4 Modulation of Cancer Cell Growth and Progression by Caveolin-1 in the Tumor Microenvironment

Hyo-Jin Yoon and Young-Joon Surh

Abstract

Caveolin-1 (Cav-1), a major structural component of cell membrane caveolae, is involved in a variety of intracellular signaling pathways as well as transmembrane transport. Cav-1, as a scaffolding protein, modulates signal transduction associated with cell cycle progression, cellular senescence, cell proliferation and death, lipid homeostasis, etc. Cav-1 is also thought to regulate the expression or activity of oncoproteins, such as Src family kinases, H-Ras, protein kinase C, epidermal growth factor, extracellular signal-regulated kinase, and endothelial nitric oxide synthase. Because of its frequent overexpression or mutation in various tumor tissues and cancer cell lines, Cav-1 has been speculated to play a role as an oncoprotein in cancer development and progression. In contrast, Cav-1 may also function as a tumor suppressor, depending on the type of cancer cells and/or surrounding stromal cells in the tumor microenvironment as well as the stage of tumors.

Keywords

Caveolin-1 · Caveolae · Cancer-associated fibroblasts · Cancer progression · Cancer stem-like cells · Epithelial-mesenchymal transition · Metastasis · Stem cells · Stromal cells · Tumor microenvironment

4.1 Introduction

Caveolae represent a flask-shaped invagination of the plasma membrane that play a role in endocytosis and forming vesicles in the cytoplasm. Caveolae are heterogeneous in normal and tumor cells, and they are most abundant in stromal cells, such as adipocytes, fibroblasts, vascular endothelial cells, and smooth muscle cells [1, 2]. A family of integral membrane proteins, called caveolins, are the principal components of caveolae. Caveolins may act by compartmentalizing and concentrating signaling molecules and are involved in receptor-independent endocytosis [3]. Caveolins have amino-terminal and carboxy-terminal domains

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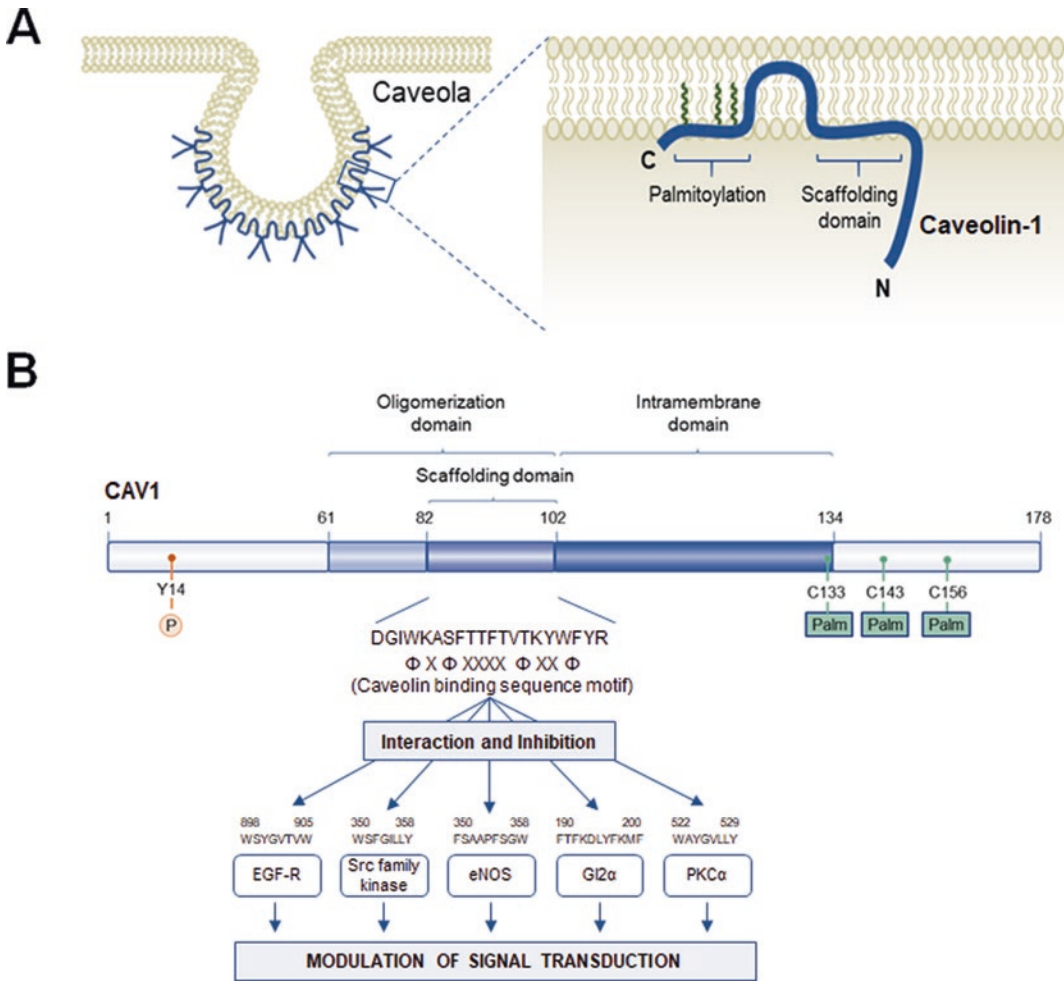

Fig. 4.1 Structures of caveolae and Cav-1. (**a**) The diagrams of caveolae and Cav-1. Cav-1 is inserted into the caveolar membrane, with the N- and C-termini facing the cytoplasm and an intramembrane domain embedded within the membrane bilayer. (**b**) The sequence of the caveolin-scaffolding domain (CSD; residues 82–102) and the caveolin binding sequence motifs within several caveolae-localized signaling molecules are shown. These include epidermal growth factor receptor (EGF-R), Src family tyrosine kinases, endothelial nitric oxide synthase (eNOS), G-protein α subunits (Gi2α), and PKC isoforms (PKCα). In most cases, such interaction is inhibitory, leading to inactivation of the signaling molecules and modulation of downstream signal transduction

localized at the cytoplasmic face of the cell membrane (Fig. 4.1a) [4]. Caveolins also contain the caveolin scaffolding domain required for binding to signaling proteins. Caveolins modulate functions of several signaling molecules, such as Src, G-protein α-subunits, and H-Ras, involved in cell proliferation and growth (Fig. 4.1b) [5]. Caveolins consist of the three core members, Caveolin-1 (Cav-1), Caveolin-2 (Cav-2), and Caveolin-3 (Cav-3). Cav-1 is highly expressed in various cells, such as adipocytes, endothelial cells, fibroblasts, and smooth muscle cells. Cav-2 shares a similar expression profile with Cav-1, as it requires Cav-1 for stabilization. Cav-3 is predominantly expressed in muscle cells [6]. Cav-1 and Cav-3 form homo-oligomers, and oligomerization is essential for caveolae biogenesis. Ablation of Cav-1 and Cav-3 causes a deficiency of caveolae in various cell types [7, 8]. Besides formation of caveolae, caveolins have multiple cellular functions by interacting with signaling molecules, such as receptors, kinases, adhesion

molecules, and G proteins. These include cholesterol homeostasis, vesicle trafficking, and endocytosis [9, 10]. Of three isoforms of caveolin family, Cav-1 is the principal structural component of caveolae, and its expression is essential for driving the formation of morphologically identifiable caveolae [10]. Cav-1, as a scaffolding protein, modulates multiple signal transduction pathways involved in cell cycle progression, cellular senescence, cell proliferation and death, lipid homeostasis, etc.

Over the past years, there has been increasing concern about the involvement of Cav-1 in the development and pathogenesis of human cancer. Cav-1 regulates cancer cell metabolism, proliferation, differentiation, resistance to apoptosis, survival, adhesion, migration, invasion, and metastasis [12–16]. On the other hand, Cav-1 can also act as a tumor suppressor in some circumstances in which its low expression favors tumor progression [17–20]. Besides epithelial Cav-1 in tumors, altered expression of stromal Cav-1 in the tumor microenvironment (TME) is observed in different types of human malignancies [12, 14]. However, the clinical significance of Cav-1 in cancer is still elusive.

This review summarizes the differential roles for Cav-1 in tumor development, migration, metastasis, therapy resistance, and cancer cell survival.

4.2 Cav-1 Expression in Human Cancer

Cav-1 expression has been extensively examined in various tumor specimens from cancer patients as well as in human cancer cell lines [14–18]. In most studies, the association between Cav1 expression levels and clinicopathological significance in terms of prognosis, metastatic status, and/or tumor resistance has been analyzed [14–18]. However, there is a contradictory profile of the Cav-1 expression in human cancer [19]. While some studies suggest the oncogenic function of Cav-1, loss or low expression of Cav-1 has been associated with poor outcomes in various tumor types. In other studies, however, there is no consistent change in Cav-1 expression between cancer cells and their normal adjacent cells. Therefore, the effects of Cav-1 expression on tumorigenicity and aggressiveness appear to vary widely among different cancer types [19].

4.2.1 Oncogenic Function

Cav-1 is frequently overexpressed or mutated in various tumor tissues and cancer cell lines. Aberrant upregulation of Cav-1 has been postulated to favor cancer cell survival and growth. Cav-1 may function as an oncoprotein commonly associated with enhanced malignant behavior, such as metastasis [15, 16, 18] and therapy resistance [14, 15, 17]. The clinicopathologic significance of upregulated Cav-1 is described below.

4.2.1.1 Role in Cancer Cell Invasiveness and Metastasis

In certain tumors, progression into a metastatic or drug-resistant form has been attributable to reexpression of Cav-1 [14–18]. Upregulation of Cav-1 is thought to contribute to cancer cell invasiveness and resistance to anoikis, properties that are essential for metastasis [20]. In non-neoplastic gastric mucosa, Cav-1 was not expressed in the epithelial compartment. However, the expression of Cav-1 was significantly correlated with cancer progression and poor prognosis in gastric cancer. This was associated with an advanced stage and lymph node metastasis [21].

Restoration of Cav-1 expression in lung adenocarcinoma cells is sufficient to promote their filopodia formation, migration, and metastatic potential [22]. Recent studies have indicated that cell invasion during tumor progression may be critically dependent on the acquisition of epithelial-mesenchymal transition (EMT) features. Multiple lines of evidence support that Cav-1 mediate the invasion and metastasis of cancer which are accompanied by EMT. Thus, Cav-1 can promote bladder cancer metastasis by inducing EMT which is linked to activation of phosphatidylinositol 3-kinase-Akt and upregulation of Slug expression [23]. Moreover, overex-

pressed Cav-1 increased vimentin expression, but downregulated E-cadherin. This accompanied the change of EMT, resulting in the increased motility and invasiveness in hepatocellular carcinoma [24]. The reduced levels of Cav-1 in hypoxia stimulate activation of epidermal growth factor receptor and consequently STAT3. This, in turn, results in the downregulation of E-cadherin and upregulation of mesenchymal markers, such as Slug, α-smooth muscle actin, N-cadherin, and vimentin, suggesting that Cav-1 can mediate the EMT and promote invasiveness in gastric cancer [24] (Fig. 4.2).

Matrix metalloproteins (MMPs) are a family of zinc-containing proteolytic enzymes that degrade various components of extracellular matrix [25]. The migration- and invasion-promoting effects of Cav-1 overexpression in hepatocellular carcinoma appear to be mediated by increasing secretion or expression of MMP-2, MMP-9, and MT1-MMP as well as inducing an EMT-like phenotype [26].

Rho-GTPases are involved in tumor metastasis and invasion [27, 28]. Previous studies have indicated the role of Cav-1 in regulating the activity of Rho-GTPases in various metastatic cancers. The interaction between Cav-1 and Rho-GTPases promotes tumor metastasis, which depends on the elevated expression of α5-integrin and the enhanced activation of Src and Ras [29]. The acquisition of the metastatic phenotype requires adhesive interaction between cancer cells and the endothelium, in which focal adhesion kinase (FAK) plays an essential role [30]. The expression of Cav-1 was positively correlated with that of FAK in gastric cancer [21]. Rho/ROCK signaling promotes tumor cell migration and metastasis by regulating focal adhesion dynamics through Cav-1 phosphorylation at the tyrosine 14 residue [31]. Cav-1 tyrosine phosphorylation is dependent on Src kinase and Rho/ROCK signaling. The phosphorylated Cav-1 stabilizes FAK association with focal adhesion and promotes cell migration and invasion [31].

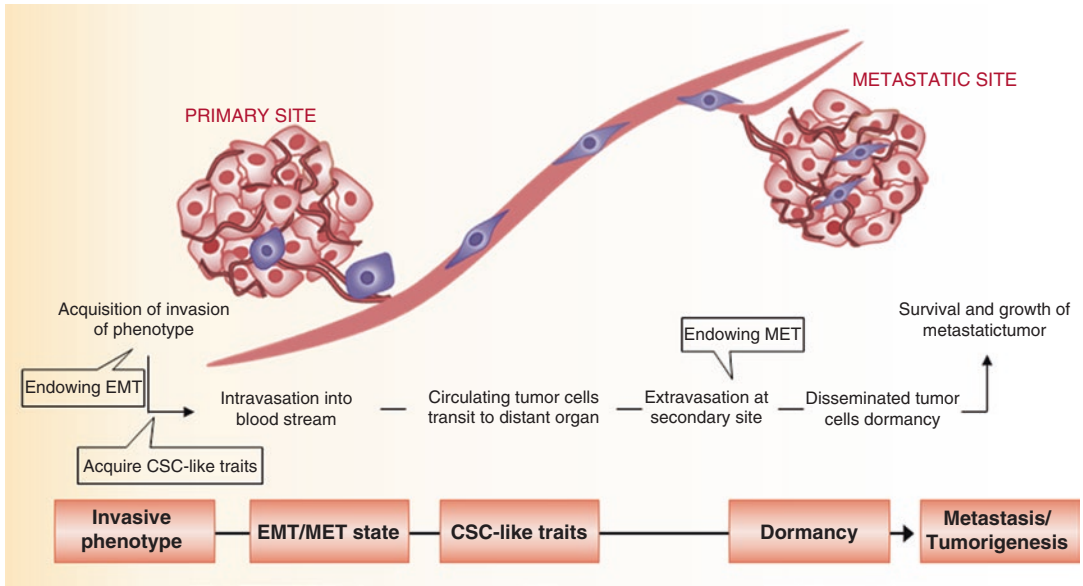

Fig. 4.2 Cancer cells within the primary tumor undergo EMT and acquire stem-like traits (CSCs) and endow invasive capacity, then intravasate into the tumor vasculature in the form of circulating tumor cells (CTCs), which must be able to survive the circulating blood and evade from the innate immune response and other defenses. Once CTCs migrate to a secondary site, the settlement in supportive niches enables them to survive and retain their stem-like tumor-initiating capacity. In the target site, disseminated cancer cells (DTCs) encounter inhibitory signals resulted in the arrested in cell cycle subsequently leading to dormancy from months to decades while they adapt to their new found microenvironment. Cancer cells undergo mesenchymal-to-epithelial transition (MET) in order to acquire feature proliferation to metastatic outgrowth in the target site

4.2.1.2 Role in Therapy Resistance

Increased expression of Cav-1 can promote development of resistance to chemo- or radiotherapy [14, 17]. In cisplatin-resistant ovarian cancer cells, both expression levels of Cav-1 and its mRNA transcript were significantly higher than those in normal ovarian cancer cells [32]. Knockdown of Cav-1 sensitized cisplatin-resistant ovarian cancer cells to apoptosis, which was attributable to downregulation of expression of Notch-1, p-Akt, and p-NF-κB/p65 [32].

4.2.1.3 Role in Cancer Stem Cells (CSCs)

CSCs represent an important subset of TME components. CSCs are responsible for tumor initiation, metastasis, and recurrence as well as resistance to chemo- and radiotherapy, which are associated with poor clinical outcomes. Because CSCs contribute to cancer development and progression, the presence of CSC population in precancerous stage is an early indicator of malignant progression. Some biological mediators (e.g., nitric oxide; NO) found in the TME could promote manifestation of CSC-like phenotypes of human nonsmall-cell lung carcinoma via Cav-1 upregulation [33].

Our recent study revealed that Cav-1 expression is significantly lower in tumorspheres derived from human breast cancer (MDA-MB-231) cells than in adherent cells [34]. In line with this notion, silencing of Cav-1 enhanced stemness of MDA-MB-231 cells as evidenced by the increased proportion of $CD44^{high}$ and $CD24^{low}$ cells. Notably, Src-mediated phosphorylation of Cav-1 at the Tyr 14 residue was found to be essential for its destabilization via the ubiquitin-proteasome degradation system which accounts for the reduced Cav-1 in a breast CSC-like state [34].

4.2.2 Tumor Suppressive Function

In some tissues, Cav-1 has been shown or speculated to function as a tumor suppressor. Several studies have shown that Cav-1 inhibits colony formation and induces apoptosis in transformed cells and cancerous cells [35–37]. In addition, forced reexpression of Cav-1 abrogated anchorage-independent growth of transformed cells [35–39].

In human breast cancer, the *Cav-1* has been considered a tumor suppressor gene associated with inhibition of tumor metastasis. Sagara and colleagues investigated the mRNA and protein expression levels of Cav-1 in 162 cases of breast cancer and found that the Cav-1 expression was suppressed at both transcriptional and translational levels in breast cancer tissues compared with the normal tissues [40]. In this study, the reduced *Cav-1* mRNA level was significantly associated with an increased tumor size, and was correlated with hormonal receptor status [40]. Overexpressed Cav-1 reduced the invasion capacity of metastatic mammary tumor cells by inhibiting the activity of MMP-2 and MMP-9 [41]. In normal breast, Cav-1 was found to be expressed in myoepithelial cells, endothelial cells, and a subset of fibroblasts. In contrast, luminal epithelial cells showed negligible staining [42].

Low levels of Cav-1 and its mRNA transcripts were detected in several colon carcinoma cell lines. Moreover, Cav-1 protein levels were markedly lower in human colon tumor epithelium than in normal colon mucosa. Ectopic expression of Cav-1 in the colon carcinoma cells attenuated tumor formation when these cells were inoculated into nude mice [43]. Moreover, Cav-1 may function as a negative regulator of metastasis by inhibiting MT4-MMP expression in colon cancer [44]. Cav-1 is not expressed in lipid rafts of the highly metastatic colon cancer cell line, but expressed in cytosolic fractions of the parental lower metastatic cell line. Xenografting Cav-1 deficient cells in nude mice induced development of bigger tumors expressing higher levels of proliferating cell nuclear antigen than in mice injected with cells expressing the higher level of Cav-1 [45]. In another study, high Cav-1 expression correlated with good clinical outcomes in head and neck cancer and extrahepatic biliary carcinoma cells [46]. In mucoepidermoid carcinoma of the salivary glands, reduced expression of Cav-1 was associated with a poor prognosis for some patients [45].

Contrary to the previous report on the association between Cav-1 and Rho-GTPases that promotes tumor metastasis [29], Lin and colleague have reported that Cav-1 expression inhibits RhoC GTPase activation and subsequently activates the p38 mitogen-activated protein kinase, leading to suppression of migration and invasion of primary pancreatic cancer cells [47].

In in vivo experiments, Cav-1 knockout mice showed increased development or progression of some cancers. A novel mouse model of colorectal cancer was generated by crossing C57BL/6 *Apc*$^{min/+}$ with B6129 Cav-1 knockout (*Cav1*$^{-/-}$) mice. Absence of Cav-1 accelerated colorectal tumorigenesis in *Apc*$^{min/+}$ mice, which was accompanied by upregulation of Wnt signaling [48].

Cav-1 null mice are much more susceptible to chemically induced skin carcinogenesis as well as epidermal hyperplasia than wild-type littermates [49]. In addition, cyclin D1 expression was upregulated during epidermal hyperplasia, which may account for the increased susceptibility of Cav-1 null mice to skin paillomagenesis [49]. Further, orthotopic implantation of B16F10 melanoma cells in the skin of Cav-1 null mice increased tumor growth [50].

Lewis lung carcinoma cells implanted into Cav-1 knockout mice had increased tumor vascular permeability compared with tumors implanted into wild-type mice. Cav-1 deficient mice also had significantly higher tumor growth rates, and this was attributable to increased tumor angiogenesis and decreased tumor cell death [51].

4.3 Stromal Versus Tumoral Cav-1 in TME

There has been increasing concern about the tumor-host interactions, which influence tumor growth, metastasis, therapy resistance, and cell survival. Understanding such tumor-stroma communication interactions may hence offer a novel therapeutic strategy to avoid or minimize therapy resistance and improve clinical outcomes [14].

Multiple lines of compelling evidence support that the heterogeneous tumor stroma in TME contributes to manifestation of a malignant phenotype of epithelial tumors, tumor recurrence, metastasis, and therapy resistance, resulting in poor clinical outcome. In this context, Cav-1 in the stroma of TME is also likely to be an important prognostic indicator of breast cancer [12, 14]. An absence or reduced stromal Cav-1 expression accounts for poor clinical outcome or therapy resistance in many different types of cancers [12, 13, 52–54].

4.3.1 Cav-1 in Cancer-Associated Fibroblasts

The stroma which constitutes at least half of the tumor mass consists of cancer-associated fibroblasts (CAFs), macrophages and other immune cells, and endothelial cells. Of the stromal cells, CAFs play a key role in tumor-stromal interaction. Loss of Cav-1 expression in CAFs results in an activated TME, thereby driving early tumor recurrence, metastasis, and poor clinical outcome in various malignancies [12]. The loss of Cav-1 in fibroblasts is sufficient to induce a CAF phenotype. In addition to CAFs, metastasis-associated macrophages in TME also express abundant levels of Cav-1, which is critical for metastasis and not for primary tumor growth [55]. The decreased expression of Cav-1 in CAFs resulted in a growth advantage and the chemoresistance of cancer cells when they were co-injected into immunodeficient mice to develop mixed fibroblast/cancer cell xenografts [56]. In this study, however, Cav-1 downregulation in cancer cells had no effect on chemoresistance and growth gain in vivo. Thus, it is likely that relative expression of tumor vs. stromal Cav-1 in TME has more precise prognostic significance than that of each alone. In this context, it is interesting to note that low expression of stromal Cav-1 was negatively associated with cytoplasmic Cav-1 expression in total tumor tissues [57]. As the colon tumor becomes more aggressive and metastatic, it looses the stromal Cav-1 and gains the cellular Cav-1 as well as the abnormal β-catenin expression [58]. In line with this notion, the high tumor/low stromal expression of Cav-1 was closely associated with poor

prognostic outcomes in primary human prostate cancer patients [59].

Sotgia and colleagues have proposed paracrine signaling mechanisms by which the loss of stromal Cav-1 promotes tumor progression to fuel the growth of adjacent tumor cells [12]. It appears that oxidative stress is the root cause of initiation of the loss of stromal Cav-1 via autophagy [12]. It is noteworthy that loss of stromal Cav-1 correlates with high epithelial Cav-1 levels and activated Akt [60]. Low stromal expression of Cav-1 increased TGF-β1 expression and induced phosphorylation and activation of Akt in human dermal fibroblasts [61].

Though the majority of studies suggest stromal Cav-1, especially of CAF origin, has tumor suppressive functions, Cav-1 expression of CAFs has been shown to be associated with patients' poor prognosis [62, 63]. Moreover, tumors with Cav-1-positive CAFs had vascular and pleural invasion significantly more frequently than those with Cav-1-negative CAF [64].

4.3.2 Cav-1 in Other Stromal Cells

Besides CAFs, Cav-1 may also functions in some other stromal cells in TME. Cav-1 is abundant in endothelial cells, adipocytes, and smooth muscle cells as well as in fibroblasts and epithelial cells. Several studies have suggested that Cav-1 may function in the main types of vascular cells in TME [51, 65–67], including pericytes, endothelial cells, and smooth muscle cells which are associated with vascular permeability and morphogenesis in tumor. Endothelial cells play a central role in angiogenesis, a process by which new vasculature is derived from preexisting blood vessels. Several studies have proposed a role for Cav-1 in the regulation of vascular development and angiogenesis [51, 65–67].

Under physiological condition, the main function of Cav-1 is to inhibit endothelial permeability. Cav-1 knockout mice were observed to exhibit a hyperpermeable vascular endothelium [66]. Likewise, tumors grown in *Cav1*$^{-/-}$ mice became leaky as evidenced by increased tumor vascular permeability, and grew faster, compared with tumors implanted into wild-type mice [51]. Cav-1 deficient mice also displayed elevated tumor angiogenesis and decreased tumor cell death, which may account for significantly higher tumor growth rates [51]. As Cav-1 is an endogenous inhibitor of endothelial NO synthase (eNOS), the loss of Cav-1 may result in hyperactivation of eNOS, and resultant NO overproduction is speculated to increase tumor vascular permeability, survival, and ultimately tumor growth [51]. Besides inhibition of endothelial NO production, there might be an alternative mechanism by which Cav-1 modulates the microvascular permeability and angiogenesis. Cav-1 has been found to interact with many intracellular signaling molecules including receptors, thereby altering their activity. For instance, Cav-1 suppresses vascular endothelial cell growth factor receptor (VEGFR)-2 signaling by inhibiting tyrosine phosphorylation of this receptor mediated by adherens junction protein, VE cadherin [51]. Therefore, the enhanced tumor permeability and growth as a consequence of loss of Cav-1 may be attributed to augmented proangiogenic signaling through inhibition of phosphorylation-dependent VEGFR-2 activation [51].

Soon after microvessels are formed, they come in close contact with mural cells of the smooth muscle cell lineage, referred to as pericytes or vascular smooth muscle cells. Such association of pericites (smooth muscle cells) with endothelial cells lining newly formed blood vessels is essential for vascular development and stability [68]. Cav-1 was found to be enriched in the lipid raft fraction of pericytes [69]. Cav-1 impaired the migration of pericytes [66]. Therefore, a decrease in Cav-1 abundance appears to stimulate the angiogenesis and prevent its termination by mural cell recruitment [66]. In another study, a cell-permeable peptide derived from the Cav-1 scaffolding domain inhibited the proliferation of pericytes, but not their survival or migration [67].

There is paucity of information on the role of Cav-1, derived from other stromal cells of TME, in cancer development and progression. Cav-1 promotes differentiation of monocytes to macrophages [70]. Downregulated Cav-1 expres-

sion in circulating monocytes has been implicated in the pathogenesis of psoriasis [71]. However, the functional role of Cav-1 in stromal macrophages in TME has been poorly understood. It has been reported that Cav-1 functions as an anti-metastatic regulator in mouse models of lung and breast cancer pulmonary metastasis [54]. Among all the recruited inflammatory cell populations, metastasis-associated macrophages (MAMs) uniquely express high levels of Cav-1. Loss of Cav-1 did not affect MAM recruitment to the metastatic site, but rather favored lung metastatic growth through increased angiogenesis [54].

4.4 Role of Cav-1 in the Cancer Cell Metabolism and Metabolic Reprogramming of the Tumor Stroma

Recent studies have highlighted the importance of Cav-1, especially of stromal origin, in metabolic alterations in cancer cells in relation to their survival advantage. Cav-1 influences tumor development or progression by modulating such metabolic pathways as glycolysis, mitochondrial bioenergetics, glutaminolysis, fatty acid metabolism, etc. [13]. Catabolic CAFs represent a key metabolic "fuel source," required for cancer cell propagation, survival, and systemic dissemination during metastasis [52]. A loss of Cav-1 has been shown to drive the metabolic reprogramming of stromal cells to support the growth of adjacent epithelial tumor cells. Stromal cells could function as providers of energy metabolites for tumor cells by undergoing the "reverse Warburg effect" [53]. The interaction between the tumoral microvesicles (TMVs) and stroma in the tumor microenvironment plays a critical role in facilitating cancer progression. After being incubated with tumoral microvesicles, normal human gingival fibroblasts acquired a phenotype switch to CAFs which was accompanied by degradation of Cav-1 [72]. Notably, Cav-1-deficient CAFs undergo autophagy to secrete energy-rich metabolites and chemical building blocks that can sustain and support the growth of tumor cells [12].

Some studies also revealed the critical role of oxidative stress in a loss of stromal Cav-1 and the metabolic reprogramming of CAFs [73]. Although Cav-1 loss is caused by elevated ROS levels, Cav-1 downregulation may result in increased oxidative stress, which represents a feed-forward mechanism [12]. Oncogenes drive the onset of the CAF phenotype in adjacent normal fibroblasts by provoking oxidative stress. This oncogene-triggered fibroblast activation is "mirrored" by a loss of stromal Cav-1. These fibroblasts exhibit elevated ROS production and elevated glucose uptake, indicative of a shift toward a glycolytic metabolism [52].

4.5 Conclusion

As a main component of caveolae, Cav-1 is involved in many biological processes that include substance uptake and transmembrane signaling. In addition, Cav-1 can modulate cancer cell proliferation, differentiation, migration, invasion, metastasis, and resistance to anticancer therapy.

Although the role of Cav-1 in cancer is still elusive, the majority of reports suggest that Cav-1 represents an important prognostic marker of tumor development and progression, and independently serves as a predictor of overall survival rate. In addition, through interaction with other biological molecules, Cav-1 modulates stem-like traits. On the other hand, a functional loss of Cav-1 in several tumor cells induces a hyperproliferative state, promoting cell proliferation, survival, and invasiveness as well as acquisition of resistance to cancer therapy [14].

Based on these findings, the roles for Cav-1 in human cancer and its suitability as a prognostic marker are controversial. Cav-1 is likely to function both as a tumor suppressor and as an oncoprotein, depending on the stage of neoplastic transformation and extent of tumor progression (Fig. 4.3). Though Cav-1 appears to be downregulated in early transformed cells, a reexpression or rather upregulation and stabilization through

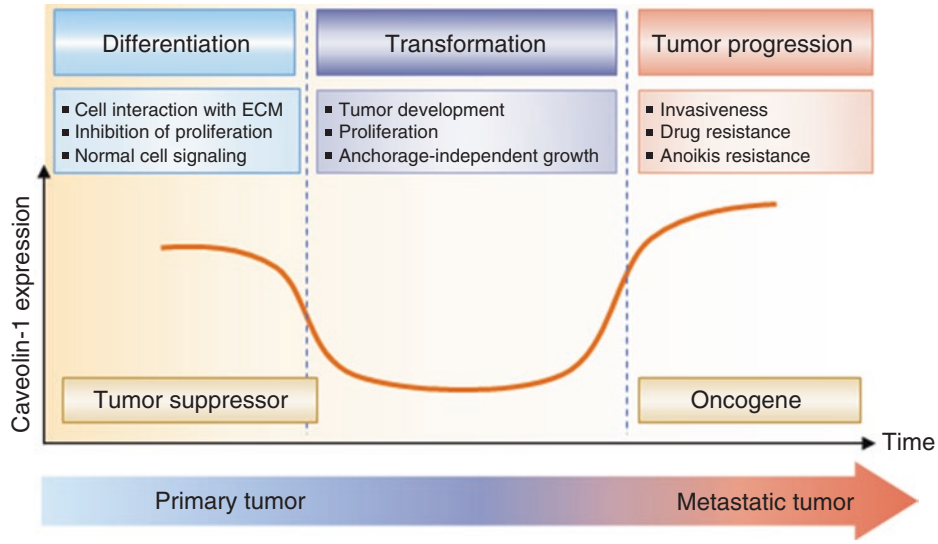

Fig. 4.3 Dual role of Cav-1 in cancer. Cav-1 may function both as a tumor suppressor and as an oncoprotein, depending on the stage of oncogenic transformation and extent of tumor progression. Cav-1 is expressed at relatively high levels in many differentiated cells. During oncogenic transformation, Cav-1 is downregulated, in certain tumors, further progression into a metastatic or drug-resistant form is associated with reexpression of Cav-1. Upregulation of Cav-1 in these tumors is thought to contribute to tumor cell invasiveness and resistance to anoikis, properties that are essential for tumor cell metastasis. Increased Cav-1 has also been associated with the development of drug resistance in tumors

phosphorylation of Cav-1, in later tumor stages, may confer invasiveness, resistance, and survival advantage of multidrug-resistant tumor cells [14].

The differential effects of Cav-1 in tumor development and progression may be related to a different profile of TME components involved in each stage of cancer, particularly in the context of tumor vs. stromal form of Cav-1. Loss of stromal Cav-1 in TME has been frequently associated with poor patient outcomes in diverse malignancies. A characteristic shift in stromal-epithelial Cav-1 in advanced and metastatic tumor stages with a loss of stromal Cav-1 and a concomitant increase in expression of epithelial isoform highlights Cav-1 as being a tissue and stage-specific tumor modulator [14]. A molecular mechanism by which Cav-1 expression is upregulated/restored in more advanced stages of cancer and how Cav-1 deficient CAFs promote this process merit further investigation. Identification and characterization of CAF-derived signaling molecules that mediate the shift in stromal-tumor Cav-1 accumulation during cancer progression will be of particular interest. Another interesting research subject would be elucidation of how metabolic reprogramming of Cav-1 deficient CAFs by CAF-addicted cancer cells is achieved.

Further studies are required to unveil the clinical value of Cav-1 as a prognostic marker and a candidate target for cancer therapy.

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