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Development or disease: duality of the mitochondrial permeability transition pore

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ABSTRACT

Mitochondria is not only a dynamic organelle that produces ATP, but is also an important contributor to cell functions in both development and cell death processes. These paradoxical functions of mitochondria are partially regulated by the mitochondrial permeability transition pore (mPTP), a high-conductance channel that can induce loss of mitochondrial membrane potential, impairment of cellular calcium homeostasis, oxidative stress, and a decrease in ATP production upon pathological activation. Interestingly, despite their different etiologies, several neurodegenerative diseases and heart ischemic injuries share mitochondrial dysfunction as a common element. Generally, mitochondrial impairment is triggered by calcium deregulation that could lead to mPTP opening and cell death. Several studies have shown that opening of the mPTP not only induces mitochondrial damage and cell death, but is also a physiological mechanism involved in different cellular functions. The mPTP participates in regular calcium-release mechanisms that are required for proper metabolic regulation; it is hypothesized that the transient opening of this structure could be the principal mediator of cardiac and brain development. The mPTP also plays a role in protecting against different brain and cardiac disorders in the elderly population. Therefore, the aim of this work was to discuss different studies that show this controversial characteristic of the mPTP; although mPTP is normally associated with several pathological events, new critical findings suggest its importance in mitochondrial function and cell development.

1. Introduction

The mitochondria is a highly dynamic organelle, commonly nicknamed “the powerhouse of the cell” for its ability to produce cellular energy in a highly efficient manner (Mattson et al., 2008). The main function of the mitochondria is to convert the energy derived from nutrients into heat and ATP, but it is also a major contributor to cell fate determination, as this organelle is able to control both apoptotic and necrotic cell death (Folmes et al., 2012; Nunnari and Suomalainen, 2012). These diametrically opposed functions of mitochondria are particularly relevant in the heart and brain, where mitochondria supply over 90% of the energy demands (Wallace, 2005). In fact, several studies have demonstrated that, in these specific organs, metabolic control through mitochondria is not only related to cell fate (Folmes et al., 2012), but also plays an important role in cell differentiation (Kasahara and Scorrano, 2014).

Interestingly, it has been shown that all these mitochondrial functions are at some point related to the opening or activation of the mitochondrial permeability transition pore (mPTP) (Bernardi et al., 1999; Hou et al., 2013; Kasahara and Scorrano, 2014; Kwong and Molkentin, 2015). The mPTP is a high-conductance channel that, upon opening, generates a sudden increase in inner mitochondrial membrane (IMM) permeability to ions and small solutes (Haworth and Hunter, 1979; Hunter and Haworth, 1979a, 1979b). These changes also affect regulation of the mitochondrial membrane potential (Galluzzi et al., 2009), calcium homeostasis (Elrod et al., 2010), reactive oxygen species (ROS) production (Hou et al., 2014), ATP production (Budd and Nicholls, 1996), and cell death (Galluzzi et al., 2009). Recent advances have determined that the mPTP could also be the principal mediator of the duality of cell development and cell death. The mPTP plays a role in cardiac and neurodegenerative pathologies (Hou et al., 2013; Kwong et al., 2015), but is also involved in heart and brain development (Hom et al., 2011; Porter et al., 2011; Mattson et al., 2008), highlighting the importance of the mPTP in health and disease.

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2. The mitochondrial permeability transition pore

The mPTP is a non-specific mega-channel that is sensitive to perturbations in intracellular calcium homeostasis, permitting the passage of molecules smaller than 1.5 kDa in size (Elrod and Molkentin, 2013). The opening of the pore results in an increase in the permeability of the IMM and permits entry of metabolites into the mitochondrial matrix space, which leads to a reduction in the efficiency of ATP production by uncoupling the electron transport system from ATP synthase activity (Elrod and Molkentin, 2013; Mnatsakanyan et al., 2016). Recent studies suggest that the mPTP is one of the principal mechanisms that leads to cell death, participating as a metabolic regulator of cell energy homeostasis, a mitochondrial calcium transporter, and a superoxide (SO) efflux channel (Izzo et al., 2016).

The original mPTP model proposed that the channel was formed by three principal proteins: cyclophilin D (CyPD), located in the mitochondrial matrix; the adenine nucleotide translocator (ANT), found in the inner membrane; the voltage-dependent anion channel (VDAC) in the outer membrane (Rao et al., 2014); and other interacting mitochondrial molecules such as the phosphate carrier, BH3 proteins, and p53 (Elrod and Molkentin, 2013). However, genetic knock-out studies showed this model to be invalid, as they demonstrated that only the deletion of the *CyPD* gene has a regulatory role in the activation of mPTP (Baines et al., 2005; Nakagawa et al., 2006). In fact, studies in mouse models lacking ANT expression showed a functional state of mPTP that held two-fold more calcium than wild-type mitochondria; this suggests that ANT has an important regulatory role in the function of the mPTP, but not in its structure (Kokoszka et al., 2004). On the other hand, the absence of one or more VDAC isoforms still allowed opening of the mPTP (Baines et al., 2007), indicating that CyPD is the major factor responsible for the activation of the mPTP (Elrod and Molkentin, 2013; Izzo et al., 2016).

Interestingly, in recent years, it has been proposed that ATP synthase is a major component of the mPTP (Jonas et al., 2015). This enzyme is a highly conserved molecular machine that catalyzes the production of ATP from ADP and P_i, powered by an electrochemical transmembrane gradient in mitochondria (Pogoryelov et al., 2009). Furthermore, ATP synthase is located in the inner membrane cristae, made up of a membrane component—known as Fo—composed of nine polypeptides (a, b, c, d, e, f, g, F6, and F8) and a soluble catalytic core complex—known as F1—consisting of five different subunits (α, β, γ, δ/OSCP, and ε) (Pogoryelov et al., 2009). The F1 subcomplex forms a catalytic head group and a rotating central stalk, and the Fo subcomplex comprises the membrane region and the peripheral stalk; the oligomycin sensitivity-conferrin protein (δ/OSCP) subunit connects the peripheral stalk to the catalytic domain (Pogoryelov et al., 2009). Regarding ATP synthase and its role in mPTP regulation, important studies have described that CyPD associates with ATP synthase specifically through the δ/OSCP subunit; this interaction is inhibited by cyclosporine A (CsA), a fungus-derived drug that reduces the probability of mPTP opening through the inhibition of CyPD (Giorgio et al., 2009, 2013). In fact, this inhibitory drug increased the activity of both ATP synthesis and hydrolysis through displacement of CyPD from ATP synthase, suggesting that the interaction of CyPD with ATP synthase may switch the enzyme to a lower catalytic activity state (Giorgio et al., 2009). On the other hand, it was suggested that the δ/OSCP subunit also influences the accessibility of mPTP calcium-binding sites. It seems that δ/OSCP affects the affinity of the metal binding sites of ATP synthase, and thus, the ability with which calcium can interact with the enzyme. Interestingly, when calcium is bound to the enzyme, ATP synthase activity is not coupled to proton translocation, suggesting that calcium induces conformational changes in ATP synthase, which could open the mPTP and stop ATP synthesis (Giorgio et al., 2013).

With respect to the mechanism for channel formation, there are two different working proposals about the structure of the pore itself. However, both models suggest that ATP synthase forms part of the functional pore of the mPTP (Alavian et al., 2014; Giorgio et al., 2013). One hypothesis indicates that the mPTP channel forms at the interface of two monomers (associated into dimers) of ATP synthase (Giorgio et al., 2013). Purified dimers of the enzyme were reconstituted into lipid bilayers and stimulated with regulators of mPTP; it was shown that dimers of ATP synthase were capable of forming a current that was electrophysiologically equivalent to that in the mPTP (Giorgio et al., 2013). Since a current is only seen in dimers, and the genetic ablation of the subunits that form the dimers did not result in opening of the mPTP (Carraro et al., 2014), it was suggested that the pore structure of the mPTP forms at the membrane interface between two adjacent Fo sectors (Giorgio et al., 2013).

Another proposed model involves the c-subunit ring of the F1 subcomplex (Alavian et al., 2014). Both a- and c-subunits form the proton channel of ATP synthase, permitting proton flux between the intermembrane space and the mitochondrial matrix (Pogoryelov et al., 2009). Interestingly, gene-silencing of isomers of the c-subunit inhibited mPTP opening, and the overexpression of these subunits accelerated the kinetics of the opening response, increasing permeabilization of the outer mitochondrial membrane (OMM) and resulting in cell death (Azarashvili et al., 2014; Bonora et al., 2013). Furthermore, in purified ATP synthase extracts, it was found that the ring structure formed by c-subunits generated a current similar to that of the mPTP. These currents were inhibited by calcium, CyPD and CsA (Alavian, 2014). Therefore, the properties of the pore formed in the c-subunit ring suggests that this structure corresponds to the mPTP itself, indicating a strong relationship between the opening of the mPTP and ATP synthase activity (Alavian, 2014).

It is still a matter of discussion whether the extraction methods and protocols used were adequate to reach a clear conclusion about the components of mPTP (Bernardi et al., 2015a, 2015b; Chinopoulos et al., 2014; Konig et al., 2016; Maltecca et al., 2015); complementary evidence has indicated new roles of ATP synthase in mPTP regulation. Although the mechanism for mPTP formation is an open question, studies suggest that ATP synthase could not only participate in mPTP opening by increasing IMM permeability, but could also directly affect respiratory chain functionality and cell survival (Alavian et al., 2014). The permeability of the IMM is a critical and decisive point between life and death in the cell; the mPTP has been suggested as a master regulator of both metabolism and cell death. With that in mind, a relative closure or opening of the mPTP could greatly affect cellular functions in organs and tissues with a high energy demand, such as the heart and brain (Mnatsakanyan et al., 2016).

3. Pathological implications of mPTP opening

As we previously mentioned, the formation and consequent opening of the mPTP is a key factor in mitochondrial dysfunction and mitochondria-driven cell death (Bernardi et al., 2015a, 2015b; Bonora et al., 2013; Jonas et al., 2015; Kroemer et al., 2007). In fact, the general consensus is that uncontrolled opening of the mPTP leads irreversibly to necrosis or apoptosis (Bernardi et al., 2015a, 2015b). Under physiological conditions, when the mitochondria is exposed to high concentrations of calcium, it can undergo a massive and permanent swelling that leads to an abrupt increase in permeability to small solutes of the IMM, resulting in the collapse of the chemiosmotic gradient across the IMM—also known as the mitochondrial permeability transition (Elrod and Molkentin, 2013). The resultant uncoupling of oxidative phosphorylation results in a decrease in ATP generation and a subsequent increase in reactive oxygen species (ROS) production. In addition, mitochondrial swelling may rupture the OMM, releasing cytochrome C and initiating apoptosis (Izzo et al., 2016; Kroemer et al., 2007; Rao et al., 2014).

Interestingly, despite their different etiologies, several neurodegen-