Caveolae as mechanoprotective and signaling organelles

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Caveolae are an abundant feature of the plasma membrane of many vertebrate cells. The surface of adipocytes, endothelial cells, smooth muscle, skeletal muscle and many other cell types has a dense covering of these small invaginations that are characterized by a striated coat, as viewed by electron microscopy, and by the presence of membrane proteins termed caveolins. Three caveolins are present in mammalian cells with caveolin-1 (CAV1) and caveolin-3 (CAV3) essential for caveolar formation in non-muscle and muscle cells respectively. Caveolins bind cholesterol and fatty acids and form homooligomers required for caveolar formation. Approximately 150 CAV1 molecules associate with a single caveola in mammalian cells and in a model prokaryotic system upon caveolin expression. Genetic ablation of caveolins in mice has diverse cellular consequences with impact upon numerous signal transduction pathways and lipid dysregulation. Human patients lacking CAV1 show a severe lipodystrophy while CAV3 mutations, many of which disrupt caveola formation in muscle, are associated with a number of muscle diseases.

Recent years have seen a dramatic increase in our understanding of caveolae with the characterization of a family of caveolar coat proteins. Cavin1/polymerase transcript release factor (PTRF), cavin2/SDR (serum deprivation response protein), cavin3/SRBC (serum deprivation response factor-related gene product that binds to C-kinase) and cavin4/MURC (muscle-restricted coiled-coil protein) are cytoplasmic proteins characterized by conserved putative N-terminal coiled coil domains. PTRF/cavin1 was originally identified as a nuclear protein that can dissociate paused ternary transcription complexes, while cavin2 and cavin3 were identified as protein kinase C (PKC) substrates and have been suggested to function in the targeting of PKC to caveolae. Cavin4/MURC is predominantly expressed in cardiac and skeletal muscle. The cavin proteins have been shown to co-associate and form a cytosolic complex(es) in cells lacking CAV1 (or CAV3), but are recruited to the cell surface to stabilize caveolae in cells expressing CAV1. Ablation of cavin1 expression causes loss of caveolae with CAV1 being released into the bulk membrane whereas expression of cavin1 or cavin2 in cells lacking cavins but expressing endogenous CAV1 is sufficient to generate caveolae. Like caveolins, cavins have also now been linked to many disease conditions including cardiomyopathies, lipodystrophy, and skeletal muscle disorders

The identification of a cytoplasmic coat that can regulate caveola formation has identified a possible mechanism for spatial and temporal regulation of caveola formation: caveolae form at the plasma membrane as caveolins and cavins associate, rather than earlier in the exocytic pathway. In addition, the dissociation of the cavin coat complex could potentially provide a mechanism to disassemble caveolae. This may be crucial for caveolar function in setting membrane tension and in mechanosensing as increased membrane tension causes caveolar flattening and dissociation of cavin1. However, the mechanisms underlying the formation of the cavin complex(es), their stoichiometry and association with caveolae, as well as the mechanisms underlying their dissociation upon membrane stress are all unknown.

We have used a number of model systems to analyse the formation of caveolae and the mechanisms of assembly/disassembly. In response to membrane stress caveolae flatten with release of cavins into the cytoplasm. In cell culture, in mammalian muscle explants, and in zebrafish embryos we demonstrate that caveolae can protect cells against mechanical damage. In addition, we show that flattening of caveolae can have profound consequences for the lipid-based microdomain organization of the plasma membrane with effects on specific signaling pathways. We propose a protective and signaling role for caveolae in response to mechanical stress.