MINI-REVIEW

Significance of Caveolin-1 Regulators in Pancreatic Cancer

Tao Chen*, Liang Liu*, Hua-Xiang Xu, Wen-Quan Wang, Chun-Tao Wu, Wan-Tong Yao, Xian-Jun Yu*

Abstract

Caveolin-1 is a scaffold protein on the cell membrane. As the main component of caveolae, caveolin-1 is involved in many biological processes that include substance uptake and transmembrane signaling. Many of these processes and thus caveolin-1 contribute to cell transformation, tumorigenesis, and metastasis. Of particular interest are the dual roles of tumor suppressor and oncogene that caveolin-1 appears to play in different malignancies, including pancreatic cancer. Therefore, analyzing caveolin-1 regulators and understanding their mechanisms of action is key to identifying novel diagnostic and therapeutic tools for pancreatic cancer. This review details the mechanisms of action of caveolin-1 regulators and the potential significance for pancreatic cancer treatment.

Keywords: Caveolae - caveolin-1 - pancreatic cancer - regulatory factor - significance

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Caveolin-1 and Pancreatic Cancer

Caveolin-1

Caveolae were originally identified as omega-shaped invaginations of the plasma membrane in epithelial cells (Smart et al., 1999), which were discovered by Palade in the 1950s (Casley-Smith et al., 1975). Currently, caveolae are considered integral transmembrane microdomains and critical components for the interactions between integrin receptors and cytoskeleton-associated signaling molecules (Cordes et al., 2007). Further, they are associated with various membranous structures, including the endoplasmic reticulum, Golgi, and plasma membranes (Parat et al., 2004). Caveolae are specialized structures mainly composed of cholesterol and sphingolipids. They are abundant in endothelial, muscle cells, adipocytes, and lung epithelial cells (Okamoto et al., 1998), and are implicated in several endocytic and trafficking mechanisms. The coat proteins required for caveolae formation are the three caveolins: caveolin-1, -2, and -3 (Fujimoto et al., 2000). Caveolin-1 and -2 are ubiquitously expressed in the human body, whereas caveolin-3 is found only in muscle tissue (Anderson et al., 1998). Caveolin-1 is the major structural protein in caveolae (Smart et al., 1994) and acts as a scaffold to organize multiple molecular complexes that regulate a variety of cellular events (Kato et al., 2004) such as cellular transformation, tumorigenesis, cell metastasis, and angiogenesis.

However, the fact that it appears to act as both a tumor suppressor and oncogene, depending on the context, is especially intriguing. In ovarian (Prinetti et al., 2010), colon (Nimri et al., 2012), and breast cancer cells (Rao et al., 2012; Simpkins et al., 2012), caveolin-1 is down-regulated and negatively correlated with the malignant potential of tumor cells. It is up-regulated and promotes cell proliferation and invasion in bladder (Thomas et al., 2011), esophageal (Kato et al., 2002), and prostate cancer cells (Li et al., 2001). High expression of caveolin-1 has favorable prognoses in bile duct cancer and breast cancer (Murakami et al., 2003; Rao et al., 2012), but is correlated with poor prognoses in prostate, esophageal, renal, and non-small cell lung carcinoma (Li et al., 2001; Kato et al., 2002; Steffens et al., 2011). In pancreatic cancer, caveolin-1 is reduced compared to normal pancreatic tissues from precancerous tumor tissue.

Pancreatic cancer

Pancreatic cancer is one of the deadliest cancers (Shi et al., 2012) and has been called the king of cancer because of its poor cure rate and prognosis (Siegel et al., 2012). Compared with other cancers, it has higher resistance to conventional treatments including surgery, radiation, and/ or chemotherapy (Diamantidis et al., 2008). Despite the fact that diagnostic techniques are rapidly developing, the early diagnosis of pancreatic cancer remains poor (Luo et al., 2008). Data indicates that the five-year survival rate ranges between 0.4 and 2 percent in the United States (Kreehler et al., 2011). Furthermore, 75 percent of the patients who are diagnosed at an advanced stage die within 1 year. Currently, surgical resection is the only treatment that results in long-term survival for pancreatic cancer patients.
Table 1. Caveolin-1 Regulators

<table>
<thead>
<tr>
<th>Regulatory Factor</th>
<th>Method</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forkhead box (FOXO)</td>
<td>PI3K/AKT/FOXO pathway</td>
<td>Promotion</td>
<td>(Boreddy et al., 2011; Roy et al., 2010)</td>
</tr>
<tr>
<td>Lipopolysaccharide (LPS)</td>
<td>Inhibit NF-κB activation by preventing the formation of IKK-γ/IKK complex and TLR4/MyD88 signaling</td>
<td>Suppression</td>
<td>(Tiruppathi et al., 2008; Ibebe et al., 2009)</td>
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<tr>
<td>High-density lipoprotein (HDL)</td>
<td>Activate MAP kinase pathway through ERK1/2</td>
<td>Suppression</td>
<td>(Frank et al., 2001)</td>
</tr>
<tr>
<td>Stimulatory protein 1 (Sp1)</td>
<td>Affect promoter activity</td>
<td>Promotion</td>
<td>(Dasari et al., 2006)</td>
</tr>
<tr>
<td>Estrogen receptors (ERs)</td>
<td>Methylation caveolin-1 promoter</td>
<td>Suppression</td>
<td>(Zschocke et al., 2003)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Sterol regulatory element binding protein (SREBP) and Sp1</td>
<td>Suppression</td>
<td>(Llaverias et al., 2004)</td>
</tr>
<tr>
<td>Carbon monoxide (CO)</td>
<td>Activate guanylylcylate and p38 MAPK</td>
<td>Suppression</td>
<td>(Kim et al., 2005)</td>
</tr>
<tr>
<td>Vascular endothelial growth factor (VEGF)</td>
<td>VEGF/MEK signal transduction pathway and protein kinase/C/MEK/c-myc gene/androgen receptor pathway</td>
<td>Suppression</td>
<td>(Liu et al., 1999)</td>
</tr>
<tr>
<td>Epithelial membrane protein 2 (EMP2)</td>
<td>Promote formation of membrane lipid rafts containing GPI-APS</td>
<td>Promotion</td>
<td>(Wadehra et al., 2004)</td>
</tr>
<tr>
<td>Endothelial NO synthase (eNOS)</td>
<td>Inhibit the catalytic activity of eNOS</td>
<td>Promotion</td>
<td>(Venema et al., 1997)</td>
</tr>
<tr>
<td>Reactive oxygen species (ROS)</td>
<td>Catalyse and N-acetylcysteine; prevent formation of caveolin-1-ubiquitin complex</td>
<td>Suppression</td>
<td>(Rungtabnapa et al., 2011)</td>
</tr>
<tr>
<td>Src kinase</td>
<td>Phosphorylate caveolin-1</td>
<td>Suppression</td>
<td>(Shields et al., 2011)</td>
</tr>
<tr>
<td>Na+/K+/ATPase</td>
<td>Separate regulation of Na+/K+/ATPase in the transport process</td>
<td>Promotion</td>
<td>(Cai et al., 2008)</td>
</tr>
<tr>
<td>Breast cancer susceptibility gene 1 (BRCA1)</td>
<td>Anti-caveolin-1 gene in caveolin-1 gene promoter</td>
<td>Promotion</td>
<td>(Wang et al., 2008)</td>
</tr>
<tr>
<td>Flotillin-1</td>
<td>Prevent lysosomal degradation</td>
<td>Promotion</td>
<td>(Vassileva et al., 2009)</td>
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Structure and Expression of Caveolin-1

Caveolin-1, a 21-24kDa integral membrane protein, is a principal component of caveolae membranes in vivo (Liu et al., 2013). Caveolae are involved in constitutive endocytic trafficking. Liquid-ordered domains are formed within the Golgi apparatus and thus the biogenesis of both caveolae and caveola-related liquid-ordered domains initiate in the Golgi and are transported to the cell surface by vesicular organelles. Caveolin-1 is formed during endocytosis and recycled back to the cell membrane (Smart et al., 1999). Immunofluorescent staining of cells transfected with caveolin-1 indicated that, like the NH2 terminus, the COOH-terminal region is located on the cytoplasmic side of the plasma membrane. Using the anti-peptide antibodies and epitope tags targeting the N- and C-terminal, Glenney et al. found that the N-terminal and C-terminal are both located on the cytoplasmic side of the plasma membrane. The NH2 terminus has a tyrosine that is phosphorylated by V-Src (Glenney et al., 1989) and the C-terminus has a cysteine palmitoylation site (Dietzen et al., 1995). Studies have revealed that COOH-terminal palmitoylation is crucial for caveolin-1 to attach to the plasma membrane (Sowa et al., 2003). Both phosphorylation and palmitoylation occur intracellularly (Sargiacomo et al., 1993). Caveolin-1 interacts with a variety of signaling molecules, including endothelial nitric oxide synthase (eNOS), heterotrimeric G proteins, adhesion molecules, nonreceptor tyrosine kinases, Src-family tyrosine kinases, and p42/44 mitogen-activated protein kinase (MAPK). Residues 82-101 in the N-terminal region are called the caveolin-1 scaffolding domain (CSD) and serve to bind other molecules to the cell membrane (Arbuzova et al., 2000). Couet et al. found that the CSD was the area where caveolin-1 interacted with signaling molecules indicating that the CSD is the most important functional area of caveolin-1 (Couet et al., 1997). Some factors have been identified that interact with the CSD and regulate caveolin-1 activity.

Caveolin-1 Regulation in the Human Body

In the pre-transcriptional and transcriptional stages, caveolin-1 is regulated mainly through cell signaling pathways. During the post-transcriptional stage, expression is mainly regulated through ubiquitination and lysosomal degradation. Caveolin-1 is degraded in the late endosome and lysosome. Generally speaking, the velocity of degradation is very slow. However, if caveolin-1 assembly is altered, the rate of decomposition is accelerated. The most likely explanation for this phenomenon is cholesterol consumption, which would inhibit the assembly of complete cytoskeletal proteins and cause caveolin-1 to be more easily decomposed (Hayer et al., 2010).

During both transcription and translation, caveolin-1 expression is influenced by a variety of factors (mainly multiple signal transduction pathways) which results in changes to cellular physiological processes. The following sections detail how caveolin-1 expression is regulated.

Significance of pre-transcriptional caveolin-1 regulation in pancreatic cancer

Pre-transcriptional regulation of caveolin-1 is mainly controlled by transcription factors and transcription-related factors.

Forkhead box (FOXO): FOXO transcription factors are of vital importance in cellular proliferation, metabolism, and apoptosis downstream of PTEN, phosphoinositide 3-kinase (PI3K), and AKT (Eijkelenboom et al., 2013). In the stationary phase of cell growth, FOXO induces stable expression of insulin receptors and regulates caveolin-1 through the PI3K/AKT/FOXO pathway (Boreddy et al., 2011). Vanden et al. found that active FOXO binds directly to the caveolin-1 promoter and activates transcription (Van et al., 2005). In pancreatic cancer, Roy SK et al. found that inhibition of the PI3K/AKT and MAPK/extracellular regulated protein kinase (ERK) pathways activates FOXO transcription and caveolin-1 expression, leading to cell cycle arrest and apoptosis (Roy et al., 2010).

Lipopolysaccharide (LPS): LPS acts with NEMO [an essential modifier-binding domain of nuclear factor-kappa B (NF-κB)] to inhibit the formation of the IKK-γ and IKK complexes, thus preventing the activation of NF-κB (a family of transcription factors) and caveolin-1 expression in vivo (Tiruppathi et al., 2008). NF-κB is a key factor in the regulation of gene expression in response to a variety of stimuli, including bacterial lipopolysaccharide (LPS).
factor connecting inflammation with cancer progression. The idea that a tumor itself can act as a stimulator of chronic inflammation is becoming more widely accepted by oncologists (Zhu et al., 2008). Maier et al. found that NF-κB promotes epithelial-mesenchymal transition, migration, and invasion in pancreatic carcinoma cells (Maier et al., 2010). Ikebe et al. found that LPS promotes NF-κB activation and increases invasive ability through the TLR4/MyD88 signaling pathway (Ikebe et al., 2009).

**High density lipoprotein (HDL):** When NIH/3T3 cells are exposed to HDL, caveolin-1 promoter activity is inhibited. This phenomenon suggests that HDL has direct negative impact on caveolin-1 transcription. Further research revealed that HDL can downregulate caveolin-1 expression without affecting caveolin-2 expression by activating the MAP kinase pathway through ERK1/2 activation (Frank et al., 2001). We also know that a high-fat diet is a risk factor for pancreatic cancer and a high-fat diet increases caveolin-1 (Yang et al., 2007).

**Stimulatory protein 1 (Sp1):** Sp1 is one of the two transcription factors that bind the caveolin-1 gene and affect promoter activity (Chen et al., 2011). Sp1 is a central transcription factor that regulates a number of pathways critical to tumorigenesis, including tumor cell-cycle progression, apoptosis, angiogenesis, metastasis, and evasion of the immune system (Huang et al., 2012). Dasari et al. showed that oxidative stress enhances Sp1-stimulated caveolin-1 expression. In addition, other studies have shown that p38 MAPK is an oxidative stress-induced upstream regulatory factor of Sp1. Inhibition of p38 MAPK prevents oxidative stress from inducing Sp1-mediated caveolin-1 gene expression and premature cell aging (Dasari et al., 2006). Sp1 activation is also essential for the differential overexpression of vascular endothelial growth factor (VEGF), which is involved in pancreatic cancer angiogenesis and progression (Shi et al., 2001).

**Estrogen receptors (ERs):** Estrogens are major promoters of cell proliferation in both normal and neoplastic epithelium. Two major ERs are ERα and ERβ (Kimbro et al., 2008). ERα acts as an estrogen transcription factor that stimulates estrogen target genes and regulates cell progression and growth, especially in breast epithelium (Singh et al., 2005). In neuroepithelioma cells, ectopic ERα inhibits caveolin-1 transcription and the caveolin-1 promoter is methylated (Zschock et al., 2003). However, because caveolin-1 mutations occur in the early stages of mammary transformation, this observation suggested that caveolin-1 might be an upstream activator of ERα (Sotgia et al., 2006). There may be negative feedback regulation of caveolin-1 as the proliferation of pancreatic cancer cells is highly sensitive to estrogen in vitro (Konduri et al., 2007).

**Significance of caveolin-1 transcription regulators in pancreatic cancer**

**p53:** p53 is the strongest tumor suppressor gene and it regulates apoptosis, cell cycle arrest, and senescence (Lee et al., 2011). p53 binds directly to the caveolin-1 promoter with the EZF/DP-1 and Sp1 transcription factors, thus increasing caveolin-1 expression (Lee et al., 2012). In human pancreatic ductal adenocarcinoma, low p53 transcript levels are associated with poor prognosis (Grochola et al., 2011). Much evidence indicates that p53 provokes a classic proapoptotic response by delaying G1-to-S progression (Gupta et al., 2010).

**Cholesterol:** Cholesterol is also a powerful regulator of gene expression. It carries out this activity by jointly binding the sterol regulatory element binding protein (SREBP) with Sp1. KLF11 [a Krüppel-like factor; also referred to as transforming growth factor-beta early inducible gene 2 (TIEG2)] inhibits Sp1/SREBP cholesterol-dependent gene expression (Llaverias et al., 2004). High cholesterol intake increases in the incidence of pancreatic cancer (Takeyama et al., 2005).

**Carbon monoxide (CO):** CO (a product of hemeoxygenase activity) is an endogenous gaseous transmitter that exerts anti-proliferative effects (Schwer et al., 2013). CO affects caveolin-1 gene expression by activating guanylate cyclase and p38 MAPK. p38 MAPK down-regulates ERKs that inhibit caveolin-1 gene transcription (Kim et al., 2005). In pancreatic cancer, CO protects cells from apoptosis. Protection is mediated through the generation of cyclic GMP (cGMP) and the activation of cGMP-dependent protein kinases and guanylate cyclase (Gunther et al., 2002).

**Vascular endothelial growth factor (VEGF):** VEGF is a key mediator of angiogenesis and promotes proliferation, survival, migration of endothelial cells, and blood vessel formation and neovascularization (Ferrara et al., 2002). On the one hand, Liu J et al. found that activation of the VEGF/MEK signal transduction pathway decreased caveolin-1 while leaving caveolin-2 unchanged in human umbilical vein endothelial cells (Liu et al., 1999). In prostate cancer cells, the protein kinase CMEK/c-myc gene androgen receptor pathway increases caveolin-1 (Wu et al., 2002). On the other hand, caveolin-1 also stimulates expression of VEGF via Akt activation (Li et al., 2009). VEGF is a well-characterized mediator of tumor angiogenesis and functions primarily by binding and activating the VEGF receptor 2. Angiogenesis is a characteristic of many malignant tumors, including pancreatic cancer (Dineen et al., 2008).

**Epithelial membrane protein 2 (EMP2):** EMP2, a tetraspan protein, facilitates plasma membrane delivery of certain integrins. EMP2 also contributes to the formation and trafficking of lipid rafts bearing glycosylphosphatidyl inositol anchored proteins (GPI-Aps), thus reducing caveolin-1 expression (Wadehra et al., 2004). Down-regulation of caveolin-1 by EMP2 does not affect caveolin-1 translational efficiency, phosphorylation, or degradation. Protein half-life analysis showed that caveolin-1 decomposition was more rapid when mediated by EMP2 (Forbes et al., 2007).

**eNOS:** The eNOS protein binds caveolin-1 through its CSD (Razani et al., 2002). Caveolin-1 also functions as an eNOS inhibitor with a calcium/calmodulin cofactor (Ju et al., 2002). Enhanced renal caveolin-1 expression is linked to poor eNOS expression (Valles et al., 2007). Increased caveolin-1 is associated with inhibition of the catalytic activity of eNOS (Venema et al., 1997). There may be a feedback regulator to caveolin-1. In the model of pancreatic cancer liver metastasis, eNOS overexpression...
attenuates both the number and size of tumors. In vitro, NO promotes tumor cell anoikis and limits invasive capacity (Decker et al., 2008).

Reactive oxygen species (ROS): ROS are produced by cellular aerobic metabolism (Gough et al., 2011). Cells treated with oxidation have increased tyrosine kinase activity and decreased phosphatase activity (Vepa et al., 1997). Rungtabnapa found that catalase and N-acetylcysteine promote the ubiquitination and degradation of caveolin-1. In addition, exogenous hydrogen peroxide prevents the formation of the caveolin-1-ubiquitin complex and inhibits caveolin-1 reduction (Rungtabnapa et al., 2011). Endogenous hydrogen peroxide also prevents the transport of newly synthesized caveolin-1 to the cell membrane. Palmitoylation of caveolin-1 is significantly inhibited in endothelial cells exposed to hydrogen peroxide (Parat et al., 2002). Park JH et al. found that hydrogen peroxide and methyl-beta-cyclodextrin down-regulate caveolin-1. In pancreatic cancer, NADPH oxidase 4-mediated generation of ROS is proposed to have anti-apoptotic activity and thus confer a growth advantage to cancer cells. ROS transmit cell survival signals through the AKT/ASK1 pathway and their depletion leads to apoptosis (Mochizuki et al., 2006).

Src kinase: Src family kinases regulate cell proliferation, adhesion, and motility. They are frequently activated in human cancers and contribute to malignancy and metastasis (Di et al., 2011). Src kinase increases as a function of tumor progression and plays a role in the transition to malignancy. Further, it is associated with phosphorylation of the caveolin-1 gene Y14. More than 60% of pancreatic cancer patients show increased c-Src activity, which is associated with poor prognosis (Shields et al., 2011). Src/Stat3 signaling plays a crucial role in tumor cell survival, proliferation, angiogenesis, and immune suppression (Nam et al., 2012).

Others: There are additional cellular signaling pathways, like transforming growth factor/PI3K, histone deacetylase, and cAMP that are associated with caveolin-down-regulation that are not mentioned here (Zschocke et al., 2005). In contrast, oxidized LDL increases caveolin-1 expression (Wu et al., 2009).

Post-transcriptional regulation
Post-transcriptional regulation of caveolin-1 mainly occurs through the deacetylase, and cAMP that are associated with caveolin-down-regulation that are not mentioned here (Zschocke et al., 2005). In contrast, oxidized LDL increases caveolin-1 expression (Wu et al., 2009).

Na+/K+-ATPase: High metabolism is a characteristic of malignancies and Na+/K+-ATPase provides energy for cellular metabolism. Na+/K+-ATPase is an important enzyme in the protein transport process. Cai T et al. found that caveolin-1 was significantly reduced on the cell surface when the Na+/K+-ATPase gene was knocked out. This is due to unilateral regulation of the transport process by Na+/K+-ATPase rather than an interaction between Na+/K+-ATPase and caveolin-1 (Cai et al., 2009).

Breast cancer susceptibility gene 1 (BRCA1): BRCA1 is involved in multiple processes, such as cell growth, apoptosis, DNA damage repair, and transcriptional activation. In immunofluorescence studies, Wang Y et al. showed that BRCA1 might inhibit the invasive and metastatic abilities of cancer cells by inducing the redistribution of caveolin-1. In addition, the BRCA1 gene inhibits redistribution of caveolin-1 in the cell membrane and cytoplasm (Wang et al., 2008). BRCA1 mutations have been shown to drastically decrease survival rate in breast and ovarian cancer patients who carry them. A number of studies have shown that the third most common cancer associated with these mutations is pancreatic cancer (Lynch et al., 2005).

Flotillin-1: Flotillins are localized to lipid rafts independent of caveolin-1 and are the principal proteins associate with lipid rafts. These microdomains function in roles such as membrane trafficking, cell morphogenesis, and cell signaling (Evans et al., 2003). Flotillin-1 regulates caveolin-1 levels by preventing its degradation in lysosomes (Vassilieva et al., 2009).

Relationship between Caveolin-1 and Pancreatic Cancer
Pancreatic cancer progression is attributed to genetic and epigenetic alterations and a chaotic tumor microenvironment (Huang et al., 2012). Recent studies suggest that caveolin-1 plays important roles in promoting cancer cell development, migration, invasion, and metastasis (Thomas et al., 2011). Further research also suggests that caveolin-1 can impact cancer biology both positively and negatively. In tumor tissue, both tumor cells and blood vessels express caveolin-1. However, in peritumoral tissue caveolin-1 is mainly expressed in blood vessels and only occasionally expressed in ductal or parenchymal cells. Overexpression of caveolin-1 is associated with tumor size, grade, stage, and increased serum levels of CA19-9 (Tanase et al., 2009).

Caveolin-1 has recently been identified as a tumor metastasis modifier gene that affects cancer cell motility (Koleske et al., 1995; Yang et al., 1999). In contrast, loss of caveolin-1 leads to RhoC-mediated migration and invasion in metastatic pancreatic cancer cells (Thomas et al., 2011). Data also indicates that caveolin-1, with its dual function in cancers, is associated with tumor progression and inhibits proliferation and invasion (Mathew et al., 2011). Tumor cells have significantly higher caveolin-1 levels, especially in the tumor stroma. Caveolin-1 knockdown significantly induces cell apoptosis and enhances the radio sensitivity of cancer cells (Hehlsgans et al., 2009).

The caveolin-1 gene inhibits invasion of pancreatic carcinoma cells likely through the Erk/MMP signal pathway, however, the mechanism remains unclear. This suggests that endogenous expression or re-expression of caveolin-1 could act to reduce the potential invasiveness of cancer cells (Han et al., 2010). Together, these findings strongly imply that caveolin-1 plays a critical role in pancreatic cancer development and progression and is a valuable biomarker for the disease. The majority of normal and adjacent normal pancreatic tissue cells are negative for caveolin-1, whereas pancreatic cancer tissue cells and stromal cells are strongly positive for caveolin-1. Caveolin-1 expression is positively correlated with tumor differentiation, disease stage, and tumor metastasis.
Caveolin-1 is also an oncogene that could promote invasion. In summary, a variety of data indicates that caveolin-1 might be a good candidate for a prognostic tumor marker and a potential target for therapeutic intervention (Bailey et al., 2008).

Five year view

Caveolin-1 is involved in a variety of cellular signal pathways and transmembrane transport. It is generally accepted that signaling proteins are proposed to use conserved caveolin-binding motifs (CBMs) to associate with caveolae via CSD. However, Collins BM et al. found CBM/CSD-dependent interactions are unlikely to mediate caveolar signaling (Collins et al., 2012). Its precise role as a tumor suppressor or oncogene in different human malignancies remains elusive. Caveolin-1 regulates a variety of cellular events that include cellular transformation, tumorigenesis, cell metastasis, and angiogenesis. It is interesting to note that caveolin-1 is reduced in pancreatic cancer compared to normal tissue in precancerous tumors, such as pancreatic intraductal papillary-mucinous neoplasms (Terris et al., 2002). Caveolin-1 contributes to cellular resistance against genotoxic agents and thus its knockdown sensitizes human pancreatic tumor cells to ionizing radiation (Cordes et al., 2007). Based on this observation, caveolin-1 appears to be a tumor suppressor in pancreatic cancer. However, it is highly expressed in invasive tumors compared to noninvasive tumors (Terris et al., 2012). Huang C et al. found the FoxM1-caveolin signaling promotes pancreatic cancer invasion and metastasis (Huang et al., 2012). This review detailed the mechanisms that regulate caveolin-1 expression in vivo and their significance in pancreatic cancer. Other mechanisms are being actively explored. At present, a variety of factors, such as HDL, SREBP1, and epidermal growth factor receptor, that regulate the expression of caveolin-1 have been identified, but the precise regulatory mechanisms remain unclear. In-depth research in this field will improve our understanding of pancreatic cancer and potentially highlight novel diagnostic methods and anti-cancer strategies.

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