Review Article CODEN: IJPRNK Impact Factor: 5.567 ISSN: 2277-8713
Jegan Sakthivel, IJPRBS, 2017; Volume 6(2): 196-209 IJPRBS

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

CAVEOLIN (CAV-1) AS A CLINICAL BIOMARKER FOR CANCER

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Accepted Date: 23/04/2017; Published Date: 27/04/2017

Abstract: More than fifty years ago caveolae were discovered and marked as a new endocytic mechanism. Later it was found that they are formed in microdomains of the plasma membrane, called lipid rafts. The caveolar endocytotic route is known to transport several molecules like, membrane components and growth receptors into the cell. The main functional components of caveolae are the caveolins, caveolin-1, caveolin-2 and caveolin-3. These proteins are not only necessary for caveolae formation and dynamics, but are also involved in the regulation of several signaling molecules. Caveolae may play a role in tumorigenesis. In this review we aim to discuss the recent progress in our understanding of the role of caveolins in cancer. Caveolin-1 is known to act as both, a tumor suppressor and an oncoprotein, here we will explain how this difference is established.

Keywords: Caveolae, Caveolin, cancer, tumour, cell lines.

PAPER-QR CODE

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Access Online On:

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How to Cite This Article:

Jegan Sakthivel, IJPRBS, 2017; Volume 6(2): 196-209

INTRODUCTION

Caveolin-1 (cav-1) is the essential constituent protein of specialized membrane invaginations called caveolae [1, 2]. The caveolin family is highly conserved with inter-species sequence homology and includes caveolin-1, 2 and 3. Caveolae occur in terminally differentiated cells, aside from lymphocytes and central nervous system neurons, with abundance in adipocytes, endothelial cells, type-I pneumocytes, fibroblasts and muscle cells. Caveolin is not only involved in endocytosis, but also in the regulation of signaling, as many signaling molecules can bind to the scaffolding domain of caveolin and others to phosphorylated caveolin (Y14). Since the late 1980's it has been suggested that caveolin is involved in cancer.

Structure of caveolin

Caveolin is a 22 kDa molecule, which was first identified in 1992 as a component of the caveolae endocytosis machinery. Almost at the same time, an integral membrane protein of transport vesicles, VIP21 (Vesicular Integral-membrane Protein of 21 kDa), was cloned. This protein is involved in trafficking from the Golgi complex to the plasma membrane in MDCK (Madin Darby canine kidney) cells. The cDNA of caveolin and VIP21 is identical which suggests that caveolin/VIP21 not only plays a role in endocytosis, but also in trafficking from Golgi to the plasma membrane. Later, two other gene family members were discovered, named caveolin-2 and caveolin-3.

Caveolin-1 is an integral membrane protein, with both the amino- and carboxy-terminus directed to the cytoplasm (figure 1). Caveolin can be phosphorylated at tyrosine residue 14 by tyrosine kinases, like Src, Fyn and Abl. Phosphorylation of this residue will increase the induction of endocytosis, signal transduction, cell migration and mechanotransduction as SH-2 domain proteins are able to bind [18].

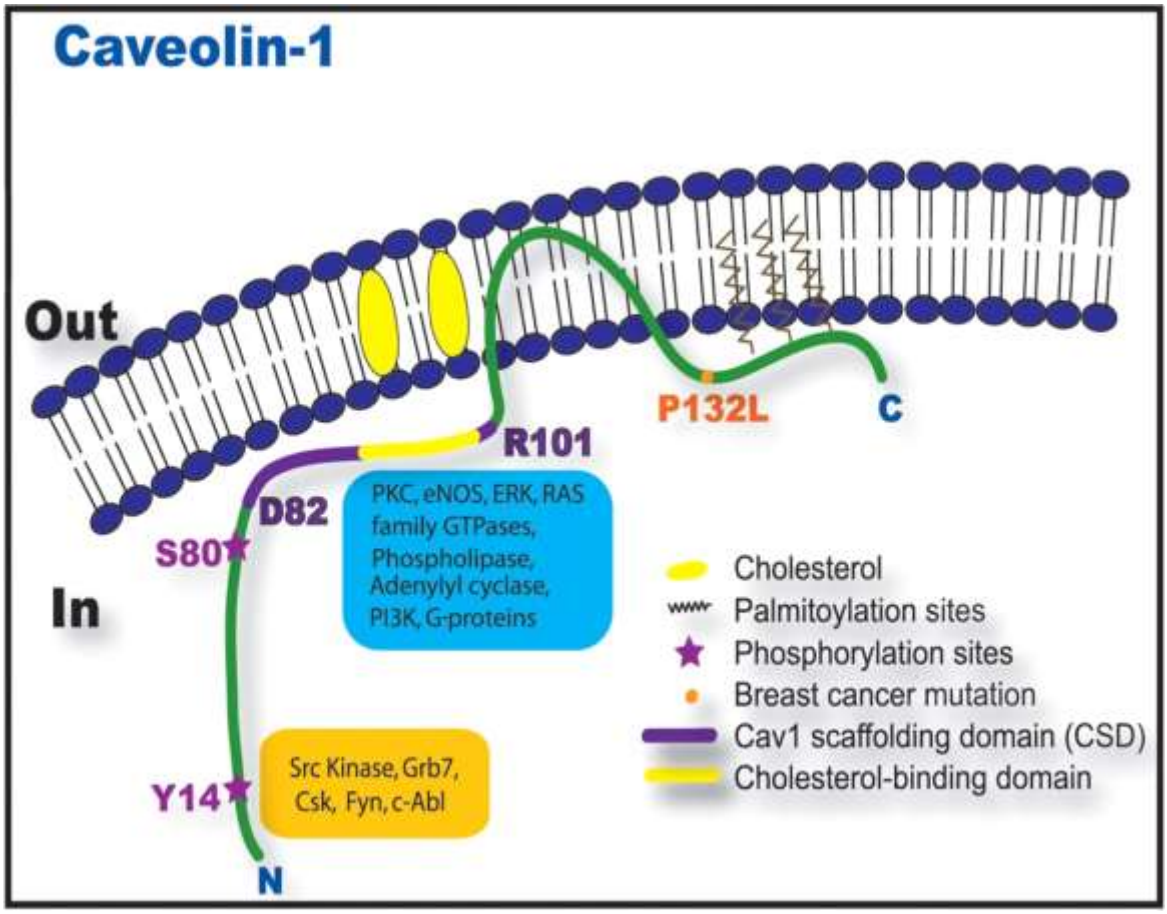

Fig. 1: Structural characteristics of Caveolin-1

Residues 82-101 of the amino terminus are called the caveolin scaffolding domain (CSD) has the sequence DGIWKASFTTFTVTKYWFYR. This domain can bind to molecules containing the caveolin-1 binding motif, ZXZXXXXZ or ZXXXXZXXZ. Z stands for the amino acids Phenylalanine (F), Tryptophan (W) or Tyrosine (Y). X stands for any amino acid [2, 19]. Several well-known signaling molecules bind to this domain, like Src family tyrosine kinases , endothelial nitric oxide synthase (eNOS), c- Neu, H-Ras and G-protein-coupled receptors (figure 2). [3-5].

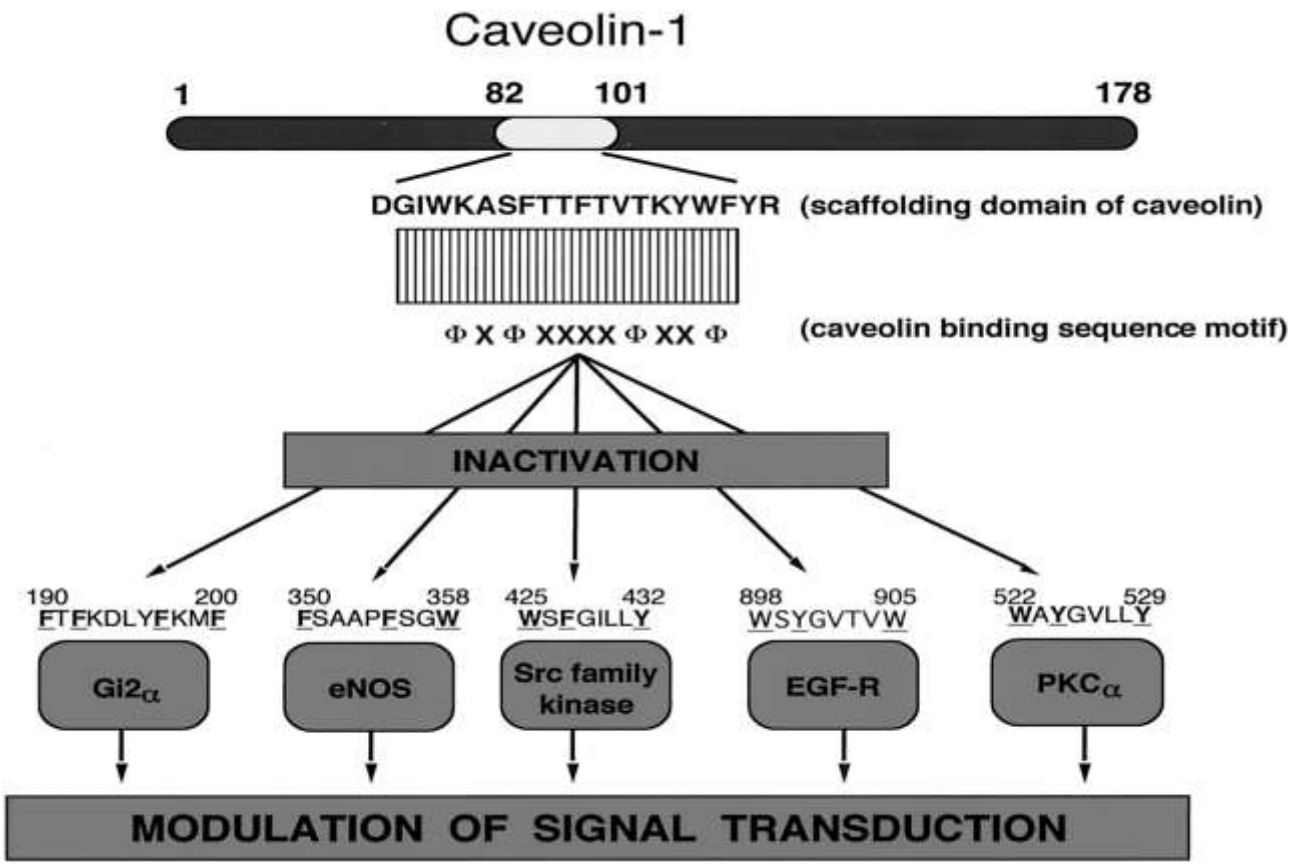

Fig. 2: Caveolin scaffolding domain (CSD) with sequence DGIWKASFTTFTVTKYWFYR. This domain can bind to molecules containing the caveolin-1 binding motif, ZXZXXXXZ or ZXXXXZXXZ

Caveolin and its link with cancer

Caveolin-1 was identified as a protein phosphorylated when studies was carried out on Rous sarcoma virus in chick embryo fibroblasts [3]. Beside Gag, Pol and Env proteins, the virus also contains Src kinase, which phosphorylates caveolin-1 on a tyrosine residue in infected cells. Due to this observation, the presence and phosphorylation of caveolin-1 were associated with events involved in cell transformation.

It was found that the Caveolin scafolding domain of caveolin can bind to many signaling proteins. Many of these signaling proteins are known as proteins encoded by proto-oncogenes, such as the tyrosine kinase Src. By the binding of the signaling molecules, proteins are clustered at the plasma membrane. Due to this clustering, signaling can be enhanced. Caveolin-1 can also interact directly with many of these molecules and thereby influence the oncogenic activity of the proteins. An example of such direct interaction is the inhibition of heterotrimeric G-proteins by the CSD. This binding will inhibit GDP/GTP exchange, whereby the protein cannot be activated

[4]. Heterotrimeric G-proteins are known proto-oncogenes as they can activate the Ras/MEK/ERK pathway. It was found later that the CSD of caveolin-1 is involved in the negative regulation of other proto-oncogenic signaling proteins, like the auto phosphorylation of Src kinase [5], EGFR cross-auto phosphorylation, H-Ras and c-Neu. These proteins are all known to be important players in cell transformation and tumor formation, as they are activators of several important pathways like the RAS/MEK/ERK, PI3kinase and JAK/STAT pathway. These pathways are involved in proliferation, survival and cell division.

The signaling proteins which are summarized above, all have the same caveolin binding domain in their kinase domain. Binding to this motif to caveolin-1 induces an inhibition of the kinase activity [6]. This suggests a general kinase inhibition activity for caveolin-1. The inhibiting role of caveolin on these proteins indicates that caveolin can be negatively involved in tumor formation.

Functional implications of caveolin signaling protein-oncogensis

During progression from a normal epithelium to invasive or metastatic cancer, cells accumulate a combination of defects, including mutational activation of oncogenes such as Ras or Myc and inactivation of tumor suppressor genes like p53 [7]. As a general consequence, several signal transduction pathways become constitutively activated, leading to enhanced cell proliferation, loss of adhesion, and a transformed phenotype coupled with insensitivity to apoptosis [8-10].

Caveolin-1 interacts directly with and inhibits or sequesters the inactive form of many key signaling molecules including heterotrimeric G proteins, Ha-Ras, c-Src, endothelial nitric oxide synthase, protein kinase C , MAPK, 3 and tyrosine kinase receptors via a motif referred to as the scaffolding domain [11 –13]. Additionally, many of the aforementioned proteins contain a consensus motif for caveolin-1 binding. Thus, caveolin-1 may induce cell tumorigenicity by virtue of its ability to bind to and inhibit or sequester inactive forms of signaling proteins [14].

CSD of caveolin-1 also inhibits growth factors by inhibition of the tyrosine kinase activity of the receptors. For example the TGF-β receptors (type I and II) colocalize with caveolin-1 positive compartments (15). Normally receptor type I phosphorylates receptor type II, which activates the SMAD pathway. If caveolin-1 is overexpressed in fibroblasts, it was found that TGF-β signaling is decreased by inhibition of the SMAD pathway. The SMAD pathway is involved in the transcription of growth factors. The CSD of caveolin-1 can interact with the TGF-β receptor type I, whereby its kinase activity is inhibited. The negative regulation of caveolin-1 on the tyrosine kinase domain of a receptor (like TGF-β, EGFR and PDGFR) can be regulated via the binding of caveolin which stabilizes the kinase compartment of the receptor in an inactive conformation.

Another possibility found was that dimerization of the receptor is inhibited (necessary for auto-phosphorylation of EGFR receptor and type I and II TGF-β receptor), whereby activation via transphosphorylation is inhibited. However, caveolin-1 can also negatively regulate the auto-activation of Src kinase, which does not need to form dimers for activation [17], suggesting that another mechanism or multiple mechanisms are used by caveolin-1 for inhibition of kinases. Via the inhibition of tyrosine kinase receptors like the TGF-β receptor type I and EGFR, caveolin-1 inhibits growth factor pathways.

Both caveolin-1 and caveolin-2 are localized on chromosome locus 7q31.1, near the often mutated D7S522 genetic marker. In several epithelial cancers (e.g. breast, ovarian, renal and prostate) mutations are found in the region around the D7S522 marker which is therefore known as a fragile region (named FRA7G), a region often affected in cancer.

Thus based on these information, it is evident that though Caveolin-1 (cav-1) is involved in multiple cellular processes such as molecular transport, cell adhesion and signal transduction, cav-1 is also contributes to malignant progression. A high level of intracellular cav-1 expression is associated with metastatic progression of human prostate cancer and other malignancies, including lung, renal and esophageal squamous cell cancer which are discussed in the remainder of these review

STUDY OF CAVEOLIN IN DIFFERENT CANCER TYPES

Role of caveolin-1 in prostrate cancer

Caveolin-1 (cav-1) is reportedly over-expressed in prostate cancer cells and is associated with disease progression. Prostate cancer cell lines reportedly secrete biologically active cav-1 protein in vitro, and cav-1 promotes prostate cancer cell viability and clonal growth. In addition to showing cav-1-mediated autocrine activities, a recent study showed that recombinant cav-1 protein is taken up by prostate cancer cells and endothelial cells in vitro and that recombinant cav-1 increases angiogenic activities both in vitro and in vivo by activating Akt- and/or nitric oxide synthase mediated signaling. Moreover, significantly higher serum cav-1 levels have been documented in men with prostate cancer than in men with benign prostatic hyperplasia [20-21].The molecular basis for the initiation of cav-1 expression in prostate cancer and other malignancies is not clear. However, it is important to note that cav-1 is expressed in most metastatic cells [22]. This focal expression in primary prostate cancer and significantly increased cav-1 expression in associated metastases fit well with the notion that cav-1 is more aligned with the criteria of a progression-related protein than with those of a protein that significantly affects localized tumor growth.

The androgen receptor (AR) is involved in the development and maintenance of the normal prostate and the development and progression of prostate cancer (PCa). Caveolin-1 (cav-1) is an AR co-regulator. The expression of this integral membrane protein is upregulated in PCa and correlates positively with its development [23]. Mechanisms for abnormal AR activation in PCa have now been identified, including somatic missense mutations of the AR gene, altered growth factor signaling and subsequent kinase activation of AR, AR gene amplification and upregulation of AR co-activators and/or downregulation of AR co-repressors [24]

In other studies, cav-1 levels have been linked to cancer aggressiveness and cell transformation. For example, although the offspring of TRAMP (transgenic adenocarcinoma of mouse prostate) and cav-1 dual knockout mice developed cancer, progression to invasive metastatic disease was significantly reduced, with reductions in tumor size, numbers and metastases in lymph nodes and lungs [25].

Role of caveolin-1 in breast cancer

Owing to the pivotal roles played by caveolin-1 in signalling cascades, it is perhaps unsurprising that overexpression has been reported to play a role in invasion, metastasis of breast cancer cell lines. There are several In vitro and In vivo studies suggesting oncogenic function and contribution to the malignant phenotype. Overexpression in the Hs578T cell line correlates with colony fomation in soft agar and reduced apoptosis [26]. MCF7 cells transfected with human CAV1 exhibit inhibition of anoikis with improved survival after detachment. There is suppression of detachment-induced p53 activation and consequent induction of cyclin-dependent kinase inhibitor p21WAF1/Cip1.

Caveolin-1 appears to enhance matrix-independent survival by upregulation of IGF-I receptor. Constitutively phosphorylated Akt is also exhibited, suggesting positive regulation of this survival pathway [27]. Rho/ROCK signalling has been shown to promote migration and invasion by regulating focal adhesion dynamics through Src-dependent caveolin-1 tyrosine-14 phosphorylation [28].

Caveolin-1 expression is inversely associated with steroid hormone receptor and HER2 positivity. Caveolin-1-positive breast cancers often exhibit a basal-like phenotype (40.5–52%) [29, 30]. In addition, 90% of metaplastic breast cancers, tumours that consistently display a triple-negative phenotype, have been shown to express caveolin-1.

The distribution of caveolin-1 expression within distinct components of breast cancer, namely, neoplastic epithelial cells or stromal tissues may be associated with compartment specific roles. Caveolin-1 expression is inversely associated with steroid hormone receptor positivity, human epidermal growth factor receptor 2 (HER2) status and cyclin D1, but positively associated with

histological grade; epidermal growth factor receptor (EGFR); cytokeratins 5/6, 14 and 17; MIB-1 and p53 positivity [31]

A change in CAV1 expression patterns was noted in the tumor microenvironments that favor cell elongation and microenvironment stiffening. In metastasized human carcinomas, CAV1 expression in enhanced in carcinoma-associated fibroblasts (CAFs) [32]. Both *in vitro* and *in vivo* models, CAV1 expression in CAFs consistently favors tumor invasiveness, thus promoting metastasis and further progression of the disease and a poor survival rate. A clinical study in patients with triple negative (ERα-, PR-, and HER2) and basal-like breast cancers, the two most aggressive types, showed an association of loss of CAV1 expression in the stroma with poor prognosis [33].

Caveolin-1 in brain tumors

The in vitro characterizations of the role of Cav-1 in Glioblastoma Multiforme **(**GBM) have largely been undertaken by Martin and colleagues, where Cav-1 was identified as a tumor suppressor, affecting proliferation in part through modulating TGFB/SMAD signaling [34]

In a new study, researchers expanded upon this previous work by creating a stable Cav-1 overexpressing cell line based on the common GBM-derived cell line U-87MG. Microarray analyses comparing Cav-1-overexpressing cells to control cells established that critical cell cycle genes and cell survival proteins and pathways, such ascyclin D1 and AKT/mTOR, respectively, were downregulated. Perhaps more importantly, using a mouse xenograft model, they found that Cav-1-overexpressing tumors were significantly less proliferative and less invasive when compared with control cells, with explanted tumors displaying marked silencing of cell cycle and protein biosynthetic pathways. Finally, Cav-1-overexpressing cells were found to be sensitized to the antitumor effects of the most commonly used chemotherapy agent, temozolomide, and were significantly more likely to undergo apoptosis after treatment as compared with controls cells. These results extend the role of Cav-1 into the prognosis and possibly the treatment of GBM. Interestingly, one of the most frequent point mutants in GBM occurs in the tumor suppressor protein, p53 [35, 36].

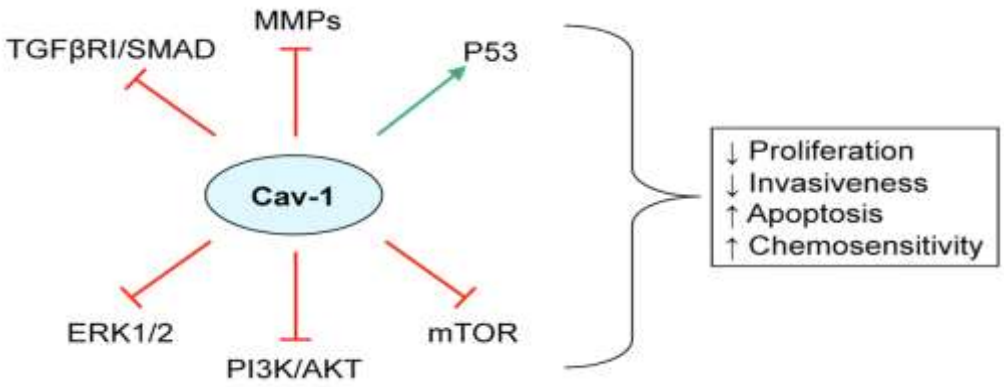

Fig. 3: Caveolin-1 plays a central role in glioblastoma multiforme onset and progression and may be a biomarker for sensitivity to chemotherapy. Red lines denote genes or pathways inhibited by Cav-1, while green lines indicate those that are upregulated.

Caveolin-1 in colon cancer

Caveolin-1 has been implicated in the process of cell transformation: caveolin-1 is a major substrate for phosphorylation on tyrosine upon cell transformation by the Rous sarcoma virus [37]; caveolin-1 mRNA and protein levels are reduced in NIH-3T3 fibroblasts transformed by several oncogenes [38]; and caveolin-1 levels are reduced in a variety of carcinoma cell lines, including human mammary carcinoma [39] and lung carcinoma cells [40]. These results suggest that reduced caveolin-1 expression may represent a general characteristic or even a requirement of transformed cells and that caveolin-1 could play a central role as an inhibitor of tumor formation.

Caveolin-1 interacts directly with and inhibits or sequesters the inactive form of many key signaling molecules including heterotrimeric G proteins, Ha-Ras, c-Src, endothelial nitric oxide synthase, protein kinase C a, MAPK,3 and tyrosine kinase receptors via a motif referred to as the scaffolding domain. Additionally, many of the aforementioned proteins contain a consensus motif for caveolin-1 binding [40, 41]. Thus, caveolin-1 may reduce cell tumorigenicity by virtue of its ability to bind to and inhibit or sequester inactive forms of signaling proteins including oncogenes.

Caveolin-1 expression and function were investigated in human colon cancer. Low levels of caveolin-1 mRNA and protein were detected in several colon carcinoma cell lines. Moreover, caveolin-1 protein levels were significantly reduced in fold) when compared with normal colon mucosa for a majority (10 of 15) of the patients characterized.

To directly assess the role of caveolin-1 in tumor development, caveolin-1 was reexpressed in the HT29 and DLD1 colon carcinoma cells, and the resulting HT29-cav-1 or DLD1-cav-1 cells were

tested for tumorigenicity in nude mice. In most experiments, tumor formation was either blocked or retarded for HT29-cav 1 cells (10 of 13 mice) and DLD1-cav-1 cells (5 of 7 mice), as compared with both mock transfected and parental HT29 or DLD1 cells. Interestingly, basal caveolin-1 levels were significantly reduced in HT29-cav-1 and DLD1-cav-1 cells isolated from tumors. Likewise, endogenous caveolin-1 mRNA and protein levels were found to be reduced in NIH-3T3 cells recovered from tumors after injection into nude mice. Thus, re expression of caveolin-1 in colon carcinoma lines reduced the probability of tumor formation *in vivo*, and when tumors did develop from either HT29-cav-1, DLD1-cav-1, or NIH-3T3 cells, lower basal levels of caveolin-1 were detected [37, 41]

CONCLUSION

CAV1 has diverse functions in relation to tumorigenesis, growth, progression, and treatment. Unfortunately, there has been much discord between researchers in providing an absolute set of definitions to CAV1 in breast cancer considering is variable effects based on tumor subtype, stage, micro environment and treatment. CAV1 expression depends of a wide variety of factors and it is becoming evident that any clinical use of CAV1 as a biomarker in conjunction with therapy has to be tumor subtype- and treatment-specific. A large volume of work so far suggests an important role for CAV1 in different subtypes of cancer, perhaps more as a potential clinical biomarker rather than a therapeutic target. With consensus and collaboration among researchers regarding the standardization of immunohistochemistry techniques, for example, it is possible to use CAV1 as a tool to select therapeutic options in cancer. Moreover, there are still many unanswered questions for CAV1 function in regulating cancer progression, for example in regulating cellular metabolism. Thus, with a clearer understanding of CAV1-mediated signaling in specific subtype of cancer, we will be better equipped to use CAV1 as a clinical biomarker for choosing therapeutic options for specific tumors.

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