Mitochondrial VDAC1 as Therapeutic Target of Inflammation-Related Diseases

Subjects: Cell Biology

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The multifunctional protein, voltage-dependent anion channel 1 (VDAC1), is located on the mitochondrial outer membrane. It is a pivotal protein that maintains mitochondrial function to power cellular bioactivities via energy generation. VDAC1 is involved in regulating energy production, mitochondrial oxidase stress, Ca^{2+} transportation, substance metabolism, apoptosis, mitochondrial autophagy (mitophagy), and many other functions. VDAC1 malfunction is associated with mitochondrial disorders that affect inflammatory responses, resulting in an up-regulation of the body's defensive response to stress stimulation. Overresponses to inflammation may cause chronic diseases. Mitochondrial DNA (mtDNA) acts as a danger signal that can further trigger native immune system activities after its secretion. VDAC1 mediates the release of mtDNA into the cytoplasm to enhance cytokine levels by activating immune responses. VDAC1 regulates mitochondrial Ca^{2+} transportation, lipid metabolism and mitophagy, which are involved in inflammation-related disease pathogenesis.

VDAC1 inflammation mitochondria metabolism mitophagy Calcium targeting therapy

1. Introduction

Inflammation is a defense response of the body to stimuli, such as infectious and non-infectious triggers. Inflammation can be beneficial when it occurs in moderation; however, excessive inflammation can easily become detrimental events that result in possible damage to local tissues. In understanding the mechanism of chronic inflammation, people know that it has a deep relationship with various diseases, for example, type 2 diabetes, atherosclerosis, asthma, neurodegenerative diseases, cancers and others [1][2][3].

Mitochondria are vital organelles in eukaryotic cells. They are not only involved in oxidative phosphorylation, thermogenesis, the biogenesis of iron–sulfur clusters, and in heme, lipid and amino acid biosynthesis [4][5][6], they can modulate programmed cell death [7][8] and control inflammation [9]. Mitochondrial malfunction is related to various diseases [10][11][12] that are mainly manifested with a reduction in metabolism, Ca^{2+} homeostatic imbalance, increased levels of reactive oxygen species (ROS), lipid peroxidation and increased apoptosis.

Voltage-dependent anion-selective channel protein was first purified from paramecium mitochondria in 1976 [13]. People now know that there are two isoforms of voltage-dependent anion channel (VDAC) in yeast, yVDAC1 and yVDAC2, with yVDAC1 being the most abundant [14][15]. Three VDAC family members in mammalian mitochondria

were observed, VDAC1, VDAC2, VDAC3. VDAC1 is the most widely expressed, and contributes to a broad and general role [16][17][18]. Notably, VDAC2 in mammals contributes to anti-apoptotic phenotypes by binding to Bcl-2 homologous antagonist killer (BAK); mitochondrial apoptosis is activated, resulting from the homo-oligomerization of BAK when VDAC2 is displaced by truncated BH3 interacting-domain death agonist (tBID), Bcl-2-like protein 11 (BIM) or Bcl-2-associated agonist of cell death (BAD) [19]. VDAC3, especially the indispensable cysteine residues, plays an important role in protecting mitochondria from oxidative stress [20]. The transcriptional factors that regulate cell growth, apoptosis, energy metabolism, etc., also regulate VDAC gene expressions [21].

VDAC1 is a multifunctional channel protein that is located in the outer membrane of mitochondria. It modulates cellular metabolism [22][23]. VDAC1 regulates metabolism between the mitochondria and other parts of the cell by transferring metabolites, such as pyruvate, malonate, succinate, nucleotides and nicotinamide adenine dinucleotide hydrogen (NADH), into the mitochondria to complete subsequent metabolic reactions [23]. VDAC1 is also involved in cholesterol transportation, regulating lipid metabolism, mediating ion channels, regulating Ca^{2+} signaling between mitochondria and the endoplasmic reticulum (ER), and regulating the redox status of mitochondria and the cytoplasm. It has also been suggested that VDAC1 is a key protein that is involved in mitochondria-induced cell death [24][25][26][27].

VDAC1 is associated with increased release of mitochondrial DNA (mtDNA) [28][29], which is a signal of impaired mitophagy [30]. Mitophagy plays a central role in maintaining mitochondrial homeostasis; the process is pivotal in the development of inflammation and apoptosis [31][32][33][34], and is highly related to cytokines release [34][35]. VDAC1 plays an important role in regulating the mitochondrial involvement in vital activities. Functional abnormalities in mitochondria may lead to mitochondria-derived pathologic diseases, including inflammation, cardiovascular disease, cancer, neurodegenerative diseases, diabetes, and so on [10][11][36][37].

2. Inflammation, VDAC1 Mediates Apoptosis and Mitochondrial Oxidative Stress

2.1. VDAC1 Regulates Inflammation via Mediating Apoptosis

The mitochondrial permeability transition pore (MPTP) is about 1.4 nm in diameter, and supports solute and ion diffusion under 1500 kDa. It is also known as the mitochondrial macro-channel that plays an important role in cell survival and apoptosis [38][39]. The voltage-dependent anion channel (VDAC) is located in the outer mitochondrial membrane (OMM); adenine nucleotide translocase (ANT) is located in the inner mitochondrial membrane (IMM). VDAC and ANT are considered to be the structural components of the MPTP [40][41][42].

The Bcl-2 family has a close relationship with mitochondria and apoptosis [43]. It is known that Bcl-2 family member, Bcl-2-associated X protein (BAX), interacts with VDAC1 to regulate the release of cytochrome c (Cyto c) during apoptosis [44][45] (**Figure 1**). Oligomerization of BAX is one of the mechanisms that is involved in the mitochondrial apoptosis pathway [46]. A rat brain model indicates BAX promotes apoptosis by interacting with VDAC1 to expand the associated pore size, resulting in the increased permeability of mitochondria [47]. During apoptosis, VDAC1

assembles into oligomeric structures, forming a channel that is sufficient to pass Cyto c and release it into the cytoplasm. Cyto c forms oligomeric apoptosomes by binding to Apaf-1, apostasy activator and deoxyadenosine triphosphate (dATP); this results in the activation of cysteine protease 9 (caspase-9) that further activates effector caspases, caspase-3, caspase-6 and caspase-7 [43][48][49]. Ultimately, the caspase-mediated apoptosis pathway proteolytic cascade begins to cleave organelles and cellular components, resulting in apoptosis [48].

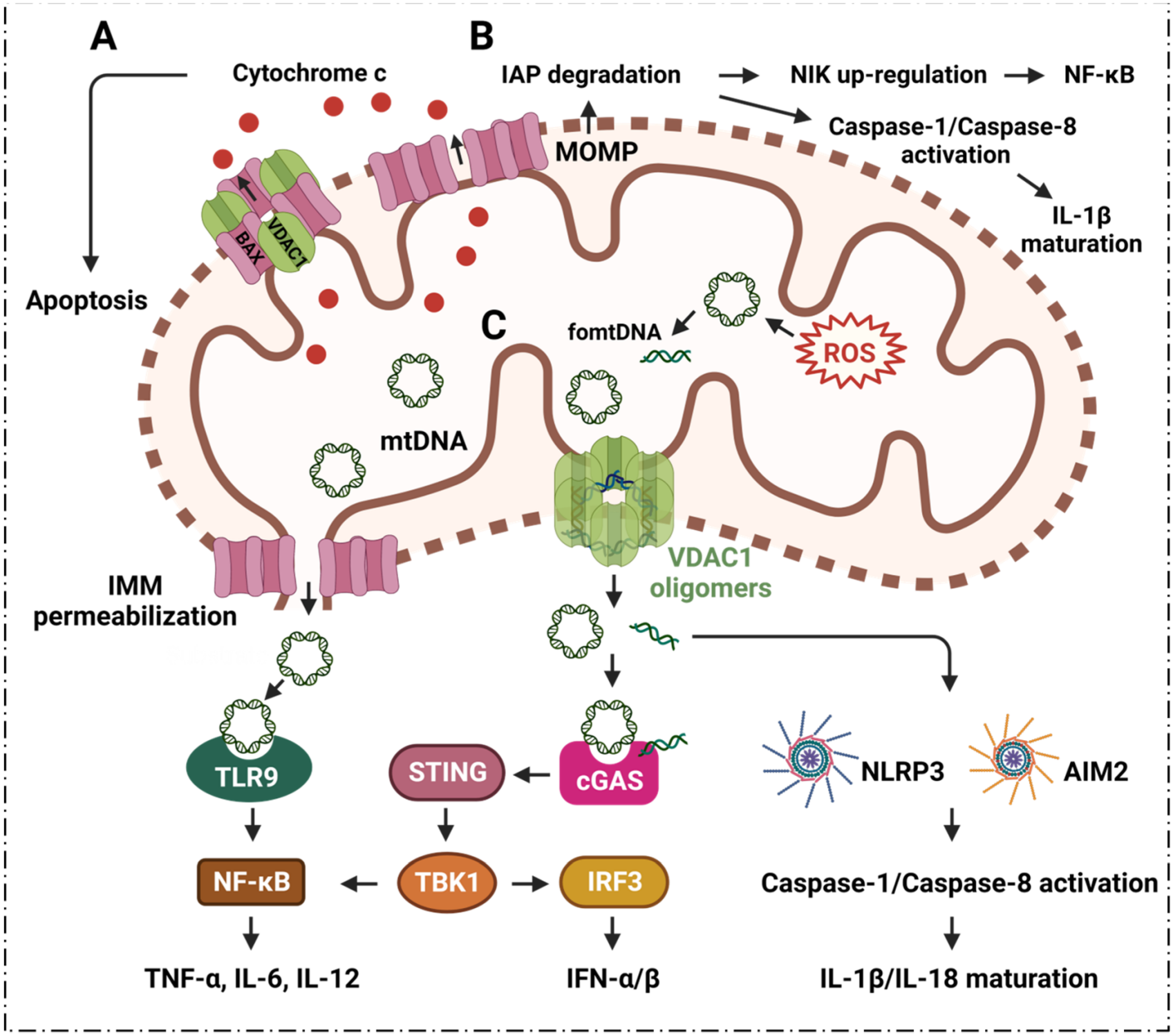

Figure 1. VDAC1 mediates apoptosis and mtDNA release to promote cytokines expression and inflammatory pathogenesis. (**A**) Bcl-2 family member, BAX, interacts with VDAC1 to release cytochrome c into the cytoplasm, promoting apoptosis. (**B**) MOMP induces proteasomal degradation of IAPs, which causes NIK to further induce the pro-inflammatory NF-κB signal and activate caspase-1/8; this in turn results in the maturation of pro-inflammatory factor IL-1β. (**C**) Mitochondrial overproduced ROS oxidize mtDNA to fomtDNA. The mtDNA and fomtDNA pass the VDAC1 oligomers channel or the oligomerization BAX pore into the cytoplasm. The released

mtDNA/fomtDNA induce the cGAS-STING pathway to promote interferon gene expressions via TBK1-IRF3 to up-regulate IFN-α/β, or through TBK1-NF-κB to enhance TNF-α, IL-6 and IL-12. Additionally, mtDNA interacts with TLR9 and promotes TNF-α, IL-6 and IL-12 expression via NF-κB signaling. Moreover, the released mtDNA induces the NLRP3 inflammasome and AIM2 inflammasome to enhance caspase-1/8 activation to promote IL-1β/IL-18 maturation. **Abbreviations:** AIM2: absent in melanoma 2; BAX: Bcl-2-associated X protein; cGAS: cyclic GMP-AMP synthase; Cyto c: cytochrome c; fomtDNA: oxidized mtDNA fragments; IAP: inhibitors of apoptosis; IFN: interferon; IL: interleukin; IRF3: interferon regulatory factor 3; IMM: inner mitochondrial membrane; MOMP: mitochondrial outer membrane permeabilization; mtDNA: mitochondrial DNA; NF-κB: nuclear factor-κB; NIK: NF-κB induced kinase; NLRP3: nucleotide-binding domain and leucine-rich repeat (LRR) containing P3; ROS: reactive oxygen species; STING: stimulator of interferon genes; TLR9: Toll-like receptor 9; TBK1: TANK-binding kinase 1; TNF: tumor necrosis factor; VDAC1: voltage-dependent anion channel 1.

2.2. VDAC1 Mediates Mitochondrial Oxidative Stress in Immune Responses

ROS from mitochondria can be dramatically induced under the stimulation of radiation, cigarette smoke, air pollution, inflammatory factors, tumor necrosis factor, hyperlipidemia, hypoxia, and so on. Notably, the ROS are mainly generated from the respiratory complex that is located in the IMM [50][51]. Malfunctioning mitochondria hyperproduce ROS which negatively affect other components of mitochondria, for example, mtDNA, membrane lipids, oxidative phosphorylation, etc. [52][53]. The mtDNA is mainly localized in the IMM, and mtDNA can easily be oxidized by ROS to generate oxidized mtDNA fragments (fomtDNA) [54]. The released mtDNA acts as ligands for different danger signal sensors, activating the innate immune response (**Figure 1**). These risk sensors include the cytoplasmic cyclic GMP-AMP synthase (cGAS); Toll-like receptor 9 (TLR9); nucleotide-binding domain and leucine-rich repeat (LRR) containing P3 (NLRP3) inflammasome; and absent in melanoma 2 (AIM2) inflammasome [50]. Through these pathways, mtDNA can induce the secretion of inflammatory cytokines, and induce the recruitment of immune cells at different sites, providing the conditions for inflammation in many diseases [50]. It has been shown that VDAC1 oligomer pores promote MOMP and allow the release of mtDNA into the cytoplasmic matrix in living cells, where mtDNA fragments escape from the mitochondria through direct interactions at the N-terminus of VDAC1 [28]. At the same time, the inhibition of VDAC1 oligomerization eliminates cytoplasmic and circulating mtDNA. Therefore, single-stranded or double-stranded DNA escapes into the cytoplasm through the permeability transition pore that is composed of VDAC1. VDAC1 indirectly participates in mtDNA induction by mediating the translocation of the subsequent mtDNA inflammatory response [28]. VBIT-3 and VBIT-4, as well as VBIT-12, were reported to interact with VDAC1 by disrupting its oligomerization, resulting in altered intracellular Ca^{2+} concentration and decreased ROS levels, thereby protecting mitochondrial malfunction related to apoptosis and inflammation [55][56]. This response was found to alleviate type 2 diabetes [57], lupus [28], atrial myocardium fibrosis [58], ulcerative colitis [59] and amyotrophic lateral sclerosis [56].

3. Inflammation and VDAC1 Mediates Mitochondrial Ca^{2+} Transportation

Mitochondrial Ca^{2+} uptake and release play a key role in cellular physiology by regulating intracellular Ca^{2+} signaling, energy metabolism and cell death [60]. The transportation of Ca^{2+} across the inner or outer mitochondrial membranes (IMM, OMM) is mainly mediated by several proteins, including VDAC1, mitochondrial Ca^{2+} monotransporter (MCU) and Na^{+}-dependent mitochondrial Ca^{2+} efflux transporter (NCLX) [61][62].

VDAC1 was shown to be highly permeable to Ca^{2+}, and contains a binding site for ruthenium red, thereby inhibiting channel opening [63][64]. VDAC1 may be a key component of the mitochondrial Ca^{2+} homeostatic mechanism, enhancing the Ca^{2+} response through different mechanisms. VDAC1 acts as a large conductance channel that allows for the rapid diffusion of Ca^{2+} across the OMM, thereby allowing the exposure of low-affinity single transporters in the inner membrane to the high Ca^{2+} microdomains that are generated by the opening of the endoplasmic reticulum (ER)-Ca^{2+} channel [63][64].

Moreover, VDAC1 has been proposed to be part of a larger complex of members, including the adenine nucleotide transporter, cyclophilin D, peripheral benzodiazepine receptors and Bcl-2 family members [65], which can interact with the ER. The structural components interact with each other, and thus become part of the molecular mechanism of mitochondrial docking with Ca^{2+}. VDAC1 is the major permeation pathway for Ca^{2+} across the OMM, and VDAC1 mediates Ca^{2+} transport through the OMM to the IMM space. It can also facilitate Ca^{2+} transport from the inner mitochondrial membrane space (IMS) into the cytoplasm [61] (**Figure 2**).

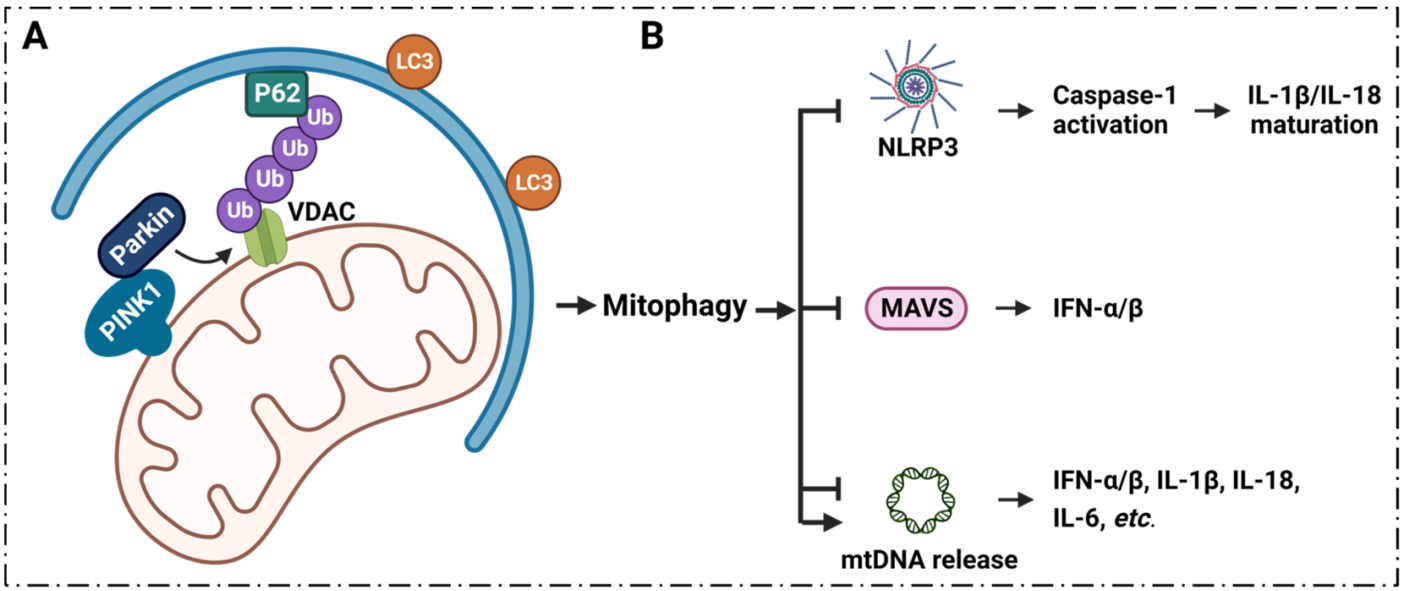

Figure 2. VDAC1 is involved in Ca^{2+} transportation, lipid metabolism, glycolysis, TCA cycleand in inflammatory responses. (**A**) VDAC1 regulates Ca^{2+} transportation, glycolysis, TCA cycle and lipid metabolism. VDAC1 transports Ca^{2+} between the mitochondria and cytoplasm to maintain calcium homeostasis. In the energy generation system, the VDAC1 pore maintains substrates, metabolites, biomolecules, etc., in a balanced manner to sustain salutogenesis. (**B**) Ca^{2+} signaling affects the inflammatory responses of neutrophils, macrophages, dendritic cells and $CD4^{+}$ T cells. (**C**) Inflammatory responses of macrophages, dendritic cells and $CD4^{+}$ T cells are promoted by glycolysis/TCA cycle energy generation pathways. **Abbreviations:** VDAC1: voltage-dependent anion

channel 1; TRPML1: also known as MCOLN1, mucolipin TRP cation channel 1; GRP75: glucose-regulated protein 75; IP3R: inositol 1,4,5-trisphosphate receptor; DJ1: deglycase DJ-1, also known as Parkinson disease protein 7, is encoded by the PARK7 gene in human; RyR2: ryanodine receptor 2; CPT1a: carnitine palmitoyltransferase 1A; ACSL: long-chain acyl-CoA synthase; TCA cycle: tricarboxylic acid cycle; HK: hexokinase; ATP: adenosine triphosphate; ADP: adenosine diphosphate; NADH: nicotinamide adenine dinucleotide hydrogen; PEP: phosphoenolpyruvate; Th: T helper.

Ca^{2+} is an important regulatory point of barrier function and inflammation. Ca^{2+} influx is involved in many steps of the inflammatory cascade, including leukocyte rolling, arrest, adhesion, and ultimately, transendothelial migration, etc. [66]. Ca^{2+} is involved in lymphocytic responses to foreign antigens, and inositol triphosphates (InsP3) are generated as a result of foreign molecules binding to antigen receptors and stimulating Ca^{2+} release from internal storage [67]. Once these stores are emptied, store-operated Ca^{2+} channels (SOCs) are activated, allowing lymphocytes to maintain a long-term increase in Ca^{2+}; this usually occurs in the form of a series of regular Ca^{2+} oscillations that activate nuclear factor of activated T cells (NF-AT) [67].

3.1. Neutrophils

Neutrophils are the most abundant type of white blood cells, and are the first responders to inflammatory stimuli, such as bacterial infection, or tissue damage medium caused by polarization and migration of mediators such as formyl-Met-Leu-Phe (fMLP) and IL-8 [68][69], whose dysfunction often leads to severe infections and inflammatory autoimmune diseases.

In neutrophils, the cytoplasmic free calcium concentration is an important determinant of cell viability, and is a marker of neutrophil activation; it is closely related to a range of neutrophil functions [70]. Rapid cell spreading in neutrophils is induced by Ca^{2+} signaling [71]; Ca^{2+} influx activates cytoplasmic calpain, which plays an important role in regulating neutrophil polarization, and in directing their migration toward chemotactic stimuli [68]. The entry of extracellular Ca^{2+} into neutrophils affects multiple functions, including phagocytosis, ROS production, vesicle secretion and degranulation, β2-integrin activation, and cytoskeletal rearrangement that leads to polarization and migration; these activities play a key role in the occurrence and development of the neutrophil inflammatory response [72][73] (**Figure 2**B).

3.2. Macrophages

Ultrasound, combined with endogenous protoporphyrin IX derived from 5-aminolevulinic acid (ALA-SDT), induce the apoptosis of macrophages [74]. The inhibition of VDAC1 by 4,4′-diisothiocyanostilbene-2,2′-disulfonic acid (DIDS) was found to prevent ALA-SDT-induced cell apoptosis in THP-1 macrophages [74]. The VDAC1 of the mycobacterium avium phagosome is associated with bacterial survival and lipid export in macrophages [75]. Macrophages are an important part of the innate immune system; their main function is to phagocytose and digest cell debris and pathogens, and they play an important role in inflammatory responses [76][77].

Ca^{2+} is an essential second messenger in phagocytosis; indeed, elevated cytosolic calcium concentrations are required for efficient phagocytosis and maturation of phagosomes [78]; blocking MCU inhibits macrophage phagocytosis [79]. Studies have shown that Ca^{2+} influx into macrophages is the trigger for macrophage activation, and that increased Ca^{2+} concentrations are associated with macrophage differentiation [80]. An influx of extracellular Ca^{2+} is required to polarize macrophages toward the pro-inflammatory M1 phenotype, while decreasing Ca^{2+} leads to anti-inflammatory M2 switching [79][81] (**Figure 2**B).

3.3. Dendritic Cells

Dendritic cells (DCs) are the most powerful antigen-presenting cells in the body. DCs uptake, process and present antigens efficiently that are crucial for initiating T cell responses. They play a central role in initiating, regulating and maintaining immune responses [82].

Ca^{2+} signaling plays a key role in the function of DCs. Migration of DCs to secondary lymphoid organs is indispensable for subsequent T helper cell-mediated adaptive immunity. It has been shown that chemokine-induced DC migration is Ca^{2+}-dependent [83]. Ca^{2+} is involved in the regulation of chemokine receptor expression, cell swelling, cytoskeletal changes and amphipod formation activities; DC migration relies tightly on the cytosolic Ca^{2+} concentration [84]. Activated DCs rapidly up-regulate chemokine receptor 7 (CCR7) expression, and acquire the ability to migrate into afferent lymphatics and drain lymph nodes [85]. CCR7 is a G protein-coupled receptor [86] that regulates DC chemotaxis, survival, migration velocity, cellularity and endocytosis; furthermore, its activation is accomplished by inducing the mobilization of intracellular calcium stores through the inositol 1,4,5-triphosphate (IP3) pathway [87][88]. Ca^{2+} plays an important role in the inflammatory response because it regulates the function of DCs in various links (**Figure 3**B).

4. Inflammatory Diseases and VDAC1 in Energy Metabolism

4.1. TCA Cycle

Metabolites in the process of energy metabolism can participate in inflammatory responses through different pathways, affecting the secretion of cytokines, the production of pro-inflammatory mediators, and the activation and differentiation of immune cells. VDAC1 plays an important role in energy metabolism, and participates in the inflammatory response by directly mediating the transport of metabolites during respiration and regulating Ca^{2+} as well as the activity of respiration-related enzymes (**Figure 2**A,C). Succinic acid is one of the metabolites that accumulates from the disturbance of the TCA cycle and the breakdown of hyperglutamine. Succinate accumulation leads to macrophage M1 polarization through the direct inhibition of proline hydrolase, prompting HIF-1α and IL-1β secretion [89][90]; it acts as an inflammatory stimulator in an autocrine-dependent manner [89][91]. Lipopolysaccharide (LPS)-induced succinate promotes IL-1β expression via HIF-1α signaling [90][92]. Extracellular succinate induces a pro-inflammatory response in diverse immune cells, increasing the migration and secretion of pro-inflammatory cytokines TNF-α and IL-1β in dendritic cells and macrophages [90].

4.2. Glycolysis

The initial and rate-limiting steps of glycolysis are mainly catalyzed by HK1, most of which is bound to the OMM, mainly through mitochondria formed by VDAC1 and adenine nucleotide translocator (ANT) intermembrane contact sites for transport [93]. It has also been shown that Hexokinase-2 (HK2) binds to VDAC1 on the OMM to facilitate the preferential entry of ATP into HK2 for glycolysis [94]. The binding of HK2 with mitochondrial VDAC1 can be inhibited by chrysin, resulting in decreased glucose uptake and lactate production [95]. VDAC1 is directly involved in the regulation of the glycolytic pathway; it affects the activation, differentiation and migration of various immune cells such as macrophages, DCs, T cells, etc., and affects the production, migration, and release of various cytokines and pro-inflammatory mediators.

VDAC1 can affect mitochondrial respiration, as a result of its important role in controlling the transportation of substances and metabolites. The intermediates in the Krebs cycle have a close relation with the inflammation process [96]. The metabolism of PEP, lactic acid, succinic acid, citric acid, etc., plays an important role in the occurrence and development of inflammation. In conclusion, VDAC1 could become a new therapeutic target for inflammation, and this necessitates further study.

5. Inflammatory Diseases and VDAC1 in Lipid Metabolism

VDAC1 is involved in cholesterol transport, and is generally considered to be part of a complex that mediates fatty acid transport through the OMM [97][98][99]. Meanwhile, VDAC1 also serves as an anchoring site for long-chain acyl-CoA synthase (ACSL), which is associated with the outer surface of the OMM, and for carnitine palmitoyltransferase 1a (CPT1a), which faces the intermembrane space [99] (**Figure 2**A). ACSL catalyzes the synthesis of fatty acyl-CoA in vivo, which is the first reaction in the human body to utilize fatty acids; meanwhile, CPT1a is involved in the process of transporting long-chain fatty acids into the mitochondria so that fatty acids can be broken down to generate usable energy for cells. It has been reported that CPT1a, ACSL and VDAC1 can form a complex, and that the long-chain fatty acyl-CoA synthesized by ACSL is transferred from the OMM to the intermembrane space through VDAC1; furthermore, CPT1a converts acyl-CoA into long-chain fatty acylcarnitine [99], followed by a series of subsequent oxidation reactions.

It has been found that the phosphorylation state of VDAC1 mediated by glycogen synthase kinase 3 (GSK3) can control the permeability of the OMM [100]. It has been observed that a loss of VDAC1 may cause mitochondria to stop oxidizing fatty acids, and VDAC1 inhibitors can inhibit palmitate oxidation [101][102]. In addition, the VDAC1-based peptide, R-Tf-D-LP4, can stimulate catabolic pathways that are involved in promoting fatty acid transfer to the mitochondria, fatty acid oxidation and increasing the expressions of enzymes and factors that are associated with fatty acid transport to the mitochondria, thereby enhancing β-oxidation and production of energy [101].

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6. Inflammatory Diseases Pathogenesis and VDAC1 in Mitophagy

6.1. Mitophagy Regulates Inflammation via VDAC1

Mitophagy plays a key role in the regulation of inflammatory signaling, and the process of mitophagy limits inflammatory cytokines secretion [32][33][103][104][105] (**Figure 3**).

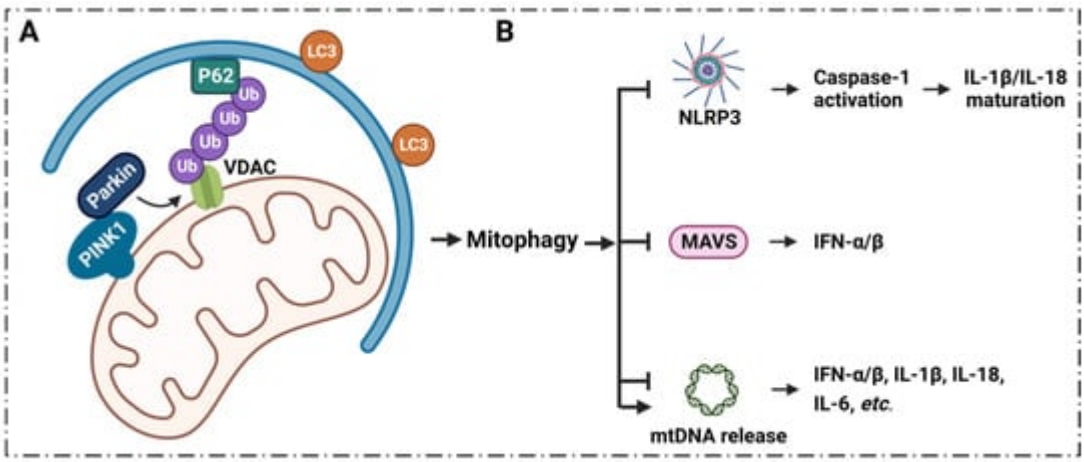

Figure 3. VDAC1, PINK1/Parkin signaling and mitophagy. (**A**) PINK1/Parkin targets damaged mitochondria, ubiquitinates VDAC1, and ultimately degrades damaged mitochondria by promoting mitophagy. (**B**) Mitophagy modulates NLRP3, MAVS and mtDNA release, affecting the immune response. NLRP3 activates caspase-1 to promote IL-1β/IL-18 maturation. MAVS enhance IFN-α/β expression. Meanwhile, mitophagy suppresses NLRP3, MAVS and mtDNA release, which results in reduced cytokines release. Additionally, mitophagy can also promote mtDNA release, which affects cytokines expression. **Abbreviations:** IL: interleukin; IFN: interferon; LC3: microtubule-associated proteins 1A/1B light chain 3; MAVS: mitochondrial antiviral signaling protein; NLRP3: nucleotide-binding domain and leucine-rich repeat (LRR) containing P3; PINK1: PTEN-induced putative kinase 1;; Ub: ubiquitin; VDAC1: voltage-dependent anion channel 1.

The PTEN-induced putative kinase 1 (PINK1) and the RING family ubiquitin ligase Parkin were found to be involved in mitophagy [106][107][108][109]. This indicates that induced mitophagy can be accomplished in cells that overexpress Parkin or overexpress PINK1. PINK1/Parkin acts as key regulator of mitophagy, and is vital in controlling infection and the inflammatory response [110]. The interaction of two Parkin domains, RING1 and ubiquitin-like (UBL), affects its activity. UBL binding with RING1 results in the inactive state of Parkin; PINK1 phosphorylates UBL-Ser65, leading to the activation of Parkin to promote substrate ubiquitination, with VDAC1 included [111].

7. Summary and Conclusions, Current Clinical Conditions and Future Perspectives

Mitochondria are fundamental organelles that execute and coordinate various metabolic processes in cells. Mitochondria are key organelles that are associated with cellular functions, and well-functioning mitochondria are critical to maintaining tissue homeostasis [112]. Mitochondrial malfunction is a sign of oxidative stress, inflammation, aging and chronic degenerative diseases [112][113][114]. VDAC1 is an important regulator of mitochondrial function, and acts as a mitochondrial gatekeeper that is responsible for cell fate [115].

Cutting-edge research confirms that VDAC is essential for the apoptotic “Find me signaling” pathway that results from the failure of apoptotic cell clearance, and leads to the pathogenesis of cystic fibrosis, followed by sterile inflammation [116]. Ulcerative colitis (UC) may be promoted by VDAC1 overexpression, and novel interacting targets for the treatment of UC based on VDAC1 are being developed for inflammatory and/or autoimmune diseases [59]. In addition, research suggests that VDAC1 is also related to cardiovascular and cerebrovascular diseases [117]. Furthermore, VDAC1 is widely involved in cancer [24][118], neurodegenerative diseases [119][120], diabetes [57][121], kidney disease [122][123], aging [124] and other areas of study. These all suggest that VDAC1 is a reasonable target to develop the next generation of therapeutic drugs.

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