A mutation in exon 7 of the human cytochrome P-4501A1 gene as marker for sensitivity to anti-cancer drugs?

Sir

One of the major problems in the anti-cancer drug treatment of patients with malignant tumours is the development of anti-cancer drug resistance. Evidence is accumulating that anti-cancer drug resistance is a multifactorial phenomenon, and (a combination of) several different mechanisms may be responsible for the drug-resistant phenotype, such as an altered expression of drug-metabolizing enzymes in tumour cells. Among other changes, compared with the parent MCF-7 WT (wild type) cells (Davies et al, 1996), low inducibility of cytochrome P-4501A1 (CYPIA1) and elevated expression of glutathione S-transferase have been detected in multidrug-resistant MCF-7 Adr breast cancer cells (Ivy et al, 1988). Many anti-cancer drugs require prior metabolic activation by CYP enzymes and, consequently, low CYP activities could result in cells being insensitive to these agents (LeBlanc and Waxman, 1989; Chen et al, 1996). On the other hand, enhancement of detoxification of the anti-cancer drugs by glutathione S-transferases may also result in less efficient cytotoxic damage of tumour cells (Hayes and Pulford, 1995).

A point mutation in exon 7 of the human CYPIA1 gene has been described which results in an isoleucine to valine substitution (Hayashi et al, 1991) and leads to an enhancement of CYPIA1 enzyme activity (Crofts et al, 1994); this can lead to a more efficient activation of anti-cancer drugs (LeBlanc and Waxman, 1989). This phenotype is present in the drug-sensitive MCF-7 WT breast cancer cells (Figure). The MCF-7 Adr multidrug-resistant cells, however, possess the non-mutated CYPIA1 genotype (Figure 1). This may explain the observed CYPIA1 inducibility of the MCF-7 WT cells, which is absent in the MCF-7 Adr cell line (Ivy et al, 1988). As discussed above, deficient (inducibility of) CYPIA1 enzyme activity could lead to failure in activation of anti-cancer drugs and thus contribute to drug resistance.

In conclusion, it may be of importance to investigate a possible relationship between the mutation in exon 7 of the CYPIA1 gene (which is present in about 17% of Dutch Caucasians) and clinical sensitivity to particular (regimens of) anti-cancer drugs. The rapid polymerase chain reaction method for detection of this polymorphism, as applied above, could then be of value in selecting patients for chemotherapy.

WHM Peters and HMJ Roelofs
Department of Gastroenterology,
St Radboud University Hospital,
PO Box 9101, 6500 HB Nijmegen,
The Netherlands

REFERENCES


