New insights into the formation and function of caveolae

R.G. Parton, Institute for Molecular Bioscience, University of Queensland, Brisbane, Queensland 4072, Australia. (Introduced by D.I. Cook)

Caveolae are flask-shaped pits of the cell surface, an abundant morphological feature of many mammalian cells. Caveolins, the major proteins of caveolae, play a crucial role in the formation of caveolae. Mutations in caveolins are associated with breast cancer and with a number of muscle diseases, including limb girdle muscular dystrophy. We have studied how caveolin-lipid interactions generate the unique architecture of the caveolar domain by studying caveola formation in caveolin-null fibroblasts by light and electron microscopy upon expression of mammalian caveolins (caveolin-1 and caveolin-3), specific mutants of these proteins, or non-mammalian caveolins (from *C. elegans* and the honey bee, *Apis mellifera*) (Kirkham *et al.*, 2008). These studies are being combined with high-resolution analysis of caveolae by electron tomography of isolated plasma membrane sheets and fast frozen cells after freeze substitution (Richter *et al.*, 2008). These studies have adefined the fine structure of caveolae and shown that caveolae are linked by actin filaments to form an interconnected network.

Our recent studies have identified an additional level of regulation of caveola formation. Using a systematic proteomic analysis we have identified a family of evolutionary-conserved coat proteins that work together with caveolins to regulate caveola formation (Hill *et al.*, 2008). Reduction of PTRF-cavin levels in cultured cells causes loss of morphological caveolae with caveolin being released into the bulk membrane. Photobleaching studies show that caveolin is now freely mobile in the plasma membrane in contrast to the immobility of caveolin in control cells. Reduction of PTRF-cavin levels also allows caveolin to be degraded more rapidly. To examine the role of PTRF-cavin in a whole animal system we have utilised the zebrafish embryo as a model organism. Formation of caveolae in the zebrafish correlates temporally with expression of PTRF-cavin in the notochord during zebrafish development. Consistent with this, knockdown of zebrafish PTRF-cavin causes a reduction in the density of caveolae in the notochord (Hill *et al.*, 2008).

We propose that PTRF-cavin family members regulate association of caveolin with caveolae and identify a cellular mechanism to regulate caveolar and non-caveolar functions of caveolins. In addition, we postulate that PTRF-cavin family members can act as molecular sensors of changes in caveola structure or composition.

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