MONITOR A 'digest' of some recent papers of interest in the primary journals TIG DECEMBER 1998 VOL. 14 NO. 12

The organelle of death

The mitochondrial FOF1-ATPase proton pump is required for function of the proapoptotic protein BAX in yeast and mammalian cells Matsuyama, S., Xu, Q., Velours, J. and Reed, J.C. Mol. Cell. 1, 327–336 A role for mitochondria in the decision-making machinery that commits cells to the cell-death (apoptotic) pathway is now generally accepted. However, exactly what that role is, and how central it is in the overall process, remain highly controversial. Depending on methodology, or the system studied, different researchers have implicated at least four distinct 'mitochondrial events' in the death decision. These are the release to the cytosol of cytochrome c and/or another caspase activator, the opening of a mitochondrial permeability pore, the activation of oxygen radical generation in the respiratory membrane, and a catastrophic failure of ATP synthesis. Death-regulatory proteins of the BCL2 super-family appear to function inside mitochondria, although exactly what they do there remains unclear, and additional roles for them elsewhere in the cell have not been excluded. Our understanding of how this puzzle fits together has been greatly advanced by the ongoing work of John Reed and colleagues, using yeast as a model system to study the action of death-inhibiting and death-promoting proteins of the BCL2 super-family. Employing a mutational approach, this group has now succeeded in defining a critical component of the death-inducing machinery that co-operates with the mammalian protein BAX. The newly identified partner turns out to be none other than the central enzyme in mitochondrial oxidative phosphorylation, ATP synthase. Loss-of-function mutations in the nuclear gene ATP4, encoding subunit b of the membrane portion of the enzyme, render cells resistant to BAX-mediated lethality. In a parallel series of experiments the same authors found that inhibition of the proton pump of mitochondrial ATP synthase with the drug oligomycin also blocks BAX-induced death. Importantly, a similar effect can be produced in mammalian cells. Exactly how proton pumping by ATP synthase activates BAX – or mediates its action – remains to be elucidated. Intriguingly, although not emphasized by the authors, BAX still functions in a rho- strain that lacks the mtDNA-encoded subunits (a, c and 8) of the ATP synthase proton pump. Therefore the role of the enzyme in the cell death pathway need not be directly related to its primary metabolic activity. Nevertheless, the demonstration that a key mitochondrial enzyme complex can regulate the life-or-death decision of cells implies that this should properly be regarded as a central function of mitochondria. -