In vitro chemoresistance profile and expression/function of MDR associated proteins in resistant cell lines derived from CCRF-CEM, K562, A549 and MDA MB 231 parental cells*

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Although cellular experiments have elucidated a number of active principles in the study of the multidrug resistance (MDR) phenomena, most of the drug resistant tumor cells were derived from different parental cell lines. This fact limits generalization of some experimental data and conclusions, and therefore we selected and characterized cell lines resistant to various anti-cancer agents derived from four parental cell lines: CEM (human T-lymphoblastic leukemia), K562 (human myeloid leukemia), A549 (human lung adenocarcinoma) and MDA MB 231 (human breast adenocarcinoma).

In total we obtained a set of 42 resistant sublines, which is an excellent tool for the future studies of different aspects of MDR. In this study we report on some basic characteristics of these sublines, namely, cross-resistance to other anti-cancer drugs investigated by *in vitro* MTT assay, expression of MDR associated proteins (Pgp, MRP1, LRP, GST-π and Topo IIα) as well as the functional activity of Pgp and MRP.

Key words: Multidrug resistance, P-glycoprotein, MDR associated proteins, MTT assay, resistant cells, anti-cancer drugs.

Resistance of human tumors to a wide range of potent chemotherapeutic agents, designated multidrug resistance, remains a major obstacle to the successful therapy of human cancer. Intensive research in this field has defined some differences between resistant and sensitive tumor cells. These cells differ in their intracellular drug distribution and kinetics. There is also a shift in the cytoplasmatic pH of the resistant cells towards alkalisation and a high intracellular transport and exocytosis through the plasmatic membrane. A decreased ability of intracellular accumulation of toxic agents, and an increased expression/activity of some cellular proteins have also been demonstrated.

Proteins, that have been identified to confer drug resistance on tumor cells, take part either in cell transportation or detoxification or DNA replication/reparation processes. ABC-transport proteins are those on which research is focused the most. These proteins are located on cell membrane where they act as ATP-dependent membrane pumps causing the excretion of cytotoxic agents (including anti-cancer drugs) out of tumor cells. Clinically the most relevant is the expression of P-glycoprotein (Pgp, P170) [22] followed by a group of Pgp homologous proteins named as multidrug resistance-related proteins (MRP 1-8) [4, 18]. A half-transporter, the breast cancer related protein (BCRP), is the newest member of the ABC transporters with a potencial role in the drug resistance in leukemia [6, 19]. Besides ABC transport proteins there is another mechanism represented by the lung resistance-related protein (LRP). It is located intracellularly in vaults and transports toxic agents from the nucleus of neoplastic cells to the lysosomes [17, 20].

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