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The mitochondrial permeability transition from yeast to mammals

Luca Azzolin, Sophia von Stockum, Emy Basso, Valeria Petronilli, Michael A. Forte¹, and Paolo Bernardi*

Department of Biomedical Sciences and CNR Institute of Neuroscience, University of Padova, Italy

¹ Vollum Institute, Oregon Health and Sciences University, Portland, Oregon

Abstract

Regulated permeability changes have been detected in mitochondria across species. We review here their key features, with the goal of assessing whether a “permeability transition” similar to that observed in higher eukaryotes is present in other species. The recent discoveries (i) that treatment with cyclosporin A unmasks an inhibitory site for Pi [Basso et al. (2008) *J. Biol Chem.* 283, 26307–26311], the classical inhibitor of the permeability transition of yeast; and (ii) that under proper experimental conditions a matrix Ca^{2+} -dependence can be demonstrated in yeast as well [Yamada et al. (2009) *Biochim. Biophys. Acta* 1787, 1486–1491] suggest that the mitochondrial permeability transition has been conserved during evolution.

1. Introduction

The permeability transition (PT) is an increase of the inner mitochondrial membrane (IMM) permeability mediated by opening of the PT pore (PTP), a putative channel that has been thoroughly characterized functionally but whose molecular nature remains elusive [1]. Long considered an *in vitro* artifact of little pathophysiological relevance, the role of the PT in disease has been reevaluated in the context of both programmed and accidental cell death [2]. PTP openings of short duration lead to transient depolarization and to rearrangement of the cristae, making more cytochrome *c* available for release even in the absence of outer mitochondrial membrane (OMM) rupture provided that the Bax-Bak pathway had been activated [3]; while long-lasting openings cause permanent depolarization, loss of ionic homeostasis, depletion of matrix pyridine nucleotides, matrix swelling, OMM rupture and triggering of the mitochondrial pathway to apoptosis [4]. Under these conditions mitochondria hydrolyze any ATP available from glycolysis, and thus substantially contribute to energy depletion.

Mitochondrial swelling, its detrimental effects on energy conservation, and the basic features of the process (stimulation by Ca^{2+} , Pi and fatty acids and inhibition by Mg^{2+} , adenine nucleotides and acidic pH) have been recognized as soon as isolated mitochondria became available for biochemical studies [5–15]. These initial indications were reported before the chemiosmotic theory of energy conservation was proposed [16,17] and generally accepted [18]. How the chemiosmotic theory influenced studies of mitochondrial cation transport and

*Corresponding Author (bernardi@bio.unipd.it).

Proofs to be sent to: Prof. Paolo Bernardi, Department of Biomedical Sciences, University of Padova, Viale Giuseppe Colombo 3, I-35121 Padova (Italy), Tel +39 049 827 6365, Fax +39 049 827 6361

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of the PTP has been covered in some detail in previous reviews, to whom the interested Reader is referred for further details [2,19].

The subsequent history of the PTP can be traced to the work of Pfeiffer and Coworkers, who proposed that it could play a role in steroidogenesis through a Ca^{2+} -dependent “transformation” of adrenal cortex mitochondria allowing extramitochondrial pyridine nucleotides to gain access to the otherwise impermeable matrix, in keeping with earlier observations [20], and support the 11- β hydroxylation of deoxycorticosterone [21–23]. Through the work of Haworth and Hunter, who coined the term “permeability transition”, the basic features of the PTP in heart mitochondria were meticulously characterized, resulting in the key insight that the PT is due to reversible opening of a proteinaceous IMM pore [24–27]. The discovery that the PT can be desensitized by submicromolar concentrations of cyclosporin A (CsA) was a turning point [28–31] because it rekindled interest on the PTP, and provided a pharmacological tool to address its role in cells and organs [32–37] as well as at the single channel level [38–40].

Most classical studies of the PT were carried out in mitochondria obtained from mammals, although permeability changes, most notably those caused by ATP and substrates, have also been studied in yeast [41–55]. In recent years, the growing interest on the PT in cell death has prompted an increasing number of studies in mitochondria from other organisms including plants [56–71], fish [72,73], amphibians [74,75], and the brine shrimp *Artemia franciscana*, a salt- and anoxia-tolerant organism that may represent an exception in that it apparently lacks a PT [76]. Whether the permeability changes observed in mitochondria from these organisms reflect the same molecular events underlying the PT of mammals is not obvious [46]. Here we compare the features of the PT in various organisms in the light of recent mechanistic advances of PTP regulation. We conclude that, with very few exceptions, regulated IMM permeability changes are a conserved feature of mitochondria across species.

2. Cyclophilin and the mechanism of PTP desensitization by Cyclosporin A

CsA is a cyclic undecapeptide produced by the fungus *Tolypocladium inflatum*; its ability to prevent the immune response against xenografts [77] has allowed organ transplantation to become a standard surgical practice. This effect of CsA is mediated by two sequential events, (i) the interaction of CsA with cytosolic cyclophilin (CyP) A followed by the formation of a CsA CyP-A complex; (ii) the binding of this complex to calcineurin, a Ca^{2+} /calmodulin-dependent cytosolic phosphatase that becomes inhibited [78–80]; as a consequence, phospho-NFAT is no longer dephosphorylated and therefore unable to translocate to the nucleus and trigger the IL-2-dependent activation of the immune response against the transplant [78–80].

CyPs are highly conserved, ubiquitous proteins sharing a common domain of about 109 amino acids, the CyP-like domain [81]; they possess peptidyl-prolyl *cis-trans* isomerase (PPIase) activity [82,83], which is inhibited after the binding of CsA [84]. Work with site-directed mutants of CyP-A has allowed the PPIase activity to be separated from CsA binding and calcineurin inhibition [85], and suggested that CyPs perform specific functions through interactions with a limited set of partner proteins rather than serving as general mediators of protein folding [81]. In keeping with this prediction, CyPs are involved in inflammation and vascular dysfunction [86–90], wound healing [91], innate immunity to HIV [92], hepatitis C infection [93], host-parasite interactions [94], tumor biology [95] and, in some species, regulation of the PTP which is mediated by CyP-D, the mitochondrial isoform of the enzyme [96–99]. Genetic ablation of the mouse *Ppif* gene (which encodes for CyP-D) has demonstrated that CyP-D is a unique mitochondrial receptor for CsA, and that it is responsible for modulation of the PTP but not a structural pore component [100–103] (see [104] for a recent review on the pathophysiology of CyP-D).

An important point should be appreciated, i.e. that CsA is *not* a *bona fide* PTP blocker. The inhibitory effect of CsA (and of CyP-D ablation) on the PTP is best described as “desensitization” in that the PTP becomes more resistant to opening after the uptake of Ca^{2+} and Pi in isolated mitochondria, yet opening still takes place for Ca^{2+} -Pi loads that are about twice those required in naïve mitochondria [2]. The mechanism through which CyP-D modulates the PTP has been recently clarified with our discovery that CyP-D ablation (or treatment with CsA) unmasks an inhibitory site for Pi, which is the actual PTP desensitizing agent [105]. It is remarkable that the PT of *Saccharomyces cerevisiae* mitochondria, which is insensitive to CsA in spite of the presence of a mitochondrial CyP, is inhibited by Pi [44]. As should become clear later in the review, we believe that inhibition by Pi is the unifying feature of the PT in all organisms, which allows to fill the gap between “CsA-sensitive” and “CsA-insensitive” PT, and to shed new light on what we regard as an evolutionarily conserved event.

3. The Permeability Transition in mammals

The PT has been characterized in a large number of tissues, cells and mitochondria of mammalian origin; due to space constraints, here we will only cover the essential regulatory features that allow a comparison to be made with other organisms, while we refer the reader to previous reviews for a discussion of the pathophysiology of the PTP and its role in cell death [1,2,19,106–113].

Matrix Ca^{2+} is perhaps the single most important factor required for PTP opening. It is difficult to separate the PTP-inducing effects of Ca^{2+} from those of Pi (and possibly of polyphosphate generated in the matrix [114,115]), because the transport of Pi (or of other species able to prevent the buildup of a relevant ΔpH such as acetate or bicarbonate, see Discussion in [105]) is required for the uptake of substantial amounts of Ca^{2+} . As discussed in detail elsewhere, matrix Ca^{2+} is best viewed as a permissive factor for PTP opening [2] in the sense that a PT is not observed in the absence of matrix Ca^{2+} , yet Ca^{2+} alone is not sufficient to induce PTP opening. The effect of Ca^{2+} is counteracted by other Me^{2+} ions that are transported by the Ca^{2+} uniporter (such as Sr^{2+} and Mn^{2+}), but the matrix Me^{2+} binding site(s) remain undefined. All divalent cations, including Mg^{2+} and Ca^{2+} itself, instead favor PTP closure through an external Me^{2+} binding site [116]. In the absence of a Ca^{2+} uniporter allowing fast Ca^{2+} uptake in energized mitochondria, it has been hard to assess the importance of matrix Ca^{2+} in *Saccharomyces cerevisiae*, but recent work with the Ca^{2+} ionophore ETH129 and of proper concentrations of Pi has recently allowed to establish a Ca^{2+} -dependence in this organism as well [52] (see the following paragraph).

As mentioned above, CsA desensitizes the PTP of mammalian mitochondria through an effect on matrix CyP-D. Binding of CsA to CyP-D unmasks an inhibitory site for Pi, which is the actual PTP antagonist [105]. At variance from what is often, and erroneously, stated CsA is not a blocker of the PTP, and a PT can readily occur in the absence of CyP-D and in CsA-treated mitochondria and cells. Another important feature of the mammalian PTP is its modulation by redox effectors, a more oxidized state favoring PTP opening. This effect is conferred by at least 3 redox-sensitive sites, i.e. (i) a matrix SH site in apparent redox equilibrium with glutathione, which can be blocked by low micromolar concentrations of N-ethylmaleimide (NEM) and monobromobimane but not by impermeant bimanies or β -hydroxybutyrate; (ii) a matrix site in apparent redox equilibrium with pyridine nucleotides, which can be blocked by NEM or β -hydroxybutyrate but not by monobromobimane [117, 118]; and (iii) an external thiol that triggers PTP opening after reaction with millimolar concentrations of NEM or low micromolar concentrations of copper-*o*-phenantroline [119]. This complex array of PTP redox-sensitive sites has recently been confirmed by careful studies based on mitochondrial photoirradiation after loading with hematoporphyrin [120].

4. The Permeability Transition in yeast

Manon and Coworkers have published a very useful review of the properties of the “yeast PTP”, also called Yeast Mitochondrial Unselective Channel (YMUC), and effectively summarized earlier literature on yeast permeability pathways [46]. They have also compared the features of the PTP of yeast and mammals as of 1998, and concluded that even if YMUC presents some functional analogies with mammalian PTP, its regulation is different enough to consider it a poor model for understanding the PTP of mammals [46]. Several new results, however, suggest that in fact the PTP of yeast and mammals may be closer than previously thought. We shall therefore reconsider the key points raised by Manon et al. in the light of these recent advances.

A first issue concerns the lack of Ca^{2+} -dependence of YMUC even in the presence of the Ca^{2+} ionophore ETH129, which allows electrophoretic matrix Ca^{2+} accumulation in *Saccaromyces cerevisiae* mitochondria [44]. It was later established that the apparent lack of effect of Ca^{2+} on the PTP of *Saccaromyces cerevisiae* in the study of Jung et al. [44] was due to the relatively high concentration of Pi (10 mM), which inhibits the yeast permeability pathway induced by ATP and substrates [41,43,44,55]. When addition of the Ca^{2+} ionophore ETH129 was performed in mitochondria incubated with 2 mM rather than 10 mM Pi, a Ca^{2+} dependence could be readily observed in yeast mitochondria as well [52]. These results match findings where a PT could be caused in *Saccaromyces cerevisiae* mitochondria at high concentrations of Ca^{2+} provided that the vicinal thiol crosslinker phenylarsine oxide [121] was used to sensitize the pore [47].

A second key point is the lack of sensitivity of the yeast PTP to CsA; as also noted by Manon et al. [46], this adds to a major discrepancy about the effect of Pi, which is an inhibitor of the yeast pore while it is an activator of the PTP in mammals. As we recently showed, however, Pi becomes a PTP inhibitor in mammalian mitochondria after they have been treated with CsA, or after CyP-D has been genetically ablated. We suspect that the yeast mitochondrial cyclophilin CYP3 [122] may not be able to bind the PTP, and thus to hinder the inhibitory site for Pi; as a result, CsA does not affect the yeast PT in spite of its binding to, and inhibition of, CYP3 [122]. As a PT can still occur in mammals in the presence of CsA or after ablation of CyP-D [100–103], we believe that the importance of sensitivity to CsA as a discriminating tool between the PT of mammals and yeast (and of the very occurrence of a PT) may have been overestimated.

A third important point is the presence of a PTP in yeast devoid of the outer membrane voltage-dependent anion channel (VDAC) or of the adenine nucleotide translocator (ANT) [45], which at the time were considered the main candidates as PTP constituents [46]. Subsequent genetic ablation studies have unequivocally shown that neither the ANT [123] nor any VDAC isoform [124] is essential for the PT to occur. We believe that this set of findings removes one of the major hurdles standing between the PTP of yeast and mammals.

Additional points are the lack of effect in yeast of several inducers of the mammalian PTP like carboxyatractylate (inhibitor of the ANT), ligands of the peripheral benzodiazepine receptor, and prooxidants [46]. While differences may certainly exist, some of these may depend on specific experimental conditions. For example the dithiol crosslinker phenylarsine oxide, one of the most powerful sensitizers of the PTP in mammals [121,125,126], was shown to induce the yeast PTP in the presence of relatively high concentrations of Ca^{2+} [47]; the efficacy of oxidants also reflects the activity of antioxidant mechanisms that may be particularly effective in yeast, a unicellular organism that can be exposed to extreme environmental conditions; and osmolarity profoundly affects yeast permeability pathways, which makes comparisons even more difficult given that what is isoosmotic for yeast is hypertonic for mammals [46].

Based on the above considerations, we believe that the yeast and mammalian PT may be the expression of very similar events, although they differ in modulation through mechanisms that will be fully understood only after the molecular nature of the PTP is defined. Hopefully this will also help understand why strain-specific differences exist (mitochondria from *Endomyces magnusii* [127] and *Yarrowia lipolytica* appear to be resistant to the PT [48,51]).

5. The Permeability Transition in other organisms

Other than in mammals and yeast, occurrence of a PT has been established in plants [56–71], fish [72,73] and amphibians [74,75]. The key features of the PTP, including desensitization by CsA, have been basically conserved in all these organisms although subtle differences may exist, such as the presence of additional effects of CsA on K⁺ channels in some plants [56, 65]. In the case of fish, the PT has been studied in the great green goby (*Zosterisessor ophiocephalus*) [72] and in the rainbow trout (*Oncorhynchus mykiss*) [73], and has revealed properties that match quite closely those of the pore of mammals. Due to its importance as a model system, we have investigated the occurrence and properties of the mitochondrial PTP in zebrafish (*Danio rerio*). Our results show that zebrafish mitochondria possess a ruthenium red-sensitive Ca²⁺ uniporter, and that they display a Ca²⁺-sensitive and redox-modulated PT. Occurrence of the PT *in situ* is modulated by binding of hexokinase like in mammals [128], and that it maintains its Pi-dependent sensitivity to CsA (Azzolin et al., manuscript in preparation). All these features make zebrafish a suitable model to study PTP modulation *in vivo*, to test its occurrence in disease models, and to evaluate its sensitivity to pharmacological treatments.

Another important model organism for which little is known about Ca²⁺ transport and the PT is *Drosophila melanogaster*. Our studies (von Stockum et al., manuscript in preparation) demonstrate that *Drosophila* mitochondria take up Ca²⁺ through a ruthenium red-sensitive mechanism, and display a ruthenium red-insensitive Ca²⁺ release following matrix Ca²⁺ loading. Ca²⁺ release was inhibited by Mg²⁺ (as is the PTP of all species) and Pi (as is the PT of yeast) but was insensitive to UbO, ADP and CsA (unlike the mammalian PTP). Fourteen CyPs have been identified in *Drosophila*; none of these has an obvious mitochondrial targeting sequence [129], and it remains to be established whether the lack of sensitivity to CsA is due to the absence of a mitochondrial CyP. Ca²⁺-induced Ca²⁺ release in *Drosophila* mitochondria could be triggered by thiol reactive compounds such as mersalyl at low concentrations (20 μM) and NEM at high concentrations (1–2 mM). Thus, *Drosophila* mitochondria may possess a Ca²⁺-regulated permeability pathway with features intermediate between the PTP of yeast and that of vertebrates (von Stockum et al., manuscript in preparation).

An interesting study has investigated Ca²⁺ transport in mitochondria from the brine shrimp *Artemia franciscana*, a crustacean that can tolerate anoxia for years, and also presents a striking resistance to osmotic stress [76]. These mitochondria displayed a high Ca²⁺ transport ability, and accumulated Ca²⁺ loads in excess of 1 micromole × mg protein⁻¹ without undergoing a PT, while under similar experimental conditions the PT was readily induced in rat liver mitochondria at the lowest tested load of 0.1 micromole × mg protein⁻¹ [76]. *Artemia franciscana* mitochondria were also resistant to a variety of classical inducers of the mammalian PTP; and resistance to PTP opening could not be ascribed to a lack of mitochondrial CyP, or of any regulators including the ANT and VDAC [76]. Lack of a PT may contribute to the extreme hypoxia tolerance in this species, and assessing the basis for PTP resistance in *Artemia franciscana* is of obvious interest for future studies on this topic.

6. Conclusions

Table I summarizes the key features of the PT in *Saccharomyces cerevisiae*, *Drosophila melanogaster*, *Danio rerio*, potato and mammals. It is apparent that the major discrepancy between *Saccharomyces* and *Drosophila* on one hand and fish, potato and mammals on the other is the sensitivity to CsA. As discussed in the review, however, we feel that this point may have been overestimated; and that inhibition by Pi (in the absence or presence of CsA), regulation by Ca^{2+} and sensitivity to redox effectors represent the minimum requirements for defining the PT, and unifying features that bridge the gap between yeast and higher eukaryotes. If our view proves to be correct, genetic strategies available in yeast, *Drosophila* and zebrafish could be of tremendous help in the identification of the molecular components of the PTP.

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List of Abbreviations

ANT	adenine nucleotide translocator
CsA	cyclosporin A
CyP	cyclophilin
IMM	inner mitochondrial membrane
NEM	N-ethylmaleimide
OMM	outer mitochondrial membrane
Pi	inorganic phosphate
PT	permeability transition
PTP	permeability transition pore
VDAC	voltage-dependent anion channel
YMUC	yeast mitochondrial unselective channel

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Table I
Properties of the Permeability Transition across species

The Table summarizes the occurrence of the permeability transition (PT), the presence of a Ca^{2+} uniporter (Unip), the dependence of the PT on matrix Ca^{2+} , sensitivity to Pi as an inducer (ind) or an inhibitor (inhib), the occurrence of PT desensitization by CsA, the presence of a mitochondrial cyclophilin (Mt CyP), and the presence of thiol-dependent, redox-sensitive (S) sites. For further explanation see text.

	PT	Ca^{2+} Unip	matrix Ca^{2+}	Pi (ind)	CsA	Mt CyP	Pi (inhib)	S Site
<i>S. cerevisiae</i>	Yes	No	Yes [†]	Yes	No	Yes	Yes	Yes
<i>D. melanogaster</i>	Yes	Yes	Yes	No	No	?	Yes	Yes
<i>D. rerio</i>	Yes	Yes	Yes	Yes	Yes	Yes	Yes [‡]	Yes
Potato	Yes	Yes	Yes	Yes	Yes	Yes	-	Yes
Mammals	Yes	Yes	Yes	Yes	Yes	Yes	Yes [‡]	Yes

[†] in the presence of ETH129

[‡] in the presence of CsA

- not tested