Caveolae in cancer: two sides of the same coin? Focus on “Hydrogen peroxide inhibits non-small cell lung cancer cell anoikis through the inhibition of caveolin-1 degradation”

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Caveolae are flask-shaped invaginations on cholesterol- and sphingolipid-rich domains of the plasma membrane that have been proposed to play a role in the localization of a wide range of signaling systems and metabolic pathways in a variety of cells. Localization of these processes to caveolae is mediated by protein-protein interactions between pathway components and caveolins, the caveolar coat proteins. Three members of the caveolin family have been described (caveolins-1, -2, and -3). Of these, caveolin-1 (Cav-1; 22 kDa) has been shown to be essential for formation of caveolae in non-muscle cells. Many proteins that interact with Cav-1 contain a caveolin-binding motif enriched in aromatic amino acids (4). Recently, an additional family of caveola-associated proteins, the cavins (cavins-1, -2, -3, and -4), has also been identified. Although the biology of cavins is just beginning to be explored, it has been suggested that cavins may regulate such diverse functions as sequestration of caveolins within caveolae, caveolar membrane curvature, intracellular movement of caveolae, and coupling of caveolae signaling with nuclear signaling (9).

It has proven very difficult to unravel the role of caveolae in health and disease, because of the complex spatial and temporal associations of macromolecules/cell functions with caveolae (10). A key (and controversial) example is the role of caveolae in cancer cell growth, drug resistance, and metastatic potential. One notable characteristic of cancer cells is their high rate of glycolysis and lactate production (the Warburg effect), and caveolae have been shown to localize the glycolytic pathway to the plasma membrane (14, 24, 25). Hypoxic tumors, which have especially high lactate production rates and are able to survive using glycolysis, are more drug resistant and metastatic (1, 5). Therefore, the role of caveolae in cancer cell drug resistance and metastatic potential is of considerable interest. In this issue, Rungtabnapa et al. (19) begin to dissect out a novel role for caveolae in enabling cancer cells to survive detachment and gain metastatic potential.

Caveolin-1: Tumor Suppressor or Oncogene?

Evidence from in vitro studies investigating the role of Cav-1 in cancer is contradictory, with some studies supporting the conclusion that Cav-1 functions as a tumor suppressor gene, while others indicate that it is an oncogene. Early studies suggested that Cav-1 functions as a tumor suppressor gene. Cav-1 levels were shown to be reduced in oncogenically transformed fibroblasts, and the ability of the transformed cells to form colonies in soft agar was inversely correlated with Cav-1 levels; furthermore, induction of Cav-1 expression inhibited colony growth and/or induced apoptosis in transformed cells and breast cancer cells (6, 7, 12). Further studies showed that Cav-1 levels were inversely correlated with metastatic potential in breast adenocarcinoma cells (20). Simultaneously, however, evidence for an oncogenic role of Cav-1 also began to accumulate. Such evidence included the demonstration that Cav-1 levels are increased in drug-resistant variants of human lung carcinoma, ovarian carcinoma, colon adenocarcinoma, and breast adenocarcinoma cell lines (13, 29). In addition, lung adenocarcinoma cells selected for a highly invasive phenotype had elevated Cav-1 levels (11). Interestingly, prostate cancer cells were found to secrete Cav-1; the secreted Cav-1 can be taken up by tumor cells and endothelial cells and may promote tumor angiogenesis (22, 23). These in vitro studies implicated elevated Cav-1 expression in the development of drug resistance and tumor metastasis.

Contradictory results have also been obtained from in vivo studies in both animal models and human patients. Genetic deletion of Cav-1 in mice with breast cancer induced by oncogenic transformation resulted in increased tumorigenesis and lung metastasis, again supporting a role for Cav-1 as a tumor suppressor (28). However, lung metastases of mice with prostate cancer were found to have increased Cav-1 expression compared with the primary tumor; likewise, Cav-1 levels in lymph node metastases of human prostate and breast cancers were shown to have higher Cav-1 expression than normal epithelia from these tissues (30). Thus, these in vivo studies supported an oncogenic, prometastatic function for Cav-1. Indeed, increased Cav-1 levels are associated with decreased survival in human patients with several types of cancer (for a review, see Ref. 8).

A model that attempts to reconcile at least some of these contradictory findings has emerged. This model proposes that Cav-1 levels vary during the course of tumor progression, with downregulation of Cav-1 in early stages facilitating oncogenic transformation, but with reexpression of Cav-1 at later stages (in some tumors) possibly contributing to the development of drug resistance and metastatic potential (18, 27). Thus, Cav-1 may function as both a tumor suppressor and an oncogene, depending on the stage of oncogenic transformation and extent of tumor progression (Fig. 1). It also seems clear that the role of Cav-1 is highly dependent on tumor type (for a review, see Ref. 27).

Hydrogen Peroxide, Cav-1, and Anoikis

The acquisition of an ability to grow without receiving signals from the extracellular matrix is a key feature of metastatic tumor cells. When deprived of contact with the extracel-
fluorescence staining and flow cytometry in cells treated with... increase in ROS. Intracellular ROS levels were examined with... that detachment of NCI-H460 cells induces a time-dependent... expression and anoikis following cell detachment. They report... Cav-1, whereas exogenous H2O2 had the opposite effect. Again, peroxide... limits anoikis in detached cells. To determine whether the effects of peroxide are mediated by a Cav-1-dependent mechanism,... Cav-1 protein levels were measured in detached cells treated with and without a ROS scavenger. Again, peroxide was found to be the key ROS involved in this signaling pathway; scavenging H2O2 decreased Cav-1 protein levels via increased ubiquitination and proteasomal degradation of Cav-1, whereas exogenous H2O2 had the opposite effect. Finally, the ability of NCI-H460 cells to form colonies in soft agar was increased by exogenous H2O2 and blocked by cata-

Cav-1 overexpression similarly enhanced colony formation, whereas knockdown of Cav-1 with a small hairpin RNA resulted in increased cell death. The results of Rungtabnapa and coauthors mesh nicely with findings from other recent studies of mechanisms mediating anoikis. One mechanism by which cell detachment is thought to induce anoikis is via inhibition of phosphatidylinositol 3-kinase (PI3K)/Akt signaling; in contrast, integrin-linked H2O2 production activates PI3K/Akt in adherent cells to prevent anoikis (16). The authors of the present paper and others have shown that increased Cav-1 levels cause constitutive activation of PI3K/Akt signaling (2, 17). Thus, the work presented in this issue provides an important link between these previous studies. Another recent report from this group describes a role for ROS in Cav-1-mediated migration and invasion of NCI-H460 cells (15). Along with that work, the present article provides new insights into how ROS may contribute to metastatic potential of tumor cells via altered regulation of Cav-1. Further characterization of this signaling pathway could eventually lead to new mechanism-based antimitastasis therapies for patients with Cav-1-expressing tumors.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).
REFERENCES


