The Tumor Metabolome by MRS: Implications for Medical Diagnosis

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Synopsis
Metabolomics, the youngest of the "-omics" sciences, is concerned with the totality of small molecules in an organism. NMR is attractive for investigating metabolic profiles, sub-sets of the metabolome, with minimal sample preparation. Metabolic profile studies are beginning on the effects of gene knockouts, inhibitions or overexpressions in cancer cells in culture as well as in experimental tumors. It is also possible to combine these data with conventional in vivo MRS studies of cancer in patients. Metabolomics can be used in drug discovery programs to indicate novel drug targets and to detect mechanisms of action or unwanted cellular side-effects.

Following the solution of the human and other genomes, a new group of sciences has developed – the "-omics". The youngest of these is metabolomics, the study of the 60,000 or so small-molecule metabolites present in living cells. Just as the genome acts through the proteome, so the proteins act through the metabolome, and we will eventually have to understand human metabolomics in order to complete our knowledge of ourselves. At present, most metabolomic studies have been performed on plants[1] or micro-organisms, and it is here that the first systematic attacks on whole metabolomes are beginning. There has been little systematic work on animal metabolomes, still less in humans. However, the power of this approach in human disease and particularly in drug development is obvious, and many such studies are beginning.

Metabolomics presents several additional challenges beyond those of the other -omic sciences. Instead of a "present or absent" readout we need to know the metabolite concentrations. There is no current method that will simultaneously measure the concentrations of thousands of metabolites but we can measure sub-sets of the metabolome, termed "metabolic profiles"[2]. As studies of the entire metabolomes of micro-organisms such as yeast are completed it will be possible to correlate metabolic profiles of human cells or tissues with them.

High Resolution NMR of tissue extracts is currently a very attractive technique for metabolic profiling as it quantifies a substantial number of metabolites, many of which show variations in disease, without the need for elaborate sample preparation. By using Magic Angle Spinning NMR one can obtain similar information from solid tissue samples – avoiding artifacts induced by the extraction process but risking scrambling of some metabolites by the still-active enzymes. MR spectroscopy, of course, also has the unique ability to monitor metabolites non-invasively *in vivo*. By combining these three NMR methods we can thus obtain metabolic profiles of models of human disease, particularly cancer. All these methods have the advantage that the relative concentrations of metabolites are known with great precision since they are all assayed simultaneously in the same sample, so the effects of perturbations such as gene knock-outs can easily be distinguished[3].

Metabolic profiling studies of genes involved in cancer are typically performed on perchloric acid (for soluble metabolites) or organic solvent (for lipids) extracts of either cultured cells or experimental tumors grown from human cancer cells in rodents. In either case one can study the effect of a gene knockout, suppression (e.g. by RNAi) or overexpression by comparing the metabolic profile of the modified cell (or tumour) with that of a control[3]. This method has great promise for anticancer drug development as many novel chemotherapeutics are intended to inhibit a particular gene or its protein product. Studies on the metabolome will suggest new drug targets, refine the results of high-throughput screens, detect side-effects and also indicate mechanisms of action. Finally, it has been possible for some years to monitor the chemistry of human cancers, both *in vivo* and from biopsies. Another recent advance has been the combination of Metabolomics by MR spectroscopy with proteomics, using small biopsies dissected from a tumor. This last method, like MRS imaging methods *in vivo*, addresses the problem of heterogeneity within tumors.

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3. Griffiths JR, *et al*. Metabolic changes detected by *in vivo* magnetic resonance studies of HEPA-1 wild-type tumors deficient in hypoxia-inducible factor-1β(HIF-1β): evidence of an anabolic role of the HIF-1 pathway. Cancer Res. 62: 688-695 (2002)