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COMMENTARY

Gold opens mitochondrial pathways to apoptosis

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Apoptosis is a form of cell death characterized by the activation of caspases (cystenyl aspartate specific proteases) that cleave multiple targets in the cell. The control of caspase activation represents a major decision point for determining whether a cell will either continue to live or die by apoptosis. The release of cytochrome *c* from mitochondria as a result of permeability changes to the mitochondrial membranes is an important pathway of caspase activation in some forms of apoptosis (reviewed by Desagher & Martinou, 2000; Gottlieb, 2000). Cytochrome *c* binds with apaf-1, ATP and procaspases in the cytoplasm to form apoptosome complexes that activate caspase 9, and in turn, other caspases. The mechanisms that control mitochondrial membrane permeability and the release of cytochrome *c* during apoptosis are becoming better understood, but are still controversial. For example, the bcl-2 family of proteins displays anti-apoptotic and pro-apoptotic functions possibly by targeting the outer membranes of mitochondria, preventing or promoting the formation of cytochrome *c* permeant pores. Opening of the mitochondrial permeability transition pore complex at contact sites of the inner and outer membranes may also cause the release of cytochrome *c* from the inter-membrane space, by allowing entry of water and solutes, inducing mitochondrial swelling and causing the rupture of the less expansive outer membrane. Thus, over the last few years mitochondria have become known for promoting apoptosis and activating caspases by undergoing membrane permeability changes and releasing cytochrome *c*.

There is now considerable interest in the potential to manipulate the mitochondrial regulation of apoptosis for therapeutic gain. For example, the induction of mitochondrial pathways to apoptosis could be used to eliminate diseased cells from the body in cancer chemotherapy (Costantini *et al*., 2000). In the most advanced approach of this type, Genasense (G3139), an antisense oligonucleotide complementary to bcl-2 mRNA, is being applied to down-regulate expression of the bcl-2 antiapoptotic protein on mitochondrial membranes. In clinical trials, Genasense therapy has been shown to be feasible and well tolerated, and to achieve down-regulation of bcl-2 protein in tumour samples, and clinical antitumour responses (Waters *et al*., 2000). Mitochondria are therefore becoming clinically validated targets for cancer chemotherapy. The same mitochondrial pathways are also of interest as drug targets for therapies aiming to prevent membrane permeability changes and the loss of cells from the body (Morin *et al*., 2001).

Auranofin and other gold (I) complexes are well known as anti-arthritic drugs, but also inhibit the growth of cultured tumour cells *in vitro* and many have antimitochondrial activity (reviewed in McKeage *et al*., 2002). Early studies of auranofin showed accumulation of tumour cellular debris in lower channels of flow cytometry DNA histograms and morphological changes (Mirabelli *et al*., 1985). In retrospect this is consistent with an *in vitro* antitumour mechanism involving the induction of apoptosis rather than growth arrest of cycling cells. Although the intracellular targets of auranofin and gold (I) complex are unclear, auranofin has recently become known as a potent and specific inhibitor of thioredoxin reductase (Gromer *et al*., 1998), an enzyme that may play an important role in the redox control of the permeability of mitochondrial membranes (Rigobello *et al*., 1998).

A paper in this issue of the *British Journal of Pharmacology*, by Rigobello *et al*. (2002) provides further linkages between the thioredoxin reductase/thioredoxin system, mitochondrial membrane permeability transition and the biological activities of auranofin and other gold (I) complexes. Auranofin is shown to be a potent inducer of swelling of freshly isolated rat liver mitochondria, indicative of a transition in the permeability status of the mitochondrial membranes. Inhibition of the effect of auranofin on mitochondrial permeability by cyclosporin A and other experimental conditions inferred a mechanism involving the mitochondrial permeability transition pore complex. Permeability changes were shown to occur at auranofin concentrations associated with the selective inhibition of mitochondrial thioredoxin reductase, and with few effects on the mitochondrial electron transport chain or glutathione reductase.

In summary, over the last few years mitochondria have become known for promoting apoptosis by releasing cytochrome *c* and other pro-apoptotic factors during mitochondrial permeability transition or *via* other release mechanisms. There is now considerable interest in the therapeutic potential of manipulating mitochondrial membrane permeability in order to prevent or promote cell death. One of the targets under investigation is the redox control of mitochondrial permeability transition that may depend upon

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the thioredoxin reductase/thioredoxin system. Gold drugs like auranofin are known for inhibiting thioredoxin reductase and for suppressing the growth of cultured tumour cells. Hence, the demonstration by Rigobello *et al*. (1998) that auranofin is a potent inducer of mitochondrial permeability transition, through the inhibition of mitochondrial thioredoxin reductase is a significant finding because it strengthens the links between the thioredoxin reductase/thioredoxin system, mitochondrial permeability transition and the cell killing properties of auranofin and other gold (I) complexes.

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