Membrane Transport of Chemotherapeutics and Drug Resistance: Beyond the ABC Family of Exporters to the Role of Carrier-mediated Processes

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Chemotherapeutic agents almost invariably require, as a prerequisite for activity, the ability to traverse the tumor cell membrane to interact with, and perturb the activity of, intracellular targets. Transport often precedes the interaction between drugs and intracellular enzymes and may regulate the rate and extent of metabolism to cytotoxic or cytostatic derivatives that achieve the pharmacological effect. Lipophilic drugs readily enter cells by passive diffusion. However, many drugs are hydrophilic, diffuse through lipid membranes very slowly, and can only enter cells by parasitizing a transporter normally used for physiological substrates. Indeed, even transmembrane flows of lipid-soluble compounds, such as cholesterol and long chain fatty acids, can be augmented by specific membrane transporters.

Early in the era of modern cancer chemotherapy, transport across cell membranes by carrier-mediated processes was recognized as an important determinant of drug activity and resistance. This was first characterized for the antifolate, methotrexate, transported by the carrier for reduced folates (3) and subsequently implicated in clinical resistance (4–6). Likewise, phenylalanine mustard activity was shown to be dependent on transport mediated by amino acid carriers (7). But over the past 2 decades, the major focus has been on the ABC superfamily of exporters, in particular, the p-glycoproteins responsible for the multidrug resistance phenotype that produces pleiotropic resistance to multiple classes of agents (anthracyclines, Vinca alkaloids, taxanes, etc.) with very different chemical structures and mechanisms of action (8, 9). These transporters couple the hydrolysis of ATP to the transport of drugs, unidirectionally, out of cells. p-Glycoprotein can capture and eject drug molecules to interact with, and perturb the activity of, intracellular enzymes and may regulate the rate and extent of metabolism to cytotoxic or cytostatic derivatives that achieve the pharmacological effect. Lipophilic drugs readily enter cells by passive diffusion. However, many drugs are hydrophilic, diffuse through lipid membranes very slowly, and can only enter cells by parasitizing a transporter normally used for physiological substrates. Indeed, even transmembrane flows of lipid-soluble compounds, such as cholesterol and long chain fatty acids, can be augmented by specific membrane transporters.

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2 The abbreviation used is: MRP, multidrug resistance-associated protein.
a monoclonal antibody to a widely expressed equilibrating nucleoside carrier (hENT1). This reagent makes possible assessment of transporter expression in tumor cells, as distinguished from vascular endothelial or other normal stromal cells present in tumor tissues that express this carrier. The article demonstrates low-carrier expression in 25–30% of the breast cancers studied as compared with normal breast epithelial cells. This was independent of clinical stage, histopathological grade, and estrogen and progesterone receptor status. Hence, resistance by this mechanism may limit drug activity across the spectrum of disease stages. As antibodies to additional nucleoside transporters become available, the potential for developing a more complete understanding of the pharmacological impact of nucleoside carriers on antimitabolite activity will be enhanced.

There is increasing emphasis on molecular characterization of tumors; in particular, the quantitation of proteins that regulate the cell cycle and apoptosis and the application of high-throughput techniques, such as DNA microarrays, to identify genes that are determinants of response to treatment modalities. It is, however, equally important and now possible to characterize, quantitate, and understand the importance of those critical prerequisites of the drug-cell interaction, such as carrier-mediated transport, that must be achieved before downstream events associated with cell death can occur. This issue now assumes greater importance as new nucleoside antimitabolites enter the clinics, some, like gemcitabine, with activities that extend beyond the hematological malignancies to the more common solid tumors (17). The same is true for new-generation antifolates currently in clinical trials that are direct inhibitors of purine and/or thymidylate synthesis (18). There is now a wealth of new information from laboratory and clinical studies on the molecular basis for antifolate drug resistance and cross-resistance patterns associated with impaired transport mediated by the reduced folate carrier along with the availability of reagents to assess carrier expression (4–6, 19–21). Whereas the focus here is on carrier-mediated processes, it is important to note that there is little information on the importance of MRPs as a resistance mechanism in clinical regimens, and much more work is required to fully understand the role of p-glycoproteins in clinical resistance.

There are other reasons for investigators to be alert to the potential importance of the Major Facilitator Superfamily of transport carriers. New combinatorial chemistry approaches are now widely applied to identify small molecules that inhibit specific protein targets. One critical determinant of the activity of these agents in intact cells will be their ability to penetrate the tumor cell membrane. Molecules that enter cells rapidly, although structurally unique, may nonetheless be substrates for well-characterized or obscure carriers, and the properties of these transporters may turn out to be important determinants of cytotoxicity, selectivity, and resistance. For those molecules that have limited cellular permeability, attempts will be made to modify structures to enhance lipid solubility and passive diffusion into cells. However, another approach can be to couple these agents to substrates of known carriers with relaxed structural requirements. These complexes will then serve as vehicles to achieve transport into cells followed by release of the active agent by endogenous enzymes. This approach may have particular potential for enhancing transepithelial transport, in particular intestinal absorption, to make more chemotherapeutic agents bioavailable by the oral route. Transporters that might be harnessed for this purpose could include, among others, the oligopeptide, anionic, or cationic carriers (22–25).

References
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