MULTIDRUG RESISTANCE REVERSAL IN CANCER CELLS AND IN PATHOGENIC MICROORGANISMS

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ATP-binding cassette proteins form a superfamily of highly conserved transmembrane transporters, and many of them are involved in the trafficking of biological molecules across cell membranes. The first known human ABC transporter, P-glycoprotein (P-gp), confers the multidrug resistance (MDR) of cancer cells to anticancer drugs. In resistant tumor cells, another type of multidrug transporter – MRP – is also often overexpressed. Multidrug transporters are also found in many other cells, for example in bacteria and yeast. These transporters protect cancer cells and pathogenic micro-organisms from antitumor and antimicrobial agents. The drug substrates of multidrug transporters are often structurally dissimilar. The biophysical properties of drugs, e.g. hydrophobicity or charge, are key factors in the substrate selectivity of these transporters. The resistance conferred by Pgp or other multidrug transporters can be reversed by various structurally unrelated compounds called modulators, chemosensitizers or alternatively resistance modifiers. In this study, two groups of new compounds that are active against P-gp or MRP efflux pumps were presented. The inhibitory activity of the compounds was examined in functional tests based on measurements of fluorescent substrate efflux mediated by these transporters. Different possible mechanisms of the action of multidrug resistance modulators was suggested. Several lines of evidence indicate that lipophilic drugs interact with multidrug transporters via membrane bilayers. The role of substrate and modulators interactions with the lipid phase of the membrane, as well as the role of passive transbilayer drug movement in multidrug resistance and its modulation, were discussed. In this study, lipid bilayer/buffer partition coefficients for different modulators were estimated. Perturbation of lipid membranes in the presence of these compounds was revealed via spectroscopic and microcalorimetric methods. The effect of modulators on lipid phase properties was correlated with their influence on fluorescence substrate accumulation in cells with expression of P-gp or MRP1. Although many substrates and inhibitors can compete for protein binding sites, our results clearly indicate that both direct membrane transporter and indirect lipid interactions should be taken into account in the evaluation of the mechanism of multidrug resistance reversal by studied compounds. In the case of microorganisms, the synergistic action of antibacterial or antifungal agents and MDR inhibitors was also discussed.