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Mitochondrial Permeability Transition: Known Phenomenon with Unknown Molecular Identity

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Mitochondria play an important role in energy metabolism of the cell. The electron transport chain linked to oxidative phosphorylation provides ATP necessary for cell metabolism. Studies over the past 30 years provide strong evidence that, in addition to their role in cell life, mitochondria are the main organelles which initiate cell death through apoptosis, necrosis, and autophagy. One of the key events that cause mitochondria-mediated cell death is the mitochondrial permeability transition (PT) that associates with formation of non-selective pathological PT pores (PTPs) in the inner membrane of mitochondria (IMM). Oxidative stress, Ca^{2+} accumulation, and ATP depletion are the main factors inducing mitochondrial PT which is accompanied by loss of membrane potential ($\Delta\psi m$) and proton gradient (ΔpH) across the IMM. Loss of electrochemical potential diminishes oxidative phosphorylation and ATP synthesis. Mitochondrial PTP formation can occur at low (or transient) conductance, and at high (or long-lasting) conductance, although the existence of a low-conductance mode (reversible opening of PTP) is still controversial. In a high-conductance mode, which has been accepted as an irreversible step, solutes, water and ions with the molecular mass up to ~1.5 kD enter through the PTPs thus enhancing colloid-osmotic pressure in the matrix [1,2] (Figure 1). Surface area of the IMM exceeds that of the outer mitochondrial membrane (OMM), and extensive matrix swelling induces unfolding of cristae causing rupture of the OMM. Damage to the OMM leads to cell death through apoptosis and/or necrosis depending on the ATP level in the cell. When ATP synthesis is partially maintained by undamaged mitochondria, release of pro-apoptotic proteins will initiate cell death through caspase-dependent (e.g. cytochrome c, Smac/DIABLO) and/or caspase-independent (e.g. AIF, EndoG) pathways. However, in the absence of ATP, cell death will preferably occur through necrosis even though mitochondrial pro-apoptotic proteins are present in the cytoplasm [3-5].

The role of mitochondrial PT in cell dysfunction has been broadly investigated in various animal models of oxidative stress caused by cardiac and cerebral ischemia/reperfusion, diabetes mellitus and other diseases. There are many methodologies to measure the opening of PTPs *in vivo* (by mitochondrial [^{3}H]-deoxyglucose entrapment technique, NADH assay in the blood) and *in vitro* (by fluorescent methods using calcein or calcium green, the spectrophotometric method by measuring Ca^{2+}-induced light scattering) [6]. Although mitochondrial PT induction has been broadly accepted as a well-known phenomenon the molecular identity of the PTP still remains unknown. Initially three proteins, the adenine nucleotide translocase (ANT) in the IMM, voltage-dependent anion channel (VDAC, also called porin) in the OMM, and cyclophilin D (CyP-D) in the matrix were proposed as the main structural components of the PTP. In addition, the benzodiazepine receptor, hexokinase, creatine kinase, Bcl2, phosphate carrier and other proteins may play regulatory roles in pore formation [3,7]. However, results of genetic studies conducted in knocked-out mice by different groups demonstrated that mitochondria containing neither VDAC nor ANT were still susceptible to Ca^{2+}-induced mPTP induction. Mitochondria from CyP-D knock-out mice exhibited PT induction at high concentration of Ca^{2+} suggesting that the protein could play a regulatory role in pore formation [8-11]. The presence of a large number of proteins in mitochondrial PTPs along with the dynamic structure of the complex presumably makes it difficult to identify the molecular composition of the pores.

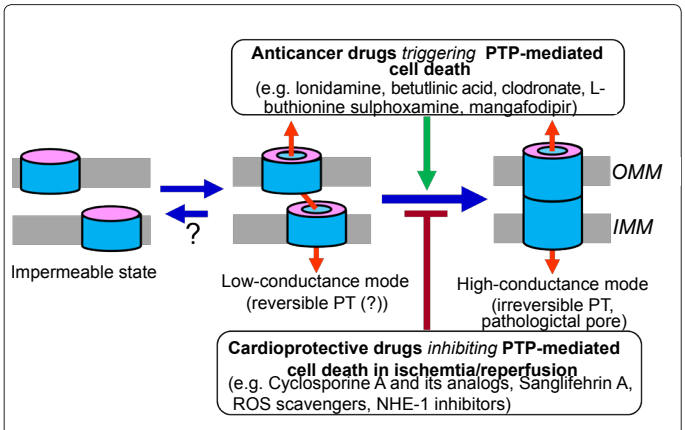

Figure 1: Mitochondrial PTPs as a target to induce or prevent cell death.

In biomedical studies, the PT induction is mainly elucidated in two ways, in an effort to further develop new pharmacological and conditional approaches for mitochondria-mediated treatment of diseases (Figure 1). The *first* group of studies is aimed to inhibit the PT induction and therefore, prevent mitochondria-mediated cell death. Immunosuppressive drugs (sanglifehrin A, cyclosporine A and its derivatives), ROS scavengers (propofol, MCI-186), ubiquinone analogues (UQ0, Ro 68-3400), Na^+-H^+ exchanger-1 (NHE-1) inhibitors (cariporide and its derivatives), and others have been shown to exert cardioprotective effects against ischemia/reperfusion in various animal models [3,5,12,13]. Furthermore, cardioprotective effects of the PTP inhibitor, cyclosporine A have been demonstrated in patients with acute myocardial infarction [14]. PTP inhibitors also exerted neuroprotective effects in a various models of brain ischemia [15,16]. The *second* group of studies, in contrary to the first group, is aimed to stimulate mPTP-induced apoptosis in cancer cells. Several pharmacological agents triggering mPTP induction have been developed in cancer chemotherapy for inhibition of carcinogenesis. Pharmacological

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agents such as lonidamine, betulinic acid, clodronate, L-buthionine sulphoxamine, β-phenylethyl isothiocyanate, mangafodipir among others that stimulate mPT induction directly or indirectly are already involved in pre-clinical and clinical (Phases I-III) trials [17-20].

Thus, existing studies indicate the importance of the PT as a target to initiate or inhibit mitochondria-mediated cell death. Notably, development of new pharmacological drugs is limited due to absence of the precise molecular identity of the pores. Targeting the PT and individual components of the pore may open new perspectives for the treatment of various diseases including myocardial infarction, cerebral ischemia, and cancer.

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