What does Multidrug Resistance (MDR) Expression Mean in the Clinic?

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Abstract

For 15 years, an overflowing literature has been published about MDR-1 gene expression in tumor cell lines and in cancerous tissues at various stages of disease and treatment (chemotherapy-naive, during treatment and at relapse). However, the clinical significance of this particular feature, if it seemed obvious in the 1980s as a factor responsible for the development of chemoresistance, is currently reconsidered. MDR-1 gene expression seems to be, at least in some instances, a hallmark of tumor cell aggressiveness and of chemoresistance rather than its cause, the mechanisms of which are probably far more complex. The failure of MDR reversal trials might result from the misunderstood or overvalued role of MDR expression in cancer cells rather than from a lack of control of pharmacological parameters.

This review summarizes recent data and hypothesis about the expression of P-170 and its clinical significance in some important human tumor types, suggesting that it should rather be considered in the future as an adverse prognostic factor. The Oncologist 1996;1:151-158

Introduction

The development of chemoresistance is a major problem in medical oncology, limiting the success of multidrug regimens in most advanced solid tumors and in some hematological malignancies. In the clinic, the most studied form of chemoresistance is undoubtedly the one mediated by the P-170 glycoprotein expressed by a broad range of human tumors at presentation or at relapse [1].

Although MDR-1 gene expression has been extensively studied in vitro from its cloning in the mid-80s, when expressed in tumor specimens its clinical relevance remains unclear and poorly investigated [2-5]. Indeed, in contrast to the experimental situation where the number of study variables is minimal, the phenomenon of drug resistance in human tumors is widely dependent on drug pharmacokinetics or tumor accessibility, and not only on altered cellular characteristics such as P-170 expression, making an isolated parameter hardly evaluable. Likewise, it is unclear whether the disappointing results of most multidrug resistance (MDR)-reversal clinical trials are to be understood as a failure of their basic theoretical concept or as a poor control of numerous intricate variables able to influence the data.

From a clinical point of view, MDR expression is currently evaluated as a prognostic factor in untreated and relapsing tumors. In the future, a better definition of the potentially important role of P-170 in chemotherapy-naive tumors and their stromal or endothelial cells may promote an understanding of why its high expression in a subset of cases accounts for inherent aggressive cell behavior, making specific therapeutic approaches mandatory in these situations.

This article reviews the current knowledge about the physiologic role and expression of the MDR product in humans and modes of its detection in practice. Also reviewed are important studies evaluating MDR product expression and clinical significance in some solid tumors and hematological malignancies. Finally, clinical trials of MDR reversal will be briefly mentioned. We have deliberately chosen not to report on studies of low clinical relevance.

MDR-1 Gene and P-170 Glycoprotein

MDR cell lines were initially derived by stepwise selection with a single natural cytotoxic drug. All these cell lines were found to be cross-resistant to several other natural drugs, including colchicine, vinca alkaloids, paclitaxel, epipodophyllotoxins, anthracyclines, mitomycin C and actinomycin D.

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All of these cell lines displayed a similar pattern of resistance, suggesting a common underlying mechanism—a decreased intracellular accumulation of the cytotoxic agent. The cytotoxic agent resulted from the action of an adenosine triphosphate (ATP)-dependent efflux pump, P-170, which is a product of the MDR-1 gene [6]. The degree to which the drug is pumped out of the cell depends upon the level of expression of P-glycoprotein in the cell lines and on the affinity of the substrate for it.

The MDR genes remain remarkably conserved across species [7, 8], suggesting a vital role played by their products in the survival of the organism. However, the normal physiologic function in humans remains unknown. The MDR-1 gene product is differentially expressed in a variety of normal tissues distributed in several categories: organs with excretory functions, such as apical surface or secretory epithelium of the jejunum and colon, bile canaliculi, renal proximal tubular epithelium, pancreatic small duct epithelium and the glandular epithelium of the gravid uterus; organs with blood-barrier function, such as capillary endothelium of the brain and testis, placenta and adrenal gland, and the hematopoietic system, such as some hematopoietic precursors and lymphocytes. Interestingly, with the exception of Wilms tumor, most of the malignant tumors derived from these tissues express high levels of P-170 and generally already exhibit a high degree of chemoresistance at diagnosis. The distribution of P-170 in normal tissue suggests a physiological role of detoxification, excretion and protection of vital organs against toxic products and xenobiotics. Endogenous substances such as steroids (cortisol, aldosterone) and signal peptides lacking signal leader sequences could also be physiologic substrates of this transporter protein.

It appears that a large number of nontoxic compounds are potential substrates for P-170 protein and can become competitive with other substrates, such as chemotherapeutic agents; therefore, they may be capable of reverting the drug efflux mechanism of the pump, accounting for the MDR-reversal ability of drugs such as verapamil, cyclosporine A, their derivatives and others.

MDR EXPRESSION AND CHEMoresistance

The causes of chemotherapy failure derive from many factors, ranging from the physical inability of the drugs to reach their critical cellular target to diverse cellular and molecular mechanisms of resistance. For the latter, the model of spontaneous mutations as a cause of drug-resistance development in a cancer cell population proposed by Goldie and Coldman [9] almost 20 years ago was corroborated later by the definition of several drug-resistance genes activated through mutational events or amplifications. Among these, the discovery of the MDR gene has raised enthusiasm because of its clinical implications and the potential pharmacological manipulations. However, it seems now that MDR-1 gene overexpression is just one of numerous potential mechanisms of drug resistance distributed among five groups: those affecting drug transport (entry or efflux); those mediated at the level of drug activation or inactivation; those mediated at the level of the target (increased, decreased or mutated); those associated with altered DNA repair, and those resulting from alteration in cell survival pathways (apoptosis, growth factors and their receptors, etc.).

Among the first group, the MDR-based pathway, although the most extensively studied, is not the only transport mechanism. The product of two more recently discovered genes, MRP (multidrug resistance-associated protein) and LRP (lung resistance protein), better known as M 110 (major vault protein), are possibly also implicated in transport mechanisms.

MRP has been described in a small-cell lung cancer cell line selected for resistance to doxorubicin [10]. MRP belongs to the same ATP-binding cassette superfamily of transporter proteins as MDR. Subsets of cells can be found where the MRP gene is amplified and the protein overexpressed in the absence of MDR-1 expression. MRP can also lead to resistance by drug transport and efflux through the membrane [11, 12].

Likewise, LRP has been identified as belonging to the same transport superfamily of genes as MDR-1 and MRP, but differs from the former by its cytoplasmic location [13-15]. This enumeration underlines the complexity of possible mechanisms of drug resistance development at the cellular level, the situation in the clinic being even more complex. In this setting, the isolated MDR-reversal approach to re-establishing chemosensitivity can no appear naive in spite of some sporadic in vitro successes.

MDR EXPRESSION IN HUMAN TUMORS

Detection of MDR Expression

A range of methods with extremely variable sensitivity and specificity can be used to detect MDR-1 expression in normal and tumoral tissues; they include assays for MDR-1 mRNA (Northern blot, slot blot, reverse transcriptase polymerase chain reaction (RT-PCR), RNAase protection assay and in situ hybridization), and assays for the presence of P-170 (immunohistochemical staining, image and flow cytometry, western blotting). Techniques regarding the function of the protein remain limited to the experimental field. Currently, the most common assays detecting MDR-1 expression in the routine are RT-PCR and immunohistochemical assays. For the latter, several monoclonal antibodies (mAb) can be used: C219, MRK-16 and JSB 1, all recognizing different epitopes
of the MDR-gene-derived proteins. More recently, the mAb UIC2 was proposed as more specific for P-170 than former ones. Different techniques have been developed to improve the sensitivity of immunohistochemical methods.

In addition to the variability among the techniques used, there are major differences in the definition of positive samples among investigators, making any interstudy comparison almost impossible.

In cases of tumoral tissues such as lymphomas, stromal cells and macrophages have been observed to express P-170 while the malignant lymphoma cells are negative [16]. The clinical significance of this particular pattern of positivity is unknown.

RT-PCR provides an exquisite sensitivity in detecting any MDR-1 expression in tumoral tissue but may give false positive results if mRNA from nonmalignant cells expressing a high level of MDR-1 is amplified as well. Thus, only negative results are highly reliable by RT-PCR. In contrast, immunohistochemical assays are less sensitive but allow direct visualization of the staining cells and differentiation of tumor cells from normal background elements.

The expression of MDR has been examined in samples from both untreated and relapsing patients with several tumor types to investigate whether:

• MDR expression at presentation is found in a high proportion of tumors and whether in the subset of positive cases it can be correlated with other tumor characteristics such as tumor grade, or histologic subtype.
• This precludes the success of first-line chemotherapy, including MDR-sensitive drugs, indicating that only MDR-insensitive agents should be used or that the former should be directly associated to MDR-reversing drugs.
• MDR expression in relapsing tumors should modify the standard therapeutic recommendations in second- or third-line chemotherapies according to the particular outcome of this subset of patients under treatment.

The following sections report on the most relevant articles on MDR expression in certain representative malignancies in which it is suspected to play a role in tumor evolution.

**Hematological Malignancies**

**Acute Leukemias**

Acute and chronic leukemias often provide good models for the study of cellular and molecular parameters, due to the availability of only malignant cells in blood or bone marrow at different phases of diagnosis and treatment.

MDR-1 expression has been largely investigated in diverse forms of acute leukemias as normal hematopoietic counterparts of leukemic cells express P-170 [17, 18], and as relapsing disease often shows an evolutionary pattern, suggesting a role for MDR expression in the development of drug resistance.

**Acute Myeloblastic Leukemias (AML)**

In AML, the incidence of P-170 overexpression by immunohistochemical methods has been estimated to range between 30% and 40% in previously untreated disease. This proportion increases up to 70% at time of relapse, correlating in this case with refractoriness to treatment [4, 19]. Several studies have clearly correlated the expression of MDR-1 in AML specimens at diagnosis with significantly lower chances of achieving induction remission. Recently, MDR-1 mRNA expression by slot blot techniques was shown in 71% of 63 untreated patients [20]. The complete remission rate to induction treatment was 89% in MDR-1+ and 53% in MDR-1− cases. Moreover, MDR-1 mRNA was higher in M4 and M5 FAB subtypes and significantly correlated with a shorter disease-free survival (DFS) and overall survival (OS). Of interest is the significant correlation of MDR-1 expression and the presence of CD34 antigen on leukemic blasts. However, both markers are shown to confer a poor prognosis independently. This may only reflect coexpression of P-170 and CD34 on some early myeloid precursors [19].

The same adverse prognostic value has been attributed to P-170 expression in myelodysplastic syndromes.

**Acute Lymphoblastic Leukemias (ALL)**

Fewer studies have been conducted to evaluate the prognostic significance of MDR-1 expression in ALL patients. In most of those, however, it seems that the proportion of adult ALL patients de novo or relapsing positive for P-170 is smaller than in AML patients [4, 21, 22].

There seem to be differences between childhood and adult ALL. There are apparently no differences in induction remission rate in positive or negative MDR-ALL in children, while in adults the difference is significant (remission rate of 56% in MDR+ cases versus 93% in MDR−, p = 0.05) [22]. The treatment-related parameters such as regimens and dose intensity can be relevant here. However, in the same study, the largest one performed in de novo ALL, an impressive difference in DFS was observed between MDR+ and MDR− patients, and this difference was maintained when children were analyzed separately. This suggests that in ALL, as in other tumor types, MDR-1 expression may be a powerful, negative prognostic factor. To underline the complexity and perhaps the lack of reproducibility of such studies, it is of note that the MDR phenotype was not prevalent in children with anthracycline-resistant ALL, nor was the anthracycline concentration lower in the resistant cells in vitro; finally, these were not influenced by verapamil and cyclosporine A [23].
**Chronic Myelogenous Leukemia (CML)**

CML represents an interesting model for study of MDR-1 expression. Indeed, blasts of CML patients in blastic crisis show a high expression of P-170, whereas little or no expression is found during the chronic phase [4, 24]. In a recent study of 38 CML patients in various phases, the same was noted: two of 14 patients were positive in chronic phase versus 11 of 22 patients in blastic crisis [25]. The lack of accumulation of P-170-expressing cells in blast crisis CML during treatment suggests that MDR is not a major mechanism leading to drug resistance in studied cases. As in AML, a positive correlation between P-170 and CD34 expression was found.

The prognostic value of MDR expression in CML has not been reported in any study. However, it should be noted that this phenotype predominates when the disease exhibits a more aggressive course.

**Myeloma**

P-170 expression is observed in about 5% of cases of untreated myeloma, but gradually increases after prolonged treatment. This was correlated to the cumulative dose of doxorubicin and vincristine given. The expression of MDR-1 being found in up to 70% to 80% of myelomas refractory to vincristine, adriamycin and dexamethasone (VAD) [26]. As in other tumor types, the question as to whether this is an induction of MDR expression in previously naive cells or a selection of MDR-expressing clones among cancer cells remains open, but some experimental and theoretical data favor the second hypothesis.

VAD is one of the most effective regimens in resistant myeloma; acquired resistance to VAD is associated with a very poor outlook, as efficient third-line treatments are lacking. Several arguments favor the hypothesis of a relevant role of MDR-1 expression in the development of chemoresistance in this setting (high proportion of MDR expressing cells, correlating with the extent of MDR expression resistance to substrates of P-170, etc.). This made the VAD-refractory myeloma a good model for the study of the MDR-reversal strategy in the clinic.

In spite of an optimistic preliminary study in which VAD was associated with i.v. cyclosporine A [27], a recent larger randomized study failed to demonstrate any benefit of adding oral verapamil to VAD [28].

**Lymphomas**

Drug resistance, including MDR-1 dependence, has been extensively reviewed in two recent papers [16, 29]. In lymphomas, possibly more than in any other tumor type, the extreme variability among techniques and definitions of MDR positivity and the clinically heterogeneous, often small, populations of patients with various histologic subtypes make any interstudy comparison hardly reliable. Moreover, in some cases, stromal cells, macrophages and nonmalignant T lymphocytes of lymphoma tissue have been observed to express P-170 while lymphoma cells were negative; the significance of this particular feature remains obscure. This makes any positive RT-PCR-based result equivocal.

Overall, it can be concluded from the published reports that in untreated lymphoma, MDR-1 expression is relatively low, ranging from 2% to 20% without any obvious histology-related pattern, but increasing up to 50% to 70% in patients with recurrent disease.

The question of whether MDR-1 expression should be retained as a prognostic factor in lymphomas has been addressed in a number of studies. Because of the above-mentioned limitations, definitive conclusions cannot be drawn. There seems to be a higher proportion of P-170 negative lymphoma patients who respond to chemotherapy as compared to P-170 positive ones in small series [30-33], but this trend is not reported by all investigators [34].

A large single study provides the most substantial data, reporting a significant correlation between P-170 status and five-year DFS in a uniform population of 141 patients with diffuse, large-cell lymphoma treated primarily with polychemotherapy [35].

**Solid Tumors**

**Breast Cancer**

From a limited number of studies, there is evidence that P-170 might play a role in chemoresistance to cytotoxic drugs used in breast cancer. A correlation has been observed between P-170 expression in breast cancer cells from treated patients and in vitro resistance to anthracyclines [36]. A high P-170 expression in 17 out of 20 patients with locally advanced disease was associated with the lack of response to neoadjuvant doxorubicin-containing chemotherapy and a shorter DFS [37]. In addition to the small size of this study, the median length of follow-up was 22.5 months. Thus, the evaluation of MDR-1 expression as a prognostic factor of response to treatment in breast cancer requires larger data sets with longer follow-up.

A recent study reported data about MDR-1 expression and several other markers of drug resistance (MRP, LRP, topoisomerase resistance, etc.) in samples obtained from 92 patients with primary breast cancer and 12 with metastatic disease. It was emphasized that P-170 expression was more often found in tumors from premenopausal women—in metastatic rather than in primary disease—and was associated in primary tumors with the presence of more than three positive axillary nodes. In this study, the strongest prognostic factors for OS with univariate analysis were the mitotic index, lymph node status, P-170 expression, and,
Interestingly, the combination of P-170-expressing tumor cells surrounded by P-170-expressing stroma—the latter being the strongest prognostic factor in a multivariate analysis [38].

In another series of 60 patients, the same group of investigators analyzed the expression of drug-resistance-related genes MDR-1 and MRP in various tumor materials, ranging from normal breast tissue to multitreated metastatic disease tissue. Their preliminary results showed that locally advanced breast carcinomas had significantly higher expression of P-170 than operable primary tumors [39]. This might account for the poorer prognosis of more advanced disease, perhaps based on progressive selection of resistant clones.

**Sarcomas**

An elevated P-170 expression has been reported as highly predictive for early relapse and poor survival in children with embryonal sarcomas [40]. Indeed, several other observations have been made about significant expression of the MDR-1 gene in a high proportion of soft tissue sarcomas and osteosarcoma; in most of them, when patients had tumors expressing high levels of P-170, the trend was toward a poorer outcome [41].

Recently, the clinical significance of MDR-1 expression in high-grade osteosarcomas was highlighted in an elegant study [42]. In this series of 92 patients treated with surgery and chemotherapy, an elevated level of P-170 expression in tumor samples at diagnosis was associated with a poorer clinical outcome and a decreased probability of event-free survival. In a multivariate analysis, this parameter was not correlated with the extent of tumor necrosis after chemotherapy (one of the most reliable predictors of prognosis in osteosarcoma). This means that P-170 expression seems to be unrelated to the response of tumor cells to chemotherapy and may just reflect tumor aggressiveness, at least in this particular setting.

**Colon Cancer**

High levels of MDR-1 expression are found in primary tumors originating from tissues which normally express the protein, such as renal cell or adrenocortical cancer. Colon cancer is usually a chemoresistant form of tumor, and MDR-based mechanisms have been suspected to participate in the general unresponsiveness of colorectal tumors to cytotoxics [43]. The most effective drugs in this setting, such as 5-fluorouracil, are not MDR-dependent, and results of clinical MDR-reversal trials are all disappointing.

Some data suggest that MDR expression in colorectal cancer should be regarded as a molecular indicator of tumor aggressiveness. A significant expression of P-170 could be demonstrated in invasive cells at the edge of the tumor of about 50% of 95 examined cases of colorectal cancer. In the positive cases, a greater incidence of vessel invasion and lymph node metastases was found [44]. In half the patients with P-170 negative tumors, the lymph nodes expressed P-170. This could be interpreted, as in breast cancer, as an indicator of invasiveness and of the high metastatic potential of P-170-expressing cells.

**Neuroblastoma**

In metastatic neuroblastoma, chemoresistance is particularly apparent when the tumor presents an amplification of N-myc, which is one of the most powerful predictors of poor outcome. The participation of the MDR-1 gene in development of drug resistance in neuroblastoma appears controversial in most of the published reports [45-47]. In a recent paper examining the prognostic value of several molecular parameters in a series of 60 neuroblastoma patients, MDR-1 expression was not predictive of survival or DFS, nor associated with N-myc amplification [48]. In contrast, the high level of expression of MRP was significantly associated with reduced DFS and OS and found in tumors with N-myc amplification, probably also accounting for the association of N-myc amplification with poor prognosis.

**Miscellaneous Solid Tumors**

P-170 expression has been reported with variable results in lung cancers [49], renal cancers [50, 51] and many other tumor types. However, most of the time, the small size of these studies or other pitfalls of the methodology used make any evaluation of MDR-1 expression as a factor in clinical chemoresistance or of any prognosis neither feasible nor reliable.

In ovarian cancers, other markers seem to be more relevant than the P-170 level as a predictive factor of outcome [15].

**Clinical Significance of MDR-1 Expression**

**Factor of Chemoresistance—MDR-Reversal Trials**

While it was tempting until recently to assume that P-170 confers or contributes to the chemorefractoriness of P-170-expressing tumors, it now appears more obvious that other mechanisms of resistance are equal, or more important, since these tumors show no particular sensitivity to cytotoxic drugs unaffected by P-170, such as antifolates, alkylators or platin compounds. However, in tumors in which a real role in clinical drug resistance is suspected, the more important question is whether overcoming drug efflux will lead to a therapeutic benefit or whether other mechanisms of drug resistance should be considered [52]. These questions about the relevance of chemosensitizers have been addressed in many experimental and clinical studies for more than ten years now.
Pharmacological reversal of P-170-mediated drug resistance was first reported in 1981, with verapamil enhancing the intracellular accumulation of vincristine, potentiating its antiproliferative activity in a multidrug-resistant murine leukemia cell line [53]. Many chemosensitizers have since been reported to antagonize multidrug resistance in vitro and some are effective in vivo upon coadministration with the appropriate chemotherapeutic agents to nude mice having multidrug-resistant tumors. Most of the MDR-reversal agents act through a competitive inhibition of the drug efflux function of P-170 by being a substrate for it.

Unfortunately, clinical studies with the so-called “first-generation” MDR modulators have indicated dose-limiting side effects of these chemosensitizers with a low therapeutic index as responsible for the failure to achieve therapeutic blood levels [54-58]. Moreover, pharmacokinetic drug interactions sometimes complicate patient dosing by decreasing elimination of cytotoxic drugs or increasing their plasma concentration by 40% to 60%, thereby increasing their toxicity [57].

Less toxic, second-generation MDR-reversing drugs, e.g., the less cardiotoxic d-verapamil and less immunosuppressive and nephrotoxic PSC 833 cyclosporine analog, are currently being evaluated in clinical studies by several investigators.

Exhaustive reviews about MDR-reversal trial data have been published [55, 56, 58, 59]. Most of the results, particularly in solid tumors, have been somewhat disappointing, leaving in question the validity of three primary concepts: the MDR hypothesis, the reversing agents themselves and the strategy for their most effective use.

It is now clear, as previously mentioned, that many other cellular and extracellular mechanisms can account for chemoresistance development in tumors, and that an efficient MDR-reversing approach alone is probably not sufficient to improve cure rates or DFS.

Many in vitro experiments are ongoing to develop a better MDR-reversal or circumventing approach in vitro that might be applied later on in vivo, such as third-generation MDR-reversal agents, anti-P-170 monoclonal antibodies, liposome-included drugs, etc. [36, 60].

Possibly the most important question currently to be answered is whether any relevant clinical application of MDR reversal should still be considered. Indeed, most clinical studies involving the use of chemosensitizers are attempting to treat patients with established MDR-positive tumors. In most instances, these patients have heavily pretreated, advanced disease. Now, as recently suggested by in vitro findings, the use of chemosensitizers early in the clinical course of the treated tumors, before any significant detection of MDR-1 expression (to prevent its appearance), may be a more appropriate strategy for assessing their clinical potential in chemotherapeutic treatment [61]. When human MES-SA sarcoma cells are coselected with doxorubicin and PSC 833, the mutation rate for doxorubicin-selected resistance is reduced tenfold compared to doxorubicin alone [62]. This suggests a decrease or suppression of the activation of the MDR-1 gene, and, possibly, a prevention of the emergence of resistant cancer cell clones with an MDR-1 phenotype in the coselection process. However, although exciting, this hypothesis appears difficult to verify in the clinic.

**Prognostic Factor**

When found, MDR-1 expression does not seem to be a major determinant of clinical response—at least not enough to shift the intended chemotherapeutic drugs to non-MDR-dependent cytoxics. In contrast, its routine detection can be included reasonably in the work-up of tumors such as high-grade osteosarcomas, acute leukemias and possibly colon and breast carcinomas. In some of these tumors, such as osteosarcomas, the predictive value of P-170 expression for drug resistance can clearly be distinguished from its role as a prognostic factor. Similarly, other pleiotropic drug-resistance gene expressions are known to correspond to reliable predictors of clinical outcome in other tumor types (such as MRP in neuroblastoma, or LRP in ovarian cancers) in which MDR-1 expression lacks any prognostic significance. These might be included in the near future in the diagnostic staging of these tumors.

The molecular mechanisms linking P-170 expression to its adverse prognostic value in some tumor types remain unclear and are largely speculative. The P-170 membrane pump can intracellularly transport substrates that are critical for cell growth and invasiveness in the tumor tissue. Possibly, there is a common molecular pathway activated by the respective substrates for MDR-1, MRP and LPR which remains to be defined.

**CONCLUSIONS**

More than ten years ago, the discovery of the MDR-1 gene and its protein product, P-170, through potential manipulation in the clinic, has raised a great enthusiasm in medical oncology. However, the experimental successes of MDR reversal observed in vitro were not translated convincingly in the clinical setting because of the poor control of many pharmacological and tumoral parameters, or, more probably, because of the overvalued (or possibly false) role attributed to MDR-based mechanisms in the development of chemoresistance. Indeed, it appears clear now that MDR expression can be a marker of the aggressiveness of cells which are inherently chemoresistant.
including non-MDR-dependent drugs. In this setting, P-170 expression may be merely an epiphenomenon of the drug resistance, making its reversal irrelevant. If so, the effort should not be against MDR expression itself, but toward more aggressive treatment of tumors that express MDR or any other drug-resistance gene.

The reasons for the poor prognosis of MDR-expressing tumors in most studies remain largely speculative. Perhaps the description of some “natural tumoral ligands” of P-170, such as auto or paracrine growth factors or cytokines, will allow a better definition of its peculiar role in cancer development and/or progression.

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