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Detection of the ATP binding cassette transporter genes in human cancers with multiple drug resistance

Anticancer drug resistance developing after prolonged exposure to a drug is a common and a significant clinical problem. The mechanisms of resistance, characteristically to multiple drugs, are multifactorial, and involve alteration of detoxification processes, apoptosis, DNA repair, drug uptake, and others. Overexpression of ATP-binding cassette (ABC) transporter genes, which include *ABCB1* (*MDR1*), *ABCC1* (*MRP1*), and *ABCG2* (*MXR* and *BCRP*), have been recognized as a major cause of acquired multidrug resistance (MDR) in many human cancers. There are at least 10 ABC transporters capable of transporting relevant drugs that have been identified in human cancers or tissues. As a result of the close correlation between the overexpression of ABC transporters and multidrug resistance, detecting their overexpression would promote a better understanding of the mechanisms underlying multidrug resistance, and clearly would be useful in guiding anticancer chemotherapies. Techniques currently employed for this purpose are mainly molecular methods including PCR, comparative genomic hybridization (CGH), and microarray assay. These detection methods, especially the conventional microarray assay, are cumbersome and need special knowledge to interpret the results. Thus, they are not suitable for routine application. To simplify the detection and the result analysis, Gillet *et al*¹ recently described a low-density DNA microarray (termed DualChip human ABC), which contained 38 gene probes of the ABC transporter family. Overexpression of the ABC transporters in a wide range of human cancer cell lines originated from leukemia and a variety of solid tumors, using this method evidently correlated well with their multidrug resistance status. The low-density microarray is a simpler and easier method, yet

comprehensive enough to detect overexpression of all possible ABC transporter genes; and hence might be a useful diagnostic test in the clinical setting.

The usefulness of this simple test, however, relies on an assumption that most, if not all, multidrug resistance is associated with the overexpression of the ABC transporters, regardless of the origin of the cancer. In human hepatocellular carcinoma (HCC), the overexpression of *MDR1* or P-glycoprotein correlates well with its resistance to doxorubicin. It is still unclear, however, if the overexpression of *MDR1* is the only or the major mechanism contributing the resistance to this particular drug. In this issue of *Laboratory Investigation*, Pang *et al*² provided evidence that overexpression of *MDR1* gene was a major genetic event acquired in five HCC cell lines resistant to doxorubicin treatment. Comparative Genomic Hybridization (CGH) revealed that the over-representations of regional chromosome 7q11–q21 coincided with the location of the *MDR1* gene. Microarray assay and RT-PCR confirmed the overexpression of *MDR1* in those five cell lines. In addition, cDNA microarray also identified an aberrant expression of a topoisomerase gene, *TOP2A*, a known target for the anticancer-effect of doxorubicin. This finding suggests the possibility of multiple complimentary pathways leading to multidrug resistance in HCC. One may posit that detection or prediction of resistance to doxorubicin using the simpler low-density microarray may greatly help in the anticancer chemotherapy of patients with HCC.

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References

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- 2 Pang E, Hu Y, Chan KY-Y, *et al*. Karyotypic imbalance and differential gene expression in the acquired doxorubicin resistance of hepatocellular carcinoma cells. *Lab Invest* 2005;85:664–674.