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REVIEW

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

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Abstract **Caveolin-1 (Cav-1) isoforms, including Cav-1α and Cav-1β, 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-β 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-1α and Cav-1β, 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-1α contains the N-terminal 31 amino acids (Kogo and Fujimoto, 2000; Scherer et al., 1995). The tyrosine(Y) 14 in Cav-1α was identified as a phosphorylation site, while this site does not exist in Cav-1β (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-1α and -1β 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-1α and-1β 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.

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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) N-attachment domain (N-MAD) Caveolin Scaffolding domain (CSD)	Stabilize CSD helical conformation Attach with membrane Interact with other protein	Le Lan et al., 2006 Schlegel and Lisanti, 2000 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	Glenney and Soppet, 1992
135–150	C-attachment domain(C-MAD)	Attachment with membrane	Schlegel and Lisanti, 2000
133, 143, 156	Cysteine	Palmitoylation Interaction with other acylated protein Bind and transport cholesterol	Dietzen et al., 1995 Lee et al., 2001 Uittenbogaard and Smart, 2000

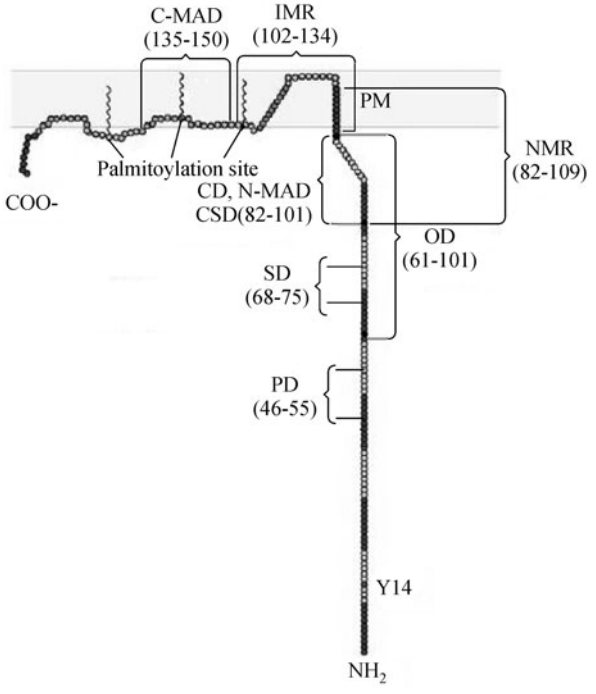

Figure 1 A structural model of Cav-1 protein (178 amino acids) from Head and Insel (2007) with some modifications. PD: polarization domain; C-MAD: C-attachment domain; IMR: intramembrane region; NMR: nuclear magnetic resonance; CSD: Caveolin Scaffolding domain; N-MAD: N-attachment domain; CD: circular 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 ΦxΦxxxxΦ, ΦxxxxΦxxΦ or ΦxΦxxxxΦxxΦ, where Φ 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-β receptor (TGF-βR), 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 (EFGR), and signal molecules including H-ras, G protein, eNOS, β-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. EFGR, 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-β-mediated transcriptional activity through direct interaction with ubiquitous TGF-βR (Razani et al., 2001a; Lee et al., 2007), but enhances the TGF-β/ALK1 signaling as shown by its activation of ALK1 (an activin receptor-like kinase and TGF-β1R) -specific reporters (Santibanez et al., 2008). Moreover, Cav-1 expression leads to the accumulation of β-catenin within caveolae membranes and thus inhibits the β-catenin/Lef-1 signaling activated by wnt-1 or the overexpression of β-catenin itself (Galbiati et al., 2000), while inducing LRP6 (a low-density lipoprotein receptor-related protein 6 and wnt receptor) internalization and activating wnt/β-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	TNFa	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
	Indiirectly	Survivin	Inhibit	Wnt	Torres et al., 2006
	Indiirectly	COX-2	Inhibit	Wnt	Rodriguez et al., 2009
	Directly	LRP6	Active	Wnt	Yamamoto et al., 2006
NF-kB	Directly	TNFa	Negative	PI3K/PKB and p44/42 MAPK NF-kB	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-1α 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-β (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-β, 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-1α and-1β exhibit overlapping but distinct expression patterns during embryogenesis of zebrafish. For example, both zebrafish *cav-1a* and *-1β* mRNAs are detected in the heart, pharyngeal vasculature, notochord, somites, skin, and neuromast tissues during the very early stages of development, whereas *cav-1α* 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-1α could not rescue the phenotype caused by knockdown of Cav-1β 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-1α and -1β are closely associated with the phosphorylation at Y14 in Cav-1α (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; Schwencke 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-β 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-β receptor and negatively control the activity of TGF-β signaling (Razani et al., 2001a). Therefore, intriguing roles of Cav-1 in tumorigenesis may be partially associated with its regulation of TGF-β 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-β 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-β/ALK1 and repression of TGF-β/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-β 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*$^{-/-}$ mice exhibited impaired liver regeneration and low survival. Hepatocytes isolated from *cav-1*$^{-/-}$ mice showed dramatically reduced lipid droplet accumulation and did not advance through the cell division cycle. Treatment of *cav-1*$^{-/-}$ 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-κB and cAMP response elements and then repress TGF-β 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.

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