Cytochrome P450 CYP1B1: a novel mechanism of drug resistance.

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4.7 CYTOCHROME P450 CYP1B1: A NOVEL MECHANISM OF DRUG RESISTANCE

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CYP1B1 is a member of the xenobiotic metabolising cytochrome P450 enzymes. This superfamily of constitutive and inducible haemoproteins are central to the oxidative metabolism of wide range of substrates including endogenous compounds involved in cell signaling, environmental carcinogens and anti-cancer drugs. Our previous studies have shown CYP1B1 protein to be to be expressed at significant levels only in tumour tissue being specifically localised to the tumour cells[1]. Our current studies are investigating CYP1B1 activity in a number of human tumours and its role in the metabolism of anti-cancer drugs in these tumours.

CYP1B1 activity can be measured by ethoxyresorufin-o-deethylase activity using the EROD assay. Our initial findings investigating ethoxyresorufin-o-deethylase activity indicate that CYP1B1 is active in a number of human tumours (100–800 fmol/min/mg of protein). Moreover, this activity can be inhibited by co-incubation with the CYP1B1 inhibitor alpha-naphthoflavone. The over-expression of active CYP1B1 in human tumours is important possibly as a mechanism of drug resistance. Several cytochrome P450 enzymes are capable of the bio-transformation of a number of anti-cancer drugs. We have recently shown several of these drugs to be substrates for CYP1B1, and our in vitro studies are now providing evidence for a functional role for CYP1B1 in drug resistance.

Using the MTT assay the cytotoxic profile of CYP1B1 with a number of anti-cancer drugs is currently being evaluated with a Chinese hamster ovary cell line known to express active CYP1B1 and a parental non-expressing CYP1B1 cell line. Our results show that on exposure to docetaxel a significant ($P = 0.03$) increase in resistance to the cytotoxic effects of docetaxel was observed between the parental cell line ($IC_{50} = 22$ nM) and the cell line expressing CYP1B1 ($IC_{50} = 100$ nM). In addition, co-incubation with alpha-naphthoflavone, reversed the resistance to docetaxel in the CYP1B1 expressing cells. The resistance to the cytotoxic effects of docetaxel in those tumours expressing CYP1B1 may have important clinical implications. It is also likely that the over-expression of active CYP1B1 is a general mechanism of drug resistance. Moreover, the ability to overcome this drug resistance with the appropriate CYP1B1 inhibitors could be developed clinically.

1. Murray GI, Melvin WT, Greenlee WF, Burke MD. 2001 *Annu Rev Pharmacol Toxicol* **41** (in press).