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REVIEW

Ca^{2+}-Dependent Mitochondrial Permeability Transition Pore: Structure, Properties, and Role in Cellular Pathophysiology

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Abstract—The Mitochondrial Permeability Transition pore (MPT pore) activated by Ca^{2+} ions is a phenomenon that has long been the subject of intense study. Cyclophilin D-dependent opening of the MPT pore in mitochondria in response to calcium overload and oxidative stress leads to swelling of the mitochondrial matrix, depolarization of the inner membrane and dysregulation of ion homeostasis. These processes are accompanied by damage to mitochondrial membranes and, ultimately, to cell death. Despite decades of research, the molecular identity of the MPT pore remains unclear. Currently, the inner membrane proteins – ATP synthase and adenine nucleotide translocator (ANT) – are considered to be its key structural components, along with the regulatory protein cyclophilin D. The involvement of the MPT pore in the progression of various pathological conditions and diseases, as well as in a number of physiological processes, such as the regulation of cellular bioenergetics and rapid release of Ca^{2+}, is widely discussed. This review summarizes modern molecular genetic data on the putative structure of the MPT pore, traces the evolution of views on its functioning – from interpreting it as a simple experimental artifact to its recognition as a putative key regulator of energy metabolism – and also considers the mechanisms of its regulation and its multifaceted pathophysiological role.

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INTRODUCTION

Mitochondria are organelles that perform a wide range of functions in eukaryotic cells. They are the primary energy generators in most types of cells, they participate in the regulation of ion homeostasis and thermogenesis, and their production of reactive oxygen species (ROS) is closely linked to aging and cell death. However, one of the most intriguing and enigmatic phenomena associated with these organelles is the formation and functioning of the Mitochondrial Permeability Transition pore (MPT pore), which is formed by a complex of mitochondrial proteins under a wide range of pathophysiological conditions.

The MPT pore is a megachannel formed in the outer and inner mitochondrial membranes as a result of exposure to high concentrations of intracellular Ca^{2+}, oxidative stress and other inducers [1]. Despite more than 70 years of studying this phenomenon, the exact molecular structure of the MPT pore has not been established yet. The main difficulty lies in identifying the protein components that form the pore in the inner mitochondrial membrane. Currently, the most abundant proteins of the inner mitochondrial membrane are traditionally considered as such components, specifically the F_0F_1–ATP synthase (complex V) and adenine nucleotide translocator (ANT) [2, 3]. At the same time, cyclophilin D, the key regulator of the MPT pore, as well as the proteins and protein subunits involved in the formation of the

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pore complex in the intermembrane space and the outer membrane of organelles, have been discussed quite rarely in recent years.

The pathophysiological significance of MPT pore formation in mitochondria is currently undisputed and highlights the dual role of these organelles in cell life and death. It is believed that a prolonged open state of the MPT pore leads to mitochondrial and cell death, whereas its short-term "flickering" opening facilitates the removal of excess Ca^{2+} ions from the mitochondria into the cytoplasm, protecting cells from the damaging effects of calcium overload on organelles [3-7].

Based on existing observations, new natural and synthetic modulators of the MPT pore are being actively investigated, and genetic manipulations of known components of the pore complex are being conducted in model systems. This allows to establish of a link between the functioning of the pore in mitochondria and the development of various cellular pathologies. This review analyzes the current state of research regarding the mechanisms of MPT pore formation, regulation and functioning, as well as the prerequisites that have led to the current understanding of the nature of this phenomenon in cells, its physiological and pathological role, and key unresolved issues.

THE HISTORY OF PORE STRUCTURE STUDIES

The history of studying the mitochondrial pore had started long before the term "mitochondrial permeability transition" (Fig. 1) was coined. As early as the 1950s, it was discovered that mitochondria have the ability to swell, which leads to impaired ATP synthesis [8, 9]. However, the observed mitochondrial permeabilization was thought to be either an *in vitro* artifact or a consequence of nonspecific damage to their inner membrane by phospholipase A_2 [10]. Ca^{2+} was found to activate phospholipase A_2, whose hydrolytic activity results in the accumulation of "defects" – lysophospholipids and free fatty acids – in mitochondrial membranes. These were believed to be the primary cause of changes in mitochondrial membrane permeability [11]. However, this hypothesis did not explain why rapid and dramatic swelling of mitochondria occurs if the accumulation of membrane defects associated with phospholipase A_2 activity occurs gradually. However, at the turn of the 21st century, studies based on this hypothesis were conducted, resulting in the discovery of a new type of mitochondrial pore – a lipid pore inducible by saturated fatty acids and Ca^{2+} [12, 13].

In the late 1970s, permeabilization of the inner mitochondrial membrane was described in detail [14-16]. It was found that when Ca^{2+} ions accumulate in mitochondria, their inner membrane becomes permeable to hydrophilic compounds with a molecular weight of up to 1.5 kDa, resulting in swelling of the organelles. The influence of the major metabolites on this process was studied, and regulation of inner membrane permeabilization was demonstrated. Based on these studies, it was suggested that a non-selective Ca^{2+}-dependent channel is formed in the mitochondrial membrane in the presence of Ca^{2+} ions,

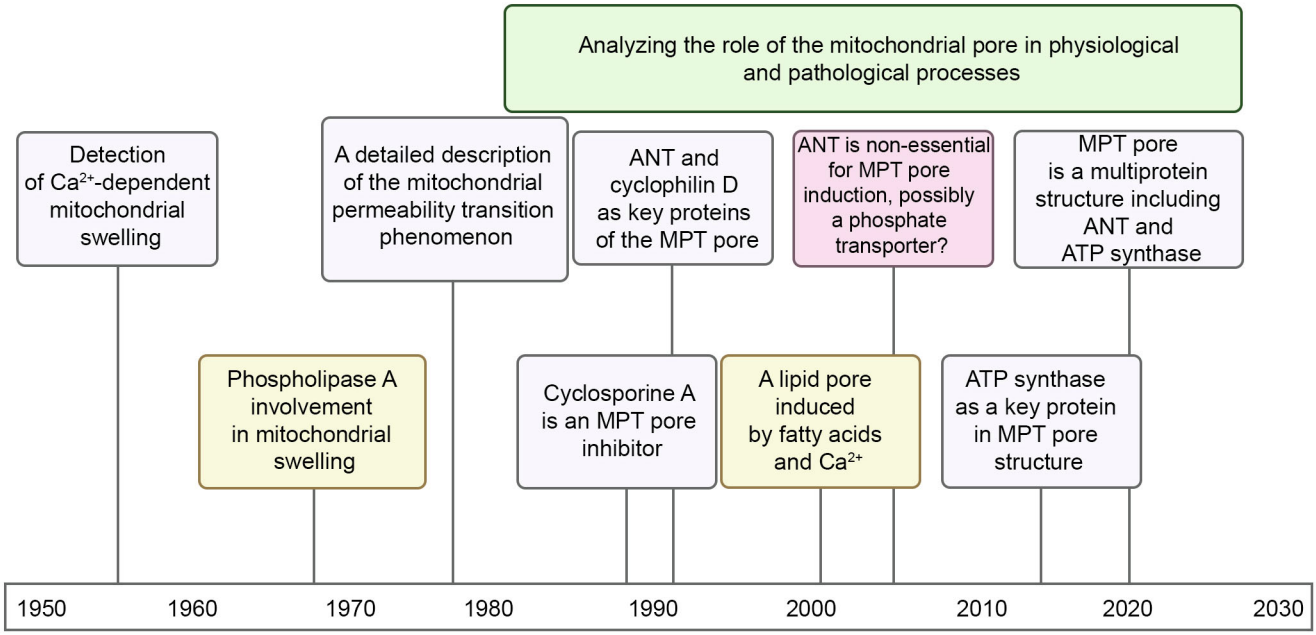

Fig. 1. Timeline of MPT pore research. ANT – adenine nucleotide translocator.

which can be inhibited by chelating agents. Since the molecular nature of the channel remained unknown, the authors proposed the term “permeability transition” to describe this phenomenon (meaning a sharp non-specific change in permeability). Since the change occurred abruptly according to the “all or nothing” principle [1, 14], it was discussed specifically as a “transition” (and, subsequently, the mitochondrial pore) and not a change in mitochondrial permeability, in order to emphasize the transitive nature of the phenomenon.

In the late 1980s, a high-affinity inhibitor of the mitochondrial pore, the cyclic undecapeptide cyclosporin A (CsA) was discovered. It completely inhibited the MPT pore opening at submicromolar concentrations [17, 18]. It was established that CsA binds to the mitochondrial matrix protein, peptidyl prolyl *cis*/*trans* isomerase cyclophilin D [19]. This discovery finally confirmed the concept of the protein nature of the mitochondrial pore.

It was initially believed that the target of cyclophilin D and the channel component of the pore is the adenine nucleotide translocator, the predominant protein of the inner mitochondrial membrane responsible for the antiport of ADP and ATP. The prerequisites for this were discovered back in the 1970s, when it became clear that the ANT modulators carboxyatractylate and bongkrekic acid activate and inhibit Ca^{2+}-dependent mitochondrial swelling, respectively [14]. Later, Halestrap and Davidson [20] proposed a mechanism of action for these inhibitors, according to which carboxyatractylate stabilized ANT in the cytosolic (*c*) conformation, and bongkrekic acid – in the matrix (*m*) conformation [20]. The hypothesis of a key role for ANT existed until the mid-2000s, when it was discovered that ANT is not an essential component of the MPT pore. In mitochondria of mice with genetic knockout of the first and second ANT isoforms (ANT1 and ANT2), the MPT pore opened and remained sensitive to cyclosporin A [21].

The search for new channel components of the MPT pore led to suggestions that such a component could be a phosphate transporter, and, later, a mitochondrial ATP synthase [22, 23]. These proteins have a common feature of being able to interact with cyclophilin D. However, interest in the phosphate transporter quickly became irrelevant, since its knockdown or overexpression did not affect pore opening.

Mitochondrial ATP synthase is currently considered a key component of the MPT pore. Its involvement (or the involvement of individual ATP synthase subunits) in membrane permeabilization has been demonstrated by various methods. Several models for the transformation of ATP synthase into the MPT pore have been proposed [3]. However, ANT has recently come to be regarded as an important component of the MPT pore once more, responsible for its low-conductance mode of operation [3].

However, even today we can only discuss a hypothetical structure of the MPT pore. This is primarily due to the limitations of current methodological approaches.

MPT PORE STRUCTURE

According to current concepts, the mitochondrial pore is a large protein megachannel formed in the outer and inner mitochondrial membranes. Depending on the conditions, the size of the MPT pore can vary from a small non-selective ion channel to a large pore with high conductivity (up to 1000 pS), through which ions and hydrophilic molecules with a mass of up to 1.5 kDa can penetrate. Prolonged MPT pore opening leads to suppression of mitochondrial energy metabolism, disruption of ion homeostasis and a drop in mitochondrial membrane potential. Furthermore, the entry of osmotically active metabolites into the mitochondrial matrix due to MPT pore opening leads to swelling, followed by rupture of the outer mitochondrial membrane. All this, along with the release of proapoptotic proteins from mitochondria, can lead to organelle destruction and cell death [1, 3, 7, 12, 24]. These mechanisms of cell death, mediated by the opening of the mitochondrial pore, play a key role in the pathogenesis of numerous diseases associated with ischemic damage to organs and tissues, neurodegenerative diseases, aging, etc. At the same time, the temporary opening of the MPT pore, characterized by a low-conductivity state, is of physiological significance for the cell. This type of pore is involved in the unloading of Ca^{2+} ions from mitochondria, a decrease in ROS production and regulation of bioenergetic metabolism [6, 24, 25]. Activation of the pore is believed to be associated primarily with an increase in Ca^{2+} concentration in the mitochondrial matrix, development of oxidative stress, an increase in cyclophilin D levels and a decrease in the pool of adenine nucleotides. At the same time, di- and trivalent cations, adenine nucleotides, SH-reducing agents and cyclophilin D inhibitors suppress MPT pore opening. More details on this can be found in the review by Zoratti and Szabo [1].

The abovementioned facts make it clear that MPT pore formation in mitochondria is a complexly regulated process that may involve a large number of proteins. Indeed, current models suggest a multiprotein nature of the pore, with ANT, ATP synthase, cyclophilin D and other proteins forming a dynamic “sensory cluster” that adapts to particular conditions in a cell (Fig. 2) [2, 3].

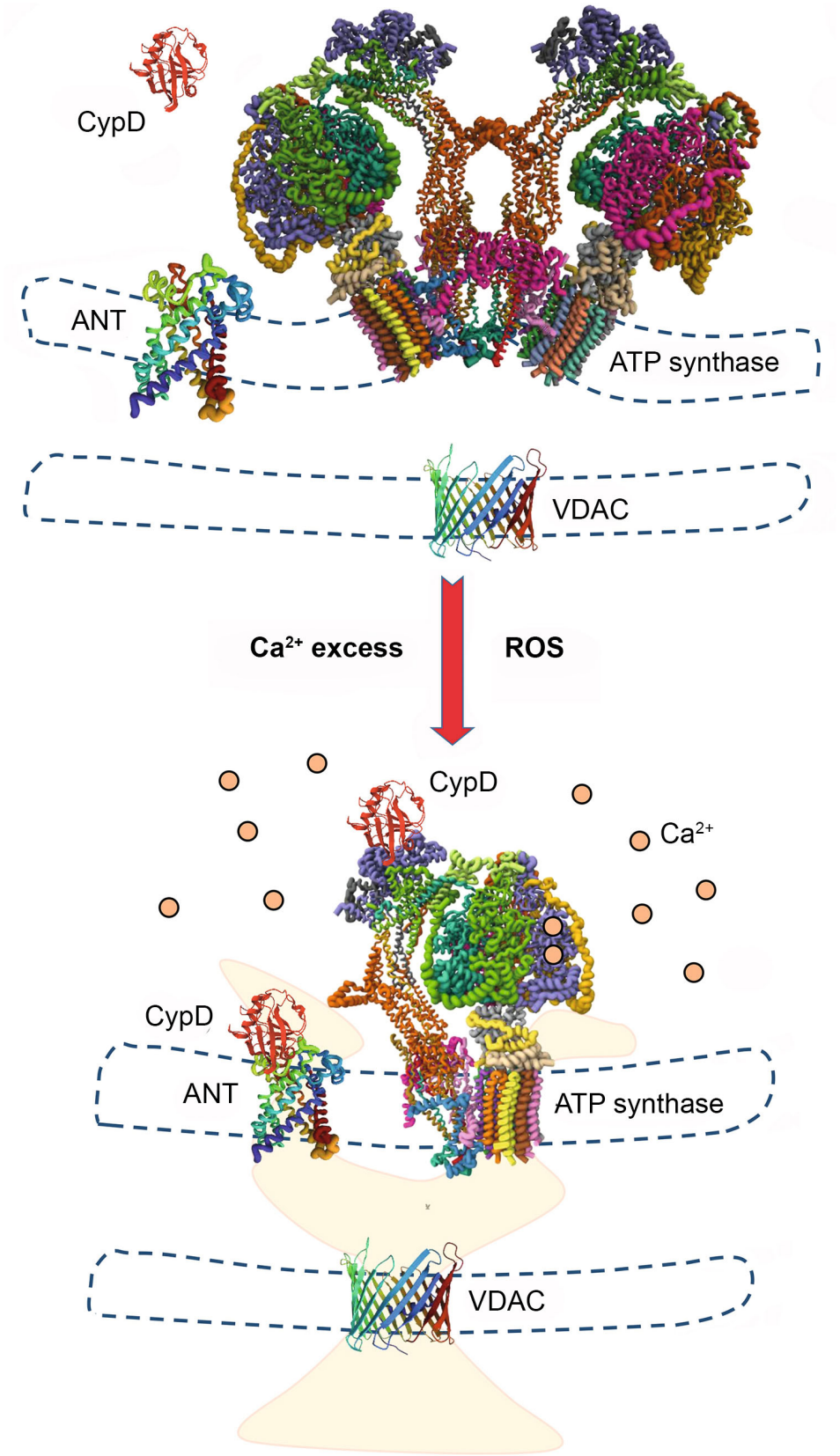

Fig. 2. The proteins forming the MPT pore in mitochondria and their transformation into pore channels under the influence of Ca^{2+} ions and/or oxidative stress. Fluxes of osmotically active molecules through the pore channels in the inner and outer membranes upon pore induction are shown. PDB IDs used: ANT – 1OKC; ATP synthase (both) – 6RD4; VDAC – 2JK4; CypD – 5CBV. Descriptions are given in the text. ANT – adenine nucleotide translocator; VDAC – voltage-dependent anion channel of the outer mitochondrial membrane; CypD – cyclophilin D.

When describing the mitochondrial pore model, three groups of proteins can be distinguished: the obligatory regulator – cyclophilin D; hypothetical channels of the inner membrane pore – ANT and ATP synthase; auxiliary proteins, which include VDAC (voltage-dependent anion channels of the outer mitochondrial membrane), TSPO (translocator protein, also known as the peripheral benzodiazepine receptor), mitochondrial creatine kinase, mitochondrial hexokinase and a number of other proteins.

Cyclophilin D is a key regulator of the MPT pore. Cyclophilin D is a protein belonging to the CsA-sensitive peptidyl prolyl *cis*/*trans* isomerase family capable of catalyzing the isomerization of proline residues, a rate-limiting step in protein folding [26]. All proteins of this family contain a highly conserved cyclophilin-like domain consisting of 8 antiparallel β-sheets that form a hydrophobic core with the catalytic center and other functional regions [19]. Cyclophilin D is encoded by the *Ppif* gene, the mature protein is localized in the mitochondrial matrix and contains 178 amino acid residues (19 kDa) [19].

Cyclophilin D is able to interact with a large number of various transporters which are associated with membrane proteins, including ATP synthase, ANT, respiratory chain complex III, the anti-apoptotic Bcl2 protein and the key metabolic protein kinases GSK-3β and Akt2 [19, 27-29]. Due to this, cyclophilin D is able to regulate the formation of various mitochondrial supercomplexes. However, its most well-described function is regulation of MPT pore formation. Cyclophilin D modulates pore formation by reducing the threshold level of calcium load required for pore opening in mitochondria; this requires the interaction of cyclophilin D with ATP synthase or ANT, which form a channel in the pore complex [2, 3]. This effect is suppressed in the presence of cyclosporin A, which is believed to cause dissociation of cyclophilin D from channel proteins [20]. Mitochondria from various tissues of mice with the knocked out *Ppif* gene (and, consequentially, lacking the interaction of pore proteins with cyclophilin D) were more resistant to Ca^{2+} overload, and the addition of CsA had no inhibitory effect in this case. At the same time, overexpression of the *Ppif* gene caused an increase in Ca^{2+}-dependent mitochondrial swelling and cell death [30].

The exact mechanism of modulation of MPT pore formation involving cyclophilin D has not been fully established. Early studies demonstrated that MPT pore formation requires interaction of cyclophilin D with ANT and VDAC proteins [29]. However, it is now recognized that cyclophilin D binds primarily to ATP synthase [3, 28] (Fig. 2). In the ATP synthase complex, cyclophilin D interacts with OSCP (oligomycin sensitivity conferring protein), which appears to be involved in peripheral stalk formation [23, 28]. The issue of whether the enzymatic activity of cyclophilin D is required also remains debatable. It was initially assumed that cyclophilin D induces MPT pore formation independently of its peptidyl prolyl *cis*/*trans* isomerase activity [31]. However, fibroblasts with inactivated cyclophilin D (Arg96Gly substitution) were insensitive to oxidative stress induction, similar to what was observed in cells with a knockout of this protein [30]. This suggests that the enzymatic activity of the protein does facilitate MPT pore activation. Furthermore, peptidyl prolyl *cis*/*trans* isomerase activity correlates with increased self-assembly of ATP synthasomes (a supercomplex consisting of ATP synthase, ANT and a phosphate transporter) in various tissues and the formation of highly ordered ATP synthase oligomeric structures, thereby reducing the likelihood of MPT pore formation [32].

The ability of cyclophilin D to modulate MPT pore opening is provided in the cell by mechanisms of post-translational protein modification [19]. For example, acetylation of Lys138 stimulates MPT pore formation [33]. It is believed that Lys138 is localized in the catalytic site of the protein and is involved in the interaction with OSCP [23]. GSK-3β increases cyclophilin D binding to OSCP and stimulates MPT pore opening by phosphorylating Ser162 [34, 35]. Cleavage of the N-terminal region of cyclophilin D by calpain 1 can also contribute to an increase in the probability of MPT pore opening by enhancing the interaction with OSCP [36]. Oxidative modification of cyclophilin D at cysteine residues (Cys174(C203) in particular) is involved in the process of activation of MPT pore formation in the presence of oxidative stress inducers [37].

ANT and ATP synthase as channel proteins of the pore complex. The adenine nucleotide translocator is a protein of the SLC25 family of mitochondrial transporters that transport metabolites, inorganic ions and cofactors [38]. ANT exchanges matrix ATP for cytoplasmic ADP across the inner mitochondrial membrane [39]. It is also believed that one of the alternative functions of ANT is fatty acid-catalyzed proton transfer, which ensures uncoupling of oxidative phosphorylation. In humans, 4 ANT isoforms are present (while mice lack the *Ant3* gene) [40], with a molecular weight of ~30 kDa. The protein structure contains 6 transmembrane α-helices [41] (Fig. 2).

As mentioned above, the involvement of ANT in MPT pore formation was suggested in the 1970s, and in the 1990s, understanding of the mechanism of ANT transformation into the mitochondrial pore was developed [14, 20, 42]. Indeed, ANT inhibitors and substrates significantly affected Ca^{2+} capacity and swelling of organelles [14]. When ANT was incorporated into giant vesicles, channel conductance (up to 600 pS) was observed [43]. It was shown that

oxidative modification of cysteine residues (Cys57 and Cys160) of ANT caused formation of disulfide bridges in the protein, increased mitochondrial sensitivity to MPT pore induction through enhanced cyclophilin D binding and suppressed the inhibitory effect of ADP [44]. All this convincingly indicated the involvement of ANT in MPT pore formation.

However, the results of certain experiments in the mid-2000s almost made mitochondriologists completely abandon the idea of ANT as a part of the MPT pore. It was shown that liver mitochondria from mice with knockouts of the *Ant1* and *Ant2* genes were still sensitive to Ca^{2+}-dependent mitochondrial swelling, which was prevented by cyclosporin A. Moreover, such mitochondria had increased Ca^{2+} capacity (compared to liver mitochondria from control animals), which was reduced by the addition of oxidizing agents, but not atractyloside (an ANT inhibitor and MPT pore inducer) [21]. Only recently it was shown that knockouts of all three ANT genes (*Ant1*, *Ant2*, *Ant4*) in mice resulted in liver mitochondria becoming virtually insensitive to Ca^{2+} ions, while the addition of cyclosporin A or knockout of the *Ppif* gene resulted in complete inhibition of the pore. Patch clamp analysis of mitoplasts isolated from mouse embryonic fibroblasts with knockouts of all three ANT genes showed virtually no channel conductance. This allowed to conclude that ANT is an essential component of the MPT pore, which induces the formation of a low-conductance pore [45].

Interestingly, increased expression of different ANT isoforms is observed in various pathologies. For example, in Duchenne muscular dystrophy, a decrease in ANT1 expression and an increase in ANT2 levels are observed in skeletal muscle cells [46]. In hepatocytes of diabetic mice (type 1 diabetes mellitus), a decrease in ANT1 levels was also observed [47]. On the other hand, suppression of ANT2 expression in HEK293T cells (a cell line derived from human embryonic kidneys) even enhanced the progression of mitochondrial dysfunction under hyperlipidemic conditions [48]. All this may indicate tissue-specific regulation of MPT pore activity in various pathologies.

It is believed that ANT is capable of transforming into a channel under the influence of Ca^{2+} ions [42]. However, ANT does not have a Ca^{2+} binding site, which suggests the effects of additional factors in the regulation of the MPT pore (possibly cardiolipin) or post-translational modification [2, 49]. There are doubts about the necessity of ANT interaction with cyclophilin D for MPT pore formation [2, 3]. All this allows to assume that another channel that ensures the opening of high-conductance MPT pore can be formed in mitochondria. Surprisingly, a slightly incorrect interpretation of the experiment conducted in the mid-2000s led to significant progress in the search for new structural components of the MPT pore. As a result, ATP synthase is currently considered as the key channel component of the MPT pore.

Mitochondrial ATP synthase is one of the key mitochondrial supercomplexes (~600 kDa), consisting of a F1 complex (ATP synthesizing) and a membrane-embedded F0. The complexes interact via a central and a peripheral stalk. The F1 complex consists of three pairs of αβ subunits arranged around the central stalk (γ, δ, and γ subunits). The central stalk is linked to the F0 complex, which consists of a lipid-filled c-ring (integral c subunits) and an α subunit. The peripheral stalk consists of OSCP, F6, b and d subunits. ATP synthase forms dimer rows in the inner mitochondrial membrane, with the key proteins being the e, f, g, A6L, j and k subunits. These dimer rows form the cristae structure of the inner membrane, giving it a positive curvature [50, 51].

The possibility of ATP synthase involvement in the formation of the mitochondrial pore was first suggested with the discovery of a CsA-sensitive interaction between cyclophilin D and OSCP (Fig. 2) [28]. This interaction resulted in inhibition of mitochondrial ATP synthase activity and stimulation of MPT pore opening. Benzodiazepine-423, a classic inhibitor of ATP synthase activity, acted in a similar manner, binding to OSCP at the same site as cyclophilin D [23, 28].

There are currently two hypotheses on ATP synthase involvement in MPT pore formation: the pore is formed either between ATP synthase dimers or within the ring of c subunits [3].

When ATP synthase was embedded in an artificial lipid membrane, a high Ca^{2+}-dependent channel conductance (1-1.3 nS) was observed, similar to the conductance of the MPT pore in mitoplasts [23, 52]. The conductance was observed only in the case of the dimeric or oligomeric form of ATP synthase, but not its monomeric form [53]. Suppression of the expression of proteins involved in the dimer formation (subunits e, g, f) led to complete inhibition of MPT pore opening [54-56]. Dimerization of ATP synthase was enhanced by the ATPase inhibitor, the IF1 protein, which inhibits MPT pore opening and protects the cell from ischemic damage [57]. All this allowed us to assume that the MPT pore is formed in the dimers of ATP synthases between the e, g and f subunits due to their destabilization or structural rearrangements in each monomer [58].

On the other hand, it was shown that ATP synthase monomers are also capable of forming high-conductance channels [59]. When purified c subunits were embedded in a lipid membrane, voltage-gated channels of varying conductance appeared in the membrane. The conductance of most channels was

at a level of 100 pS, but in some cases, high conductance at a level of 1.5-2 nS was also observed [60], which is also similar to the conductance of the MPT pore [52]. Knockdown of the c subunit of ATP synthase resulted in inhibition of MPT pore opening in mitochondria [61].

However, the possibility of the c-ring involvement in MPT pore formation remains debatable. This is due to the fact that the inner space of the ring is filled with lipid molecules and is hydrophobic [62]. The "death fingers" hypothesis attempts to circumvent this limitation and combine the two mechanisms described above [63]. According to this hypothesis, the binding of Ca^{2+} to the β subunit of the F1 complex of ATP synthase and the binding of cyclophilin D to OSCP causes a chain of conformational changes in the F_1 complex, which are transmitted through the peripheral stalk to the inner mitochondrial membrane in the region of the e subunit. Simultaneous displacement of the central stalk subunits and the F_1 complex away from the c-ring can also occur. The e subunit expels lipids from the c-ring lumen, which may lead to its expansion and the emergence of channel activity. Indirect evidence for such a mechanism may be provided by the data showing that mutations weakening the c-ring packing led to an increase in the internal diameter of the ring, an increase in channel conductance and an increase in the sensitivity of various cells to cell death inducers [60, 64]. This hypothesis describes both the reversible opening of the pore, which can be observed under physiological and sublethal pathological conditions, and the irreversible opening of the pore. In the latter case, dissociation of the F_1 and F_0 subunits may occur, which will lead to mitochondrial swelling and cell death. However, it should be noted that displacement of lipids from the c-ring lumen into the hydrophilic region of the intermembrane space is a thermodynamically unfavorable process [3].

J. Walker's group demonstrated that knocking out various ATP synthase proteins involved in MPT pore formation does not suppress its activity. For example, genetic knockout of each of the e, f, g, k subunits and of the 6.8 kDa proteolipid (6.8PL) disrupted the dimerization of the complex, but the probability of MPT pore opening did not decrease [58]. Knockout of three nuclear genes, *ATP5G1*, *ATP5G2*, and *ATP5G3*, encoding the c subunits, rendered mitochondria in HAP1-A12 cells sensitive to MPT pore induction [65]. Knocking down peripheral stalk proteins (β subunits and OSCP) either did not affect the induction of the mitochondrial pore in cells, or ionic currents were observed that were insensitive to cyclosporin A, but underwent inhibition by bongkrekic acid [54, 55]. All this allowed us to consider ANT as a channel of the MPT pore once again.

Recently, a consensus has emerged that adding Ca^{2+} to mitochondria can activate the formation of the MPT pore, whose channel in the inner membrane can be either ANT or ATP synthase [3, 66, 67]. It has been suggested that the opening of the pore associated with ATP synthase occurs at physiological pH values, while the action of ANT regulators (and, consequently, ANT-mediated pore opening) is enhanced by decreasing the pH from 7.4 to 6.5 [68]. In this case, the two structures can function as an ATP synthasome. ANT and ATP synthase embedded in an artificial lipid membrane are able to induce channel conductivity upon the addition of high concentrations of Ca^{2+} ions.

However, the precise molecular structure of the mitochondrial pore remains far from being resolved. This is due to the numerous contradictions and phenomena which are difficult to explain observed in experiments with mitochondria. This has been mentioned above in regards to the studies when suppression of the activity of the same genes encoding ATP synthase proteins led to different effects in different experiments. Meanwhile, the removal of ANT or various ATP synthase subunits leads to a decrease in energy metabolism, suppression of respiratory activity and membrane potential generation [55, 65]. This may be an additional factor influencing pore formation in mitochondria even in the absence of certain subunits. In addition to these discrepancies, no precise answers to questions posed several decades ago are present yet. For example, it is still unclear why pore induction in mitoplasts and artificial membranes requires Ca^{2+} ion amounts 2-3 orders of magnitude higher than in the case of intact mitochondria. Moreover, it is still not entirely clear what the binding site for Ca^{2+} ions is [3]. Another mystery is the ratio of the number of opening pores (up to 10) to the number of ANT and ATP synthases (several thousand copies) per mitochondrion [69, 70]. Which particular events lead to a very small number of ANT or ATP synthases undergoing transformation and changing their physiological function to pathological? The answers to these questions may be one of the cornerstones which will allow us to understand the structure of the pore in the future.

The accessory proteins required for MPT pore induction in mitochondria. The ability of mitochondrial outer membrane proteins to regulate MPT pore opening has been known for a long time. VDAC is a family of β-barrel proteins of the mitochondrial outer membrane (~30-35 kDa). These are the most abundant outer membrane proteins that regulate the transport of metabolites and ions from cytoplasm to mitochondria. VDAC has long been considered one of the main components of the MPT pore, since the conductance of VDAC channels is similar to that of the MPT pore (Fig. 2) [71]. It was believed that the pore

is formed in the contact site region where the connection of outer and inner mitochondrial membranes occurs. However, in isolated mitochondria, VDAC is not required for MPT pore formation [5]. Thus, mitochondrial pore opening can be induced in mitoplasts and submitochondrial particles [72, 73]. Furthermore, pore opening occurs in mitochondria isolated from mice in which all three VDAC isoforms were knocked out [74]. However, the role of VDAC in MPT pore formation in a living cell should not be underestimated, since these channels provide the main pathway for Ca^{2+} ions influx into mitochondria. Various cytoplasmic protein kinases (e.g., GSK3β, PKA (protein kinase A), etc.) lower the threshold for MPT pore opening to various inducers by phosphorylating VDAC [71].

TSPO is another protein (18 kDa) localized in the outer mitochondrial membrane [75], for which participation in MPT pore formation has been described. TSPO is involved in the regulation of many metabolic processes, the key one of which is cholesterol transport into mitochondria [76, 77]. It was believed that this protein facilitates the formation of the contact site between VDAC and ANT [77]. Meanwhile, in rat brain mitochondria, cholesterol binding to TSPO resulted in suppression of cyclosporin A-insensitive membrane potential decrease and Ca^{2+} release from mitochondria [78]. Antibodies against TSPO caused an increase in Ca^{2+} capacity of mitochondria [78, 79]. A number of TSPO ligands caused MPT pore activation [76]. At the same time, there is evidence that suppression of TSPO expression in animal tissues did not cause a significant change in MPT pore induction [79]. Therefore, the role of TSPO in MPT pore formation cannot be considered proven yet, and the stimulating effects of ligands may be associated with the presence of other mitochondrial targets in the latter [23].

The involvement of other proteins of the outer mitochondrial membrane (in particular, proteins of the Bcl2 family) in MPT pore regulation has also been shown [5]. It has been suggested that the Bax and Bid proteins stimulate the pore opening in mitochondria, since their genetic knockout leads to inhibition of MPT-induced mitochondrial swelling and cell death [80]. However, it should be noted that these proteins induce the formation of large pores in the outer mitochondrial membrane primarily as a result of oligomerization with each other or with VDAC [71]. This can surely promote MPT pore opening, but it rather appears to be a parallel process.

As mentioned above, in the mid-2000s, a phosphate transporter capable of interacting with cyclophilin D was considered as a possible structural unit of the MPT pore in the inner membrane [22]. Today, it is believed that even if the phosphate transporter is involved in pore formation, its expression level does not limit the process of MPT pore opening [81]. It can be assumed that, being part of the ATP synthasome, this transporter may be indirectly involved in pore induction mediated by ANT or ATP synthase [2]. Other proteins (aldehyde dehydrogenase (*Aldh6a1* gene) and prohibitin 2) associated with ATP synthase can also modulate ATP synthase-mediated MPT pore [82].

A 2015 study showed that, in addition to cyclophilin D, spastic paraplegia 7 (SPG7) is also an essential component [83]. This is a protein of the AAA protease family, localized in the inner mitochondrial membrane. Genetic knockout of SPG7 resulted in suppression of MPT pore opening in mitochondria induced by Ca^{2+} or oxidative stress and also prevented cell death. There are several possible explanations for SPG7 involvement in MPT pore induction, ranging from its effect on mitochondrial Ca^{2+} transport to suppression of SIRT3 (sirtuin 3) expression and, a consequently, suppression of cyclophilin D deacetylation [84, 85]. Other studies found that increasing or decreasing SPG7 expression by using siRNA did not affect MPT pore induction in mitochondria [86]. All these facts allow us to say that SPG7 may indirectly participate in the induction of the MPT pore, but it is not an essential component of the pore.

Another group of enzymes involved in MPT pore regulation are various kinases, including mitochondrial creatine kinase, hexokinase, and GSK-3β [87-89]. Their ability to regulate the pore is believed to be associated primarily with their interaction with VDAC and ANT. Thus, increased expression of creatine kinase and hexokinase suppresses MPT pore opening and prevents the development of cell death [49]. Due to this, one of the cancer cell markers is overexpression of mitochondria-associated hexokinases I and II [90]. Kinases can interact with VDAC either directly (the hydrophobic N-terminus of hexokinase interacts with Glu73 of VDAC, preventing its oligomerization) or through Ser and Thr residue phosphorylation (inhibition or phosphorylation of GSK-3β prevents mitochondrial ROS production, MPT pore induction and cell death) [71, 89].

Alternative mechanisms of mitochondrial pore induction which are insensitive to cyclosporin A. The possibility of inhibiting mitochondrial pore formation by cyclosporin A allowed researchers to focus their attention on the MPT pore phenomenon. Thus, studies of the role of the mitochondrial pore in various diseases are often determined by the effect of CsA or other MPT inhibitors on the process. However, it is possible to induce non-specific mitochondrial permeability that is insensitive to cyclosporin A. This suggests that regulation of such permeability is not associated with cyclophilin D. Exogenous amphipathic peptides (e.g., signaling proteins), certain prooxidants,

hormones (thyroxine) and fatty acids have the ability to induce Ca^{2+}-dependent permeability of the inner mitochondrial membrane that is insensitive to cyclosporin [12, 91].

The possibility of inducing a Ca^{2+}-dependent pore mediated by fatty acids and phospholipase A_2 activity was established quite a long time ago [11-13, 92, 93]. The insensitivity of this phenomenon to CsA was demonstrated in the early 2000s: saturated palmitic acid in the presence of Ca^{2+} ions induced swelling of mitochondria isolated from various tissues. At the same time, it was shown that palmitic acid similarly induces Ca^{2+}-dependent permeabilization of both natural (mitochondrial and erythrocyte plasma membranes) and artificial lipid membranes (unilamellar liposomes and bilayer lipid membranes) [13]. Based on these and a number of other characteristics, we concluded that the pore induced by saturated fatty acids and Ca^{2+} is of lipid origin [93]. It was shown that the mechanism of palmitate/Ca^{2+}-induced pore formation is based on the ability of saturated fatty acid anions to form strong complexes with Ca^{2+} in the lipid bilayer, followed by their separation into solid crystalline membrane domains and the appearance of hydrophilic lipid pores [12, 93]. Importantly, lipid pores are characterized by their self-sealing ability, which may be of physiological significance for the mechanism of mitochondrial Ca^{2+} unloading [13]. The formation of such pores in a living cell can occur due to phospholipase A_2 activation [13, 94]. More details on the lipid pore induced by palmitic acid and Ca^{2+} can be found in the review by Mironova and Pavlov [13].

MPT PORE INHIBITORS IN MITOCHONDRIA

Understanding the mechanisms of MPT pore activation and its involvement in pathological processes naturally leads us to the question of the possibilities of modulating this pore's function. One of the most detailed analyses of MPT pore modulators was given in the review by Zoratti and Szabo [1] in 1995. Today, the development of MPT pore inhibitors has entered the phase of targeted design: using structural modeling, high-throughput screening and analysis of interactions with both the regulators of its opening (cyclophilin D, TSPO) and the discussed direct components of the pore (such as ANT and ATP synthase).

The most studied MPT pore inhibitor is cyclosporin A [17-19]. Its discovery not only confirmed the role of the MPT pore in cell death but also provided a direction for further research. However, the use of CsA as a cardio- or neuroprotector is limited by its side effects, including immunosuppression, nephrotoxicity and its lack of selectivity regarding other cyclophilins. Furthermore, its low permeability across the blood-brain barrier limits its potential use against neurological diseases [95]. Other natural cyclosporins B, C, D, and E have also been studied for their ability to modulate MPT pore opening. They differ by minor variations in amino acid sequences, which, however, have a significant impact on their activity. For example, cyclosporins A, B, C, and D exhibit significant conformational dynamics, whereas cyclosporin E, being more rigid due to the absence of a methyl group at Val11 position, loses the ability to inhibit MPT pore opening [96].

One of the ways to enhance the selective properties of cyclosporin A was elimination of immunosuppressive activity. Thus, in 1994, a cyclosporin derivative, N-methyl-4-isoleucine-cyclosporin (NIM811 or GNX-4975) [1, 97], was obtained. It retained high affinity for cyclophilin D but did not suppress calcineurin, which deprived it of immunomodulatory activity and could potentially expand its therapeutic window. This allowed NIM811 to reach the stage of preclinical and early clinical trials against myocardial infarction and stroke. Another promising compound lacking any immunosuppressive properties is alisporivir (Debio 025), which has shown higher selectivity for cyclophilin D, having successfully performed in models of diabetes, Duchenne muscular dystrophy [98, 99], collagenopathy [100], Alzheimer's disease [101] and having passed clinical trials for hepatitis C. However, like cyclosporin A, alisporivir exhibited non-selective effects on mitochondrial bioenergetics (already at micromolar concentrations, which are classical for *in vitro* experiments), which is due to its hydrophobic nature and the ability to accumulate in the lipid phase of membranes and affect their physical properties [102].

Cyclophilin D is not the only regulatory molecule through which MPT pore status is modulated. The involvement of TSPO in pore opening and its modulation by the synthetic agent TRO40303, which is capable of preventing pathological opening of the MPT pore, is being discussed [103].

In addition to cyclosporins, the natural macrolide compound sanglifehrin A, isolated from actinomycetes, is among the classic MPT pore inhibitors. Sanglifehrin A is capable of binding to cyclophilin D, but at a different site than cyclosporin A, and does not inhibit calcineurin. Furthermore, unlike CsA, sanglifehrin A does not affect the binding of cyclophilin D to ANT [104]. In experiments on cardiac tissue, sanglifehrin A reduced myocardial damage during reperfusion, decreasing infarction size and protecting cells from oxidative stress if the compound was administered during the first minutes of reperfusion [105]. However, like CsA, sanglifehrin A also has immunosuppressive properties, which limits its use. Another

example is bongkrekic acid, produced by *Burkholderia gladioli pathovar cocovenenans* bacteria. It blocks MPT pore opening binding to ANT. However, its high toxicity limits its clinical applications.

In addition to well-known ANT modulators capable of inhibiting MPT pore opening, agents capable of influencing the pore-forming activity of ATP synthase are currently being developed. For example, a new class of MPT pore inhibitors based on 1,4,8-triazaspiro[4.5]decan-2-one has recently been presented [106]. The most promising compound, **14e**, demonstrated high inhibitory activity at micromolar concentrations and a pronounced cytoprotective effect in a model of cardiomyocyte hypoxia/reoxygenation. The effect is apparently due to the influence of the compounds on ATP synthase which is a structural component of the MPT pore. Molecular modeling revealed a potential binding site for the compounds at the junction of the c-ring and the a subunit of ATP synthase, and in this case, the structural features of **14e** provided the greatest affinity for this site [106].

High-throughput screening also identified efficient MPT pore inhibitors among cinnamyl anilides, isoxazoles and benzamides [107-110]. These compounds are more potent than cyclosporin A and exhibit marked specificity, acting independently of cyclophilin D. However, these compounds are characterized by low metabolic stability (e.g., isoxazoles) and, in some cases (benzamides), toxicity, meaning that further optimization of their structure is required.

It should be noted that pore inhibitors are being actively developed for at least two main reasons: the emergence of new scientific hypotheses about the pore structure and the identification of the role of the mitochondrial pore in the development of pathologies.

THE ROLE OF MPT PORES IN THE DEVELOPMENT OF CELLULAR PATHOLOGIES

The first papers suggesting the involvement of the MPT pore in the development of cellular pathologies appeared in the late 1970s, when it was discovered that a sharp increase in the permeability of the inner mitochondrial membrane can be triggered by Ca^{2+} overload and oxidative stress and is closely associated with cell death. At that time, it was already shown that MPT pore opening leads to mitochondrial swelling, rupture of outer mitochondrial membrane and activation of apoptosis or necrosis, which was believed to be associated with tissue damage during cardiac ischemia/reperfusion and other acute conditions. In the following decades, research confirmed the key role of the MPT pore in the pathogenesis of a wide range of diseases, including neurodegenerative and neuromuscular diseases, cardiovascular diseases, diabetes, bone remodeling pathologies and cancer (Fig. 3). Although the molecular structure of the pore is still under debate, its involvement in pathologies is widely accepted, and modulation of its activity is considered a promising therapeutic strategy [111]. Moreover, accumulated data suggest that the occurrence of pathologies associated with the process of aging, primarily neurodegenerative disorders, metabolic and cardiovascular pathologies, is also due to an age-related increase in cell sensitivity to MPT pore induction. Indeed, indirect measurements show that the MPT pore is activated more efficiently in tissues of old organisms, especially when exposed to high concentrations of Ca^{2+} and inorganic phosphate ions [112]. In addition, experiments on model organisms such as *Caenorhabditis elegans* demonstrate that stimulation of MPT pore induction shortens lifespan, while its inhibition can have a protective effect [113]. However, the mechanisms that determine the transition from the physiological to the pathological role of the MPT pore remain not fully understood.

Participation of the MPT pore in the pathogenesis of neurodegenerative diseases. The MPT pore plays a key role in the development of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis (ALS), as well as in the processes of axonal degeneration and neuronal death. It is believed that MPT pore induction in Alzheimer's and Parkinson's diseases is caused by accumulation of aggregates of pathological proteins in nerve cells, such as β-amyloid, tau protein and α-synuclein, which are able to interact with MPT pore components (e.g., cyclophilin D, VDAC, ANT, and ATP synthase) [7, 114-116]. Experimental models of ALS (G93A-mSOD1 mice) revealed structural rearrangements of motor neuron mitochondria, accompanied by an increase in the number of contacts between the inner and outer membranes, which is believed to contribute to the induction of the MPT pore [116]. Since such mitochondria cease to produce ATP efficiently, cells with high energy demands (e.g., dopaminergic neurons in Parkinson's disease or motor neurons in ALS) begin to experience energy deficiency, which leads to their degeneration. Furthermore, mitochondrial dysfunction promotes increased ROS formation and development of oxidative stress. Opening of the MPT pore promotes the release of cytochrome *c* and other proinflammatory molecules, such as mitochondrial DNA, which increases neuroinflammation and further contributes to nerve tissue damage [7]. Moreover, mitochondrial sensitivity to MPT pore opening increases with age. This is associated with impaired calcium homeostasis, increased oxidative stress and changes in the composition of mitochondrial proteins,

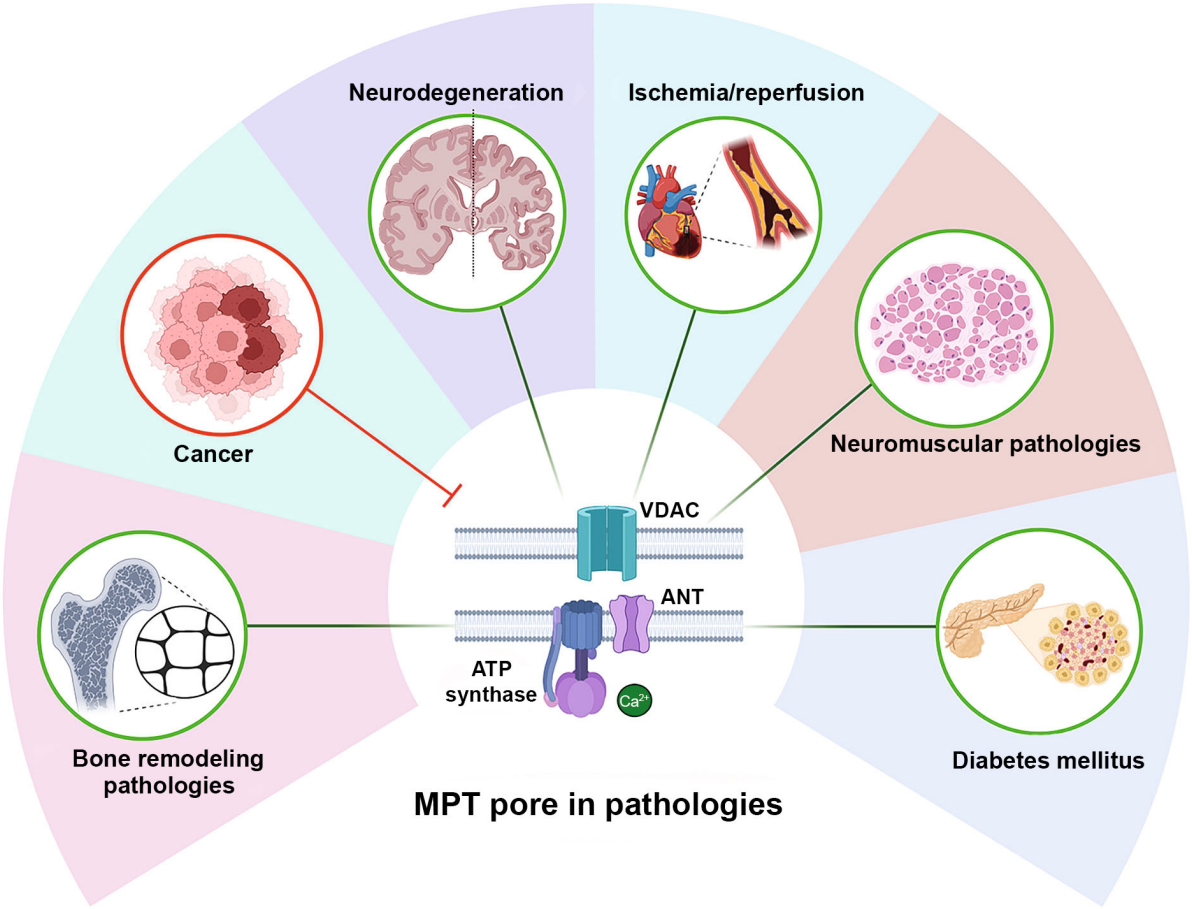

Fig. 3. A scheme illustrating MPT pore participation in the development of various pathological processes. Explanations are given in the text. ANT, adenine nucleotide translocator; VDAC, voltage-dependent anion channel of the outer mitochondrial membrane. The image was created by using BioRender.

which may explain the age-related vulnerability of the brain to neurodegeneration [7]. These effects can be eliminated by pharmacological inhibition of the MPT pore with cyclosporin A [117] and olesoxime [118].

Participation of the MPT pore in the development of pathologies caused by tissue ischemia/reperfusion. The role of the MPT pore in damage caused in tissues highly sensitive to hypoxia and subsequent reoxygenation (heart, brain, kidneys) is currently being actively discussed [3, 4]. Specifically, during myocardial infarction, which occurs due to ischemic damage to the heart muscle, Ca^{2+} ions and inorganic phosphate accumulate in cardiomyocytes, creating preconditions for MPT pore induction in mitochondria. However, in the initial period of pathology development, low intracellular pH and high ADP levels temporarily suppress pore opening, delaying the onset of consequences. The situation changes drastically under reperfusion conditions, when restoration of blood flow leads to normalization of pH values and the "washout" of inhibitory factors, creating favorable conditions for MPT pore formation. It is also important to note that, in addition to the classical Ca^{2+}-dependent mechanism, oxidative stress plays a significant role in regulating MPT pore formation in mitochondria in cardiovascular pathologies. For example, accumulation of intracellular succinate during ischemia can lead to increased ROS formation as a result of reverse electron transfer in the mitochondrial respiratory chain during subsequent reperfusion, which further facilitates MPT pore opening in organelles [4]. Subsequently, pore induction under such conditions causes a collapse of mitochondrial membrane potential, swelling and destruction of mitochondria, which triggers a cascade of events leading to necrosis of cardiomyocytes and other types of cells in the myocardium. This process is directly related to the localization and volume of the infarction zone: the more mitochondria undergo MPT pore induction, the larger the area of necrotic tissue. Experimental models convincingly demonstrate that preventing MPT pore formation with cyclosporin A, using cyclophilin D gene knockout methods or initiating the ischemic preconditioning effect significantly reduce tissue damage during ischemia/reperfusion [119, 120]. However, clinical studies based on pharmacological

inhibition of the MPT pore in patients with myocardial infarction have shown conflicting results [121], indicating the need to optimize therapeutic approaches.

MPT pore involvement in neuromuscular diseases. The idea of mitochondrial dysfunction being involved in the pathogenesis of neuromuscular diseases was proposed for the first time almost 50 years ago [122]. Currently, the main focus is on how MPT pore induction caused by Ca^{2+} overload and oxidative stress in dysfunctional mitochondria leads to muscle fiber damage and death. It has been found that the MPT pore may play an important role in the development of muscular dystrophies associated with deficiency of collagen VI (e.g., Bethlem myopathy, Ullrich congenital muscular dystrophy, myosclerosis), dystrophin (Duchenne and Becker muscular dystrophy), δ-sarcoglycan (limb-girdle muscular dystrophy), and laminin [123, 124]. In all these cases, the absence of structural proteins leads to a disruption of the stability of muscle fiber sarcolemma (both its integrity and the function of ion channels and signaling molecules) and an excessive influx of calcium ions from the extracellular space [125]. Excessive calcium uptake by mitochondria under these conditions combined with oxidative stress makes them extremely sensitive to MPT pore opening and triggers a cascade of pathological events, from the loss of mitochondrial membrane potential to the release of proapoptotic factors and, ultimately, muscle fiber death [46]. In addition, mitochondria overloaded with calcium phosphate can act as foci of tissue calcification, thereby promoting tissue degeneration [126]. It is interesting to note that mitochondria in the hearts of dystrophic *mdx* mice (a model of Duchenne muscular dystrophy) exhibit resistance to MPT pore induction, which may be linked to tissue-specific expression of proteins associated with its formation and regulation (cyclophilin D, ANT, ATP synthase subunits) [127]. This is supposed to contribute to the delayed development of cardiac pathologies, which is characteristic of both model animals and patients. Meanwhile, MPT pore inhibitors (CsA, alisporivir, NIM) are able to slow the development of muscle pathology in model animals and also improve the condition of skeletal muscles in patients [98, 99, 110, 124]. A similar effect is achieved by blocking mitochondrial calcium overload with inhibitors of Ca^{2+}-transporting proteins [125]. A number of pharmacological inhibitors are currently in early clinical trials. Recent studies involving inactivation of genes of cyclophilin D and ANT, the presumed protein components of the pore, also confirm the role of the MPT pore in the development of muscle pathologies [124, 128].

It has been shown that the MPT pore may be involved in pathogenesis of multisystem diseases, including those affecting muscle tissue. Early stages of ALS are characterized by disrupted calcium homeostasis and oxidative stress in the brain, spinal cord, and skeletal muscles, which contributes to increased susceptibility of mitochondria in the cells of these tissues to MPT pore opening [129]. The involvement of the MPT pore formation in age-related muscle degeneration has also been described [130]. The lack of effective therapy for these pathologies, which are in most cases sporadic and multifactorial, allows us to consider the MPT pore as one of the promising pharmacological targets. Further research in this area may also contribute to improving the diagnostic approaches to most neuromuscular pathologies accompanied by mitochondrial dysfunction already in the early stages.

The role of the MPT pore in the development of diabetes mellitus. In type 1 and type 2 diabetes mellitus, hyperglycemia, hyperlipidemia, and oxidative stress increase mitochondrial sensitivity to MPT pore opening in most tissues, which leads to a loss of membrane potential, increased ROS production and the release of proapoptotic factors [131]. Pathological induction of the MPT pore in diabetes has been described for pancreatic β-cells [132], cardiomyocytes [133] and neurons [134]. The involvement of this phenomenon in diabetic complications, such as cardiomyopathy, is also being discussed. Meanwhile, sensitivity to MPT pore opening in diabetes varies depending on the tissue type. For example, mitochondria of the heart and skeletal muscles become more susceptible to the opening of the pore in diabetes, which increases oxidative stress and cell damage [135, 136]. At the same time, an increase in resistance to MPT pore induction is observed in the liver, which may also be associated with tissue-specific expression of pore proteins and is considered an adaptive mechanism which prevents acute toxic organ damage [137]. Interestingly, this significantly distinguishes the pathology of diabetes from other metabolic diseases, such as non-alcoholic fatty liver disease, which is characterized by accumulation of free fatty acids in hepatocytes and the development of lipotoxicity, which contributes to the disruption of the respiratory chain, increased ROS formation and a significant increase in the sensitivity of liver cells to MPT pore induction [138]. It has been shown that both genetic and pharmacological inhibition of the MPT pore by using cyclophilin D blockers (CsA and alisporivir) can protect against mitochondrial damage caused by diabetes or other metabolic pathologies, improve glucose utilization and reduce oxidative stress, thereby alleviating cardiac and skeletal muscle dysfunction [131, 133, 139-141]. We have shown that blockers of VDAC (VBIT-4) and ANT (bongkrekic acid), potential channel components of the MPT pore, exhibit a cytoprotective effect under these conditions [48, 142].

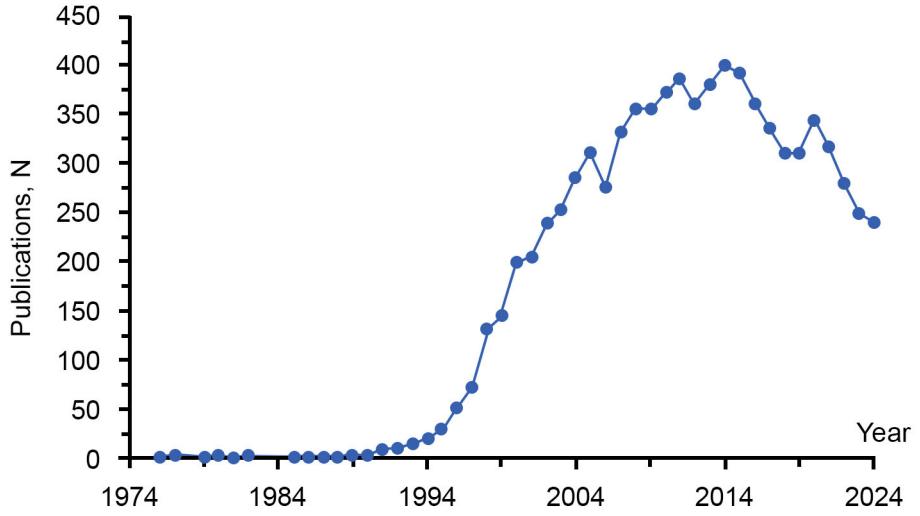

Fig. 4. Number of publications by year in the PubMed database in response to the query "Mitochondrial Permeability Transition". https://pubmed.ncbi.nlm.nih.gov/?term=mitochondrial+permeability+transition&sort=date.

It should be noted that diabetes mellitus is a chronic disease. In this regard, mitochondrial pore induction in a high-conductivity state may be a feature of such extremely pathological manifestations as diabetic foot syndrome. In all other cases, however, MPT pore activation occurs in a low-conductivity "flickering" state which rather represents a mechanism of adaptation to mitochondrial calcium overload.

MPT pore participation in bone remodeling pathologies. Recent data indicate that the MPT pore is involved in the regulation of bone cell metabolism, including mesenchymal stem cells, osteoblasts and osteoclasts [143]. In mesenchymal stem cells, decreased MPT pore opening activity promotes osteogenic differentiation, which is associated with the suppression of cyclophilin D expression via the BMP/Smad signaling pathway [144].

Pathological opening of the MPT pore is observed in age-related osteoporosis, which is accompanied by a decrease in bone mass and impaired mitochondrial function. Knockdown of cyclophilin D or its pharmacological inhibition (e.g., by using NIM811) improves bone health in aged mice, preventing loss of bone mass [145]. Osteoporosis induced by excessive glucocorticoid (e.g., dexamethasone) intake has also been shown to be associated with MPT pore activation, which promotes osteoblast apoptosis. This effect, observed in gum tissue, is believed to be due to an increase in cyclophilin D levels in tissues and is removed by cyclosporin A or knockdown of this pore protein [146].

In models of periodontitis and osteoarthritis, excessive induction of the MPT pore facilitates activation of inflammatory pathways and bone resorption. Meanwhile, MPT pore inhibition reduces the intensity of inflammation and bone tissue loss [147].

MPT pore and oncological diseases. Unlike other pathologies discussed above, in which the MPT pore acts as an unambiguous driver of cell, tissue, and organ damage, its activity in carcinogenesis is subject to complex regulation, reflecting tumor cell adaptation to stress. The Warburg effect, which is characteristic of many tumors and involves increased glycolysis in cells even in the presence of oxygen, creates a unique metabolic background (cytoplasmic acidosis and decreased inorganic phosphate levels) that helps to block MPT pore induction [148]. Furthermore, oncogenic signaling pathways (e.g., Bcl-2 family proteins, Akt or mutant p53) actively suppress the pore's sensitivity to calcium and oxidative stress. This allows malignant cells to maintain viability even under conditions that would inevitably lead to mitochondria-mediated death in normal tissues [4].

Expression of many MPT pore components is significantly increased in tumor cells [71]. It is suggested that this may provide cancer cells with the capability of fine regulation, ranging from complete suppression of MPT pore formation (for cell survival) to its controlled activation (for adaptation to changing microenvironmental conditions). This may underlie the heterogeneity of many tumor types and explain their resistance to therapy. Nevertheless, a number of approaches involving the use of oxidative stress inducers and calcium homeostasis modulators may be used to combat tumors, provided that the issue of their selectivity is addressed [4].

Is it possible to accurately decipher the structure of the MPT pore, determine the molecular mechanism of its formation and visualize this phenomenon in a living cell? It should be acknowledged that the prospects, given current capabilities and experimental approaches, as well as the known limitations (including

the rarity of this event in mitochondria), are not very promising. This is indirectly evidenced by the trend in publications: despite the recognized role of the MPT pore in the development of cellular pathologies and socially significant diseases, as well as active research in this area, the number of articles has been gradually decreasing since 2015 (Fig. 4). The emergence of new methodological approaches and selective inhibitors could not only allow to establish the precise structure of the pore complex but also to provide a new direction for therapy and diagnosing various cellular pathologies associated with MPT pore induction and associated organelle dysfunction.

Abbreviations

ANT	adenine nucleotide translocator
CsA	cyclosporin A
MPT	mitochondrial permeability transition pore
OSCP	oligomycin sensitivity conferring protein
ROS	reactive oxygen species
SPG7	spastic paraplegia 7
TSPO	peripheral benzodiazepine receptor
VDAC	voltage-dependent anion channel

Contributions

K. N. Belosludtsev – concept; N. V. Belosludtseva, M. V. Dubinin, and K. N. Belosludtsev – writing the manuscript; N. V. Belosludtseva and K. N. Belosludtsev – editing the manuscript; M. V. Dubinin and K. N. Belosludtsev – creating the figures.

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Ethics approval and consent to participate

This work does not contain any studies involving human and animal subjects.

Conflict of interest

The authors of this work declare that they have no conflicts of interest.

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