Caveolae at a glance

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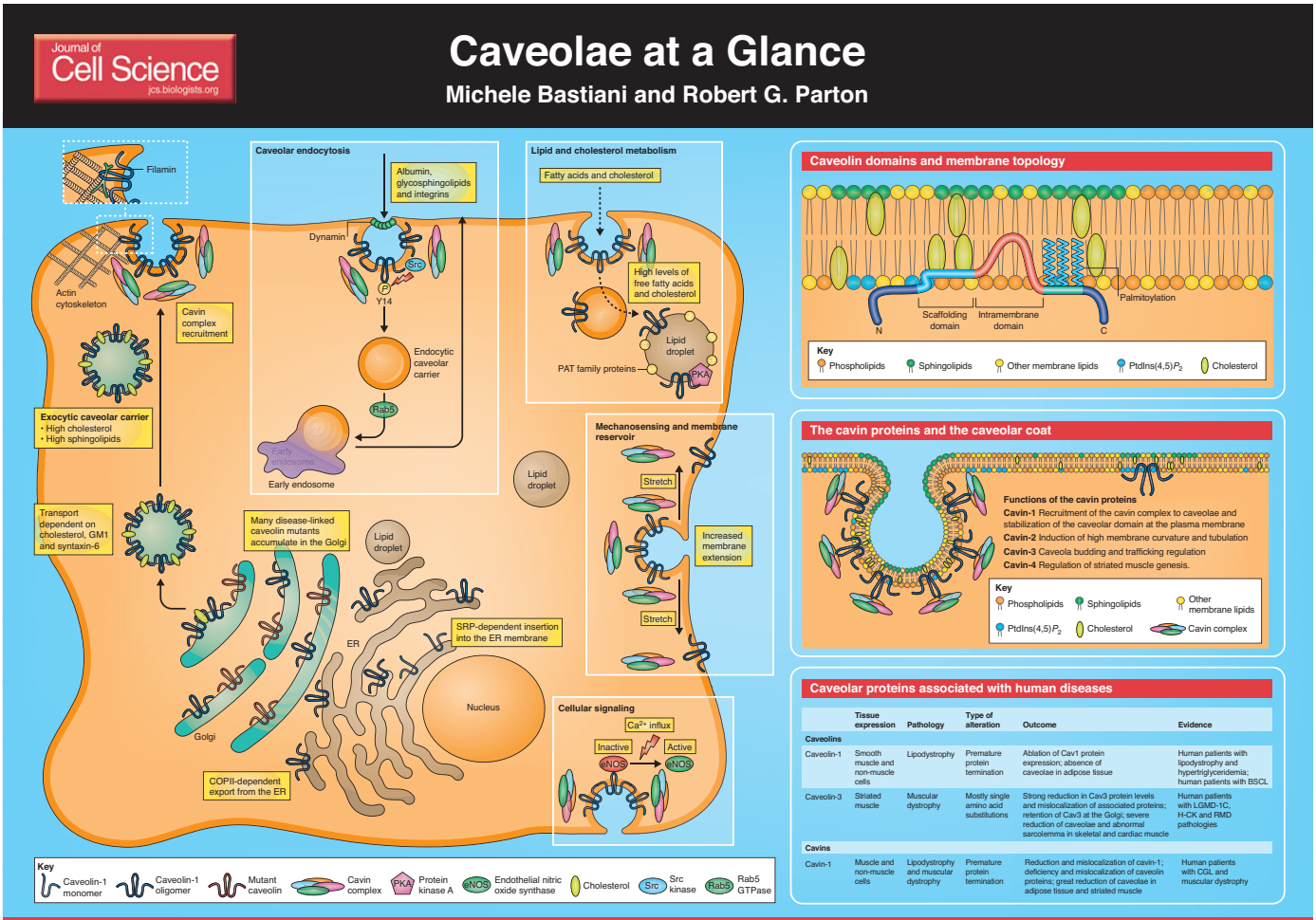
The plasma membrane is more than a simple delimitation of the boundary of the cell but is a dynamic multi-domain membrane system participating in numerous cellular processes. In many different cell types, the plasma membrane is heavily decorated with small pits of 60–80 nm in diameter, which constitute a specialized type of microdomain called caveolae. Nowadays, almost 60 years after the first observation of caveolae (Palade, 1953), these enigmatic structures are still a hot topic in cellular biology with questions remaining regarding their formation, regulation, and functions in different cell types and in pathological scenarios.

The discovery of the caveolin proteins greatly advanced the study of caveolae, particularly with the subsequent demonstration that caveolin expression induces, and is required for, the formation of caveolae (Drab et al., 2001; Fra et al., 1995; Razani et al., 2001). Caveolins are now known to constitute a family of integral membrane proteins that form the principal membrane components of caveolae. The first reported caveolin protein (also independently described as VIP-21) is now called caveolin-1 (Cav1), after the discovery of the related proteins caveolin-2 (Cav2) and caveolin-3 (Cav3). Cav1, together with Cav2, is expressed in a wide range of tissues with the highest levels of expression in endothelial cells, adipocytes, fibroblasts and smooth-muscle cells. Cav3 appears to be the sole isoform expressed in skeletal and cardiac muscle. The essential role of caveolins for caveola formation was made evident with the generation of *Cav1*- and *Cav3*-knockout mice, which completely lack caveolae in the respective tissues and, consequently, exhibit a range of phenotypes including muscle, pulmonary and lipid disorders (Le Lay and Kurzchalia, 2005).

The recent characterization of cavin-1 (also known as polymerase I and transcript release factor, PTRF) – a protein initially described as a transcription factor and associated with caveolae in adipocytes – as an essential factor required for the stabilization of caveolae at the plasma membrane (Hill et al., 2008; Liu and Pilch, 2008) brought new insights into caveola biogenesis and suggested that caveola formation can be a dynamically regulated process. Moreover, further investigation of cavin-1 and the other three members of the cavin family in the past two years (Bastiani et al., 2009; Hansen



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et al., 2009; Hill et al., 2008; McMahon et al., 2009) have revealed additional levels of complexity in the regulation of caveola formation and function.

In this review, we summarize the events leading to caveola formation as well as the roles of caveolae in different cell types. The accompanying poster illustrates the biosynthetic pathway for caveola formation, the role of the recently characterized cavin complex in caveola formation, and also proposed functions of caveolae and the association of caveolar proteins with disease conditions.

Caveola biogenesis and the caveolin biosynthetic pathway

Caveolae at the plasma membrane are characterized by a highly uniform structure, originally described as 'flask-shaped' but more recently shown to be 'cup-shaped', with an open neck as demonstrated in unfixed fast-frozen material (Richter et al., 2008; Schlormann et al., 2010). Although considered uncoated (in comparison with clathrin coated pits), a coat structure can be observed when specialized techniques are used (Richter et al., 2008; Rothberg et al., 1992). Approximately 144 caveolin molecules have been suggested to be incorporated in a single caveolar structure (Pelkmans and Zerial, 2005).

Caveolin is synthesized in the endoplasmic reticulum (ER) in a signal recognition particle (SRP)-dependent manner as an integral membrane protein, and it adopts an unusual hairpin configuration in which the N- and C-termini are exposed to the cytoplasm (Monier et al., 1995) (see poster). Caveolin forms low molecular weight oligomers in the ER and travels to the Golgi complex, in a process dependent on the coat protein complex-II (COPII), where it undergoes another round of oligomerization (Hayer et al., 2009; Pol et al., 2005). Later on in the biosynthetic pathway, caveolin is palmitoylated in the C-terminal region (Dietzen et al., 1995; Parat and Fox, 2001). Exocytic caveolar carriers, containing a defined number of caveolin monomers, were shown to directly travel from the Golgi complex to the plasma membrane (Parton and Simons, 2007; Tagawa et al., 2005). Glycosphingolipids and cholesterol have been suggested to be crucial factors for the budding of these caveolar domains from the Golgi complex, and cholesterol has been shown to be a rate-limiting component for caveolin trafficking from the Golgi complex to the plasma membrane (Pol et al., 2005). The exact mechanisms underlying exit from the Golgi complex and the precise nature of the exocytic carriers are still to be elucidated, but it is apparent that mutations in a number of regions of the caveolin protein disrupt the transport from the Golgi to the cell surface (Kirkham et al., 2008), resulting in the development of diseases (Mercier et al., 2009). The SNARE protein syntaxin-6 also regulates post-Golgi caveolin transport through the control of membrane fusion events (Choudhury et al., 2006), and the ganglioside GM1 has been recently shown to be required for caveolin trafficking and maintenance of caveolae at the plasma membrane (Singh et al., 2009). Once at the plasma membrane, caveolae form a specialized lipid domain that is enriched in sphingolipids, specifically sphingomyelin and the glycosphingolipids ganglioside GD3, GM1 and GM3 (Ortegren et al., 2004; Pitto et al., 2000), cholesterol (Fujimoto et al., 1997) and phosphatidylinositol (4,5)-bisphosphate [PtdIn(4,5)P_2] (Fujita et al., 2009), and remain in close association with microtubules and actin microfilaments (Head et al., 2006; Richter et al., 2008). The actin-binding protein filamin, which directly interacts with Cav1, might be involved in linking caveolae to the actin cytoskeleton (Stahlhut and van Deurs, 2000).

The role of the cavin proteins in caveola formation and function

The essential role of a newly characterized multi-protein complex – the cavin complex – for caveola formation at the plasma membrane has been highlighted in the past few years (Bastiani et al., 2009; Hansen et al., 2009; Hill et al., 2008; McMahon et al., 2009); for a recent review see (Hansen and Nichols, 2010). The cavin complex is formed through the direct interaction of the four cavin family members, namely cavin-1 or PTRF, cavin-2 or SDR (serum deprivation response protein), cavin-3 or SRBC (serum deprivation response factor-related gene product that binds to C-kinase) and cavin-4 or MURC (muscle-restricted coiled-coil protein). The different components of this complex regulate distinct aspects of caveola formation and function.

The cavin proteins are highly conserved among mammals and the homology among different family members is mostly found in two regions within the N-terminal part of the proteins (Bastiani et al., 2009). Moreover, the cavins are predicted to contain PEST domains (sequences enriched in proline, glutamic acid, serine and threonine), which are known to serve as recognition domains for regulating signaling proteins through proteolysis. In addition, cavin-1, cavin-2 and cavin-3 were predicted to contain putative leucine zippers (dimerization and protein-protein interaction modules generally involved in DNA-binding), and cavin-1 and cavin-4 also contain putative nuclear localization signals (Aboulaich et al., 2004; Bastiani et al., 2009; Hansen and Nichols, 2010).

Cavin-1 was originally described as a transcription regulatory factor (Jansa et al., 1998; Mason et al., 1997) and shown to interact with the transcription factor BFCOL1, which binds the type-I collagen promoter, in specific tissues (Hasegawa et al., 2000). Cavin-1 has also been independently characterized as cav-p60, a protein initially found to be localized to caveolae in adipocytes (Vinten et al., 2005; Vinten et al., 2001) and, subsequently, also in a range of other tissues (Voldstedlund et al., 2001). This indicates that cavin-1 is not associated with caveolae in a tissue-specific manner and, therefore, could associate with both Cav1 and Cav3. Further characterization of cavin-1 has demonstrated that this protein is an essential regulator of caveola biogenesis and thus opened the way for further investigation of caveola regulation. Making use of both cell culture systems, and animal models that include mice and zebrafish embryos, it has been demonstrated that caveola formation is dramatically reduced in cells lacking cavin-1 (Hill et al., 2008; Liu et al., 2008; Liu and Pilch, 2008). In these models, caveolin exhibits an increased mobility and is associated with a flat plasma membrane (Hill et al., 2008). In addition, the loss of caveolae caused by the lack of cavin-1 was associated with degradation of caveolin and with lipid and muscle disorders (Dwianingsih et al., 2010; Hayashi et al., 2009; Hill et al., 2008; Liu et al., 2008; Rajab et al., 2010).

Cavin-2 (Gustincich et al., 1999) and cavin-3 (Izumi et al., 1997) are both protein kinase C (PKC) substrates and have been suggested to function in the targeting of PKC to caveolae. Like cavin-1, cavin-2 and cavin-3 are expressed in muscle and non-muscle cells, and their expression profile closely parallels that of Cav1 (Bastiani et al., 2009). The recently characterized fourth member of the cavin family, cavin-4, is a caveolar protein highly enriched in skeletal and cardiac muscle plasma membranes (Bastiani et al., 2009), and shown to be able to regulate ERK1/2 signaling and myogenesis (Ogata et al., 2008; Tagawa et al., 2008).

The cavin complex, comprising an estimated 60–80 cavin molecules (Hayer et al., 2009), is recruited to the plasma membrane in a cavin-1-dependent fashion by caveolin (Bastiani et al., 2009) but does not associate with the pool of caveolin in the Golgi complex (Hayer et al., 2009; Hill et al., 2008). This indicates that cavin-1 recognizes and associates specifically with a mature form of caveolin present in surface caveolae or with the plasma membrane environment that is generated by the caveolin-

enriched domains (e.g. the lipid environment or the caveola shape). All four cavin proteins can interact with phosphatidylserine (PtSer) in vitro (Bastiani et al., 2009; Burgener et al., 1990; Gustincich et al., 1999; Hill et al., 2008; Izumi et al., 1997). Caveolin might generate PtSer-enriched domains at the plasma membrane (Wanaski et al., 2003) and therefore the stabilisation of caveolae by the cavin complex could be the result of the sum of the many – but relatively weak – binding interactions between PtSer and cavin molecules (Bastiani et al., 2009). Such a mechanism, termed coincidence detection, relies on a large number of low-affinity interactions for the generation of a high-avidity interaction and has been proposed for the formation of clathrin-coated pits, where accessory proteins interact with cargo molecules and with PtdIn(4,5)P_2 (Carlton and Cullen, 2005). The fact that cavins can recognize the specific pool of caveolin associated with caveolae also raises the interesting possibility that changes to the caveolar domain at the surface can result in the dissociation of the cavin proteins from caveolae with the consequent flattening of the caveolar membrane. The experimentally induced loss of cavin-caveolin interactions upon disruption of caveolae by cholesterol depletion (Hill et al., 2008) is consistent with this possibility, and suggests that a similar disruption of caveolae occurs under physiological cellular conditions of membrane perturbation to release the cavin complex and allow its interaction with other thus far unidentified targets.

Cavin-1 has an essential role in targeting the cavin complex to the plasma membrane (Bastiani et al., 2009) but the other members of the cavin family perform distinct and specific functions. Cavin-2 has been suggested to be important for membrane curvature and tubulation, and has a direct role in the formation of the caveolar invaginations (Hansen et al., 2009), although it appears that morphologically normal caveolae can be detected in cells that express only Cav1 and cavin-1 (Bastiani et al., 2009; Hill et al., 2008). Cavin-3 regulates caveola endocytosis, and the knockdown of cavin-3 limits the budding and the intracellular trafficking of Cav1-positive vesicles (McMahon et al., 2009). Cavin-4 expression increases with the differentiation of myoblasts into myotubes (Bastiani et al., 2009; Tagawa et al., 2008) and transgenic mice that overexpress cavin-4 show cardiac contractile dysfunction (Ogata et al., 2008), possibly indicating impairment of the T-tubule system.

Functions of caveolae

Although the presence and abundance of caveolae in mammalian cells has been known for decades, their function is yet to be completely elucidated. Caveolae have been implicated in endocytosis, cholesterol and lipid metabolism, mechanosensation and cellular signaling. The proposed physiological roles of caveolae, however, are vastly different depending on the cell type and organ system examined (for reviews, see Parton and Simons, 2007; van Deurs et al., 2003).

Cellular signaling pathways

Caveolae have been proposed to be a platform for many different signaling pathways, and have been linked to molecules as diverse as platelet-derived growth factor (PDGF), epidermal growth factor receptor (EGFR), and the small GTPase H-Ras (Patel et al., 2008). In this model, caveolin acts as a scaffold to interact with and to regulate signaling molecules located in caveolae. However, many of these interactions need to be confirmed by using independent techniques that can clearly show the association of these molecules with caveolae and their functional dependence on caveolin. In addition, roles for caveolar and non-caveolar pools of caveolin must be considered.

Despite the lack of clear evidence in many cases, the interaction of endothelial nitric oxide synthase (eNOS) with caveolae and with caveolin is well characterized. In endothelia, eNOS is targeted to caveolae by palmitoylation and is negatively regulated by its association with caveolin (Garcia-Cardena et al., 1997; Sowa et al., 2001). Caveolin interacts with eNOS through a region called the caveolin scaffolding domain (amino acids 82–101 of Cav1) and this interaction is sufficient to inhibit eNOS function in vivo (Bucci et al., 2000; Garcia-Cardena et al., 1997). This region of the caveolin scaffolding domain has also been suggested to interact with the inactive conformations of Src tyrosine kinases and of H-Ras (Li et al., 1996). It has been recently suggested to form an in-plane amphipathic helix buried within the membrane in mature caveolae (Kirkham et al., 2008), thus challenging the idea that this domain has a role in mature caveolae but compatible with a role for non-caveolar caveolin in regulating signaling.

Caveolar endocytosis

Caveolae have been described as relatively immobile structures and it has even been proposed that Cav1 works as a negative regulator of lipid raft (and caveolar) endocytosis (Le et al., 2002) by inducing caveola formation with the consequent stabilisation of the rafts at the plasma membrane. However, caveolar endocytosis has been implicated in the internalisation of integrins and glycosphingolipids as reviewed in (Cheng et al., 2006). The non-enveloped Simian virus 40 (SV40) has also been proposed to exploit caveolar endocytosis for its own internalisation (Pelkmans et al., 2001; Pelkmans et al., 2002). More recent findings, however, indicate that SV40 is internalized in vesicles that lack Cav1 (Ewers et al., 2010) and that it is more rapidly internalized in Cav1$^{-/-}$ cells (Damm et al., 2005). Regardless of the internalized agent, caveolar endocytosis involves a subsequent reorganization of the actin cytoskeleton and appears to be mediated by dynamin, Src kinases (which phosphorylate Cav1 at the Tyr14 residue) and PKC (Mayor and Pagano, 2007). The analysis of kinases involved in SV40 internalization revealed that some of these are also associated with the regulation of cellular adhesions, suggesting a connection between endocytosis via caveolae and cell adhesion (Pelkmans et al., 2005). Corroborating this connection, glycosphingolipids, which stimulate caveolar endocytosis (Sharma et al., 2004), can lead to clustering and internalisation through caveolae of β1-integrin, a key integral membrane protein that mediates cellular adhesion in many cell types (Sharma et al., 2005). It has been further suggested that the clustering and activation of β1-integrins can initiate caveolar endocytosis with the subsequent removal of β1-integrins from the plasma membrane (Sharma et al., 2005). Supporting a role for β1-integrin signaling in caveolar endocytosis, downregulation of β1-integrin reduces activation of Src and caveolar endocytosis (Singh et al., 2007). However, it has been reported that integrins are negative regulators of caveolae internalization and, therefore, active integrins actually inhibit caveolar internalization (Echarri et al., 2007). Whether these differences are dependent on the attachment status of the cell or on the trigger for caveolae internalization remains to be unraveled. It is, however, clear that caveolar endocytosis participates in the regulation of cellular adhesion, and caveolin itself has a particularly important role in detaching cells, in which the internalization of specific membrane domains and the consequent downregulation of growth signaling pathways is dependent on Cav1 phosphorylation and caveolar endocytosis (del Pozo et al., 2005).

Lipid and cholesterol regulation

Caveolae also function in lipid and cholesterol regulation; the plasma membrane of adipocytes (cells specialized in lipid storage) contains high levels of Cav1 and an extremely high numbers of caveolae, which cover up to 40% of the cellular surface. As caveolae are detergent-resistant membrane domains that are not dissolved by the mild detergent properties of fatty acids, it has been hypothesized for many

years that caveolae can regulate trafficking of fatty acids and their accumulation into the cells; for a more comprehensive review of this aspect see Pilch et al. 2007 (Pilch et al., 2007). Support for this role comes from the expression of Cav1 in cells that normally have no endogenous caveolin; expression was shown to facilitate the uptake of fatty acids into cells as well as to increase the levels of free cholesterol and of cholesterol export (Fielding and Fielding, 2001; Fu et al., 2004; Meshulam et al., 2006). In vivo experiments further implicate caveolae in lipid and cholesterol metabolism. For example, *Cav1*-knockout mice are resistant to diet-induced obesity and show decreased adiposity as well as decreased levels of free cholesterol in adipocytes (Le Lay et al., 2006; Razani et al., 2002). Cav1 is an important plasma membrane fatty-acid binding protein in adipocytes (Trigatti et al., 1999) and it moves from the plasma membrane to lipid droplets (intracellular organelles specialized for lipid storage) in response to free fatty acids (Ostermeyer et al., 2001; Pol et al., 2001; Pol et al., 2004). Reinforcing the significance of Cav1 in lipid droplets and in lipid metabolism, *Cav1*-null mice show a dramatic reduction in the formation of lipid droplets during liver regeneration and decreased survival after partial hepatectomy (Fernandez et al., 2006). Studies using a model system (HEK293 cells heterologously expressing Cav1) have confirmed a role for Cav1 (and Cav3) in increasing lipid storage in lipid droplets (Meshulam et al., 2006; Simard et al., 2010). These studies also demonstrated that Cav1 modulates fatty acid flux across the plasma membrane (Meshulam et al., 2006) through a C-terminal region in caveolin that is enriched in positively charged amino acids (Simard et al., 2010). These effects are accompanied by a significant protection against lipotoxicity in the caveolin-expressing cells. In addition, it has been proposed that caveolae themselves function as sites for the uptake of fatty acids and their subsequent conversion to triacylglycerols (Ost et al., 2005), which subsequently are stored in the Cav1-containing lipid droplets. Studies in adipocytes have shown that the association of Cav1 with lipid droplets is stimulated by cholesterol and dependent on the dynamin-dependent budding of caveolae mediated by PKC and Src activation (Le Lay et al., 2006). Altogether, these results suggest that caveolae can coordinate fatty acid uptake and storage in lipid droplets, and raise the possibility that lipodystrophy associated with loss of Cav1 in patients (Cao et al., 2008; Kim et al., 2008) reflects the increased sensitivity of adipose tissue to fatty acids in the absence of caveolins.

Mechanosensing

Caveolae and caveolin have also been implicated in mechanosensing, the cellular sensing and response to force or geometry stimuli, and have been shown to be required for signaling events in response to mechanical cues. In Cav1-deficient cells, release of Cl^-, taurine and ATP in response to hypo-osmotic cellular swelling is defective and can be recovered by exogenous Cav1 expression (Ullrich et al., 2006). Moreover, Cav1 has been shown to be essential for mechanoactivation of protein kinase B (Akt) and for cell cycle progression under cyclic stretch in vitro and in vivo (Sedding et al., 2005). Recently, Kozera and colleagues demonstrated a direct role for caveolae in mechanosensing and showed that caveolae can act as a membrane reserve and attenuate volume-regulated channels activation by limiting the increase in membrane tension during cellular swelling (Kozera et al., 2009). These reports endorse the hypothesis that caveolae can sense and respond to changes in membrane tension. An intriguing possibility is that caveolae work not only as membrane reservoirs, but also as structural mechanosensors, in that the interaction between caveolin and cavin-1 functions as a regulator for caveola disassembly and reassembly in response to membrane tension. Apart from the elementary benefit of providing additional surface area, the flattening of caveolae and the dissociation of the caveolin-cavin complexes could release these proteins for modulating a cellular response at the molecular level in response to mechanical stimuli.

Perspectives

It is now clear that cavins work in conjunction with caveolins to regulate caveola formation and function. This knowledge has not only provided new insights into the cell biology of caveolae, but also pointed to an increasing number of disease conditions that are associated with caveolar dysfunction. For example, as mentioned above, deficiency in Cav1 protein leads to severe and generalized lipodystrophy (Cao et al., 2008; Kim et al., 2008), whereas mutations in Cav3 lead to the development of several different muscle disease conditions (for a review, see Gazzerro et al., 2010). Cavin-1 mutations are associated with both lipodystrophy and muscle disease (Dwianingsih et al., 2010; Hayashi et al., 2009; Rajab et al., 2010) in agreement with the proposed role of cavin-1 in regulating caveola formation in both muscle and non-muscle tissues. Although the table in the accompanying poster highlights the dystrophic phenotypes directly associated with caveolins and cavin-1 inherited mutations in patients, it should be noted that malfunctioning or changes in the expression levels of these proteins have also been associated with a variety of other diseases both in vitro and in mice models (for a review see Mercier et al., 2009). Cav1 appears to function as either a tumor suppressor or promoter depending on the cell type, and might be involved in the development of human breast and prostate cancers (Goetz et al., 2008). The somatic mutation P132L in Cav1 has been associated with invasiveness and malignant progression in human breast cancer (Hayashi et al., 2001), but there is some controversy as a recent study questioned the association of this mutation with breast cancer (Koike et al., 2010). In prostate cancer, elevated expression of Cav1 appears to correlate with metastatic progression (Thompson et al., 2010). Loss of cavin-1 has also been recently linked to the development of prostate cancer (Gould et al., 2010; Hill et al., 2008), whereas the lack of cavin-2 and cavin-3 has been suggested to be involved in the development of cancer in several tissues (Li et al., 2008; Xu et al., 2001), indicating that cavin proteins are also connected to pathologies that have been linked to caveola.

The characterization of cavins also provides new insights into possible caveolar and non-caveolar roles of caveolins (Head and Insel, 2007). Caveolin protein expression starts well before the onset of cavin-1 expression and caveola biogenesis during embryonic development of the zebrafish *Danio rerio* (Hill et al., 2008), which strongly suggests that caveolin has roles independent of those of caveolae. For example, phosphorylated Cav1 has been recently suggested to be involved in focal adhesion turnover and cell migration even in cells that lack caveolae (Joshi et al., 2008). It is important to note that cavins might also have non-caveolar functions – for example, after they are released from the plasma membrane upon disruption of caveolae – whereas other functions might be entirely independent of caveolae. Although expression patterns of cavins generally correlate well with the expression of *Cav1* and *Cav3*, exceptions exist that suggest additional tissue-specific functions (Bastiani et al., 2009).

In the light of these findings it is clear that the study of the mechanisms underlying caveola biogenesis and function, as well as of the individual proteins involved in caveola assembly and function, promises exciting new discoveries in the field of cellular biology. Numerous questions remain to be answered, for example, what is the role of the characteristic shape of caveolae? What is the role of non-caveolar caveolin and how important is the interplay between caveolar and non-caveolar caveolin? Do cavins orchestrate cytoplasmic or

nuclear events in response to changes in caveolae? Any advances are likely to be of great importance in understanding a range of physiological and pathological conditions associated with caveolar proteins.

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