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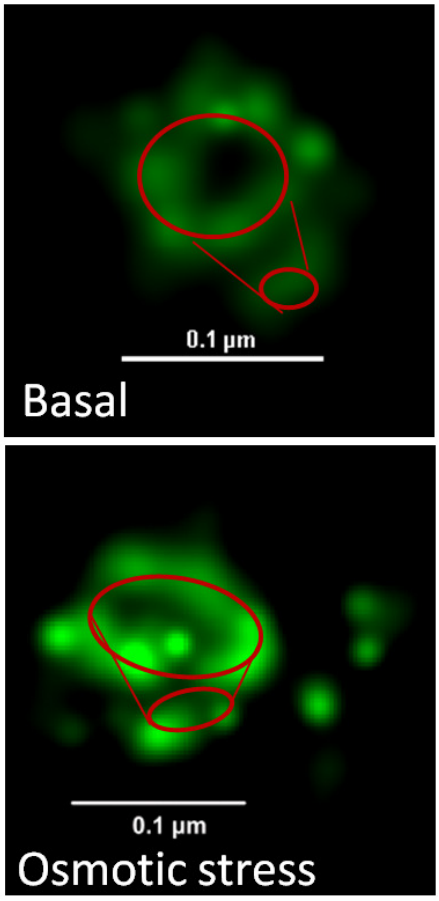
Watching caveolae under stress

The plasma membrane of many cells contain many protein-dense invaginations called caveolae or 'little caves'. Caveolae are composed of ~140 molecules of caveolin proteins along with other components. Caveolae are thought to act like springs and flatten when cells are stretched to relive membrane tension by providing more membrane to the cell. In this way, caveolae give strength to cells. In addition to this mechanical function, it has been observed that proteins involved in different cell signaling pathways can localize to these domains. Our research has shown that caveolae enhances calcium signals that are generated through the Gαq family of heterotrimeric G proteins which is initiated by agents such as acetylcholine, endothelin I, dopamine and angiotensin II. Enhancement of Gαq signals occurs because caveolin molecules bind and stabilize the activated state of Gαq proteins. This stabilization results in prolonged and enhanced calcium signals which has a host of effects on cell growth and function. Thus, the ability of caveolae to regulate calcium responses may play a role in regulating critical cell functions.



Many cells, especially muscle cells, undergo routine cycles of stretch and relaxation during their daily functions which may destabilize the structure of caveolae. Our previous studies showed that the enhancement of calcium signals by caveolae is reversibility lost when cells are subjected to mild hypo-osmotic stress. These observations led us to ask whether stress can impact calcium signals by stretching and deforming caveolae. To answer this question we wanted to determine changes in caveolae structure that may occur with stretch. The problem is that caveolae are very small (50-100 nm) and hard to visualize in their native environment. Therefore, we viewed changes in caveolae structure using super-resolution fluorescence imaging. In this method, we immunostained cells with fluorescent-labeled antibodies for caveolin-1 to view caveolae domains, Gαq and one of its coupled receptors, the bradykinin type 2 receptor (B2R) and Gαi and on its coupled receptors, the β2-adrenergic receptor (βAR). We imaged the cells so that the fluorescence of only a few probes were collected in each image. The center of the point spread functions of the intensities were assigned. This process was carried out for 50,000 raw images and these were merged to generate images below the diffraction limit. In the Figure 1 we show a single caveola where the larger opening is on the extracellular side of the membrane, and the conical structure protrudes into the cell interior (the red diagram is simply to guide the eye). We find that subjecting cells to mild osmotic stress increases the opening of the mouth of the domain and increases the fluorescence intensity in the center of the domain corresponding with a flattening of the caveolae invagination (Fig. 1). Although the caveolae deform with stress, we find that the G proteins and their receptors remain associated with domains. Our results show that cells can regulate their mechanical properties and calcium signals by regulating the amount of caveolae.

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