VDAC1

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The voltage-dependent anion channel 1 (VDAC1) protein, is an important regulator of mitochondrial function, and serves as a mitochondrial gatekeeper, with responsibility for cellular fate.

Apoptosis VDAC metabolisim Mitochondria

1. Introduction

Mitochondria as cellular energy powerhouses provide a central location for the multiple metabolic reactions required to satisfy the energy and biomolecule demands of cells, and serve to integrate the diverse metabolic pathways and provide cells with metabolic flexibility. The appreciation of mitochondria as sites of biosynthesis and bioenergy production has dramatically expanded in recent years, and they are now known to play a crucial role in almost all aspects of cell biology and to regulate cellular homeostasis, metabolism, innate immunity, apoptosis, epigenetics, cellular fate, and more[1][2]. Mitochondrial dysfunction induces stress responses, which link the fitness of this organelle to the condition of the whole organism. Mitochondria are also integrators and amplifiers of the death program These functions typically center around the metabolic traffic in and out of the mitochondria, and they are likely to contribute to the exceptional variability of mitochondrial disease manifestations. The voltage-dependent anion channel 1 (VDAC1) protein, which is located in the outer mitochondrial membrane (OMM), serves as a gatekeeper that can regulate the metabolic and energetic cross-talk between mitochondria and the rest of the cell, and plays a role in mitochondria-mediated apoptosis[3][4][5].

Other different aspects of VDAC1 structures[6] and functions, such as in cell stress[5], Ca^{2+} regulation[7][8], metabolism[5], and apoptosis[7][9], and as a therapeutic target[10][11][12][13][14][15], were presented in ours and others' recent reviews.

2. VDAC1 Structural Elements: The N-Terminal Domain and its Oligomeric State

Three mammalian isoforms of VDAC (VDAC1, VDAC2, and VDAC3) that share a number of functional and structural attributes have been identified[16][17][18]. Information about VDAC isoform function and structure was obtained from channel activity of purified and reconstituted protein and, using cell-based assays for survival, metabolism, reactive oxygen species (ROS), and cellular Ca^{2}+ regulation, and by gene knockout mouse models[17]. VDAC1 is the most abundant isoform and the focus of this review. VDAC2 knock out is lethal and is considered to be an anti-apoptotic protein. VDAC3 is the least known, active as channel. While VDAC1 contains

two cysteines, VDAC2 and VDAC3, with nine and six cysteines, respectively, are proposed to function as oxidative stress sensors[17]. The crystalline structure of the most prevalent and studied isoform, VDAC1, was solved at atomic resolution, revealing a β-barrel composed of 19 transmembrane β-strands connected by flexible loops. The β1 and β19 strands, together, are arranged in parallel, where the N-terminal region (26-residues) lies inside the pore[19][20][21], but can flick out of it[22][23] and interact with hexokinase (HK) [4][5][24][25][26][27][28][29][30], Aβ[31][32], and other proteins, such as the anti-apoptotic proteins, Bcl-2 and Bcl-xL[4][19][33][34][35][36][37]. Thus, this region of the protein is well positioned to regulate the traffic of materials through the VDAC1 channel[19][21].

The diameter of the channel pore has been estimated as 2.6–3.0 nm[26], but this can decrease to about 1.5 nm when the N-terminal flexible region is located inside the pore[26][27][28]. The sequence of rich with glycine residues (21GlyTyrGlyPheGly25)[26][27][28] connecting the N-terminal region to β1 strand is thought to confer the flexibility needed for this region to move in and out of the VDAC1 channel[30]. This mobility has been reported to be important for channel gating, dimerization of VDAC1[30], and interaction with hexokinase (HK) and members of the apoptosis regulating Bcl-2 family (i.e., Bax, Bcl-2, and Bcl-xL)[30][19][33][34][38][39].

Membranal and purified VDAC1, can form dimers, trimers, tetramers, hexamers, and higher-order oligomeric forms [4][23][40][41][42][43][44][45][46][47] through contact sites that have been identified[48]. We have demonstrated this oligomerization to be a dynamic process that occurs in response to a variety of apoptotic stimuli, acting through a range of signaling processes[28][40][44][45][47][48][49][50][51][52][53] , as presented below (Section 5.1).

3. VDAC1 Extra-Mitochondrial Localization, Function, and Association with Pathological Conditions

In addition to the mitochondrial membrane, VDAC1 has also been detected in other cell compartments[16] [54][55][56] [57][58][59][60][61][62][63][64], including the plasma membrane[16][57], the sarcoplasmic reticulum (SR) of skeletal muscles[65], and the endoplasmic reticulum (ER) of the rat cerebellum[64][66].

Antibodies raised against the N-terminus of VDAC1 interacted with the plasma membrane of bovine astrocytes and blocked a high conductance anion channel[61]. Interestingly, when detected in the plasma membrane (pl-VDAC1), the amino acid residues that were exposed to the cytosol in the mitochondrial protein were found to face the extracellular space[55][60][67][68][69][70]. This was demonstrated in epithelial cells, astrocytes, and neurons[56][57]and in differentiated hippocampal neurons[55]. VDAC1 has also been identified in the brain post-synaptic membrane fraction[59] and in the caveolae or caveolae-related domains of established T-lymphoid-like cell lines[58]. The protein has also been found to participate in the multi-protein complexes found in lipid rafts, together with the estrogen receptor α (mERα) and insulin-growth factor-1 receptor (IGF-1R)[58][62][63][64]. In red blood cells that do not possess mitochondria, VDAC1 has been found in the endoplasmic reticulum, and Golgi apparatus[59].

The plasma membrane form of VDAC1 may have an extended N-terminal signal peptide which is responsible for its targeting to the cell membrane[70][71]. Alternatively, the human plasminogen kringle 5 (K5) may induce translocation of VDAC1 to the cell surface, where the protein was recently identified as the receptor for K5 on

HUVEC membrane[72][73]. Additional mechanisms, such as the presence of alternative mRNA untranslated regions, have also been suggested[57][64].

The levels of pl-VDAC1 were reported to be increased under pathological conditions such as Alzheimer's disease (AD)[73][74][75], where it has been suggested that pl-VDAC1 serves as an "amyloid-regulated" apoptosis related channel[61][62][63][64]. We recently described a direct interaction between Aβ and the N-terminal region of VDAC1, and demonstrated that VDAC1 is required for Aβ entry into the cells[76] and apoptosis induction[31][32]. We have also recently demonstrated that VDAC1 is overexpressed in type 2 diabetes (T2D)[77][78][79][80] and mistargeted to the β-cell plasma membrane[81]. This overexpression under pathological conditions is also seen in cancer[3][15][81][82], autoimmune diseases such as lupus[83], non-alcoholic steatohepatitis (NASH)[84], inflammatory bowel disease (IBD) (unpublished data), and cardiac diseases[85][86], as presented below (Section 8).

The exact functions of extra-mitochondrial VDAC are unknown, although several possible roles have been proposed (reviewed in[63][86][87]), and include regulation of tissue volume in the brain[88], and other cell types [70,93,94], or release of ATP in β-cells and in human erythrocytes[89].

4. VDAC1, a Multi-Functional Channel Controlling Cell Energy, Metabolism, and Oxidative Stress

To reach the mitochondrion matrix or to be released to the cytosol, all metabolites and ions must traverse the OMM via VDAC1, the sole channel mediating the flux of ions, nucleotides, and other metabolites up to ~5000 Da. In this way, VDAC maintains control of the metabolic and ion cross-talk between the mitochondria and the rest of the cell (Figure 1). Nucleotides and metabolites transported include pyruvate, malate, succinate, and NADH/NAD+, as well as lipids, heme, cholesterol, and ions such as Ca^{2+}[3][4][5][90]. In contrast, there are over 50 mitochondrial substrate-specific carrier proteins of the family solute carrier family 25 (SLC25) in the inner mitochondrial membrane (IMM), such as the (ADP/ATP) antiporter, the adenine nucleotide translocator (ANT) , the transporter of Pi (PiC), as well as transporters of aspartate/glutamate, pyruvate, acyl carnitine, and citrate, among others[91].

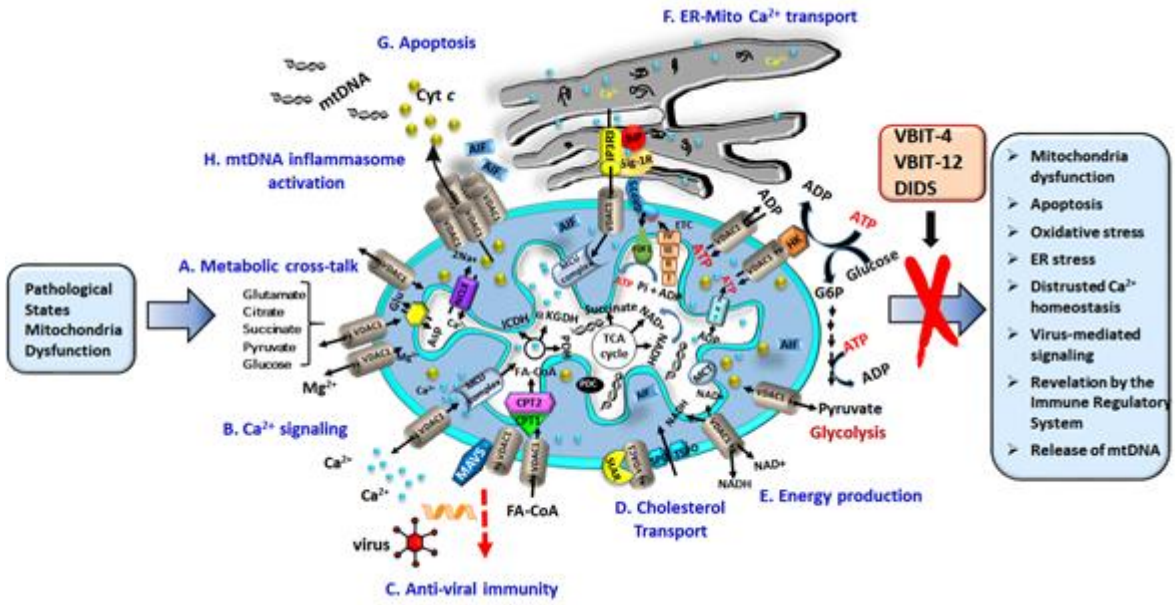

Figure 1. Voltage-dependent anion channel 1 (VDAC1) as a multi-functional channel mediates metabolites, nucleotides, and Ca^{2+} transport, controlling energy production, endoplasmic reticulum (ER)-mitochondria cross-talk, and apoptosis. VDAC1 is responsible for a number of functions in the cell and mitochondria including: (**A**) transfer of metabolites between the mitochondria and cytosol; (**B**) passage of Ca^{2+} to and from the intermembrane space (IMS) to facilitate Ca^{2+} signaling; (**C**) Mitochondrial antiviral-signaling protein (MAVS) associated with VDAC1 enable anti-viral signaling. (**D**) Transfer of acetyl coenzyme-A (acyl-CoAs) across the outer mitochondrial membrane (OMM) to the IMS, for conversion into acylcarnitine by CPT1a for further processing by β-oxidation. Together with Star and translocator protein (TSPO), VDAC1 forms the multi-protein transduceosome, which transports cholesterol. (**E**) Recycling ATP/ADP, NAD+/NADH, and acyl-CoA between the cytosol and the IMS, and regulating glycolysis via association with HK; (**F**) contributing to ER-mitochondria contacts, where Ca^{2+} released by IP3 activation of inositol 1,4,5-trisphosphate receptors (IP_3R) in the ER is directly transferred to IMS via VDAC1, and then is transported to the matrix by the Ca^{2+} uniporter (MCU complex). In the matrix Ca^{2+} regulates energy production via activation of the tricarboxylic acid cycle (TCA) cycle enzymes: pyruvate dehydrogenase (PDH), isocitrate dehydrogenase (ICDH), and α-ketoglutarate dehydrogenase (α-KGDH). The electron transport chain (ETC) and the ATP synthase (FoF1) are also presented. (**G**) VDAC1 oligomers forming a hydrophilic protein-conducting channel capable of mediating the release of apoptogenic proteins (e.g., Cyto c and apoptosis-inducing factor (AIF)) from the mitochondrial IMS to the cytosol, leading to apoptosis. (**H**). VDAC1 oligomers allow mtDNA release triggering inflammasome activation. Pathological conations lead to dysfunction of the mitochondria as reflected in the activities presented in the box on the right. These altered activities can be prevented by VDAC1-interacting molecules, such as DIDS, VBIT-4 and VBIT-12.

Closure [98] or down-regulation of VDAC1 channel expression reduced the exchange of metabolites between the mitochondria and the rest of the cell and inhibited cell growth[82][92], indicating the importance of the protein to the maintenance of physiological cellular function.

As already described, the mitochondria are the energy source of the cell. They are responsible for the ATP generated during glycolysis and oxidative phosphorylation (OXPHOS). This is then exported to the cytosol and exchanged for ADP, which is recycled again in the mitochondria to generate ATP. This shuttling process that also involves ANT and creatinine kinase (CrK), located between the IMM and OMM[93], and may be regulated by tubulin αβ heterodimers[94], but it is ultimately facilitated by VDAC1, which thereby controls the electron transport chain[4] (Figure 1) and the energy state of the cell [95].

In addition to ATP, VDAC1 is also involved in the transfer of a number of other essential molecules across the OMM. These include Ca^{2+}, cholesterol, fatty acids, and reactive oxygen species (ROS). Controlling the flow of Ca^{2+} allows VDAC1 to regulate mitochondrial Ca^{2+} homeostasis, oxidative phosphorylation, and Ca^{2+} cross-talk between the VDAC1 in the OMM and the IP3 receptor in the ER. This takes place through the mitochondria associated membranes (MAM) and involves the chaperone GRP75[66][96][97].

VDAC1[98] is a necessary component of the cholesterol transport multi-protein complex, the transduceosome, composed of the translocator protein (TSPO), and the steroidogenic acute regulatory protein (STAR)[84][99] (Figure 1).

VDAC1 is also part of a complex mediating the transport of fatty acids through the OMM[84][99][100] composed of carnitine palmitoyltransferase 1a (CPT1a), which faces the intermembrane space (IMS), and the long chain acetyl coenzyme-A (acyl-CoA) synthetase (ACSL) protein. Once activated by ACSL, VDAC1 transfers acyl-CoAs across the OMM to the IMS, where they are converted into acylcarnitines by CPT1a (Figure 1). They are then transferred across the IMM by carnitine/acylcarnitine translocase, and converted back into acyl-CoA by CPT2 in the IMM, and, subsequently, undergo β-oxidation in the matrix[99][101]. In this respect, VDAC1 has recently been reported to serve as a lipid sensor[102]. Finally, VDAC is also involved in regulating oxidative stress[5]. ROS formed by reaction with $O_2^{\bullet-}$ at complex III are released through VDAC1 where they activates c-Jun N-terminal kinase (JNK), the extracellular signal-regulated kinase (ERK 1/2), and p38, members of the mitogen-activated protein kinase (MAPK) family of serine/threonine kinases whose signaling may be detrimental to mitochondrial function[103][104]. Importantly, ROS release and consequent cytotoxicity are decreased when HK-I and HK-II bind to VDAC1[105][106][107][108].

VDAC1 is also affected by hypoxic conditions. The C-terminal end of VDAC1 is cleaved (VDAC1-ΔC), with silencing of hypoxia inducible factor 1A (HIF-1α) prevents such cleavage[109][110]. This formation of VDAC1-ΔC, is thought to prevent apoptosis and permit the maintenance of ATP and cell survival in hypoxia[111].

As described, the location of VDAC1 in the OMM provides the perfect opportunity to preside over the traffic of metabolites between the mitochondria and the cytosol, where it interacts with other proteins in order to orchestrate and integrate mitochondrial functions with other cellular activities[3][4][40][41][112][113](Figure 1).

VDAC1 activities are modulated by Ca^{2+}, ATP, glutamate, and NADH, as well as by a variety of proteins (see Section 7)[114][115][116][117]. Using a photo-reactive ATP analog, we identified three potential nucleotide binding sites

[115]. Subsequent NMR spectroscopy and site-directed mutagenesis revealed that hVDAC1 possesses one major binding region for ATP, UTP, and GTP that is formed by the N-terminal α-helix, the linker connecting the helix to the first β-strand, and adjacent barrel residues[118]. The crystal structure of mouse VDAC1 in the presence of ATP, revealed an additional low-affinity binding site[119]. With respect to a high and low affinity ATP binding site, it should be noted that the cellular concentration of ATP is 1–2 mM.

In addition, Ca^{2+} binds to VDAC1 although the physiological function of this connection is not clear. Binding of Ca^{2+} to purified and bilayer reconstituted VDAC1 maintained the channel in an open configuration, which could be useful in upregulating the exchange of metabolites[120]. The divalent cation-binding sites bind the lanthanides, La^{3+} and Tb^{3+}, as well as ruthenium red (RuR), and its analogue Ru360[121][122][123], the photo-reactive analogue azido ruthenium (AzRu)[124]. All reduce the conductance of native, but not mutant, VDAC1.

VDAC1 undergoes all known types of post-translational modifications (PTMs), including nitrosylation, acetylation, carbonylation, and phosphorylation[118]. TVDAC1 contains two cysteines; Cys^{232} is found in the carboxyamidomethylated form, while Cys^{127} is in the oxidized form of sulfonic acid[125]. VDAC1 possesses several potentially phosphorylatable serine and threonine residues, many of which have indeed been shown to undergo phosphorylation[126][127][128] by protein kinase A (PKA)[127], protein kinase C (PKC)ε[126], and GSK3b[129] Both VDAC1 and VDAC2 are phosphorylated at a specific Tyr residue under hypoxic conditions[128].

Under pathological conditions, such as oxidation, aging, or after ischemic reperfusion injury, VDAC was shown to undergo nitration[130][131][132], while the protein undergoes carbonylation in the Alzheimer's disease-affected brain or after exposure to acrolein, produced by lipid peroxidation[133].

Thus, VDAC1, a protein that plays a pivotal role in regulating cellular energy and metabolism and when over-expressed, leads to cell death can be considered as a therapeutic target for initiating or inhibiting cell death.

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