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Nuclear Encoded Mitochondrial Proteins in Metabolite Transport and Oxidation Pathway Connecting Metabolism of Nutrients

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Additional information is available at the end of the chapter

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Abstract

In the mitochondria, there are ongoing processes essential to the survival of cells associated with the production of energy ending in the oxidative phosphorylation and the formation of ATP, constituting a form of energy for majority of metabolic processes. Except for nutrient oxidation in the citric acid cycle interfacing with the process of oxidative phosphorylation, mitochondria are linked to a number of metabolic pathways ongoing directly in mitochondria or indirectly in cell compartments by serving substrates. Mitochondrial activities maintenance requires continual draw of intermediates from cytosol through the double mitochondrial membrane as well as transport in the reverse direction. Interconnection and regulation of all the processes are mediated by transporters and carriers, activities of which are affected by cell and body requirements. In the chapter, the main transport systems localized in membranes of mitochondria, their regulation, affection, and disorders in the background of mitochondria aberrant functions are described. Voltage-dependent anion channels, translocase of mitochondrial outer membrane, deoxynucleotide carrier, ADP/ATP nucleotide translocase, and phosphate carrier in mitochondrial inner membrane are among them. In more detail, the pyruvate carrier and its abnormal activity, but also others as di- and tri-carboxylate, glutamate, and ornithine carriers, are characterized. The uncoupling protein, as solute carrier family members, involvement is also mentioned.

Keywords: carrier, mitochondria, mitochondrial inner membrane, mitochondrial outer membrane, transporter

1. Introduction

Mitochondria are two membrane organelles present in all cells that have a nucleus. They are the energy center of the cells. Their primary role is the production of ATP in oxidative

phosphorylation, and the basis of the aerobic oxidation is the citric acid cycle interconnection representing the final metabolic pathway of oxidation of all major nutrients to the respiratory chain where oxidation of reduced coenzymes results in ATP formation. The nutrient to be oxidized must transfer the mitochondria by means of the transporters, as pyruvate produced in glycolysis in the cytosol. After fatty acids released by hydrolysis of lipoproteins or triacylglycerols transport across the mitochondrial membranes, acetyl-CoA arising from β -oxidation enters the citric acid cycle. Similarly, amino acids or their catalytic products enter the citric acid cycle at different sites. The production of energy in mitochondria from various nutrients is controlled by the availability of the individual nutrients that a given organ or tissue can use. For example, in excess of carbohydrates, the energy is obtained from glycolysis rather than from fatty acids and amino acids. The needs for ATP produced in oxidative phosphorylation vary in different cell compartments, and therefore it is efficiently transported out of mitochondria. Through the activity of uncoupler proteins, mitochondria also regulate energy production in the form of heat. In addition to providing different forms of energy, mitochondria are involved in other important metabolic processes. In the excess of saccharides, the acetyl-CoA resulting from pyruvate is not used in the citric acid cycle but is transported to the cytosol for the synthesis of more energy-efficient reserve, triacylglycerols. When there is a lack of glucose, mitochondria provide the intermediates for gluconeogenesis, but also participate in the synthesis of various substances, such as urea, heme, and polyamines. Reactive oxygen and nitrogen species production and triggering the intrinsic apoptotic pathway are other significant functions. They synthesize proteins from their own DNA, but most mitochondrial proteins are encoded by nuclear genes. Mitochondria are the sole site for Fe-S cluster biogenesis, which is also the only fully conservative function. The diversity and importance of biochemical pathways taking place in the mitochondria require the access of substrates and transport products generated outside the mitochondria. In terms of ensuring the normal physiological functions of the mitochondria, it is therefore crucial to ensure the transfer of the substances through the mitochondrial membranes separating the organelle from the cytoplasm, thus allowing the course of these specialized metabolic processes. Therefore, the chapter is focused on the mitochondrial transport proteins, transporters of citric acid cycle intermediates, localized in mitochondrial outer and inner membrane, since their activities significantly affect the functions of mitochondria and subsequently functions of the given organ, tissues, and the whole organism.

2. Mitochondrial outer membrane transport proteins

The mitochondrial outer membrane (MOM) is characterized by higher lipid content than inner membrane and is permeable to small molecules such as sucrose, salts, adenine nucleotides, coenzyme A, and tRNA. It is not permeable to larger molecules such as inulin, polyglucose, cytochrome c, or albumin [1]. The outer mitochondrial membrane contains three integral membrane protein families. The entire translocation and insertion of nearly all newly synthesized proteins destined to the mitochondrial organelle is mediated through channels as part of larger protein complexes, translocase of the outer membrane (TOM complex), the sorting and assembly machinery (SAM) complex (followed by translocase of the inner membrane of mitochondria (TIM)) [2]. Channels, generally, are used to conduct ions and cycle between open and closed states, with

some also exhibiting an inactivation step forming a completely continuous tunnel through a bilayer that allows for rapid conductance of many ions [3]. The third protein family are voltage-dependent anion channels (VDAC), which are permanently open under physiological conditions with some evidence-based regulations [4]. VDAC is the most abundant protein of outer mitochondrial membrane (~10 thousand copies per mitochondrion), whose functions in permeability of compounds between cytosol and mitochondria have been shown to be related either to physiological or pathological states [5–7]. Many cases of abnormal manifestations of mitochondria are the consequence of this type of regulation of the mitochondrial outer membrane permeability [8].

2.1. Voltage-dependent anion channel

The functions of VDAC related to four main aspects are controlling of transport of metabolites and ATP transport between mitochondria and cytoplasm, forming part of mitochondrial permeability transition pore; modulation of inner mitochondrial Ca^{2+} level through connection to endoplasmic reticulum calcium release channel IP3R with glucose-related protein 75 and through phosphorylation cluster sorting protein 2 (PACS2), regulating Bid of Bcl2 pro-apoptotic factor family-mediated apoptotic pathways; and regulation of intracellular redox substances [9]. VDAC is a way of transiting reactive oxygen species (ROS) from mitochondria to cytoplasm, though it reacts directly with the NO leading to decrease in permeability and inhibition of mitochondrial transition pore [10].

VDAC, mitochondrial porin, forms a barrel comprised of a transmembrane alpha helix and 13- and more transmembrane beta strands. Beta barrel encloses a channel large in diameter (~3 nm), which is permeable to molecules up to ~5 kDa in the open configuration [11]. *In vitro* studies have shown a conserved property of eukaryotic VDAC channels to adopt multiple conductance states [12]. In humans, three isoforms of VDAC (VDAC 1–3) located on chromosome 5, each of 30 kDa, are known [13]. VDAC1 and 2 have prototypic voltage gating, but VDAC2 also has a second discrete lower conductance and ion selective state. VDAC3 is not fully voltage-dependent [14], and unlike the previous two types, VDAC3 is evenly distributed [15].

The role of membrane potentials (Ψ) in the physiological regulation of VDAC conductance is considered with regard to appearance of Donnan potential across the outer membrane [16]. However, ambiguity is not confirmed due to the presence of charged macromolecules on both sides of outer membrane, and high ionic strength of intracellular environment decreasing Donnan potentials and causing closure of channels. Differences in pH across the outer membrane indicate the presence of Donnan potential of ~–40 mV, close to a gating potential for VDAC [17]. Positive and negative $\Delta\Psi$ close VDAC symmetrically with half maximal closure at ± 50 mV. In the open state, anions are favored over cations, but the selectivity is weak. In the closed state, VDAC becomes a cation selective pore of 1.8 nm in diameter that still conducts small cations, such as K^+ , Na^+ , and Ca^{2+} , as well as Cl^- , whose movement through VDAC collapses electrical potentials [16]. In most conductive, open state, VDAC shows significant preference especially for metabolic anions. The states of lower conductance reduce permeability to metabolic anions, thus greatly diminishing metabolite flux across the outer mitochondrial membrane [18]. The flux of charged metabolites does not significantly contribute to the membrane potential because it is confined by the internal mitochondrial membrane transport, which

is even 2 orders of magnitude less than the flux of small ions through VDAC in the closed state. However, when VDAC closes, the transition of major anionic metabolites (as creatine phosphate, ATP, ADP, Pi, and respiratory substrates) is prevented [19]. A number of papers have been published that confirm the VDAC conductance regulation by several factors contributing to the explanation of mitochondria dysfunction and affection by the energy metabolism of cells.

3. Physiological implication of VDAC affection by membrane bound proteins

It has been shown that the disruption of mitochondrial functions is linked to the occurrence of mutations in genes encoding various types of intermediate filament proteins. In humans, the different morphology, distribution, and function of mitochondria in patients with neurological disorder [20, 21], types of myopathies [22, 23], or epidermolysis bullosa simplex [24] were documented. The cytoskeleton proteins as tubulin, desmin, vimentin, and plectin have been found to interact with mitochondrial outer membrane, where they are involved in the ATP/ADP transmission control through VDAC, thus mediating or influencing mitochondrial functions.

3.1. Tubulin

Tubulin binds with high affinity to cellular membranes, and bound to mitochondrial membranes represent ~ 2% of total cellular tubulin [25]. It is important for ensuring intracellular transport and DNA segregation in cell division. Rostovtseva et al. [19] have found induction of fast, reversible blockade of VDAC conductance by tubulin at nanomolar concentration in 1–100 ms range. Closing occurs in concentration-dependent manner and negative potential as low as 5 mV. The type of VDAC, phosphorylation level, and membrane lipid composition have an impact on VDAC blocking. Change in channel selectivity in blocked state results in impermeability to ATP [26]. The restriction of ATP/ADP and other respiratory substrates fluxes leads to reduction of oxidative phosphorylation and promotion of apoptosis. Therefore, signals that enhance VDAC-tubulin binding by kinase-regulated phosphorylating VDAC or by increasing the concentration of available free tubulin in the cytosol would reduce mitochondrial respiration [27].

3.2. Desmin

One other regulating mitochondria affinity to ADP and oxygen consumption through direct binding to VDAC is the muscle-specific intermediate filament protein, desmin. The function of desmin is to form a three-dimensional scaffold that interconnects the contractile apparatus to the nucleus, cellular organelles, and the sarcolemma [28]. Proximity of sarcoplasmic reticulum and mitochondria by desmin scaffold allows facilitation of direct protein and metabolite targeting to mitochondria [29–31]. Interaction of desmin with contact sites (VDAC, adenine nucleotide translocator (ANT) and mitochondrial contact site complex) affects mitochondrial permeability transition pore (mtPTP) behavior and respiratory function [32, 33]. Studies on mice have shown that desmin deficiency leads to development of skeletal and myocardial defects associated with a deteriorated structure and function of mitochondria [22, 34].

Mitochondrial abnormalities cause cardiomyocyte death and myocardial degeneration, accompanied by inflammation and fibrosis, resulting in dilated cardiomyopathy and heart failure [35–38]. The cardiac-specific small heat-shock protein, α B-crystallin, was proven to rescue desmin-deficient heart failure and maintain mitochondrial functions through inhibition of mtPTP. In addition, similarly as tubulin, desmin affects mitochondrial bioenergetics through interaction with VDAC and ATP synthase [39].

3.3. Vimentin and plectin

Association of vimentin with mitochondria increases mitochondrial membrane potential and has an important function in controlling the production of ATP to various sites in the cytoplasm [40]. As a possible mechanism of action, the similarity of the mitochondrial binding site on vimentin with the domains targeting outer mitochondrial membrane is reported. The domains interact with the VDAC, increasing its permeability for several negatively charged compounds (such as pyruvate, succinate, ADP, etc.), thus compensating decreasing membrane potential effects of hexokinase [41], or tubulin. A study by Winter et al. [42] suggests that plectin 1b also plays an important role in regulating mitochondrial outer membrane permeability to ADP and ATP through VDAC.

4. VDAC regulation by mitochondrial kinases

4.1. Hexokinases

Mitochondrial localized kinases, hexokinase, and creatine kinase have been shown to regulate outer VDAC conductance [43–45]. There are three isoforms of hexokinases (fourth is glucokinase) known to mammals, whose role is to retain glucose in the cell by phosphorylation at position 6, thereby subsequently metabolizing in glycolysis and pentose phosphate pathways. Isoenzymes are of different subcellular localization: I and II are localized in the outer mitochondrial membrane reflecting controlling glycolysis, and III and IV in the nuclei and cytoplasm more reflecting the synthesis of glycogen and the pentose-phosphate pathway. Along with highly elevated levels of aerobic glycolysis (and suppression of mitochondrial respiration, Warburg effect) when compared to healthy tissue, high expression of hexokinase and more than doubled activity concurrently with VDAC closure were found in cancer cells [8, 46–48].

Both glucose phosphorylation reaction and hexokinase binding to VDAC have been found to pronounce protective effects against cell death [49]. A study by Azoulay-Zohar et al. [41] shows hexokinase-I acting through its N-terminal mitochondrial binding domain block conductance of rat liver mitochondrial VDAC and block opening of mtPTPs. An outer membrane potential generation (OMP) by hexokinase bound to VDAC allows electrical suppression of mitochondria and calcium extrusion from mitochondrial intermembrane space (IMS). Interestingly, a significant limitation on the permeability of the MOM is the reaction velocity of hexokinase binding to VDAC that is only mild per se but the OMP becomes high enough to prevent release of ADP from mitochondrial inner membrane (MIM), which should lead to inhibition of the hexokinase reaction. Yet, OMP values directly depend on percentage bounds

formed, glucose concentration, metabolic conditions, and the presence of tubulin-like effectors increasing VDAC voltage sensitivity [4]. Prevention of ATP production together with higher hexokinase activity favors glycolysis. Research has shown that cancer cells respire in the absence of glucose, suggesting that VDAC blocking is not absolute, and the respiration increases with the addition of glucose. Increase in respiration is attributed to the formation of ADP in the hexokinase-catalyzed reaction and subsequent stimulation of oxidative phosphorylation. Since not all VDACs are closed, preferential access to mitochondrial ATP may be allowed for the hexokinase reaction [8]. Another principle applies if ATP from cytosol is readily available for hexokinase, leading to so-called turbo effect of uncontrolled glycolysis activation and development of metabolic burst [4].

The product hexokinase-catalyzed reaction, glucose-6-phosphate, was found to potentiate ATP release from mitochondria with the recovery of normal metabolism, and substrate replacement, even increased by induction of release of hexokinase and glucokinase from bound to VDAC [4, 41, 50]. Therefore, the effect of hexokinase dissociation from VDAC is the subject of many studies dealing with the development of potent chemotherapy of cancer diseases.

Most interestingly, there is a view of influencing metabolism of the mitochondria by blocking VDAC after binding of glucokinase in pancreatic beta cells. The glucokinase acts as a glucose sensor to maintain glucose homeostasis also in neurons, pituitary, and endocrine K and L cells [51], as its K_m of approximately 5 mM matches the set point of blood glucose [52]. An alternatively spliced glucokinase with an additional N-terminal sequence that promotes glucokinase binding to both mitochondria and secretory granules is expressed in pancreatic beta cells [53]. Glucose-6-phosphate formed after glucose enters beta cells acts to dissociate glucokinase from mitochondria and open VDAC permitting mitochondrial uptake of ADP, Pi and respiratory substrates, formation of ATP, and release of ATP into the cytosol. Increased cytosolic ATP/ADP then inhibits K_{ATP} channels, which causes plasmalemmal depolarization, activation of Ca^{2+} channels, and Ca^{2+} -dependent exocytosis of insulin granules [8]. Then, respiratory substrates that require the passage through VDAC, such as pyruvate, lactate, and long-chain fatty acids, do not trigger insulin synthesis directly. But their permeable substrates without the need for VDAC transport such as short-chain fatty acids or methylpyruvate are capable of insulin synthesis induction [54]. Ahmed et al. [55] found that under glucotoxic conditions upregulation of VDAC1 expression occurs initiating a mitochondrial death cascade and beta cell dysfunction.

4.2. Creatine kinases

Two creatine kinase (CK) isoforms are expressed in vertebrate tissues, namely dimeric cytosolic and octameric mitochondrial located in the peripheral intermembrane space and the cristae MIM (MtCK) [56]. In addition, there are tissue-specific mitochondrial isoforms in the sarcomers of striated muscles (sMtCK), and in most other tissues, they are present as ubiquitous MtCK (uMtCK) [57]. Similar to hexokinase, creatine kinase acts as energy sensor and mediates antiapoptotic effect through VDAC-ANT complexes with preferential use of mitochondrial ATP [41, 58].

Isoenzymes are associated to subcellular structures, forming microcompartments that facilitate a functional coupling, e.g., a direct exchange of ADP and ATP between the association partners

without mixing with bulk [59]. In IMS, MtCK renders a high affinity to cardiolipin and other anionic phospholipids forming a cross-link of two peripheral mitochondrial membranes [60] and to ANT, thus forming a complex of MtCK-VDAC-ANT and cardiolipin. The MtCK-VDAC association is enhanced at physiological calcium concentrations [61]. MtCK associates only with inner membrane and ANT in the cristae space. MtCK preferentially uses mitochondrial ATP that is exported via ANT to phosphorylate creatine, which has a higher diffusion rate in comparison to ATP, thus providing spatial energy shuttle. The locally produced ADP is immediately reimported into the mitochondrial matrix space via ANT, and phosphocreatine is then released into the cytosol via VDAC [62]. It keeps maintaining a relatively low [ATP]/[ADP] ratio in the mitochondrial matrix to stimulate oxidative phosphorylation. The degree of such metabolite channeling varies among different tissues, species, and developmental states [63].

Changed functionality of the CK essentially leads to changes in energy flows as well as calcium homeostasis, leading in particular to changes in muscle activity. Up to 40% of the cellular volume of the heart consists of mitochondria, with sMtCK activity being the highest among all tissues and representing up to 25% of CK activities [64]. Reducing its activity is the cause of congestive heart failure [65]. As is well reviewed in Schlattner et al. [62] with impairment of the CK system, dilated cardiomyopathy, hypertrophy, and heart failure were found in animal models. In addition, the protective effect of creatine supplementation and hence the enhancement of the CK system have been found to be beneficial in human Duchenne muscular dystrophy, mitochondrial cytopathies, and phosphorylase deficiency and in animal models of amyotrophic lateral sclerosis, Huntington's disease, Parkinsonism, and brain ischemia. However, as found in the study by Qian et al. [66], overexpression of uMtCK increased survival ability of cancer cells and downregulation of mitochondrial apoptotic pathway proteins.

5. Some other factors affecting VDAC conductance

Besides the aforementioned intermediate filament proteins and mitochondrial kinases, the conductivity of VDAC as described by Lemasters et al. [67] is regulated by a number of other factors, for example, Bcl-2 family members, protein kinase A, glycogen synthase 3 β , protein C kinase ϵ , NADH, Ca²⁺, ATP, and glutamate [68].

Protein kinase A phosphorylates VDAC and thus increases its sensitivity to tubulin and decreases VDAC conductance [69]. Glycogen synthase 3 β -mediated VDAC phosphorylation promotes VDAC opening [70].

The Bcl-2 protein family belongs to the key factors in the regulation of apoptosis, modulation of Ca²⁺ and signal transduction pathway. The Bcl-2 protein as anti-apoptotic protein prevents the release of cytochrome c and the activity of caspase. Bax, the main regulator of Bcl-2 activity, can interact with VDAC to increase VDAC aperture and increases mitochondrial permeability, promoting apoptosis [71]. The proper proportion of Bax and Bcl-2 maintains the cell homeostasis to ensure cell survival [72].

Lemasters et al. [67] introduced a concept of aldehyde-dependent VDAC closure, mitochondrial uncoupling, and disruption of normal mitochondria functioning resulting from ethanol

metabolism effects. Aldehydes derivation during lipid peroxidation, VDAC closure is probably a common feature leading to liver pathologies as was pointed out on almost indistinguishable histopathological manifestations in alcoholic liver disease, nonalcoholic fatty liver disease, non-alcoholic steatohepatitis, and toxicant-associated steatohepatitis. Ethanol is metabolized predominantly by the liver in two-step oxidation: first to acetaldehyde (AcAld) by catalytic action of alcohol dehydrogenase (ALD) followed by oxidation to acetate by aldehyde dehydrogenase (ALDH). The first step undergoes in cytosol and peroxisomes by effect of cytochrome P4502E1 and catalase. Although the oxidation is prevalent over ALD, the consequence of cytochrome P450 metabolism is overwhelmingly negative due to the formation of ROS, e.g., hydroxyethyl radicals. Of the 19 known mammalian ALDH genes, mitochondrial ALDH2 with high affinity for AcAld ($K_m < 1 \mu\text{M}$) is the most important for AcAld oxidation (and detoxification) to acetate [73]. In both reactions, by oxidation of 1 mole of ethanol, 2 moles of NADH are formed, further requiring oxidation in the respiratory chain. As little as 2.5 h after a single bolus dose of ethanol ingestion a swift increase of alcohol metabolism (SIAM), an adaptive increase of hepatic ethanol metabolism occurs [74]. Mitochondrial respiration causing NADH oxidation nearly doubles, but it does not lead to increased ATP generation. To the contrary, hepatic ATP decreases, glycolysis is stimulated, and glycogen stores are depleted. Furthermore, mitochondrial β -oxidation of fatty acids becomes inhibited, promoting fat accumulation within hepatocytes (steatosis) [75]. This is probably the result of decrease in MOM permeability most likely by VDAC closure, promoting selective oxidation of AcAld, since VDAC closure blocks mitochondrial ATP release, respiratory substrates uptake, and uptake of fatty acids for β -oxidation [67]. Adrenergic hormones release free fatty acids from adipose tissue, which serve as substrates for long-chain fatty acid peroxisomal β -oxidation. The ensuing peroxisomal H_2O_2 formation then can promote catalase-dependent alcohol metabolism [67]. AcAld is toxic to mitochondria and aggravates oxidative stress by binding to GSH and promoting GSH leakage [76]. Moreover, as mentioned before, ethanol metabolism and also NADH overproduction cause formation of ROS, lipid peroxidation, onset of the mitochondrial permeability transition, and apoptosis [77]. However, as has been showed, short- and medium-chain fatty acids can cross mitochondrial membrane freely using carnitine shuttle or other transport system [78] and therefore are presented in diet capable to prevent steatosis development.

5.1. Translocase of the MOM

The endosymbiotic relationship of α -proteobacteria and archaic eukaryotic cell results in massive loss and transfer of coding sequences from mtDNA to the nucleus and only less than 1% is retained in today's mtDNA. Thus, most mitochondrial proteins (1000–1500) undergo cytosol translation and are subsequently transferred to mitochondria, requiring membrane complexes of protein translocators, translocases, or translocons. They include TOM and TIM for large conductance channels with almost identical properties [79]. In addition, other mitochondria protein translocators like TOB/SAM complex in MOM and Mia40/Tim401-Erv1 redox translocator in MIM have been identified [80, 81].

The general entry gate for mitochondrial proteins is thought to be TOM40 complex in MOM consisting of core sequence Tom40, Tom22, Tom7, Tom6, Tom5, peripheral associated receptors Tom20, Tom70, and a minor component Tom71. Among them, only Tom40, Tom22, and

Tom7 commonly occur in eukaryotic organisms [82]. To prevent misfolding and aggregation, hydrophobic segments of mitochondrial precursor proteins are shielded in cytosol by chaperones that escort them to the mitochondria surface [83]. These chaperones are Hsp70 (and its partner J proteins), Hsp90, and mitochondrial import stimulation factor (MSF) [84]. MSF with precursor proteins loaded was suggested to bind to Tom70 and forward proteins to Tom20, with ATP consumption, while Hsp70 transfers proteins to Tom70 without ATP hydrolysis [85]. In addition, it was found that mitochondrial proteins are also allowed to bind Tom20 directly without Hsp70 [86]. Except for some α -helical outer membrane proteins, virtually all precursors initially enter mitochondria by passing a TOM complex. As also discussed by Dudek et al. [2], many IMS proteins are imported by the mitochondrial intermembrane space import and assembly (MIA) machinery, which couples sorting of client proteins to their oxidative folding through a disulfide bridge formation. Small Tim chaperones of IMS bound to outer membrane β -barrel proteins transfer preproteins to the sorting and assembly machinery (SAM), allowing their integration into the MOM. Tim chaperones also convoy mitochondrial metabolite carrier proteins through the IMS, which are then integrated into the MIM by translocase of the inner membrane 22 (TIM22) complex in a membrane potential-driven manner. Preproteins of matrix-targeted proteins are directly transferred from TOM to TIM23 (presequence translocase) without IMS chaperones, ensuring their translocation into the matrix or later sorting into the MIM. The only source of energy for lateral membrane integration is membrane potential. Complete import of preproteins into the matrix requires the ATP-dependent presequence translocase-associated import motor (PAM).

Affection by the TOM40 complex functions leads to dysfunction of mitochondria and oxidative damage and is in the background of misfolding protein diseases. Bender et al. [87] found a significantly reduced TOM40 in the brain of Parkinson's disease patients in connection with increased mtDNA damage and α -synuclein transgenic mice together with altered levels of complex I proteins. The stable complexes of accumulated truncated amyloid precursor protein and TOM40 cause mitochondrial dysfunction in brains of Alzheimer disease patients [88]. Other diseases in humans associated with abnormal mitochondrial transport of proteins, as reviewed in MacKenzie and Payne [89], are primary hyperoxaluria type I (caused by alanine/glyoxylate aminotransferase 1 deficiency), pyruvate dehydrogenase deficiency, susceptibility to severe alcoholic liver disease (caused by increased Ala-MnSOD activity due to inability to transfer Val-MnSOD through MIM), deafness dystonia syndrome (caused by mutations in IMS protein deafness dystonia peptide 1), dilated cardiomyopathy with ataxia (caused by dysfunctional import of matrix proteins through the TIM23 complex), spastic paraplegia (dysfunction of Hsp60), and atypical mitochondria disease involving multisystem failure (deficiency in Hsp60 causing decrease in mitochondrial metabolic pathways).

6. Mitochondrial inner membrane carriers

The inner mitochondrial membrane is relatively low permeable to ions in order to minimize energy dissipation formed on complexes through generation of electrochemical proton gradient, in its direct link with ADP phosphorylation. Random flow of charged metabolites

via MIM would lead to a reduction in the membrane potential and ATP formation [1]. The relative impermeability of the MIM is the basis of chemiosmotic hypothesis proposed by Mitchell. As discussed in O'Rourke [90], Mitchell recognized three modes of ion transport. Symporters cotransport multiple ions (or an ion and a metabolite) in the same direction across the membrane often utilizing the asymmetric electrochemical ion gradient to drive the transport in a thermodynamically favorable direction, as for example mitochondrial P_i/H^+ carrier. Antiporters exchange ions on different sides of the membrane. Antiporters can be electro-neutral (the Na^+/H^+ antiporter of the mitochondrial or plasma membrane) or electrogenic. For electrogenic transporters, ion flux is driven by both the electrochemical gradients of the transported ions and the membrane potential. For uniporters, the transport rates are in the range of 10^4 – 10^6 ions s^{-1} , based on ions flowing down their electrochemical gradient.

Mitchell and Moyle [91] reported that anions, including P_i , succinate, and malonate, accelerated the rate of decay of the pH gradient induced by a pulse of oxygen. This suggested the presence of anion transport systems coupled to proton movement, leading to the identification of the anion/metabolite-coupled cotransporter family. Inner membrane anion uniporters have been less well studied, but in the 1980s, an inner membrane anion channel was postulated to account for anion-selective mitochondrial swelling responses [92]. Moreover, some mitochondrial membrane proteins (e.g., mitochondrial uncoupling protein) were identified to display anion channel activity [90]. Based on the research, seven metabolite-specific mitochondrial transporters or carriers were proposed. Studies of amino acid sequence composition showed that the carriers form a well-defined family (in humans known as the solute carrier 25 family (SLC25)), with the one defining feature, a tripartite structure of three homologous sequence repeats of about 100 amino acid residues each, which was first noted in the published sequence of the bovine ADP/ATP carrier [93]. A signature motif containing P-X-[D/E]-X-X-[R/K] sequence is conserved in all members and in all three sequence repeats [94]. According to typical sequence repeats and signature motif, eukaryotic mitochondria were found to contain 35–55 different carriers when compared to genomic DNA database [95]. The human genome encodes 48 members of the SLC25 family, of which 30 are identified [96]. The isoforms of carrier members are encoded by different genes, and only the phosphate carrier has two alternatively spliced isoforms [97].

6.1. Mitochondrial nucleotide transporter

Several proteins have been identified as carriers for purine nucleotides, their analogues, as well as pyrimidine nucleotides. The ANT was identified by Kramer and Klingenberg [98]. Other specific proteins as GTP/GDP carriers, peroxisomal adenine nucleotide transporter, CoA and S-adenosylmethionine transporters belong in [99–102].

6.1.1. ADP/ATP translocase

Deoxynucleotide carrier ((DNC) SLC25A19) transports all dNDPs in exchange for ATP or ADP [103]. The protein was later identified as thiamine pyrophosphate carrier (TPC) [104], transporting thiamine pyrophosphate, thiamine monophosphate, and deoxynucleotides in descending order of potency $dNDP > dNTP > dNMP$. The protein is also capable of nucleotide transport, though less efficiently. The protein is ubiquitously expressed within tissues, with the highest levels in the kidney and lung [103].

The mutation in gene-encoded DNC (chromosomal localization 17q25.1) is known to be associated with Amish microcephaly. Amish microcephaly has only been observed in Old Order Amish community in Pennsylvania, U.S.A, with a high prevalence of about 1:500. The disease is characterized by severe congenital microcephaly, elevated levels of α -ketoglutarate in urine, and premature death. The only non-CNS physical anomaly is moderate micrognathia. Patients manifest no orientation to sight or sound and no fine or gross motor development and have metabolic acidosis enhanced by episodic viral illnesses, and in some cases patients have mild hepatomegaly and difficulty maintaining normal body temperature and develop increasing irritability [97]. Study on SLC25A19 knock-out mice has shown that metabolic abnormalities in humans are due to absent TPC activity [104].

6.1.2. Deoxynucleotide carrier

Four ANT isoforms are encoded in human genome on the chromosome X. ANT1–3 are structurally similar and proteins are about 90% identical, and ANT4 only shares 66–68% consistency in the amino acid composition with other isoforms. Isoforms are specifically expressed in different types of cells and tissues. ANT1 (SLC25A4) is expressed in the skeletal muscle, brain, and heart. ANT2 (SLC25A5) is expressed in the liver and proliferating cells and is over-expressed in various types of cancer cell lines. ANT3 (SLC25A6) is ubiquitous in all tissues, and ANT4 (SLC25A31) is specific to the testis and germ cells [105]. The translocase is highly selective of the adenine nucleotide and provides a continuous shift of ADP to the mitochondria required to maintain oxidative phosphorylation and membrane potential. ANT is also implicated in leakage of protons and inducible proton leakage [106, 107].

Impaired translocase activity affects the energy metabolism of the cell by decreasing mitochondrial ATP synthesis and increasing mitochondrial membrane potential [108], thus contributing to the promotion of apoptosis. The rate-limiting factor of apoptosis is mtPTP formation, which is actually increased permeabilization of the mitochondrial membrane for all the solvents up to 1.5 kDa. It is a nonspecific pore, where ANT, VDAC, cyclophilin D, hexokinase, creatine kinase, and peripheral benzodiazepine receptor are effective but not as direct components or core structures. Moreover, there is an evidence for apoptosis regulators of the Bcl-2 family, Bak and Bax, requirement for mtPTP-dependent MOM permeabilization [109]. PTP opening is linked to mitochondrial dysfunction because its occurrence leads to the set of consequences that will arise, as mitochondrial depolarization, cessation of ATP synthesis, Ca^{2+} release, pyridine nucleotide depletion, inhibition of respiration and matrix swelling, MOM rupture, and release of pro-apoptotic proteins such as cytochrome c, endonuclease G, and AIF [110, 111]. Detrimental effects are seen for long-lasting mtPTP opening, while short-term effects are involved in physiological regulation of Ca^{2+} and ROS homeostasis [112, 113].

Cancer cells are able to survive suppression of mitochondrial oxidative phosphorylation under hypoxic conditions through higher rate of glycolysis; however, it depends on ATP uptake especially for mitochondrial potential generation and Ca^{2+} exchange [114]. The expression of ANT isoforms is related to the adaptation of metabolic properties of cancer cells. ANT2 is over-expressed in various types of human cancer cells and in several hormone-dependent cancers [115, 116]. It was found that ANT2 proves properties allowing the import of ATP into mitochondria (in coexpression with hexokinase II and a subunit of mitochondrial F₀F₁-ATPase, ATPsyn β),

increased glycolysis, maintaining mitochondrial membrane potential, and finally prevention of apoptosis [115]. The effect of hexokinase has been described in Section 4.1. Similarly, the ATP synthasome, a complex of ANT, F₀F₁-ATPase, and phosphate carrier (PiC), facilitates a mechanism for adenine nucleotide and pyrophosphate release. Under pathological conditions, the imported ATP may also be hydrolyzed by F₀F₁-ATPase to maintain mitochondrial membrane potential [115]. This type of hydrolysis has also been reported in order to prevent neurodegeneration [117] and in activated macrophages [118].

Roussel et al. [119] found isoforms ANT1 and 2 to mediate uncoupling by fatty acids and to lower mitochondrial membrane potential in heart and skeletal muscle in rats. ANT is inhibited by competitive displacement of the nucleotide by long-chain acyl-carnitines (LCAC) [120]. LCAC may accumulate under pathological conditions with excess lipid supply, obesity, and mitochondrial β -oxidation defects [121]. ANT inhibition is thought to contribute to mitochondrial defects in metabolic syndrome [122].

The ANT function in subcellular compartment energy supply is important and therefore it is not surprising that the altered structure and subsequently properties of this solute carrier protein associated with DNA mutations are also associated with serious clinical conditions. Mutations linked to mitochondrial disorders with autosomal recessive inheritance cause mitochondrial myopathy and cardiomyopathy presented in childhood or early adulthood. It is characterized by lactic acidosis, fatigue, proximal muscle weakness, and exercise intolerance [123, 124]. Several different autosomal-dominant mutations in ANT1 gene have been associated with an adulthood-onset disorder, autosomal-dominant progressive external ophthalmoplegia, characterized by ptosis, restriction of eye movement, and accumulation of clonally expanded mtDNA deletions in postmitotic tissues [125, 126]. Thompson et al. [127] have recently described recurrent *de novo*-dominant mutation with severe early-onset of mitochondrial disease. Mutations in the gene encoding ANT1 are associated with the presence of mtDNA deletions. The most likely mechanism of how the defective carrier affects the appearance of mtDNA mutations is the insufficient adenine nucleotide availability for dATP synthesis and consequent imbalance in dNTP pools [127].

6.2. Mitochondrial phosphate carrier

The role of mitochondrial phosphate carrier (PiC, SLC25A3) is importing inorganic phosphate into the mitochondrial matrix. A part of ATP synthasome enables efficient energy production, since Pi is essential for F₁F₀-ATP synthase to catalyze formation of ATP from ADP. For PiC, two isoforms differing in alternative splicing of mutually exclusive exon are documented in tissue-specific expression pattern. PiC-A is expressed in heart and skeletal muscle, while PiC-B is expressed in liver, kidney, and other tissues [128]. The PiC gene is located on chromosome 12q23.1. In 2007, the presence of a homozygous mutation in PiC-A was found in two siblings of nonconsanguineous Turkish parents. Given the role of PiC in energy production, the clinical manifestation of PiC deficiency is associated with multisystemic disorder characterized by muscle hypotonia, lactic acidosis, severe hypertrophic cardiomyopathy, and shortened lifespan [129, 130]. Besides that, PiC has been suggested to impact mtPTP opening [131].

6.3. Mitochondrial pyruvate carrier

Important one is another of the mentioned carriers. Pyruvate is the end product of glycolysis in the cytosol. In mitochondria, pyruvate entering the tricarboxylic acid cycle supports the ATP generation but also serves as a link to anabolic pathways for lipid, amino acid biosynthesis, and gluconeogenesis. The main sources of pyruvate in the cytoplasm are reactions catalyzed by pyruvate kinase. Two more sources are lactate dehydrogenase (LDH) and alanine aminotransferase (ALT), which are important to mention in terms of linking metabolic pathways between tissues. Reversible transamination of pyruvate and glutamate to alanine and α -ketoglutarate catalyzed by ALT converts the pyruvate from muscles into a transport form, alanine, which is reused in the liver for gluconeogenesis. LDH reversibly catalyzes reduction of pyruvate to lactate concurrently with oxidation of NADH to NAD⁺. Enzyme gains importance especially in muscle tissue in conditions requiring excessive energy production and in cancer cells. During increased need for ATP for muscle activity, the energy requirements to support continued muscle activity exceed mitochondrial capacity for ATP production. As glycolysis requires NAD⁺, ATP production is limited when NAD⁺ depletes and NADH accumulates. In this case, LDH ensures ATP production in glycolysis by regenerating NAD⁺. With a steady supply of NAD⁺, and until acidosis becomes limiting, glycolysis can produce ATP to support work rates exceeding those that could be supported by oxidative phosphorylation alone [132]. The lactate is transported to the circulatory system from where it is taken up by the liver and converted back into pyruvate.

The cross-connection of pyruvate with catabolic and anabolic pathway in mitochondria depends on its passage through mitochondrial membranes. Pyruvates cross MOM through VDAC; however, transport through MIM requires specific carrier. Although the existence of carrier was known earlier, the existence of genes on chromosome 6q27 encoding of mitochondrial pyruvate carrier (MPC) formed by hetero-oligomeric complex of two proteins, MPC1 and MPC2, has been revealed recently. Both proteins are needed for sufficient activity [133, 134]. Proteins do not contain any sequence homology to other mitochondrial carriers. Instead, they have been proposed to belong to the PQ-loop/MtN3/MPC superfamily [135]. Members of PQ-loop family are located in a variety of organelles performing diverse functions. They combine common characteristic features that are seven transmembrane domains and two conserved glutamine motifs. Subunits MPC1 and 2 contain three of seven transmembrane domains and are only half size of other PQ-loop family members [136]. Pyruvate uptake has been proposed to be coupled with the electrochemical gradient, occurring with the symport of one proton, or exchange with one hydroxide ion [137].

MPC activity increases in response to glucagon and decreases in response to insulin. Adrenaline and cortisol also have been found to increase pyruvate carboxylation by increasing mitochondrial pyruvate import [138]. The MPC2 transcript levels have been found to increase up to 1.5-fold under fasting conditions. In a physiological response to fasting (e.g., excessive exercise or prolonged food deprivation), hepatic mitochondrial ketone export and pyruvate import through MPC allows to enhance hepatic gluconeogenesis and maintains membrane potential [132]. Conversely, unregulated rate of gluconeogenesis contributes to chronic hyperglycemia in diabetes. Except for some substances (e.g., α -cyano-4-hydroxy cinamate, UK-5099, and several thiazolidinediones) acting as specific MPC inhibitors, inhibitory

effects of α -ketoacids and phenylpyruvate were found [139, 140]. The accumulation of phenylpyruvate in phenylketonuria prevents pyruvate transfer to mitochondria. Malate was shown to significantly increase mitochondrial pyruvate uptake while not affecting affinity. A genetic background of diminished pyruvate utilization due to pyruvate transport deficiency accompanied by lactic acidosis resulting also from the described metabolic possibilities of pyruvate are the mutations in MPC1 and/or MPC2 genomic loci [133, 141].

A ^{13}C metabolic flux analysis of cells after transcriptional or pharmacological inhibition of MPC, published by Vacanti et al. [142], revealed that inhibition of MPC activity leads to shift from glucose to amino acid and fatty acid oxidation. Citric acid cycle and fatty acid synthesis were maintained due to malic enzyme flux, glutaminolysis, fatty acid, and branched chain amino acid oxidation. Alternatively, pyruvate interconversion into gluconeogenic substrates (e.g., alanine) that can enter mitochondria independently of the MPC could compensate for loss of the MPC [143].

7. Aberrant pyruvate transfer

Altered metabolism of pyruvate resulting from the inability to transfer pyruvate is present in cancer and other metabolic diseases. Pyruvate metabolism and carbon flux are altered in many cancer cells. Metabolic switch to enhanced glycolysis and decreased oxidative phosphorylation (Warburg effect) leads to elevated lactate production, which is advantageous for cancer cells. The first advantage is regeneration of NAD^+ for the continuation of glycolysis. Another is proton-linked transport of lactate out of the cell, increasing the acidity of the extracellular space. Acidification of the extracellular environment provides protection from the immune system [144]. Furthermore, lactic acid appears to influence the activity of matrix metalloproteinases breaking down the extracellular matrix aiding in tumor proliferation and metastasis [145] and can be utilized as fuel source by cancer cells located at the surface of the tumor [146]. Schell et al. [147] found *MPC1* genomic locus as the most frequently deleted region across cancer cells, while *MPC2* locus does not appear to be frequently lost. *MPC1* underexpression correlates with poor survival in almost all cancers examined, including colon, kidney, lung, bladder, and brain [147]. The correlation of survival with *MPC2* expression is more variable, but associated with poor prognosis in kidney and colon cancer [147].

Increased pyruvate levels in cerebrospinal fluid reflecting an impaired metabolism of pyruvate have been detected in neurodegenerative disorders including Leigh's syndrome, Alzheimer's disease, and Parkinson's disease [148, 149]. Neuronal metabolism depends upon the uptake of lactate produced by astrocytes (astrocyte-neuron lactate shuttle), its conversion to pyruvate by LDH, and subsequent oxidation in mitochondria to form energy. Glucose is shifted into the pentose phosphate pathway for the NADPH generation to maintain reduced glutathione levels [150]. Due to the lack of pyruvate metabolism in neurodegenerative diseases, synthesis of acetylcholine is also insufficient because it requires acetyl-CoA [143]. To the present, there are not many findings available about MPC inhibition in neuronal cells except for α -cyano-4-hydroxy cinnamate or phenylpyruvate effects. Most likely, MPC efficacy and susceptibility to disease progression are also related to genetic predisposition. Mitochondrial pyruvate supply restriction can also display a neuroprotective effect by increase in glutamate oxidation. Maintaining the levels of synaptic glutamate during glutamatergic neurotransmission comes at energetic cost leading

to periods of increased levels of glutamate. High levels of glutamate cause complex I inhibition through receptor-stimulated Ca^{2+} overload, which is an attribute of acute neuropathologies [151].

MPC1 and MPC2 are highly expressed in brown adipose tissue compared with other tissues [152]. Brown adipocytes use predominantly fatty acids as an energy source for uncoupled respiration and thermogenesis, which requires replenishment of oxaloacetate through pyruvate carboxylation to enter citric acid cycle. MPC is supposed to be important in shifting between formation and oxidation of fatty acids in fat cell metabolism.

Alteration in pyruvate metabolism plays a conspicuous role in heart disease. Heart muscle predominantly metabolizes fatty acids, ketone bodies, lactate, and glucose depending on their availability and neurohormonal signaling. Up to 95% of the heart's ATP generation comes from mitochondrial oxidation, and typically approximately 60–90% of this mitochondrial ATP production comes from fatty acids, whereas 10–40% is from pyruvate oxidation. The myocardium is a significant consumer of lactate even at the maximum load, because of specific expression of LDH-B isoform preferring reaction catalysis toward pyruvate [153]. It was found that acute stress (such as ischemia) and chronic stress (hypertrophy and heart failure) change substrate availability and metabolism [143]. Reduction in pyruvate oxidation leads to increased anaerobic glycolysis and lactate formation. However, age-related decrease in MPC activity was observed [154]. Shift in substrate utilization in order to maintain citric acid cycle can lead to serious states of energy deficiency called “starved heart.” The effect was observed in cancer treatment with doxorubicin reducing carnitine transport followed by reduced fatty acid oxidation [155].

7.1. Mitochondrial di- and tricarboxylic acid transport

7.1.1. Tricarboxylate carrier

The tricarboxylate carrier (SLC25A1) catalyzes an electroneutral exchange of the dibasic form of a tricarboxylic acid (citrate, isocitrate, and cis-aconitate) with proton for another tricarboxylate- H^+ , dicarboxylate (malate and succinate), or phosphoenolpyruvate [156]. An importance of the citrate carrier (CiC) results from formation of a link between carbohydrate catabolism and lipogenesis. The CiC overlaps with oxoglutarate carrier ((OGC) SLC25A11) by transporting the 2-oxoglutarate in exchange for malate and malonate [157]. CiC facilitates transport of citrate across MIM, followed by passive diffusion through VDAC in MOM into the cytosol. In the cytosol, fatty acids and cholesterol are synthesized from citrate. Citrate also acts as inhibitor of phosphofructokinase 1, thus affecting the rate of glycolysis, positive allosteric modulator of acetyl-CoA carboxylase in fatty acid synthesis pathway, and serves as a substrate for the formation of malate, the conversion of which into pyruvate facilitates NADPH production necessary for lipogenesis [158]. High CiC mRNA levels in liver, kidney, and pancreas; lower levels in heart, skeletal muscle, and placenta; and no detectable mRNA in brain and lung were detected [128]. High liver and kidney CiC mRNA levels are supposed to be due to gluconeogenesis and lipogenesis. Moreover, CiC plays a role in gluconeogenesis from lactate where phosphoenolpyruvate carboxykinase is located in mitochondria. Similarly as in other animals, mitochondrial phosphoenolpyruvate isoforms are present mainly in the liver, kidney, and adipose tissue [159]. The relatively high CiC mRNA level in pancreas could be explained with the role of CiC in regulation of insulin secretion. On the other hand, the low CiC mRNA level in skeletal muscle correlates to the very low activity of gluconeogenesis and fatty acid synthesis [160].

Except for decisive interconnection between lipogenesis, gluconeogenesis, and glycolysis, CiC has been proposed to play a role in the maintenance of chromosome integrity and in the regulation of autophagy [161]. A particularly important role played by the CiC is in the regulation of insulin secretion by providing isocitrate for NADP-dependent isocitrate dehydrogenase [162].

The studies have shown that the CiC activity and properties could be changed under specific conditions: starvation-induced decrease of CiC activity and considerable reduction of CiC mRNA in starved rats. The reduced CiC mRNA levels were ascribed to shortened half-life and accelerated degradation of CiC mRNA. Refeeding, however, leads to renewal of mRNA and increased activity of CiC [163]. The polyunsaturated fatty acid (PUFA) administration also dramatically affects CiC gene expression by transcriptional and posttranscriptional mechanisms. Rat liver mitochondria showed more decreased CiC activity and reduced transcriptional rate of CiC mRNA when affected by n-3 PUFA than by n-6 [164]. During the inflammation, CiC gene expression is activated by NF- κ B, which causes an increased availability of cytosolic acetyl-CoA and NADPH + H⁺ for synthesis and activity of compounds and enzymes involved in inflammatory response (e.g., COX2, iNOS, and NADPH oxidase) [156].

The human SLC25A1 gene is localized on chromosome 22, within the region associated with allelic losses in DiGeorge/22q11 syndrome, velo-cardio-facial syndrome, and a subtype of schizophrenia [165]. To date, recessive mutations of CiC gene in 20 persons with combined D,L-hydroxyglutaric aciduria were described. The clinical phenotype of disorder is characterized by severe developmental delay, hypotonia, seizures, secondary microcephaly, hypoplasia or agenesis of the corpus callosum, optic nerve hypoplasia, dysmorphic feature, lactic acidosis, and recurrent apneic crises [166]. CiC has also been reported to be upregulated in ovarian and colon cancer [167].

7.2. Dicarboxylate carrier

Dicarboxylate carrier protein ((DIC) SLC25A10) transporting malate and succinate out of mitochondria in exchange for P_i is ubiquitously expressed in mammalian mitochondria. The carrier is inhibited by P_i and other phosphate and substrate analogues. Malate exchange for P_i provides a cytosolic source of malate for CiC and therefore plays a significant role in fatty acid synthesis [168]. DIC interacts with malate dehydrogenase by acting as an oxaloacetate shuttle, thus improving functional coupling of citric acid cycle with shuttle. In the cytosol, malate is converted into oxaloacetate following conversion into phosphoenolpyruvate by carboxykinase-catalyzed reaction. The reaction is rate-limiting for gluconeogenesis. No less important role of the carrier is the transport of reduced glutathione into the mitochondria shared with OGC. Therefore, limiting protein expression results in significantly reduced levels of glutathione in the mitochondria and subsequent altered redox conditions [169]. It was found that the activity of DIC is increased in type I diabetes, in contrast to decreased activities of CiC [170].

8. Oxoglutarate carrier

The OGC mediates transfer of oxoglutarate across MIM in exchange for dicarboxylate. OGC is a component of malate-aspartate shuttle; thus, dicarboxylate is usually malate. After export, malate is converted into oxaloacetate, which is in transamination reaction with glutamate converted into

oxoglutarate and aspartate. The oxoglutarate is then transported by OGC. Binding the succinate to the matrix side of the carrier increases the affinity for malate, while phenylsuccinate, pyridoxalphosphate, retinoic acid, or alcohol was found to inhibit OGC [171, 172]. The OGC inhibition causes a decrease in mitochondrial reduced glutathione levels by 40–50% [138]. The carrier has also been proposed as a porphyrin transporter, and its inhibition blocks porphyrin conversion to heme in mitochondria. The downregulation of OGC has been reported in horse muscle with recurrent exertional rhabdomyolysis [173].

8.1. Mitochondrial glutamate carriers

8.1.1. Glutamate carrier

Another one from SLC25 family is a glutamate carrier. Two glutamate-transfer isoforms are known for the glutamate carrier: GC1 (SLC25A22) and GC2 (SLC25A18). They transport glutamate across the MIM in symport with a proton or in exchange for hydroxyl ions. In mitochondria, glutamate is converted by glutamate dehydrogenase into α -ketoglutarate while reducing NAD (P)⁺. Ammonia is released and reduced coenzyme enters the complex I of respiratory chain. The mRNAs of GC1 have been found to be highly expressed than that of GC2 in liver, pancreas, and kidney but are similar in the brain. Moreover, the K_m and V_{max} values are higher than those of GC2 (5.2 vs. 0.26 mM; 12.2 vs. 3.9 μ mol/min/g of proteins). Therefore, an acceptable explanation, for the expression pattern is that GC2 is responsible for the basic function, whereas GC1 functions in tissues with increased demands [174].

GC1 has been demonstrated to have an important physiological function in the control of glucose-stimulated insulin secretion in pancreatic β cells [96]. The signaling mechanism leads to adjustment of insulin release to levels greater than the sole contribution of Ca²⁺-induced triggering pathway in rats. Stimulation of β cells with high glucose might result in rapid saturation of the respiratory chain [175], favored by glucokinase properties (as mentioned in Section 4.1.) and low lactate release. Saturated electron transport chain would then promote export of metabolites (GTP, citrate, NADH, and glutamate) out of the mitochondria compensated by activity of anaplerotic pathways [176]. Energetic sufficiency favors the glutamate dehydrogenase reaction from α -ketoglutarate toward glutamate formation. Glutamate is taken up by secretory granules, which are consistent with the expression of vesicular glutamate transporters (VGLUT1 and 2) in insulin-secreting cells [177]. Inside the secretory granule, glutamate could induce pH changes and activate metabotropic receptors mGlu5, thereby mediating insulin release [178]. Alternative mechanisms include activation of acetyl-CoA carboxylase and inhibition of phosphatase activities involved in insulin exocytosis [179].

GC1 is highly expressed in astrocytes from different structures (retina, spinal cord, and cortex) [180] and represents the principal gate for glutamate entry into the mitochondria of astrocytes. Restricting glutamate access to mitochondria results in reduced ATP and NAD(P)H formation. A defective glutamate carrier may lead to glutamate accumulation in the astrocytes cytosol and then to glutamate liberation in the synaptic cleft. The release could result in neuronal synchronicity, which may contribute to the generation of epileptic-like discharges in the brain [181]. Mutations in the human GC1 gene (localized on chromosome 11p15.5) are responsible for the autosomal recessive form of early infantile epileptic encephalopathy

caused by complete loss of transport and uniport activity of the protein [182–184]. Clinical manifestations are similar to epileptic spasms and focal seizures associated with suppression bursts beginning in the first days of life, microcephaly, hypotonia, abnormal retinogram recording, and psychomotor retardation [183].

9. Aspartate/glutamate carrier

Glutamate can also enter mitochondria through aspartate/glutamate carrier (AGC1 and 2 isoforms, known as aralar and citrin) combining the input of glutamate to the release of aspartate [185]. The export of aspartate is favored in energized mitochondria. Moreover, in increased cytosolic calcium concentration, respiration is strongly increased associated with the reduction of mitochondrial membrane potential [185]. A decrease in ROS production could be expected given the opposite relationship between the mitochondrial membrane potential and ROS production [186]. Another attribute contributing to this effect is glutamate entry through AGC1 (SLC25A12) in cotransport with proton. The loss of membrane potential is compensated by the extrusion of four protons by the respiratory chain when one molecule of glutamate is processed through the citric acid cycle generating two molecules of NADH [187]. AGC together with the OGC plays a crucial role in the transport of NADH from cytosol to the mitochondria as a part of malate-aspartate shuttle [188]. Therefore, AGC1 and AGC2 (SLC25A13) are expressed in tissues differently according to their demands for maintenance of the redox balance between anaerobic and aerobic glycolysis. An interesting finding is that expression of AGC1 and AGC2 is almost completely restricted to neurons and photoreceptor cells [180, 189], in contrast to GC1 expressed in astrocytes. Cytosolic Ca^{2+} has a direct role in the regulation of AGC1 gene expression via cAMP response element-binding protein in neuronal cells, underlining the key role of AGC1 in the central nervous system by upregulation in neuronal differentiation and downregulation in neuroinflammation [190]. AGC1 is also highly expressed in skeletal and heart muscle [191]. Upregulation of both isoforms was found in several cancers, which is also related to the change in glycolytic metabolism [187].

9.1. Ornithine carriers

Translocation of the ornithine and related substrates is mediated by mitochondrial ornithine carrier (ORC). The physiological importance of this carrier reclines on urea production, delivery-rate control of arginine, and interferential formation of NO, agmatine, creatine, glutamine, glutamate polyamines, and proline [192]. The human isoforms ORC1 (SLC25A15), ORC2 (SLC25A2), and ORC3 (SLC25A29) [193, 194] provide transport by exchange or by exchange for H^+ but differ in substrate transport rates, substrate specificity, and tissue expression. They all facilitate passage of L-ornithine, L-lysine, and L-arginine. The ORC1 prefers transport of amino acid substrates with shorter and noncyclized side chains. It does not enable transport of L-homoarginine, D-ornithine, D-histidine, and D-arginine. The ORC2 transports all substrates with the same efficiency (L,D-forms of ornithine, lysine, histidine, arginine, and L-citrulline, L-homoarginine). The ORC3 enables transport of L-forms with longer side chains across MIM, e.g., lysine, arginine, and histidine [192]. The isoform expresses lower affinity to ornithine and does not transport citrulline [194].

Activity of ORC1 and 2 is enhanced by P_i , malate, and dicarboxylates and inhibited by pyridoxal 5'-phosphate (PLP), mercurials, spermine, and spermidine. The affinity of ORC2 to lysine and arginine is lower and to ornithine and citrulline is higher in comparison to ORC1. Moreover, ORC2 has been reported to be about three times less active than ORC1. The dispositions are also related to protein expression. The ORC1 is expressed in most tissues, with the highest levels in the liver, pancreas, lungs, kidney, and testis, unlike the ORC2 being more restricted to these organs [193]. ORC3 is expressed in heart, brain, liver, and kidney and is induced after partial hepatectomy or fasting [195, 196]. The import of arginine, lysine, and histidine allows for protein synthesis in mitochondria and that for ornithine enables degradation of arginine surplus. Transfer of ornithine out of the mitochondria allows for synthesis of polyamines reversibly inhibiting ORC activity. Ornithine is synthesized in mitochondria from glutamate in tissues with low arginase activity (except for the liver), from glutamine in intestinal mitochondria or when deficient in the diet [193]. Considering ornithine and citrulline transport efficiency and level of protein expression in the liver, the ORC1 isoform is of highest importance in urea cycle continuance [193].

Mutation in the gene encoding ORC1 isoform (localized on 13q14.1 chromosome) causes hyperornithinemia-hyperammonemia-homocitrullinuria (HHH syndrome), characterized by early-onset neurological deficits. Hyperammonemia results from impaired urea cycle due to ORC1 malfunction. Ornithine accumulates in the cytosol leading to hyperornithinemia and increases polyamine synthesis. Carbamoyl phosphate condensates with lysine in the absence of ornithine inside the mitochondria, leading to homocitrullinuria, or enters pyrimidine synthesis, thus increasing excretion of orotic acid and uracil [97, 197]. Overexpression of ORC2 might only partially compensate defective function of ORC1 due to lower affinity for ornithine and citrulline [196, 198]. ORC3 has not been found to compensate lack of ORC1 function but is probably responsible for lysine transport in patients with HHH syndrome [194].

9.2. Mitochondrial uncoupling proteins

Uncoupling proteins (UCP) sharing the same tripartite structure belongs to the family of the mitochondrial anion carriers. Six families of UCP members encoding by 45 genes have been described [199]. In mammals, UCPs consist of five homologs: UCP1 (SLC25A7), UCP2 (SLC25A8), UCP3 (SLC25A9), UCP4 (SLC25A27), and UCP5 (SLC25A14, BMCP1). *UCP1* genes are localized on human chromosome 4. The human and mouse *UCP2* genes are located 7–20 kb downstream of the *UCP3* stop codon, as the result of a duplication; the *UCP3-UCP2* locus is located on human chromosome 11q13 (between the genetic markers D11S916 and D11S911). The UCP5 homolog *Bmcp1* is located on Xq25–26 chromosome (between the markers DXS1206 and DXS1047), and *UCP4* on 6p11.2-q12 (close to the genetic marker SHGC-34952) [200].

UCPs are ubiquitous, except for UCP2 [201], however, exhibiting tissue-specific expression pattern. As reviewed in Gutiérrez-Aguilar and Baines [202], UCP1 is unique to brown adipose tissue, UCP3 to heart and skeletal muscle, and UCP4 and 5 are typical to the brain. The general designation of this carrier family is derived from observed function of the first member, UCP1 in brown fat tissue—the heat production in the nonshivering thermogenesis [199]. According to Mitchell's theory, any proton leak not coupled with ATP synthesis would provoke uncoupling of respiration and thermogenesis. The discharge of proton gradient formed

in respiratory chain causes dissipation of energy of oxidation as heat. Besides adaptive thermogenesis, uncoupling of respiration allows continuous reoxidation of coenzymes that are essential to metabolic pathways [203], prevents inhibition of mitochondrial respiration from excessive ATP production, and decreases ROS formation [204].

The activity of UCPs requires ubiquinone as a cofactor [205] and is regulated by two ligands. UCP1 is activated by fatty acids and inhibited by purine nucleoside di- and triphosphates. UCP2 and 3 can be activated by fatty acid and are less sensitive to purine inhibition. There are not many findings about UCP4 and 5 regulation; however, they were reported to be GDP-sensitive [206]. The mechanism of proton transport is still controversial. The UCP is referred to act as a pure proton transporter activated by fatty acids, while by other mechanism, UCP facilitates protonated fatty acid transbilayer movements, flip-flop, to the matrix where they release the proton and are then transported back to the IMS by UCP [199, 206]. Consistently with transport of fatty acid anion, UCP1 was shown to transport a variety of ions, suggesting that UCP1 is a hydroxyl anion transporter rather than a proton carrier [207].

As has already been mentioned, the physiological function of UCP1 is the production of heat in brown adipocytes. The UCP1 induction is influenced by thyroid hormones and sympathetic nerves and therefore also by drugs activating adrenoceptors [203]. Capsaicin was found to increase levels of all UCPs [206]. A mutation in gene encoding UCP1 is associated to diabetic retinopathy [208].

Although, UCP2 and 3 are not involved in thermogenesis, polymorphisms in the coding region of the *UCP2* gene are associated with the level of energy expenditure during sleep [209]. These two members reduce ROS formation by mild uncoupling [208] and related to function to decrease mitochondrial oxidative stress load and transport fatty acid peroxides to MOM [210]. Cytokines and thyroid hormone upregulate UCP2 and UCP3 [211]. Thus, physiological response of macrophages is lowering the UCP levels and enhancing the ROS production. Moreover, UCP2 was proposed to act as carrier for the superoxide anion [205]. The expression of UCP2 is induced under starvation when there are elevated levels of fatty acid in the circulation. The expression of UCP3 increases during fasting [212]. In leptin-induced lipolysis, fatty acids are not exported to the liver but are oxidized in adipocytes, where UCP2 initiates fat oxidation that is not associated with energy-requiring processes [213]. Pharmacological inhibition and genetic mutations in UCP2 and UCP3 have been shown to reverse damaging consequences of obesity and diabetes-induced pancreatic β -cell dysfunction [214, 215].

UCP4 and 5 have been shown to be upregulated by oxidative stress, while insulin downregulates their levels [216]. Mutations in *UCP4* gene have been linked to schizophrenia [217]. For all UCPs, a continuity of upregulation of the expression and incidence of tumor diseases has been described [202].

10. Conclusion

As it follows from this review, the proper course of metabolic processes in the mitochondria requires direction of transport systems to the needs of the organism. The activities of transporters can be regulated differently by hormones, phosphorylation and dephosphorylation,

cytokines, concentration of metabolites, and individual nutrition components, which can alter their amount and activity. Most metabolites or their precursors can be mutually transported by different transport systems to provide the desired concentrations on both sides of the mitochondrial membranes. The specificity of transport and regulation of compounds in different organs and tissues provide various isoforms encoded by different nuclear genes. More detailed knowledge of transport mechanisms can contribute to better diagnosis and treatment of metabolic disorders.

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