A Novel Conceptual Model for the Dual Role of $F_0F_1$-ATP Synthase in Cell Life and Cell Death

Abstract: The mitochondrial permeability transition (MPT) has been one of the longstanding enigmas in biology. Its cause is currently at the center of an extensive scientific debate, and several hypotheses on its molecular nature have been put forward. The present view holds that the transition arises from the opening of a high-conductance channel in the energy-transducing membrane, the permeability transition pore (PTP), also called the mitochondrial megachannel or the multiconductance channel (MMC). Here, the novel hypothesis is proposed that the aqueous access channels at the interface of the c-ring and the a-subunit of $F_o$ in the $F_0F_1$-ATP synthase are repurposed during induction of apoptosis and constitute the elusive PTP/MMC. A unifying principle based on regulation by local potentials is advanced to rationalize the action of the myriad structurally and chemically diverse inducers and inhibitors of PTP/MMC. Experimental evidence in favor of the hypothesis and its differences from current models of PTP/MMC are summarized. The hypothesis explains in considerable detail how the binding of Ca$^{2+}$ to a β-catalytic site (site 3) in the $F_1$ portion of ATP synthase triggers the opening of the PTP/MMC. It is also shown to connect to longstanding proposals within Nath’s torsional mechanism of energy transduction and ATP synthesis as to how the binding of MgADP to site 3 does not induce PTP/MMC, but instead catalyzes physiological ATP synthesis in cell life. In the author’s knowledge, this is the first model that explains how Ca$^{2+}$ transforms the $F_0F_1$-ATP synthase from an exquisite energy-conserving enzyme in cell life into an energy-dissipating structure that promotes cell death. This has major implications for basic as well as for clinical research, such as for the development of drugs that target the MPT, given the established role of PTP/MMC dysregulation in cancer, ischemia, cardiac hypertrophy, and various neurodegenerative diseases.

Keywords: Mitochondria; Permeability transition; ATP synthase; Calcium Ca$^{2+}$; Apoptosis; Nath’s torsional mechanism of energy transduction and ATP synthesis; Nath’s two-ion theory of energy coupling; Oxidative phosphorylation (OXPHOS); Magnesium Mg$^{2+}$.

Introduction

The $F_0F_1$-ATP synthase is the universal enzyme that provides cellular energy in the form of ATP [1−5]. It catalyzes the process of ATP synthesis by oxidative phosphorylation (OXPHOS) and photophosphorylation, the fundamental pathways of cell energy generation in animals, plants, and microorganisms [1−9]. The enzyme is composed of eight subunits in *Escherichia coli*, and seventeen subunits in animal mitochondria. Coupled ion translocation through aqueous half-channels in the membrane-bound $F_o$ domain formed at the interface of the c-ring (consisting of eight c-subunits in mitochondria [10]) and the conserved, hydrophilic amino acids of the a-subunit which electrostatically interact with two c-subunits as visualized in pioneer cryo-EM structures [11,12] and drive the rotation of the c-ring [13], the rotational dynamics of which has been described and analyzed quantitatively [2,14]. The torque produced in $F_o$ by the process of ion-protein interactions [3] is transmitted from $F_o$ to $F_1$ in the nanomachine and stored as torsional energy in the central shaft of the γ-subunit as first proposed by Nath’s torsional mechanism of energy transduction and ATP synthesis [15]. The release of torsional energy is used to cause conformational changes in the β-catalytic sites of $F_1$ and make ATP by a unique tri-site catalytic cycle detailed within the torsional mechanism [16,17]. The full name of the mechanism was given by other researchers and book authors over the past decade [7,18−30].

In addition to the central physiological function of the $F_0F_1$-ATP synthase as the energy currency in cell life, it has recently been proposed to be directly involved in
the induction and permeability increase of mitochondria by the phenomenon of permeability transition (MPT) during apoptosis and cell death [31,32]. Following MPT, mitochondria cannot generate electrochemical ion gradients and therefore can no longer support the vital process of OXPHOS. The permeability increase was first discovered in the 1950s [33–35] but regarded as damage of the inner mitochondrial membrane by elevated Ca\(^{2+}\). Subsequently, it was suggested by the groups of Pfeiffer, Hunter, and Crompton that the “damaging” effects of high matrix Ca\(^{2+}\) concentration on mitochondria might have physiological significance [36–38]. In particular, the pioneering work of Hunter and colleagues showed that energy coupling in mitochondria was reversibly lost upon induction of Ca\(^{2+}\)-induced swelling and transition [36]. The findings were assimilated in a series of influential papers by Haworth and Hunter in the 1970s, who first proposed that the process of swelling undergone by isolated mitochondria could be due to the opening of a regulated protein channel at mitochondrial contact sites of the inner and outer mitochondrial membranes, and named it the permeability transition pore (PTP) [39–41].

Strong evidence for the involvement of a pore/channel arose from the finding that the MPT is inhibited with high affinity by cyclosporin A [38,42,43]. Further important evidence for the channel hypothesis was provided by the discovery of high conductance channels in the inner mitochondrial membrane (termed as the mitochondrial megachannels (MMC) or multiconductance channels) using electrophysiological techniques [44–47]. The channels displayed the same properties as the PTP, i.e., activation by Ca\(^{2+}\), desensitization by cyclosporine A, and inhibition by mildly acidic matrix pH [47–49]. Today’s research defines the PTP as a Ca\(^{2+}\)-dependent non-selective channel permeant to cations, anions, and neutral solutes with molecular masses ≤ 1500 Da that shows a maximal conductance of ~1.5 nS and also displays several subconductance levels [45–50].

Despite the scientific advances traced above, the molecular nature of the PTP has remained shrouded in mystery. Several hypotheses of its molecular nature have been put forward, and several hypotheses have been rejected or contradicted by experimental work [51–55]. The molecular composition of the PTP/MMC is currently a subject of intense debate in the scientific literature [54,55]. A unifying molecular explanation for the complex regulation of the PTP/MMC has not been provided, and new ideas or hypotheses may be required. A better understanding of the structure, function, and regulation of the PTP/MMC is very important both for basic and applied medical research, given that the channel’s dysregulation and malfunction plays a key role in various pathological conditions and diseases, including cancer, ischemia, cardiomyopathies, diabetic encephalopathy, and neurodegeneration such as in Parkinson’s disease [56–62].

**Activators and inhibitors of PTP/MMC**

In addition to the almost absolute requirement of matrix Ca\(^{2+}\) to open the pore/channel, numerous studies in the field of apoptotic cell death have identified a large number of activators or inhibitors of the PTP/MMC. These activators or inducing agents accelerate the induction of the transition and/or lower the Ca\(^{2+}\) concentration required for induction. A comprehensive list of almost 50 chemical inducers of PTP/MMC has been tabulated previously [63]. Here we have selected a subset of the commonly used inducing agents, classified these inducers as endogeneous or external, and have tried to arrange them into chemical classes (Table 1). We have also collected some newly discovered chemical inducers of PTP/MMC and have included them in Table 1 with appropriate reference [64–70]. A shorter, but nonetheless impressive list of inhibitors of the pore/channel is also available [63]. These are included in Table 2 along with some subsequently discovered inhibitors for which the original references have been provided [71–73]. Rationalization of the mechanism of action of such a chemically diverse set of activators and inhibitors of the PTP/MMC poses a huge challenge to scientists who wish to understand the structure and regulation of the pore.

Inspection of Tables 1 and 2 reveal the chemically diverse nature of the effectors of the PTP/MMC. In addition, the set of activating and inhibiting agents are structurally diverse and do not show any structural similarity. One approach would be to postulate that these diverse agents act at unique sites and regulate the PMT/MMC. However, the almost absolute requirement of Ca\(^{2+}\) for pore/channel opening and the almost universal inhibitory action of cyclosporine A on the PMT/MMC that maintains a closed pore/channel constitute very strong evidence for a common mechanism of regulation. Moreover, agent-specific interaction sites have not been identified for the array of chemical effectors of PTP/MMC (Table 1 and Table 2). The question arises how an array of structurally and chemically diverse effector molecules produce common regulatory actions and effects.
Current hypotheses of PTP/MMC composition and regulation have recently been reviewed [54,55]. These hypotheses can be classified as mechanisms involving mechanical force transmission. The major challenge appears to be in the identification of the elusive molecular entities forming the PTP/MMC and thereafter to arrive at a unified principle of regulation of the pore/channel. An examination of the net charge, i.e. of the electrical aspects of the system that serves to regulate the voltage sensor of the constituents of the pore/channel may be instructive. This aspect seems to have been recognized previously in the vast scientific literature on apoptosis [74]. However, it was only stated as one among several possibilities, and the interpretations were sufficiently ambiguous leading to the consequence that this aspect was not elaborated or its elements developed further by subsequent research in the field. In this author’s view, a detailed consideration of local electrical potentials generated in the vicinity of the \( F_0F_1\)-ATP synthase by the action of activators and inhibitors in apoptotic cell death conditions is central to a unifying regulatory principle. Moreover, the common mechanism should obey the general correspondence principle, i.e., it should reduce to the mechanism of regulation of energy coupling by the ATP synthase during physiological ATP synthesis. The details of such a mechanism of regulation in cell life have already been proposed within Nath’s torsional mechanism of energy transduction and ATP synthesis and the two-ion theory of energy coupling [2,3,6,15–17,75–81].

### Unifying hypothesis

Here, the novel and exciting hypothesis is advanced that the aqueous access channels at the interface of the \( F_0F_1\)-ATP synthase are repurposed during induction of apoptosis and constitute the elusive permeability transition pore/mitochondrial megachannel. The next sections will explain in detail how this hypothesis is supported by evidence from both physiological and pathological situations.

### Table 1: Activators/Inducers of PTP/MMC

| Endogenous inducers | External inducers |
|---------------------|-------------------|
| Ca\(^{2+}\)         | Acids, e.g. arachidonic acid [67], bile acids [70], palmitic acid [67] |
| Inorganic phosphate (Pi) | Arsenate [63] |
| Oxaloacetate        | Atractyloside, Carboxyatractyloside [63] |
| Acetoacetate        | Dopamine [63] |
|                      | Free fatty acids [63] |
|                      | Heavy and transition metal cations, e.g. Zn\(^{2+}\) [68] |
| Ibuprofen           | Ibuprofen [65] |
|                      | Other cations, e.g. Al\(^{3+}\) [69] |
| Parabens            | Parabens [66] |
| Pesticides          | Peptides, e.g. mastoparan [64], MP14 [64] |
| Salicylates         | Salicylates [63] |
| Trialkyltin compounds | Salicylates [63] |

The wide-ranging structural and chemical diversity of the array of activator molecules has as unifying feature a negative local potential induced at the voltage sensor on the matrix side of the aqueous access pore/channel constituted by the polar interface of the c-ring and the \( F_0 \)-subunit in the membrane-bound \( F_0F_1 \)-ATP synthase. In special cases, other mechanisms of action are possible.

### Table 2: Inhibitors of PTP/MMC

| Endogenous inhibitors | External inhibitors |
|-----------------------|---------------------|
| Mg\(^{2+}\)           | Bonkrekate [63]     |
| ADP                   | Ca\(^{2+}\) chelators [63] |
| ATP                   | Cinnarizine [71]    |
|                       | Cyclosporin A [63]  |
|                       | Flunarizine [71]    |
|                       | Long chain acyl cations, e.g. sphingosine [74], psychosine [74], stearylamine [74] |
|                       | Polyamines, e.g. spermine [74] |
|                       | Oligomycin [72]     |
|                       | Oligomycin derivatives [73] |

The wide-ranging structural and chemical diversity of the array of inhibitor molecules possesses as unifying feature a positive local potential induced at the voltage sensor on the matrix side of the aqueous access channel formed by the polar interface of the c-ring and the \( F_0 \)-subunit in the membrane-bound \( F_0F_1 \)-ATP synthase. In special cases, other mechanisms of action are possible.
how exactly this transformation is conceived to occur. The presence and placement of these two mutually non-colinear half-access channels at the a-c interface with exquisite ion selectivity had been predicted in our earliest works during the formulation of Nath’s torsional mechanism of energy transduction and ATP synthesis [2,13,14,82], more than fifteen years before state-of-the-art cryo-EM structures of F$_0$, proved their existence by direct visualization [11,12]. The novelty of the proposal had been emphasized [6,76,78–80]. At that time, these access channels were generally believed to be located either within the a-subunit or in the c-ring [83,84].

Careful inspection of the myriad diverse regulators of the PTP/MMC (Tables 1 and 2) lead to the unifying principle that agents that by their action generate a positive local potential on the mitochondrial matrix side in the neighbourhood of the F$_0$F$_1$-ATP synthase are associated with PTP/MMC inhibition/closure. Similarly, agents that produce a negative local potential on the matrix side in the vicinity of the synthase lead to PTP/MMC activation/opening. Regulation by such a mechanism of action predicts a lack of structural and chemical specificity among activators and inhibitors of the PTP/MMC, as found (Tables 1 and 2). The principle of regulation is also attractive in that there is no need to postulate that diverse effectors of permeability change act at effector-specific sites on the F$_0$F$_1$-ATP synthase. Nor is there a necessity to stipulate that these agents mediate their effects on the permeability transition by a direct physical interaction between the F$_0$F$_1$-ATP synthase and other presumed constituents of the PTP/MMC or the ATP synthasome, for example, the adenine nucleotide translocator, ANT. Thus the principle rationalizes the effects of the numerous regulators and modulators of the PTP/MMC without making additional assumptions, or postulating additional specific sites of interaction.

**Key role of Mg$^{2+}$ in catalysis of ATP synthesis in cell life**

Interestingly, a key role of the establishment of positive absolute local/surface potentials for the regulation of energy coupling during steady-state $V_{\text{max}}$, ATP synthesis by the F$_0$F$_1$-ATP synthase is already a part of the torsional mechanism in cell life [2,3,6,76–79]. The mechanism considers Mg$^{2+}$ binding as the initiation step of substrate MgADP binding [16,17]. The binding of Mg$^{2+}$ to the open β-catalytic site of least affinity (site 3, β$_0$) in the F$_1$ portion and the interaction of Mg$^{2+}$ with its identified ligands creates a site with the correct conformation for ADP$^-$ binding [16,17], thanks to the strict six-ligated octahedral coordination and rigid stereochemistry of Mg$^{2+}$, upon which the site adopts a half-closed conformation, β$_{HC}$ [75,85]. This sequestration and closing off of a net negative charge due to MgADP$^-$ binding at the enzyme catalytic site creates a net positive local potential on the matrix side at the F$_0$−F$_1$ interface (Fig. 1) that triggers coupled ion translocation in F$_{\text{v}}$. Upon several cycles of ion translocation in F$_0$ depending on the ion to ATP ratio, torsional energy is stored in the γ-subunit according to the mechanism [2,7,14−18,21,22,86–88]. Release of torsional energy stored in the γ-subunit adds to MgADP$^-$ binding energy and forces the catalytic site to adopt a closed conformation (β$_c$) around MgADP by...
a process of induced fit [2,15–17,51,86]. The maintenance of a positive local potential on the matrix side keeps the half-access channels functioning in the ATP synthesis mode with its intrinsic exquisite selectivity, and does not trigger the opening of PTP/MMC as per the unifying principle enunciated above (Fig. 1). Hence Mg$^{-2}$ in the presence of ADP$^{3-}$ is a strong inhibitor of the PTP/MMC, and the common observation of a complete block of PTP/MMC by MgADP [51] is readily explained. The local potential becomes zero, and the positive local potential on the matrix side only disappears after MgATP$^{2-}$ release from the catalytic site, which once again adopts its open conformation $\beta_{\,c}$, and a new catalytic cycle is initiated by binding of the Mg$^{2+}$ ion [2,15–17].

### Key role of Ca$^{2+}$ in opening the PTP/MMC and triggering cell death

So what happens when Ca$^{2+}$, which is considered the universal trigger that opens the PTP/MMC under apoptotic conditions, is present in the mitochondrial matrix beyond a threshold concentration? Ca$^{2+}$ competes for binding to the same site in $\beta_{\,c}$ as Mg$^{2+}$. However, an irregular geometry is induced by the (7 – 9)-liganded coordination of Ca$^{2+}$, and the generally longer average bond lengths of Ca$^{2+}$ with its ligands in enzyme catalytic sites. Hence the binding of Ca$^{2+}$ in $\beta_{\,c}$ does not provide sufficient binding energy to enable ADP$^{3-}$ to bind tightly in the catalytic site, and the catalytic site cannot adopt the closed conformation $\beta_{\,c}$, unlike in the physiological cell life situation with Mg$^{2+}$, as explained recently [75]. In fact, in experiments on isolated $\beta$-subunits, virtually no ADP binding was detected (< 0.1 mol bound ADP per mol $\beta$-subunit), compared to 1.0 mol bound ADP per mol $\beta$-subunit in the presence of Mg$^{2+}$ [75]. Hence binding and sequestration of Ca$^{2+}$ in a $\beta$-catalytic side without subsequent ADP binding inhibits ATP synthesis and also nucleates a net negative local potential on the matrix side in the vicinity of the $F_{0}F_{1}$-ATP synthase molecule (Fig. 2).

The negative local potential generated as described above (Fig. 2) is sensed by the voltage sensor and constitutes the trigger for the PTP/MMC to open, in accordance with the unifying hypothesis formulated here. For details please see the text. The subunit structure of mitochondrial ATP synthase is simplified and modified from [104] with permission. For the sake of clarity, and in order to show the interaction of the $\alpha$-subunit with the $c$-ring that forms the aqueous access ion half-channels, the membrane-bound subunits e, f, g, A6L, DAPIT, and 6.8 kDa (or 6.8 PL) have been pooled together. These latter subunits have no known role in either synthesis or hydrolysis of ATP.

Figure 2: Opening of the PTP/MMC constituted by the polar interface of the $c$-ring and the $\alpha$-subunit in apoptosis and cell death. Ca$^{2+}$ binds in $\beta$-catalytic site (site 3) in the $F_{0}$ portion of mitochondrial $F_{0}F_{1}$-ATP synthase. However, Ca$^{2+}$ binding does not provide sufficient binding energy to enable ADP$^{3-}$ to bind tightly in the catalytic site, as explained recently [75]. The binding and sequestration of Ca$^{2+}$ in the $\beta$-catalytic side without subsequent ADP binding inhibits ATP synthesis [2,3,15–17,79] and generates a negative local potential on the matrix side at the $F_{0}$$-$$F_{1}$interface (with respect to zero potential on the other side of the membrane). The negative local potential distorts the structure of the normally selective transporter in cell life. This potential is sensed by the voltage sensor and constitutes the trigger for the PTP/MMC to open, in accordance with the unifying hypothesis formulated in this work. For details please see the text. The subunit structure of mitochondrial ATP synthase is simplified and modified from [104] with permission. For the sake of clarity, and in order to show the interaction of the $\alpha$-subunit with the $c$-ring that forms the aqueous access ion half-channels, the membrane-bound subunits e, f, g, A6L, DAPIT, and 6.8 kDa (or 6.8 PL) have been pooled together. These latter subunits have no known role in either synthesis or hydrolysis of ATP.
as proposed earlier [86; pp. 1829–1832]. Note that this can happen if crista junctions are associated with contact sites or even if formation of stable and/or dynamically labile contact sites do not cluster about crista junctions and are non-proximal to them. Such release of cytochrome c is also supported by a lot of experimental data [89,90], and hence the subsequent downstream steps in the apoptosis cascade can be readily catalyzed. In this new light, the PTP is now visualized with greater clarity than previously as a spatially extended structure that connects the mitochondrial matrix through the now open channels of the $F_0F_1$ synthase molecules to the intracristal spaces of cristae and onward through the cristae junctions via the open contact sites/ruptured outer membrane to the cytosol. Such a conceptual model of the PTP appears to be consistent with the available information in the field and would be of value for integration of various studies on the MPT. As far as initiation of PTP/MMC is concerned, Ca$^{2+}$ binding to $F_1$ triggers the induction of PTP/MMC by a local potential mechanism (Fig. 2). Moreover, in addition to its well-recognized function in cell life, the $F_0F_1$-ATP synthase is specifically present to enable a second physiological function: the opening of PTP/MMC for its participation in apoptosis and programmed cell death. It appears that nature uses and re-uses the same structures and principles for performing various physiological functions, as eloquently stated by Channakeshava [21].

**Experimental evidence in support of the hypothesis and discussion**

In addition to the extensive experimental support for the proposed hypothesis (Figs. 1, 2) in cell life, not all of which can be covered here [for reviews, see refs. 2, 86], considerable experimental evidence can be adduced from studies on cell death [31,32,47–55]. These include numerous biochemical experiments [36,38,42,43,48–53], experiments based on electrophysiology on mitochondria [44–47], and several state-of-the-art electrophysiological experiments on the $F_0F_1$-ATP synthase in reconstituted systems [31,32]. The various experimental evidences that have been offered for the involvement of the ATP synthase in forming the PTP/MMC [for reviews, see refs. 54,55] also support the present hypothesis. This is because these experiments relate to the entire $F_0F_1$-enzyme complex, and do not specifically address which subunits of the $F_0F_1$-ATP synthase are responsible for constituting the PTP/MMC. In that sense, a very large number of combination/complexes of the ATP synthase subunits could constitute the pore. The present hypothesis presents a specific combination, and helps us converge to a particular solution.

It ought to be stressed that genetic loss of function and indirect swelling studies, experimental studies on mitochondrial $\rho^0$ cells lacking mitochondrially-encoded $F_0F_1$ subunits [91], and c-ring knockdown experiments [92] do not disprove the role of ATP synthase in formation of the PTP/MMC; in fact, they provide strong arguments in favor of formation of the PTP/MMC by the ATP synthase or its specific subunits, as explained also by other researchers [54]. This is due to the fact that such deletions interfere with the assembly of a functional ATP synthase [92], and moreover, such experiments fail to detect the physiological high-conductance PTP/MMC channel. Channel formation is a general property of many membrane-bound complexes. Recent experiments show that deletion of $F_0$ subunits leads to loss of the PTP/MMC, and only significantly lower conductance channels (such as in ANT) could be detected by direct electrophysiological recordings [93], the gold standard for quantifying channel activity. Hence the largest conductance PTP/MMC channel is indeed located within the $F_0F_1$-ATP synthase.

There are other salient differences between current hypotheses of the molecular composition of the PTP/MMC and the hypothesis presented here, in addition to their classification above as mechanical- or electrical-centric respectively. Current models place the PTP/MMC at the dimer/tetramer interface of ATP synthase [54] or within the core of the c-ring [55]. However, the interface or the core possess a hydrophobic nature and are normally occupied by membrane lipids, which would need to be ejected out upon PTP/MMC activation in order to form an aqueous channel and allow the passage of ions. These models do not specify where the free energy for such an energy-intensive extrusion process comes from. Such difficulties do not arise in the model proposed here.

The change from the prevailing positive local electrical potential on the matrix side due to the binding of MgADP at an $F_1$-catalytic site/action of inhibitors (Fig. 1) to a negative local potential due to binding of Ca$^{2+}$ ions in $F_1$/action of activators (Fig. 2) can be expected to alter the structure of a normally specific channel/transporter. An influence of net surface charge, or of a reversal of polarity has been emphasized in a number of biological contexts and fields, including apoptosis and transport [88,94–103]. Thus, the action of valinomycin transforms a channel normally transporting anions into a K$^+$-translocating channel [88]. Replacement of a single negatively charged atom in bacteriorhodopsin alters the ion specificity completely from cations to anions, as in halorhodopsin.
Transformation of physiologically selective transporters to less selective forms is also quite common. A well-known example is the Ca$^{2+}$ channel of sarcoplasmic reticulum which begins to transport neutral molecules such as glucose upon a slight increase in ionic strength [102]. Another example is the modification of transporter properties by incubation with mercurials [103]. Hence it is quite reasonable to propose that reversal of polarity (Figs. 1, 2) can, by a distortion of channel structure, transform a normally selective channel in cell life to its less selective avatar in cell death.

Summary and conclusion

In summary, it has been proposed that aqueous access channels known to exist at the interface of the c-ring and the a-subunit of F$_{0}$ in the F$_{0}$F$_{1}$-ATP synthase are repurposed during induction of apoptosis and constitute the elusive PTP/MMC. A unifying principle for the action of structurally and chemically diverse regulators of PTP/MMC has been postulated. The central role of Ca$^{2+}$ binding in the F$_{1}$ portion of ATP synthase in triggering the opening of the PTP/MMC has been highlighted. This has been compared and contrasted with the specific binding of Mg$^{2+}$ and ADP$^{3-}$ in F$_{1}$ and its role in forming the normally selective access pathway in the F$_{0}$ portion of ATP synthase during physiological ATP synthesis in OXPHOS. To the best of the author’s knowledge, this is the first model that explains how Ca$^{2+}$ transforms the F$_{0}$F$_{1}$-ATP synthase from an energy-conserving nanomachine vital for cell life into an energy-dissipating structure involved in apoptosis and cell death. The model should prove useful to scientists carrying out basic research and also to clinicians because PTP/MMC dysregulation is implicated in diseases and pathological conditions such as neurodegeneration including Parkinson’s disease, cancer, cardiac hypertrophy, diabetic encephalopathy, and ischemia/reperfusion [56–62].

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