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Review

Caveolae: One Function or Many?

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Caveolae are small, bulb-shaped plasma membrane invaginations. Mutations that ablate caveolae lead to diverse phenotypes in mice and humans, making it challenging to uncover their molecular mechanisms. Caveolae have been described to function in endocytosis and transcytosis (a specialized form of endocytosis) and in maintaining membrane lipid composition, as well as acting as signaling platforms. New data also support a model in which the central function of caveolae could be related to the protection of cells from mechanical stress within the plasma membrane. We present evidence for these diverse roles and consider *in vitro* and *in vivo* experiments confirming a mechanoprotective role. We conclude by highlighting current gaps in our knowledge of how mechanical signals may be transduced by caveolae.

Trends

Loss of caveolae causes phenotypes in endothelium, muscle, and adipose tissue. Molecular explanations for these phenotypes have been lacking.

Caveolae do not make a major direct contribution to overall endocytic flux but could indirectly regulate other endocytic pathways via changes in membrane lipid composition.

Structural and proteomic analysis undermines models invoking the involvement of specific peptide motifs within caveolin and other proteins in protein–protein interactions.

Disassembly and flattening of caveolae occurs in physiologically relevant contexts and caveolae protect the plasma membrane of cells from mechanical damage.

Caveolae are likely to have a role in signaling during mechanical and other types of membrane stress. Relevant signaling pathways are not fully understood.

Caveolar Architecture and Phenotypes

Caveolae, named from the Latin for 'little caves', are 50–100-nm, bulb-shaped invaginations of the plasma membrane that are most abundant in endothelia, smooth muscle, and adipocytes [1]. In 1992, the discovery of caveolin 1, an integral membrane protein that was the first defining component of caveolae, enabled a surge of biochemical and cell biological experiments and consequent assignment of additional functions in processes such as signal transduction, lipid trafficking, and endocytosis [2]. Over the past several years, the characterization of protein complexes responsible for generating caveolae has proceeded rapidly and the reader is referred to recent reviews [3,4]. There are three caveolin isoforms, caveolins 1–3. Caveolin 1 is expressed in many cell types, excluding striated muscle, and is essential for caveolar biogenesis. Caveolin 3 is a striated muscle-specific caveolin isoform required for caveolar morphogenesis [2,5–7]. Caveolin 2 has a similar expression profile to caveolin 1 but appears to be dispensable for caveolar formation. Caveolins are not the sole structural component of caveolae [8–11]. Four related proteins with previously identified functions have been identified and are now known as 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 the striated muscle-specific cavin 4 [muscle-restricted coiled-coil protein (MURC)] [12–16]. Cavins form higher-order hetero-oligomeric assemblies, which are essential for caveolar architecture and function [17–20]. Cavins and caveolins can be isolated after chemical crosslinking as large 80S complexes that are likely to represent the stable coat around the bulb of caveolae [19].

Surprisingly, *caveolin 1* knockout mice are viable, fertile, and, at least under laboratory conditions, healthy [21–23]. This basic genetic observation has posed a continuing challenge for various models of caveolar function. There is, however, a large literature on the diverse phenotypes induced by altered caveolar gene function (summarized in Table 1). The broad-brush conclusion that emerges from these studies is that adipocytes, endothelial cells, and myocytes are dysfunctional without caveolae. However, phenotypes themselves are not directly indicative of specific molecular functions. A full molecular description of caveolar function should

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Table 1. Phenotypes of Humans and Mice with Mutations in Caveolar Genes[a]

Phenotype	Caveolin 1		Caveolin 2	Caveolin 3		Cavin 1	
	Mouse[b]	Human[c]	Mouse	Mouse	Human	Mouse	Human
Vascular and Pulmonary Tissue							
Cardiomyopathy	[21]			[140]	[141]		
Cardiac (myocyte) hypertrophy	[142]			[140]			
Pulmonary hypertension	[21,108, 143,144]		[136,145]			[146]	
Interstitial fibrosis	[142]						
Endothelium-dependent relaxation	[23]						
Thickened alveolar septae	[22,23,144]	[147]					
Altered NO	[22,23,143]						
Exercise intolerance	[23]	[147]					
Cardiac arrhythmias			[148]		[149,150]		[83,151]
Macrophage accumulation in lungs						[138]	
Vascular morphology defect	[143]						
Muscle Tissue							
Muscular dystrophy				[140]	[133,134, 152]		[135]
Rippling muscle disease					[134,153, 154]		[83,151]
Muscle hypertrophy							[151]
Myopathy				[155]			
Adipose Tissue							
Defective lipid metabolism	[156]					[157]	
Resistant to diet-induced obesity	[156]		[158]				
Hypertriglyceridemia	[156]		[81,158]			[8]	
Lipodystrophy	[156]		[81]			[8]	[83,135, 151,159, 160]
Macrophage infiltration	[161]					[138]	
Insulin resistance/glucose intolerance			[81,142]			[8,157]	[151,160]

[a]Mouse refers to mice that are homozygous for the specified knocked-out caveolar gene.
[b]Human refers to mutations of the specified caveolar gene.
[c]Blank entries indicate that the phenotype has not been reported.

help to unify these diverse phenotypes. It is this gap between molecular function and phenotype that provides the focus of this review.

Endocytosis

Whether caveolae engage in endocytosis, and what the cellular function of caveolar endocytosis is, are longstanding questions. Given the centrality of endocytosis (see Glossary) in the regulation of many signaling pathways, alterations in the uptake of specific receptors could potentially

Glossary

Annexin A1: part of the Annexin family that comprises a set of Ca^{2+} and phospholipid binding proteins. Proteomic analysis of endothelial membranes from tumour vasculature identified annexin A1, present within caveolae, as a preferentially expressed protein in tumors compared with wild type vasculatures [75]. Antibodies against Annexin A1 have been used to visualize transendothelial transport specifically in tumors, from caveolae at the luminal side of endothelial cells into the interstitium.

Cholera toxin: a multimeric protein secreted by *Vibrio cholerae*, it binds to the ganglioside GM1, a glycosphingolipid with a single sialic acid residue that is present on the plasma membrane. GM1 is found within caveolae but is also localized throughout the plasma membrane, and hence internalized by caveolae-dependent and -independent pathways.

Clathrin-independent endocytosis: methods of endocytosis that occur separately from clathrin, a protein that forms a triskelion assembly around vesicles for the enrichment of cargo molecules via adaptor proteins and their subsequent internalization into the cell. Mechanisms that are independent of clathrin are thought to comprise a small percentage of the total cellular endocytic flux. These alternative mechanisms include but are not limited to caveolae, receptor-mediated endocytosis, and CLIC-GEEC and are responsible for the internalization of a diverse set of cargoes required for various cellular processes such as polarity and proliferation.

Endocytosis: the process by which cells uptake molecules such as proteins and lipids through their engulfment and sequestration into a vesicle derived fromthe plasma membrane.

Endothelial nitric oxide synthetase (eNOS): an enzyme produced by endothelial cells that is reported to localize to caveolae. eNOS converts O_2 and L-arginine to nitric oxide (NO) and L-citrulline. Activation of eNOS and the subsequent generation of NO is associated with increased vascular permeability in response to inflammatory agents such as vascular endothelial growth factor (VEGF).