Mitochondrial Permeability Transition Pore Assembling Does Not Require the Participation of Outer Mitochondrial Membrane Proteins

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Mitochondrial permeability transition (MPT) is characterized by Ca^{2+}-induced opening of a nonselective proteinaceous membrane pore, the permeability transition pore (PTP) sensitive to cyclosporin A (CyA). Data from our laboratory provided evidence that PTP is assembled by the aggregation of cyclophylin D with inner membrane proteins due to the formation of thiol cross-linking. Alternatively, literature data propose the participation of a number of other outer membrane proteins in the composition of the PTP, such as, voltage-dependent anion channel (VDAC), creatine kinase, hexokinase and the benzodiazepinic receptor. In order to ascertain the independence of outer membrane proteins to generate the PTP we performed experiments with liver mitoplasts by using digitonin to eliminate the outer membrane. Mitoplasts retained less than 5% of monoamine oxidase activity, a marker of the outer membrane. These mitoplasts were able to generate and sustain a membrane potential enough to phosphorylate ADP and to take up Ca^{2+}. As hypothesized, these mitoplasts were as susceptible to PTP opening by Ca^{2+} as the intact mitochondria. Mitoplasts PTP were sensitive to the known PTP "inducers" such as inorganic phosphate, thiol and NAD(P)H oxidants, reactive oxygen and "inhibitors", such as, CyA, Ca^{2+} chelators, adenine nucleotides, dithiol and NAD(P) reductants, and reactive oxygen scavengers. Altogether, the data indicate that the outer membrane is not necessary for PTP assembling or opening.

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