. TLR signaling is a known regulator of
AML differentiation (12). Notably, TLR4 induces expres-
sion of NKG2D ligands (107). Also, induced expression of
MHC class I by differentiation of cancer stem cells has been
reported (108), and leukemia initiation selectively mediated
by TIM3+ AML cells (109) suggests that induced differentia-
tion of LSCs may result in loss of TIM3. Collectively, these
studies suggest a connection between cancer stem cell differ-
etiation and immunogenicity.

It is noteworthy that mutations in metabolic enzymes may
also influence immune recognition through a similar path-
way. As noted above, the metabolic enzyme IDH2 catalyzes
the conversion of isocitrate to α-KG in the TCA cycle. Mutations
in IDH2 are associated with AML and glioblastoma (34, 110).
Mutations in the catalytic site of IDH2 result in the formation of a neomorphic enzyme that converts α-KG to the oncometabolite R-2-HG. Accumulation of R-2-HG suppresses the activity of α-KG–dependent dioxygenases, many of which
are demethylating enzymes. Hypermethylation of NKG2DLS is a mechanism employed by glioma stem/progenitor cells bearing IDH2 mutations, rendering them more resistant to
NK cell– and possibly other immune cell–mediated cytotoxic-
ity (110). Interestingly, wild-type glioma cells treated with
2-HG became resistant to NK cells (110). These results sug-
gest an additional immune-mediated role for the effects of
IDH2 mutations in malignancies. Enasidenib, which inhibits
mutant IDH2 and reverses the differentiation block by reduc-
ing R-2-HG accumulation in IDH2-mutant AML, may render
cells more susceptible to immune cell–mediated clearance via
upregulation of NKG2DL.

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Mitochondrial and Metabolic Pathways Affect Immune Cell Activity

Mitochondrial and metabolic pathways also influence
the anticancer activity of immune cells, and targeting these pathways
can enhance the anticancer activity of immune cells.
For example, naïve and memory T cells preferentially rely
on oxidative phosphorylation as their energy source. In con-
trast, activated T cells are more dependent on glycolysis with
increased expression of nutrient transporters, such as GLUT1
(Fig. 3). Inhibiting glycolysis in T cells with 2-deoxy-D-glucose
(glucose analogue) skews T cells toward a memory response
(111). In contrast, as T cells are metabolically flexible, inhibit-
ing oxidative phosphorylation shifts T cells to a more effec-
tor phenotype (112, 113). Likewise, itaconate is a metabolite
produced in activated macrophages by diverting aconitate
away from the TCA cycle. In peritoneal tumors, increased
itaconate skewed macrophages toward an anti-inflammatory
M2 phenotype and promoted tumor growth. Conversely,
inhibiting itaconate production reduced tumor burden (114).
These results also highlight how the flux and competition for
metabolites influence antitumor immunity. Recently, Bian
and colleagues showed that tumor cells outcompete T cells
for methionine by overexpressing the methionine receptor
SLC43A2 (115). Lower intracellular level methionine in T
cells altered their epigenetic profile, in particular demeth-
ylation of H3K79me2, which resulted in impaired T-cell
function. Finally, metabolites in the microenvironment can
also influence immune cell function. For example, lactic acid
generated by tumor cells results in the acidification of the
cancer microenvironment. The acidic environment impairs
the activation and anticancer activity of T and NK cells by
reducing levels of NFAT (116).

Thus, targeting mitochondrial and metabolic pathways by
anticancer agents can prime cancer cells for killing by increas-
ing their recognition by immune cells. Given the increasing
importance of immunotherapies in the treatment of hema-
tologic malignancies and solid tumors, understanding how
mitochondrial and metabolic pathways influence immune
response will be an important field of study.

SUMMARY

Emerging evidence indicates that mitochondrial and meta-
abolic pathways have functions beyond biomass and energy
production. Mitochondrial and metabolic pathways regulate
nuclear gene expression to control differentiation, stem cell
function, and immune response. A subset of cancer cells, such
as AML, have increased reliance on mitochondrial pathways
and a heightened sensitivity to inhibiting these pathways
(23, 24). Inhibiting mitochondrial pathways kills malignant
cells through multiple mechanisms. A subset of cancer cells
are metabolically inflexible with decreased reserve in their
respiratory chains (26). As such, inhibiting mitochondrial
and metabolic pathways in these cells deprives them of criti-
cal energy supply. Moreover, mitochondrial and metabolic
pathways alter metabolites that influence epigenetic marks
to control gene expression. Aberrancy in these pathways leads
to alterations in histone and DNA methylation and histone
acetylation, which promote tumor development and pro-
gression (34). Inhibiting abnormal mitochondrial pathways
can reverse these changes, restore normal gene expression,
and promote the differentiation of malignant cells. Finally,
dysregulated metabolic pathways help tumor cells evade
immune detection. Targeting mitochondrial and metabolic
pathways increases the immunogenicity of the tumor cells
(88) and the effector activity of T cells (112). Thus, mitochon-
drial and metabolic pathways have wide-ranging impact on
cancer cell growth and differentiation, and these pathways
remain important areas for new investigation.
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Authors’ Disclosures

J.B. Lee reports a patent for US62/971,534 pending. L. Zhang reports grants from Canadian Cancer Society and grants from Canadian Institutes of Health Research during the conduct of the study; grants and personal fees from WYZE Biotech Co. Ltd. outside the submitted work; WYZE Biotech Co. Ltd licensed the Chinese rights for one of the patents for which L. Zhang is named as one of the co-inventors; and L. Zhang owns stock in AbbVie Pharmaceuticals. A.D. Schimmer reports personal fees from Takeda Pharmaceuticals and stock ownership in AbbVie during the conduct of the study; personal fees from Novartis, personal fees from Jazz Pharmaceuticals, personal fees from Medivir AB outside the submitted work; in addition, A.D. Schimmer has a patent for DNT for ship in AbbVie during the conduct of the study; personal fees from Takeda Pharmaceuticals and stock ownership in AbbVie during the conduct of the study; personal fees from Novartis, personal fees from Jazz Pharmaceuticals, personal fees from Medivir AB outside the submitted work; in addition, A.D. Schimmer has a patent for DNT for

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Mitochondria and Metabolism Regulate Gene Expression


Mitochondrial and Metabolic Pathways Regulate Nuclear Gene Expression to Control Differentiation, Stem Cell Function, and Immune Response in Leukemia

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