From Genome to Metabolome

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Synopsis
With the completion of a growing number of genome sequences attention is now turning to functional genomics, the elucidation of gene function from studies of the effects of gene modification on cellular phenotype. Magnetic resonance has an important role to play in this enterprise, from imaging changes in tissue morphology to spectroscopic measurements of changes in tissue biochemistry. This lecture will deal with MRS analysis of the small-molecule metabolite complement of the cell, the metabolome, and how this might be used, in conjunction with gene modification, to deduce gene function.

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The metabolome, defined by some as the metabolite complement of the cell, is, like the transcriptome and proteome, context dependent, being dependent on the genotype of the cell and the conditions to which it is exposed. However unlike these other two omes, where there is a fairly direct relationship between a gene and its resulting transcript or protein, although this may be complicated by alternative splicing and post-translational modification, there is no simple relationship between genome and metabolome. So how can we use MRS analysis of the metabolome, in genetically modified organisms, to give us information about gene function?

From its development in the early 1970s the advantages of "in vivo NMR" seemed obvious, most notable amongst these were its facility to study biochemistry in intact biological systems, including human beings. However another major benefit, which was in stark contrast to the metabolic techniques of the time, which tended to be target oriented i.e. they measured the levels of single metabolites, was that the spectra contained information about the levels of multiple metabolites. This was true particularly for ^{1}H spectra of tissue and cell extracts and body fluids. MRS techniques were thus able, quickly and easily, to produce metabolite profiles of the cells or tissue of interest. Another key advance was the introduction of multivariate statistical methods to look for patterns amongst these multiple metabolites which were correlated, for example, with the action of a drug (see the lecture by Jeremy Nicholson) or with tumor type (see the lecture by John Griffiths). We can use these techniques in a similar way to look for patterns of metabolite changes that are correlated with changes in gene expression. But how can we use this approach to elucidate the role of genes of unknown function? One possible way might be to use an approach that has been adopted in the analysis of changes in mRNA expression (the transcriptome) using microarrays, i.e. by cluster analysis of linear relationships between variables. Thus mRNAs which show similar patterns of expression are assumed to be transcripts of genes with similar function. If the function of one of the genes is known then the function of the others can be inferred. A similar concept can be applied to metabolome analysis. If gene deletion (or knock-down) mutations produce the same pattern of metabolite changes then this might suggest that they affect a similar area of cellular metabolism, and the function of the unknown genes can be inferred. We are currently testing this hypothesis with a systematic study in the yeast *Saccharomyces cerevisiae*. The advantages of yeast as a model organism in this context are that it is a simple unicellular eukaryote whose genome has been completely sequenced and, most importantly, there are strains available in which each of the ~6000 open reading frames have been deleted. Initial studies suggested that this approach had some potential [1] and the results of current studies will be reported. Studies on the effects of gene modification in mice and tumors will also be discussed.

1. Raamsdonk, L. M. *et al.* Functional genomics via the metabolome: a FANCY approach to characterising mutations with a silent phenotype. *Nature Biotech.* **19**, 45-50 (2001).