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Aspirin disrupts acetyl-CoA metabolism in redox-compromised yeast cells – implications for its role in cancer chemoprevention

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Introduction: Acetyl-coenzyme A (acetyl-CoA) drives the energy-generating tricarboxylic acid (TCA) cycle in eukaryotes. Likewise, it plays an acutely important role in satisfying the high energy demands of proliferating cancer cells. Hence, we investigated the effect of aspirin, which has promising cancer-preventive properties, on acetyl-CoA metabolism using yeast cell eukaryotic models, due to their considerable advantages for laboratory research.

Methods: Wild-type Saccharomyces cerevisiae EG103 and manganese-superoxide dismutase (MnSOD)-deficient EG110 yeast strains were grown in aspirin-treated and untreated ethanol medium (YPE). Microarray analysis was performed and validated by RT-qPCR and functional enzyme assays. The response to aspirin, of yeast strains with induced overexpression of alcohol dehydrogenase (ADH2), was assessed by measuring culture growth, cell viability and Adh2 enzyme activity.

Results: We observed that in MnSOD-deficient yeast cells, aspirin significantly impairs transcription and activity of enzymes involved in acetyl-CoA synthesis and its transport to the mitochondria. Moreover, induced overexpression of active Adh2 enzymes, which catalyze the most upstream reaction of acetyl-CoA synthesis during growth in YPE, conferred no benefit to transformed yeast cells, failing to prevent aspirin-induced death.

Conclusion: Aspirin impairs acetyl-CoA metabolism in MnSOD-deficient, redox-compromised yeast cells, causing energy failure linked to critical mitochondrial damage, resulting in apoptosis. Because core cellular processes, including apoptosis, are conserved among yeast and mammalian cells, aspirin possibly behaves similarly in early-stage cancer cells, which manifest downregulated MnSOD and are redox-compromised. Hence, this work may provide further mechanistic insight into aspirin's chemopreventive behaviour, since acetyl-CoA is one of the least-studied targets of aspirin in its propensity to prevent cancer.

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Inhibition of Wnt-supressing genes regulates non-Canonical Wnt signalling in Pituitary Adenomas (PA)

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Introduction: The Wnt developmental pathway has been implicated in tumour development in numerous tissues. Both the canonical and non-canonical Wnt pathways, namely the Wnt-Calcium signalling pathway and the Wnt- planar polarity pathway have also been found de-regulated in a number of cancers (Katoh et al, 2017). Microarray analysis on locally resected PAs revealed strong down-regulation of a number of Wnt antagonists. The aim of this study was to functionally assess the role of WIF1 in PA in relation to the different Wnt signalling pathways using two established cell lines in the presence Wnt3, Wnt4 and Wnt5a ligands.

Methods: Proliferation analysis was used to assess the effect of Wnt pathway antagonists on cell models of PA. Luciferase reporter, hormone secretion and calcium signalling assays were then used to assess which downstream pathways could mediate these effects. Finally, quantitative expression of target genes was used to identify activated pathways that mediate the effects of non/canonical Wnt signalling.

Results: Preliminary findings indicate that Wnt antagonists reduce GH3 and MMQ proliferation. Additionally, the canonical Wnt pathway appears to be completely inactive in these two PA cell models using real-time PCR and reporter assays. Conversely, free calcium fluxes are clearly influenced by the addition of Wnt ligands and co-treatment with Wnt antagonist Wnt Inhibitor Factor 1 (WIF1) represses these calcium fluctuations, with concomitant effects on hormone secretion.

Conclusion: Preliminary data reveals that the Wnt agonists may activate the Wnt-Calcium signalling pathway and WIF1 could play a role in PA by inhibiting specific aspects of this pathway.

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