MODULATION OF MITOCHONDRIAL MEMBRANE PERMEABILITY IN PATHOGENESIS AND CONTROL OF METABOLISM

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Mitochondrial inner and outer membranes have contrasting permeability. The outer membrane is nonspecifically permeable to low molecular weight solutes, whereas the inner membrane is impermeable to hydrophilic solutes and ions except through specific transporters. After stresses and sometimes in normal physiology, the permeability of the two membranes can change abruptly. In the inner membrane, permeability transition pores conducting solutes up to 1500 Da open to induce the mitochondrial permeability transition (MPT). As the MPT involves more and more mitochondria, autophagy, apoptosis and necrosis progressively develop linked to the proportion of injured mitochondria, cytochrome *c* release after mitochondrial swelling and the extent of ATP depletion. In apoptosis, the outer membrane can also increase its permeability to cause release of cytochrome *c* and other intermembrane proteins. By contrast, outer membrane permeability may decrease after certain stresses by closure of voltage dependent anion channels (VDAC). VDAC closure may globally suppress mitochondrial metabolism to prevent futile ATP hydrolysis in hypoxia-ischemia and release of toxic superoxide during oxidative stress. VDAC closure also appears to facilitate selective acetaldehyde oxidation after ethanol ingestion and may promote aerobic glycolysis (Warburg effect) in cancer cells. VDAC opening, by contrast, is proposed to stimulate ATP release from mitochondria during glucose-stimulated insulin secretion by pancreatic beta cells. Thus, VDAC is a global regulator, or governator, of mitochondrial metabolism. The mechanisms by which these mitochondrial membrane permeability changes occur and are regulated remain incompletely understood and require future study.