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## Caveolae, caveolin-1 and cavin-1: Emerging roles in pulmonary hypertension

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### Abstract

Caveolae are flask-shaped invaginations of cell membrane that play a significant structural and functional role. Caveolae harbor a variety of signaling molecules and serve to receive, concentrate and transmit extracellular signals across the membrane. Caveolins are the main structural proteins residing in the caveolae. Caveolins and another category of newly identified caveolae regulatory proteins, named cavins, are not only responsible for caveolae formation, but also interact with signaling complexes in the caveolae and regulate transmission of signals across the membrane. In the lung, two of the three caveolin isoforms, *i.e.*, cav-1 and -2, are expressed ubiquitously. Cavin protein family is composed of four proteins, named cavin-1 (or PTRF for polymerase I and transcript release factor), cavin-2 (or SDPR for serum deprivation protein response), cavin-3 (or SRBC for sdr-related gene product that binds to-c-kinase) and cavin-4 (or MURC for muscle restricted coiled-coiled protein or cavin-4). All the caveolin and cavin proteins are essential regulators for caveolae dynamics. Recently, emerging evidence suggest that caveolae and its associated proteins play crucial roles in development and progression of pulmonary hypertension. The focus of this review is to outline and discuss the contrast in alteration of cav-1 (cav-1),-2 and cavin-1 (PTRF) expression and downstream signaling mechanisms between human and experimental models of pulmonary hypertension.

### Keywords

Caveolae; Caveolin-1; Cavin-1; Pulmonary hypertension; Lipid rafts

## INTRODUCTION

The cell membrane is a dynamic, fluid structure containing lipids and proteins that are asymmetrically distributed between the outer and inner leaflets of the membrane. It

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functions not only as a protective boundary to the cell, but also aids in selective molecular transport and transduction of signals across the membrane. These processes are facilitated by membrane proteins that form macromolecular complexes and are highly organized with respect to time and position. In some cases, these complexes are localized to specific regions of the cell membrane, such as lipid rafts and caveolae<sup>[1]</sup>. Caveolae are (Ω)- or flask-shaped invaginations of the plasma membrane. While the surrounding plasma membrane contains mostly lipids with kinked-unsaturated fatty acids, the caveolae have a high concentration of saturated straight chain fatty acids and cholesterol, which makes the structure rigid and highly organized<sup>[1]</sup>. This organization is maintained by proteins called caveolin, lining the inner leaflet; sometimes referred to as “caveolin-coat”. Three distinct caveolin proteins have been identified in humans: caveolin-1 (cav-1), caveolin-2 (cav-2) and caveolin-3 (cav-3)<sup>[2]</sup>. Cav-3 is mostly expressed in skeletal and smooth muscle cells, while cav-1 and -2 are widely expressed in many cell types.

In addition to the coat protein caveolin, caveolae also have an inner lining of adapter proteins called cavin. The cavin family consists of four members (cavin-1 to -4) with common structural features including leucine zipper motifs, PEST (Pro-Glu-Ser-Thr-rich) sequence and phosphoregulatory sites<sup>[3]</sup>. Among the different cavin, cavin-1 is the most abundantly expressed and extensively studied.

As discussed above, signaling protein complexes are organized and concentrated in the caveolae which serve to receive, concentrate and transmit extracellular signals across the cell. And since caveolae are covered with a “caveolin-coat”, it is imperative that caveolin plays an important role in transmitting these signals *via* interaction with the signaling protein complexes.

In this review we will discuss the role of cav-1 and cavin-1 as a regulator in lung disease, specifically pulmonary hypertension.

Pulmonary hypertension is a chronic and progressive disease characterized by high mean pulmonary arterial pressure (> 25 mmHg at rest). Common symptoms include shortness of breath, dizziness, edema and fatigue. Right heart catheterization and six-minute walk test are often performed to diagnose the disease. However, due to the non-specific nature of symptoms of the disease, by the time patients are diagnosed, frequently, they are at an advanced stage of the disease. Endothelial dysfunction, pulmonary vasoconstriction and vascular remodeling are the common features of pulmonary hypertension of different etiologies. Dysfunctional endothelial cells in PH patients have an altered production of endothelial vasoactive mediators such as NO, endothelin-1, prostacyclin, thromboxane and serotonin<sup>[4]</sup>. Pulmonary vasoconstriction in response to airway hypoxia is a physiological response to redirect blood flow from poorly ventilated regions of the lungs to well oxygenated regions<sup>[5]</sup>. Pulmonary vascular remodeling refers to a process that causes thickening of the arterial wall, wherein phenotypic and morphological changes occur in all three layers of the vessel wall: intima, media and adventitia. In more severe forms of PH, such as that in idiopathic and heritable PAH, the additional formation of complex cellular and fibrotic neointimal and plexiform lesions in distal pulmonary arteries is often identified, which involve the proliferation of both PSMCs and PAECs<sup>[6-8]</sup>. Without treatment, these

conditions lead to right ventricular hypertrophy, right heart failure and premature death. Currently, the exact molecular mechanisms underlying the development of pulmonary vasoconstriction and pulmonary arterial remodeling are still unclear. This is mostly due to the fact that pulmonary hypertension is a disease condition that is associated with a wide range of underlying medical conditions and environmental exposures<sup>[9]</sup>. Interestingly, many of the signaling proteins implicated in the pathobiology of PH such as eNOS, VEGF receptor and prostacyclin receptors are known to interact with the membrane protein, cav-1 in caveolae of endothelial cells<sup>[10–13]</sup>, as reviewed below in detail.

## CAV-1 STRUCTURE AND FUNCTION

Cav-1 is a 22 kDa phosphoprotein present in many cell types in the lung including endothelial cells, type I epithelial cells, airway and vascular smooth muscle cells, fibroblasts, macrophages and neutrophils<sup>[14]</sup>. The *CAVI* gene on chromosome 7 encodes a 178 amino acid protein<sup>[15]</sup>. Cav-1 protein exists in two isoforms: cav-1 $\alpha$  and cav-1 $\beta$  that are derived from the use of two distinct transcription initiation sites<sup>[16]</sup>. Pulse-chase analysis studies have shown that soon after the cav-1 protein is synthesized in the ER, it forms homooligomers of approximately 14–16 monomers before being translocated to the plasma membrane<sup>[17,18]</sup>. The oligomerization is brought about by a series of 40 amino acids from residues 61–101 of cav-1. This is called the oligomerization domain (OD). The OD also contains the caveolin scaffolding domain (CSD) which spans from residues 82–101 (Figure 1). The CSD interacts with several other membrane proteins, most of which are signaling proteins that have a cav-1 binding motif<sup>[19]</sup>. Cav-1 also has a membrane spanning segment (residues 102–134), also called the transmembrane domain (TMD), formed by a hydrophobic loop configuration exposing the N- and C-termini to the cytoplasm<sup>[17,20]</sup>. The TMD is flanked by membrane attachment domains on each side called the N-terminal membrane attachment domain (N-MAD, residues 82–101) and C-terminal membrane attachment domain (C-MAD, residues 135–150) (Figure 1). Interestingly, N-MAD and C-MAD are minimal regions required to mediate attachment to the membrane. While the N-MAD targets cav-1 attachment to caveolae membrane, C-MAD facilitates trans-golgi targeting<sup>[21]</sup>. Additionally, the C-terminus has three palmitoylation sites on cysteine residues (133, 143 and 156)<sup>[22]</sup>, and the N-terminus has a phosphorylation site on tyrosine-14<sup>[23]</sup> (Figure 1).

Various studies have shown that cav-1 plays an important role in the formation of caveolae (Figure 2). Most importantly: (1) Mice lacking the *CAV1* gene (*CAV1*<sup>-/-</sup>) do not have caveolae on the plasma membrane<sup>[24]</sup>; (2) Cells that do not have detectable cav-1 and endogenous caveolae on their membranes, were able to form plasma membrane invaginations *de novo*, upon transient expression of cav-1 in these cells<sup>[25,26]</sup>. Cav-1 also aids in cellular transport namely, transcytosis<sup>[27,28]</sup>, endocytosis<sup>[29,30]</sup> and exocytosis<sup>[31]</sup>. Caveolins have also been implicated in cholesterol homeostasis. Since its discovery, cav-1's association with cholesterol has been demonstrated in several studies<sup>[32–34]</sup>. Cholesterol binds to cav-1 in the ER and is then transported to caveolae where it can be either released outside the cell or added to the plasma membrane layer<sup>[35,36]</sup>. The three palmitoylation sites on C-terminus are required for cholesterol binding of cav-1 and transport to caveolae<sup>[37]</sup> (Figure 2). Numerous plasma membrane-signaling protein complexes have been reported to

concentrate in caveolae in different cell types. These proteins have caveolin binding sequence motif that allows them to interact with CSD on cav-1. Some of the cav-1-associated proteins that have been reported are: endothelial-NO synthase (eNOS), G-protein  $\alpha$ -subunits, insulin receptor, Rho A and TGF $\beta$  receptors<sup>[34,38–41]</sup>.

## CAV-1 IN HUMAN PULMONARY HYPERTENSION

Geraci *et al*<sup>[42]</sup> in 2001, first reported a decrease in cav-1 mRNA level, in lung tissue samples from severe PH patients, in a gene expression profiling study. Further, immunohistochemical studies in lungs from severe PH patients show a lack of cav-1 staining in complex plexiform lesions and muscularized precapillary arterioles. Cav-2, a protein that normally co-localizes with cav-1 also shows decreased expression in plexiform lesions<sup>[43]</sup>. Plexiform lesions are mainly composed of highly proliferative endothelial cells and are characteristic features of pulmonary vascular remodeling<sup>[44,45]</sup>. Dysfunctional endothelial cells of pulmonary arteries play a key role in initiation and progression of PAH<sup>[46,47]</sup>. Interestingly, endothelial and smooth muscle cells of the surrounding normal-appearing vessels in the severe PH lungs express cav-1 ubiquitously<sup>[43]</sup>. In contrast, the increase in cav-1 staining is specifically seen in the vascular smooth muscle cells lining the remodeled arteries<sup>[48]</sup>. In whole lung tissue extract, cav-1 expression (by immunoblotting) is lower in IPAH lungs as compared to normal lungs<sup>[11]</sup>. This could be due to the fact that human IPAH is a complex disease and the changes in cav-1 expression are cell-specific. Endothelial cells are the majority cell type in the lung expressing abundant cav-1<sup>[49]</sup>. Therefore, the decreased cav-1 level in whole lung tissue extract reflects mainly the level of cav-1 in endothelial cells. In the pulmonary artery smooth muscle cells (PASMC) of IPAH patients, increase in cav-1 and caveolae formation enhances the capacitative calcium entry and  $[Ca^{2+}]_i$  which is attributable to the up-regulation of TRPC channels and localization to caveolae<sup>[48,50,51]</sup>. A sustained increase in  $[Ca^{2+}]_i$  is known to trigger vasoconstriction in PASMCs and also stimulate cell growth<sup>[48,52]</sup>. Therefore cav-1 up-regulation in PASMCs may also contribute to increase in pulmonary vascular resistance and pulmonary vascular remodeling.

Another interesting observation in the lungs of IPAH patients is the high level of eNOS derived NO<sup>[11]</sup> (Figure 3). NO can have beneficial or adverse effect in a disease setting like PH depending on the relative amounts of NO and reactive oxygen species (ROS)<sup>[53]</sup>. eNOS activity in the lungs of IPAH patients is substantially increased because of the reduction in cav-1 levels. Under basal conditions, cav-1 interacts with eNOS and inhibits NO production. eNOS binds to Cav-1 at a specific amino acid stretch (90–99 residues) in the caveolin scaffolding domain and inhibits its activity<sup>[54]</sup>. Loss of cav-1 in the lungs of IPAH patients leads to high NO levels and hypoxia-independent ROS production which causes peroxynitrite formation. This induces nitration of PKG at tyrosine (residues 345, 549) which impairs its kinase activity<sup>[11]</sup>, subsequently, leads to pulmonary vasoconstriction and vascular remodeling of the pulmonary arteries. Taken together, the decrease of cav-1 expression in endothelial cells and increase of cav-1 level in smooth muscle cells may both contribute to the development of severe pulmonary vascular remodeling in the pathogenesis of human PAH.

## CAV-1 IN EXPERIMENTAL MODELS OF PULMONARY HYPERTENSION

Involvement of cav-1 in pulmonary hypertension has also been demonstrated in different rodent models of severe pulmonary hypertension. Decreased cav-1 and cav-2 expression has been reported in SU5416-hypoxianormoxia<sup>[43,55]</sup> and myocardial infarction<sup>[56]</sup> models. SU5416 {3-[(2,4 dimethylpyrrol-5-yl) methylidanyl]-indolin-2-one}, is a vascular endothelial growth factor receptor-2 (VEGFR-2/Flk-1/KDR) inhibitor<sup>[57]</sup>. In the SU5416-hypoxia-normoxia model, many complex plexiform lesions show diminished immunohistochemical staining for cav-1 (Figure 3). However, in chronic hypoxia model of PH (without adding SU5416), there is no diminution in cav-1 expression<sup>[58]</sup>. Given that the plexiform lesions are prominent features in SU5416-hypoxia-normoxia models, this observation suggests that cav-1 may play an essential role in regulating pulmonary vascular remodeling. Interestingly, cav-1 has been shown to regulate the activity of VEGFR-2. Cav-1 forms a complex with VEGFR-2 in the caveolae of endothelial cells and inhibits its basal activity<sup>[12]</sup>. Similarly, overexpression of cav-1 in endothelial cells blocks VEGF-dependent activation of Elk-1 promoter activity<sup>[41]</sup>. Conversely, treatment of endothelial cells with VEGF causes a marked decrease in cav-1 protein expression<sup>[41]</sup>. Furthermore, endothelial cells isolated from cav-1 knockout mice, as compared to WT endothelial cells, show a robust and sustained increase in the tyrosine phosphorylation of VEGFR-2 upon stimulation with VEGF<sup>[59]</sup>. Apparently, although SU5416 and cav-1 depletion have opposite effects on VEGFR-2, both of these factors play a role in development of pulmonary hypertension. Further studies are required in order to dissect the signaling between SU5416 inhibition of VEGFR-2, and role of cav-1 in the SU5416-hypoxianormoxia model of severe PAH.

In the relatively older monocrotaline (MCT) model of PAH, a decrease in caveolae was first reported in 1988 where, a reduction in percent volume of caveolae was observed in endothelial cells<sup>[60]</sup>. Later on, another study showed a decrease in cav-1 protein in the caveolae fraction of MCT treated rat lungs<sup>[61]</sup>. This was accompanied by hyperactivation of the transcription factor STAT3 (PY-STAT3) and an increase in DNA synthesis (Figure 3). As seen in human IPAH lungs, there is an increase in cav-1 expression in smooth muscle cells of remodeled pulmonary arteries<sup>[62]</sup>. In this report, the authors studied the sequential events occurring after administration of MCT through the progression of PAH up to 4 wk. After administration of MCT, there is a progressive decline in endothelial cav-1, PECAM-1 and soluble guanylate cyclase (sGC) along with a progressive increase in PY-STAT3 and prosurvival protein, Bcl-xl up to 4 wk. However, endothelial vWF and smooth muscle cav-1 remain unchanged until 2 wk post-MCT. With further loss of endothelial cav-1 at 4 wk post-MCT, there is severe endothelial deterioration indicated by loss of vWF. This exposes the smooth muscle cells to shear stress and high pressure prevalent in the hypertensive pulmonary arteries. Further, this leads to an increase in smooth muscle cav-1 expression in 70% of the vWF-lacking arteries, accompanied by an increased expression and activation of MMP2 which facilitates the proliferation and migration of smooth muscle cells, eventually leading to vascular remodeling<sup>[62]</sup> (Figure 3). eNOS protein expression increases soon (48 h) after MCT administration up to one week and then decreases by about 50% by 3–4 wk post MCT<sup>[63,64]</sup>. Similarly, NO production in the lung is decreased by about 50% by 3–5 wk post-MCT<sup>[65,66]</sup>. Mechanistically, MCT treatment in endothelial cells *in vitro* leads to hypo-

oligomerization of cav-1 (< 8-mers) in the Golgi compartment and inhibits its trafficking from the Golgi compartment to caveolae on the plasma membrane<sup>[61]</sup>. Interestingly, administration of a peptide corresponding to cav-1 scaffolding domain to MCT rats is able to restore cav-1 expression in whole lung extracts and subsequently normalize right ventricular hypertrophy and pulmonary artery medial hypertrophy that is seen in MCT-PAH rats. Hyperactivation of STAT3 and increase in cyclin D1, D3 protein expression is also suppressed in the lungs of MCT treated rats after the administration of this peptide<sup>[67]</sup>.

## CAV-1 KNOCKOUT MOUSE AND PULMONARY HYPERTENSION

Cav-1 knockout mice are viable and fertile. The lung parenchyma of these mice show a multilayered, thickened alveolar septa due to increased pulmonary endothelial cell proliferation and fibrosis<sup>[24,68]</sup> possibly due to the lack of inhibition of mitogenic signals in the absence of cav-1. The highly disorganized alveolar septum comprise of mostly incompletely differentiated cells as evidenced by lack of vWF (differentiated endothelial cell marker) staining and prominent Flk-1 staining (endothelial progenitor marker)<sup>[68]</sup>. In the absence of cav-1, cav-2 expression is also reduced by up to 95%. Cav-1 is known to heterooligomerize with cav-2 and recruit it to the caveolae on plasma membrane. Depletion of cav-1 halts the trafficking of cav-2 to the plasma membrane thereby sequestering the residual cav-2 mostly in the Golgi compartments<sup>[24]</sup>. However, depletion of cav-2 in the cav-2 knockout mouse does not affect the expression and trafficking of cav-1 to plasma membrane. Also, caveolae formation is not affected by the absence of cav-2. But cav-2 knockout mice demonstrate alveolar septal thickening, endothelial hyperproliferation and exercise intolerance similar to cav-1 knockout mice, without any altered lipid homeostasis and vascular dysfunction<sup>[69]</sup>. This observation suggests that cav-2 has selective function in lung homeostasis and is independent of caveolae formation. The depletion of cav-1 gene in the knockout mice however, does not affect the presence of clathrin-coated pits in the cells of these animals<sup>[24]</sup>. This could be one of the workaround mechanisms by which these cells overcome the lack of caveolae that could make the cav-1 knockout mice viable. These cav-1 knockout mice also exhibit remarkable exercise intolerance as assessed by a forced swimming test. Cav-1 knockout mice develop marked right ventricular hypertrophy indicating a chronic elevated pulmonary artery pressure<sup>[70]</sup>. Indeed pulmonary artery pressure is increased in cav-1 knockout mice by 90% as compared to wild type mice.

As observed in MCT-PAH rat models, cav-1 knockout mice lungs also showed increased tyrosine phosphorylation of STAT3 and a dramatic upregulation of cyclin D1 and D3 levels<sup>[56]</sup>, that could promote cell proliferation and perhaps contribute to structural remodeling in the lung. Unlike in the MCT-PAH model, in cav-1 knockout mice there is 5-fold increase in systemic NO, while in the lungs, eNOS derived NO is increased by at least 3-fold as compared to wild type mice<sup>[11,70,71]</sup>. However eNOS protein expression is not changed in the heart and lungs of these mice. Mechanistically, the high NO levels from impaired eNOS activity leads to tyrosine nitration of PKG and thereby decreasing PKG bioavailability (figure 3). This could abolish its vasodilatory effect, perhaps contributing to development of PH<sup>[11]</sup>. This speculation is supported by the fact that NOS inhibition or superoxide scavenging in cav-1 knockout mice is able to rescue the PH phenotype in these mice. Similarly, PKG-1 overexpression in the lungs of these mice significantly decreases the

right ventricular systolic pressure and pulmonary vascular resistance. Furthermore, endothelial specific reconstitution of cav-1 in cav-1 knockout mice not only restores eNOS activity to normal levels, it is also able to suppress pulmonary hypertension and right ventricular hypertrophy<sup>[72]</sup>. Taken together, these observations clearly demonstrate that loss of cav-1 plays an important role in the development of pulmonary hypertension in mouse PH models.

## CAVIN-1 AND PULMONARY HYPERTENSION

Cavin-1, also called as polymerase I and transcript release factor (PTRF), is known to be expressed mostly in endothelial cells, fibroblasts and epithelial cells in the lungs and also in heart, adipocytes and skeletal muscle<sup>[73]</sup>. Since its discovery in 1998, cavin-1 was known to aid in the dissociation of paused ternary transcription complexes in the nucleus<sup>[3]</sup>. However, in recent years cavin-1/PTRF has been associated with caveolae and reported to regulate caveolae membrane curvature by anchoring cav-1 to the cytoskeleton *via* its C-terminal region<sup>[74]</sup>. Also, cavin-1 is required to mediate the normal oligomerization of cav-1<sup>[73]</sup>. More recent evidence suggests that cavin-2 plays an important role in generating caveolae specifically in the endothelial cells of the lung which is supported by the fact that endothelial cells lacking cavin-2 have flattened or shallow caveolae, but show cavin-1 co-localizing with oligomerized cav-1<sup>[73]</sup>. While cav-1 knockout mice have almost no cavin-1 expression<sup>[73,75]</sup>, cavin-1 knockout mice also have diminished cav-1 expression<sup>[73]</sup> suggesting that the expression of cav-1 and cavin-1 are interdependent. Cavin-1 knockout mice have increased lung tissue density and show hypertrophic remodeling of pulmonary arteries. They also exhibit symptoms of pulmonary hypertension, *i.e.*, increased RV-to-RV +LV ratio and increased pulmonary artery pressure as assessed by right ventricular systolic pressure<sup>[76]</sup>. Microarray analysis in new born lungs of cavin-1 knockout mice show changes in Arg1 (arginase 1) and Ddah1 (dimethylarginine dimethylaminohydrolase) genes. Increase in Arg1 and decrease in Ddah1 have been previously implicated in acquired forms of PAH<sup>[77,78]</sup>. Although the reciprocal changes in Arg1 and Ddah1 are known to limit the increase in NOS activity decreasing NO levels, this study did not measure changes in NO levels after cavin-1 knockout. Interestingly, silencing cavin-1 in endothelial cells *in vitro* enhances basal NO release from these cells, which could possibly be the effect of subsequent decrease in cav-1 levels<sup>[79]</sup>. Collectively, these data suggest that cavin-1 plays an important role in caveolae function in the lungs and could contribute to the development of pulmonary hypertension. However, changes in cavin-1 have not yet been studied in human and experimental models of PAH to date and these studies will help us better understand the role of cavin-1, as well as cav-1, in the development of pulmonary hypertension.

## CONCLUSION

As evidenced in several reports summarized here, cav-1 plays a central role in the development and progression of PH and PAH. The signaling pathways that are affected by cav-1 are diverse in different animal models and in humans, while chronic hypoxia-induced PH mice do not show any change in cav-1 levels. Although the cav-1 knockout mouse is not an experimental model of PH, these mice do exhibit symptoms of PH among other abnormalities. Similar effects are seen in cavin-1 knockout mice whose expression is also

diminished in cav-1 knockout mice. SU5416-hypoxia-normoxia PAH mice and IPAH lungs in humans show a decrease in cav-1 in plexiform lesions but not in surrounding normal pulmonary arteries. Moreover, there is a robust increase in cav-1 in the medial smooth muscle of remodeled pulmonary arteries in both animal models and in humans. Therefore, the differential expression and function of cav-1 in specific cells (*i.e.*, endothelial cell *vs* smooth muscle cell) may all together contribute to the development of pulmonary vascular remodeling, subsequently resulting in PH.

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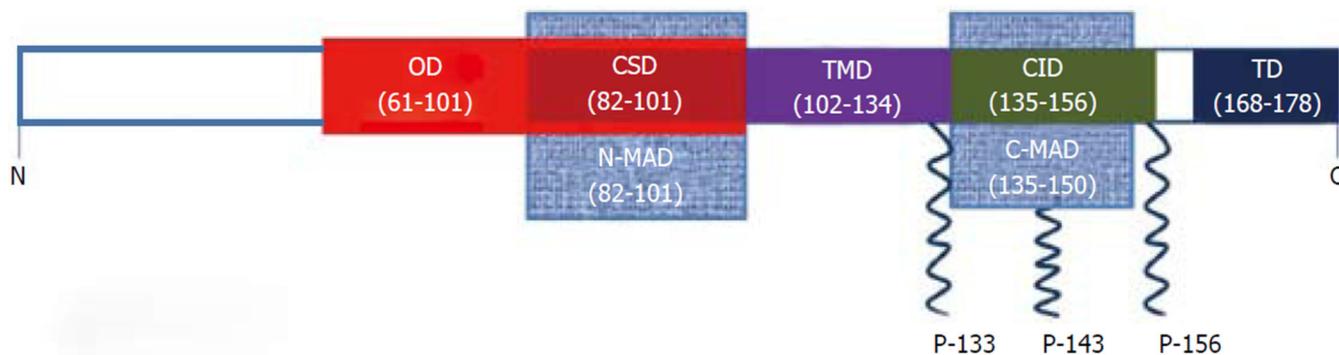
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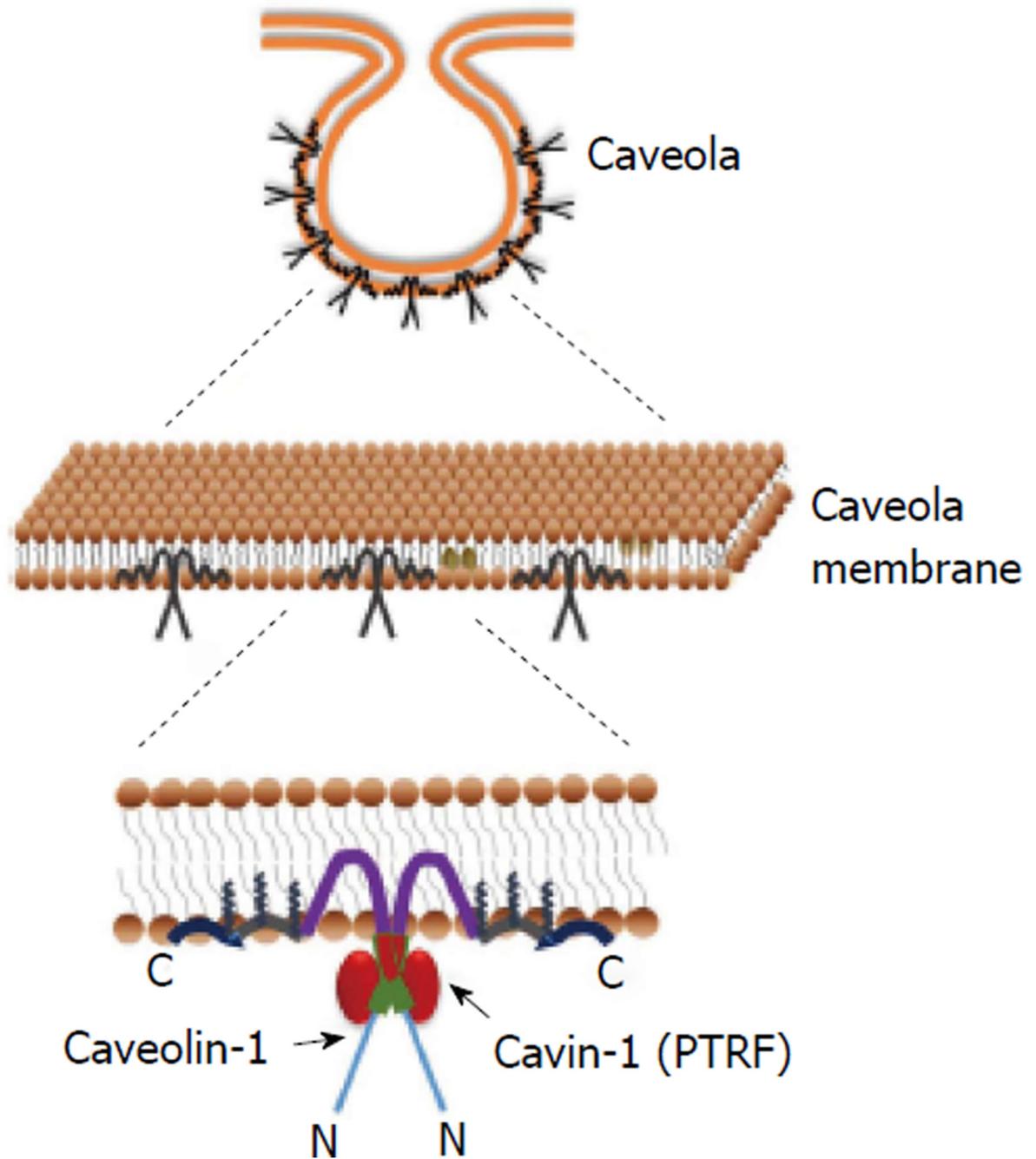
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**Core tip**

Pulmonary hypertension is a disease condition that is associated with a wide range of underlying medical conditions and environmental exposures. Currently, the exact molecular mechanisms underlying the pathogenesis of pulmonary hypertension remain unclear. This review is to outline and discuss the current understandings on the novel roles of a group of cell surface proteins, cav-1, -2 and cavin-1, on the development of pulmonary hypertension and vascular remodeling.



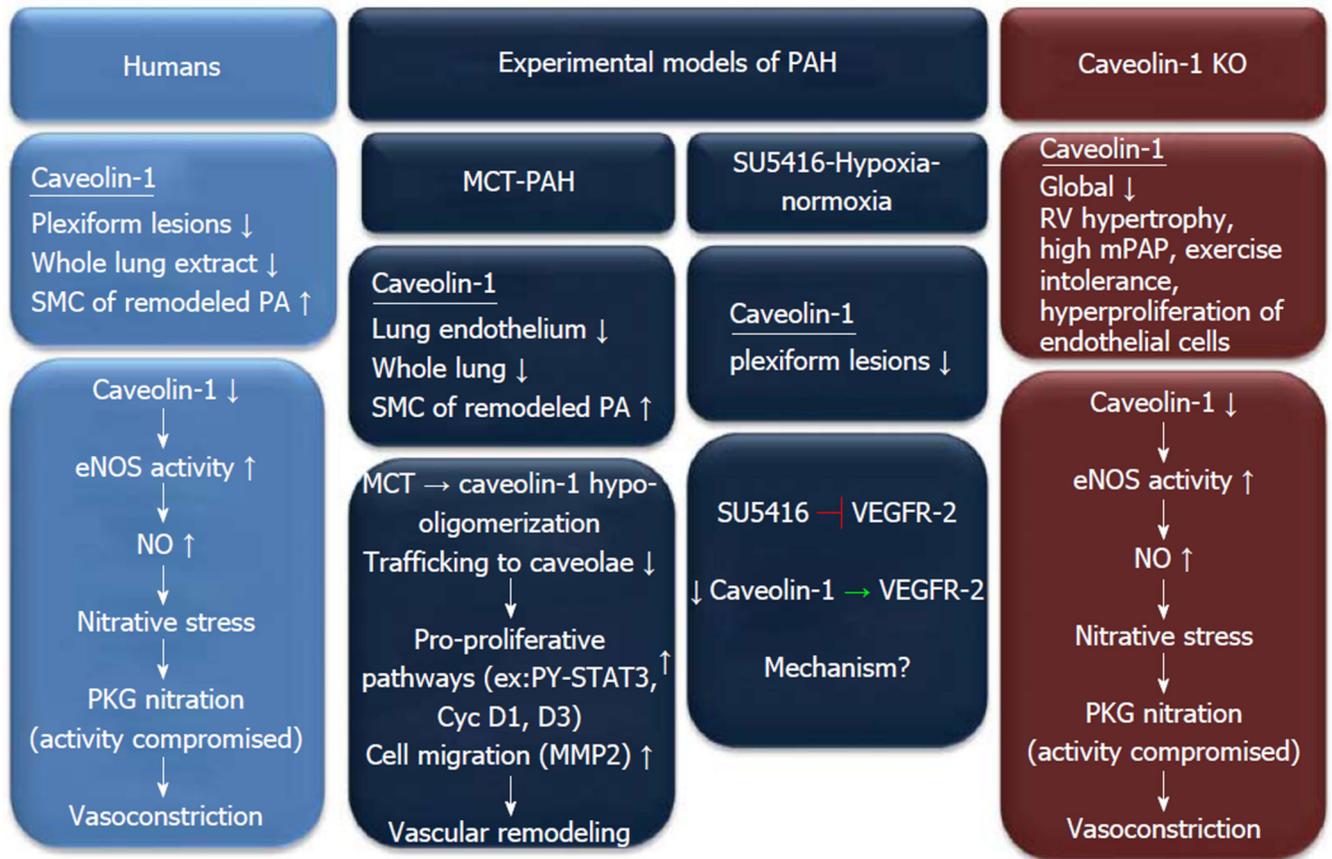
**Figure 1. Diagram summarizing the different functional domains of caveolin-1 protein**  
Cav-1 contains seven known functional domains. It contains an oligomerization domain (OD), a caveolin scaffolding domain (CSD), a transmembrane domain (TMD), a caveolin inhibitory domain (CID) (eNOS, Src kinase and PKA), a terminal domain (TD), an N-terminal membrane association domain (N-MAD), and a C-terminal membrane association domain (C-MAD). P-133, 143, 156: Palmitoylation sites.



**Figure 2. Structural organizations of a caveola, caveolin-1 and cavin-1**

Caveola are specialized lipid raft that are structurally maintained by caveolin-1 to form flask-shaped invaginations. In addition to these coat protein caveolin, caveolae contains an inner lining of adapter proteins called cavins, which regulate caveolin. PTRF: Polymerase I and transcript release factor.

## Role of Caveolin-1 in PAH



**Figure 3. Schematic representation of alterations in caveolin-1 and the downstream pathways affected by caveolin-1 in human idiopathic pulmonary arterial hypertension and experimental models of pulmonary hypertension**

Cav-1 expression is decreased in the lung. Downstream signaling pathways that are affected by cav-1 are diverse in different animal models of pulmonary hypertension (PH) and in humans. However, they eventually lead to vasoconstriction, vascular remodeling and development of PH. PAH: Pulmonary arterial hypertension; VEGFR: Vascular endothelial growth factor receptor; Cav-1: Caveolin-1.