Lung Resistance-Related Protein: Determining Its Role in Multidrug Resistance

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Resistance to cytotoxic drugs remains a major obstacle for the successful treatment of cancer (1). Over the past two decades, a great deal of information has emerged that elucidates how cancer cells become drug resistant. At least one prominent drug-resistance mechanism in cancer cells is the reduction of intracellular drug concentration at the putative drug target. There are at least two mechanisms capable of reducing drug concentration at the target site. The most obvious mechanism involves an overall reduction in intracellular drug concentration by reducing drug uptake or enhancing drug efflux. A second mechanism could be a redistribution of drug away from the target. In this case, the total concentration of drug may not be reduced, but the intracellular distribution may be altered, thereby reducing the drug concentration at the site of action.

To date, most mechanisms associated with reduced drug concentration at the active site have involved membrane transport proteins. The most well known of these proteins is P-glycoprotein, a 170-kd adenosine triphosphate (ATP)-dependent transmembrane efflux pump (2). P-glycoprotein has been observed in a number of drug-resistant cell lines, and strategies to overcome P-glycoprotein-mediated resistance are currently undergoing clinical trials (3). Undoubtedly, P-glycoprotein contributes to clinical drug resistance in cancer patients; however, it clearly is not the sole mechanism of drug resistance. Since the discovery of P-glycoprotein, a number of other transport proteins have been identified as being involved with the multidrug-resistant phenotype. The multidrug resistance-associated protein (MRP1) is another member of the same superfamily and is structurally related to P-glycoprotein (4). Like P-glycoprotein, MRP1 transports cancer drugs out of the cell, reducing the concentration at the intracellular target. Recently, another membrane transporter called breast cancer-resistant protein was cloned (5). This particular drug-resistance protein appears to be associated with resistance to anthracycline-type drugs, such as doxorubicin and mitoxantrone. Like P-glycoprotein and MRP1, breast cancer-resistant protein is associated with enhanced drug efflux, which is ATP dependent. However, in addition to enhanced drug efflux, a number of studies using drug-resistant cell lines have demonstrated alterations in intracellular drug distribution (6,7).

These changes in drug distribution are most notable for DNA-interacting drugs, where in drug-resistant cells the drug is redistributed from the nucleus to the cytoplasm. It is not known how the ATP-binding cassette family members of transmembrane proteins, which are primarily located in the plasma membrane, are able to redistribute drug from the nucleus to the cytoplasm. One possibility is that the transporters are located in intracytoplasmic vesicles, and these vesicles somehow “trap” drugs in the cytoplasm and prevent them from reaching their target in the nucleus. A second possibility involves the participation of other novel proteins responsible for the transport of substrates between the cytoplasm and nucleus.

In this issue of the Journal, Kitazono et al. (8) provide evidence implicating the lung resistance-related protein (LRP) in multidrug resistance. In this case, LRP expression is associated with a redistribution of doxorubicin from the nucleus to the cytoplasm without changes in total drug intracellular concentrations.

In 1993, Scheper et al. (9) first described LRP in non-P-glycoprotein drug-resistant cell lines. Since its original description, LRP has been identified as the major vault protein (10). Vaults are complex ribonucleoprotein particles containing at least two high-molecular-weight proteins and a small RNA molecule in addition to the 110-kd major vault protein (11). Most vaults are present in the cytoplasm, but a small portion is localized in the nuclear membrane and nuclear pore complex. The structure and localization of the vaults have led to the speculation that vaults mediate the bidirectional transport of a variety of substrates between the nucleus and the cytoplasm. It is conceivable that these substrates could include cytotoxic drugs.

Determining whether LRP is causally related to multidrug resistance is problematic for at least two reasons. First, transfection of cells with complementary DNA constructs encoding the major vault protein does not result in drug resistance. However, because the vault is a multiprotein complex structure, perhaps it is not surprising that overproduction of a single component may not be sufficient to increase vault activity and thereby confer drug resistance. Second, LRP is very often expressed concomitantly with other drug-resistance genes, especially multidrug-resistance protein and breast cancer-resistant protein. Excluding the involvement of these other drug-resistance proteins so that the role of LRP can be determined has been problematic. The results obtained by Kitazono et al. are noteworthy because their experimental approach allowed them to overcome both obstacles by use of LRP-specific ribozymes. Reduction of LRP expression in a cell line induced to overexpress LRP, as well as MRP1 and P-glycoprotein, by exposing cells to sodium butyrate was enough to reverse drug resistance. Moreover, MRP1 and P-glycoprotein were found to be nonfunctional when induced by sodium butyrate. Therefore, to our knowledge, this is the first study providing evidence demonstrating a possible causal relationship between LRP expression and drug resistance.

While these findings are very interesting, they require confirmation by other investigators using similar experimental approaches. In addition, the actual mechanism by which vaults might confer drug resistance is unknown. There is no evidence that vaults transport or even bind drugs. The experiments by Kitazono et al. (8) that use anti-LRP polyclonal antibodies to increase drug concentration in the nuclei of drug-resistant cells are provocative but do not conclusively demonstrate that vaults

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are involved with transport of drugs from the nucleus to the cytoplasm.

Finally, studies have demonstrated that vaults are overexpressed in multidrug-resistant cancer cell lines, and clinical studies (12–15) have reported that LRP expression predicts for drug resistance and poor outcome in patients with acute myelogenous leukemia, ovarian cancer, and possibly other cancers. The article by Kitazono et al. now provides evidence that the expression of LRP may actually be causally related to clinical drug resistance. This determination is extremely important if we are to design approaches to overcome LRP-mediated resistance or merely use the expression of LRP as a marker for the presence of other drug-resistance mechanisms. Both basic science and clinical studies are needed to address this important issue.

REFERENCES