Factors determining cellular mechanisms of resistance to antimitotic drugs

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Abstract With the rapidly expanding use of paclitaxel and related taxanes to treat malignant diseases, comes the realization that development of resistance to this class of agents will become an increasingly significant clinical problem. Studies have indicated that acquisition of resistance to the cytotoxic action of these drugs can occur by limiting the drug's ability to accumulate in cells, altering the stability of cellular microtubules, diminishing the drug's ability to bind tubulin, or varying the expression of specific tubulin genes. This review will critically evaluate the selection methods used to generate drug resistant mutants in tissue culture and focus on the various factors that determine which resistance mechanisms are most likely to be encountered. It is anticipated that clinical drug resistance will be complicated by pharmacokinetic considerations and variability among individuals, but that underlying genetic mechanisms will be similar to those found in culture. © 2001 Harcourt Publishers Ltd

It is generally accepted that tumor cell resistance to chemotherapeutic drugs represents the single most significant reason for the failure of drug therapy to cure cancer.[1] Paclitaxel should prove no different in this regard. In this article I will discuss approaches currently being used to study drug resistance while emphasizing that emerging mechanisms are highly influenced by the selections used to obtain resistant cell lines. Throughout the text I will use paclitaxel as the prototype for the increasingly broad class of drugs known as taxanes, but will include other antimitotic drugs as needed to illustrate specific points. This review is not intended to be comprehensive; instead I will cite a few experiments to illustrate various principles or mechanisms. Although the discussion will focus on mechanisms of resistance to antimitotic drugs, some of the general principles may have relevance to other drug classes as well. I apologize in advance to those whose work is not included here. It is not meant to diminish the importance of their work, but rather to limit the scope of the review. For a more comprehensive summary of the literature, the reader is referred to another recent review.[2]

Tumor cells from patients are frequently very heterogeneous, slow growing, and difficult to culture. For these reasons most information about drug resistance mechanisms has come from studying established cell lines in culture. Although these are far removed from a true in vivo situation, the ease with which resistant cells can be generated and studied, the ability to maintain tight controls, and the flexibility with which treatment protocols can be varied, combine to make cell culture the system of choice for the study of drug resistance mechanisms. It should be remembered, however, that mechanisms discovered in cell culture may not always represent the most commonly encountered mechanisms in patients undergoing treatment. Nonetheless, cell culture systems are a good place to begin examining the genetic basis and relative frequencies of potential cellular-based mechanisms of resistance.

INFLUENCE OF THE SELECTION METHOD

One of the biggest advantages of the cell culture model for drug resistance, namely the flexibility to manipulate the drug treatment protocol, can also lead to one of its biggest pitfalls. A variety of selection protocols for isolating drug resistant mutants has been employed, but seldom have the implications of choosing a particular method of selection been discussed. Most studies have used multiple step procedures in which cells are initially selected under low, minimally toxic drug concentrations, but are then exposed to many further stepwise increases until cells with very high levels of resistance are obtained. While this method offers the advantage of producing biochemical changes that are relatively easy to detect and study, one must recognize that the method is biased in favor of resistance mechanisms that are capable of producing high levels of resistance. Furthermore, it is likely that multiple genetic changes have contributed to the drug resistance, but the individual contributions are not always easy to sort out. In many cases, they are not even acknowledged.

The problem of bias is significant because chemotherapeutic drugs are typically administered to patients in an amount that is close to the maximum tolerated dose, and so the clinician rarely has the option of increasing the drug concentration when a patient relapses. For this reason, single-step selections with a concentration of drug only a few-fold higher than the minimal toxic dose should reveal resistance mechanisms that are most clinically relevant. At the same time, single-step selections should be less biased, i.e. mechanisms that produce high and low levels of resistance should be retained, and the resulting phenotypes should be more easily ascribed to specific biochemical and genetic changes.

An example of how selection methods can bias the kinds of mutants that are isolated is provided by resistance to antimitotic drugs. Most cell lines resistant to paclitaxel, a drug that stabilizes microtubules and blocks cells in mitosis, have been obtained using a multiple step procedure.[2] Typically, these cells are hundreds or even a thousand-fold resistant to paclitaxel and exhibit cross-resistance to a variety of hydrophobic drugs with diverse mechanisms of action. Analysis of the molecular defect in these cells has revealed increased production of P-glycoprotein, an ATP-driven plasma membrane pump that actively extrudes hydrophobic drugs from the cell and is responsible for a major form of multidrug resistance.[3] On the other hand, laboratories using selections that give lower levels of resistance have reported resistance mechanisms based on tubulin mutations that affect microtubule assembly and stability[4–8] or binding of the drug to tubulin.[9] Indeed, in our own studies

using single-step selections for paclitaxel resistance, most resistant cell lines had altered microtubule stability and less than 10% were multidrug resistant.[8]

In retrospect, the predominance of the multidrug resistance mechanism in multiple step, but not single step, selections was predictable. Tubulin is a highly conserved and tightly regulated protein that is essential for cell survival; therefore, only subtle mutations that minimally disturb its ability to assemble into microtubules are retained. Such mutations produce modest effects on drug resistance, and so, cells with tubulin alterations are typically only 2–3-fold resistant to the selecting agent. P-glycoprotein is under no such constraints. It is a non-essential protein (to a tumor cell) and its level in the plasma membrane is not highly regulated. Multiple step selections producing high levels of resistance therefore retain cells with highly elevated production of normal or mutant P-glycoprotein because the cells suffer no adverse effects. Clearly then, multiple step selections favor multidrug resistant cells over those with tubulin alterations, whereas single step procedures exhibit no such bias.

A second problem with multiple step selections is the difficulty in ascribing a specific genetic or biochemical change to the drug resistance phenotype. The growth of cells between rounds of selection allows the introduction of multiple mutations that may be contributing to drug resistance. Thus, identification of a single biochemical change may not be sufficient to define what could be a complex mechanism of resistance or overlapping mechanisms of resistance. Studies in mouse macrophage J774.2 cells selected to grow in high concentrations of paclitaxel, for example, identified a clear increase in P-glycoprotein as the mechanism of resistance.[10] Later studies, however, reported that these cells grew better in the presence of paclitaxel than in its absence,[11] a phenotype previously described among Chinese hamster ovary (CHO) cells with altered tubulin that had been selected for resistance in a single step.[4,5,8] It thus appears that during selection, the J774.2 cells acquired tubulin alterations that affected assembly and subsequently acquired further mutations leading to increased production of P-glycoprotein to produce the complex phenotype.

A more recent example of problems in interpretation that can be encountered in multiple step selections is provided by reports of increased β-tubulin production as a mechanism of paclitaxel resistance. Mammals express at least seven distinct genes producing highly homologous β-tubulin isoforms that differ primarily in their carboxyl terminal sequences.[12] Biochemical studies have suggested that the various β-tubulin isoforms have differing assembly and drug binding properties.[13] It would therefore be reasonable to expect that altered production of specific β-tubulin isotypes might allow a cell to become resistant to specific antimitotic drugs. A number of studies support this idea. For example, various cell lines have been exposed to increasing concentrations of paclitaxel and then analyzed for β-tubulin expression using quantitative PCR. This approach has led to publications reporting an increase in β2-tubulin in J774.2 cells,[14] an increase in β1, β2, β3, and β4a-tubulin in human lung cancer cells,[15] an increase in β1, β3, and β4a in human ovarian tumors,[15] and an increase in β4a in human leukemia cells.[16] Additionally, an increase in β3 and β4a was found in human prostate cancer cells selected for resistance to estramustine, a drug that inhibits microtubule assembly.[17]

Although several independent laboratories have reported these changes, there is as yet no compelling evidence that altered tubulin expression is sufficient to produce resistance to antimitotic drugs. First, of the seven isotypes of β-tubulin produced in vertebrates, four have been implicated in resistance to paclitaxel, a seemingly high number. Second, increased expression of β3 and β4a tubulin has been implicated in resistance to paclitaxel and to estramustine even though the two drugs have opposing actions on microtubules and bind to different sites on tubulin. Third, one study reported changes in tubulin expression in human sarcoma cells, but these did not correlate with paclitaxel resistance.[18] Finally, transfection and overexpression of β1, β2 or β4b-tubulin was found to have no effect on paclitaxel resistance in CHO cells.[19] How is one to explain these conflicting results? One possibility is that tubulin expression varies from cell to cell in heterogeneous populations and that isolation of a subclone with altered expression is unrelated to drug resistance. A second and perhaps more likely possibility is that the increased expression of tubulin is linked to some other change such as a mutation in the highly expressed tubulin gene, and the mutation is actually responsible for the resistance. Whatever the eventual explanation, these ambiguities in interpretation point out the need to firmly establish a cause and effect relationship between any biochemical change that is identified and the drug resistance phenotype of the mutant cells.

CHOICE OF DRUG

The bias introduced in multiple step selections suggests that the prominence of multidrug resistance may be overstated in the literature: a conclusion supported by the observation that paclitaxel has been highly successful in patients previously treated with anthracycline antibiotics, which are well known substrates for the P-glycoprotein pump.[20–22] This argument, however, is not meant to diminish the potential importance of multidrug resistance mechanisms even in single step selections. Our laboratory has examined the prevalence of tubulin alterations versus multidrug resistance mechanisms in single step selections using various antimitotic drugs.[8,23] The studies (Table 1) demonstrated that the prevalence of a particular drug resistance mechanism is highly dependent on the selecting drug. Despite the fact that all the drugs tested are affected by the multidrug resistance mechanism, the frequency with which this mechanism was seen

Table 1 **Frequency of MDR in single step selections using the indicated drug**

Drug	MDR[a]	Tubulin[b]	%MDR
Colchicine	17	3	85
Vinblastine	17	5	77
Paclitaxel	10	129	8

[a]Number of cell lines with the multidrug resistance phenotype. [b]Number of cell lines with properties indicating a tubulin alteration.

in single step selections varied from a high of 75–85% for vinblastine and colchicine, to a low of 8% for paclitaxel. Although the reasons for this variability are uncertain, one plausible explanation is that tubulin mutations conferring paclitaxel resistance destabilize microtubule structure and are relatively common. On the other hand, tubulin mutations that confer resistance to colchicine and vinblastine would need to stabilize microtubule structure and these are relatively rare. The lesson from these studies is that one cannot *a priori* assume that a resistance mechanism identified for a particular drug will apply equally to all drugs within the same class.

CHOICE OF CELLS

The cell line used in studies of drug resistance may also influence the kinds of mutants that are ultimately obtained. Differences in membrane properties, tubulin composition, and other less obvious factors may all combine to determine the relative frequencies with which various mechanisms are seen. As already mentioned, most human tumor cell lines are relatively heterogeneous and it is likely that significant variability in biochemical and genetic properties exists from one cell to the next. This can even be a problem with well established cell lines and can complicate interpretation of mutant phenotypes. For this reason, it is wise whenever possible to clone cells before beginning a mutant selection as this will minimize the influence of genetic drift and make the assignment of a biochemical change to the phenotype of the mutant less ambiguous.

Our studies have used Chinese hamster ovary (CHO) cells for mutant isolation. This is a well established, stable cell line that is easily cloned and has been well studied. CHO cells express 3 β-tubulin isoforms (β1, β4b, and β5) with relative abundances of 70%, 25%, and 5% respectively.[24,25] To date, every β-tubulin mutation we have identified in cells selected for resistance to antimitotic drugs was found in the β1 isoform. This may not be surprising because β1 is the most abundant isoform and is therefore positioned to have the greatest effect on microtubule assembly. More recent studies using site directed mutagenesis and transfection of β-tubulin cDNA to explore the kinds of changes that allow acquisition of paclitaxel resistance, however, indicate that some highly toxic mutations can confer resistance but only when expressed at low levels (F. Cabral, unpublished studies). It is therefore possible that further sequencing of mutant cell lines will uncover some of these more toxic mutations in less highly expressed tubulin genes. A tentative conclusion from this work is that less disruptive mutations will be found in highly expressed genes and the more disruptive mutations will be found in less highly expressed genes. Thus, the kinds of mutations that are found are likely to be influenced by the tubulin composition of the cell line used for mutant selection.

It should be noted that our CHO cells with mutant tubulin are resistant to antimitotic drugs because of altered stability of their microtubules.[26,27] Moreover, recent selections using human KB3 cells produced mutant cell lines with properties that mimic those we've seen in CHO cells (F. Cabral, unpublished studies). Despite the isolation of hundreds of drug resistant cells, we have to date not identified any mutants that have altered drug binding even though such changes are common in lower eukaryotes.[28,29] This discrepancy can be explained by the observation that antimitotic drugs poison microtubule assembly at substoichiometric concentrations.[30] Thus, a decrease in drug binding affinity can confer resistance in yeast because they grow as haploid cells that express a single β-tubulin gene. Mammalian cells, on the other hand, are diploid and express multiple tubulin genes. In this case, a mutation that decreases the drug binding affinity will affect only a small portion of the total tubulin, leaving sufficient wild-type tubulin to bind the drug with normal affinity and poison microtubule assembly. In short, decreased drug binding affinity is a recessive phenotype that should not be observed in mammalian cells.

Contrary to this expectation, mutant 1A9 cells have been reported to contain altered β1-tubulin with decreased binding of paclitaxel.[9] This human ovarian carcinoma cell line was subjected to several rounds of exposure to increasing concentrations of paclitaxel leading to the isolation of two mutant cell lines with approximately 20-fold resistance to the drug. Although isolation of these mutants would appear to contradict the idea that decreased drug binding is a recessive phenotype, further analysis of the cells revealed that the wild-type allele of the β1-tubulin gene was not expressed.[9] Because the authors estimate that the β1 isoform accounts for about 85% of the total, most of the β-tubulin in the cells is altered; and this may explain why drug binding alterations were recovered in their selections. Subsequent selection of cells resistant to epothilone A or B by the same authors again led to the isolation of drug binding mutations.[31] These studies present a dramatic example of how the choice of a particular cell line can influence the mechanism of resistance that is seen.

CLINICAL PERSPECTIVES

Taking into account the previous discussion, one might ask what kind of mutant tumor cells are likely to be found in patients undergoing therapy with one of the antimitotic drugs. Given that a patient is likely to receive a single concentration of drug, the single-step selection model should be the best predictor for the relative frequencies with which the various drug resistance mechanisms are encountered. As already pointed out, the most frequently encountered mechanism will depend on which drug is being administered. For vinca alkaloids and many other drugs that inhibit microtubule assembly, it is expected that multidrug resistance will predominate. For paclitaxel, epothilone, and other drugs that promote microtubule assembly, on the other hand, tubulin mutations should be seen most frequently. The development of methods to overcome multidrug resistance and the identification of new antimitotic drugs that are not affected by this phenomenon have all been extensively discussed in the literature and will not be reviewed here. It should be noted, however, that as methods to circumvent multidrug resistance become adopted, tubulin alterations as a mechanism of resistance will become increasingly prevalent.

Tubulin mutations can confer resistance to antimitotic drugs by at least two mechanisms. One of these, decreased

drug binding, is rarely if ever seen in a well behaved cell line. Tumors, however, are anything but well behaved and frequently exhibit genomic instability.[32] It is therefore possible that some fraction of large tumors will have become functionally haploid at the β-tubulin locus and thereby be able to survive cancer therapy by acquiring mutations that decrease drug binding. Two considerations suggest that such mutants will be infrequently encountered. First, this phenotype requires at least two independent changes (haploidization of the β-tubulin locus and mutation of the expressed β-tubulin). Second, these mutants have only been reported in multiple step selections to approximately 20-fold resistance. Nevertheless, if this mechanism is encountered in a patient, the resistance should exhibit some specificity for the drug used in the selection. In cell lines with decreased binding of paclitaxel, for example, only low cross-resistance to epothilones was reported even though both drugs act by stabilizing microtubules and bind to the same region of tubulin.[9] Similarly, cell lines with altered binding of epothilones exhibited much lower cross-resistance to paclitaxel.[31]

A second mechanism by which tubulin alterations can confer resistance is through changes in microtubule stability. This phenotype can arise from a single mutation in either α- or β-tubulin[6,26] and should therefore be encountered more frequently than drug binding mutations. As already mentioned, this is the mechanism most commonly found in single step selections for paclitaxel resistance.[8] The mechanism is most easily understood by considering that microtubules are metastable, highly dynamic structures that can only function within a limited range of stability (Fig. 1). This limited stability is reflected in the fact that the microtubule polymer exists in a steady state with free heterodimers. In CHO cells only 38% of the cellular tubulin is in the polymer pool.[33] Drugs like vinblastine that destabilize microtubules decrease the amount of polymer. These drugs become toxic when their concentration reduces the amount of microtubules to the point they become nonfunctional (point L, Fig. 1). Drugs like paclitaxel, on the other hand, increase the amount of polymer and become toxic at concentrations that abrogate the ability of the cell to control tubulin polymerization (point H, Fig. 1). Cells may become resistant when tubulin is altered in a way that counteracts drug action. Thus, mutations that stabilize microtubules confer resistance to vinblastine and other inhibitors of polymerization because more drug is needed to reduce microtubule stability below point L. Mutations that destabilize microtubules confer resistance to paclitaxel and other agents that promote assembly because more drug is needed to raise microtubule stability beyond point H.

The same mutations that confer resistance to one drug may make the cell more sensitive to another. For example, we frequently find that cells selected for resistance to a drug that enhances microtubule stability (e.g. paclitaxel) are cross-resistant to other drugs that enhance stability (e.g., epothilones), but are more sensitive to drugs that destabilize the polymer (e.g. vinblastine). Conversely, cells that are resistant to drugs that destabilize microtubules are cross-resistant to all drugs that destabilize microtubules, but are more sensitive to paclitaxel, epothilone, and other microtubule stabilizing drugs. Thus, it might be anticipated that patients who relapse following treatment with paclitaxel might be good candidates for follow-up therapy with vinblastine, but not epothilones. This prediction has not yet been well tested.

One problem in applying these principles to patient management is the difficulty in knowing the mechanism by which a patient has relapsed. Although good molecular tools are available to determine whether P-glycoprotein is elevated in resistant tumors, determining whether mutations exist in tubulin is far more challenging. Recent work, however, suggests that development of methods to detect tubulin mutations in a cost effective way might be feasible. Although it is reasonable to think that a mutation destabilizing microtubule structure and conferring paclitaxel resistance can occur anywhere on β-tubulin, it has been reported that such mutations affect only three amino acids, all leucine, at positions 215, 217, and 228 of the protien.[34] This observation suggests that it should be possible to devise a diagnostic assay for these mutations and thereby provide the clinician with important information about the mechanism of resistance in a tumor and potential follow-up therapies that could be used to attack the malignancy.

CAVEATS

This review has focused on mechanisms of resistance likely to be encountered in a well behaved cell line in culture; but

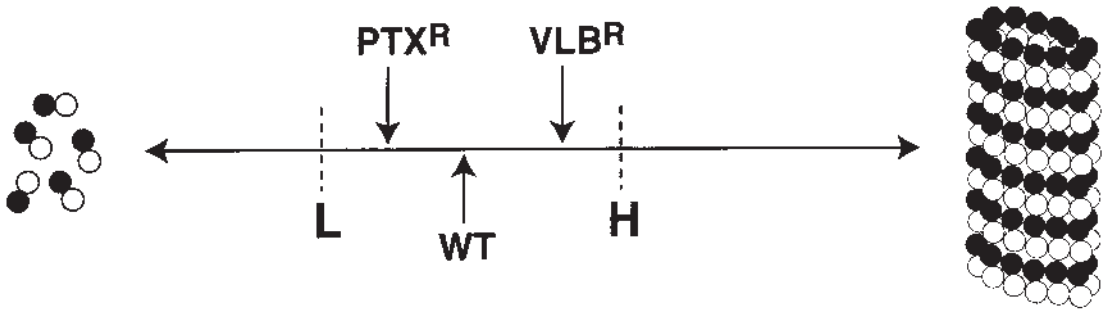

Fig. 1 **Mechanism by which changes in microtubule stability confer resistance to antimitotic drugs. Function is maintained when microtubule stability falls between points L and H. Wild-type (WT) CHO cells have microtubule stability that leads to 38% assembly of the total tubulin. PTX^R, extent of assembly in paclitaxel resistant cells; VLB^R, extent of assembly in vinblastine resistant cells.**

Table 2 **Potential mechanisms of resistance to antimitotic drugs**

Resistance mechanism	Comments
Cellular	
Increased drug efflux	Common for microtubule inhibitory drugs, less common for stabilizing drugs
Altered tubulin assembly	Common for microtubule stabilizing drugs, less common for inhibitory drugs
Altered tubulin synthesis	Not proven as mechanism of resistance
Altered drug binding	Common in haploid cells, rare in diploid
Pharmacological	
Increased drug metabolism	
Increased drug excretion	
Decreased delivery to tumor	e.g. poor vascularization of tumor; cells in pharmacological sanctuaries (CNS, testes, ovaries)
Cytokinetic	e.g. drug not present at appropriate stage of cell cycle

tumor cells are more heterogeneous and exist in much more complex environment. Thus, tumor cells in patients could escape therapy because of pharmacological considerations I have not addressed (Table 2). Problems in drug delivery to the tumor or metabolism of the drug are likely to vary from patient to patient and may lead to treatment failure. It should be easier, however, to circumvent these problems when they occur. The genetic changes leading to drug resistance are likely to affect all patients and may be more difficult to attack.

I have also not addressed a growing body of literature indicating that changes in cell cycle parameters or apoptosis might be involved in drug resistance. While these kinds of changes may yet prove to be important stumbling blocks to successful chemotherapy, it is too soon to assess their significance in relation to the more specific mechanisms I have discussed. It should be pointed out, however, that in our selections for resistance to antimitotic drugs, we have found no evidence for the existence of these alternative mechanisms at any appreciable frequency.

Finally, I should point out that the changes I have discussed assume continuous exposure to a single cytotoxic drug; but patients undergoing chemotherapy receive intermittent therapy with several drugs in combination. This might suggest that mechanisms capable of conferring resistance to different classes of drugs simultaneously should be most common in patients. As already mentioned, however, the observation that patients refractory to anthracycline treatment respond well to paclitaxel provides evidence that drug specific mechanisms of resistance may be more common than is presently appreciated.

CONCLUSION

A large body of work has established the most common mechanisms of cellular resistance to antimitotic drugs. The challenge in the future will lie in devising methods to detect these mechanisms in drug resistant human tumors, establishing their prevalence, and working out alternative therapies to circumvent their emergence. As already mentioned, the identification of tubulin mutations that confer resistance to paclitaxel and related drugs suggests that tools will become available in the next few years to begin screening patients for the presence of these genetic alterations. At the same time, it will become increasingly important to assess the role of pharmacological changes in mediating resistance. The inability to experimentally manipulate a patient population poses a serious obstacle to carrying out these studies; but the use of heterotransplanted tumors in rodents may provide a convenient model in which to determine the importance of pharmacokinetic alterations in drug resistance, and to test strategies for overcoming these kinds of changes. Given the rate at which new information is becoming available, it is possible to foresee a day in the near future when a patient will be evaluated for preexisting mechanisms of resistance, receive customized therapy based on that evaluation, be re-tested at regular intervals for the possible emergence of new mechanisms of resistance, receive an altered course of therapy to combat emerging resistant cells, and enjoy a more favorable outcome than is currently attainable.

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