Fatty acid treatment induced cell death is associated with decreasing reduced-to-oxidized glutathione in colon cancer but not breast cancer or non-cancerous cells

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Introduction The shift towards glycolysis rather than mitochondrial oxidative phosphorylation is a hallmark of many cancers (Warburg Effect). Evidence suggests that mitochondrial activation through palmitoylcarnitine (PCarn) incubations in colorectal adenocarcinoma causes cell death, yet non-cancerous cells are resistant. The mechanism of PCarn-induced cancer cell death is unclear, but may be associated with elevated H$_2$O$_2$ associated with activating mitochondrial oxidation of fatty acids. Reduced glutathione (GSH) is the main intracellular antioxidant, and we hypothesize that cancers with low glutathione will be susceptible to PCarn-induced mitochondrial H$_2$O$_2$, whereas cancer with higher glutathione will be resistant.

Methods We exposed HT29 colon adenocarcinoma (GSH: 41μmol/g protein), MCF7 breast adenocarcinoma (GSH: 104μmol/g protein) and non-cancerous CCD841 epithelial cells (GSH: 35μmol/g protein) to PCarn (50μM, 100μM, 200μM) for 48hrs. We measured the effect of PCarn on clonogenicity, real-time mitochondrial H$_2$O$_2$ emission and GSH and oxidized (GSSG) glutathione.

Results There were less cells following incubation of 200μM PCarn in all lines (p<0.05). All PCarn concentrations below 200μM did not decrease cells in non-cancerous CCD841 and cancerous MCF7. HT29s decreased with 50uM and 100uM PCarn (p<0.05). CCD841 had increases in H$_2$O$_2$ emission at 100μM and 200μM PCarn. At 100μM and 200μM PCarn, HT29 increased H$_2$O$_2$ emission, whereas MCF7 had a modest increase at 200μM PCarn (p<0.05). HT29 had decreased GSH relative to GSSG at 50μM, 100μM, 200μM PCarn. Concurrent incubation with the antioxidant N-acetylcysteine blunted the effect of PCarn on cell count in HT29, while the glutathione depleting L-buthionine-sulfoxomine increased sensitivity to PCarn causing a greater reduction in cell count (p<0.05).

Discussion and Conclusion This suggests that PCarn decreases cell number in low-glutathione HT29 but not in high-glutathione MCF7 or non-cancerous CCD841. This relationship may be related to changes in GSH/GSSG caused by H$_2$O$_2$ released during fat oxidation but more work is required to test this possibility.