Challenges in molecular analysis for individualized cancer therapy

Chemotherapy is an important component of cancer treatment regimes, but cure rates are constrained not only by the limited range of agents currently available and their adverse side effects, but also by variations in individual responses. This variation might be due to individual host factors, such as drug metabolism and clearance, or to resistance (inherent or acquired) of the tumour cells to drugs [1]. Laboratory tests that could predict individual tumour sensitivity or resistance to chemotherapy would be valuable, and would allow optimal choice of therapeutic agents and/or circumvention therapy (although options in both are still somewhat limited). In a recent article in Drug Discovery Today [2], Huang and Sadée review developments in the use of DNA microarrays for prediction of individual sensitivity and for identification of gene expression sets relevant to chemoresponsiveness in cancer patients.

Theoretically at least, DNA microarrays should allow the assessment of resistance-associated genome-wide mRNA expression patterns, which should in turn permit the design of smaller arrays for more economic routine use. However, the data available so far are insufficient for routine application. Practical difficulties will include tumour progression over time and differences in gene expression between primary tumours and metastases; we still do not know the proportion of cases in which surgical or biopsy material (even pure tumour tissue obtained from laser capture microdissection) will predict the overall behaviour of a tumour over the course of the treatment cycle.

The analysis of tumour-derived proteins in blood has its own set of technical and interpretational problems, but has the attraction of allowing repeated sampling and monitoring of response to treatment; recent technical advances might make this approach more feasible [3,4]. Somewhat surprisingly, well-controlled studies have shown the presence in serum of tumour-derived mRNA for some genes [5]; the possible diagnostic potential of these findings is not yet clear. It should also be remembered that resistance to therapy might relate to physical factors, such as poor vascularity and associated poor supply of drug and oxygen, and it is not clear to what extent microarrays and related techniques might detect such mechanisms. The current range of therapeutic responses to such diagnoses is also unclear. Indeed, in spite of the impressive technical advances in ‘chemogenomics’, the collection of agents effective against, for example, cancers of the lung, colon, brain and prostate is small. The therapeutic options for dealing with multidrug-resistant tumours, whether resistance is inherent or acquired, are also severely limited. The immediate benefits arising from DNA microarray and proteomic analysis of tumours could, therefore,

References

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