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SPOTLIGHT REVIEW

Caveolae, caveolins, and cavins: complex control of cellular signalling and inflammation

John H. Chidlow Jr and William C. Sessa*

Vascular Biology and Therapeutics Program, Department of Pharmacology, Yale University School of Medicine, Amistad Research Building, 10 Amistad Street, New Haven, CT 06520, USA

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Caveolae are specialized lipid rafts that form flask-shaped invaginations of the plasma membrane. They are involved in cell signalling and transport and have been shown critically regulate vascular reactivity and blood pressure. The organization and functions of caveolae are mediated by coat proteins (caveolins) and support or adapter proteins (cavins). The caveolins, caveolin-1, -2, and -3, form the structural backbone of caveolae. These proteins are also highly integrated into caveolae function and have their own activity independent of caveolae. The cavins, cavins 1–4, are involved in regulation of caveolae and modulate the function of caveolins by promoting the membrane remodelling and trafficking of caveolin-derived structures. The relationships between these different proteins are complex and intersect with many aspects of cell function. Caveolae have also been implicated in chronic inflammatory conditions and other pathologies including atherosclerosis, inflammatory bowel disease, muscular dystrophy, and generalized dyslipidaemia. The pathogenic role of the caveolins is an emerging area, however, the roles of cavins in disease is just beginning to be explored. This review will examine the relationship between caveolins and cavins and explore the role of caveolae in inflammatory signalling mechanisms.

Keywords Caveolin • Caveolae • Cardiovascular • Cell biology • Nitric oxide

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1. Introduction

Caveolae are flask-shaped invaginations of the plasma membrane which participate in and are the site of regulation for many cellular functions. They were first discovered by Palade[1] and Yamada,[2] who noted non-clathrin coated, plasmalemmal vesicles of 50–100 nm. Caveolae occur at different densities in different cell types, being most prominent in vascular endothelial cells (ECs), adipocytes, fibroblasts, and epithelial cells. These specialized lipid rafts can function as cell signalling platforms and regulate the kinetics of vesicle transport, making them both versatile and highly integrated into cellular physiology. Enhanced cellular signalling within caveolae is due to the target rich environment formed through clustering of receptors and signalling molecules, thereby permitting efficient signal transduction. For purposes of macromolecule transport, multiple caveolae can form *trans*-endothelial channels and vesiculo-vacuolar organelles and/or cavicles.[3] In terms of EC function, caveolae are important regulators of vascular tone through modulation of endothelial nitric oxide synthase (eNOS) activity. Specifically, regulation of eNOS within caveolae by the coat protein, caveolin-1 (Cav-1), is an important physiological mechanism for control of vascular reactivity, and this pathway is intimately involved with the progression of pathologies likely through suppression of pro-inflammatory signalling pathways.

Caveolae are specialized forms of lipid rafts. Contained within the plasma membrane, lipid rafts are dynamic assemblies of sphingolipids and cholesterol, and individual lipid raft domains can have differing affinities for proteins resulting in different functions. These rafts are highly important to cellular signal transduction as they can concentrate or segregate receptors and signalling intermediates and form a microenvironment where local kinases and phosphatases can modify downstream signalling events.[4] In the case of caveolae, organelle size and specificity have been shown for several protein pairs, and clearly demonstrated for the Cav-1/eNOS interaction.[5,6] Importantly, Cav-1 contained within non-caveolar, lipid rafts fails to exert its inhibitory effect on eNOS, whereas Cav-1 within caveolae is able to inhibit NO release due to its closer proximity to eNOS.[7] Caveolae-mediated endocytosis differs mechanistically from clathrin-dependent endocytosis and other clathrin-independent (rhoA-dependent and cdc2 regulated) endocytosis; these differences involve cargo, biochemical sensitivities and specific adaptor and signalling proteins.[8] A unique mechanism by which exogenous cholesterol and glycosphingolipids selectively stimulate caveolar endocytosis has also been suggested.[8]

The caveolae coat proteins, caveolins, have specific functional roles which can vary in different cell types. These coat proteins, Cav-1, caveolin-2 (Cav-2), and caveolin-3 (Cav-3), are the major structural

* Corresponding author. Tel: +1 203 737 2291; fax: +1 203 737 2290, Email: william.sessa@yale.edu

components of caveolae.[9,10] Cav-1 is present in most cell types of the cardiovascular system as is Cav-2, whereas Cav-3 is expressed primarily in vascular smooth muscle, cardiac and skeletal muscle. Evidence shows that Cav-1 or Cav-3 expression is necessary for the formation of caveolae, whereas Cav-2 expression is not required and its role less obvious.[11–13] Endothelial Cav-1 is responsible for caveolae formation throughout the endothelium lining the entire cardiovascular system. Cav-1 regulates endothelial NO production,[14] microvascular permeability, cellular Ca^{2+} entry, vascular remodelling, and angiogenesis.[15–18] Cav-1 localizes at the plasma membrane and in the Golgi.[19,20] Although a clear picture of Cav-1 trafficking to the plasma membrane is yet to emerge, several proteins involved in this process have been identified. Sato *et al.*[21] show that ARF-1 is necessary for Cav-1 targeting to embryonic Cav-1 bodies in *Caenorhabditis elegans*. It has also recently been shown that amyloid beta protein stimulates the trafficking of Cav-1 from the Golgi to the plasma membrane, and insulin can acutely regulate Cav-1 trafficking.[22,23] Furthermore, the endocytotic trafficking of Cav-1 has been shown to be regulated by Na/K-ATPase activity.[24] Smart *et al.*[25] suggested that Cav-1 targeting to the membrane is likely stabilized by its C-terminal palmitoylation.

The role of Cav-2 in the formation of caveolae is less clear, it is not necessary for lung endothelium or adipose tissue caveolae formation, but it is suggested to have a support role in caveolae assembly via its hetero-oligomerization with Cav-1.[26,27] Additionally, Cav-2 is almost always co-expressed with Cav-1. Cav-2 can regulate the number of plasma membrane attached caveolae[28] and is a regulator of mitosis through serine 36 phosphorylation, a process regulated by Cav-1.[11] Cav-3 is expressed highly in striated muscle, localized to the sarcolemma, and is critical to caveolae formation and eNOS regulation in muscle cells, in the same manner as Cav-1 elsewhere.[29–31] The caveolin support proteins, cavin-1 (polymerase transcript release factor, PTRF), cavin-2 (serum deprivation protein response, SDPR), cavin-3 (srd-related gene product that binds to c-kinase, SRBC), and cavin-4 (muscle-restricted coiled-coil protein, MURC), are newly documented and play important roles in the regulation of caveolin expression and caveolae morphology. The remainder of this review will focus on new information regarding caveolae regulatory proteins, and the involvement of caveolae and these proteins in vascular function and inflammation.

2. Caveolae regulatory proteins

Cavins act as regulators of caveolin function and organization, each of them has been assigned different roles based on caveolae morphologies and cell type. Importantly, these proteins function primarily as scaffolding proteins, though they also regulate availability of the caveolins.[32,33] It should be noted that all cavin proteins share certain characteristics; namely leucine zipper-like domains for protein–protein interactions, PEST domains for protein turnover, and phosphorylation motifs.[32] Additionally, all of the cavins can bind phosphatidylserine and are phosphorylated upon insulin stimulation.[32] This section will focus on the individual contributions of the cavins to caveolae structure and function.

2.1 Cavin-1 (PTRF)

The first of the caveolin regulatory proteins to be identified was cavin-1, also known as PTRF.[34] Upon its original identification, PTRF was thought to be a transcript release factor.[35,36] The requirement of cavin-1 for caveolae formation and organization has been previously demonstrated.[33,37,38] Early studies showed that cavin-1 co-localizes with Cav-1 in adipose tissue and co-distributes with Cav-1 in lipid rafts.[33,39] Importantly, interactions between cavin-1 and Cav-1 are apparently not direct, as solubilization of caveolae disrupts the interactions and the interaction of cavin-1 with Cav-1 may be mediated by cytoskeletal interactions dependent on microtubules and actin filaments.[33] Regulation of Cav-1 bioavailability by cavin-1 was demonstrated *in vitro*, as cavin-1 over-expression causes increased levels of Cav-1, and cavin-1 knockdown reduces Cav-1 levels.[33] These data are similar to the well-appreciated stabilizing effect of Cav-2 with Cav-1 and visa versa.[40] Liu *et al.*[38] showed that genetic deletion of cavin-1 results in global loss of caveolae through decreased availability of all caveolin proteins, dyslipidaemia, reduced adipose tissue, and glucose intolerance, similar phenotypes to Cav-1/Cav-3 knockout mice. Hill *et al.*[41] showed that cavin-1 associates with caveolae at the plasma membrane, where it is required for the formation of caveolae via sequestration of caveolins into caveolae. Additionally, these authors demonstrated that the loss of cavin-1 enhances the lateral mobility of Cav-1 and its accelerated lysosomal degradation.[41] A recent study confirmed these results using live-cell imaging to show that Cav-1 scaffolds are trafficked to the plasma membrane independently from cavin-1, suggesting that cavin-1 interacts with Cav-1 once it is already in the membrane to direct the formation of caveolae.[42] Importantly, in humans, mutations in cavin-1 result in a secondary deficiency of caveolins and muscular dystrophy; effects likely mediated via cavin-1/Cav-3 interactions.[43]

2.2 Cavin-2 (SPDR)

Cavin-2 or SDPR is required along with cavin-1 for caveolae formation.[44,45] Gustincich and Schneider[46] identified a gene they called serum deprivation response (called sdr) in 1993, and in 1998 Mineo *et al.*[47] isolated the sdr protein and showed that it is a protein kinase C (PKC)α binding protein and localizes to caveolae. Hansen *et al.*[45] showed that cavin-2 directly binds cavin-1 and recruits it to the plasma membrane, and that cavin-2 is required for the stable expression levels of both Cav-1 and cavin-1 proteins. Cavin-1/cavin-2 binding results in the formation of complexes containing Cav-1 contributing to stable caveolae structures.[45] Interestingly, the over-expression of cavin-2 in cultured cells results in the formation of elongated tubular caveolae implying that it provides an organizational role to generate membrane curvature.[45] Cavin-2 also exhibits functionality in caveolae signalling as a known substrate of PKC, and it is involved in the compartmentalization of PKC to caveolae.[48] Additionally, pleckstrin, a platelet PKC substrate has been shown to directly bind cavin-2.[49]

2.3 Cavin-3 (SRBC)

Cavin-3, or SRBC, was initially identified as a PKCδ binding protein and separately as a BRCA1-interacting protein.[50,51] McMahon *et al.*[52] were the first to show that cavin-3 is localized to caveolae and examine its role in caveolar function. Cavin-3 co-precipitates with Cav-1, has a similar distributions to Cav-1 and that either Cav-1 or Cav-3 must be present for cavin-3 localization to the plasma membrane.[52] Furthermore, cavin-3 participates in the formation of caveolar vesicles (cavicles) based on two observations; cavin-3 remains associated with caveolae when budding occurs and the absence of cavin-3 impairs intracellular cavicle trafficking.[52] This role for cavin-3, when compared with those of cavins-1 and -2,

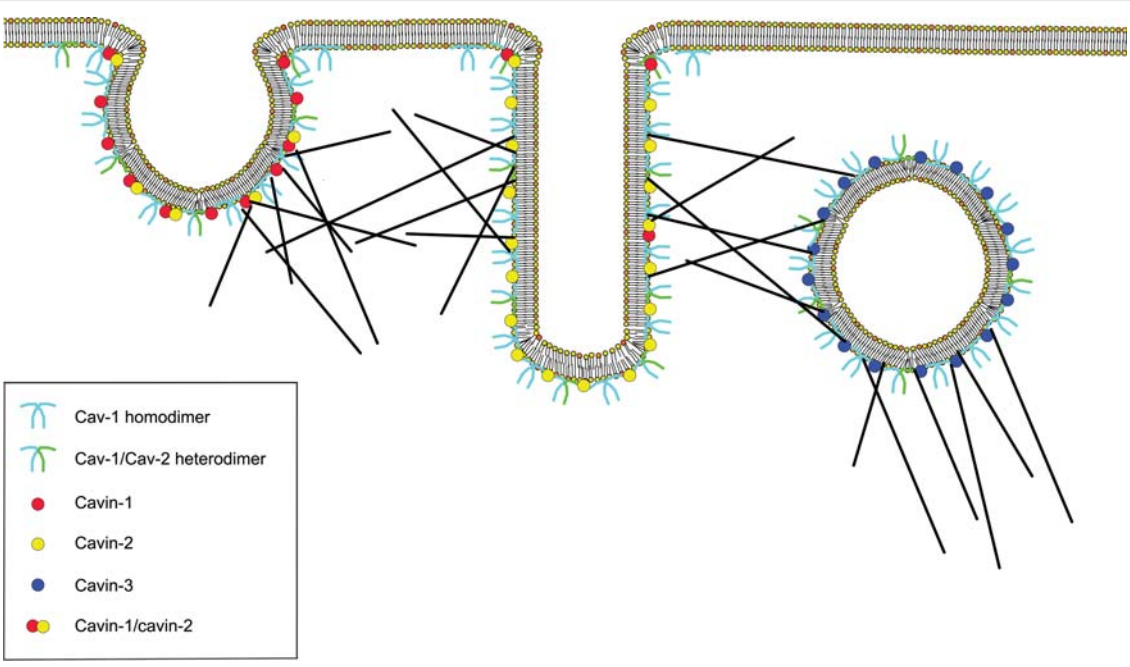

Figure 1 Dynamic roles of the cavins in determining caveolae structure. Cav-1 and Cav-2 (light blue and green lines) dimerize to form the backbone of caveolae. Cavins as supports proteins then determine the final shape of this structure. Cavin-1 (red circle) directs formation of normal flask-shaped caveolae alone and through interactions with cavin-2 (combined red and yellow circles). Cavin-2 when expressed at higher levels than cavin-1 causes the formation of elongated caveolae which may be involved in channel formation. Finally, cavin-3 (blue circles) directs vesicle formation by caveolae. Dark lines show cytoskeletal components which are thought to mediate the interaction between cavins and caveolins.

paints an interesting picture where cavin-1 in conjunction with normal levels of cavin-2 regulate the formation of traditional flask-shaped caveolae, excess of cavin-2 causes the formation of elongated tubular caveolae, and cavin-3 directs the budding and formation of cavicles (*Figure 1*).

2.4 Cavin-4 (MURC)

The most recent addition to the Cavin family is cavin-4, MURC. This cavin was discovered as a cardiac and skeletal muscle-specific cytosolic protein and sequence homology searches identified it as a cavin family member.[53–55] Bastiani *et al.*[55] characterized cavin-4 as a predominantly muscle expressed protein component associated with sarcolemmal caveolae complexes. On the basis of its expression in muscle and co-localization with Cav-3, a role is suggested for cavin-4 in caveolin-associated muscle disease due to altered cavin-4 distribution in patients with caveolinopathies.[55] Although the cavin proteins have not yet been extensively studied their, as of now, known roles in caveolae regulation indicate their importance to the physiological roles of caveolae.

3. Caveolae and vascular function

3.1 Caveolae and eNOS

The only direct protein–protein interaction demonstrated *in vivo* between Cav-1 and a non-homologous protein is with eNOS. Other proteins have been shown to bind Cav-1 *in vitro* including dynamin-2 during Cav-1-mediated endocytosis.[56] Evidence suggests that Src phosphorylates Cav-1 at tyrosine 14 suggesting a direct interaction in response to growth factor stimulation and cellular stress.[57–59] Furthermore, the insulin receptor has been shown to phosphorylate Cav-1 at the same site.[60] Interactions of phosphoCav-1 with Csk resulting in negative regulation of Src, and Cav-1 with fatty acid synthase have also been demonstrated.[61,62] Lastly, Feng *et al.*[63] showed that Cav-1 associates with TRAF2 enhancing TNFR signalling.

The relationship between caveolae and eNOS is one of the cornerstones of caveolae involvement in cardiovascular function. Loss of Cav-1 leads to persistent eNOS activation and high levels of NO in cells through the loss of Cav-1 inhibitory effect on eNOS. The Cav-1/eNOS interaction tonically inhibits eNOS activity resulting in sequestering of eNOS in caveolae and reduced NO production. Our group showed that eNOS dysregulation in global Cav-1 KO mice is normalized with EC-specific reconstitution of Cav-1.[16,17,64] Previous studies from our laboratory using AP-Cav-1 peptides, the Cav-1 scaffolding domain fused to the cellular internalization peptide, antennopedia (AP), showed that the amino acids 82–101 of Cav-1 contain the binding site for eNOS[5,6,30,65] and that F92 is the key residue for this inhibitory effect.[14] It has also been shown that the genetic deletion of eNOS or pharmacological blockade, prevents many of the physiological changes observed in Cav-1 KO mice,[66] highlighting the importance of Cav-1 regulation of eNOS function. The mechanism for reducing the inhibitory action of Cav-1 on eNOS under normal circumstances is regulated by the activator calcium-–calmodulin, hsp90 complex.[30,67,68]

3.2 Caveolae, vascular reactivity, and blood pressure

The genetic deletion of Cav-1, and concurrent loss of caveolae, results in dysregulation of NO synthesis, enhanced or reduced vascular

permeability, impaired vascular reactivity and mechanotranduction, cell proliferation, and severe cardiovascular and pulmonary phenotypes.[12,13,17,69–73] These phenotypes include cardiac hypertrophy, pulmonary hypertension, and pulmonary hyperplasia. Murata *et al.*[16] examined vascular reactivity in Cav-1 KO and EC-specific Cav-1 reconstituted mice and found that reconstitution of Cav-1 restored vascular reactivity resulting in normal smooth muscle contractility and endothelium-dependent relaxation in response to phenylephrine and acetylcholine, respectively. Additionally, Cav-1 reconstitution partially rescues the cardiovascular and pulmonary phenotypes seen in Cav-1 KO mice, and corrected vascular leakage.[16] The conditions seen in Cav-1 KO mice have been linked to hyperactivation of Akt and p42/p44 ERK signalling, and reduced signalling by these messengers in Cav-1 EC-specific reconstituted mice has been shown.[16] Zhao *et al.*[66] have recently shown that pulmonary hypertension, and seen in Cav-1 KO mice, is dependent on PKG nitration. Specifically, they showed that genetic deletion of eNOS in Cav-1 KO mice prevents pulmonary hypertension and that the activation of eNOS in Cav-1 KO mice causes nitrosative stress leading to the nitration of and the inactivation of PKG.[66] EC-specific transgenic expression of Cav-1 reduces microvascular permeability when compared with that of Cav-1 KO, adding another aspect to caveolae regulation of vascular function.[15]

Caveolae are implicated in mechanosignalling[74] and to sense changes in shear flow, indeed, genetic evidence shows that Cav-1 is required for short- and long-term mechanotransduction in the vasculature.[17] Reduced systemic blood pressure (BP), as measured by conventional methods, with anaesthesia, in Cav-1 KO mice has been documented and we have shown that the restoration of Cav-1 to the endothelium returned systemic BP to normal, suggesting a role for caveolae in the regulation of BP.[16] Recently, Desjardins *et al.*[75] examined blood pressure in Cav-1 KO by implanted telemetry in awake mice and determined that Cav-1 regulation of eNOS NO production is important for control of central BP. They saw no differences in BP between Cav-1 KO and WT mice, and they showed increased levels of circulating Hb-NO and vessel relaxation in response to increased NO production by eNOS in Cav-1 KO mice, both of which were reversible with NOS inhibition.[75] They suggest that Hb-NO acts as a 'buffer' for systemic BP, further indicating Cav-1 as an important target in vascular regulation.[75]

4. Caveolae and inflammation

4.1 Caveolae as a signalling platform for inflammation

The microdomain created by caveolae is ideal for promoting cell signalling both through localization of many different types of receptors and bioavailability of signalling molecules and through the direct actions of the caveolin proteins.[76] Sequestered within caveolae, through interaction with Cav-1, are many G protein receptors, Gα subunits, tyrosine kinases and receptor tyrosine kinases (RTKs), GTPases, components of the MAPK pathway, and others.[77,78] As far as specific actions of the caveolin proteins are concerned, Cav-1 modulation of eNOS regulates inflammatory signalling through local control of NO production.[79,80] Cav-1 has also been shown to sequester p42/44 MAPK cascade members including EGFR, raf, MAP-1, and ERK-2, inhibiting the activity of this pathway.[81] Another important inflammatory signalling mediator cyclooxygenase-2 (Cox-2) has recently been shown to be regulated by Cav-1 through Cav-1 binding of Cox-2 at the endoplasmic reticulum (ER) enhancing its degradation.[82] Caveolae and Cav-1 are also involved in integrin signalling, a key component of mechanotransduction and the inflammatory response. Co-precipitation of Cav-1 and integrins in cell culture has been demonstrated.[83,84] Additionally, Salani *et al.*[85] have recently shown that Cav-1 is necessary for integrin-β1 localization to caveolae upon IGF signalling.

Ca^{2+} regulation and signalling can also be involved in inflammatory responses. ECs sequester and store Ca^{2+} in the ER and it is used in receptor-induced signalling involving rapid release of these Ca^{2+} stores and then sustained entry of extracellular Ca^{2+}. There are three phases to this process, initial ER Ca^{2+} release, sustained entry of Ca^{2+} into the cell, and tonic Ca^{2+} entry. The first can be stimulated by G protein-coupled receptors and RTKs. The major signalling pathway involved in calcium release is phospholipase C activation of inositoltriphosphate (IP_3) and diacylgylcerol, where IP_3 then activates receptors on the ER causing Ca^{2+} release. The sustained entry of Ca^{2+} is mediated by Ca^{2+} release activated Ca^{2+} channels and receptor-operated Ca^{2+} channels to promote signalling, and the tonic phase allows long-term Ca^{2+} signal propagation and replenishes intracellular Ca^{2+} stores. Importantly, Murata *et al.*[16] have shown that Cav-1 is necessary for Ca^{2+} entry into ECs. In intact endothelium lining blood vessels, the loss of Cav-1 impairs Ca^{2+} entry and reconstitution of endothelial Cav-1 selectively rescues this phenotype. This evidence further indicates the importance of caveolae in cell signal transduction involved in maintaining vascular homeostasis. An impairment of Ca^{2+} signalling may be critical to pathological angiogenic processes which occur during chronic inflammation.[86] Interestingly, recent data show that Cav-1 and Ca^{2+} antagonistically regulate eNOS in intact microvessels, agreeing with the above data, and they further show that the level of NO production directly determines the degree of vascular permeability increases which occur during inflammation.[87]

There are additional lines of evidence that indicate caveolae participate in inflammatory signalling. Garrean *et al.*[88] show that Cav-1 can regulate NF-κB activation via its effects on eNOS resulting in reduced lipopolysaccharide (LPS)-driven lung inflammation in Cav-$1^{-/-}$ mice. Whereas its interaction with eNOS is the only direct protein–protein interaction that can be demonstrated *in vivo* at this time, implications from other studies suggest several other direct and indirect Cav-1 interactions that may have bearing on the evolution of the inflammatory response. Wang *et al.*[89] have shown that the regulation of Cav-1/TLR4 interaction due to haemeoxygenase-1/carbon monoxide activity reduces the production of tumour necrosis factor-α and interleukin-6 in response to LPS-induced inflammation in macrophages suggesting an anti-inflammatory role here. Additionally, caveolae have also been shown to play a role in EC barrier dysfunction in the brain resulting in increased permeability through caveolae-mediated claudin-5 and occludin internalization.[90]

4.2 Caveolae and disease

The loss of caveolae through Cav-1 deletion is protective against atherosclerosis and inflammatory bowel disease (IBD). Frank *et al.*[91] initially have shown that Cav-1 protects against atherosclerosis and LDL transcytosis in ECs implicating it as a regulator of plasma LDL level and composition suggesting a role in dislipidaemia. Our group has shown that genetic loss of caveolae results in reduced LDL

uptake by the endothelium *in vivo* preventing development of atherosclerosis in Cav-1 KO mice, an effect that is reversed with endothelial-specific restoration of Cav-1.[64] Additionally, Catalan *et al.*[92] have indicated that Cav-1 is involved in inflammation associated with obesity, and Cav-1 regulates aspects of PMN activation, adhesion, and transmigration during lung inflammation.[93]

During IBD the loss of Cav-1, and thus caveolae, results in reduced tissue pathology likely due to decreased inflammatory and angiogenic signalling; this protection is also lost with EC-specific restoration of Cav-1.[86] The reduction in angiogenesis signalling is also manifested in limb ischaemia studies[73] perhaps via mislocalization of the vascular endothelial growth factor (VEGF)-R2 receptor. During chronic inflammation, as occurs during atherosclerosis, IBD, rheumatoid arthritis, age-related macular degeneration, and other diseases, angiogenic vascular responses are not properly regulated and contribute to the inflammatory conditions.[94,95] In fact, our studies of Cav-l in experimental colitis models indicate that the protection seen in Cav-1 KO mice is conferred through a reduction in angiogenesis resulting secondarily in reduced inflammatory pathology.[86] Important to this concept, Cav-1 is known to enhance tube formation *in vitro* by regulating EC differentiation, and to be important for the maturation of newly formed blood vessels.[96,97] VEGF-R2, the major ligand for $VEGF_{164}$, the pathological isoform of VEGF-A, has been shown to be sequestered in caveolae and is known to be involved in the pathological progression of IBD, rheumatoid arthritis, and others.[94,98] Yu *et al.*[17] have shown that Cav-1 over-expression reduces $VEGF_{164}$-stimulated angiogenic responses *in vivo* demonstrating direct Cav-1 regulation of angiogenesis. Cav-1 at physiological levels is a positive regulator of angiogenic responses by coordinating the fidelity of signalling, however the loss or over-expression of Cav-1 in cases mentioned in this review results in impaired angiogenic responses, which may be due to the lack of the organelle, impaired signalling or excess levels of the scaffolding function of Cav-1.

Cav-1 has also been in the pathological sequelae diabetes and fibrosis. Cav-1 has been shown to bind insulin receptor-β as a necessary component of receptor activation, and Cav-1 loss results in insulin resistance,[99] and recently Fagerholm *et al.*[100] have shown that tyrosine phosphorylation of Cav-1 causes endocytosis of activated insulin receptors. Although neither of these findings are directly related to caveolae-dependent-inflammatory signalling, this close relationship between Cav-1 and insulin regulation suggests that Cav-1 may be involved in diabetes-associated inflammation. In the context of fibrosis, the loss of Cav-1 promotes pulmonary and cardiac fibrosis, perhaps via regulation of angiotensin/TGF-β signalling pathways.[101,102]

Cav-3 defects have been closely tied to muscular dystrophy. Early studies showed that mutation of the Cav-3 gene results in autosomal dominant limb girdle muscular dystrophy characterized by calf hypertrophy and muscle weakness.[103] Cav-3 has also been implicated in idiopathic hyperCKemia due to a sporadic Cav-3 gene mutation, in rippling muscle disease due to missense mutations of Cav-3, and in distal myopathy due to a heterozygous 80 G to A mutation of the Cav-3 gene.[104–106] While not inflammatory conditions, these findings implicate the importance of caveolae in muscle homeostasis and show that Cav-3-dependent muscle caveolae are important to disease. Combined the data reviewed here shows significant evidence for caveolae and caveolin involvement in disease pathologies through inflammatory signalling, regulation of angiogenic responses and genetic control. While the role that cavins play in disease is as presently being explored is it likely that further study of their functions will shed mechanistic light on caveolae regulation of inflammation and disease.

5. Concluding remarks

Caveolae are clearly important to vascular function and homoestasis as are the caveolins and the cavin proteins. Caveolae support transcytosis in certain cell types and a plethora of signalling events, through sequestration of messengers and localization of receptors and their mere presence seems to be important during disease for inflammatory and angiogenic signalling making then critical regulators of vascular function from the single cell to the system wide level. As indicated herein the caveolins are directly responsible for many of the regulatory mechanisms attributed to caveolae. With the discovery of cavins, many caveolae functions can now begin to be mechanistically understood. Interestingly, cavins directly determine the shape of caveolae and the budding of cavicles making them key proteins for the regulation of all caveolae functions. The roles that cavins play in caveolae formation and signalling bear further investigation, research that will undoubtedly reveal new mechanisms of caveolae and caveolin function. Caveolae are clearly important during inflammation. Most studies of Cav-1 in inflammation indicate that the direct effects of Cav-1 regulation of other proteins is anti-inflammatory, however, genetic deletion of Cav-1 is protective against atherosclerosis and IBD. Although these findings seem to conflict, they underscore the overall importance of caveolae as a regulator of cell signalling. It could be that without caveolae inflammatory and angiogenic signalling are perturbed to the point where signalling becomes impossible, or conflicting signals override one another, resulting in protection more through inability to respond than differential regulation of signalling. Evidence for an extra-caveolar role (i.e. scaffolding functions) of caveolins is plentiful, and it is possible that Cav-1 itself can effect protein and vesicle trafficking, angiogenic and inflammatory signalling, and other cellular processes, however, more sophisticated approaches to delineate caveolae vs. caveolin/cavin functions are needed. Similarly, it is feasible that cavins may also function outside caveolae/cavicles, perhaps independent of caveolins. Regardless, the evidence for caveolae and Cav-1 regulation during inflammation is clear and additional studies will shed light on mechanisms of caveolae-dependent inflammatory responses and the new roles of cavins in these processes.

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