Spotlight

By Caroline Seydel

Mitochondrial Defect Opens Door to Destruction

Stockwin *et al*.
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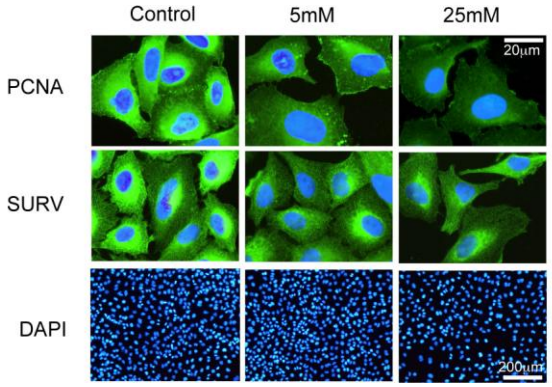
To create therapies that efficiently take out tumors without harming the healthy tissue nearby, researchers continuously seek new ways to exploit features unique to cancer cells. One such feature could be reliance on glycolysis for ATP production, even when ample oxygen is available; researchers have been very interested in agents that hamper glycolysis, and a recent study investigated one such agent, dichloracetate (DCA), for its ability to induce apoptosis selectively in cancer cells. Stockwin *et al.* set out to verify these data, and found that DCA induces apoptosis only at high concentrations and does not specifically target cancer cells.

Cancer cells appear able to generate ATP by glycolysis, rather than oxidative phosphorylation, even in the presence of oxygen. This shift may provide certain advantages, such as switching on pro-survival pathways. DCA stimulates oxidative phosphorylation, by inhibiting the enzyme pyruvate dehydrogenase kinase (PDK). When PDK is limited, less pyruvate is available in the cell to fuel glycolysis. Previous reports have suggested that DCA can act against cancer – a tantalizing proposition, but still controversial.

To weigh in on the debate, Stockwin *et al.* attempted to induce apoptosis in cancer cells and found that it required a very high dosage before apoptosis increased; they also saw no growth inhibition at pharmacologically relevant doses. Next, the team analyzed the effects of DCA on cancer cells and normal cells *in vitro* and found that, although the tumor lines were hyperpolarized relative to the normal cells, DCA depolarized all cell types. Interestingly, however, DCA appears most effective in cells with defects in the electron transport chain. When treated with DCA, these cells must turn to a deficient pathway for ATP production, and perhaps they can't satisfy their metabolic needs. Further work is needed to establish the clinical usefulness of DCA, but combining it with agents that interfere with the electron transport chain could be a promising strategy.



Even at high dose (25 mM) of DCA, cells do not show nuclear condensation indicative of apoptosis