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Gene Expression Profiling of the cancer chemotherapeutic agent, Cisplatin, compared with its ineffective Isomer, Transplatin

Vincent Murray and Anne M. Galea

School of Biotechnology and Biomolecular Sciences,University of New South Wales, Australia

Cisplatin, cis-diamminedichloridoplatinum(II), is extensively used as a cancer chemotherapeutic agent to treat testicular, ovarian and other cancers. Cisplatin is thought to act by forming covalent adducts with DNA that inhibit DNA replication, RNA transcription and cell division. However, the detailed mechanism of action of cisplatin has yet to be determined. The aim of this study was to investigate the effect of cisplatin on the gene expression profile of human cells using microarrays. In this project, we identified hundreds of human genes that were down-regulated by cisplatin as well as genes that were up-regulated. Several statistical techniques were employed to analyse the microarray data including: the 'Robust Spline' method of intra-array normalisation, calculation of a log-odds of differential expression (B-statistic) for each gene, 'One-sample' and 'two-sample' assessments of differential gene expression, and the EASE expression analysis for classification into gene ontology groups. In particular, we utilised a powerful technique to determine the genes that are crucial for the anti-tumour activity of cisplatin. This technique involved the cisplatin analogue, transplatin, that does not possess any anti-tumour activity but produces DNA adducts. The gene expression profiles of cisplatin and transplatin were compared and the crucial genes that were important in the anti-tumour activity of cisplatin were determined. With this method, 27 genes that were up-regulated and 12 genes that were down-regulated by cisplatin (but not transplatin) treatment of human cells were revealed. Hence we have discovered 39 genes that are uniquely transcriptionally altered by cisplatin but not transplatin. This knowledge could ultimately result in the elucidation of the detailed mechanism of action of the cancer chemotherapeutic agent, cisplatin.

Biography

Vincent Murray obtained his PhD from the National Institute for Medical Research in London. After post-doctoral fellowships at Princeton University and the Cancer Institute, Melbourne, Australia, he was appointed as an academic at the University of NSW, Sydney, Australia. His lab has concentrated on several areas including:- the DNA sequence specificity of drugs used as cancer chemotherapeutic agents; the development of more efficient anti-tumour agents based on cisplatin; and the use of gene chip microarrays to examine the effects of anti-tumours agents on gene expression. He has published over 70 papers in internationally peer-reviewed journals.