The Mitochondrial Permeability Transition Pore

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Abstract The mitochondrial permeability transition (MPT) consists of an abrupt increase in the permeability of the inner mitochondrial membrane to low molecular weight solutes, resulting in the osmotic breakout of the organelle. MPT drives cell death and provides an etiological contribution to several human disorders characterized by the acute loss of post-mitotic cells. These conditions include ischemia/reperfusion injury, cancer and neurodegenerative disorders. However, precise knowledge of the structure and regulators of the supramolecular entity that induces MPT, the so-called *permeability transition pore complex* (PTPC), is lacking and this constitutes a substantial obstacle in the development of MPT-targeting agents with clinical applications. Here we report the current evidences about molecular structure and regulatory components of PTPC. In particular we pay attention on new two proteins which recently were added to the list of PTPC components: the mitochondrial F_1F_O ATP synthase, particularly and the SPG7 paraplegin matrix AAA peptidase subunit. At least a detailed overview of MPT contribution to pathological condition is provided, focusing on the idea that to develop therapeutic drugs, it will be fundamental to understand the molecular composition of the PTPC.

Keywords Mitochondrial permeability transition · Permeability transition pore complex · F1FO ATP synthase · Mitochondrial disorders

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1 Mitochondrial Permeability Transition

The concept of the *mitochondrial permeability transition* (MPT) refers to a sudden and irreversible increase in the permeability of the inner mitochondrial membrane (IMM) to small solutes up to 1.5 kDa, leading to the progressive dissipation of mitochondrial transmembrane potential ($\Delta\psi_m$). This unregulated passage of water into the mitochondrial matrix results in the osmotic breakdown of the organelle (Bonora et al. 2015); this implies the suspension of mitochondrial functions, including ATP production.

In the 1990s, the mechanism by which the MPT ultimately initiates a form of regulated cell death (RCD) that often (but not always) manifests with necrotic morphological features was shown (Galluzzi et al. 2015; Crompton and Costi 1990). The MPT also constitutes a central checkpoint in the apoptotic pathway; it can generate apoptotic waves. For example, when outer mitochondrial membrane (OMM) rupture occurs upon mitochondrial swelling, the release of proteins involved in the effector phase of apoptosis (such as cytochrome C, AIF, SMAC/DIABLO and EndoG) into the cytosol is inevitable. This notion is supported by various studies in which isolated mitochondria and living cells treated with MPT-inducing stimuli clearly show apoptotic-like features, and MPT targeting protects against cell death (Marchetti et al. 1996; Kroemer 1997).

A frequently discussed problem involves what determines the induction of necrosis or apoptosis upon MPT onset. The answer may reside in the ATP levels of the cell (Eguchi et al. 1997); when cellular ATP content is high, apoptosis can initiate and proceed, but when the energy level is low or insufficient, the necrotic pathway prevails. In addition, and related to the ATP level, necrosis may be caused by a prolonged and irreversible MPT event experienced by all mitochondria in the cell. Conversely, the MPT may affect only one or few mitochondria (Duchen et al. 1998) allowing the cell to either recover completely or initiate the apoptotic pathway. However, it has recently been demonstrated how transient MPT events (called tPTPs or MitoWinks) are also correlated with normal physiologic manifestations that allow the resetting of mitochondria (Lu et al. 2016) that is essential for cell survival.

For these reasons, the MPT is a significant event in different human pathologies (e.g., reperfusion injuries, neurodegeneration, and cancer). However, precise knowledge of the structure and mode of action of the supramolecular entity that induces MPT, the so-called *permeability transition pore complex* (PTPC), is lacking, and this constitutes a substantial obstacle in the development of MPT-targeting agents with clinical applications.

The best-characterized MPT is triggered by the accumulation of Ca^{2+} ions in the cytosol and then in the mitochondria (Izzo et al. 2016). Thus, besides the accumulation of mitochondrial Ca^{2+}, major MPT stimulators include reactive oxygen species (ROS), inorganic phosphate, intracellular alkalinization, long-chain fatty acids, atractyloside and carboxyatractyloside. The latter two inhibit members of the adenine nucleotide translocase (ANT) protein family by locking them into a cytoplasmic-side open conformation (Brenner and Grimm 2006).

Conversely, MPT inhibitors include ATP and ADP, NADH and NAD^+, glutamate, bongkrekic acid, which locks ANT family members into a matrix-side open conformation, 5-isothiocyanato-2-[2-(4-isothiocyanato-2-sulfophenyl) ethenyl]benzene-1-sulfonic acid (DIDS), an inhibitor of voltage-dependent anion channel (VDAC), and cyclosporine A (CsA), which targets peptidylprolyl isomerase F (PPIF, best known as cyclophilin D, CyPD) (Martel et al. 2012).

The MPT-inhibitory potential of CsA has been documented so extensively, in vitro and in vivo, that this molecule is currently considered the gold standard method for the confirmation of presumed instances of MPT (Kepp et al. 2011).

2 Mitochondrial Permeability Transition Pore Complex: Molecular Structure

Despite the intense experimental interest generated by MPT throughout the last two decades, the precise molecular composition of the PTPC remains elusive.

Accordingly, the first PTPC model proposed at the end of 1990s was a supramolecular entity assembled at the juxtaposition of the inner and outer mitochondrial membranes, composed by VDAC, ANT, and regulatory components including hexokinase 1 (HK1) and creatine kinase mitochondrial 1 (CKMT1) (Beutner et al. 1996, 1998). Moreover, CyPD was supposed to have a central role in the PTPC due to its interacting partners (Crompton et al. 1998), which include VDAC and ANT, and its pharmacological profile (Tanveer et al. 1996).

This model was substantially challenged by genetic approaches. Indeed, the genetic co-inactivation of three distinct VDAC isoforms (Vdac1, Vdac2 and Vdac3) failed to protect murine fibroblasts from MPT induction by hydrogen peroxide (an MPT inducer) and did not influence the ability of their mitochondria to undergo MPT in response to Ca^{2+} (Baines et al. 2007).

Similarly, the simultaneous knockout of the genes coding for two distinct ANT isoforms, namely, Slc25a4 (encoding Ant1) and Slc25a5 (encoding Ant2), failed to abolish the ability of murine hepatocytes to succumb to several MPT inducers, including the Ca^{2+} ionophore Br-A23187, in a CsA-inhibitable manner. Moreover, mitochondria isolated from $Slc25a4^{-/-}Slc25a5^{-/-}$ hepatocytes retained the ability to undergo MPT in vitro upon exposure to a depolarizing agent (Kokoszka et al. 2004).

The only component to survive genetic analysis was CyPD (Baines et al. 2005; De Marchi et al. 2006), confirming its role as a modulator of the PTPC. Indeed, it is unlikely that CyPD, which is mainly localized within the mitochondrial matrix, would constitute the pore-forming component of the PTPC. Therefore, CyPD is currently viewed as the major gatekeeper of the MPT, regulating the opening of the PTPC but not lining up the pore that physically allows for the entry of low-molecular-weight solutes into the mitochondrial matrix. Additionally, CyPD played a central role in the identification of (or attempts to identify) the channel-forming components of the PTPC core, primarily through the identification of CyPD-interacting proteins.

For instance, in 2008, the phosphate carrier PiC was shown to bind CyPD and ANT1, an interaction that was potentiated by MPT-inducing conditions and inhibited by CsA (Leung et al. 2008).

Inorganic phosphate has been known since 1965 as an MPT-promoting metabolite (Tedeschi et al. 1965), suggesting that the PTPC would possess a specific binding site. In physiological conditions, inorganic phosphate is transported across the inner mitochondrial membrane by members of the SLC protein family, including SLC25A3 (best known as PHC or PiC) and SLC25A24 (also known as APC1) (Palmieri 2004).

A high-throughput genetic screen showed that PiC overexpression promotes apoptotic cell death and that a small-interfering RNA-mediated depletion of PiC has cytoprotective effects (Alcala et al. 2008). Later, Baines and coworkers demonstrated that PiC is not a core component of the PTPC, although in its absence, the MPT occurred more slowly (Gutierrez-Aguilar et al. 2014; Kwong et al. 2014). Although the ability of PiC to influence mitochondrial dynamics may be involved in this process (Pauleau et al. 2008), the exact molecular mechanisms by which PiC promotes cell death under some circumstances remain to be elucidated.

Concerning APC1, it is known that it can respond to increases in cytosolic Ca^{2+} levels, favoring the mitochondrial uptake of ATP and ADP and consequently inhibit MPT (Traba et al. 2012).

Recently, thanks to monitoring MPT in living cells using fluorescence-imaging-based techniques (Bonora et al. 2016), two proteins were added to the list of PTPC components: the mitochondrial F_1F_O ATP synthase, particularly the c subunit of the F_O domain (which in humans is encoded by three genes, ATP5G1, ATP5G2 and ATP5G3), and the SPG7 paraplegin matrix AAA peptidase subunit (Giorgio et al. 2013; Bonora et al. 2013; Alavian et al. 2014; Shanmughapriya et al. 2015) (in Fig. 1 a model of PTPC is reported).

The mitochondrial F_1F_O ATP synthase is a multiprotein complex consisting of a globular domain that protrudes into the mitochondrial matrix (F_1 domain) and an inner mitochondrial membrane-embedded domain (F_O domain); the domains are interconnected by a central and a lateral stalk (Yoshida et al. 2001). Mammalian ATP synthases contain 15 different subunits: α, β, γ, δ, ε, a, b, c, d, e, f, g, A6L, F6 and O (also known as oligomycin sensitivity-conferring protein, OSCP). These subunits form a fully functional holoenzyme with a total molecular weight of ~ 600 kDa.

The interest in the mitochondrial F_1F_O ATP synthase as the possible molecular identity of the PTPC is the result of assays screening for potential CyPD binding partners. The screen identified CyPD as co-migrating with the mitochondrial F_1F_O ATP synthase in blue native gels (Giorgio et al. 2009) and the subunit OSCP (oligomycin sensitivity conferring protein) as a binding site (Giorgio et al. 2013).

In this study, Giorgio et al. proposed that the PTPC forms from dimers of the F_1F_O ATP synthase (Giorgio et al. 2013). Indeed, the mitochondrial F_1F_O ATP synthase dimers excised and extracted from blue native gels and reconstituted into lipid bilayers have been reported to provoke currents that are consistent with the known electrophysiological properties of the PTPC. However, no PTPC-like currents were observed after the addition of monomeric F_1F_O ATP synthase that was extracted from the same

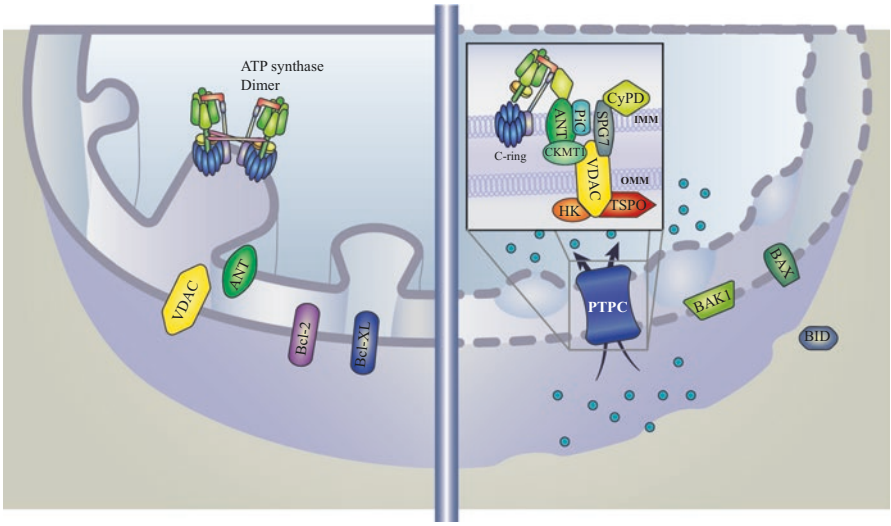

Fig. 1 Hypothetical PTPC molecular structure. MPT is mediated by the opening of a supramolecular entity, called PTPC, assembled at the juxtaposition between mitochondrial membranes. Structural and functional studies show that multiple mitochondrial and cytosolic proteins intervene in the formation or regulation of the PTPC, yet the actual pore-forming unit of the complex remains elusive. These proteins include VDAC, ANT, HK, CYPD, PiC, TSPO, CKMT1; in the text a detailed explanation is reported

blue native gel. These data have not been reproduced by independent investigators and appear to contradict several studies demonstrating, for instance, the cytoprotective effects of endogenous molecules that promote F_1F_O ATP synthase dimerization (Garcia et al. 2006). Interestingly, in 2016, Gerle highlighted that a straightforward alternative explanation could be the loss of PTPC-specific subunits during extraction from the excised gel bands or reconstitution into the black membrane. Indeed, bovine F_1F_O ATP synthase comprises 17 different subunits of which the two F_O subunits DAPIT and 6.8 kDa are easily lost during extraction of this fragile multisubunit membrane complex from the inner mitochondrial membrane (Gerle 2016). However, robust evidence excluding a key role for F_1F_O ATP synthase dimers in the MPT has not yet been provided. Only recently, it was reported that MPT induction is linked to F_1F_O ATP synthase dimers dissociation and that stabilizing F_1F_O ATP synthase dimers by genetic approaches inhibits PTPC opening (Bonora et al. 2017).

An alternative proposal for a pore-forming entity within the components that make up the mitochondrial F_1F_O ATP synthase highlights its proton-transporting c-ring.

F_1F_O ATP synthase c-rings consist of multiple copies of c subunits, varying between species (8–15), that are arranged as a circle (Pogoryelov et al. 2012). As describe above, the c subunits of F_1F_O ATP synthase are encoded by three genes, ATP5G1, ATP5G2 and ATP5G3, and it has been shown that cells depleted of ATP5G1 or ATP5G3 exhibit reduced sensitivity to MPT-driven RCD (Bonora et al. 2013; Alavian et al. 2014).

In 2013, Bonora et al. examined PTPC formation after depletion of the c-subunit mediated by small interfering RNA knock-down, demonstrating, for the first time, that the c subunit of F_O is required for MPT, mitochondrial fragmentation and cell death induced by mitochondrial Ca^{2+} overload and oxidative stress (Bonora et al. 2013).

One year later, the proposal that the c-ring formed the core of the PTPC was supported by Alavian et al., who demonstrated how the c-ring could generate a non-specific current that was attributable to the PTPC because of a rearrangement that promoted an increase in the c-ring diameter.

Nevertheless, it seems unlikely that the c-ring itself constitutes the PTPC. Indeed, Alavian et al. proposed that this event required CypD activity, but they did not propose a molecular mechanism through which this activity could be transmitted to the c subunit.

In 2016, Elustondo et al. provided an elegant confirmation of previous reports and a more defined mechanism of action for the MPT. Specifically, during Ca^{2+}-induced MPT, the c subunit associates with inorganic polyphosphate (polyP) and polyhydroxybutyrate (PHB), promoting the generation of a water-permeable channel (Elustondo et al. 2016). The c subunit is a hydrophobic protein with properties that are similar to those of lipids, and it is not expected to be able to form water-filled pores in its c-ring. Therefore, these data suggest that the c subunit is responsible for forming the calcium-dependent channel with the help of polyP possibly serving as the hydrophilic coating of the pore (Morciano et al. 2017).

Despite the increasing evidence for the pivotal roles of c subunits in the MPT (Halestrap 2014), a study in March 2017, by the Walker group showed the MPT in the absence of a c subunit (He et al. 2017). Specifically, they generated a clonal cell, HAP1-A12 (near-haploid human cell), in which ATP5G1, ATP5G2, and ATP5G3 were disrupted. They reported that the HAP1-A12 cells were incapable of producing the c subunit, but they preserved the characteristic properties of the PTPC. These data are the results of a single cell clone, so clonal adjustment cannot be excluded. Indeed, they reported that HAP1-A12 cells assembled a vestigial ATP synthase, with intact F_1-catalytic and peripheral stalk domains and supernumerary subunits e, f, and g but without membrane subunits ATP6 and ATP8. The authors did not exclude the possibility that the PTPC could be associated with the ATP synthase complex, but they speculated that the most likely components available to form the pore were the b, e, f, and g subunits (He et al. 2017). Although these data should be confirmed and strictly challenged before excluding the c subunits from the list of PTPC components, the creation of a cell clone characterized by ATP5G1, ATP5G2, and ATP5G3 deletion will improve experimental research regarding the involvement of c-subunits in the MPT.

Finally, SPG7, an integral protein of the inner mitochondrial membrane with metalloprotease activity, has recently been identified as a PTPC component (Shanmughapriya et al. 2015). A phenotypic screen based on the mitochondrial Ca^{2+} retention capacity (CRC) of digitonin-permeabilized cells after treatment with siRNAs designed to suppress translation of a set of mitochondrial proteins was used to identify regulators of the PTPC. The screen identified 13 proteins whose

suppression caused desensitization of the PTPC to Ca^{2+}, among which well-known modulators that do not take part in PTPC core formation, such as CyPD, were revealed. Stable depletion of CyPD, VDAC1, or SPG7 appeared to be equally effective in protecting cultured human cells from hydrogen peroxide-dependent PTPC opening. Moreover, it was shown that SPG7 could be co-immunoprecipitated with CyPD in a complex that also included VDAC1. The interaction between CyPD and SPG7 depends on the C-terminus of SPG7 (but not on its catalytic activity) and is sensitive to CsA. Indeed, a CyPD mutant lacking the seven highly conserved residues that constitute the CsA binding site is unable to bind to SPG7. Conversely, the transmembrane domain of SPG7 is responsible for VDAC1 binding and does not depend on CyPD–SPG7 interactions. Finally, deletion of SPG7 resembles the deletion of CyPD in terms of resistance to MPT-inducing stimuli (Shanmughapriya et al. 2015). Thus, SPG7 might constitute a key regulator of MPT. However, these findings have been obtained in cultured cells only, and they have not yet been reproduced by independent investigators.

2.1 Regulatory Components

Several proteins have been shown to regulate the activity of the core PTPC, including cytosolic and mitochondrial proteins.

The translocator protein (18 kDa) (TSPO), a protein of the outer mitochondrial membrane, constitutes the benzodiazepine-binding component of the so-called peripheral benzodiazepine receptor, an oligomeric complex involving VDAC and ANT (Mcenery et al. 1992).

The physiological role of TSPO involves steroid biosynthesis regulation (Mukhin et al. 1989). Moreover, several studies have implicated TSPO in the MPT. Indeed, the ability of a series of endogenous (e.g., protoporphyrin IX) (Pastorino et al. 1994) and exogenous (e.g., PK11195, Ro5–4864, diazepam) (Hirsch et al. 1998; Chelli et al. 2001) TSPO agonists to cause an MPT has been reported. Although their roles in modulating the MPT are clear, the effects of TSPO ligands are variable, ranging from cytoprotective to cytotoxic (Kugler et al. 2008; Shargorodsky et al. 2012; Campanella et al. 2008; Decaudin et al. 2002).

Various kinases have been shown to interact with the core PTPC, such as CKMT1, HK1, HK2, glycogen synthase kinase 3β (GSK3β) and protein kinase Cε (PKCε) (Verrier et al. 2004).

Some of these kinases, including CKMT1, HK1 and HK2, do not phosphorylate protein substrates, implying that their MPT-modulatory activity originates either from their physical interaction with core PTPC components or from their ability to catalyze metabolic reactions.

CKMT1 is localized to the mitochondrial intermembrane space, and it can bind to VDAC1 and ANT1 (Beutner et al. 1996, 1998). Additionally, CKMT1 phosphorylates creatine to generate phosphocreatine, a reaction that is tightly

coupled to oxidative phosphorylation and of consequence to the availability of ATP and ADP (Wallimann et al. 1998; Dolder et al. 2003). It remains to be formally demonstrated whether the MPT-modulatory activity of CKMT1 originates from its physical interaction with the PTPC components or its catalytic activity.

HKs catalyze the rate-limiting step of glycolysis, converting glucose into glucose-6-phosphate in an ATP-dependent manner (Wilson 2003). Both HK1 and HK2 interact with VDAC isoforms (Pastorino and Hoek 2008). These interactions are associated with an optimal flux through glycolysis and with major cytoprotective effects (Pastorino and Hoek 2003).

Conversely, PKCε and GSK3β exert MPT-modulatory functions by phosphorylating core PTPC components (Pastorino et al. 2005; Baines et al. 2003).

PKCε has been reported to phosphorylate VDAC1, promoting HK2 binding and consequent PTPC inhibition (Baines et al. 2003).

Activation of GSK3β has been reported to disrupt the binding of HK2 to mitochondria by phosphorylating VDAC1, resulting in an enhancement of chemotherapy-induced MPT-related cytotoxicity (Pastorino et al. 2005). Moreover, the activation of GSK3β has also been linked to the MPT-triggering phosphorylation of CyPD (Chiara et al. 2012). However, inactivation of GSK3β caused by phosphorylation on Ser9 has been shown to inhibit the PTPC by physically disrupting the ANT1/CyPD interaction (Nishihara et al. 2007). In addition, the activation of several upstream signal transducers, such as AKT1, mammalian target of rapamycin (mTOR), protein kinase A and protein kinase cGMP-dependent type I (PRKG1), has been reported to converge with the inactivation of GSK3β, mediating MPT-inhibitory effects (Juhaszova et al. 2004; Takuma et al. 2001; Pediaditakis et al. 2010).

Interestingly, multiple components of the MOMP-regulatory machinery have been shown to physically and functionally interact with core components of the PTPC, suggesting a tight relationship between the two RCD processes, including mutually regulatory crosstalk.

For instance, BCL-2 and BCL-2-like 1 (BCL-2L1, best known as BCL-XL) have been shown to inhibit MPT by regulating the open state of VDAC1 (Shimizu et al. 1999; Vander Heiden et al. 1999), but the MPT-regulating activity of anti-apoptotic BCL-2 family members remains questionable.

Instead, BAX, BAK1 and BCL-2-like 11 (BCL-2L11, a BH3-only protein best known as BID) reportedly promote MPT-driven apoptosis by interacting with ANT1 and/or VDAC1 (Marzo et al. 1998; Zamzami et al. 2000; Narita et al. 1998). Similarly, BCL-2-associated agonist of cell death (BAD, another BH3-only protein) can trigger a VDAC1-dependent, BCL-XL-responsive mechanism of the MPT. Indeed, the MPT appears to result from BAD-dependent displacement of BCL-XL from VDAC1 rather than from a physical BAD/VDAC1 interaction (Roy et al. 2009).

Furthermore, in 2012, a pool of p53 localized to the mitochondrial matrix was shown to participate in the MPT; in response to oxidative stress, p53 accumulated in the mitochondrial matrix and triggered PTPC opening and necrosis through a physical interaction with CyPD (Vaseva et al. 2012).

3 Pathological Relevance

Throughout the last two decades, several studies have implicated the MPT as a major etiological determinant in a wide variety of acute and chronic disorders characterized by an unwarranted loss of postmitotic cells. These conditions include ischemia/reperfusion injury, cancer and neurodegenerative disorders (in Fig. 2 a schematic summary of involvement of MPT in pathologies is reported).

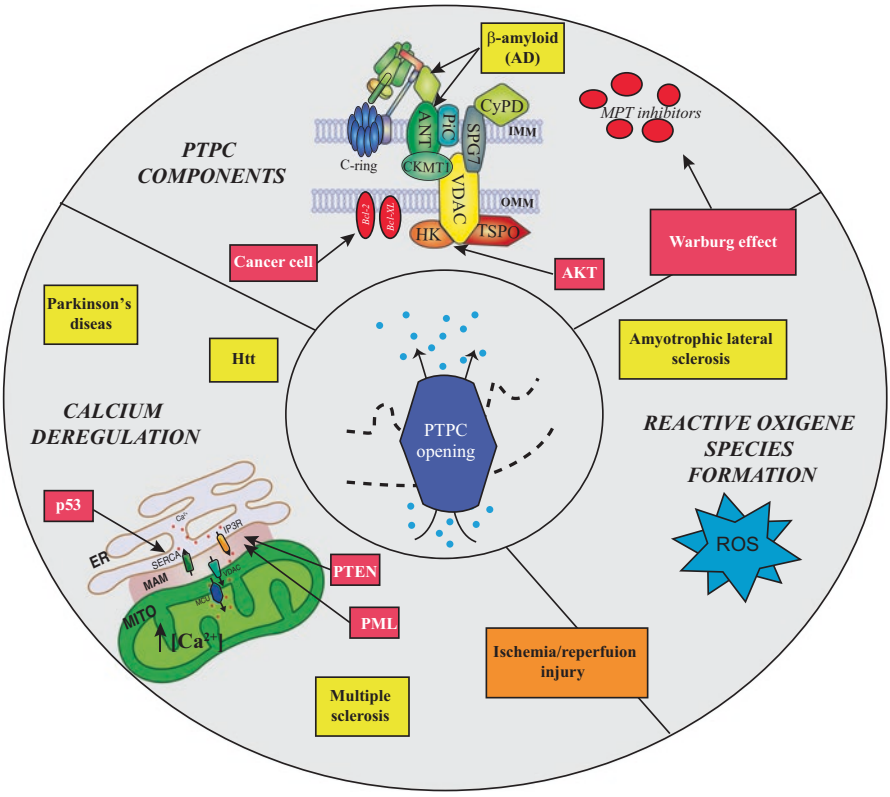

Fig. 2 Involvement of MPT in pathologies. The MPT is been identify as a major etiological determinant in a wide variety of acute and chronic pathologies. The PTPC opening could be caused by (1) changes in PTPC components and regulators, (2) calcium deregulation and/or (3) ROS formation increment. Here it is shown a summary of the most common alterations (deeply described in the text) reported in ischemia/reperfusion injury (orange box), cancer (red boxes) and neurodegenerative disorders (yellow boxes) which link MPT to disease onset

3.1 Ischemia/Reperfusion Injury

In 2012, the World Health Organization estimated 7.4 million deaths from coronary heart diseases (CHDs) worldwide, particularly in low- and middle-income countries. Accounting for nearly 13% of all deaths globally, CHDs have since been in the spotlight of cardiovascular research. Although the risk factors that promote CHDs have been identified (Akhabue et al. 2014), not all players involved in this pathology are well characterized. Generally, the pathophysiological effects of CHD are imputable to the debilitating consequences of coronary occlusions, followed by additional damage due to reperfusion, which as a whole, is known as ischemia-reperfusion injury (Kawajiri et al. 2011; Araszkiewicz et al. 2013; Frank et al. 2012).

In cardiomyocytes, the deprivation of oxygen following myocardial infarction (MI) results in a mitochondrial oxidative phosphorylation blockade, leading to a reduction in available ATP, which is indispensable for cellular energy metabolism (Hausenloy and Yellon 2013). In this situation, cellular metabolism is forced to switch to anaerobic glycolysis to recover the ATP levels, causing accumulation of lactate and hydrogen ions, which in turn leads to intracellular acidosis. The latter increases the intracellular Na^+ concentration through the Na^+/H^+-exchanger, which extrudes protons, to restore pH, in exchange for Na^+ (Avkiran and Marber 2002). Na^+ overload is exacerbated by the ceased activity of Na^+/K^+ ATPase due to the reduced ATP availability, while the reverse mode activity of the sarcolemmal Na^+/Ca^{2+} exchanger induces intracellular Ca^{2+} overload (Piper et al. 2003). The intracellular accumulation of Ca^{2+} and Na^+ ions and protons H^+, followed by losses of K^+ and Mg^{2+} ions, results in intracellular edema, cell swelling and disruption of cellular membranes (Haunstetter and Izumo 1998; Moe and Marin-Garcia 2016). In prolonged ischemia and in response to an increase in the Ca^{2+} ion concentration, proteases (such as calpains) are activated and contribute to myocardial ischemic injury by degrading myofibrillar proteins and regulatory enzymes; this ultimately results in cardiac contractile dysfunction (Neuhof and Neuhof 2014).

According to the current knowledge, the major contributing actors of the lethal reperfusion injury are oxidative stress and increased Ca^{2+} overload (Piper et al. 2003), which are also the best characterized MPT inducers (Morciano et al. 2015).

Oxidative stress, determined by the reoxygenation of the ischemic heart, reduces the bioavailability of nitric oxide (NO), which is indispensable for inhibiting neutrophil accumulation and inactivating superoxide radicals (Granger and Kvietys 2015; Kvietys and Granger 2012). Moreover, reduced levels of nitric oxide diminish myocardial blood flow reperfusion through the coronary circulation. The oxygen burst at the reperfusion time stimulates xanthine oxidase- and NADPH oxidase-dependent reactive oxygen species (ROS) formation. Intracellular Ca^{2+} overload, initiated during ischemia, is exacerbated at the time of reperfusion due to the oxidative stress-mediated impairment of the sarcoplasmic reticulum and damage to the plasma membrane (Hausenloy and Yellon 2013). In addition, the recovery of oxygen levels following the reperfusion re-energizes the mitochondria, enhancing their ability to accumulate Ca^{2+} ions (Lemasters 1999; Giorgi et al. 2012). Upon reperfusion,

the rapid restoration of intracellular pH, favored by the reactivation of the Na^+-H^+ exchanger and the consequent washout of lactic acid, stimulates the opening of the PTPC. As demonstrated in 1995 by Griffiths and Halestrap (1995), despite the presence of pro-opening factors (such as Ca^{2+}, inorganic phosphate, oxidative stress and ADP), the PTPC remains closed during ischemia due to low pH levels (<7.0), since H^+ inhibits Ca^{2+} binding to the PTPC trigger site (Lemasters et al. 1996). At the reperfusion time, the opened PTPC can be permeated by protons and any molecule less than 1.5 kDa. This event favors mitochondrial membrane potential dissipation, uncoupling oxidative phosphorylation and ATP depletion, whose generation is also prevented by reversal of the ATPase (Halestrap and Richardson 2015). In this way, energy metabolism is impaired, leading to further intensification of Ca^{2+} deregulation and PTPC opening.

In the last few decades, the PTPC has emerged as a promising therapeutic target. In 2002, Hausenloy et al. confirmed PTPC opening at the onset of reperfusion and demonstrated that exclusive administration of CsA at the onset of reperfusion could limit the infarct size (Hausenloy et al. 2002). One year later, using the immunosuppressant sanglifehrin-A, it was shown that the mPTP-opening inhibition was effective in limiting the infarct size in isolated perfused rat hearts if performed in the first few minutes of reperfusion (Hausenloy et al. 2003). Long-term cardioprotective effects of PTPC inhibition were shown in a study by Gomez et al., in which the PTPC inhibitor Debio-025, a CsA analog, was administered to mice that underwent IRI. They have demonstrated that inhibition of the PTPC at the reperfusion time improves functional recovery and mortality in mice at 30 days (Gomez et al. 2007). In 2014, a clinical study, conducted in patients undergoing aortic valve surgery, showed that cyclosporine administration at the time of reperfusion protects against reperfusion injury by reducing the levels of cardiac troponin I (Chiari et al. 2014).

Moreover, ischemia induces the release of cell membrane receptor ligands, such as adenosine, generated by the breakdown of ATP (Leung et al. 2014) and bradykinin, which induces production of ROS and NO (Sharma et al. 2015). Subsequently, the activation of a set of kinases known as RISKs (reperfusion injury salvage kinases), including Akt, Erk1/2, PKG, PKC-ε and p70s6K, is triggered. By activating the Akt/eNOS pathway, ischemic preconditioning results in S-nitrosylation of multiple mitochondrial proteins; S-nitrosylation is a modification that is thought to protect sensitive sites from subsequent ROS-induced oxidation (Sun et al. 2015). These proteins include CypD, which can be nitrosylated at cysteines 103, 156 and 203 (Gutierrez-Aguilar and Baines 2015). The RIS kinases deliver an inactivating phosphorylation onto GSK3β, which is constitutively active and phosphorylates, among other substrates, CyPD, favoring its interaction with the PTPC (Rasola et al. 2010). A cardioprotective role is attributed to hydrogen sulfide (H_2S), which can function through the Akt/GSK3β axis (Andreadou et al. 2015). In this case, ischemia causes a decrease in endogenous H2S production, which can be antagonized by preconditioning protocols. Recently, mitochondrial calpain was proposed to contribute to the onset of the MPT after IRI, following its activation by a matrix Ca^{2+} concentration increase (Shintani-Ishida and Yoshida 2015).

Finally, another regulatory pathway has been shown to involve CyPD acetylation/deacetylation (Bochaton et al. 2015). Deacetylation of Lys166 of CyPD by mitochondrial deacetylase SIRT3 (Hafner et al. 2010) favors CyPD interaction with PTPC components and thus, the MPT. In addition, SIRT3 downregulation sensitizes mitochondria to PTPC opening, and SIRT3-mediated deacetylation of CyPD is reportedly enhanced downstream of postconditioning (Bochaton et al. 2015). Interestingly, the knockdown of SIRT4, another mitochondrial isoform that lacks deacetylase activity but has ADP ribosyl-transferase activity, has been reported to have the opposite effect, increasing resistance to PTPC induction (Verma et al. 2013).

3.2 Cancer

Apoptosis is recognized as a hallmark of cancer, and loss of its control is required for the development and progression of the pathology (Hanahan and Weinberg 2011). Considering the role of the MPT in cell death induction, it is logical to speculate that alterations to the PTPC exist in cancer.

Experimental data that corroborate this hypothesis have been collected and are discussed below.

As previously mentioned, the best-known MPT inducer is intra-mitochondrial calcium, which is provided to mitochondria by the endoplasmic reticulum through MAMs (Marchi et al. 2014; Patergnani et al. 2011; Giorgi et al. 2015c).

Cancer develops several mechanisms to inhibit toxic Ca^{2+} signaling. Two oncosuppressors, PML (Bernardi and Pandolfi 2014) and PTEN (Pulido et al. 2014), in cooperation with protein phosphatase 2A, sustain the transfer between the ER and mitochondria through the mitochondrial Ca^{2+} uniporter (MCU) complex by regulating the phosphorylation state of the channel responsible for Ca^{2+} release, the inositol-3-phosphate receptor (IP3R) (Bononi et al. 2013; Giorgi et al. 2010). A different mechanism, but a similar result, occurs with the loss (or mutation) of the master oncosuppressor p53. Indeed, p53 stabilization leads to stimulation of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) and maintains elevated levels of Ca^{2+} in the endoplasmic reticulum ($[Ca^{2+}]$er). Loss of p53, PML and PTEN (as well as several of their oncogenic mutations) leads to a decrease in $[Ca^{2+}]$er resulting in reduced signaling to the mitochondria (Giorgi et al. 2015a, b). In contrast, oncogenes can display the opposite effect. Indeed, tumor progression can be sustained by the accumulation of a series of changes in the Ca^{2+} regulatory machinery that decrease the cytotoxic Ca^{2+} signal. An in vitro mimicking of tumor transformation induced by activation of H-RAS is accompanied by a progressive reduction in the amount of intracellular Ca^{2+} that is transferable to the mitochondria. This effect can be counteracted by a controlled increase in the extracellular Ca^{2+} level that causes an increase in the intracellular Ca^{2+} level and impedes H-RAS-induced transformation (Rimessi et al. 2015). For example, Bcl-2 reduces the Ca^{2+} content in the ER (Pinton et al. 2000), and the mitogenic kinase AKT strongly inhibits the IP3R.

Interestingly, AKT and PTEN are both members of the PI3K pathway, one the most studied survival signaling pathways, which plays a critical role in resistance to anticancer therapies (Slomovitz and Coleman 2012; Fresno Vara et al. 2004; Wolin 2013).

AKT can also phosphorylate and consequently inhibit GSK3β. This kinase has a significant stimulatory effect on the PTPC and can act as a tumor suppressor in several tumors. Indeed, as already mentioned, its inactivation by AKT promotes the association between HK2 and VDAC, causing inhibition of PTPC and an increase in cell survival (Juhaszova et al. 2004). In addition, the WNT, PKC and ERK pathways regulate GSK3β phosphorylation, which potentially connects the MPT to signals involved with growth factors, G protein-coupled receptor ligands and the extracellular matrix (Graber et al. 1999; Kang et al. 2007).

These data suggest that kinase cascades that are significantly activated in cancers can keep the PTPC closed, especially when acting on HK2.

Apart from their phosphorylation statuses, different PTPC components are differentially expressed in cancer cell lines and tumor models (Brenner and Grimm 2006; Fulda et al. 2010). VDAC isoforms are significantly higher in malignant tumor cells (Shinohara et al. 2000); ANT-2 is upregulated in renal tumors and transformed hepatocytes (Faure Vigny et al. 1996). HK2 is upregulated in multiple tumors (Shinohara et al. 1991; Rempel et al. 1996; Azoulay-Zohar et al. 2004; Gudnason et al. 1984), and there is a positive correlation between tumorigenesis and the expression level of TSPO (Beinlich et al. 2000; Maaser et al. 2001). Such alterations in gene expression would lead to the erroneous conclusion that the MPT should be favored in tumors. Nonetheless, tumor cells also contain alterations to the expression levels of the BCL-2 family members that keep the MPT probability low. Indeed, antiapoptotic members, such as BCL-XL and Mcl-1, are overexpressed in cancer (Quinn et al. 2011). BCL-XL has been shown to negatively regulate PTPC opening by directly interacting with VDAC (Arbel et al. 2012) from the cytoplasmic side, while a mitochondrial-matrix-located BCL-XL interacts with the β-subunit of F_1F_O ATP synthase inhibiting PTPC opening (Beinlich et al. 2000). Additionally, Mcl-1 plays a role in inhibiting the MPT (Thomas et al. 2013) even though the mechanism is not clearly elucidated. Furthermore, it is proposed that antiapoptotic members BCL-2, BCL-XL and Mcl-1 interfere with the proapoptotic interactions formed by BAX and BAK, which are known positive regulators of the MPT (Narita et al. 1998; Brenner et al. 2000; Karch et al. 2013).

Upregulation in HK2 expression can also be linked to the Warburg effect, a well-known metabolic hallmark of cancer. This term (“Warburg effect”) usually refers to the atypical increase in glucose uptake and lactic fermentation observed in tumor masses regardless of the aerobic environment in which they are observed (Warburg et al. 1927; Boland et al. 2013). Glucose is converted to pyruvate, which is further reduced to lactate and completes the lactic fermentation process. The findings reported by Warburg (and confirmed by other groups) result in two main consequences for the MTP: (1) an increase in glucose uptake that allows for the continued synthesis of ATP, which impedes the depletion of adenine nucleotides

and Pi accumulation and (2) the accumulation of lactate and lowering of pH as described for the MPT inhibitor. This suggests that the Warburg effect may result in the accumulation of PTPC inhibitors.

Another hypothesis, which is poorly investigated, is that the Warburg effect would simply make the MPT inefficient toward stressing cells sufficiently to induce cell death. Indeed, the large dependence on glycolytic metabolism would allow cells to continue surviving even with the loss of the mitochondrial functions induced by the MPT (at least to some extent). The observation that osteosarcoma cells with overt Warburg effects also display signs of the MPT supports this hypothesis.

The Warburg effect causes alterations in mitochondrial redox potential, ultimately changing ROS generation (Locasale and Cantley 2011). Indeed, ROS, the second most important MPT inducer, appears at higher levels in tumor cells, where they promote several other hallmarks of cancer, such as proliferation, invasion and metastasis (Gupta et al. 2012; Yang et al. 2013). However, ROS also reduces the PTPC threshold for Ca^{2+} and should increase tumor cell sensitivity to MPT induction, leading to an apparent paradox.

Nonetheless, several cancer cell types display higher levels of antioxidants, which could inhibit ROS toxicity. Specifically, increased levels of superoxide dismutase (SOD2) and thioredoxin reductase 2 (TRX-2) were observed in mitochondria from cancer samples (Dvorakova et al. 2002; Biaglow and Miller 2005; Pani et al. 2004). These data, together with the impaired Ca^{2+} signals already discussed, may allow the ROS level to increase without alerting the cell's regulatory mechanisms. Evading these regulatory mechanisms would then allow the tumor cell to undergo the cancer-promoting changes induced by a high ROS level.

Finally, a chaperone network could be an additional adaption mechanism for allowing cancer cells to escape MPT induction. Indeed, the PTPC relies on the activity of a well-known chaperone, CyPD, as its inhibition by CsA dramatically reduces the probability of PTPC opening.

3.3 Neurodegenerative Diseases

Mitochondria participate in various fundamental cellular processes, including energy production, regulation of cell death, and metabolism. There is no protagonist of life whose cellular fate is so strongly dependent on mitochondrial functions as the neuronal cell. The involvement of mitochondrial dysfunctions in neuronal damage associated with neurodegenerative diseases and brain damage has become increasingly relevant.

As already mentioned, the MPT is activated in response to pro-apoptotic stimuli, such as ROS and Ca^{2+} overload, that are common important pathological features of multiple diseases of the nervous central system (Martin et al. 2009). Despite the origin of its discovery (Crofts and Chappell 1965), the PTPC function in neurodegenerative diseases was uncovered rather recently (Du et al. 2008; Gautier et al. 2012).

Here, we describe neurodegenerative diseases that are characterized by dysfunctions in Ca^{2+} and ROS homeostasis that induce PTPC.

Alzheimer's disease (AD) is the most common form of dementia related to aging, and it caused by chronic neurodegenerative processes. AD is characterized by the accumulation and deposition of amyloid plaques formed by the β-amyloid peptide (Aβ), a cleavage product of the amyloid precursor protein (Haass and Selkoe 2007), and by phosphorylation of the tau protein in the brain (Rao et al. 2014). It has been shown that Aβ oligomers alter intracellular Ca^{2+} homeostasis, accelerating global neuropathological cascades (Demuro et al. 2010). Moreover, Aβ can be imported into the mitochondria (Hansson Petersen et al. 2008), where it promotes PTPC opening upon binding to CyPD. Consistent with this notion, neurons derived from CyPD knockout mice are protected from cell death induced by amyloid-dependent PTP opening, and the CyPD deficiency is associated with alleviation of neuronal cell death and improvements in cognitive function in AD mice (Du et al. 2008). Interestingly, Elkamhawy et al. reported that CyPD selective inhibitors, which are novel quinazoline-urea analogs, show protective effects in neuronal cells, blocking amyloid-dependent PTP opening (Elkamhawy et al. 2014). Furthermore, the selective loss of the oligomycin sensitivity conferring protein (OSCP) subunit of the F_1F_O-ATP synthase and the physical interaction of OSCP with Aβ constitute the major OSCP alterations in the brains of AD patients and the AD mouse model. Loss of OSCP leads to a reduction in ATP production, which increases oxidative stress and activation of MPT, whereas its restoration reportedly ameliorates Aβ-mediated mouse and human neuronal mitochondrial impairments, opening up new therapeutic implications for AD based on the stabilization of the OSCP protein (Beck et al. 2016). Other critical components of the PTPC appear to have a role in AD development. ANT can bind directly to Aβ, reducing the ATP/ADP exchange rate and energy metabolism in AD (Singh et al. 2009). VDAC can form complexes with Aβ and phosphorylated tau in AD mouse models, although its involvement in PTPC formation is unclear (Crompton et al. 1998; Zheng et al. 2004; Baines et al. 2007).

The second most common disease among the neurodegenerative pathologies and the most frequent movement disorder is Parkinson's disease (PD) (Bernardi et al. 2015). It is caused by the death of dopaminergic neurons in the mesencephalic region known as the "substantia nigra pars compacta", which is characterized by the presence of α-synuclein and aggregates of protein included in neuronal cells known as Lewy bodies (Rasheed et al. 2017). Dopaminergic neurons have a peculiar mechanism for controlling intracellular Ca^{2+} fluctuations and the Ca^{2+} storage capacity of their mitochondria that involves an autonomous pace-making activity that relies on voltage-dependent L-type Ca^{2+} channels that modulate the release of the neurotransmitter dopamine (Winklhofer and Haass 2010). Accordingly, these neurons are particularly sensitive to mitochondrial Ca^{2+} perturbations, and it has been proposed that the increased sensitization of PTPC opening is a major cause of neurodegeneration in PD patients and a mouse model of the pathology (Luth et al. 2014; Martin et al. 2014). Furthermore, an altered mitochondrial Ca^{2+} storage capacity, impaired respiratory complex I, and altered mitophagy, which exacerbate the sensitization of the MPT, are observed when the complex I activity is suppressed as in the case of patients with PD (Beal 2000; Greenamyre et al. 2001; Seaton et al. 1998) and when the PINK1 Ser/Thr kinase is inactivated by RNA interference-mediated downregulation

or by PINK-1 knockout in mice (Rasola and Bernardi 2011; Valente et al. 2004; Kawajiri et al. 2011). Moreover, there is a reduced capacity for this mechanism to buffer intracellular ROS in dopaminergic neurons, which could induce an increase in the PTPC activity (Brundin et al. 2008). Interestingly, a reduction in the degeneration of dopaminergic neurons has been observed in patients treated with dopamine agonists rather than with L-dopa. This effect could be due to a neuroprotective effect of the direct inhibition of the MPT, as demonstrated after treatment with pramipexole, ropinirole and rasagiline in vitro (Sayeed et al. 2006; Youdim et al. 2005; Schonfeld et al. 2013).

Huntington's disease (Forte et al. 2007) is caused by autosomal dominant mutations that lead to translation of an expanded polyglutamine tract in the gene encoding the huntingtin (Htt) protein. Patients display progressive uncontrolled movements, psychiatric disturbances, and dementia; this disease is invariably lethal (Landles and Bates 2004). Choo et al. demonstrated that mitochondrial dysfunctions, caused by pathogenic Htt mutations, depend on PTPC opening after Ca^{2+} overload in isolated mitochondria from an HD mouse model (Choo et al. 2004), and these effects are inhibited by the addition of CsA and ADP (Milakovic et al. 2006). Therefore, neurons with the mutated Htt protein reportedly show an altered Ca^{2+} homeostasis, mtDNA damage and mitochondrial fragmentation that could trigger the MPT (Quintanilla et al. 2017). Interestingly, a significant association of Htt with the mitochondria in synaptic extracts (Hamilton et al. 2015) has been observed; this may indicate a possible interaction with several elements of the PTPC that affects mitochondrial function.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by motor neuron degeneration, especially in the brain and spinal cord, which rapidly leads to the loss of voluntary muscle control and subsequent paralysis and mortality (Lezi and Swerdlow 2012). Some forms of ALS are inherited and caused by mutations in the superoxide dismutase-1 (SOD1) gene (Martin et al. 2009). Transgenic mice expressing the mutant SOD1 were shown to display mitochondrial alterations, including swollen megamitochondria with cristae remodeling and matrix vacuolization, respiratory chain inhibition, a reduced mitochondrial Ca^{2+} buffering capacity and fragmentation, and an elevated generation of ROS (Leal and Gomes 2015; Kawamata and Manfredi 2010). Interestingly, regulatory components of the PTPC, such as ANT and CyPD, were found to be highly expressed in the same mouse model, indicating that the MPT might be the triggering cause of neuronal cell death (Martin et al. 2009).

Multiple sclerosis is the most common chronic inflammatory disease of the central nervous system, where the myelin sheath of neurons is destroyed by endogenous myelin-associated antigens, such as myelin oligodendrocyte glycoprotein, proteolipoprotein, and myelin basic protein (Stys et al. 2012). During an active inflammatory attack in MS, large quantities of glutamate, an essential excitatory neurotransmitter, are produced by activated immune cells, such as macrophages and microglia. Overstimulation of glutamate receptors leads to mitochondrial Ca^{2+} overload and a consequent bioenergetics dysfunction and MPT stimulation (Su et al. 2009). Experimental autoimmune encephalomyelitis is widely used as an animal model of multiple sclerosis. For example, decreased levels of axonal damage and a marked

protection from the inflammatory response have been observed in CyPD knockout mice compared to wild-type mice (Forte et al. 2007). Moreover, to highlight the central role of the PTPC in neurodegeneration, experimental autoimmune encephalomyelitis was performed in p66Shc-null mice, where ROS-induced PTP opening was abrogated (Savino et al. 2013).

Although neurodegenerative diseases constitute a large portion of the research focus, it is also important to underline the role of mitochondria in neuronal degeneration and brain damage caused by acute and chronic abuse of alcohol, which is a serious public health problem. Recently, an in vitro study by Lamarche and co-workers (Lamarche et al. 2013) revealed a close correlation between stimulation of the PTPC and neuronal damage induced by chronic administration of ethanol. Moreover, CsA is reportedly able to attenuate ethanol withdrawal-induced cell death in the HT22 cultured hippocampal cell line (Jung et al. 2009).

4 Conclusions

Along with the recognition that the MPT has a critical role in multiple pathophysiological scenarios, there has been strong interest in the therapeutic potential of the MPT. MPT pharmacological inhibitors could be used to prevent the cell death caused by PTPC opening. Conversely, pharmacological activators of the MPT could be used to selectively kill neoplastic cells based on their intrinsically elevated levels of stress. To develop therapeutic drugs, it will be fundamental to understand the molecular composition of the PTPC. The recent key discoveries surrounding the composition of the PTPC, particularly the F_1F_O ATP synthase, have opened new perspectives into the molecular definition of its role in pathophysiology and will rapidly enhance the understanding of pore structure and function, which will bring about the design and validation of PTP-active compounds to treat cancer and cardiac and degenerative diseases.

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