Caveolin-1: a critical regulator of pulmonary vascular architecture and nitric oxide bioavailability in pulmonary hypertension

Stefan W. Ryter1 and Augustine M. K. Choi2

1Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Pittsburgh, Pennsylvania, and 2Division of Pulmonary and Critical Care Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts

Caveolae are 50- to 100-nm o-shaped invaginations of the cell surface plasma membrane enriched in glycosphingolipids and cholesterol that occur in a variety of cell types including epithelial and endothelial cells, fibroblasts, smooth muscle cells, and adipocytes (1). These structures facilitate endocytosis of particles and participate in vesicular trafficking. Caveolin-1 (cav-1), a 21- to 24-kDa protein, is the major resident scaffolding protein constituent of caveolae (1). In addition to providing the structural integrity of caveolae, cav-1 exerts major regulatory functions on intracellular signaling pathways, in particular, those that originate at the plasma membrane. Cav-1 can form complexes with many signaling-associated proteins that reside in the caveolae, resulting in the modulation and usually inhibition of corresponding enzymatic activities. Among these are the endothelial (constitutive) nitric oxide synthase (eNOS; Ref. 5), heme oxygenase-1 (9), phosphatidylinositol 3-kinase, GTPases, estrogen receptors, the EGF and PDGF receptors, and others (1, 16).

The profound involvement of cav-1 in cellular and tissue homeostasis is evident by the aberrant pulmonary and vascular phenotypes observed in cav-1 (cav-1−/−) animals, among which include hypercellularity in the lungs and heart (2, 4, 17–18). Although cav-1−/− mice are viable, they display a dramatically shortened life span and a distinct loss of caveolae structures (4, 13). Furthermore, cav-1−/− mice exhibit insulin resistance and hyperproliferation of adipose tissue (3). Significant cardiac defects were observed in cav-1−/− mice including increased right ventricular volume and hypertrophy, left ventricular wall thickening, loss of systolic function, and evidence of cardiac fibrosis (2, 4, 22). The lungs of cav-1−/− mice display a thickening of the parenchyma and alveolar septae resulting from bronchial and alveolar epithelial cell hyperproliferation (12, 17), evidence of endothelial cell proliferation (17), and pulmonary fibrosis (4).

Despite systemic hypotension, cav-1−/− animals develop significant pulmonary hypertension and associated increases in pulmonary artery pressure and right ventricular hypertrophy as described in this issue of AJP-Lung by Maniatis et al. (11) and by others (4, 17, 23). Endothelial cell-specific reconstitution of cav-1 expression in cav-1−/− mice restored the pulmonary and vascular defects observed in these animals, as evident by the reversal of the pulmonary hypertension and cardiac hypertrophy (12). Alveolar hypercellularity was also partially compensated by cav-1 reconstitution, which inhibited the endothelial cell proliferation (12). These studies illustrate a major role for endothelium-expressed cav-1 in vascular homeostasis, although the importance of this molecule is not limited to endothelial cells.

Extensive experimentation with cav-1−/− mice has revealed the critical role of cav-1 in the regulation of signaling processes. Cav-1−/− mice display increased eNOS expression in cardiac tissue, increased eNOS activity in aortic rings and responsiveness to acetylcholine-induced relaxation, increased systemic nitric oxide (NO) production, as well as increased NO release from vascular smooth muscle cells derived from these animals (2, 4, 17). The increased NO bioavailability for vascular processes has also been associated with increased nitrosative stress in these animals, as evidenced by increased nitrotyrosine formation in cardiac tissue (22). Further evidence of deregulated signaling pathways were evident by increased p42/44 MAPK (ERK1/2) activation in cardiac fibroblasts from cav-1−/− mice as well as increased Akt activation in lung vasculature, which promote the cardiac and pulmonary hypercellularity (2, 12).

Cav-1 is known to reduce cell growth and influence apoptosis by inhibiting the activation of growth factor receptors and their downstream signaling pathways (1, 16). In addition, cav-1−/− negatively regulates smooth muscle cell proliferation (10, 15) and arrests mouse embryonic fibroblasts in the G0/G1 phase (6). Consistently, cav-1−/− mice show increased vascular smooth muscle cell proliferation and intimal hyperplasia in response to vascular injury (8), whereas stimulation of cav-1 expression decreases intimal hyperplasia (10). Cav-1 expression is increased in senescent cells and aged animals (14, 18). Furthermore, cav-1 has been identified as a candidate tumor-suppressor gene, such that mutations in the cav-1 gene have been associated with the growth of tumors (1). Wang et al. (19) have recently shown a critical antifibrotic potential of cav-1, such that cav-1 expression inhibited bleomycin-induced pulmonary fibrosis in mice. Furthermore, cav-1 expression was reduced in lung tissues and in primary pulmonary fibroblasts from idiopathic pulmonary fibrosis patients compared with controls (19). These reports, taken together, indicate that cav-1 plays important roles in the suppression of cellular proliferation, which can contribute to various vascular and pulmonary diseases.

The current article in focus by Maniatis et al. (11) further demonstrates an antihypertensive and homeostatic function of cav-1 with respect to the pulmonary vascular architecture. In agreement with previous studies, cav-1−/− mice developed pulmonary hypertension as evidenced by increased vascular resistance, which the authors localized to the precapillary bed, with associated right ventricular hypertrophy. The development of pulmonary hypertension in cav-1−/− animals occurred despite the increased vascular NO production as the conse-
quence of the loss of cav-1-dependent inhibition of eNOS activity. Chemical inhibition of NO production by acute treatment with Nω-nitro-l-arginine methyl ester (l-NNAME) increased pulmonary vascular resistance in both wild-type and cav-1−/− strains, although the effect was more pronounced in cav-1−/− mice. Furthermore, cav-1−/− were relatively resistant to vasoconstrictor-mediated responses relative to wild-type mice. These experiments are consistent with the measured twofold increase of plasma NO levels in cav-1−/− mice (11).

Consistent with previous observations (4), cav-1−/− mice exhibited increased hypercellularity of the lung, thickening of the alveolar septae, and increased matrix deposition in the lung parenchyma with increases in α-smooth muscle actin and redistribution of collagen expression in lung parenchyma (11). Fluorescence imaging and electron microscopic studies revealed profound disruption of the pulmonary vasculature including remodeling and disorganization of precapillary vessels, decreased arterial density, and increased artery-filling defects in cav-1−/− mice. Additionally some evidence of perivascular fibrosis was observed (11).

Based on these observations, Maniatis et al. (11) conclude that the increased NO production in cav-1−/− mice can provide a counter-regulatory mechanism that partially compensates for the increased vascular resistance observed in these animals. The hypertension in cav-1−/− mice was attributed primarily to morphological changes of the vasculature. Whereas NO, in addition to stimulating vasodilation, is known to inhibit smooth muscle cell proliferation, the increases in NO production in cav-1−/− mice apparently do not serve to inhibit the vascular remodeling that occurs with loss of cav-1 (11).

The question remains as to whether the increased NO production contributes to disease pathogenesis in these animals, despite beneficial reversal of pulmonary artery resistance. This issue has been further addressed in the recent studies of Wunderlich et al. (21), which show that chronic application of l-NNAME since the time of birth reduced pulmonary hypertension and vascular remodeling in cav-1−/− mice, which implies a role for aberrant NO production in the early progression of vascular remodeling in these mice. It should be noted that eNOS-deficient mice, which are not viable, also display severe defects in pulmonary vascular development and pulmonary hypertension, thus illustrating potential contributory roles for both NO deficit and NO overproduction in the pathogenesis of this disease (7).

In conclusion, the influence of cav-1 on vascular processes and vascular disease pathogenesis appears to be complex, potentially involving the modulation of signaling pathways that regulate cellular proliferation as well as vascular tone but are not necessarily restricted to modulation of NO bioavailability alone. Other potentially important sequelae of cav-1 deletion may include altered regulation of apoptosis and inflammation as suggested by other recent studies (20, 22). These additional functions of cav-1 may be relevant since pulmonary hypertension is associated with endothelial cell-specific apoptosis and considerable vascular inflammation. The studies of Maniatis et al. (11) provide an in-depth analysis of the pulmonary vascular defects that occur in cav-1−/− mice. From this work, it is evident that more research is required to understand the complex roles of cav-1 and its interrelationships with NO production in the context of pulmonary hypertension and other vascular disorders involving hyperproliferative responses.

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REFERENCES


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