Molecular determinants of MRP1/ABCC1 expression and transport

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The 190-kDa Multidrug Resistance Protein 1 (MRP1/ABCC1), first cloned by our group in 1992 from a drug resistant lung cancer cell line (Cole *et al.*, 1992), is a member of the 'C' branch of the ATP-binding cassette (ABC) superfamily of polytopic membrane proteins. MRP1 belongs to a subset of ABCC proteins comprising five domains: 3 membrane spanning domains (MSDs), containing 5, 6, and 6 transmembrane (TM) α-helices, respectively, and two cytoplasmic nucleotide binding domains (NBDs) (Leslie, Deeley & Cole, 2005). In addition to its drug efflux properties, MRP1 mediates the ATP-dependent transport of a broad array of exogenous and endogenous organic anions, including the cysteinyl leukotriene C4 (LTC4), an eicosanoid derivative that mediates inflammation and is involved in human bronchial asthma (Leslie, Deeley & Cole, 2005; Cole & Deeley, 2006). Thus MRP1 plays important roles in the cellular efflux of physiologically important signalling molecules as well as participating in the tissue disposition and elimination of drugs and their conjugated metabolites (Leslie, Deeley & Cole, 2005; Cole & Deeley, 2006). A substantial number of individual amino acids in different regions of MRP1 have been demonstrated to be critical for its substrate specificity and transport activities, as well as its stable expression in the plasma membrane. While some mutation-sensitive residues are found in the cytoplasmic loops (CLs) of MRP1, many are in, or are closely associated with, the TM helices of the core region of the transporter that likely forms part of a substrate/inhibitor binding pocket and/or substrate translocation pathway through the membrane. Particularly crucial for LTC4 binding and transport are Lys332 in TM6 (Haimeur, Deeley & Cole, 2002; Haimeur *et al.*, 2004; Maeno *et al.*, 2009). Current evidence suggests that TM6-Lys332 is involved in the recognition of the γ-Glu portion of LTC4 and other substrates/modulators containing GSH or GSH-like moieties (Maeno *et al.*, 2009). These and other data indicate that MRP1 has at least three substrate binding pockets. In contrast, residues involved in the proper assembly and/or structural stability of MRP1 have thus far been found in the CLs that mediate the coupling of the ATPase activity at the NBDs to the substrate translocation through the MSDs. Thus non-conservative substitutions of several ionizable amino acids in CL7 in MSD1 (Conseil, Deeley & Cole, 2006) and CL5 in MSD1 (Iram & Cole, 2010) profoundly diminish the levels of MRP1 at the plasma membrane of mammalian cells. Many (but not all) of these residues are predicted by homology models of MRP1 to be located in an environment where they could form bonding interactions with residues in the opposing NBD. We propose that these and other interdomain interactions are critical to the proper assembly and trafficking of MRP1 to the plasma membrane of mammalian cells.

Cole SP, Bhardwaj G, Gerlach JH, Mackie JE, Grant CE, Almquist KC, Stewart AJ, Kurz EU, Duncan AM, Deeley RG. (1992) *Science* **258,** 1650-4.

Cole SP, Deeley RG. (2006) *Trends Pharmacological Sciences* **27,** 438-46.

Conseil G, Deeley RG, Cole SP. (2006) *Journal of Biological Chemistry* **281,** 43-50.

Leslie EM, Deeley RG, Cole SP. (2005) *Toxicology and Applied Pharmacology* **204,** 216-37.

Haimeur A, Conseil G, Deeley RG, Cole SP. (2004) *Molecular Pharmacology* **65,** 1375-85.

Haimeur A, Deeley RG, Cole SP.(2002) *Journal of Biological Chemistry* **277,** 41326-33.

Iram S, Cole SPC. (2010) unpublished observations

Maeno K, Nakajima A, Conseil G, Rothnie A, Deeley RG, Cole SP. (2009) *Drug Metabolism and Disposition* **37,** 1411-20.

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