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Educational Corner

The mitochondrion as an integrator/coordinator of cell death pathways

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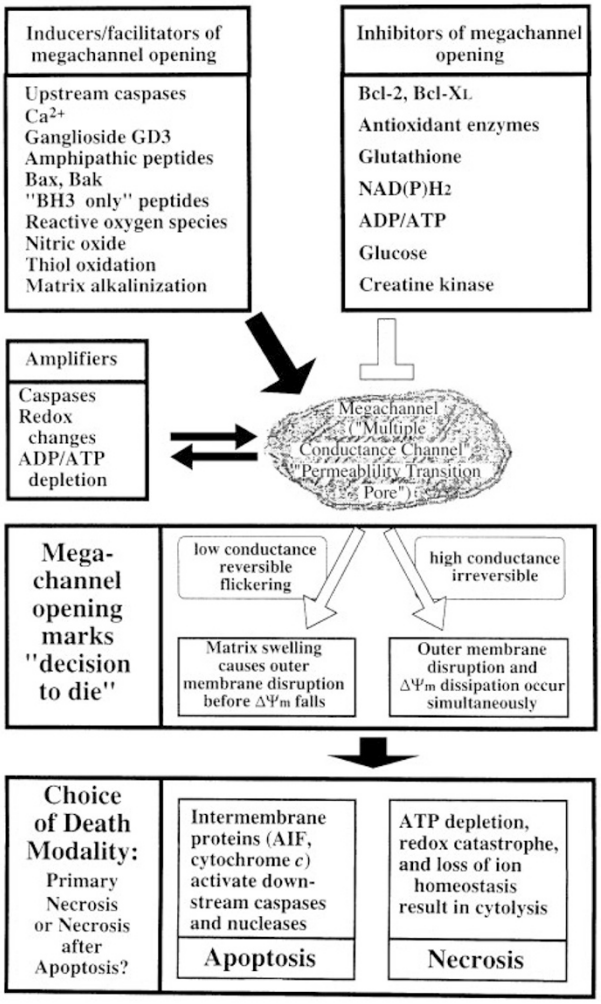
Although it has been a widely accepted dogma that mitochondria are not involved in the process of apoptosis, recent evidence indicates that mitochondria do play a decisive role in both apoptosis and necrosis. Indeed, mitochondria can function as integrators of different pro-apoptotic signaling pathways and, simultaneously, constitute the target of a number of apoptosis-inhibitory molecules. It appears that the mitochondrial megachannel also called 'multiple conductance channel' or 'permeability transition pore') is activated in response to different pro-apoptotic signal transduction molecules. The megachannel is a composite channel formed by apposition of several proteins in the contact site between the inner and the outer mitochondrial membranes, and it is directly regulated by the Bcl-2/Bax complex. It participates in the regulation of matrix Ca^{2+}, pH, and volume and functions as a Ca^{2+}-, voltage-, pH-, and redox-gated channel with several levels of conductance and little if any ion selectivity. Opening of the megachannel (maximum molecular weight cut-off: 1500 Da) causes colloidosmotic swelling of the mitochondrial matrix. Since the inner mitochondrial membrane has a larger surface area than the outer membrane, matrix swelling causes physically disruption of the outer membrane. At its low level of conductance, the megachannel can flicker and respiration can restablish the proton gradient responsible for the $\Delta\Psi_m$. At its high level of conductance, it causes irreversible loss of the $\Delta\Psi_m$. As a consequence of the liberation of intermembrane proteins through the outer mitochondrial membrane, caspases and nucleases are activated. As a result of the bioenergetic consequences of megachannel, the cells will ultimately undergo cytolysis. The availability of caspases and the maintenance of a minimum of energy, redox- and ion homeostasis is required for the acquisition of the apoptotic phenotype before cytolysis occurs. When caspases are inhibited and/or basic energy requirements are not met (e.g. low intracellular ATP levels), the consequence of megachannel opening gives rise to a necrotic phenotype.



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