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Multidrug resistance in cancer: Role of caveolin, caveolae and lipid rafts

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Background

Systemic chemotherapy is a widely used treatment modality in oncology that has limited efficacy, due to multidrug resistance (MDR), defined as cellular resistance to multiple, structurally and functionally divergent drugs. MDR is often mediated by expression of drug transporters that catalyze an energy-dependent efflux of drugs, thus reducing intracellular drug concentration. P-glycoprotein (P-gp; MDR1), is a prototypic drug-efflux ATPase. This and additional MDR mechanisms are often employed concurrently by MDR tumor cells to circumvent the lethal effects of chemotherapeutic drugs (Fig. 1).

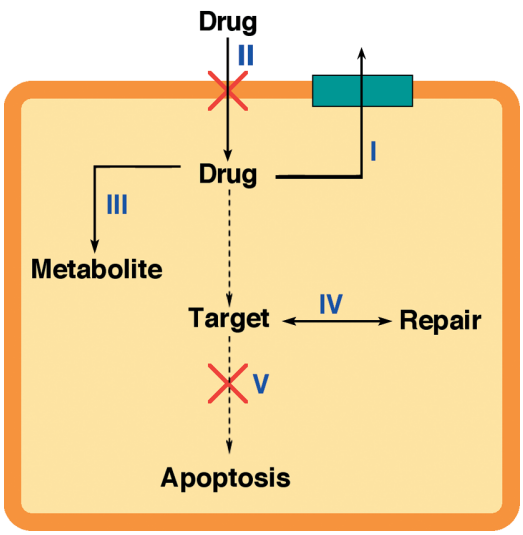

Fig. 1 *Cells adopt multiple MDR strategies: (I) expression of drug efflux pumps; (II) altered cellular drug pharmacokinetics; (III) increased drug detoxification; (IV) increased DNA damage repair; and (V) suppression of drug-induced apoptosis.*

Biological membranes contain sphingolipid- and cholesterol-rich microdomains termed lipid 'rafts'. Rafts are related in their lipid composition to caveolae, which are nonclathrin-coated plasma membrane invaginations that have a characteristic striated coat structure containing a 22 kDa protein called caveolin-1. Rafts are present in all cell types while caveolae are found mostly in epithelial and muscle cells. Caveolae have been implicated in clathrin-independent endocytosis and cholesterol efflux. Many signaling molecules are enriched in lipid rafts and caveolae, implicating them as platforms for assembly and launching of signaling cascades.

A role for caveolin-1 in MDR?

We have recently demonstrated that expression of caveolin-1 is dramatically up-regulated in several MDR human cancer cell lines. This is accompanied by elevated surface density of caveolae and other lipid and protein constituents of caveolae such as glucosylceramide and phospholipase D2. We have also observed that P-gp is localized in part in lipid rafts. These results were later confirmed in additional MDR cells lines, strongly suggesting that caveolae play a role in the acquisition of multidrug resistance in cancer cells. Our current studies are aimed to examine the role of caveolin-1 in MDR cells. We employ a caveolin-1-directed antisense oligodeoxynucleotide (Cav1-αS) to down-regulate caveolin-1 expression in human MDR cancer cells. The effects of Cav1-αS on caveolin-1 expression, the sensitivity of the cells to chemotherapeutic drugs and drug-induced apoptosis are being examined. In addition, changes in lipid raft-association of P-gp and cellular drug transport are tested. Another important aspect under study is the regulation of caveolin-1 expression by orphan nuclear receptors (i.e. PPAR-γ and PXR) and other factors (Fig. 2).

Impact of caveolin-1 expression in cancer cells

Caveolin-1 has dramatic 'oncosuppressive' effects in tumor cells. Thus, expression of caveolin-1 is likely to have important consequences on MDR tumor cell biology (Fig. 2). Utilizing MCF-7 human breast adenocarcinoma cells stably transfected with caveolin-1 (MCF-7/Cav1), we have shown that caveolin-1 attenuates MCF-7 cell proliferation and markedly reduces their capacity to form colonies in soft agar. The loss of anchorage-independent growth is not associated with stimulation of anoikis. In fact, MCF-7/Cav1 cells exhibit increased survival after detachment, indicating that caveolin-1 inhibits anoikis in MCF-7 cells. Matrix metalloprotease release and matrix invasion, two important metastasis-related phenomena, were also inhibited by caveolin-1 (in collaboration with Dr. Reuven Reich, HUJ). Additionally, laminin induced activation of ERK1/2 was inhibited in MCF-7/Cav1 cells. The inhibitory effect of

caveolin-1 on these processes suggests that caveolin-1 may impose major phenotypic changes in human cancer cells. We have found that NCI/AdrR human MDR cancer cells are indeed incapable of anchorage-independent growth, indicating that they have an essential requirement for an extracellular matrix-derived growth signal. Furthermore, like MCF-7/Cav1 cells, NCI/AdrR cells are resistant to anoikis. Currently we are studying the involvement of caveolin-1 in mediating these phenotypes. Another important goal of our future work is to identify the matrix-derived signal and how it is transduced inside the cell. This requirement for a matrix-derived signal may prove to be a previously unsuspected Achilles' heel of MDR cells, enabling future development of much needed novel drugs for treatment of multidrug resistant cancer.

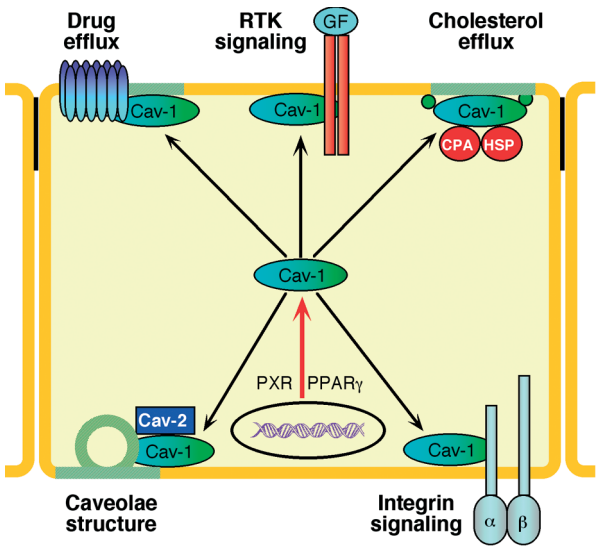

Fig. 2 *Caveolin-1 has been implicated in modulation of signaling by receptor tyrosine kinases (RTK) and integrins and in transport pathways (drug transporter(s), cholesterol efflux), processes which may be relevant in caveolin-1-expressing MDR cells.*

Selected Publications

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Fiucci, G., Ravid, D., Reich, R. and M. Liscovitch (2002) Caveolin-1 inhibits anchorage-independent growth, anoikis and invasiveness in MCF-7 human breast cancer cells (submitted).

Fiucci, G., Ravid, D. and M. Liscovitch (2002) Adhesion-dependent association of caveolin-1 and Shc in NCI/AdrR human multidrug resistant cancer cells. (submitted).

Acknowledgements

Our work is supported by grants from the U.S.-Israel Binational Science Foundation, the Israel Ministry of Science, the German Cancer Research Center, the Harry Levine Fund, the Mary Ralph Fund and the Willner Center for Vascular Biology. M.L. is incumbent of the Harold L. Korda Professorial Chair in Biology.

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