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Mass spectrometry based metabolic profiles of brain cancer

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Introduction: The author will present highly selective and sensitive LC and GC methods for quantification of intracellular metabolites involved in tricarboxylic acid cycle (TCAs) metabolism including the configuration of the enantiomers of *(L/D)*-2-hydroxyglutaric (2-HG). These are applied to the analysis of brain cancer cells and tissues in order to look for metabolic differences between mutant and wild type cells.

Method: The author has developed two novels LC-MS methods for studying changes in TCA cycle intermediates and their concentrations in cells. The first method focuses on the quantification of metabolites involved in TCA cycle metabolism and the second uses chiral separation for enantiomeric selectivity of (*L/D*)-2-HG and some amino acids associated with TCA reactions. In addition, third method for untargeted metabolites by using GC-MS for studying Fold changes on all brain metabolic profiles.

Results: All isomers and enantiomeric forms of the metabolites were well separated with baseline resolution. Method validation provided limits of detection (LODs) for L/D-2HG ≤3μM (±2SD, Accuracy (%) ±4, %CV ±1.5, STD <5). calibration curves showed good linearity mainly over six orders of magnitude with a correlation coefficient R2 > 0.99.

Conclusions: These methods were developed and applied to the analysis of brain cancer cells and tissues to investigate changes in TCA cycle intermediates identifying selected identifying selected enantionmer concentrations and studying isocitrate dehydrogenase (IDH) metabolon. We describe the methodology used and give examples from the analysis of selected wild-type and modified cancer cell lines which show highly specific enantiomeric changes in 2-hydroxyglutarate and 2-oxoglutarate taking place in mutant cell lines. There were statistically significant differences in TCAs metabolites (*D*-2HG, *L*-HG, 2-oxoglutarate, Oxaloacetate) levels between the IDH^{wt} and $IDH1^{R132H}$ and $IDH2^{R172K}$ cells. There were significant differences in metabolite concentrations seen with IDH inhibition (shRNA, AGI-5198) and also when adding individual TCA cycle metabolites individually into culture media.

Biography

Khalid Al-Qahtani has completed his PhD at the age of 32 years from University Oxford. He was awarded the delegate's choice prize for best young person's poster presentation at the BMSS annual meeting, April 2014. He has published more than 9 papers in peer reviewed journals and is focussing on building a database for cancer metabolomics linking this with changes in metabolic pathways for studying regulation in cancer cells.

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