P-glycoprotein and Tumor Progression

Samuel Benchimol, Victor Ling*

Development of resistance to chemotherapy is a hallmark of many advanced human cancers. The molecular basis of clinical resistance is not well understood. Over the past 15 years, a number of different molecular mechanisms of resistance to anticancer drugs have been identified in many cell lines.

One mechanism involves the increased expression of the plasma membrane P-glycoprotein (Pgp), which is thought to function as an adenosine triphosphate-dependent efflux pump that reduces the cellular accumulation of a wide range of chemotherapeutic drugs (1-2). Studies (1-3) of biopsy samples from patients have demonstrated that elevated levels of Pgp can be detected in tumors of every histologic type. In addition, numerous studies have been conducted to determine whether or not Pgp expression is associated with clinical outcome. The conclusions of such studies have varied; however, the basis for these differences in conclusions may be attributed in part to differences in the techniques used for detecting Pgp in tumor samples. Nevertheless, several studies (3-7) on leukemias, lymphomas, and some childhood solid tumors have demonstrated a strong association between the detection of Pgp in tumor samples and poor response to chemotherapy. The observed association between Pgp expression and poor outcome in the clinical studies raises the question of how changes in Pgp expression are regulated in malignant cells. At present, mechanisms involved in the regulation of Pgp expression in human cancers and in normal human tissues are unknown.

In this issue of the Journal, Schneider et al. (8) address the question of whether or not Pgp expression was associated with p53 mutation and HER-2/neu expression in a number of human gynecological tumors. The rationale for their study was based on the hypothesis that MDR1 gene expression is regulated by p53 (8). Studies (1-5) of biopsy samples from patients have demonstrated that elevated levels of Pgp can be detected in tumors of every histologic type. In addition, numerous studies have been conducted to determine whether or not Pgp expression is associated with clinical outcome. The conclusions of such studies have varied; however, the basis for these differences in conclusions may be attributed in part to differences in the techniques used for detecting Pgp in tumor samples. Nevertheless, several studies (3-7) on leukemias, lymphomas, and some childhood solid tumors have demonstrated a strong association between the detection of Pgp in tumor samples and poor response to chemotherapy. The observed association between Pgp expression and poor outcome in the clinical studies raises the question of how changes in Pgp expression are regulated in malignant cells. At present, mechanisms involved in the regulation of Pgp expression in human cancers and in normal human tissues are unknown.

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lack of association in B-cell chronic lymphocytic leukemia. If p53 were the sole regulator of MDR1 expression, one might reasonably have expected to see low levels of MDR1 protein in tumor cells containing wild-type p53 protein (p53-mediated repression), higher levels in tumor cells expressing no p53 protein (lack of p53-mediated repression), and even higher levels in tumor cells expressing missense mutant p53 protein (mutant p53-mediated stimulation).

Regulation of Pgp expression in tumor cells is likely to be complex. In cultured cell lines selected for drug resistance, elevated Pgp expression can be mediated via gene amplification, increased messenger RNA (mRNA) content, or increased protein levels (18). At these levels, Pgp expression appears to be highly responsive to modulation by various intrinsic and extrinsic factors.

Pgp expression is responsive to a variety of stimuli. For example, in renal carcinoma cell lines, an increase in Pgp mRNA expression was observed after heat shock or sodium arsenite treatment; this increase was thought to be mediated via an increase in transcriptional activity (19). Treatment of colon carcinoma cell lines with sodium butyrate or treatment of neuroblastoma cell lines with retinoic acid appears to result in an increased level of mRNA without an increase in transcriptional activity (20,21). Other investigators have observed an increase in Pgp protein expression in cell lines treated with repeated doses of X radiation. Such treatment did not result in an increase in the level of mRNA but rather increased the level of the protein (22). These are only a few examples of studies that have shown that Pgp expression is highly responsive to a variety of factors. It is likely therefore that in a complex heterogeneous tumor cell environment, different factors may affect Pgp expression.

Mutant p53 is often identified indirectly on the basis of overexpression in immunohistochemical assays or by single-strand conformation polymorphism (SSCP) DNA analysis directed at exons 5 to 8 where most mutations reside. Conversely, lack of immunohistochemical staining and/or absence of abnormal band patterns by limited SSCP analysis is used to identify wild-type p53.

Conclusions derived from the assays described above must be considered provisional until they are confirmed by complete sequence analysis. Tumors containing wild-type p53 alleles present a further challenge. Is the gene expressed, and is the p53 protein functional? For example, in cervical carcinomas, many of which contain and express human papillomavirus (HPV) sequences, the HPV E6 protein binds p53 protein and promotes its degradation through a ubiquitin-dependent pathway. Hence, HPV E6 protein effectively reduces the intracellular level of p53 protein and, in so doing, interferes with its function. A number of other viral (e.g., simian virus 40 large T antigen and adenovirus E1B) and cellular proteins (e.g., Mdm2) have been shown to bind wild-type p53 protein, resulting in functional inactivation (23). It would be of interest to determine the HPV status and the functional state of p53 protein in the eight cervical tumors studied by Schneider et al. (8), seven of which expressed MDR1 protein.

It is noteworthy that Schneider et al. (8) observed a statistically significant association between the expression of the HER-2/neu gene and Pgp in mammary carcinomas. The basis for this connection is not known; however, it would be of interest to determine if both the HER-2/neu and Pgp genes are regulated by a common mechanism. Schneider et al. found the coexpression of Pgp and HER-2/neu gene in a subgroup of aggressive, locally advanced, inoperable mammary carcinomas; however, they did not find a statistically significant association in the operable tumors. This finding is consistent with Pgp overexpression being associated with an advanced tumor phenotype. A similar conclusion has been made by Weinstein et al. (24) in human colon cancer and by Bradley et al. (25) in rat liver cancer.

One may speculate as to what role Pgp might play in highly malignant cancers. There is little controversy that an elevated expression of Pgp provides the tumor cells with a growth advantage during treatment with lipophilic anticancer drugs. However, since Pgp is able to transport a wide variety of other substrates, including hormones, peptides, and ions (1,2), it is possible that the export of some as yet unidentified Pgp substrates may provide a growth advantage to malignant cells expressing high levels of Pgp. For example, it is possible that Pgp may be implicated in the secretion of autocrine growth factors or factors involved in stimulating angiogenesis. Current studies (4,5,7,26) to inactivate Pgp function using chemosensitizing agents (multidrug resistance-reversing agents) may provide further insights into the postulated dual role of Pgp in chemotherapy and in tumor progression.

References

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Philip Pizzo, M.D.
Chief, Pediatric Branch
National Cancer Institute
Bethesda, Maryland 20892
(301) 402-0696
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