

# New glimpses of caveolin-1 functions in embryonic development and human diseases

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**Abstract** Caveolin-1 (Cav-1) isoforms, including Cav-1 $\alpha$  and Cav-1 $\beta$ , were identified as integral membrane proteins and the major components of caveolae. Cav-1 proteins are highly conserved during evolution from *Caenorhabditis elegans* to human and are capable of interacting with many signaling molecules through their caveolin scaffolding domains to regulate the activities of multiple signaling pathways. Thus, Cav-1 plays crucial roles in the regulation of cellular proliferation, differentiation and apoptosis in a cell-specific and contextual manner. In addition, Cav-1 is essential for embryonic development of vertebrates owing to its regulation of BMP, Wnt, TGF- $\beta$  and other key signaling molecules. Moreover, Cav-1 is mainly expressed in terminally differentiated cells and its abnormal expression is often associated with human diseases, such as tumor progression, cardiovascular diseases, fibrosis, lung regeneration, and diseases related to virus. In this review, we will further discuss the potential of Cav-1 as a target for disease therapy and multiple drug resistance.

**Keywords** Caveolin-1, signal transduction, embryonic development, human diseases

## Introduction

Caveolae are flask-shaped vesicular invaginations of plasma membrane with diameters of 50–100 nm (Yamada, 1955). Important components of caveolae include three identified caveolin members: Cav-1, -2 and -3. Cav-1 was identified as an integral membrane protein and the major molecular marker for caveolae (Rothberg et al., 1992). Cav-1 and -2 are co-expressed in almost all tissues except lymphocytes, while Cav-3 expression is limited to striated muscles (Head and Insel, 2007). Cav-1 contains several functional domains that are necessary for its roles in cell surface signaling, endocytosis and cholesterol transport (Table 1 and Fig. 1).

Cav-1 isoforms, including Cav-1 $\alpha$  and Cav-1 $\beta$ , are translated from two distinct mRNAs and contain a hydrophobic stretch of amino acids, a scaffolding domain, and an acylated C-terminal region, but only Cav-1 $\alpha$  contains the

N-terminal 31 amino acids (Kogo and Fujimoto, 2000; Scherer et al., 1995). The tyrosine(Y) 14 in Cav-1 $\alpha$  was identified as a phosphorylation site, while this site does not exist in Cav-1 $\beta$  (Li et al., 1996). Phosphorylated tyrosine 14 is thought to be a specific tyrosine kinase substrate (Lee et al., 2000) and is associated with cell (including tumor cell) migration (Joshi et al., 2008). It has been shown that Cav-1 $\alpha$  and -1 $\beta$  have different subcellular distributions (Scherer et al., 1995; Kogo et al., 2004) and play distinct roles in caveolae formation (Fujimoto et al., 2000) and development of lung and liver (Kogo et al., 2004; Wang et al., 2010a). In addition, Cav-1 $\alpha$  and -1 $\beta$  show different activities in regulation of BMP and phosphatidylinositide 3-kinase (PI3K)/Akt signaling (Ono et al., 2004; Nohe et al., 2005). Cav-1 proteins have important roles in vesicular transport, cholesterol homeostasis and signal transduction and biochemically interacting with many signaling cascades in multiple signaling pathways to regulate cellular proliferation, differentiation and apoptosis in a cell-specific and contextual manner (Cohen et al., 2004). In this review, we will focus on the recent understanding of Cav-1 functions in signal transduction, embryonic development and human diseases.

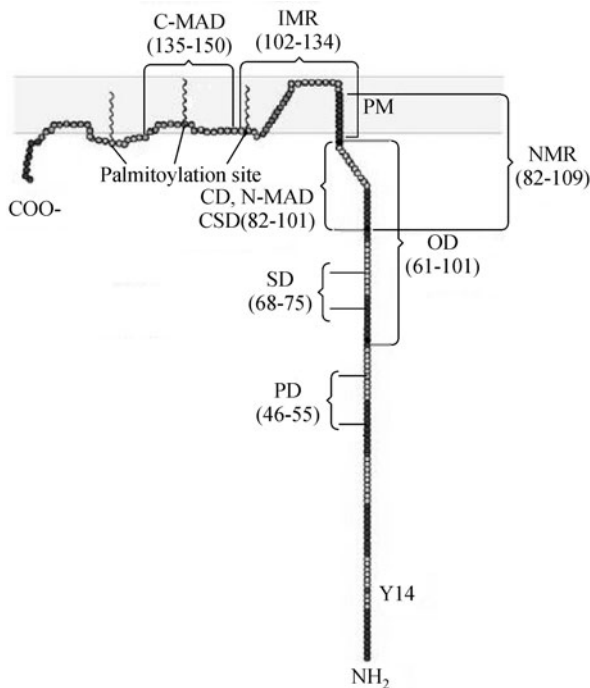
Received December 14, 2010; accepted December 30, 2010

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**Table 1** Caveolin-1 structure and domain functions

Domain locations	Names	Known functions	References
14	Tyrosine 14	Phosphorylation and caveolae internalization	Sun et al., 2007
46–55	Polarization domain (PD)	Cav-1 polarization and caveolae formation	Sun et al., 2007
68–75	Signature domain (SD)	Release Caveolin-1 from endoplasmic reticulum	Machleidt, et al., 2000
61–101	Oligomerization domain (OD)	Oligomerization with himself or Cav-2	Sargiacomo et al., 1995; Scherer et al., 1997
82–101	Circular dichroism (CD)	Stabilize CSD helical conformation	Le Lan et al., 2006
	N-attachment domain (N-MAD)	Attach with membrane	Schlegel and Lisanti, 2000
	Caveolin Scaffolding domain (CSD)	Interact with other protein	Couet et al., 1997
82–109	Nuclear magnetic resonance (NMR)	Solution of phosphatidylserine	Le Lan et al., 2006
102–134	Intramembrane region (IMR)	Plasma membrane location	Glenny and Soppet, 1992
135–150	C-attachment domain(C-MAD)	Attachment with membrane	Schlegel and Lisanti, 2000
133, 143, 156	Cysteine	Palmitoylation	Dietzen et al., 1995
		Interaction with other acylated protein	Lee et al., 2001
		Bind and transport cholesterol	Uittenbogaard and Smart, 2000



**Figure 1** A structural model of Cav-1 protein (178 amino acids) from Head and Insel (2007) with some modifications. PD: polarization domain; C-MAD: C-attachment domain; IMR: intramembrane region; NMR: nuclear magnetic resonance; CSD: Caveolin Scaffolding domain; N-MAD: N-attachment domain; CD: circular dichroism; SD: signature domain; OD: oligomerization domain; Y14: tyrosine 14.

## Caveolin-1 and signal transduction

The scaffolding domain of Cav-1 (CSD) can recognize and bind proteins containing the sequence motif  $\Phi x \Phi x x x \Phi$ ,  $\Phi x x x \Phi x x \Phi$  or  $\Phi x \Phi x x x \Phi x x \Phi$ , where  $\Phi$  is an aromatic

residue and x is any amino acid (Couet et al., 1997). Through the CSD, Cav-1 interacts with a number of growth factor receptors such as transforming growth factor- $\beta$  receptor (TGF- $\beta$ R), fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), insulin-like growth factor receptor (IGFR), platelet-derived growth factor receptor (PDGFR) and epidermal growth factor receptor (EGFR), and signal molecules including H-ras, G protein, eNOS,  $\beta$ -catenin and p53 (Table 2) (Liu et al., 2002). It is well known that roles of Cav-1 in the regulation of cellular proliferation, differentiation and apoptosis are closely associated with this CSD domain.

Mechanistically, Cav-1 is able to control activities of multiple signaling pathways by its participation in the internalization of growth factor receptors and transcriptional factors. In general, Cav-1 acts as a negative regulator to control the basal activity of many signaling molecules. For example, Cav-1 inhibits activities of growth factor receptors (e.g. EGFR, PDGFR, IGFR and FGFR), the downstream mitogen-activated protein kinase (MAPK), PI3K/Akt and Wnt signaling (Han et al., 2009; Matthews et al., 2008; Cabrita et al., 2006; Galbiati et al., 2000). However, Cav-1 sometimes plays distinct roles in a signaling pathway through interaction with different signal molecules. For instance, Cav-1 suppresses the TGF- $\beta$ -mediated transcriptional activity through direct interaction with ubiquitous TGF- $\beta$ R (Razani et al., 2001a; Lee et al., 2007), but enhances the TGF- $\beta$ /ALK1 signaling as shown by its activation of ALK1 (an activin receptor-like kinase and TGF- $\beta$ 1R) -specific reporters (Santibanez et al., 2008). Moreover, Cav-1 expression leads to the accumulation of  $\beta$ -catenin within caveolae membranes and thus inhibits the  $\beta$ -catenin/Lef-1 signaling activated by wnt-1 or the overexpression of  $\beta$ -catenin itself (Galbiati et al., 2000), while inducing LRP6 (a low-density lipoprotein receptor-related protein 6 and wnt receptor) internalization and activating wnt/ $\beta$ -catenin signaling (Yamamoto et al.,

**Table 2** Signaling molecules and pathways regulated by Cav-1

Molecules	Interact	Substrate	Regulate	Signaling pathway	Reference
Growth factor receptors					
TGFR	Directly	most of TβR	Suppress	TGF-β	Razani et al., 2001a
	Directly	ALK1	Promote	TGF-β	Santibanez et al., 2008
	Directly	BRII	inhibit (β isoform)	BMP	Nohe et al., 2005
EGFR	Directly	EGFR	inhibit	EGF	Couet et al., 1997
	Indirectly	EGFR	inhibit	EGFR-MAPK	Han et al., 2009
	Directly	EGFR	promote	EGF	Agelaki et al., 2009
FGFR	Directly	Sprouty1-4	inhibit	p42/44 MAPK	Cabrita et al., 2006
IR	Directly	IR	Active	Insulin	Nystrom et al., 1999
	Directly	IRS-1	active	Insulin	Chen et al., 2008
IGFR	Directly	IGF-IR	upregulate	IGF	Ravid et al., 2005
VEGFR	Directly	VEGFR-2	no action	VEGF	Labrecque et al., 2003
	Directly	VEGFR-2	inhibit	p42/44 MAPK	Fang et al., 2007
	Directly	Elk-1	block	VEGF	Liu et al., 1999
PDGFR	Indirectly	PDGFR	inhibit	PDGF	Tamai et al., 2001
TNFR	Directly	TRAIL	Negatively	–	Zhao et al., 2009
	Directly	TRAF2	Active	–	Feng et al., 2001
Growth factors					
EGF	Indirectly	EGF	Inhibit	p42/44 MAPK	Zhang et al., 2000
	–	EGF	Inhibit	PI3K/Akt	Park and Han, 2009
IGF	Directly	IGF-I	Deficiency Promote	PI3K/Akt	Matthews et al., 2008
PDGF	Directly	PDGF	Inhibit	PDGF	Peterson et al., 2003
TNF	Directly	TNFα	Negative	MKK3/p38 MAPK	Wang et al., 2006
VEGF	–	VEGF	Stabilize	PI3K/Akt	Li et al., 2009
TGF	–	TGF-β1	Stabilize	PI3K/Akt	Li et al., 2009
FGF	–	FGF2	Stabilize	PI3K/Akt	Li et al., 2009
Transcriptional factors					
β-catenin	Directly	β-catenin	Inhibit	Wnt	Galbiati et al., 2000
	Indirectly	Survivin	Inhibit	Wnt	Torres et al., 2006
	Indirectly	COX-2	Inhibit	Wnt	Rodriguez et al., 2009
	Directly	LRP6	Active	Wnt	Yamamoto et al., 2006
NF-κB	Directly	TNFα	Negative	PI3K/PKB and p44/42 MAPK NF-κB	Fakhrzadeh et al., 2008
	Directly	–	Active	–	Garrean et al., 2006
p53	Directly	Mdm2	Stabilize	p53/p21(Waf1/Cip1)	Bartholomew et al., 2009
	–	p53	Inhibit	–	Linge et al., 2007
	Indirectly	p53	Inhibit	IGF	Ravid et al., 2005
	Directly	MEK-1, ERK-2	–	p42/44 MAPK	Engelman et al., 1998a

Abbreviations: EGF: epidermal growth factor; TNF: tumor necrosis factor; PDGF: platelet-derived growth factor; VEGF: Vascular endothelial growth factor; IGF: Insulin-like growth factor; FGF2: basic fibroblast growth factor; TGF: transforming growth factor; EGFR: epidermal growth factor receptor; TNFR: tumor necrosis factor receptor; PDGFR: platelet-derived growth factor receptor; VEGFR: vascular endothelial growth factor receptor; FGFR: fibroblast growth factor receptor; TGFR: transforming growth factor receptor; IGF-IR: Insulin-like growth factor-I receptor; TβR: transforming growth factor-β receptor; BRII: bone morphogenetic protein receptor type II; IR: Insulin receptor; IGFR: Insulin-like growth factor receptor; IRS-1: insulin receptor substrate-1; TRAIL: tumor necrosis factor-related apoptosis-inducing ligand; TRAF2: tumor necrosis factor (TNF) receptor-associated factor 2; COX-2: cyclooxygenase-2; BMP: Bone morphogenetic proteins; MKK3/p38 MAPK: mitogen-activated protein kinase kinase 3/p38 mitogen-activated protein kinase; PI3K/Akt: phosphatidylinositol 3-kinase/Akt; NF-κB: nuclear factor kappa B; PI3K/PKB: PI3K/protein kinase B; MEK-1: MAP kinase/ERK kinase 1; LRP6: low-density lipoprotein receptor-related protein 6; ALK1: Activin receptor-like kinase 1; Elk-1: Ets-like protein 1; “–” indicates “no clear statement”

2006). Furthermore, Cav-1 inhibits EGF signaling by direct interaction with EGFR (Couet et al., 1997), but promotes

EGF signaling in a breast cancer cell line, MCF-7 (Agelaki et al., 2009). Thus, Cav-1 appears to control the activity of

multiple signaling pathways in a cell-specific and contextual manner.

In addition, it has been shown that Src-mediated phosphorylation of Cav-1 $\alpha$  on Y14 is required for stretch-induced EGFR and Akt activation in mesangial cells (Zhang et al., 2007). Phosphorylation of this site is also implicated in other signaling responses including TGF- $\beta$  (Peng et al., 2008) and IGF (Chen et al., 2008) signaling.

## Caveolin-1 and embryonic development of vertebrates

Cav-1 proteins exist in a wider range of eukaryotic systems including nematodes *Caenorhabditis elegans* (Tang et al., 1997) and *Trichinella spiralis* (Hernández-Bello et al., 2008), frog *Xenopus laevis* (Razani et al., 2002), zebrafish *Danio rerio* (Fang et al., 2006), pig (Wang et al., 2008), mouse (Engelman et al., 1998b) and human (Engelman et al., 1999). Amino acid sequence alignment reveals that Cav-1 proteins are highly conserved from *Caenorhabditis elegans* to human (Frank and Lisanti, 2006; Wang et al., 2010a), suggesting conserved physiological and/or developmental functions of Cav-1 during evolution.

It has been shown that Cav-1 is expressed in germ cells during embryonic development from nematode to human. For example, Cav-1 is expressed in most cells throughout embryonic and larval development of *C. elegans* and is essential for Ras/MAP-kinase-dependent progression through the meiotic cell cycle (Scheel et al., 1999). In zebrafish, *cav-1* mRNAs are detected during the very early stages of development (Fang et al., 2006). Cav-1 is also expressed in oocytes of *C. elegans* (Scheel et al., 1999) and a high level of *cav-1* mRNA was detected in the developing ovaries but not testes of mouse (Bullejos et al., 2002). In addition, expression of Cav-1 is detected in oocytes and embryos and plays a role in oocyte maturation and embryogenesis of *Trichinella spiralis* (Hernández-Bello et al., 2008). These data suggest that Cav-1 may play important roles in embryonic development of vertebrates. Indeed, multiple lines of evidence indicate that Cav-1 is able to modulate activities of key developmental signaling pathways including TGF- $\beta$ , BMP, Wnt and MAPK (Razani et al., 2001a; Nohe et al., 2005; Scheel et al., 1999). However, Cav-1 null mice are viable and fertile (Drab et al., 2001; Razani et al., 2001b), although they display some distinguishable phenotypes including loss of invaginated caveolae, vascular and skeletal muscle abnormalities, thickened alveolar septa, dilated cardiomyopathy, reduction in life span, leanness, and resistance to diet-induced obesity (Cohen et al., 2003; Schubert et al., 2007). Therefore, the detailed developmental progression of the Cav-1-deficient mouse embryos has yet to be defined (Frank and Lisanti, 2006).

Current knowledge about functions of Cav-1 during embryonic development mainly comes from research using

zebrafish. During zebrafish embryogenesis, transcripts of Cav-1 are mainly found in Kupffer's vesicle, tailbud, intersomite boundaries, heart, branchial arches, pronephric ducts and perithelium (Fang et al., 2006; Frank and Lisanti, 2006; Nixon et al., 2007). In contrast to Cav-1 null mice, knockdown of Cav-1 expression leads to lethal zebrafish embryos, which could result from major reduction of caveolae numbers on the cellular membrane, abnormal anterior-posterior (AP) patterning, severe disruption of actin cytoskeleton, defects in development of somites, and neuromasts (Fang et al., 2006; Frank and Lisanti, 2006; Nixon et al., 2007). Similarly, inhibition of Cav-1 expression by RNAi in embryos of *C. elegans* leads to early larval lethality (Scheel et al., 1999). Further studies indicate that abnormal phenotypes caused by the absence of each zebrafish Cav-1 isoform could be partially rescued by the corresponding human counterpart, suggesting that functions of Cav-1 proteins are highly conserved throughout evolution (Fang et al., 2006; Frank and Lisanti, 2006; Nixon et al., 2007). Recently, we demonstrate that both Wnt and BMP signals act coordinately to negatively control transcriptional expression of *cav-1* during embryonic development and provide the first biochemical and genetic evidence that Cav-1 regulates the dorsoventral patterning of zebrafish (Mo et al., 2010).

Cav-1 $\alpha$  and -1 $\beta$  exhibit overlapping but distinct expression patterns during embryogenesis of zebrafish. For example, both zebrafish *cav-1a* and -1 $\beta$  mRNAs are detected in the heart, pharyngeal vasculature, notochord, somites, skin, and neuromast tissues during the very early stages of development, whereas *cav-1a* mRNA is the only isoform detectable in the intestinal epithelium of late-stage embryos (Fang et al., 2006). Similar expression patterns of Cav-1 are also found in *Xenopus laevis* (Razani et al., 2002). Additionally, overexpression of Cav-1 $\alpha$  could not rescue the phenotype caused by knockdown of Cav-1 $\beta$  isoform in zebrafish and vice versa (Fang et al., 2006), suggesting non-overlapping functions of Cav-1 isoforms. Thus, Cav-1 isoforms appear to play differential roles in a cell- or tissue-specific manner. It is suggested that distinct functions of Cav-1 $\alpha$  and -1 $\beta$  are closely associated with the phosphorylation at Y14 in Cav-1 $\alpha$  (Frank and Lisanti, 2006).

## Caveolin-1 and human diseases

Cav-1 is mainly expressed in terminally differentiated cells such as epithelia, endothelia, adipocytes, fibroblasts and smooth muscle cells (Lisanti et al., 1994). It plays important roles in vesicular transport, cholesterol homeostasis and signal transduction and is able to biochemically interact with many signaling cascades in multiple signaling pathways to regulate cellular proliferation, differentiation and apoptosis in a cell-specific and contextual manner (Cohen et al., 2004). Therefore, abnormal expression of Cav-1 is often associated with tumor progression (Williams and Lisanti, 2005) and

many other disease-related phenotypes in the lung, vasculature, heart, adipose tissue, and the mammary gland (Cohen et al., 2004; Drab et al., 2001; Fujimoto et al., 2000; Hashimoto et al., 2003; Kasper et al., 1998; Kim et al., 2006; Schwenneke et al., 2006).

### **Caveolin-1 and tumorigenesis**

Cav-1 was considered as a key molecule in oncogenic cellular transformation, hyperplasia and metastasis during tumor progression (Juhász et al., 2003) due to its modulation of many signaling pathways in human tumors. In human breast cancer-derived cells, Cav-1 enhances matrix-independent cell survival through upregulation of IGF-IR expression and activation of IGF-I signaling (Ravid et al., 2005). Cav-1 was also found to regulate the activity of EGFR in human glioblastoma, squamous carcinoma and epidermoid carcinoma (Abulrob et al., 2004; Kim and Bertics, 2002). Cav-1 was downregulated in breast, lung, colon, stomach and ovarian cancer, but upregulated in prostate, kidney and breast cancer (reviewed by Williams and Lisanti, 2005). In addition, Cav-1 plays distinct roles in different tumor cell types or tumors derived from the same cell type or tissue (Hino et al., 2003; Liu et al., 2002; Scherer et al., 1995). Thus, Cav-1 appears to act as both a tumor suppressor and an oncogene in a contextual manner. Three distinct mechanisms have been proposed to explain why Cav-1 functions either as a tumor suppressor or as an oncogene, depending on the tumor type and/or tumor stage (Williams and Lisanti, 2005). It is known that TGF- $\beta$  signaling functions are different in the early stage of transformation and carcinogenesis and in the later stage of tumor progression (Williams and Lisanti, 2005). Cav-1 has been shown to interact with the Type I TGF- $\beta$  receptor and negatively control the activity of TGF- $\beta$  signaling (Razani et al., 2001a). Therefore, intriguing roles of Cav-1 in tumorigenesis may be partially associated with its regulation of TGF- $\beta$  signaling activity.

Cancer chemotherapy always leads to the development of multidrug resistance (MDR), a process that is commonly associated with overexpression of P-glycoprotein (P-gp). It has been shown that P-gp is often co-localized with Cav-1 (Bélanger et al., 2004). Overexpression of Cav-1 decreases the drug resistance through suppression of MDR1 gene expression since upregulation of Cav-1 in numerous human MDR cancer cells almost abolished expression of P-gp protein (Lavie et al., 1998; Zhu et al., 2004). Additionally, downregulation of Cav-1 by siRNA reduced its interaction with P-gp and enhanced P-gp transport activity; while transfection of a mutant cav-1Y14F decreased the P-gp/Cav-1 interaction (Barakat et al., 2007). These results suggest that regulation of P-gp function by Cav-1 may depend on the phosphorylation of Cav-1. However, expression of caveolin-1 and caveolin-2 in several MDR cell lines were not detectable, indicating that Cav-1 expression is not associated with expression of P-gp or MDR1 mRNA (Davidson et al.,

2002). Thus, Cav-1 appears to modulate MDR in a cell-specific and contextual manner.

### **Cav-1 and cardiovascular diseases**

Cav-1 is also expressed in endothelial cells, smooth muscle cells and macrophages, which are known to play key roles in cardiovascular diseases including atherosclerosis, hypertrophy cardiomyopathy (HCM), heart failure, cardiac hypertrophy (Williams and Lisanti, 2004). Several signal transduction pathways, regulated by Cav-1, were associated with fates of those cells. For instance, TGF- $\beta$  and p42/44 MAPK signaling pathways are involved in vascular remodeling and angiogenesis (Fang et al., 2007; Santibanez et al., 2008). It has been shown that Cav-1 is able to negatively regulate the proliferation of human endothelial cells by inhibition of the activity of VEGFR-2 (KDR) and downstream p42/44 MAP kinase (Fang et al., 2007). In addition, Cav-1 is suggested to control the angiogenic process by potentiation of TGF- $\beta$ /ALK1 and repression of TGF- $\beta$ /ALK5 responses (Santibanez et al., 2008). Moreover, Cav-1 holds a dual role toward modulation of proliferation of vascular smooth muscle cells, depending on the stimulus the cells are exposed to (Sedding and Braun-Dullaeus, 2006).

### **Cav-1 and fibrosis**

Fibrosis is the formation or development of excess fibrous connective tissue in an organ or tissue as a reparative or reactive process. Multiple lines of evidence indicate that Cav-1 is closely involved in fibrogenesis of various tissues. Cav-1 was identified as an early indicator of serious type I cell injury during lung fibrogenesis (Kasper et al., 1998) and its CSD motif is responsible for the antifibrotic properties *in vitro* and *in vivo* (Tourkina et al., 2008). Depletion of Cav-1 in mice leads to hyperproliferation of embryonic fibroblasts and formation of fibrotic lung (Drab et al., 2001; Galbiati et al., 2001). In fibrotic diseases, decreased Cav-1 expression likely leads to increased deposition of IGFBP-5 (insulin-like growth factor binding protein-5) in the ECM with subsequent reduction in ECM degradation (Yamaguchi et al., 2010). Cav-1 is able to regulate activities of several signaling pathways involved in the pathogenesis of fibrosis. For example, Cav-1 suppresses the activity of TGF- $\beta$  signaling and participates in the pathogenesis of systemic sclerosis and idiopathic pulmonary fibrosis (Del Galdo et al., 2008). In summary, Cav-1 acts as an inhibitor of fibrogenesis.

### **Cav-1 and liver regeneration**

Liver regeneration is an orchestrated cellular response that coordinates activation, migration and division of various cells (Frank and Lisanti, 2007). Evidence from recent studies indicates that Cav-1 is involved in liver regeneration through regulation of triglyceride accumulation (Fernández et al.,

2006). After a partial hepatectomy (PH), *cav-1*<sup>-/-</sup> mice exhibited impaired liver regeneration and low survival. Hepatocytes isolated from *cav-1*<sup>-/-</sup> mice showed dramatically reduced lipid droplet accumulation and did not advance through the cell division cycle. Treatment of *cav-1*<sup>-/-</sup> mice with glucose, a predominant energy substrate when compared to lipids, drastically increased survival and reestablished progression of the cell cycle. Thus, caveolin-1 plays a crucial role in the coordination of lipid metabolism with the proliferative response occurring in the liver after cellular injury.

In addition, Fernández et al. (2006) found that two coordinated main signaling pathways, a cytokine-mediated pathway and a growth factor-mediated pathway, were affected after PH in *cav-1* deficient mice. These signaling cascades include signal transducer and activator of transcription 3 (STAT3), c-myc, and Jun N-terminal kinase (JNK). However, other researchers suggest that Cav-1 is dispensable for liver regeneration since Cav-1 redistributes from the caveola-enriched domain to the noncaveolar fraction after PH and this redistribution mechanism depends on the phosphorylation on tyrosine 14 (Mayoral et al., 2007).

### Cav-1 and infectious diseases associated with virus

Cav-1 is not only involved in regulation of homeostatic cellular functions, but also associated with pathogenesis caused by infection of microbes. Zaas et al. (2009) have shown that Cav-1 plays a role in immunity against bacterial pathogens. Here, we will focus on the roles of Cav-1 in regulation of viral pathogens.

Rotavirus (RV) is the major etiologic agent of virally induced gastroenteritis in children and infants worldwide. Mir et al. (2007) found that the RV non-structural protein 4 (NSP4) binding site (residues 114–135) was localized to Cav-1 residues 2–22 and 161–178, at the amino and carboxyl termini, respectively. Cav-1 is also coexpressed with human immunodeficiency virus (HIV) and blocked expression of HIV-1 and HIV-2 (Llano et al., 2002). The inhibition of HIV-1 and HIV-2 expression by Cav-1 is depending on the intramembrane region (IMR), while the 100 most N-terminal amino acids of Cav-1 (including OD and CSD) is dispensable (Llano et al., 2002). Huang et al. (2007) demonstrate that Cav-1 is able to interact with the gp41 of HIV envelope and then modulate HIV-1 envelope-induced bystander apoptosis (Wang et al., 2010b). It is known that overexpression of Cav-1 can reduce HIV production, and in contrast, HIV infection enhances the expression of Cav-1 (Lin et al., 2010). Recently, it is shown that hepatitis B virus (HBV) also requires a Cav-1-mediated entry pathway to initiate productive infection in HepaRG cells (Macovei et al., 2010).

Cav-1 also influences the activity of virus associated with respiratory tract infections. Cai et al. (2003) demonstrate that the severe acute respiratory syndrome coronavirus (SARS-CoV) contains eight caveolin binding sites, which are located

in replicase 1AB, spike protein, orf3 protein, and M protein, respectively. Padhan et al. (2007) showed that the caveolin binding sites in orf3a were sufficient for its interaction with Cav-1. In addition, Cav-1 is incorporated into influenza virus. Cav-1 colocalizes with the paramyxovirus parainfluenza virus 5 (PIV-5) nucleocapsid (NP), matrix (M), and hemagglutinin-neuraminidase (HN) proteins and affects the virus assembly and/or budding (Ravid et al., 2010). Moreover, Cav-1 was identified as a cellular partner of human influenza A viruses and pandemic influenza A virus (H1N1) through interaction with the influenza M2 (Sun et al., 2010).

Adult T cell leukemia (ATL) is a T cell malignancy causatively associated with human T cell leukemia virus type 1 (HTLV-1). The viral protein Tax is able to transcriptionally activate Cav-1 through NF- $\kappa$ B and cAMP response elements and then repress TGF- $\beta$  signaling (Sawada et al., 2010). In several cell lines derived from lung and cervical cancer, human papilloma virus (HPV) E6 viral oncoprotein down-regulates Cav-1 expression via inactivation of p53 and Cav-1 overexpression can partially revert HPV-mediated cell transformation (Razani et al., 2000). Moreover, Smith et al. (2007) have found that HPV31 entry and initiation of early infection events require both Cav-1 and Dynamin 2. Thus, Cav-1 regulates activities of some viruses closely associated with many carcinomas.

### Perspectives

Cav-1 is able to regulate activities of key signaling pathways that are involved in embryonic development and human diseases. Knockdown of Cav-1 in zebrafish leads to dorsalization of early embryos and finally results in embryonic lethality, while Cav-1 null mice are viable and fertile. The functional difference of Cav-1 in embryonic development between zebrafish and mouse raises a crucial question as to whether an unidentified compensatory mechanism by other caveolin family members exists during the embryonic development of mice. In addition, tissue-specific expression suggests potential roles of Cav-1 in organogenesis of vertebrates. Given the essential role of Cav-1 in the regulation of liver regeneration, Cav-1 might be a novel player and indicator of wound healing. Moreover, Cav-1 appears to be closely associated with tumorigenesis and MDR development in tumor cells. It will be of great interest to investigate the effects of Cav-1 on activity and regulation of key signaling molecules in pathological contexts. Although multiple lines of evidence indicate that Cav-1 influences activities of bacteria and virus associated with human diseases, it remains largely unknown about the roles of Cav-1 in the process of pathogenesis. Thus, extensive investigation of mechanisms underlying the interactions of Cav-1 with signaling molecules in cells and functional proteins in bacteria and virus will offer plenty of opportunities to design small molecule drugs in the treatment of human

diseases and it is expected that we will witness many exciting new discoveries about Cav-1 functions in the coming years.

## References

- Abulrob A, Giuseppin S, Andrade M F, McDermid A, Moreno M, Stanimirovic D (2004). Interactions of EGFR and caveolin-1 in human glioblastoma cells: evidence that tyrosine phosphorylation regulates EGFR association with caveolae. *Oncogene*, 23(41): 6967–6979
- Agelaki S, Spiliotaki M, Markomanolaki H, Kallergi G, Mavroudis D, Georgoulas V, Stournaras C (2009). Caveolin-1 regulates EGFR signaling in MCF-7 breast cancer cells and enhances gefitinib-induced tumor cell inhibition. *Cancer Biol Ther*, 8(15): 1470–1477
- Barakat S, Demeule M, Pilorget A, Régina A, Gingras D, Baggetto L G, Béliveau R (2007). Modulation of p-glycoprotein function by caveolin-1 phosphorylation. *J Neurochem*, 101(1): 1–8
- Bartholomew J N, Volonte D, Galbiati F (2009). Caveolin-1 regulates the antagonistic pleiotropic properties of cellular senescence through a novel Mdm2/p53-mediated pathway. *Cancer Res*, 69(7): 2878–2886
- Bélanger M M, Gaudreau M, Roussel E, Couet J (2004). Role of caveolin-1 in etoposide resistance development in A549 lung cancer cells. *Cancer Biol Ther*, 3(10): 954–959
- Bullejos M, Bowles J, Koopman P (2002). Extensive vascularization of developing mouse ovaries revealed by caveolin-1 expression. *Dev Dyn*, 225: 95–99
- Cabrita M A, Jäggi F, Widjaja S P, Christofori G (2006). A functional interaction between sprouty proteins and caveolin-1. *J Biol Chem*, 281(39): 29201–29212
- Cai Q C, Jiang Q W, Zhao G M, Guo Q, Cao G W, Chen T (2003). Putative caveolin-binding sites in SARS-CoV proteins. *Acta Pharmacol Sin*, 24(10): 1051–1059
- Chen J, Capozza F, Wu A, Deangelis T, Sun H, Lisanti M, Baserga R (2008). Regulation of insulin receptor substrate-1 expression levels by caveolin-1. *J Cell Physiol*, 217(1): 281–289
- Cohen A W, Park D S, Woodman S E, Williams T M, Chandra M, Shirani J, Pereira de Souza A, Kitsis R N, Russell R G, Weiss L M, Tang B, Jelicks L A, Factor S M, Shtutin V, Tanowitz H B, Lisanti M P (2003). Caveolin-1 null mice develop cardiac hypertrophy with hyperactivation of p42/44 MAP kinase in cardiac fibroblasts. *Am J Physiol Cell Physiol*, 284(2): C457–C474
- Cohen A W, Razani B, Schubert W, Williams T M, Wang X B, Iyengar P, Brasaemle D L, Scherer P E, Lisanti M P (2004). Role of caveolin-1 in the modulation of lipolysis and lipid droplet formation. *Diabetes*, 53(5): 1261–1270
- Couet J, Li S, Okamoto T, Scherer P S, Lisanti M P (1997). Molecular and cellular biology of caveolae: paradoxes and plasticities. *Trends Cardiovasc Med*, 7(4): 103–110
- Davidson B, Goldberg I, Givant-Horwitz V, Nesland J M, Berner A, Bryne M, Risberg B, Kopolovic J, Kristensen G B, Tropé C G, van de Putte G, Reich R (2002). Caveolin-1 expression in ovarian carcinoma is MDR1 independent. *Am J Clin Pathol*, 117(2): 225–234
- Del Galdo F, Sotgia F, de Almeida C J, Jasmin J F, Musick M, Lisanti M P, Jiménez S A (2008). Decreased expression of caveolin 1 in patients with systemic sclerosis: crucial role in the pathogenesis of tissue fibrosis. *Arthritis Rheum*, 58(9): 2854–2865
- Dietzen D J, Hastings W R, Lublin D M (1995). Caveolin is palmitoylated on multiple cysteine residues. Palmitoylation is not necessary for localization of caveolin to caveolae. *J Biol Chem*, 270(12): 6838–6842
- Drab M, Verkade P, Elger M, Kasper M, Lohn M, Lauterbach B, Menne J, Lindschau C, Mende F, Luft F C, Schedl A, Haller H, Kurzchalia T V (2001). Loss of caveolae, vascular dysfunction, and pulmonary defects in caveolin-1 gene-disrupted mice. *Science*, 293(5539): 2449–2452
- Engelman J A, Chu C, Lin A, Jo H, Ikezu T, Okamoto T, Kohtz D S, Lisanti M P (1998a). Caveolin-mediated regulation of signaling along the p42/44 MAP kinase cascade *in vivo*. A role for the caveolin-scaffolding domain. *FEBS Lett*, 428(3): 205–211
- Engelman J A, Zhang X L, Galbiati F, Lisanti M P (1998b). Chromosomal localization, genomic organization, and developmental expression of the murine caveolin gene family (Cav-1, -2, and -3). Cav-1 and Cav-2 genes map to a known tumor suppressor locus (6-A2/7q31). *FEBS Lett*, 429(3): 330–336
- Engelman J A, Zhang X L, Lisanti M P (1999). Sequence and detailed organization of the human caveolin-1 and -2 genes located near the D7S522 locus (7q31.1). Methylation of a CpG island in the 5' promoter region of the caveolin-1 gene in human breast cancer cell lines. *FEBS Lett*, 448(2–3): 221–230
- Fakhrzadeh L, Laskin J D, Laskin D L (2008). Regulation of caveolin-1 expression, nitric oxide production and tissue injury by tumor necrosis factor-alpha following ozone inhalation. *Toxicol Appl Pharmacol*, 227(3): 380–389
- Fang K, Fu W, Beardsley A R, Sun X, Lisanti M P, Liu J (2007). Overexpression of caveolin-1 inhibits endothelial cell proliferation by arresting the cell cycle at G0/G1 phase. *Cell Cycle*, 6(2): 199–204
- Fang P K, Solomon K R, Zhuang L, Qi M, McKee M, Freeman M R, Yelick P C (2006). Caveolin-1 $\alpha$  and -1 $\beta$  perform nonredundant roles in early vertebrate development. *Am J Pathol*, 169(6): 2209–2222
- Feng X, Gaeta M L, Madge L A, Yang J H, Bradley J R, Pober J S (2001). Caveolin-1 associates with TRAF2 to form a complex that is recruited to tumor necrosis factor receptors. *J Biol Chem*, 276(11): 8341–8349
- Fernández M A, Albor C, Ingelmo-Torres M, Nixon S J, Ferguson C, Kurzchalia T, Tebar F, Enrich C, Parton R G, Pol A (2006). Caveolin-1 is essential for liver regeneration. *Science*, 313(5793): 1628–1632
- Frank P G, Lisanti M P (2006). Zebrafish as a novel model system to study the function of caveolae and caveolin-1 in organismal biology. *Am J Pathol*, 169(6): 1910–1912
- Frank P G, Lisanti M P (2007). Caveolin-1 and liver regeneration: role in proliferation and lipogenesis. *Cell Cycle*, 6(2): 115–116
- Fujimoto T, Kogo H, Nomura R, Une T (2000). Isoforms of caveolin-1 and caveolar structure. *J Cell Sci*, 113(Pt 19): 3509–3517
- Galbiati F, Volonte D, Brown A M, Weinstein D E, Ben-Ze'ev A, Pestell R G, Lisanti M P (2000). Caveolin-1 expression inhibits Wnt/beta-catenin/Lef-1 signaling by recruiting beta-catenin to caveolar membrane domains. *J Biol Chem*, 275(30): 23368–23377
- Galbiati F, Volonté D, Liu J, Capozza F, Frank P G, Zhu L, Pestell R G, Lisanti M P (2001). Caveolin-1 expression negatively regulates cell cycle progression by inducing G(0)/G(1) arrest via a p53/p21(WAF1/Cip1)-dependent mechanism. *Mol Biol Cell*, 12(8): 2229–2244

- Garrean S, Gao X P, Brovkovich V, Shimizu J, Zhao Y Y, Vogel S M, Malik A B (2006). Caveolin-1 regulates NF-kappaB activation and lung inflammatory response to sepsis induced by lipopolysaccharide. *J Immunol*, 177(7): 4853–4860
- Glenny J R Jr, Soppet D (1992). Sequence and expression of caveolin, a protein component of caveolae plasma membrane domains phosphorylated on tyrosine in Rous sarcoma virus-transformed fibroblasts. *Proc Natl Acad Sci U S A*, 89(21): 10517–10521
- Han F, Gu D, Chen Q, Zhu H (2009). Caveolin-1 acts as a tumor suppressor by down-regulating epidermal growth factor receptor-mitogen-activated protein kinase signaling pathway in pancreatic carcinoma cell lines. *Pancreas*, 38(7): 766–774
- Hashimoto M, Takenouchi T, Rockenstein E, Maslia E (2003). Alpha-synuclein up-regulates expression of caveolin-1 and down-regulates extracellular signal-regulated kinase activity in B103 neuroblastoma cells: role in the pathogenesis of Parkinson's disease. *J Neurochem*, 85(6): 1468–1479
- Head B P, Insel P A (2007). Do caveolins regulate cells by actions outside of caveolae? *Trends Cell Biol*, 17(2): 51–57
- Hernández-Bello R, Bermúdez-Cruz R M, Fonseca-Liñán R, García-Reyna P, Le Guerhier F, Boireau P, Ortega-Pierres G (2008). Identification, molecular characterisation and differential expression of caveolin-1 in *Trichinella spiralis* maturing oocytes and embryos. *Int J Parasitol*, 38(2): 191–202
- Hino M, Doihara H, Kobayashi K, Aoe M, Shimizu N (2003). Caveolin-1 as tumor suppressor gene in breast cancer. *Surg Today*, 33(7): 486–490
- Huang J H, Lu L, Lu H, Chen X, Jiang S, Chen Y H (2007). Identification of the HIV-1 gp41 core-binding motif in the scaffolding domain of caveolin-1. *J Biol Chem*, 282(9): 6143–6152
- Joshi B, Strugnell S S, Goetz J G, Kojic L D, Cox M E, Griffith O L, Chan S K, Jones S J, Leung S P, Masoudi H, Leung S, Wiseman S M, Nabi I R (2008). Phosphorylated caveolin-1 regulates Rho/ROCK-dependent focal adhesion dynamics and tumor cell migration and invasion. *Cancer Res*, 68(20): 8210–8220
- Juhász M, Chen J, Tulassay Z, Malferteiner P, Ebert M P (2003). Expression of caveolin-1 in gastrointestinal and extraintestinal cancers. *J Cancer Res Clin Oncol*, 129(9): 493–497
- Kasper M, Reimann T, Hempel U, Wenzel K W, Bierhaus A, Schuh D, Dimmer V, Haroske G, Müller M (1998). Loss of caveolin expression in type I pneumocytes as an indicator of subcellular alterations during lung fibrogenesis. *Histochem Cell Biol*, 109(1): 41–48
- Kim H A, Kim K H, Lee R A (2006). Expression of caveolin-1 is correlated with Akt-1 in colorectal cancer tissues. *Exp Mol Pathol*, 80(2): 165–170
- Kim Y N, Bertics P J (2002). The endocytosis-linked protein dynamin associates with caveolin-1 and is tyrosine phosphorylated in response to the activation of a noninternalizing epidermal growth factor receptor mutant. *Endocrinology*, 143(5): 1726–1731
- Kogo H, Aiba T, Fujimoto T (2004). Cell type-specific occurrence of caveolin-1alpha and -1beta in the lung caused by expression of distinct mRNAs. *J Biol Chem*, 279(24): 25574–25581
- Kogo H, Fujimoto T (2000). Caveolin-1 isoforms are encoded by distinct mRNAs. Identification of mouse caveolin-1 mRNA variants caused by alternative transcription initiation and splicing. *FEBS Lett*, 465(2–3): 119–123
- Labrecque L, Royal I, Surprenant D S, Patterson C, Gingras D, Béliveau R (2003). Regulation of vascular endothelial growth factor receptor-2 activity by caveolin-1 and plasma membrane cholesterol. *Mol Biol Cell*, 14(1): 334–347
- Lavie Y, Fiucci G, Liscovitch M (1998). Up-regulation of caveolae and caveolar constituents in multidrug-resistant cancer cells. *J Biol Chem*, 273(49): 32380–32383
- Le Lan C, Neumann J M, Jamin N (2006). Role of the membrane interface on the conformation of the caveolin scaffolding domain: a CD and NMR study. *FEBS Lett*, 580(22): 5301–5305
- Lee E K, Lee Y S, Han I O, Park S H (2007). Expression of Caveolin-1 reduces cellular responses to TGF-beta1 through down-regulating the expression of TGF-beta type II receptor gene in NIH3T3 fibroblast cells. *Biochem Biophys Res Commun*, 359(2): 385–390
- Lee H, Volonte D, Galbiati F, Iyengar P, Lublin D M, Bregman D B, Wilson M T, Campos-Gonzalez R, Bouzahzah B, Pestell R G, Scherer P E, Lisanti M P (2000). Constitutive and growth factor-regulated phosphorylation of caveolin-1 occurs at the same site (Tyr-14) *in vivo*: identification of a c-Src/Cav-1/Grb7 signaling cassette. *Mol Endocrinol*, 14(11): 1750–1775
- Lee H, Woodman S E, Engelman J A, Volonté D, Galbiati F, Kaufman H L, Lublin D M, Lisanti M P (2001). Palmitoylation of caveolin-1 at a single site (Cys-156) controls its coupling to the c-Src tyrosine kinase: targeting of dually acylated molecules (GPI-linked, transmembrane, or cytoplasmic) to caveolae effectively uncouples c-Src and caveolin-1 (TYR-14). *J Biol Chem*, 276(37): 35150–35158
- Li L, Ren C, Yang G, Goltsov A A, Tabata K, Thompson T C (2009). Caveolin-1 promotes autoregulatory, Akt-mediated induction of cancer-promoting growth factors in prostate cancer cells. *Mol Cancer Res*, 7(11): 1781–1791
- Li S, Seitz R, Lisanti M P (1996). Phosphorylation of caveolin by src tyrosine kinases. The alpha-isoform of caveolin is selectively phosphorylated by v-Src *in vivo*. *J Biol Chem*, 271(7): 3863–3868
- Lin S, Wang X M, Nadeau P E, Mergia A (2010). HIV infection upregulates caveolin 1 expression to restrict virus production. *J Virol*, 84(18): 9487–9496
- Linge A, Weinhold K, Bläsche R, Kasper M, Barth K (2007). Downregulation of caveolin-1 affects bleomycin-induced growth arrest and cellular senescence in A549 cells. *Int J Biochem Cell Biol*, 39(10): 1964–1974
- Lisanti M P, Scherer P E, Vidugiriene J, Tang Z, Hermanowski-Vosatka A, Tu Y H, Cook R F, Sargiacomo M (1994). Characterization of caveolin-rich membrane domains isolated from an endothelial-rich source: implications for human disease. *J Cell Biol*, 126(1): 111–126
- Liu J, Razani B, Tang S, Terman B I, Ware J A, Lisanti M P (1999). Angiogenesis activators and inhibitors differentially regulate caveolin-1 expression and caveolae formation in vascular endothelial cells. Angiogenesis inhibitors block vascular endothelial growth factor-induced down-regulation of caveolin-1. *J Biol Chem*, 274(22): 15781–15785
- Liu P, Rudick M, Anderson R G (2002). Multiple functions of caveolin-1. *J Biol Chem*, 277(44): 41295–41298
- Llano M, Kelly T, Vanegas M, Peretz M, Peterson T E, Simari R D, Poeschla E M (2002). Blockade of human immunodeficiency virus type 1 expression by caveolin-1. *J Virol*, 76(18): 9152–9164
- Machleidt T, Li W P, Liu P, Anderson R G (2000). Multiple domains in caveolin-1 control its intracellular traffic. *J Cell Biol*, 148(1): 17–28

- Macovei A, Radulescu C, Lazar C, Petrescu S, Durantel D, Dwek R A, Zitzmann N, Nichita N B (2010). Hepatitis B virus requires intact caveolin-1 function for productive infection in HepaRG cells. *J Virol*, 84(1): 243–253
- Matthews L C, Taggart M J, Westwood M (2008). Modulation of caveolin-1 expression can affect signalling through the phosphatidylinositol 3-kinase/Akt pathway and cellular proliferation in response to insulin-like growth factor I. *Endocrinology*, 149(10): 5199–5208
- Mayoral R, Fernández-Martínez A, Roy R, Boscá L, Martín-Sanz P (2007). Dispensability and dynamics of caveolin-1 during liver regeneration and in isolated hepatic cells. *Hepatology*, 46(3): 813–822
- Mir K D, Parr R D, Schroeder F, Ball J M (2007). Rotavirus NSP4 interacts with both the amino- and carboxyl-termini of caveolin-1. *Virus Res*, 126(1–2): 106–115
- Mo S, Wang L, Li Q, Li J, Li Y, Thannickal V J, Cui Z (2010). Caveolin-1 regulates dorsoventral patterning through direct interaction with beta-catenin in zebrafish. *Dev Biol*, 344(1): 210–223
- Nixon S J, Carter A, Wegner J, Ferguson C, Floetenmeyer M, Riches J, Key B, Westerfield M, Parton R G (2007). Caveolin-1 is required for lateral line neuromast and notochord development. *J Cell Sci*, 120(Pt 13): 2151–2161
- Nohe A, Keating E, Underhill T M, Knaus P, Petersen N O (2005). Dynamics and interaction of caveolin-1 isoforms with BMP-receptors. *J Cell Sci*, 118(Pt 3): 643–650
- Nystrom F H, Chen H, Cong L N, Li Y, Quon M J (1999). Caveolin-1 interacts with the insulin receptor and can differentially modulate insulin signaling in transfected Cos-7 cells and rat adipose cells. *Mol Endocrinol*, 13(12): 2013–2024
- Ono K, Iwanaga Y, Hirayama M, Kawamura T, Sowa N, Hasegawa K (2004). Contribution of caveolin-1 alpha and Akt to TNF-alpha-induced cell death. *Am J Physiol Lung Cell Mol Physiol*, 287(1): L201–L209
- Padhan K, Tanwar C, Hussain A, Hui P Y, Lee M Y, Cheung C Y, Peiris J S, Jameel S (2007). Severe acute respiratory syndrome coronavirus Orf3a protein interacts with caveolin. *J Gen Virol*, 88(Pt 11): 3067–3077
- Park J H, Han H J (2009). Caveolin-1 plays important role in EGF-induced migration and proliferation of mouse embryonic stem cells: involvement of PI3K/Akt and ERK. *Am J Physiol Cell Physiol*, 297(4): C935–C944
- Peng F, Zhang B, Wu D, Ingram A J, Gao B, Krepinsky J C (2008). TGFbeta-induced RhoA activation and fibronectin production in mesangial cells require caveolae. *Am J Physiol Renal Physiol*, 295(1): F153–F164
- Peterson T E, Guicciardi M E, Gulati R, Kleppe L S, Mueske C S, Mookadam M, Sowa G, Gores G J, Sessa W C, Simari R D (2003). Caveolin-1 can regulate vascular smooth muscle cell fate by switching platelet-derived growth factor signaling from a proliferative to an apoptotic pathway. *Arterioscler Thromb Vasc Biol*, 23(9): 1521–1527
- Ravid D, Leser G P, Lamb R A (2010). A role for caveolin 1 in assembly and budding of the paramyxovirus parainfluenza virus 5. *J Virol*, 84(19): 9749–9759
- Ravid D, Maor S, Werner H, Liscovitch M (2005). Caveolin-1 inhibits cell detachment-induced p53 activation and anoikis by upregulation of insulin-like growth factor-I receptors and signaling. *Oncogene*, 24(8): 1338–1347
- Razani B, Altschuler Y, Zhu L, Pestell R G, Mostov K E, Lisanti M P (2000). Caveolin-1 expression is down-regulated in cells transformed by the human papilloma virus in a p53-dependent manner. Replacement of caveolin-1 expression suppresses HPV-mediated cell transformation. *Biochemistry*, 39(45): 13916–13924
- Razani B, Engelman J A, Wang X B, Schubert W, Zhang X L, Marks C B, Macaluso F, Russell R G, Li M, Pestell R G, Di Vizio D, Hou H Jr, Kneitz B, Lagaud G, Christ G J, Edelman W, Lisanti M P (2001b). Caveolin-1 null mice are viable but show evidence of hyperproliferative and vascular abnormalities. *J Biol Chem*, 276(41): 38121–38138
- Razani B, Park D S, Miyana Y, Ghatpande A, Cohen J, Wang X B, Scherer P E, Evans T, Lisanti M P (2002). Molecular cloning and developmental expression of the caveolin gene family in the amphibian *Xenopus laevis*. *Biochemistry*, 41(25): 7914–7924
- Razani B, Zhang X L, Bitzer M, von Gersdorff G, Böttinger E P, Lisanti M P (2001a). Caveolin-1 regulates transforming growth factor (TGF)-beta/SMAD signaling through an interaction with the TGF-beta type I receptor. *J Biol Chem*, 276(9): 6727–6738
- Rodriguez D A, Tapia J C, Fernandez J G, Torres V A, Muñoz N, Galleguillos D, Leyton L, Quest A F (2009). Caveolin-1-mediated suppression of cyclooxygenase-2 via a beta-catenin-Tcf/Lef-dependent transcriptional mechanism reduced prostaglandin E2 production and survivin expression. *Mol Biol Cell*, 20(8): 2297–2310
- Rothberg K G, Heuser J E, Donzell W C, Ying Y S, Glenney J R, Anderson R G (1992). Caveolin, a protein component of caveolae membrane coats. *Cell*, 68(4): 673–682
- Santibanez J F, Blanco F J, Garrido-Martin E M, Sanz-Rodriguez F, del Pozo M A, Bernabeu C (2008). Caveolin-1 interacts and cooperates with the transforming growth factor-beta type I receptor ALK1 in endothelial caveolae. *Cardiovasc Res*, 77(4): 791–799
- Sargiacomo M, Scherer P E, Tang Z, Kübler E, Song K S, Sanders M C, Lisanti M P (1995). Oligomeric structure of caveolin: implications for caveolae membrane organization. *Proc Natl Acad Sci USA*, 92(20): 9407–9411
- Sawada S, Ishikawa C, Tanji H, Nakachi S, Senba M, Okudaira T, Uchihara J N, Taira N, Ohshiro K, Yamada Y, Tanaka Y, Uezato H, Ohshima K, Sasai K, Burgering B M, Duc Dodon M, Fujii M, Sunakawa H, Mori N (2010). Overexpression of caveolin-1 in adult T-cell leukemia. *Blood*, 115(11): 2220–2230
- Scheel J, Srinivasan J, Honnert U, Henske A, Kurzchalia T V (1999). Involvement of caveolin-1 in meiotic cell-cycle progression in *Caenorhabditis elegans*. *Nat Cell Biol*, 1(2): 127–129
- Scherer P E, Lewis R Y, Volonte D, Engelman J A, Galbiati F, Couet J, Kohtz D S, van Donselaar E, Peters P, Lisanti M P (1997). Cell-type and tissue-specific expression of caveolin-2. Caveolins 1 and 2 colocalize and form a stable hetero-oligomeric complex *in vivo*. *J Biol Chem*, 272(46): 29337–29346
- Scherer P E, Tang Z, Chun M, Sargiacomo M, Lodish H F, Lisanti M P (1995). Caveolin isoforms differ in their N-terminal protein sequence and subcellular distribution. Identification and epitope mapping of an isoform-specific monoclonal antibody probe. *J Biol Chem*, 270(27): 16395–16401
- Schwencke C, Braun-Dullaeus R C, Wunderlich C, Strasser R H (2006). Caveolae and caveolin in transmembrane signaling: Implications for

- human disease. *Cardiovasc Res*, 70(1): 42–49
- Schlegel A, Lisanti M P (2000). A molecular dissection of caveolin-1 membrane attachment and oligomerization. Two separate regions of the caveolin-1 C-terminal domain mediate membrane binding and oligomer/oligomer interactions *in vivo*. *J Biol Chem*, 275(28): 21605–21617
- Schubert W, Sotgia F, Cohen A W, Capozza F, Bonuccelli G, Bruno C, Minetti C, Bonilla E, Dimauro S, Lisanti M P (2007). Caveolin-1 (-/-)- and caveolin-2(-/-)-deficient mice both display numerous skeletal muscle abnormalities, with tubular aggregate formation. *Am J Pathol*, 170(1): 316–333
- Sedding D G, Braun-Dullaeus R C (2006). Caveolin-1: dual role for proliferation of vascular smooth muscle cells. *Trends Cardiovasc Med*, 16(2): 50–55
- Smith J L, Campos S K, Ozbun M A (2007). Human papillomavirus type 31 uses a caveolin 1- and dynamin 2-mediated entry pathway for infection of human keratinocytes. *J Virol*, 81(18): 9922–9931
- Sun L, Hemgård G V, Susanto S A, Wirth M (2010). Caveolin-1 influences human influenza A virus (H1N1) multiplication in cell culture. *Virol J*, 7(1): 108
- Sun X H, Flynn D C, Castranova V, Millecchia L L, Beardsley A R, Liu J (2007). Identification of a novel domain at the N terminus of caveolin-1 that controls rear polarization of the protein and caveolae formation. *J Biol Chem*, 282(10): 7232–7241
- Tamai O, Oka N, Kikuchi T, Koda Y, Soejima M, Wada Y, Fujisawa M, Tamaki K, Kawachi H, Shimizu F, Kimura H, Imaizumi T, Okuda S (2001). Caveolae in mesangial cells and caveolin expression in mesangial proliferative glomerulonephritis. *Kidney Int*, 59(2): 471–480
- Tang Z, Okamoto T, Boontrakulpoontawee P, Katada T, Otsuka A J, Lisanti M P (1997). Identification, sequence, and expression of an invertebrate caveolin gene family from the nematode *Caenorhabditis elegans*. Implications for the molecular evolution of mammalian caveolin genes. *J Biol Chem*, 272(4): 2437–2445
- Torres V A, Tapia J C, Rodríguez D A, Párraga M, Lisboa P, Montoya M, Leyton L, Quest A F (2006). Caveolin-1 controls cell proliferation and cell death by suppressing expression of the inhibitor of apoptosis protein survivin. *J Cell Sci*, 119(Pt 9): 1812–1823
- Tourkina E, Richard M, Gööz P, Bonner M, Pannu J, Harley R, Bernatchez P N, Sessa W C, Silver R M, Hoffman S (2008). Antifibrotic properties of caveolin-1 scaffolding domain *in vitro* and *in vivo*. *Am J Physiol Lung Cell Mol Physiol*, 294(5): L843–L861
- Uittenbogaard A, Smart E J (2000). Palmitoylation of caveolin-1 is required for cholesterol binding, chaperone complex formation, and rapid transport of cholesterol to caveolae. *J Biol Chem*, 275(33): 25595–25599
- Wang C, Mei Y, Li L, Mo D, Li J, Zhang H, Tian X, Chen Y (2008). Molecular characterization and expression analysis of caveolin-1 in pig tissues. *Sci China C Life Sci*, 51(7): 655–661
- Wang L, Mo S, Li J, Li Q, Cui Z (2010a). Preliminary study on functions of zebrafish Caveolin-1. *Acta Hydrobiologica Sinica*, 34(4): 1083–1090
- Wang X M, Kim H P, Song R, Choi A M (2006). Caveolin-1 confers antiinflammatory effects in murine macrophages via the MKK3/p38 MAPK pathway. *Am J Respir Cell Mol Biol*, 34(4): 434–442
- Wang X M, Nadeau P E, Lo Y T, Mergia A (2010b). Caveolin-1 modulates HIV-1 envelope-induced bystander apoptosis through gp41. *J Virol*, 84(13): 6515–6526
- Williams T M, Lisanti M P (2004). The Caveolin genes: from cell biology to medicine. *Ann Med*, 36(8): 584–595
- Williams T M, Lisanti M P (2005). Caveolin-1 in oncogenic transformation, cancer, and metastasis. *Am J Physiol Cell Physiol*, 288(3): C494–C506
- Yamada E (1955). The fine structure of the gall bladder epithelium of the mouse. *J Biophys Biochem Cytol*, 1(5): 445–458
- Yamaguchi Y, Yasuoka H, Stolz D B, Feghali-Bostwick C A (2010). Decreased caveolin-1 levels contribute to fibrosis and deposition of extracellular IGFBP-5. *J Cell Mol Med*,
- Yamamoto H, Komekado H, Kikuchi A (2006). Caveolin is necessary for Wnt-3a-dependent internalization of LRP6 and accumulation of beta-catenin. *Dev Cell*, 11(2): 213–223
- Zaas D W, Swan Z, Brown B J, Wright J R, Abraham S N (2009). The expanding roles of caveolin proteins in microbial pathogenesis. *Commun Integr Biol*, 2(6): 535–537
- Zhang B, Peng F, Wu D, Ingram A J, Gao B, Krepinsky J C (2007). Caveolin-1 phosphorylation is required for stretch-induced EGFR and Akt activation in mesangial cells. *Cell Signal*, 19(8): 1690–1700
- Zhang W, Razani B, Altschuler Y, Bouzahzah B, Mostov K E, Pestell R G, Lisanti M P (2000). Caveolin-1 inhibits epidermal growth factor-stimulated lamellipod extension and cell migration in metastatic mammary adenocarcinoma cells (MTLn3). Transformation suppressor effects of adenovirus-mediated gene delivery of caveolin-1. *J Biol Chem*, 275(27): 20717–20725
- Zhao X, Liu Y, Ma Q, Wang X, Jin H, Mehrpour M, Chen Q (2009). Caveolin-1 negatively regulates TRAIL-induced apoptosis in human hepatocarcinoma cells. *Biochem Biophys Res Commun*, 378(1): 21–26
- Zhu H, Cai C, Chen J (2004). Suppression of P-glycoprotein gene expression in Hs578T/Dox by the overexpression of caveolin-1. *FEBS Lett*, 576(3): 369–374