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Review Article

Caveolin-1: an essential modulator of cancer cell radio- and chemoresistance

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Abstract: Caveolin-1 is a ubiquitously expressed integral membrane protein and essential for the formation of so-called Caveolae, small invaginations of the plasma membrane. Caveolae are involved in major physiological functions of the mammalian cell, including endocytosis and transcytosis processes, signal transduction and cholesterol homeostasis. During the last decade, it became evident that Caveolin-1 plays a key role in cancer progression and metastasis. As it has also been described as a tumor suppressor, the plethora of intracellular processes Caveolin-1 contributes to remains to be fully identified. Differences in pathophysiological protein function have been ascribed to cell-specific roles of Caveolin-1 and to cancer stage dependency. An important aspect of the protein in terms of cancer cure seems to be its relevance as a prognostic marker and for induction of metastasis. These diverse functions of Caveolin-1 were expanded by recent data showing its role in radio- and chemoresistance of tumor cells, a new aspect this review will concentrate on. Since resistance of tumor cells to conventional treatment regimes is still a major obstacle in cancer treatment, new targeting approaches in combination with conventional radio- and chemotherapy are highly desirable and of great interest to improve cancer patient cure.

Keywords: Caveolin-1, cancer, chemoresistance, ionizing radiation, metastasis, radioresistance

Introduction

Radioresistance of tumor cells is a multifactorial characteristic. One critical factor is the intrinsic cellular radiosensitivity, which depends on the repair capacity of radiation-induced DNA lesions [1]. Additional essential factors are hypoxia [2], differential gene expression [3], growth factor receptors, mutations in proto-oncogenes and tumor suppressor genes [4], expression of receptor tyrosine kinases [5] and adhesion of cells to extracellular matrix (ECM) molecules mediated by cell surface receptors named integrins [6-8]. Interactions between integrins and receptor tyrosine kinases are rendered possible by specific intracellular signaling and scaffolding proteins, of which the integral membrane protein named Caveolin is one [9].

Caveolins comprise a family of three proteins named Caveolin-1, -2 and -3. While Caveolin-1 and -2 are ubiquitously co-expressed with high expression levels especially in epithelial and endothelial cells, fibroblasts, smooth muscle cells, adipocytes and pneumocytes, is the expression of Caveolin-3 mainly restricted to striated, cardiac and smooth muscle cells [10] and has also been described in C6 glioma cells [11]. Caveolin oligomerizes at the plasma membrane and its main function is that of a structural and functional element of small glycolipid-/cholesterol-rich invaginations of the plasma membrane named Caveolae. Approximately 100 to 200 Caveolin molecules are present per Caveola [12]. Caveolae are responsible for membrane trafficking, endocytosis and lipid homeostasis but also serve in signaling processes as a compartment where receptors and signaling proteins are concentrated [13-17]. Caveolin-1 in endothelial cells regulates angio-

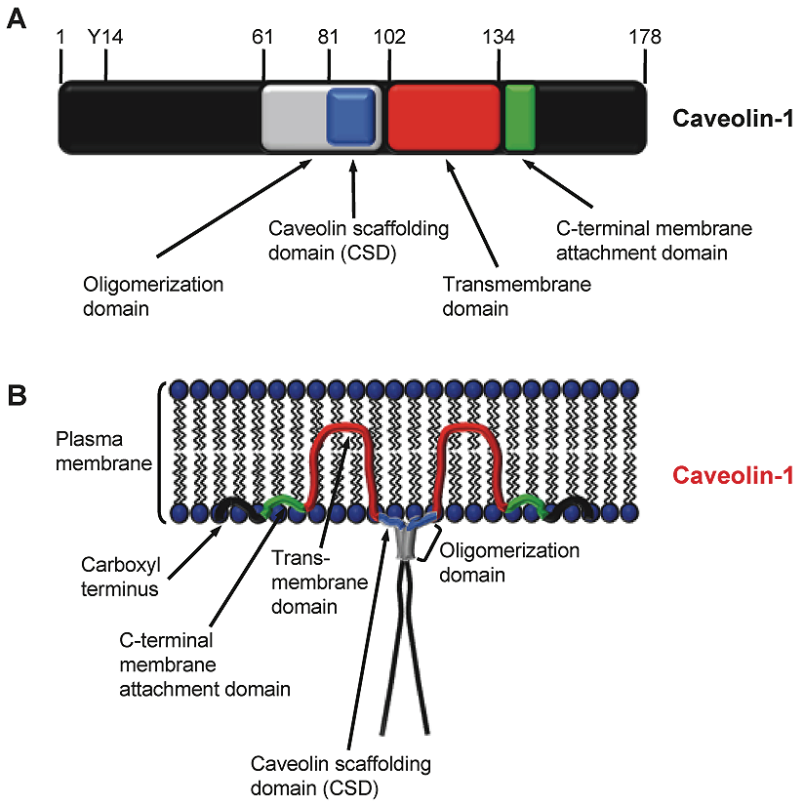

Figure 1. Structure of Caveolin-1. **A**, Important functional domains and phosphorylation site of Caveolin-1. Amino acid positions are depicted above the scheme. Y14, phosphorylation site at tyrosine 14. **B**, Localization of Caveolin-1 in the plasma membrane (modified from Williams and Lisanti [32]).

genesis, microvascular permeability and vascular remodeling [16, 18-20]. Caveolin-1 and -3 seem to be essential for Caveolae formation while the function of Caveolin-2 is less clear [21-23].

Apart from its signaling function in normal cells, Caveolin-1 takes part in pathophysiological processes such as inflammation [24], atherosclerosis and oncogenic transformation. Moreover, Caveolin-1 is thought to exert anti-apoptotic and tumor-promoting properties, stimulation of metastasis and to have prognostic value for patient survival and cancer recurrency. Contrariwise, Caveolin-1 also functions as tumor suppressor and pro-apoptotic protein [25-30]. Reasons for this Janus-like properties are postulated to be mainly due to cell-specific properties, physiological context, cellular transformation processes and cancer stage [31].

Since Caveolin-1 is the first identified and most widely explored family member, we focused in the following on the emerging role of Caveolin-1 as prognostic marker for cancer cure and on its impact on chemo- and radioresistance of cancer cells.

Caveolin structure and function

Caveolin protein family members Caveolin-1, -2 and -3 are integral membrane proteins with a molecular weight between 18 and 24 kDa [31, 32]. All three proteins are associated with membranes including the plasma membrane, endoplasmic reticulum and Golgi apparatus [31]. They possess a similar structure consisting of N- and C-terminal cytosolic domains, an oligomerization domain (residues 61-101 of Caveolin-1), including a Caveolin scaffolding domain (CSD; residues 82-101 of Caveolin-1) responsible for dimerization and interaction with signaling partners, a central transmembrane domain and a C-terminal membrane attachment domain [31-34]. Schematics of the Caveolin-1 domain structure and its localization in the plasma membrane are depicted in **Figure 1A** and **Figure 1B**. Moreover, Caveolin-1 is present in the cell in two isoforms, named α and β. Due to alternative splicing or initiation, Caveolin-1β is distinct from Caveolin-1α through a 31 amino acid residue deletion at the amino terminus [35-37].

Caveolin-1 contains a tyrosine (Y) phosphorylation site at residue 14, which is apparently not present in Caveolin-1β. Phosphorylation at this amino acid residue leads to accumulation of the protein at focal adhesion sites and subsequent transmission of extracellular signals via intracellular pathways [38, 39]. Important to note is that activation of e.g. EGFR or Akt requires previous Src-mediated phosphorylation of Caveolin-1 at Y14 [40]. Also direct activation of the insu-

lin receptor by Caveolin-1 and -3 has been observed [41]. As mentioned previously, Caveolin-1 has been shown to interact with β1 integrins and to promote Fyn-dependent Src homology containing (Shc) and mitogen-activated protein kinase (MAPK) phosphorylation [42-44]. How essential Caveolin-1 and its interaction with β1 integrin is can be seen from embryonic stem cell growth. Here, both proteins cooperate with p38 MAPK and the integrin signaling mediator Focal adhesion kinase (FAK) to provide optimal growth regulation [45]. Owing to its function as scaffold protein, Caveolin-1 seems also able to maintain a specific activity status of, for example, the important prosurvival protein Akt. Probably this action is facilitated by inhibitory binding of the Akt-regulating phosphatases protein phosphatase 1 and 2A to the CSD domain of Caveolin-1 [46]. This finding is supported by experiments in human pancreatic cancer cell lines, in which siRNA-mediated depletion of Caveolin-1 resulted in Akt dephosphorylation [47].

This short summary nicely exhibits the multifunctionality of Caveolin-1 and that most mechanisms this integral membrane protein serves in remain to be elucidated.

Caveolin-1 is associated with cancer progression and metastasis

First reports analyzing Caveolin-1 expression in different tumor entities such as breast cancer [48], colon cancer [49], ovarian carcinoma [50] and soft-tissue sarcomas [51] showed a downregulation of Caveolin-1 expression as well as a tumor suppressor function of Caveolin-1. In addition, a more recent publication found that stromal loss of Caveolin-1 expression is associated with poor clinical outcome and survival of patients with basal-like and estrogen receptor/progesterone receptor/HER2-negative breast cancers [52]. The most likely explanation of the discrepancies between Caveolin-1´s role as tumor promoter versus tumor suppressor consists of a tumor stage dependency [31, 53, 54]. Similar hypotheses and evidence have been published for the cell-cell contact protein E-cadherin. A link between Caveolin-1 and E-cadherin is suggested by a recent study evaluating oncogenic transformation [31, 53]. In detail, Caveolin-1 seems to inhibit the expression of the anti-apoptotic protein Survivin only in the presence of E-cadherin via the β-catenin-Tcf/Lef pathway in human colon cancer and mouse melanoma cells [53] involving Cyclooxygenase-2 (COX-2) and prostaglandin E2 [54].

In contrast, later reports added further functional facets to Caveolin that indicate this protein to be overexpressed in different cancers, that it might serve as a prognostic factor for patient outcome and that it may contribute to metastatic spread (reviewed in: [31, 55-58]). Examples for increased expression of Caveolin-1 in tumor cells in comparison to normal tissues are prostate cancer (reviewed in [55]), ductal adenocarcinoma of the pancreas [47, 59], squamous cell carcinoma of the esophagus [60, 61], glioblastoma [62], renal cell carcinoma [27] and non-small cell lung carcinoma (NSCLC) [63] (summarized in **Table 1**).

Concerning Caveolin-1 as prognostic marker, low Caveolin-1 expression levels in adenocarcinomas of the rectum were strongly associated with better local control rates at 5 years and increased overall survival after treatment [64]. In contrast, increased expression of Caveolin-1 in meningiomas and esophageal squamous cell carcinomas was associated with worse patient survival [60, 62]. As metastatic spread still severely hampers patient cure and survival and pursues to present a major obstacle in cancer treatment, studies have been performed to connect Caveolin-1 to this event. In NSCLC [26, 65], lung adenocarcinoma [25], esophageal squamous cell carcinoma [60] and renal cell carcinoma cells under doxorubicin treatment in a mouse model [27], Caveolin-1 expression showed a contribution to metastases formation. Studies to prove Caveolin-1 as essential determinant of migration and invasion of e.g. human head and neck squamous cell carcinoma (HNSCC) cells [66] and lung adenocarcinoma cells [25][67] supported this notion.

Functioning in such a great variety of physiological and pathophysiological cellular processes, researchers then asked the question if Caveolin-1 might also contribute to therapy resistance in cancer cells – a subject dealt with in the next section.

Role of Caveolin-1 in radio- and chemoresistance of human tumor cells

In recent years, the molecular mechanisms how Caveolin-1 is involved in cancer cell radio- and

Table 1. Role of Caveolin in cancer progression and metastasis

Authors	Year	Tumor entity	Main findings	Reference
Chen et al.	2011	lung	Increased Caveolin-1 expression indicated malignant progression and high invasion capability of NSCLC	[65]
Park et al.	2010	kidney	Caveolin-1 was upregulated in human renal cell carcinoma in comparison to adjacent tissue using cDNA microarray analysis	[27]
Li et al.	2010	lung	Caveolin-1 promoted lymph node metastasis in NSCLC	[26]
Rödel et al.	2009	rectum	Low Caveolin-1 expression in adenocarcinomas of the rectum was significantly related to better local control rates at 5 years and to an increased overall survival rate after preoperative chemoradiation	[64]
Hehlgans et al.	2009	pancreas	Caveolin-1 was overexpressed in pancreatic tumor cells compared to tumor stromal cells and pancreatic parenchymal cells	[47]
Tanase et al.	2009	pancreas	Caveolin-1 was overexpressed in ductal adenocarcinoma of the pancreas when compared to peritumoral tissue and associated with grade, stage and size of tumor	[59]
Ho et al.	2008	lung	Caveolin-1 expression was associated with a poor prognosis and with drug resistance in advanced NSCLC patients after Gemcitabine-based chemotherapy	[63]
Ando et al.	2007	esophagus	Caveolin-1 and -2 mRNA expression was significantly higher in esophageal squamous cell carcinoma than in corresponding normal esophageal mucosa	[61]
Barresi et al.	2006	brain (meningiomas)	Increased Caveolin-1 expression was correlated with worse patient survival and biological aggressiveness of meningiomas	[62]
Kato et al.	2002	esophagus	Caveolin-1 expression was correlated with a poor prognosis and lymph node metastasis in esophageal squamous cell carcinoma after surgery	[60]

chemoresistance has been increasingly explored (summarized in **Table 2**). This interest arose from a study examining effects in whole body irradiated Caveolin-1 knockout mice [68]. The authors showed a significant decreased survival rate of Caveolin-1 deficient mice relative to Caveolin-1 wild-type mice. This decreased survival rate was ascribed to increased apoptosis and abnormal proliferation of intestinal crypt stem cells of the small intestine.

In 2007, our group reported radiosensitization and antiproliferative effects by siRNA-mediated knockdown of Caveolin-1 in pancreatic cancer cells MiaPaCa2, Panc1 and PATU8902, while overexpression of Caveolin-1 conferred radioresistance in these cell lines [69]. Mechanistically, Caveolin-1 knockdown was associated with changes in expression or phosphorylation of Akt, glycogen synthase kinase 3β, Paxillin, Src, c -Jun N-terminal kinase and mitogen-activated protein kinase. DNA microarray technology assisted us to detect Caveolin-1 overexpression in a subset of biopsies from human ductal adenocarcinoma of the pancreas as well as in human pancreatic tumor cell lines as compared to normal tissues. Interestingly, we found an interrelation between Caveolin-1 and β1 integrin and FAK. Following up on these observations, we continued in three-dimensional laminin-rich extracellular matrix (3D lrECM) based cell culture models using pancreatic tumor cells [47]. The radiosensitizing effects generated under 3D lrECM growth conditions corroborated our previous findings. Concerning the underlying mechanisms, we showed a connection of Caveolin-1 to DNA repair processes as silencing of Caveolin-1 resulted in increased levels of residual DNA double strand breaks in irradiated 3D cell cultures. Despite enhanced apoptosis in unirradiated and irradiated Caveolin-1 knockdown cell cultures, neither basal clonogenic cell survival nor radiosensitization were eventually affected by apoptotic processes [47]. Thus, how does

Table 2. Role of Caveolin in radio- and chemoresistance

Authors	Year	Tumor entity	Main findings	Reference
Park et al.	2010	kidney	Caveolin-1 knockdown sensitized human renal carcinoma cells to doxorubicin-induced apoptosis and reduced lung metastasis in a mouse model	[27]
Hehlgans et al.	2009	pancreas	Caveolin-1 knockdown sensitized pancreatic tumor cell lines grown in 3D lrECM to X-rays	[47]
Dittmann et al.	2008	lung, head & neck (SCC)	EGFR receptor internalization and transport into the nucleus upon irradiation depended on Src activation and Caveolin-1	[70]
Ho et al.	2008	lung (NSCLC)	Caveolin-1 expression was associated with a poor prognosis and with drug resistance in advanced NSCLC patients after Gemcitabine-based chemotherapy	[63]
Cordes et al.	2007	pancreas	Knockdown of Caveolin-1 radiosensitized pancreatic cancer cell lines to ionizing radiation	[69]
Li et al.	2005		Enhanced radiosensitivity of Caveolin-1 deficient mice was associated with increased apoptosis and abnormal proliferation of intestinal crypt stem cells of the small intestine	[68]

Caveolin-1 participate in DNA repair? First findings suggested EGFR internalization into the cell nucleus to be Src-dependent and somewhat key to removal of DNA lesions by the DNA-Protein Kinase (DNA-PK) [70, 71]. Nevertheless, this issue is still under debate not only due to the fact that cell membrane to-cell nucleus translation of the EGFR seems not a general phenomenon but rather specific for selected cell lines in vitro.

Evaluating the data generated in 3D lrECM cell culture more deeply, a decreased expression of integrin subunits was revealed upon Caveolin-1 depletion [47]. These results further supported the dependence of both, integrins and EGFR, on the integral membrane protein Caveolin-1, its putative role in resistance of tumor cells to ionizing radiation and chemotherapy and cellular signal transduction [6-8, 72, 73]. Histologically, several studies demonstrated co-localization of β1 integins and Caveolin-1 in human chondrocytes [74], endothelial cells [75] and human pancreatic adenocarcinoma [47]. With regard to tumor cell multidrug resistance, most of the examinations have been performed in colon and breast cancer cell lines. Obviously, upregulation of Caveolin-1 expression in these cell lines mediated significant drug resistance [31, 49, 76]. In concordance with these findings, siRNA-mediated knockdown of Caveolin-1 decreased the incidence of lung metastasis from injected renal cell carcinoma cells under doxorubicin treatment in mouse experiments [27]. On the basis of the association of elevated Caveolin-1 expression with poor prognosis and Gemcitabine drug resistance of patients with advanced NSCLC [63], we investigated the chemosensitivity to Gemcitabine in Caveolin-1 knockdown pancreatic cancer cell cultures and found MiaPaCa2 to be chemosensitized to Gemcitabine, while the more resistant pancreatic cancer cell line Panc1 remained unaffected (**Figure 2A** and **B**).

Summary

Differential expression and/or function are prerequisites to be fulfilled by a specific target molecule to be designated as potential cancer target. Similarly important are these criteria for monotherapy application or combined application with conventional radio- and chemotherapy of a targeted drug against such a particular molecule. Consequently and in parallel, targeting efficacy is increased and normal tissue toxicity is reduced. As easily seen from this short review, Caveolin-1 is frequently overexpressed in a large range of tumor entities and the data point at a critical role of this integral membrane protein in carcinogenesis, tumor progression, metastatic spread and therapy resistance.

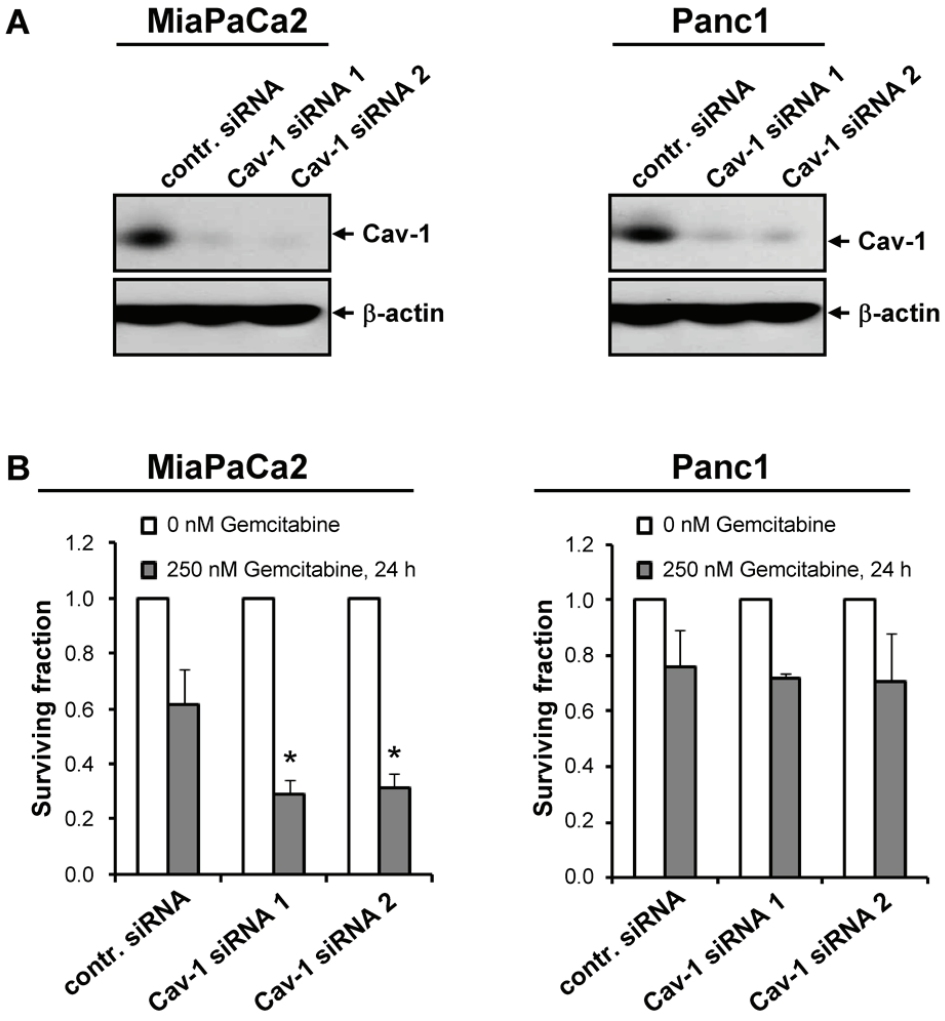

Figure 2. Cell line-dependent chemosensitization by Caveolin-1 knockdown of human pancreatic tumor cells to Gemcitabine. **A**, Confirmatory Western blot analysis of siRNA-mediated knockdown of Caveolin-1 in human pancreatic cancer cell lines MiaPaCa2 and Panc1 with two specific siRNAs directed against human Caveolin-1 (Cav-1 siRNA 1, 5'-GCUUCCUGAUUGAGAUUCAtt-3' [47]); Cav-1 siRNA 2, 5'-UGUGAUUGCAGAACCAGAAtt-3' [69]) (negative control siRNA #1 (Applied Biosystems, Darmstadt, Germany), contr. siRNA). **B**, For analysis of clonogenic survival, MiaPaCa2 or Panc1 cells were transfected with Caveolin-1 specific siRNA (Cav-1 siRNA 1/2) or control siRNA (contr. siRNA), plated as single cells on 6-well plates (BD, Heidelberg, Germany) and treated for 24 h with 250 nM Gemcitabine (Lilly Deutschland, Bad Homburg, Germany) 48 h after siRNA transfection. Colonies were counted microscopically after 9 days (MiaPaCa2) or 12 days (Panc1). Results are means ± s.d. (n = 3). Student's t-test compared Cav-1 siRNA transfected cells to siRNA controls. *$P < 0.05$.

Whether a targeted anti-Caveolin-1 therapy might be feasible, reasonable and effective for optimization of cancer cure requires detailed clarification in future studies.

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Abbreviations: COX-2, Cyclooxygenase-2; CSD, Caveolin scaffolding domain; DNA-DSB, DNA-double strand break; DNA-PK, DNA-Protein Kinase; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; FAK, Focal adhesion kinase; HNSCC, head and neck squamous cell carcinoma; lrECM, laminin-rich ex-

tracellular matrix; MAPK, mitogen-activated protein kinase; NSCLC, non-small cell lung carcinoma; Shc, Src homology containing; Y, tyrosine

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