Review

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Role of Mitochondrial Dysfunction in Cellular Lipid Homeostasis and Disease

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Mitochondria-associated membranes (MAMs) play a significant role in multiple cellular processes including lipid metabolism and neuronal survival. Fatty acids constitute 80% of the dry mass of the brain and are vital for life. Apart from mitochondrial β-oxidation, fatty acids are metabolized in part by peroxisomes to regulate the generation of acyl Coenzyme A and adenosine triphosphate (ATP). Ablation of mitochondria and its associated genes tether endoplasmic reticulum (ER)-Mitochondria contact and results in loss of function leading to aberrant lipid metabolism. Additionally, an increase in reactive oxygen species (ROS) levels along with free radicals' generation may lead to alteration in the integrity of membrane phospholipids, proteins, and DNA. Hence, it is critical to understand the effect of structural and functional aspects of mitochondria on lipid homeostasis. This review explains the role of mitochondrial dysfunction in lipid metabolism and its impact on various neurodegenerative diseases and metabolic disorders.

Keywords: mitochondria dysfunction; lipid metabolism; neurodegenerative disease

Introduction

Lipid metabolism is central to all forms of life and its study is particularly important because 80% of the dry mass of the brain is composed of lipids [1]. Not surprisingly, the alteration of lipid metabolism in the brain and in the liver which controls systemic glucose homeostasis is directly linked to a plethora of neurodegenerative diseases [2] and metabolic disorders [3]. Nevertheless, the role of mitochondria in the control of metabolism varies based on the tissue under study. Mitochondria mainly control apoptosis of the cell by free radical generation [4], calcium [5] and adenosine triphosphate (ATP) levels [6] and thus provide cells not only energy, and metabolic redox status but also initiate various biochemical pathways involved in cell metabolism. Any dysfunction of mitochondrial activity can affect body and energy homeostasis leading to vulnerability to various diseases [7]. This review will explain the features of inter-organelle contact sites with an emphasis on the role of mitochondria in lipid biology and mitochondrial dysfunction-associated diseases including diabetes, obesity, atherosclerosis, and renal failures.

Role of Mitochondria in Lipid Homeostasis

ER and Mitochondria Inter Organelle Contact Sites

Phospholipid biosynthesis is dependent on the contact sites between two organelles of mitochondria and endoplasmic reticulum (ER) [8]. This was confirmed by the transfer of hydrophobic molecules between cell organelles by cytosolic vesicles or via active transport and proved that a specific biochemical activity occurs at the contact site [9]. Indeed, this distance can affect the physiological function (calcium transport) of mitochondrial-associated membranes (MAMs) [10]. MAMs are well-characterized and present between the outer mitochondrial membrane and that of the ER at which contacts occur in each cell under a specific condition. The distance between these contact sites impacts the function of cell signaling between two organelles [11]. The ER along with MAMs not only harbors enzymes cholesterol and triacyl glycerides (TAG) synthesis but also the distribution of lipids to other cellular organelles via secretory pathways and contact sites. In the liver and other specialized tissues, TAG is also packaged in the ER into very low-density lipoproteins (VLDL) [12] to be distributed to peripheral organs. Thus, ER and its associated MAMs play a vital role in the synthesis of lipids.

Role of Mitochondria in Fatty Acid Oxidation

Mitochondria are bi-membrane cell organelles of respiration lined with two layers, an outer mitochondrial membrane (OMM), and an inner membrane that is divided into inter mitochondrial space with matrix [13]. Mitochondria are essential for fatty acid oxidation (FAO) and ATP production through oxidative phosphorylation with the Krebs cycle and synthesis of lipids [14]. Despite glucose, fatty acid (FA), and amino acids being key substrates for energy

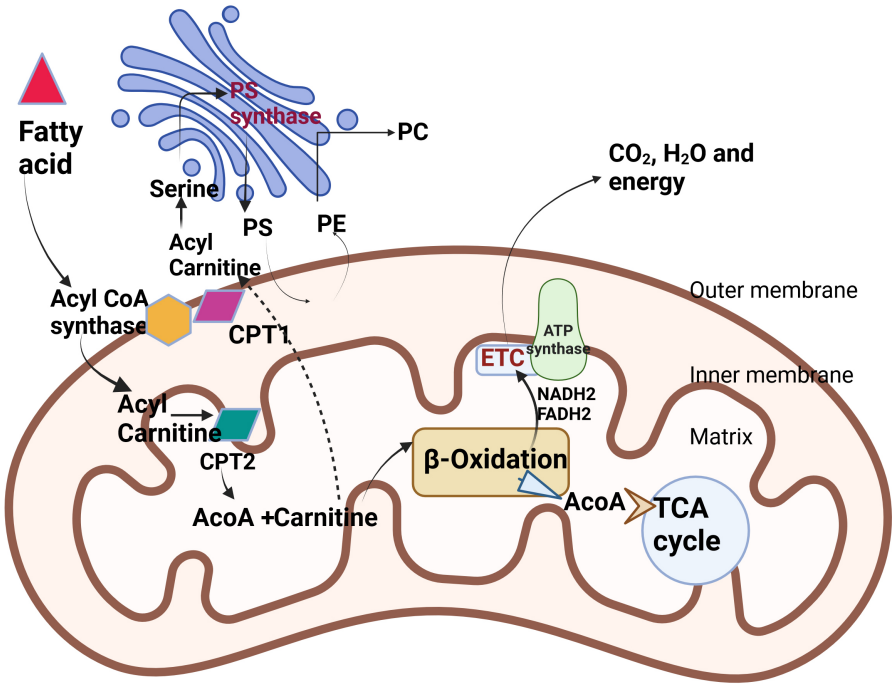

Fig. 1. Role of mitochondria in the oxidation of fatty acids. Lipid synthesis and transfer between the endoplasmic reticulum (ER) and the mitochondria are initiated by the formation of Phosphoserine (PS) which is made from serine on the ER by the enzyme PS synthase which is later transferred to the mitochondria for decarboxylation to Phosphatidyl ethanolamine (PE) by PS decarboxylase. The PE is then translocated back to the ER where it is methylated to Phosphatidylcholine (PC) by the phosphatidylethanolamine methyltransferase. Fatty acid (FA) metabolism includes the formation of acyl-CoA and later esterification by the carnitine palmitoyltransferase (CPT1) enzyme. Subsequently, there is the transport of acylcarnitine by carnitine palmitoyltransferase 2 (CPT2) which replaces carnitine with CoA which enters β-oxidation and later participates in the tricarboxylic acid (TCA) cycle or forms B-hydroxy butyrate and nicotinamide adenine dinucleotide (reduced) (NADH2)/flavin adenine dinucleotide (FADH2) are utilized in the electron transport chain. All the figures in this manuscript were created with BioRender scientific illustration software (BioRender, Toronto, ON, Canada).

sources, during fasting conditions, when glucose levels are low, most tissues use FA to generate energy [15]. ER metabolizes serine molecules by phosphoserine synthase to form Phosphatidyl serine (Fig. 1). This molecule along with acylcarnitine enters the mitochondrial through carnitine palmitoyltransferase (CPT1) of OMM and is converted to acyl-CoA by the carnitine palmitoyltransferase 2 (CPT2) enzyme located on the inner membrane of mitochondria [16] that is later degraded into acetyl-CoA by a series of enzymatic reactions of β-oxidation [17]. From each cycle of fatty acid oxidation, two acetyl-CoA electrons are carried to nicotinamide adenine dinucleotide (reduced) (NADH) and flavin adenine dinucleotide (FADH2). The newly synthesized acyl-CoA will form the basis to start a new fatty acid cycle to generate redox potential that is used in the electron transport chain in one complete cycle of glucose oxidation [18]. Thus, mitochondria play a significant role in FA import from ER to mitochondria and β-oxidation of fatty acids [19] (Fig. 1).

Control of Mitochondrial Fatty Acid Oxidation

The control of mitochondrial β-oxidation depends on the entry of acyl groups and substrate supply. Firstly, the enzyme CPT1 controls hepatic β-oxidation which depends on nutritional rate [18]. Normally, hepatocytes are supplied with high glucose by increased insulin levels and initiate glucose oxidation to form NADH2/FADH2 along with acyl-CoA [19]. Secondly, control of acetyl-CoA and other enzymes allows fatty acids to rapidly undergo β-oxidation in different tissues [20]. Thirdly, citrate is transported out from the matrix, through a carrier along with the import of oxaloacetate and cytoplasmic acetyl-CoA and is utilized in cholesterol biosynthesis [21]. In addition, CPT1 is also controlled by malonyl-CoA, a product of acetyl-CoA carboxylase, an inhibitor of CPT1 [22]. Fatty acids can be incorporated into glycolipids due to condensation of glycerol3-P derived from glucose to form lysophosphatidic acid and later to phosphatidic acid. These triglycerides are added to apolipoprotein B100 to form VLDL by the action of microsomal triglyceride transfer protein (MTTP) [23]. Thus, mitochondrial matrix metabolism controls glucose and fatty acid oxidation and controls cross-talks between the cell organelles of ER and mitochondria.

Role of Mitochondria in the Generation and Breakdown of Reactive Oxygen Species

Lipid homeostasis is maintained by a process of removal and replacement of altered lipids (lipid peroxidation) done by reactive oxygen species (ROS) [24–26]. The mitochondrial respiratory chain is the most important site of free radical generation [27]. Superoxide anion is generated by complexes I and III, through electron leakage, and by a single electron reduction of oxygen. ROS can interact with nitric oxide (another radical) to form peroxynitrite which causes oxidative stress [28]. Thus, an increase in ROS levels may have harmful effects on the integrity of membrane homeostasis. To counter this, mitochondria have developed defenses against ROS by enriching the membrane with vitamin E, ubiquinone, glutathione peroxidases and reductases [29]. Furthermore, superoxide dismutases (SODs) that can neutralize ROS are compartmentalized in mitochondrial intermembrane space [30,31]. In addition to glutathione and SOD enzymes, peroxyredoxin-3 (RX 3) located in mitochondria can also initiate the anti-oxidant defense activity that can initiate hydrogen peroxide-driven signaling pathways including apoptosis [32].

Mitochondrial Dysfunction and Disease

Dysfunctional Lipid Metabolism

In addition to the ability of mitochondria to play an important role in fatty acid oxidation and energy production, blockage of CPT1, substrate overflow, or synthetic inhibitors can lead to an imbalance in FA oxidation [33]. Enhancement of intracellular fatty acids can induce the formation and release of ROS and peroxides [34]. Fatty acid binding proteins (FABP), which are present in the liver, heart, and brain; combine with fatty acids to form a complex (FABP/fatty acid). This complex regulates the uptake of fatty acids, cell signaling and subsequent target genes [35]. Furthermore, fatty acyl-CoA binding proteins (ACBP) also regulate the binding of the product of the acyl-CoA synthetase located in the mitochondrial outer membrane [36]. Thus, mitochondrial dysfunction can lead to disruption in lipid homeostasis and ultimately result in the development of various pathophysiological conditions/diseases as discussed below.

Skeletal Muscle Mitochondrial Dysfunction and Obesity

Skeletal muscle remains the first link between insulin resistance and mitochondrial dysfunction and this was confirmed by reduced mitochondrial size [37] and oxidative capacity [38] analyzed by electron microscopy studies [39]. Proteomic analysis of skeletal muscle confirmed the depletion of mitochondrial proteins in obese and Type 2 diabetes (T2D) mellitus individuals [40–42]. Previous studies by Holloway *et al*. [43] demonstrated that a high fat diet (HFD) can elevate muscle mitochondrial oxidative capacity in rodents. Paradoxically, after HFD treatment mice overexpressing muscle-specific peroxisome proliferator activated receptor gamma coactivator-1 alpha (PGC-1α) became insulin resistance (IR), with a 60% increase in ATP synthesis [44]. On the contrary, in some studies, mitochondrial content was normal along with respiratory function [45] However, as mitochondrial function is traditionally evaluated as a maximal rate of respiration [45] using submaximal Adenosine Diphosphate (ADP) concentrations may better represent physiological conditions. Similarly, studies on obese Zucker rats showed reduced ADP-stimulated respiration despite having similar mitochondrial content as lean controls [45]. Subsequent work has shown that dietary n-3 polyunsaturated fatty acids (PUFAs) (e.g., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) supplementation can enhance mitochondrial ADP sensitivity in control subjects, and thus can be protective against diet-induced IR following PGC-1α transfection in muscle [46]. Obesity is a metabolic disorder caused by chronic adipocyte inflammation and ectopic lipid deposition leading to insulin resistance [47,48]. Alteration of lipid homeostasis might be caused by (i) mitochondrial dysfunction, (ii) differentiation of pre-adipocytes to adipocytes, and (iii) accumulation of triglycerides [49]. Furthermore, reduced mitochondrial biogenesis, and ATP formation with increased ROS production, and inflammatory cytokines aid in obesity [50]. Moreover, the studies of Wolfgang *et al*. (2011) [51] confirmed that obesity might be due to hypothalamic dysfunction leading to negative effects on mitochondrial biogenesis.

Mitochondrial Dysfunction and Diabetes

Diabetes Mellitus (DM) is caused by complex interactions of genetics, environmental factors, and lifestyle changes [52]. Sometimes, disrupted insulin production/secretion and insulin resistance in the liver and skeletal muscle can cause DM. Apart from type 1 and type 2 diabetes, mitochondrial diabetes might be inherited which is associated with a mutation in A3243G in the mitochondrial tRNA [53]. Generally, mitochondrial oxidative metabolism is a major resource for ATP production which controls insulin secretion. On the contrary, when ATP is low due to mitochondrial dysfunction, it leads to inhibition of calcium entry and later to inhibition of insulin secretion and initiation of glucose utilization and lipogenesis [54]. Mitochondrial dysfunction in skeletal muscle has a significant effect on the pathogenesis of type 2 DM with reduced oxidation of fatty acids, mitochondrial contents, oxidative phosphorylation and high levels of ROS [54]. To counter this, SOD along with uncoupling protein-1 (UCP-1), inhibit subsequent activation of protein kinase C (PKC) [55]. Furthermore, studies from Sharma (2015) [56] confirmed that mitochondrial oxidative phosphorylation (OXPHOS) was increased by activation of AMP-activated protein kinase (AMPK) [57], sirtuins (SIRT) 1/3, and PGC-1α and this could be attributed to insulin secretion by pancreatic β-cells

and increase insulin sensitivity in skeletal muscle and liver and this strategy can be used in treatment for mitochondrial dysfunction in diabetics.

MAMs' Role in Cardiovascular Disease

CVD is a multifactorial disorder initiated by mitochondrial dysfunction and high reactive oxygen species production along with the activation of apoptosis pathways [58]. Mitofusin-2 (MFN2) localized at ER and mitochondrial membrane's active contact sites not only increases MAM and calcium transfer but also can decrease the distance between ER and mitochondria membranes, impairing calcium uptake (Fig. 2) into the mitochondria.

Downregulation of MFN2 was observed in rat models of cardiac hypertrophy with myocardial infarction leading to cardiomyocyte remodeling [59]. On the other hand, its upregulation is induced by the formation of angiotensin II. Studies by Sun *et al*. (2019) [60] confirmed the role of MFN2 in cardiac differentiation from embryonic stem cells and coronary lumen [61,62]. After FA oxidation, via a cluster of differentiation 36 (CD36) the non-esterified FAs enter cardiomyocytes and are subsequently converted to fatty acyl-co A esters by long-chain acyl-CoA synthetases (ACSL) [63] and catalyze the hydrolysis of TAG into diacylglycerol (DAG). The released FAs are thus used for ATP formation via OXPHOS in mitochondria and thus any imbalance between FA uptake and utilization (Fig. 2) could result in an ectopic lipid accumulation in the heart associated with cardiomyocyte dysfunction and apoptosis, a process termed lipotoxicity [64].

Mitochondrial Dysfunction in Cancer

Mitochondrial dysfunction including genetic or metabolic alterations may lead to an imbalance in lipid homeostasis and eventually to cancer. While in some, mitochondrial fatty acid oxidation is stimulated as energy supplying source in cases of prostate cancer [65] and breast cancer [66,67], and in some others, mitochondrial CPT1 activity is reduced [68] and contributes to an imbalance in the energy homeostasis state favoring fatty acid synthase (FASN) activity [69] leading to tumor formation [70]. To overcome this fatty acids-driven lipotoxicity, cancer cells initiate a cross-signaling between the tyrosine kinase human epidermal growth factor receptor (HER2) and FASN [71,72]. This interaction initiates the activation of peroxisome proliferator-activated receptor gamma (PPAR-γ) and subsequent activation of the lipogenic triacylglycerol synthesis pathway [73–75]. Furthermore, the interaction between HER2 and FASN might lead to adipogenesis in some cancers [76]. Finally, oncogenic induced ROS levels can also cause replicative stress and altered mitochondrial dynamics with stabilization of hypoxia-inducible factor 1-alpha (HIF-1α), and inactivation of Pten [77]. To counter these effects caused by mitochondrial dysfunction in various disorders and diseases, the following approaches can be considered.

Potential Approaches in the Treatment of Imbalance in Mitochondrial Lipid Homeostasis

Exercise and Lifestyle Changes

Obesity and other lifestyle disorders caused by mitochondrial dysfunction can be modified with the intervention of calorie restriction and exercise. Physical activity not only enhances ATP turnover, and oxygen consumption but also increases calcium cycling and thus alters ROS production [78]. These biochemical changes, in turn, might activate kinases that enhance post-translational modifications to nuclear transcription factors, AMPK [79] and mitogen-activated protein kinase p38 (p38 MAPK) [80] and increase PGC-1α promoter activity [80] and thus impact mitochondrial biogenesis. Collu-Marchese *et al*. (2015) [81] work examining myocyte differentiation revealed that greater mitochondrial transcription factor A (TFAM) mRNA stability increased mRNA concentration throughout differentiation, and was in parallel with mitochondrial biogenesis. In another study by Steiner *et al*. (2011) [82] they proved that exercise training in 8-week-old male Institute of Cancer Research (ICR) mice enhanced mitochondrial biogenesis of mtDNA, and PGC-1α, SIRT1, and citrate synthase (CS) mRNA and endurance capacity. Thus, exercise remains a therapeutic option to attenuate the negative effects of mitochondrial dysfunction and associated neuro disorders as well.

Effect of PUFAs on Mitochondrial Dysfunction

Omega-3 fatty acids are essential fatty acids that act as direct ligands for peroxisome proliferator-activated receptors (PPARs) and can stimulate FA oxidation, and enhance mitochondrial content [83]. This is supported by the observation that 10 weeks of fish oil treatment (EPA/DHA) increased the muscle PPARα/γ nuclear respiratory factor 1 (NRF-1) and mitochondrial markers [84–86]. Johnson *et al*. (2015) [87] proved that EPA and DHA produce a significant effect on mitochondrial dysfunction. In another study, EPA (100 µM) supplementation for 24 h to 3T3-L1 adipocytes showed increased fatty acid β-oxidation in parallel with a rise in Carnitine Palmitoyltransferase 1A (CPT-1A) activity [88]. In other studies, n-3 PUFAs induced a decrease in body weight and fat mass along with a lowering of triglyceride levels [89–91]. Furthermore, some studies also confirmed improvement in glucose or insulin tolerance in models treated with EPA/DHA [92]. CPT-I is the main control point for β-oxidation because it facilitates the transfer of acyl groups into the mitochondria, and its expression is regulated by peroxisome proliferator-activated receptors (PPARs) and AMPK. It has been confirmed that there was a synergistic association with CPT-1 in the activation of AMPK by EPA (200 µM for 24 h) in primary cultured rat adipocytes [93].

Previously, it was shown that n-6 fatty acid linoleic acid (LA, 18:2 n-6) can restore mitochondrial dysfunction

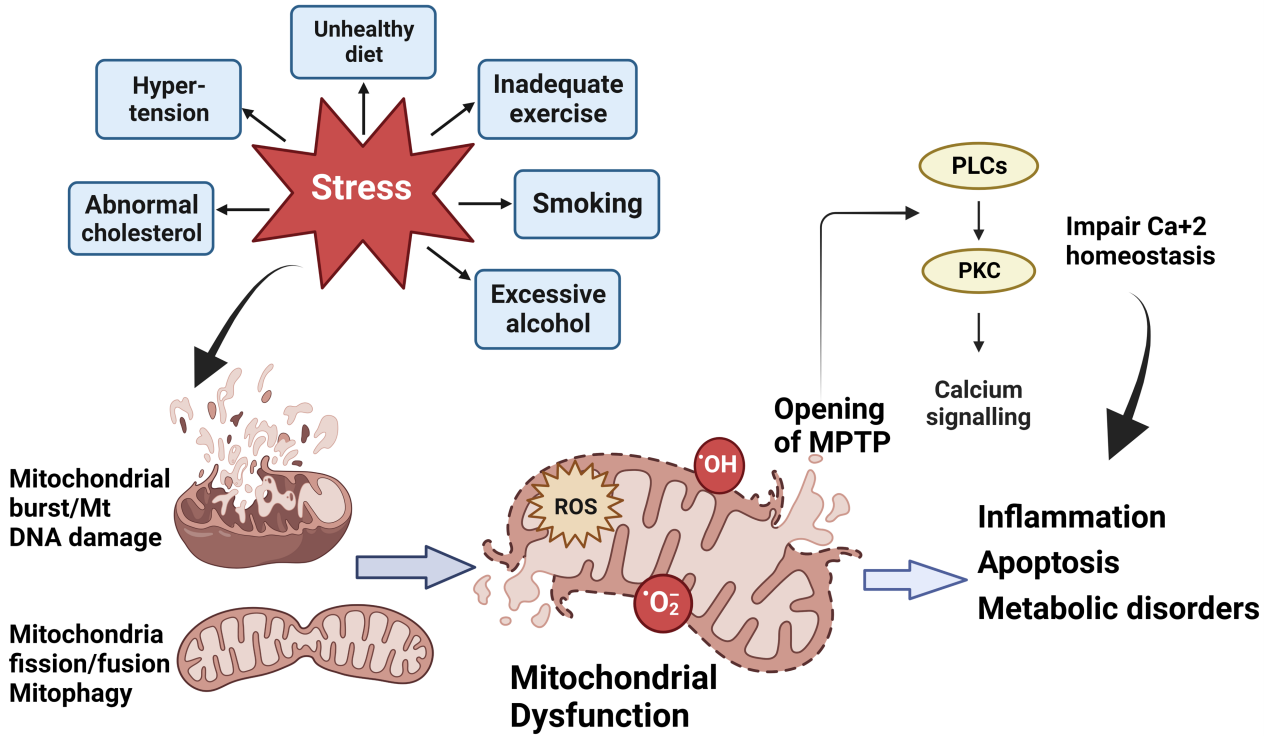

Fig. 2. Effect of mitochondrial dysfunction on Obesity, Type 2 diabetes (T2D), and Ischemia. In obesity, there is an increase in fatty acyl-CoA resulting in fatty acid peroxidation and ceramide formation. This leads to a decrease in insulin sensitivity. On the other hand, diabetes complications enhance the production of reactive oxygen species (ROS), peroxisome proliferator-activated receptor alpha (PPAR-α), fatty acid oxidation, calcium production, and formation of oxysterols and ROS and eventually to diabetes/cardiomyopathy.

in the heart and improve heart contraction especially in hypertensive animals [94]. This beneficial action of LA in heart failure has been attributed to its ability to improve the assembly of the CII subunit and CIII2/CIV complex of the mitochondrial oxidative phosphorylation system [95]. It is possible that other n-6 fatty acids gamma-linolenic acid, dihomo-gamma-linoleic acid and arachidonic acid may also have similar beneficial actions.

Effect of PUFAs on Warburg Effect of Cancer

In normal cells, oxidization of pyruvate generates 36 ATP and redox power. But in cancer cells under hypoxia conditions, they generate the redox power predominantly not through the citric acid cycle, but by aerobic glycolysis (Warburg effect) which involves uptake of high levels of glucose and glycolysis followed by lactic acid formation in cytosol [96,97]. Until now this hypothesis as to why cancer cells undergo aerobic glycolysis is not explained. But this can be justified by the fact that creating an acidic environment in the surrounding extracellular matrix of cancerous cells and concomitant enhanced fatty acid synthesis might facilitate tumor progression leading to metastasis of cancer [98,99]. In oncogenic signaling, genes of c-Myc and p53, and HIF-1α have been linked to the altered glycolytic phenotype, tricarboxylic acid (TCA) cycle, and hypoxic protection [100]. As explained in Fig. 3, the phosphatidylinositol 3-kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) pathway plays a central role in growth factor signaling of cancer and elevation of HIF-1α protein to activate downstream genes of aerobic glycolysis to yield lactate and promote cell growth and lipid synthesis [100]. Subsequently, AKT might also activate the mammalian target of rapamycin complex 1 (mTORC1) through the indirect inhibition of the AMPK, the crucial regulator of cell metabolism. We propose in this review that the beneficial aspect of ω-3 PUFAs (Fig. 3) is mainly due to its interaction with the cell survival pathway. Firstly, PUFAs might release/activate PPAR-gamma which inhibits the factors (HIF-1α) involved in downstream signaling to nullify the Warburg effect and lactate formation [101]. Additionally, the expression of Heat Shock Protein 70 (HSP70) is also inhibited which is the primary activator of HIF-1α. PUFAs might activate the gene liver kinase B1 (LKB1) of breast cancer which encodes a serine-threonine kinase that directly phosphorylates and activates AMPK, which in turn, suppresses the mTORC1 signaling and the relative downstream targets and expression of glycolytic enzymes [102,103]. Consequently, with the decrease of these enzymes, there is ablation of lactate production and migration potential of the cancer cells. This property of DHA and other PUFAs may be considered as one potential mechanism for their protective action against cancer.

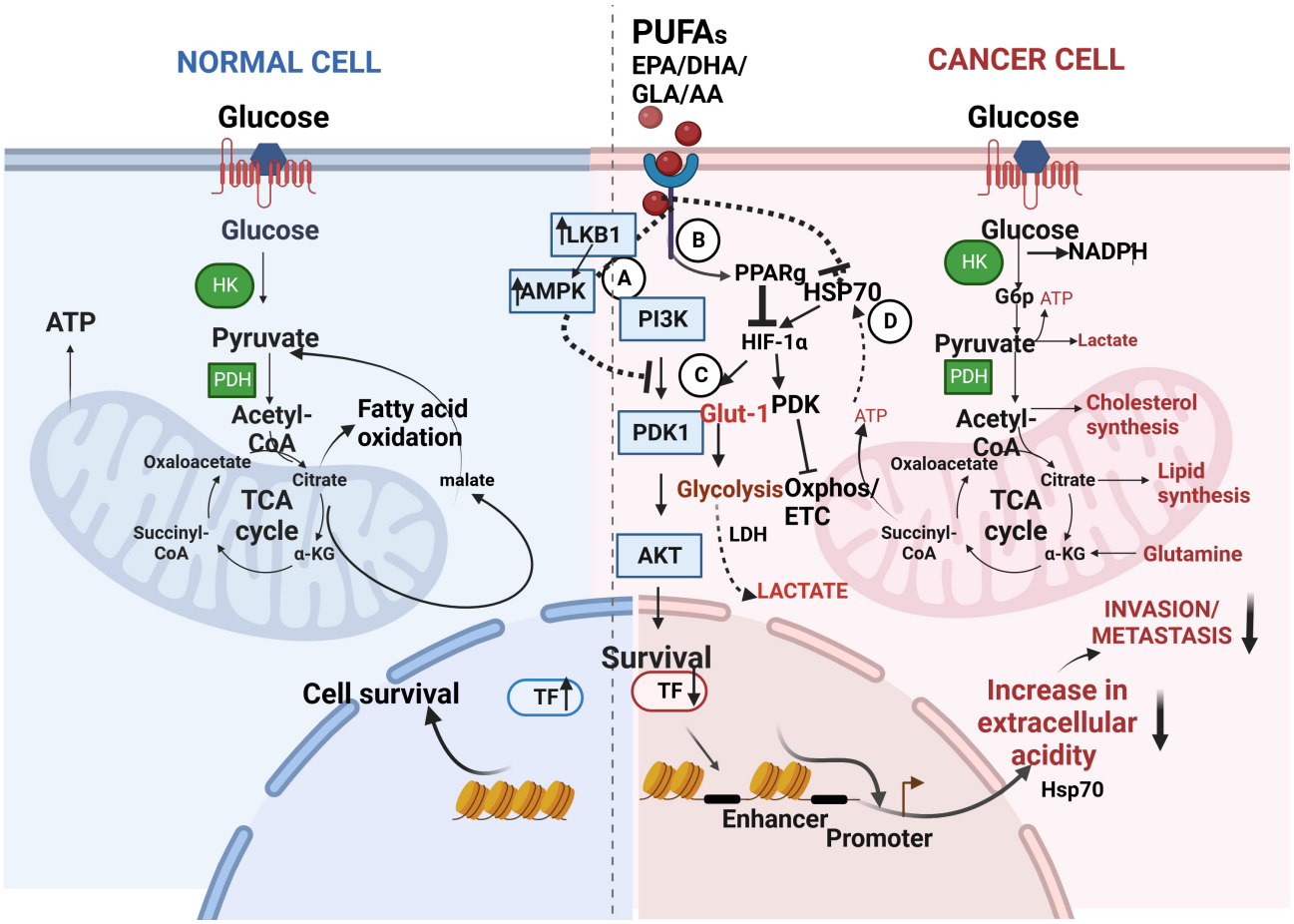

Fig. 3. Possible mode of action of polyunsaturated fatty acids (PUFAs) (eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA)/gamma-linolenic acid (GLA)/arachidonic acid (AA)) and respective interference with molecular signaling pathways. (A) Activation of phosphatidylinositol 3-kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin complex 1 (mTORC1) pathway promotes transcription factor hypoxia-inducible factor 1-alpha (HIF-1α) which later dimerizes with hypoxia-inducible factor 1-beta (HIF-1β) to active HIF-1 complex. DHA treatment increases the liver kinase B1 (LKB1) protein expression and activates the activated protein kinase (AMPK) pathway. This active AMPK inhibits mTORC1 signaling. (B) PUFAs destabilize HIF-1α promoting its proteolytic degradation via the activation of PPARα and (C) PUFAs interfere at various sites of this pathway and thus can attenuate bioenergetic function and Warburg metabolism. (D) PUFAs also alter cancer cell metabolism by blocking Heat Shock Protein 70 (HSP70), a crucial molecular chaperon necessary for the folding of HIF-1α. Thus, due to a block in the cell survival signaling pathways and Warburg effect deletion, PUFAs aid in the decrease of extracellular acidity and metastasis of cancer.

Alteration in Mitochondrial Dynamics

The balance between the fission and fusion process is called mitochondrial dynamics and this depends on the physiological shape, structure, and energy metabolism along with mitophagy and apoptosis [100–102]. In cardiac function, mitochondrial dynamics play a significant role in myocardial tissue in terms of energy supply and might be influenced by mitochondrial dysfunction, altered lipid homeostasis, and increased mitochondrial ROS production [103]. MAMs modulate calcium transport, mitochondrial damage, ER stress, and mPTP pore during the reperfusion damage caused by cardiovascular disorders [104]. Studies by Angebault *et al.* [105] found an improvement in hypoxia injury in cardiomyocytes through glycogen synthase kinase 3 beta (GSK3β) and induction of mitochondrial calcium levels. Excess deposition of lipids on cardiomyocytes might be the cause of diabetic cardiomyopathy (DCM) characterized by apoptosis. The beneficial role of MAM in the prevention of DCM needs to be explored in the near future.

Studies found a positive correlation between mitochondrial dynamics and tumor phenotype via upregulation of Drp1 confirmed by reduced proliferation and increased apoptosis in lung cancer cell lines and activated by oncogenic Ras [106]. This might subsequently activate the mitogen-activated protein kinase (MAPK) pathway and lead to extracellular signal-related kinase 1/2 (ERK1/ERK2) phosphorylation of Drp1 at serine [107]. Inhibition of Drp1 activity is sufficient to reduce xenograft tumor growth driven by oncogenic Ras [106,108]. Thus,

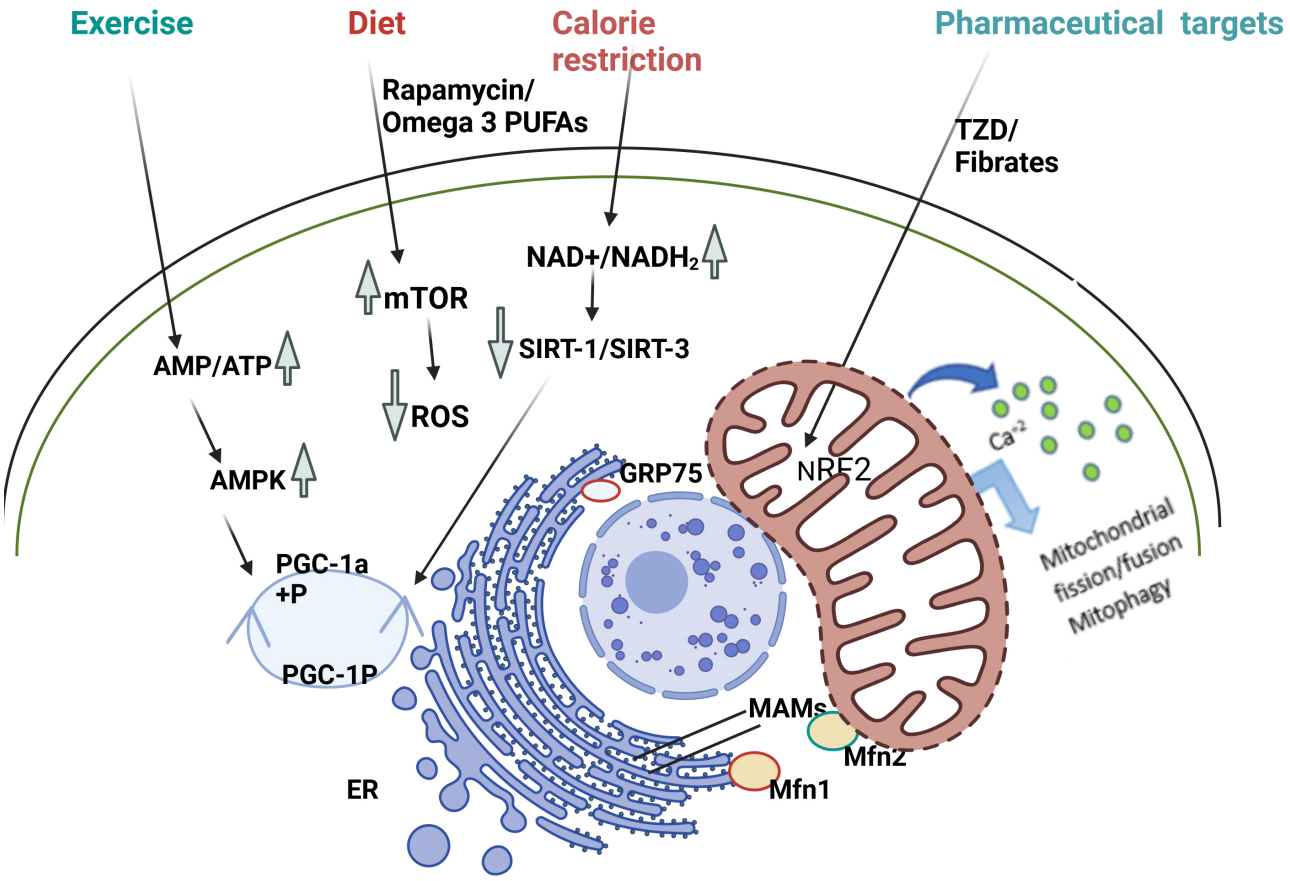

Fig. 4. Schematic representation of possible therapeutic targets of mitochondrial dysfunction in disease. Diet, exercise, calorie restriction, or diet with PUFAs increase the mammalian target of rapamycin (mTOR) signaling pathways of cell survival and energy production (adenosine triphosphate (ATP)/NADH2) and AMPK production, in turn, activate peroxisome proliferator activated receptor gamma coactivator-1 alpha (PGC-1α) (phosphorylation) and Nuclear respiratory factor 2 (NRF2) activation. Along with pharmacological targets of thiazolidines (TZD) and rapamycin, the reserve to mitochondria and their associated membranes and mitofusins (MFNs) also alter mitochondrial fission/fusion, leading to therapy against mitochondrial dysfunction.

insights/research into the role of mitochondrial dynamics in pathogenesis have important therapeutic implications [109,110].

Pharmaceuticals Targeting Mitochondrial Biogenesis

Other targets in the prevention and treatment of obesity and diabetes include AMPK/SIRT activators [111,112] resveratrol, and cyclic guanosine monophosphate (cGMP) modulators [113] that act on mitochondrial dysfunction as the primary target. The factors illustrated in Fig. 4 can stimulate/regulate the OXPHOS function, mitochondrial DNA replication, and biogenesis. Interestingly, patients with type 2 diabetes and obesity demonstrated reduced expression of MFN2, which may be related to the reduced function of mitochondria in skeletal muscle [114]. Pharmacological approaches to enhance or block specific target sites in injured mitochondria or mitophagy are attractive treatment strategies for diabetic vascular diseases like myocardial infarction and diabetic nephropathy [115]. Furthermore, drugs that have actions similar to but more specific and potent compared to thiazolidinediones, fibrates, metformin, sirtuins (SIRTs), and rapamycin can be developed along with Mdivi-1 and S3 that may prove to be beneficial against diabetic nephropathy [112,116,117].

Conclusion

This review outlines the mitochondrial role in β-oxidation and maintenance of lipid homeostasis and its effect on metabolic disorders such as diabetes, obesity and cancer which have an alteration in MAMs leading to mitochondrial dysfunction. We also explored the significance of PUFAs which can alter cell survival by acting on the mTOR pathway, oncogenes, ROS production, regulation of lactic acid production and modulating the Warburg effect, and ultimately affects energy production and homeostasis, which in turn regulates cell proliferation and metastasis. Our studies revealed that PUFAs (especially gamma-linolenic acid, arachidonic acid, eicosapentaenoic acid and

docosahexaenoic acid) at the doses tested do not affect normal cell survival but could selectively suppress tumor cell proliferation and induce their apoptosis. This differential action of PUFAs on normal and tumor cells seems to be related to the ability of these fatty acids to selectively enhance free radical generation and consequent formation and accumulation of toxic lipid peroxides only in the tumor but not in normal cells. Based on the discussions in the preceding sections, we suggest that potential pharmaceutical targets that can act on mTOR/AMPK pathways leading to changes in mitochondrial fission/fusion and thus provide a unifying therapy against mitochondrial dysfunction and metabolic diseases as outlined above.

Availability of Data and Materials

All have been included in the manuscript.

Author Contributions

SB and UND designed, drafted, and finalized the manuscript. Both authors contributed to editorial changes in the manuscript, and read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

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Conflict of Interest

Undurti N Das is the founder of UND Life Sciences and the authors declare no conflict of interest. Undurti N Das is serving as one of the Editorial Board Members and Guest Editors of this journal. We declare that Undurti N Das had no involvement in the peer review of this article and has no access to information regarding its peer review.

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