CHAPTER 3

CAVEOLIN-1:
Role in Cell Signaling

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Abstract: Caveolins (Cavs) are integrated plasma membrane proteins that are complex signaling regulators with numerous partners and whose activity is highly dependent on cellular context. Cavs are both positive and negative regulators of cell signaling in and/or out of caveolae, invaginated lipid raft domains whose formation is caveolin expression dependent. Caveolins and rafts have been implicated in membrane compartmentalization; proteins and lipids accumulate in these membrane microdomains where they transmit fast, amplified and specific signaling cascades. The concept of plasma membrane organization within functional rafts is still in exploration and sometimes questioned. In this chapter, we discuss the opposing functions of caveolin in cell signaling regulation focusing on the role of caveolin both as a promoter and inhibitor of different signaling pathways and on the impact of membrane domain localization on caveolin functionality in cell proliferation, survival, apoptosis and migration.

INTRODUCTION: COMPLEXITY OF CAVEOLIN MEMBRANE DOMAINS

Whereas caveolae were identified in the 1950s by electron microscopy as plasma membrane invaginations, caveolin-1 (Cav1) was initially identified as a 22kDa phosphoprotein substrate of Src kinase and subsequently localized to caveolae.1,2 Cav1 was also observed in the Golgi apparatus, the plasma membrane and vesicles suggesting a role as a trans Golgi network transporter.3 Cav1 was then quickly characterized as a raft-enriched protein responsible for signaling regulation.4 Cav1α is a 178 amino
acid protein (24 kDa) whereas Cav1β is encoded from methionine 32 and contains only 148 amino acid (21 kDa). Cav1α is the best characterized in terms of function. Cav2 and Cav3 are encoded by different conserved genes and display a high degree of similarity with Cav1.5 Cav1 and Cav2 are coexpressed in many tissues (adipocytes, endothelial cells and fibroblasts) whereas Cav3 is enriched primarily in differentiated muscle cells.5,7 The role of Cav2 in signaling regulation is poorly characterized while Cav3 appears to function similarly to Cav1,7,9 This chapter will therefore focus on the role of Cav1 in cellular signaling.

**Structure of Cav1**

Cav1 is a hairpin membrane protein with N and C-terminal cytoplasmic tails separated by a hydrophobic segment (amino acids 102-134) that does not cross the membrane.10,11 Cav1 displays two main functional domains: the tyrosine 14 phosphorylation site and the oligomerization domain that also contains the scaffolding domain. Cav1α (but not Cav1β lacking the first 32 amino acids) is phosphorylated on tyrosine 14 (Y14) by Src kinase as well as Fyn, Yes and e-Abl.12-14 This phosphorylation can occur chronically or punctually in response to growth factor treatment or integrin activation, with various consequences as detailed in the other sections.15,16 Cav1 is also phosphorylated on serine 80 which has been proposed to regulate Cav1 and cholesterol trafficking.17,18 Cav1 oligomerizes through amino acids 1-101; oligomers can include Cav2 and interact with the actin cytoskeleton through filamin A.19-21 This region contains the scaffolding domain (juxtamembrane 82-101 amino acids) which is responsible for Cav1 interaction with Src family proteins, G proteins, phospholipases, protein kinase A, protein kinase C, adenylyl cyclase, nitric oxide synthases, tyrosine kinase receptors and Ras family GTPases.22-25 Moreover, this domain and the C-terminal 135-178 amino acids are responsible for Cav1 localization at the plasma membrane.11 The scaffolding domain allows direct binding to cholesterol which participates in raft organization and cholesterol transport.26-29 Finally, Cav1 is palmitoylated on cysteines 133, 143 and 156 which is required for cholesterol binding and transport to caveolae and for interaction with Src leading to Cav1 Y14 phosphorylation.30,31 Here, we detail the functions of the Cav1 scaffolding domain and tyrosine 14 as critical regulators of cell signaling.

**Cav1-Associated Membrane Domains: Rafts, Caveolae and Cav1 Scaffolds**

Lipid rafts are plasma membrane domains enriched in cholesterol and sphingolipids where multiple signaling and responses are regulated. Rafts were initially characterized biochemically as detergent resistant membranes (DRMs), however they have since been shown to be very dynamic and transient structures. Cav-associated structures represent subdomains of lipid rafts and include caveolae but also Cav1 scaffolds, flat oligomerized Cav1-associated domains that do not form caveolar invaginations at the cell surface (Fig. 1).

Noncaveolar rafts are planar 1-1000 nanometer ordered structures enriched in glycosylphosphatidylinositol (GPI)-anchored proteins. They are difficult to visualize because of their transient properties and flat shape. Tools have been developed to study rafts, such as fluorescent B subunit of Cholera toxin, which binds the ganglioside GM1, GFP-tagged GPI-proteins and drugs such as filipin and nystatin that sequester cholesterol, or β-methylocyclodextrin that extracts cholesterol. Recently new dyes such as Laurdan