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Caveolin-1: Multiple actions in human cancer cells

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Background and rationale

Caveolin-1 is an essential protein constituent of plasma membrane caveolae, which are non-clathrin-coated, flask-shaped invaginations of the plasma membrane. Caveolin-1 is a principal component of the caveolar coat and a regulator of caveolae-dependent signaling and endocytosis. The expression of caveolin-1 is tightly controlled: it is up regulated in terminally differentiated epithelial cells and, conversely, down regulated upon oncogenic transformation. In addition, heterologous expression of caveolin-1 inhibits mitogenic signaling in cancer cells, while antisense suppression of caveolin-1 expression leads to fibroblast transformation. Finally, caveolin-1-null mice exhibit tissue-specific hyperplasia and increased sensitivity to oncogene- and carcinogen-induced tumorigenesis. These results led to the suggestion that caveolin-1 is a growth-inhibitory protein that may act as a tumor-suppressor. However, this idea is inconsistent with the fact that caveolin-1 is highly expressed in many cancer cell lines. A large body of data that has accumulated over the last 5 years reveals that in some forms of cancer caveolin-1 expression is down regulated, but in many other cancers caveolin-1 levels are high. The expression of caveolin-1 is positively correlated with the tumor cell grade and its progression stage (see Liscovitch et al., 2004).

These data highlight an important question: Why a putative tumor suppressor protein like caveolin-1 is highly expressed in so many cancer cells? One possibility is that in such cancer cells caveolin-1 promotes cell survival. Indeed, the ability of caveolin-1 to effect both growth-inhibitory and survival-promoting actions may explain its divergent expression in human cancers (Fig. 1). Therefore, the main focus of our current research is to elucidate the function(s) of caveolin-1 in human cancer cell lines and to examine the hypothesis that its expression in advanced stage, multidrug resistant and/or metastatic cancer is related to its pro-survival actions.

Summary of current research

To study the role of caveolin-1 in human cancer cells we have taken two approaches: (i) Overexpression of caveolin-1 in caveolin-negative cells and, conversely, (ii) gene-specific suppression of caveolin-1 expression or function in caveolin-positive cells. We have shown recently that stable expression of caveolin-1 in MCF-7 cells results in abrogation of anchorage-independent growth (Fiucci et al., 2002). Surprisingly, further studies revealed that expression of caveolin-1 results in inhibition of anoikis (detachment-induced apoptosis), indicating that caveolin-1 promotes matrix-independent survival. Caveolin-1 expression also prevents detachment-induced activation of p53. Our data suggest that caveolin-1 enhances matrix-independent cell survival by a mechanism that could be mediated by up-regulation of IGF-I receptor expression and signaling (D. Ravid).

In parallel studies we are testing the effect(s) of a dominant negative caveolin-1 mutant ($Cav1^{P132L}$) in HT29-MDR cells. Our preliminary results indicate that stable expression of $Cav1^{P132L}$ reduces clonal colony size in HT29-MDR cells. As clonal growth of cancer cells is largely dependent on autocrine growth/survival factors, the results suggest that caveolin-1 may positively regulate cell response to an autocrine factor that remains to be identified. We are also testing whether caveolin-1-specific down-regulation by RNA interference has a similar effect in other human cancer cell lines (M. Shatz).

Caveolin-1 is up regulated in numerous human MDR cancer cells (Lavie et al., 1998). P-glycoprotein (P-gp), a prototypical MDR transporter (Liscovitch and Lavie, 2002), is partially co-localized with caveolin-1 in lipid rafts and is co-

immunoprecipitated with caveolin-1. To elucidate the functional relationship of caveolin-1 and P-gp we are testing the possible role of caveolin-1 in regulating the endocytosis of P-gp in human MDR cancer cells (N. Jain). In addition, caveolin-1 may affect the ability of MDR cells to withstand genotoxic and/or oxidative stress. In this context, we have recently shown that specific activators of peroxisome proliferator-activated receptor (PPAR)-γ induce caveolin-1 mRNA and protein expression in both MCF-7 breast and HT29 colon cancer cells (Burgermeister et al., 2003). More recently we have shown that PPARγ activation increases cellular resistance to oxidative stress and reduces cancer cell sensitivity to high concentrations of doxorubicin. Our current studies are aimed to define the mechanisms involved in regulation of caveolin-1 by PPARγ ligands and in mediating their effect on cancer cell resistance to stress stimuli (L. Tencer).

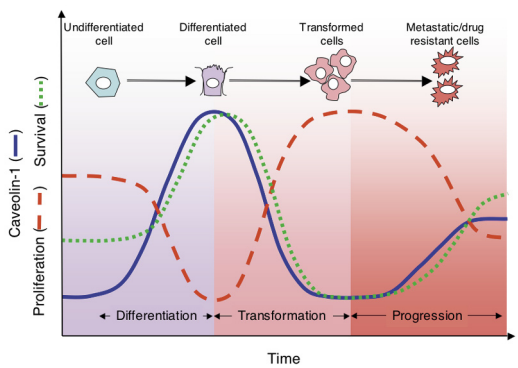

Fig. 1 *Dynamic changes in caveolin-1 expression during cell differentiation, tumor initiation and tumor progression*

Phospholipase D2 (PLD2) is a caveolae-resident enzyme that has been implicated in cell signaling and membrane trafficking events (Liscovitch et al., 2000) and is up-regulated in MDR cancer cells (Fiucci et al., 2000). PLD1 and PLD2 gene-specific suppression reagents are being generated, that will be utilized to evaluate the actions of PLD1 and PLD2 in mediating growth factor-dependent signaling and changes of the transformed phenotype of human cancer cells (G. Lustig and J. Troost).

Finally, we designed and are developing a novel method for engineering ligand-sensitive conditional mutant proteins, that could be applied in exploring the functional role of the proteins in various cellular contexts. This method will be used to determine the role played by selected proteins, including caveolin-1, in mediating the phenotypic changes that are associated with cancer cell progression to a full-fledged malignant state (O. Erster and J. Penso).

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. Oncogene 21, 2365-2375.

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Burgermeister, E., Tencer, L. and M. Liscovitch (2003) Peroxisome proliferator-activated receptor-γ upregulates caveolin-1 and caveolin-2 expression in human carcinoma cells. Oncogene 22, 3888-3900.

Liscovitch, M., Burgermeister, E., Jain, N., Ravid, D., Shatz, M. and L. Tencer (2004) Caveolin and cancer: a complex relationship. In: Membrane Microdomain Signaling: Lipid Rafts in Biology and Medicine, M.P. Mattson (Ed.), Humana Press, Totowa, New Jersey (in press).

Shatz, M. and M. Liscovitch (2004) Caveolin-1 and cancer multidrug resistance: Coordinate regulation of pro-surival proteins? Leukemia Res. (in press)

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