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Multidrug-Resistance Transporters

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1. INTRODUCTION

Approximately half of the one million new cancer cases annually in the United States will be treated with systemic chemotherapy. Unfortunately, this therapy will fail for the majority of these patients due to resistance of the tumors to the drugs. There are numerous mechanisms through which tumors become resistant to drugs; this chapter is limited to the action of a set of proteins known as the multidrug resistance (MDR) transporters. Following a brief discussion of the structure and function of the multidrug resistance transporters, this chapter focuses on the role of these proteins in the absorption and disposition of drugs and the potential consequences of modification of their function.

Several MDR transporters have been identified and characterized and the list of these proteins continues to grow as investigators seek new drug transporters. The first identified and best-characterized MDR transporter is the P-glycoprotein (p-gp) encoded by the MDR1 gene (Endicott and Ling, 1989; Borst et al., 1993; Gottesman and Pastan, 1993; Germann, 1996). This P-gp is an active drug export pump which mediates the resistance to a large group of diverse compounds. P-gp is widely expressed in many organs, leading to the hypothesis that the physiological role of this protein is a protective mechanism against xenobiotics and endogenous metabolites. Recent investigations also suggest that P-gp-mediated transport of both parent drug and metabolites are important in absorption and disposition of drugs in tissues which express this protein such as the liver, kidney, and
intestine (Cavet et al., 1996; Mayer et al., 1996; Su and Huang, 1996; Wacher et al., 1996). Alternative multidrug-resistance transporters such as MRP1, the multidrug-resistance-related protein, have been identified in multidrug-resistant cells which do not express P-gp (Cole et al., 1992). Additional MRP family members have recently been identified and are adding to our understanding of drug resistance, absorption, and disposition. The MRP1 and MRP2 (cMOAT) transporters secrete conjugated compounds and organic anions (Müller et al., 1996a, b). Both the MDR and MRP proteins interact with numerous compounds, suggesting that these transporters may affect the pharmacokinetics of many drugs in addition to those used in cancer therapy.

2. MDR GENE FAMILY

The phenomenon of drug resistance has been investigated for nearly 30 years (Biedler and Riehm, 1970; Biedler, 1994). During this time, experiments in several laboratories have resulted in the identification, isolation, and characterization of P-glycoprotein, a major drug transporter, and the multidrug-resistance genes which encode it. Ling and co-workers observed that multidrug-resistant Chinese hamster ovary cells overexpress a cell surface protein which was subsequently named P-glycoprotein for its role in affecting the permeability of cytotoxic drugs (Juliano and Ling, 1976; Kartner et al., 1983). Production of a monoclonal antibody, C219, against P-gp and subsequent screening of a cDNA expression library constructed from mRNA isolated from a multidrug-resistant cell line led to the isolation of a cDNA, pCHP1, which partially encodes a hamster P-gp (Kartner et al., 1985; Riordan et al., 1985). Use of this cDNA as a probe on Southern blots foretold the subsequent identification of the MDR multigene family. A molecular cloning approach employing the technique of in-gel renaturation and assignment of fragments to their homologous regions permitted Gros and co-workers to isolate a 120-kb domain from multidrug-resistant hamster cell lines and to demonstrate that the hamster mdr gene resides within that segment (Gros et al., 1986c). Isolation of human carcinoma cell lines which were independently selected but cross-resistant to colchicine, vinblastine, and adriamycin led to the isolation of the human MDR gene and subsequently to the full-length cDNA (Roninson et al., 1986; Shen et al., 1986; Ueda et al., 1987b). Screening of a mouse cDNA library constructed from a drug-sensitive cell line with the hamster mdr sequences led to the isolation of the first mouse mdr gene and demonstrated that expression of the wild-type protein, and not a mutant, is sufficient to acquire a drug-resistant phenotype (Gros et al., 1986a).

Subsequently additional members of the mdr gene family have been isolated