Molecules and Cells

Minireview

The Role of Pyruvate Metabolism in Mitochondrial Quality Control and Inflammation

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Pyruvate metabolism, a key pathway in glycolysis and oxidative phosphorylation, is crucial for energy homeostasis and mitochondrial quality control (MQC), including fusion/fission dynamics and mitophagy. Alterations in pyruvate flux and MQC are associated with reactive oxygen species accumulation and Ca^{2+} flux into the mitochondria, which can induce mitochondrial ultrastructural changes, mitochondrial dysfunction and metabolic dysregulation. Perturbations in MQC are emerging as a central mechanism for the pathogenesis of various metabolic diseases, such as neurodegenerative diseases, diabetes and insulin resistance-related diseases. Mitochondrial Ca^{2+} regulates the pyruvate dehydrogenase complex (PDC), which is central to pyruvate metabolism, by promoting its dephosphorylation. Increase of pyruvate dehydrogenase kinase (PDK) is associated with perturbation of mitochondria-associated membranes (MAMs) function and Ca^{2+} flux. Pyruvate metabolism also plays an important role in immune cell activation and function, dysregulation of which also leads to insulin resistance and inflammatory disease. Pyruvate metabolism affects macrophage polarization, mitochondrial dynamics and MAM formation, which are critical in determining macrophage function and immune response. MAMs and MQCs have also been intensively studied in macrophage and T cell immunity. Metabolic reprogramming connected with pyruvate metabolism, mitochondrial dynamics and MAM formation are important to macrophages polarization (M1/M2) and function. T cell differentiation is also directly linked to pyruvate metabolism, with inhibition of pyruvate oxidation by PDKs promoting proinflammatory T cell polarization. This article provides a brief review on the emerging role of pyruvate metabolism in MQC and MAM function, and how dysfunction in these processes leads to metabolic and inflammatory diseases.

Keywords: macrophage, mitochondria-associated membranes, mitochondria quality control, pyruvate dehydrogenase complex, pyruvate dehydrogenase kinase, T cell

INTRODUCTION

Mitochondria are the primary sites of energy production in cells. Pyruvate metabolism is a key function of mitochondria (Spinelli and Haigis, 2018): under physiological conditions, cells oxidize pyruvate, the end-product of glycolysis, to form acetyl-CoA within the mitochondria; acetyl-CoA then efficiently produces adenosine triphosphate (ATP) through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. Under anaerobic conditions, pyruvate can be reduced to lac-

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tate by anaerobic glycolysis; however, in certain circumstances, cells redirect pyruvate from oxidation to reduction to meet metabolic demands, despite aerobic conditions (Martínez-Reyes and Chandel, 2020). These metabolic adaptations are called the Warburg effect, or aerobic glycolysis; during this process, mitochondria coordinate and execute the changes in metabolic processes to maintain energy homeostasis (Palikaras et al., 2018). During this process, mitochondria undergo morphological transformation, characterized by fusion/fission cycles and inter-organelle crosstalk (Cho et al., 2019; 2020; Giacomello et al., 2020; Picca et al., 2018; Srinivasan et al., 2017; Yu and Pekkurnaz, 2018).

Recent evidence suggests that pyruvate dehydrogenase complex (PDC) flux and pyruvate dehydrogenase kinase (PDK) are strongly associated with mitochondria-associated membrane (MAM) function, Ca^{2+} flux, mitochondrial quality control (MQC) and several metabolic disorders (Thoudam et al., 2019).

In this review, we summarize current understanding of the molecular signaling pathways that require mitochondrial adaptation and the metabolic reprogramming that occurs to meet metabolic demands. First, we describe how critical PDC flux and mitochondrial respiration are in response to pathological conditions. Second, we discuss the association between pyruvate metabolism and mitochondrial inter-organelle communication and how mitochondrial morphological adaptations are relevant to cell health and disease. Lastly, we examine how dysfunction of mitochondrial PDC flux leads to inflammation in macrophages and T cells.

THE ROLE OF PYRUVATE METABOLISM IN METABOLIC FLUX AND ANAPLEROSIS

The PDC consists of multiple copies of three catalytic enzymes (E1, E2, and E3) that function sequentially to oxidatively decarboxylate pyruvate at the expense of NAD^+ and CoA, which results in the formation of acetyl-CoA, NADH, and CO_2. The activity of the PDC is regulated by four protein kinases (PDK1, 2, 3, and 4) that inactivate E1, the rate-limiting enzyme of the complex, and two protein phosphatases (pyruvate dehydrogenase phosphatases; PDP1 and PDP2) that stimulate activity of E1 (Patel et al., 2014). Therefore, the overall catalytic

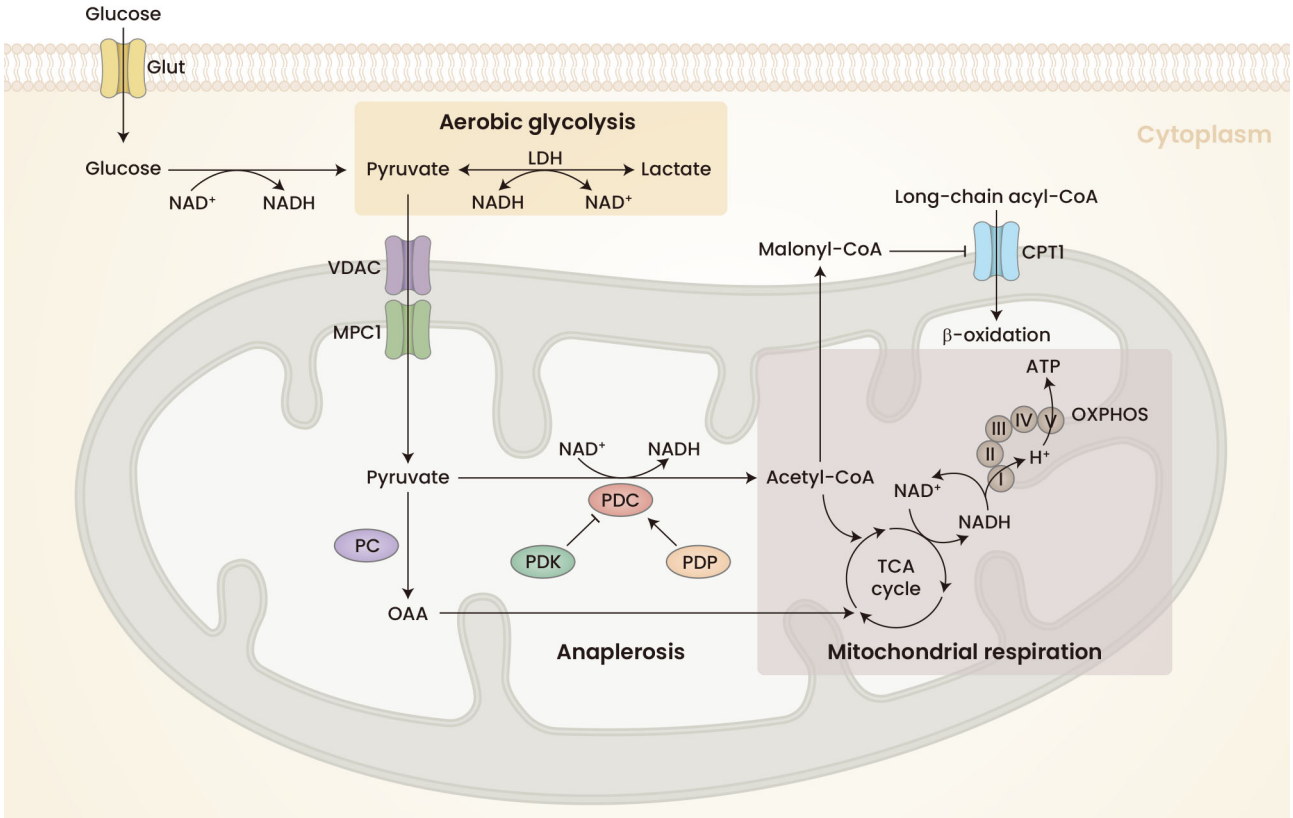

Fig. 1. Glucose metabolites are tightly regulated by pyruvate metabolic flux. Metabolism of pyruvate has two fates: reduction by LDH or oxidation by PDC. Mitochondrial pyruvate is transported by MPC1. Activity of PDC is regulated by PDK and PDP. The conversion of pyruvate to Ac-CoA by the PDC is utilized for mitochondrial respiration, which generates ATP via the TCA cycle and oxidative phosphorylation. Greater PDC activity may lead to an increase in malonyl-CoA, which suppresses FFA oxidation via CPT1 inhibition. LDH, lactate dehydrogenase; PDC, pyruvate dehydrogenase complex; MPC1, mitochondrial pyruvate carrier 1; PDK, pyruvate dehydrogenase kinase; PDP, pyruvate dehydrogenase phosphatate; Ac-CoA, acetyl-CoA; ATP, adenosine triphosphate; TCA, tricarboxylic acid cycle; FFA, free fatty acid; CPT1, carnitine palmitoyltransferase 1; VDAC, voltage-dependent anion channel; PC, pyruvate carboxylase; OAA, oxaloactetic acid; OXPHOS, oxidative phosphorylation.

activity of PDC is determined by the balance between PDKs and PDPs (Harris et al., 2002).

Since pyruvate occupies a central position in essential metabolic pathways, both catabolic and anabolic, the activities of the PDC and PDKs require tight regulation (Fig. 1). Genetically induced deficiency and pharmacologically induced inhibition of PDKs often produce beneficial effects in pathological conditions, which has led to an interest in the therapeutic potential of PDK inhibitors. For example, in *Pdk4*-deficient mice, which exhibit elevated PDC activity, glucose oxidation in diaphragms was greater than in wild-type mice (Jeoung et al., 2006); *Pdk4* deficiency also increased blood levels of free fatty acids and inhibited fatty acid oxidation (FAO) in the muscle of these mice (Jeoung et al., 2006). This effect likely resulted from greater PDC activity leading to increased malonyl-CoA production, an inhibitor of the rate-limiting enzyme in FAO, carnitine palmitoyltransferase I (Foster, 2012). In the liver, enhanced PDC activity by PDK2 inhibition and a high fat diet limited TCA anaplerosis and oxaloacetate synthesis, thereby promoting keteogenesis (Go et al., 2016). Corresponding reductions in hepatic glucose production and lipogeneic capacity in this study suggest that PDC activation is a potential therapeutic target for diabetes and non-alcoholic fatty liver disease (Go et al., 2016); indeed, enhanced PDC flux by PDK4 inhibition reduces gluconeogenesis in mice with diabetes (Park et al., 2018a). Mechanistically, this is also induced by reduced FAO and ATP production, resulting in greater p-AMPK-sensitive phosphorylation of phosphodiesterase 4B and cAMP degradation (Park et al., 2018a). Overall, PDC enhances glucose oxidation, inhibits FAO and promotes lipogenesis in muscle; in the liver, PDC activation limits gluconeogenesis, as well as oxaloacetate synthesis and TCA cycle anaplerosis, which subsequently enhances ketogenesis.

THE ROLE OF PDKs IN MAMs, CELLULAR ORGANELLE MEMBRANE CONTACT SITES

Mitochondria–endoplasmic reticulum (ER) contact sites are generally referred to as MERCs (mitochondria–ER contacts) or MAMs when studied at a biochemical level. Mitochondria and ER actively communicate with MAMs understood to be important hubs for several key cellular processes such as lipid trafficking, mitochondrial dynamics, Ca^{2+} signaling, ER stress, apoptosis, and macroautophagy (Gordaliza-Alaguero et al., 2019). Prior to being studied at the molecular level, evidence suggested that specific regions of mitochondria were sometimes found in close proximity to the ER. This active communication appeared to initiate reactive oxygen species accumulation at the MAM interface as a consequence of Ca^{2+} flux from the ER, resulting in mitochondrial ultrastructural changes (Rizzuto et al., 1998). Subsequent studies established a key role of MAMs in mitochondrial Ca^{2+} signaling. Mitochondrial Ca^{2+} regulates and activates the PDC, and as a result, the TCA, by promoting PDC dephosphorylation (Balaban, 2009); a finely-tuned mitochondrial Ca^{2+} uptake mechanism following its release from ER is thus necessary to maintain cellular bioenergetics (Cardenas et al., 2010; 2016; Csordas et al., 2006). Recent results suggest a complex relationship between metabolic perturbations and inter-organelle interactions; while some evidence suggests that metabolic changes cause defects in inter-organelle crosstalk, other studies show that deficiency in proteins that tether or facilitate the interaction between mitochondria and the ER lead to metabolic perturbations in various tissues. Further study of inter-organelle interactions will allow identification of key proteins, elucidate novel pathways, and unravel their implications in human disease.

The structural scaffold of MAMs consists of several proteins residing on the outer mitochondrial membrane that interact with those in the ER membrane. Our current understanding points towards the following protein complexes governing mitochondria–ER bridging: inositol 1, 4, 5-triphosphate receptors (IP3R1/2/3), vesicle-associated membrane protein-as-

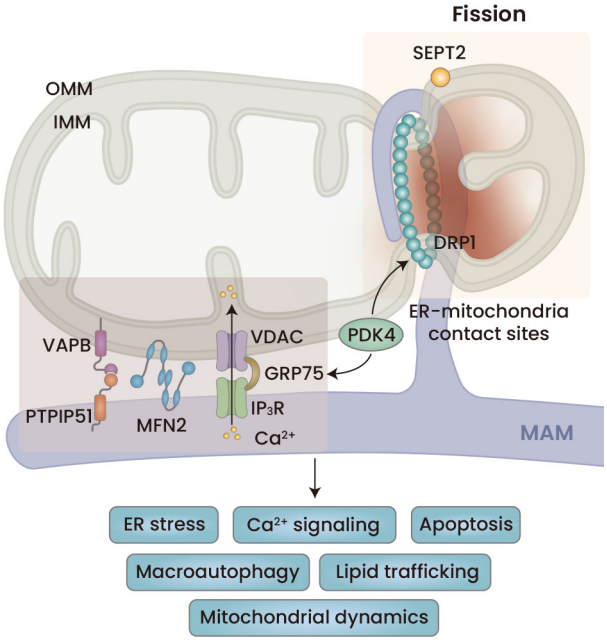

Fig. 2. ER-mitochondria contacts and functions. Mitochondria make contact with many organelles, including the ER, in the cell. ER-mitochondria contacts and the functions pertaining to these contacts are shown; VAPB and VDAC are expressed in the ER; PTPIP51, GRP75, IP3R and PDK4 are primarily localized at the mitochondria; MFN2 is expressed in both ER and mitochondria. The novel functions of PDK4 have been discovered recently; (i) enhancing Ca^{2+} transfer between ER and mitochondria via VDAC1/GRP75/IP3R1 complex and (ii) regulating mitochondrial fission by phosphorylating SEPT2 and recruiting DRP1. ER, endoplasmic reticulum; VAPB, VAMP-associated protein B; VDAC, voltage-dependent anion-selective channel protein; PTPIP51, protein tyrosine phosphatase interacting protein 51; GRP75, chaperone 75 kDa glucose-regulated protein; IP3R, inositol-1,4,5-triphosphate receptor; PDK4, pyruvate dehydrogenase kinase 4; MFN2, mitofusin 2; SEPT2, septin 2; DRP1, dynamin-related protein 1; OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; MAM, mitochondria-associated membrane.

sociated protein B and B-cell receptor-associated protein 31 in the ER; glucose-regulated protein (GRP)75, voltage-dependent anion channel (VDAC)1, protein tyrosine phosphatase interacting protein (PTPIP)51 and mitochondrial fission 1 protein in mitochondria; and mitofusin (MFN)2 in both the ER and mitochondria (Iwasawa et al., 2011). Not only do these proteins shape MAM architecture, they also participate in functions associated with these domains. Motile sperm domain containing 2 is a recently identified MAM tethering protein located in the ER that interacts with PTPIP51 (Di Mattia et al., 2018). IP3Rs, GRP75, and VDAC1 form a Ca^{2+} channeling complex that acts as a gateway through which Ca^{2+} leaves the ER and enters mitochondria (Szabadkai et al., 2006). Recently, our group identified that MAM tethering capacity and calcium flux are sustained by the mitochondrial protein PDK4 (Thoudam et al., 2019) (Fig. 2).

Human, animal, and cellular studies have revealed that metabolic perturbations affect MAM function in liver and muscle cells. Genetic ablation of tethering proteins influences MAM architecture: *GRP75* silencing disrupts IP3R1–VDAC1 interaction at the MAM interface both in HT22 mouse hippocampal neurons cells and in HuH7 human hepatocarcinoma cells (Honrath et al., 2017; Tubbs et al., 2014). Similar effects are observed upon *MFN2* ablation in HuH7 cells and H9c2 rat cardiomyoblasts (Paillard et al., 2013; Tubbs et al., 2014); partial ablation of *VDAC1* also reduces GRP75–IP3R1 interaction in HuH7 cells (Tubbs et al., 2014). Furthermore, disruption to MAM interactions can impact disease etiology; we demonstrated that *Pdk4* ablation decreases MAM formation in skeletal muscle and protects against the development of diet-induced insulin resistance (Thoudam et al., 2019). In healthy cells, nutrient availability plays a key role in determining mitochondria–ER contact dynamics; however, genetic obesity disrupts this process, resulting in obese (*ob/ob*) mouse hepatocytes failing to replicate mitochondria–ER uncoupling during transitions between nutrient states (i.e., fed to fasting or vice versa) (Theurey et al., 2016).

THE ROLE OF PDKs IN MQC

Dysfunction of MQC is emerging as a central mechanism in the pathogenesis of various metabolic diseases, such as neurodegenerative diseases, cancer, diabetes, and aging (Picca et al., 2018). Several reports suggest that PDKs play a role in MQC besides their canonical function, i.e., regulation of PDC activity (Deng et al., 2020; Pajuelo-Reguera et al., 2015; Park et al., 2015; Shi and McQuibban, 2017; Thoudam et al., 2022). Recently, we identified a unique role of PDK4 in modulating mitochondrial dynamics, where PDK4-deficient mouse embryonic fibroblasts showed delayed mitochondrial fission in response to mitochondrial electron transport chain toxins compared with wild-type cells. Interestingly, overexpression of PDK4 alone was able to promote mitochondrial fission in the absence of mitochondrial stressors. Mechanistically, PDK4 acts to induce phosphorylation of septin 2 at Ser218, which promotes recruitment of dynamin-related protein 1 (DRP1), mediating mitochondrial fragmentation (Thoudam et al., 2022) (Fig. 3). Additionally, we found that the suppression of septin 2-DRP1 axis by knocking down PDK4 reduced KRAS mutant lung cancer cells growth. Furthermore, knock down of PDK4 was shown to inhibit KRAS mutant cancer cells growth without affecting PDC phosphorylation, supporting a critical role of non-canonical PDK4 action in promoting KRAS mutant cancer growth.

Previously, a genome-wide siRNA screening revealed that PDK1 and PDK4 may play a role in carbonyl cyanide m-chlorophenyl hydrazone (CCCP)-induced mitophagy (Orvedahl et al., 2011). PDK4-mediated pyruvate accumulation was implicated in promoting CCCP-induced mitophagy via stabilization of the mitophagy adaptor protein PTEN-induced kinase 1 (PINK1). Additionally, PDK4 overexpression or addition of pyruvate strongly stimulated CCCP-induced mitophagy in a PINK1/Parkin dependent manner. However, pyruvate alone failed to stimulate mitophagy in the absence of mitochondrial stress (Park et al., 2015). Overall, this implicates PDK4-pyruvate axis in promoting mitophagy during mitochondrial stress. In contrast, PDK2 inhibits mitophagy by phosphorylating PARL to promote PINK1 degradation, while depletion of mitochondrial ATP decreased PDK2 activity leading to induction of PINK1-mediated mitophagy (Fig. 3). Interestingly, in this study, induction of PDK2 did not affect cellular pyruvate levels (Shi and McQuibban, 2017), suggesting a pyruvate-independent mechanism. Together, these findings suggest that individual PDKs may function independently to sense mitochondrial dysfunction depending on cellular status to regulate MQC, since activity of PDKs can be affected by the availability of several factors, including pyruvate, ATP, NADH, and acetyl-CoA (Park et al., 2018b).

THE ROLE OF PYRUVATE METABOLISM IN MACROPHAGES AND T CELLS

During inflammation, activated immune cells undergo metabolic reprogramming to facilitate cell proliferation, cytokine production, differentiation and immune responses. A key feature of metabolic reprograming is an increased rate of aerobic glycolysis and decreased rate of mitochondrial respiration. Aberrant metabolic regulation in immune cells can therefore impair immune homeostasis and cause immune disorders, meaning that targeting metabolic mechanisms may offer therapeutic opportunities to resolve inflammation (Palsson-McDermott and O'Neill, 2020).

Macrophages play an essential role in innate immunity and are involved in a variety of immune functions. Macrophages are commonly divided into two lineages, M1 macrophages (classically activated macrophages) and M2 macrophages (alternatively activated macrophages). M1 macrophages produce proinflammatory cytokines in response to lipopolysaccharide (LPS) or interferon-γ, while M2 macrophages display an anti-inflammatory signature in response to interleukin (IL)-4 or IL-10. Macrophage polarization (M1/M2) requires metabolic reprogramming to enhance glycolysis and repurpose mitochondrial function. Several studies have shown that regulation of pyruvate oxidation plays an important role in macrophage polarization. For example, PDK1 is required for metabolic reprograming towards aerobic glycolysis and M1 polarization in macrophages (Tan et al., 2015). Inhibition of mitochondrial pyruvate oxidation, either via depletion of

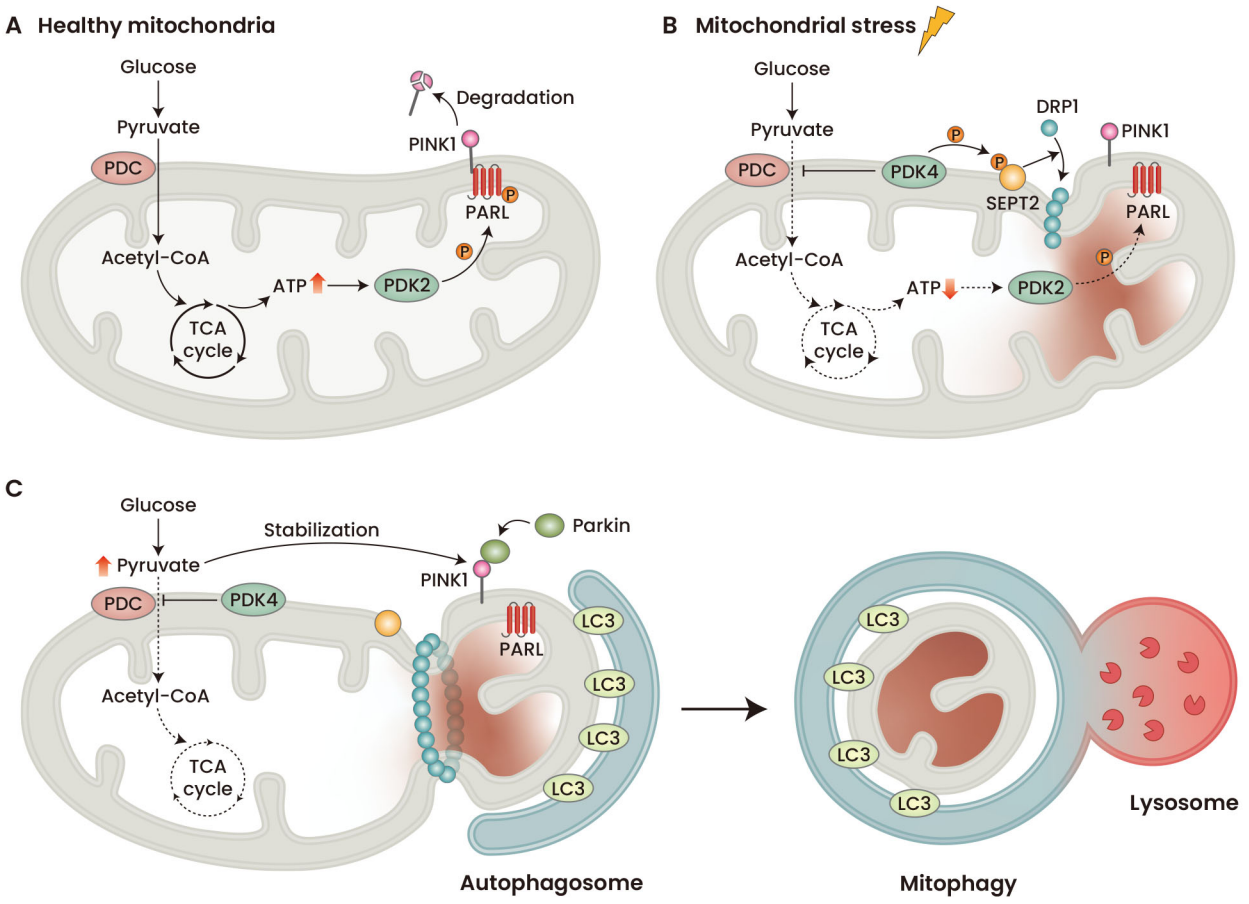

Fig. 3. Pyruvate metabolism facilitates mitochondrial quality control. (A) Healthy and metabolically active mitochondria rapidly convert pyruvate into acetyl-CoA to replenish the TCA cycle and promote ATP production. Optimal amounts of ATP in the mitochondria prevent activation of mitophagy via PDK2-mediated PARL activation and rapid degradation of PINK1. (B) Depletion of ATP during mitochondrial energy stress initiates the PDK4-mediated mitochondrial fission process via activation of the SEPT2-DRP1 axis to separate the defective part of the mitochondria. Defective mitochondria with depleted ATP levels suppress PDK2-induced PARL activation leading to the stabilization of PINK1. (C) Pyruvate accumulation induced by PDK4-mediated inhibition of PDC activity further enhances PINK1 stability. PINK1-mediated recruitment of Parkin, a cytosolic E3 ubiquitin ligase initiates the clearance of defective mitochondria via mitophagic processes. TCA, tricarboxylic acid cycle; ATP, adenosine triphosphate; PDK2, pyruvate dehydrogenase kinase 2; PARL, presenilins-associated rhomboid-like protein; PINK1, PTEN-induced kinase 1; PDK4, pyruvate dehydrogenase kinase 4; SEPT2, septin 2; DRP1, dynamin-related protein 1; PDC, pyruvate dehydrogenase complex.

mitochondrial pyruvate carrier (MPC) or the PDC, has proinflammatory effects, rewiring mitochondrial respiration to aerobic glycolysis and enhancing Nod-like receptor family pyrin domain containing 3 (NLRP3) activation and IL-1β secretion in nigericin-stimulated macrophages (Lin et al., 2021). By contrast, deletion of PDK2/4 diminishes M1 polarization *in vitro* and reduces infiltration of macrophages into adipose tissue *in vivo*, which reduces tissue inflammation and improves insulin resistance (Min et al., 2019); similarly, treatment with a pan-PDK inhibitor, dichloroacetate (DCA), promotes the secretion of the immunosuppressive cytokine IL-10 in LPS-stimulated macrophages (Na et al., 2020).

Recent studies have also shown that mitochondrial dynamics and MAM formation are critical in macrophage function: LPS-stimulated macrophages display DRP1-dependent mitochondrial fragmentation and correspondingly elevated inflammatory cytokines (Gao et al., 2021; Jiang et al., 2022; Kapetanovic et al., 2020). Additionally, defects in MAM formation by MFN2 deficiency significantly enhance proinflammatory responses in macrophages (Khodzhaeva et al., 2021).

Pyruvate oxidation is also involved in T cell development. Defects in mitochondrial pyruvate transport via deletion of MPC1 in T cells impairs mitochondrial respiration and affects early T cell development in the thymus (Ramstead et al., 2020); consequently, MPC1 deficiency results in irregular peripheral T cell homeostasis (Ramstead et al., 2020). Consistent with this, mitochondrial pyruvate oxidation via PDC is required for normal T cell development: PDHA1 deletion leads to pyruvate accumulation, oxidative stress and reductions in double-positive thymocytes during T cell development (Jun et

al., 2021). Pyruvate oxidation also regulates T cell activation early in the T cell receptor signaling pathway; within an hour of T cell receptor activation, T cells initiate aerobic glycolysis by activating PDK1, inhibiting pyruvate oxidation (Menk et al., 2018). In line with this, treatment with DCA, a pan-PDK inhibitor, prevents the rapid activation of aerobic glycolysis in T cells (Menk et al., 2018).

T cell subsets have distinct metabolic patterns. Several studies have shown that manipulation of metabolism towards aerobic glycolysis is required for proinflammatory T cell differentiation, while metabolic reprograming towards pyruvate oxidation is required for anti-inflammatory Treg differentiation. DCA treatment inhibits the expression of transcription factors (T-bet, GATA3, and RORγt), differentiation and effector function of proinflammatory Th1, Th2, and Th17 cells, whereas it enhances Treg cell differentiation, Foxp3 expression and immunosuppressive function (Eleftheriadis et al., 2016; Gerriets et al., 2015; Makita et al., 2017; Ostroukhova et al., 2012). Interestingly, Hif1α, a transcription factor regulating PDK expression, is exclusively expressed in Th17 cells (Shi et al., 2011) and deletion of Hif1α downregulates glycolytic enzyme transcription, thereby compromising Th17 cell differentiation and promoting Treg cell polarization (Shi et al., 2011). In line with the effect of pyruvate metabolism on Th17 cell function, overexpression of PDP2 (a PDC activator) decreases aerobic glycolysis and Th17 polarization but deletion of PDP2 increases aerobic glycolysis and Th17 polarization (Kono et al., 2018).

Collectively, evidence suggests that pyruvate oxidation is a key pathway orchestrating immunometabolism and T cell function, suggesting that pyruvate oxidation may provide a novel target for therapeutic intervention in T cell-mediated immune disorders. Indeed, inhibition of aerobic glycolysis by DCA attenuates rheumatic disorders such as collagen-induced arthritis (Bian et al., 2009). DCA treatment also selectively inhibits Th17 cell differentiation and attenuates multiple sclerosis in a mouse model of experimental autoimmune encephalomyelitis (Gerriets et al., 2015). In addition, $CD4^+$ T cells from patients with lupus (Gergely et al., 2002; Tsokos, 2011; Yin et al., 2015) and inflammatory bowel disease (Dumitru et al., 2018; Gerriets et al., 2015; Imam et al., 2018; Lee et al., 2023), display higher levels of Th17 cells, mitochondrial dysfunction and aerobic glycolysis. However, DCA treatment failed to resolve inflammation effectively in an

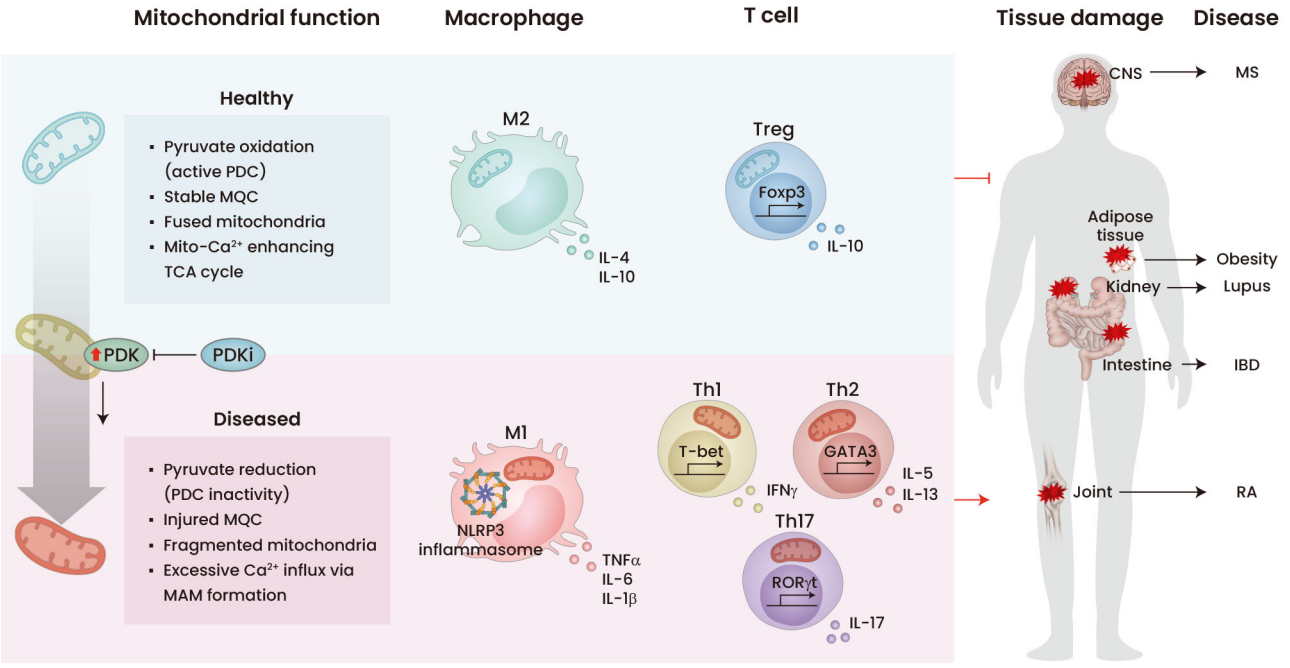

Fig. 4. PDC flux is a mitochondrial checkpoint in macrophages and T cells. Pyruvate oxidation through the PDC is critical in polarization of macrophages and T cells. Enhancement of mitochondrial PDC flux by DCA treatment or PDK inhibition polarizes macrophages into M2 macrophages, which manifest anti-inflammatory functions. Conversely, blockage of PDC flux, either by PDC or MPC deletion, inhibits M1 polarization. In T cells, PDC flux is differentially regulated in Th cell subsets. Immunosuppressive regulatory T cells (Tregs) use PDC flux to express Foxp3 transcription factors and the cytokine IL-10. Proinflammatory T cells including Th1, Th2, and Th17 utilize aerobic glycolysis instead of pyruvate oxidation. Enhancement of PDC flux by DCA treatment decreases Th1, Th2, and Th17 differentiation. PDP inhibition reduces Th17 differentiation. Aberrant and uncontrolled innate and adaptive immune activation interrupts immune homeostasis in tissue such as the CNS, adipose tissue, kidney, intestines, and joints, which leads to tissue damage and diseases including MS, obesity, lupus, IBD, and RA. PDC, pyruvate dehydrogenase complex; DCA, dichloroacetate; PDK, pyruvate dehydrogenase kinase; MPC, mitochondrial pyruvate carrier; IL, interleukin; PDP, pyruvate dehydrogenase phosphatate; CNS, central nervous system; MS, multiple sclerosis; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; MQC, mitochondrial quality control; TCA, tricarboxylic acid; PDKi, pyruvate dehydrogenase kinase inhibitor; MAM, mitochondria-associated membrane; TNF, tumor necrosis factor; IFN, interferon.

animal models of colitis (Gerriets et al., 2015) and lupus (Yin et al., 2016), despite diminished Th17 differentiation. These contradictory findings suggest further study is required.

A recent investigation has illuminated the role of PDK4 in colitogenic $CD4^+$ T cells. The study indicates that PDK4 and phosphorylated PDHE1a are augmented in gut-infiltrating $CD4^+$ T cells obtained from inflamed intestinal tissues in both DSS-induced colitis models and patients with IBD (Lee et al., 2023). Furthermore, utilizing DSS-induced colitis models and adoptive T cell transfer colitis models, CD4-specific PDK4 knockout mice exhibited a reduced extent of gut inflammation, with a decrease in Th1 and Th17 cells and an increase in Treg cells (Lee et al., 2023). The *in vitro* study also demonstrates that PDK4 deficiency in $CD4^+$ T cells leads to a disruption of the mitochondria-ER associated membrane structure, diminished mitochondrial calcium levels, reduced aerobic glycolysis, and a defect in T cell effector function (Lee et al., 2023). Significantly, treatment with the PDK4 specific inhibitor GM-10395 prevents DSS-induced colitis in animal models (Lee et al., 2023). These findings suggest a pathogenic role for PDK4 in lamina propria $CD4^+$ T cells.

PDK2 also plays an important role in survival of proinflammatory T cells under hypoxic stress. Kidney tissue-infiltrating T cells from lupus-prone mice display distinct metabolic phenotypes linked to mitochondrial dysfunction and T cell exhaustion (Tilstra et al., 2018). Under hypoxic conditions, T cells from the renal tissue of lupus-prone mice express Hif1α-dependent PDK2, which promotes alternative splicing of BCL2 interacting protein 3, increasing T cell adaptation and survival in the presence of hypoxia-induced mitochondrial dysfunction (Chen et al., 2020). By contrast, inhibition of Hif1α by T cell-specific genetic deletion or pharmacological intervention (with PX-478) attenuates T cell infiltration and tissue damage, improving survival in lupus-prone mice (Chen et al., 2020) (Fig. 4).

Finally, the role of mitochondrial dynamics (Buck et al., 2016; Cogliati et al., 2013; Simula et al., 2018) and MAM, as discussed above and previous (Bantug et al., 2018), has been intensively studied in T cell immunity. However, whether pyruvate metabolism is directly or indirectly linked to such mitochondrial scaffolds in immune cells is largely unknown, although pyruvate flux is known to decline due to mitochondrial fission and cristae disorganization in T cells (Buck et al., 2016).

CLOSING REMARKS

Mitochondria are the primary source of energy production in cells. However, mitochondria are also actively involved in the metabolic response to energy supply and subsequently adapt to metabolic changes, including via morphological changes such as fission/fusion cycles and MAM formation. Evidence suggests that mitochondrial dysfunction, including metabolic reprograming, mitochondrial dynamics and inter-organelle mislinkage, is observed in metabolic syndromes and inflammation; therefore, recent studies suggest that targeting mitochondrial dysfunction could be a promising therapeutic strategy for treating these disorders. In this Minireview, we have discussed the role of PDC flux in mitochondrial dysfunction and disease manifestation. Although targeting PDC flux may offer therapeutic opportunities to treat metabolic syndrome and inflammation, molecular mechanisms between PDC flux and mitochondrial dysfunction have not been elucidated in detail. However, our group has shown that PDK4 has non-canonical roles in MAM formation (Thoudam et al., 2019) and MQC (Thoudam et al., 2022), suggesting further investigation is needed to uncover other functions of metabolic enzymes involved in PDC flux and their potential impact on metabolic syndromes and inflammatory disease.

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AUTHOR CONTRIBUTIONS

M.-J.K., H.L., D.C., T.T., H.-J.K., and R.A.H. wrote the manuscript and designed the figures. I.-K.L. conceived and supervised the overall process.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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