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Letter to the editors

A physiological function for multidrug-resistant membrane glycoproteins: a hypothesis regarding the renal organic cation-secretory system

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Sirs,

Multidrug resistance (MDR: pleiotropic drug resistance) as defined by Gerlach et al. [5] is a "phenotype whose predominant feature is resistance to a wide range of structurally unrelated cytotoxic compounds, many of which are anticancer agents." MDR is characterized by the amplification of genes encoding the synthesis of high-molecular-weight membrane glycoproteins. The sequence of one such gene in mouse and human cells has recently been determined (i.e., the MDR1 gene) [3, 4, 6]. The inferred primary structure of the protein encoded by the MDR1 gene (designated gp 170) bears striking homology with several bacterial-transport systems. By analogy with the bacterial transport proteins, it is postulated [1] that several drug-binding proteins exist in excess in the cytoplasm. These proteins would function to "trap" drugs of a given class and present them to gp 170. If gp 170 is the limiting component, increasing its level in multidrug-resistant cells would result in increased rates of transport of several drugs. The "amplitifcation" of the gp 170 gene would account for the pleiotropic drug resistance, as is suggested by experimental observations.

These and related findings strongly suggest that the basic mechanism underlying MDR is the enhanced active transport (outward) of the drugs by this system. In effect, therefore, the MDR phenomenon is amplification of a pleiotropic drug-transport system in cell membranes. Renal pharmacologists have been studying pleiotropic active drug transport – the organic cation- and anion-secretory systems in mammalian kidneys – for many years [12]. These renal secretory systems are not well defined in terms of the structures of the carrier proteins involved. It is known that the secretion of large numbers of structurally unrelated organic anions (e.g., methotrexate, penicillin G) and cations (e.g., morphine, *N*-methyl nicotinamide) occurs. Relatively specific inhibitors of these systems are probenecid (anion system) and cimetidine (cation system). It is hypothesized that the highly conserved gp 170 (or related protein) is the carrier for the renal organic cation system. The drugs for which MDR has been demonstrated are generally lipid-soluble, organic cations [2], and recent studies using antibodies toward the gp 170 protein [11] have localized the gp 170 to that portion of the nephron in which the secretion of organic cations occurs (namely, proximal tubule cells). Further, the protein resides in the brush border membrane, the site of predicted active transport of organic cations [9]. Specifically, organic cations should enter proximal tubule cells via the peritubular membrane down their electrochemical gradient; however, energy must be expended for their transport from the cell to the lumen. Localization of the gp 170 to apical membranes of other epithelia, such as pancreatic ductal cells, colon, jejunum, and liver, has also been observed [11]. Some of these tissues demonstrate organic anion- and cation-transport functions similar to that in the kidney. Other tissues for which such drug transport has been demonstrated include choroid plexus and anterior uvea, and localization of the gp 170 protein in these tissues would be of interest.

A major distinction in transport of drugs between the tissues described above is that the active transport of a substance in MDR is across the cell membrane, whereas renal secretion involves the active transport of a substance across an epithelial cell barrier (the proximal tubules). At least one paradigm exists in which the same protein performs two similar purposes. Specifically, the enzyme Na-K ATPase appears to be largely responsible for maintaining low intracellular sodium concentrations by active extrusion of this cation across cell membranes and for the renal transepithelial reabsorption of sodium, the major work load of the mammalian kidney [10].

Using classic protein purification techniques, considerable effort has been expended in attempts to purify the renal organic cation carrier [7, 8], with only limited success. The above hypothesis suggests an alternative means whereby the structure of this particular carrier might be ascertained. Also, if the analogy drawn for the gp 170 and bacterial permeases [1] proves operative, identification of the intracellular proteins recognizing "classes" of drugs should also be a major focus of future research.

References

1. Ames GFL (1986) The basis of multidrug resistance in mammalian cells: homology with bacterial transport. Cell 47: 323
2. Beck WT (1987) The cell biology of multiple drug resistance. Biochem Pharmacol 36: 2879
3. Chen CJ, Chin JE, Ueda K, Clark DP, Pastan I, Gottesman MM, Roninson IB (1986) Internal duplication and homology with bacterial transport proteins in the mdrl (*P*-glycoprotein) gene from multidrug-resistant human cells. Cell 47: 381
4. Gerlach JH, Endicott JA, Juranka PF, Henderson G, Sarangi F, Deuchars KL, Ling V (1986) Homology between *P*-glycoprotein and a bacterial haemolysin transport protein suggests a model for multidrug resistance. Nature 324: 485

5. Gerlach JH, Kartner N, Bell DR, Ling V (1986) Multidrug resistance. Cancer Surv 5: 25
6. Gros P, Croop J, Housman D (1986) Mammalian multidrug resistance gene: Complete cDNA sequence indicates strong homology to bacterial transport proteins. Cell 47: 371
7. Holohan PD, Pessah NI, Warkentin D, Ross CR (1976) The purification of an organic cation-specific binding protein from dog kidney. Mol Pharmacol 12: 494
8. Holohan PD, Pessah NI, Pessah IN, Ross CR (1979) Reconstitution of *N*-methylnicotinamide and *p*-aminohippuric acid transport in phospholipid vesicles with a protein fraction isolated from dog kidney membranes. Mol Pharmacol 16: 343
9. Kinesella JL, Holohan PD, Pessah NI, Ross CR (1979) Transport of organic ions in renal cortical luminal and antiluminal membrane vesicles. J Pharmacol Exp Ther 209: 443
10. Nelson JA (1970) The role of Na and K ATPase in the renal reabsorption of Na (PhD dissertation). The University of Texas Medical Branch, Galveston
11. Thiebaut F, Tsuruo T, Hamada H, Gottesman MM, Pastan I, Willingham MC (1987) Cellular localization of the multidrug-resistance gene product *P*-glycoprotein in normal human tissues. Proc Natl Acad Sci USA 84: 7735
12. Weiner IM (1971) Excretion of drugs by the kidney. Springer, Berlin Heidelberg New York (Hdb Exp Pharmacol 28: 328)

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