Drug Resistance as a Biochemical Target in Cancer Chemotherapy
Bristol-Myers Squibb Cancer Symposia, vol. 13
XXV+ 342 pp.; $55.00 ISBN 0-12-702295-3

Multidrug resistance (MDR) to cancer chemotherapy was the dominant theme of the 13th Bristol-Myers Squibb Symposium on Cancer Research in Tokyo in 1991. Actually, thanks to new techniques, MDR can now be understood at the membrane, cellular and genetic levels, and there is hope for a successful clinical attack on this problem.

Selection for resistance to a single anticancer agent, mainly from the class of natural products, can confer resistance to a group of unrelated compounds having dissimilar mechanisms of action. Mediators of MDR are mainly P-170 glycoprotein (GP), DNA topoisomerases, protein kinases and glutathione transferase.

Functionally, as explained in the Introduction by G.A. Court, the main biochemical feature of MDR is an increased capacity of resistant cells to transport drug out of the cells, conferred by overexpression by the P-170 GP. This can be induced e.g. by selecting MCF-7 cells in vitro with Adriamycin. This overexpression is accompanied with resistance also to tamoxifen and estrogen.

P. Borts et al. start Part I of the book – Genetic aspects of MDR – with data on the P-GP gene family, drug-transporting P-GP. As shown by Roninson et al., in the human genome there are two related MDR genes which are highly amplified in MDR cells as shown by gene transfer by transfection with genomic DNA followed by selection with Adriamycin, colchicine or vinblastine. Gottesman et al. describe in detail the function of this ‘multidrug transporter’, P-GP, which might be involved in the extraction of hydrophobic drugs from lipid bilayers. Greenberger et al. present data on the expression of P-GP coded by MDR genes. V. Ling describes, with color pictures, gene families of P-GP in humans.

The second part of the book deals with the reversal of MDR. T Tsuruo, one of the editors, deals with the basic approaches for reversal of MDR, i.e. with P-GP as a target of cancer chemotherapy.

Benedetti et al. present data on DNA topoisomerases as targets for therapeutic agents and on the expression of human topoisomerases in yeasts for drug screening to overcome MDR.

The implications of glutathione transferase in carcinogenesis and drug resistance are discussed by Mura-matsu et al.

Part III – Basic approaches against clinical MDR – starts with an article on clinical detection of MDR (Fojo et al.) in human cancer cells with monoclonal antibodies (Shimoyama). It deals with receptors for interleukin-2 (Taniguchi et al.), the interaction of steroid hormones with their receptors, with cytokines and drugs in breast cancer (Clarke and Dickinson).
Part IV deals with the clinical approaches against drug failure, e.g. with the clinical detection of MDR and its reversal with ‘chemosensitizers’. Salmon et al. show that calcium channel blockers, like verapamil, as well as oral quinine, could reverse MDR to vincristine, Adriamycin and dexamethasone. Verapamil and quinine are classified as first-generation chemosensitizers. Further approaches to block MDR pharmacologically are feasible (e.g. with cyclosporine analogs, monoclonal antibodies or anti-sense RNA).

MDR is one of the greatest dangers for successful anticancer chemotherapy. New discoveries and measures in this field are both exciting and promising. The 13th volume from Bristol-Myers Squibb Cancer Symposia is an excellent guide to them.

V. Krcmery, Bratislava