The Caveolin-1 Connection to Cell Death and Survival

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Abstract: Caveolins are a family of membrane proteins required for the formation of small plasma membrane invaginations called caveolae that are implicated in cellular trafficking processes. In addition to this structural role, these scaffolding proteins modulate numerous intracellular signaling pathways; often via direct interaction with specific binding partners. Caveolin-1 is particularly well-studied in this respect and has been attributed a large variety of functions. Thus, Caveolin-1 also represents the best-characterized isoform of this family with respect to its participation in cancer. Rather strikingly, available evidence indicates that Caveolin-1 belongs to a select group of proteins that function, depending on the cellular settings, both as tumor suppressor and promoter of cellular traits commonly associated with enhanced malignant behavior, such as metastasis and multi-drug resistance. The mechanisms underlying such ambiguity in Caveolin-1 function constitute an area of great interest. Here, we will focus on discussing how Caveolin-1 modulates cell death and survival pathways and how this may contribute to a better understanding of the ambiguous role this protein plays in cancer.

Keywords: Caveolin-1, cell death, metastasis, multi-drug resistance, proliferation, tumor suppression.

INTRODUCTION

Caveolins

Caveolins are 21-24 kDa membrane-associated proteins that are highly enriched in specialized, 50-100 nm omega-shaped invaginations of the plasma membrane referred to as caveolae [1]. Importantly, however, caveolae morphology can vary considerably from being flattened out within the plasma membrane, to individual invaginations of the membrane, multi-vesicular rosette-like structures or even tubule-like structures (see below). This family of proteins includes the three principle members, Caveolin-1, Caveolin-2 and Caveolin-3. Caveolin-1 and Caveolin-2 are present in many cell types and often co-expressed, while Caveolin-3 distribution is far more restricted and essentially limited to muscle and glia cells [2]. Caveolin-1 and -3 form homo-oligomers, and oligomerization is essential for caveolae biogenesis. Double knock-out mice for Caveolins-1 and -3 completely lack caveolae. Caveolin-2 forms hetero-oligomers with Caveolin-1 and requires Caveolin-1 presence for stability. Thus, Caveolin-1 knock-out mice also lack Caveolin-2 [3-5]. While Caveolins are essential, they are not necessarily sufficient for caveolae formation. In the absence of proteins called cavins, the formation of morphologically detectable caveolae or tubule structures is impaired [6-9]. In the absence of cavins, Caveolins associate with microdomains of the plasma membrane and persist there as planar caveolae [10].

Caveolins have been attributed multiple roles in cells besides caveolae formation, including vesicle trafficking, endocytosis, cholesterol homeostasis, as well as regulation of signal transduction, gene expression and protein turnover [10-11]. Since much of the information available with respect to these additional roles stems from studies dealing with the isoform Caveolin-1, we will center the rest of our discussion here on this isoform.

Caveolin-1

The Caveolin-1 sequence harbors a central hydrophobic domain (residues 102-134), which is thought to adopt a hairpin-like conformation that inserts into the inner leaflet of the plasma membrane. Consequently, both carboxy- and amino-termini face the cytoplasm. A modular sequence, referred to as the “Caveolin Scaffolding Domain” (CSD; residues 82–101) is located adjacent to the hydrophobic domain, in the amino-terminal region, and is required for homo- and hetero-oligomerization, as well as for interaction with a plethora of signaling proteins [3]. In the carboxy-terminal region, Caveolin-1 contains three palmitoylated cysteine residues that are important for oligomerization, but not localization to caveolae [12-13], as well as a putative WW-like domain (residues 98-132), in analogy to that described for Caveolin-3 [14-15].
Two variants of Caveolin-1 referred to as 1α (residues 1-174) and 1β (residues 34-174) can be distinguished, which are generated either from alternative transcripts or by alternative initiation from the same transcript [3, 16]. Both proteins are ascribed different roles in cells. Most notably, Caveolin-1α contains a tyrosine residue in position 14 that is phosphorylated in response to a large number of different stimuli. Often, but not always, non-receptor tyrosine kinases of the Src family are involved and phosphorylation is triggered as part of a so-called stress response [11]. The importance of Caveolin-1 in this context is underscored by the fact that Caveolin-1 knock-out mice display a remarkably reduced ability to regenerate specific tissues like the liver and also a dramatic decrease in life span [17-18]. Rather intriguingly, phosphorylation of Caveolin-1 is also considered highly relevant to cell migration and metastasis (see discussion later on). These examples suggest that Caveolin-1 is also important player in the regulation of signaling in cells.

Indeed, a large number of signaling pathways have been shown to be regulated by Caveolin-1 and such versatility highlights the importance of this protein and the potential for involvement in many pathologies, including cancer, where Caveolin-1 plays a highly ambiguous role that depends on a variety of factors as will be discussed [19]. An additional complexity is that, Caveolin-1 is found at the plasma membrane and also in other sub-cellular compartments, such as endoplasmic reticulum (ER), Golgi, endosomes, mitochondria and associated with the nucleus [20-22]. Thus, much of the existing confusion related to Caveolin-1 function that will be discussed, likely reflects the fact that it is often unclear which pool of Caveolin-1 is implicated in a specific event.

Initially, Caveolin-1 was proposed to behave as a tumor suppressor, since presence of the protein was associated with inhibition of signaling pathways that favored cell proliferation and viability, while promoting basal or stimuli-induced cell death. Moreover, Caveolin-1 expression was shown to revert characteristics associated with cell transformation and inhibit tumor growth. Conversely, at later stages of tumor progression, Caveolin-1 has been shown to promote tumor cell migration, multi-drug resistance and, therefore its presence correlates with poor patient prognosis. Whether Caveolin-1 elicits one or the other response seems dependent on the tumor type and the cellular context [11, 19]. In this review, we will focus predominantly on discussing the ability of Caveolin-1 to modulate processes associated with cell death and survival.

The Tumor Suppressor Hypothesis

Caveolin-1 was first described as a highly tyrosine phosphorylated substrate in Rous sarcoma virus-transformed fibroblasts, suggesting a role for the protein in the transformation process [23-25]. Later on, Caveolin-1 mRNA and protein levels were shown to be down-regulated in oncogene-transformed fibroblasts in culture [26] and re-expression of Caveolin-1 was sufficient to revert the transformed phenotype as well as prevent anchorage-independent growth of these cells [27]. In addition, Caveolin-1 down-regulation using antisense oligonucleotides is sufficient to drive NIH3T3 cell transformation [28]. Also, Caveolin-1 expression is reduced in several human tumors, including lung [29], mammary [30], colon [15, 31] and ovarian carcinomas [32], as well as sarcomas [32] and re-expression of Caveolin-1 often (but not always) results in reversal of characteristics associated with the transformed phenotype. Consistent with these results, lung hyperplasia and predisposition to mammary, as well as carcinogen-induced skin hyperplasia and tumor formation are observed in Caveolin-1 knock-out mice [4-5, 33-35]. These results indicate that Caveolin-1 displays properties and characteristics of a tumor suppressor molecule in a variety of cellular settings. However, data to the contrary is also available (see subsequent section).

Initially, loss of Caveolin-1 in tumors was associated with the observation that the Caveolin-1 gene localizes to the D7S522 locus, a site frequently deleted in human cancers [36]. Generally, however, loss of Caveolin-1 expression in tumors is now thought to occur via epigenetic mechanisms, including DNA methylation, rather than mutational changes. A detailed discussion of such mechanisms, as well as transcriptional pathways controlling Caveolin-1 expression can be found elsewhere [11]. However, a P132L mutation in Caveolin-1 was detected in 16% of human breast cancer patients analyzed in one study [37]. Rather intriguingly, this mutation results in a protein that acts as a dominant negative by promoting degradation of wild-type Caveolin-1 [38]. Additional mutations have been described in breast cancer since then [39]. Also, Caveolin-1 expression is regulated at the post-transcriptional level in a differential manner by ROS species and subsequent proteasome-mediated degradation [40]. To what extent this might be a relevant mechanism in the tumor environment remains to be established.

In summary, a variety of mechanisms have been described that may contribute to loss of Caveolin-1 without implicating the need for mutations. In conjunction, these posit Caveolin-1 as a non-conventional tumor suppressor protein.

Caveolin-1 in Multi-Drug Resistance and Metastasis

Caveolin-1 is reportedly also a protein that promotes more aggressive traits in tumor cells, such as metastasis and multidrug resistance. In normal prostate tissue Caveolin-1 is not expressed, but levels increase upon tumor formation in mouse models and human patients [41-44]. Moreover, Caveolin-1 favors metastasis of prostate cancer cells via an autocrine/paracrine mechanism [45-46]. Likewise, Caveolin-1 expression is increased in multi-drug resistant MCF7 breast cancer cells [47] and promotes anchorage-independent survival by preventing anoikis [48-49]. In patients, Caveolin-1 presence is associated with elevated
metastasis, multi-drug resistance and poorer prognosis [50-52]. Interestingly, Caveolin-1 is associated with polarized distribution of cell signaling components and Caveolin-1 is required for cell polarization and migration in two and three dimensions [53-55]. Additionally, re-expression of Caveolin-1 in lung adenocarcinoma cells is sufficient to promote filopodia formation, cell migration and enhance the metastatic potential of these cells [56]. Furthermore, phosphorylation of Caveolin-1 on tyrosine favors cell migration and anchorage-independent growth via the adaptor protein Grb7 [57].

These observations strongly favor the notion that Caveolin-1 displays traits that cannot be reconciled with its definition as a tumor suppressor. Indeed, Caveolin-1 is known to promote tumor formation and, in prostate cancer, its presence correlates with poor patient prognosis and survival. Indeed, Caveolin-1 expression increases in primary tumors from prostate [44] and certain leukemia derived cell lines [58]. Also, in prostate cancer cells Caveolin-1 presence enhances tumor growth and favors metastasis [41-42, 46, 59]. Importantly, Caveolin-1 expression in tumor samples is not restricted to tissues, like the prostate, where Caveolin-1 levels are low under normal conditions. For example, increased expression is also observed in colon [31] and breast cancer [48, 52, 60], cancer cells where tumor development is associated with initial Caveolin-1 loss (see Fig. 1).

A possible explanation for these discrepancies is that Caveolin-1 functions as a tumor suppressor in systems where negative signaling events downstream of Caveolin-1 prevail. Alternatively, Caveolin-1-mediated positive signaling is likely to be important in those cases where

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**Fig. (1).** Dual role of Caveolin-1 in cancer. The ability of Caveolin-1 to participate in events that favor cell proliferation or apoptosis is reflected in the dual role the protein is proposed to play in cancer. In some tissues (breast, lung, colon), consistent with function as a tumor suppressor, Caveolin-1 expression is reduced (light gray dashed line) in the early stages of cell transformation and tumor development. However, as tumors progress, changes occur that generate a “permissive” cellular context. These may include alterations within the cell associated with epithelial-mesenchymal transition, such as the loss of E-cadherin. Alternatively, changes in the tumor cell environment due to inflammation (see text) may also contribute to generating such a “permissive” context. Upon re-expression of Caveolin-1 (black dashed line), triggered by mechanisms that remain to be defined, the protein may develop radically different characteristics (note transition in cell morphology) and promote traits associated with enhanced malignancy (multidrug resistance and metastasis). In this context, phosphorylation of Caveolin-1 on Tyrosine-14 is likely to represent a process that promotes tumor cell migration and enhances metastasis. In other tissues, including prostate, Caveolin-1 is not normally expressed; however, as tumors progress, increased expression may be detected, which is then associated with enhanced tumor cell malignancy, as indicated in the above model.
presence of the protein is associated with more aggressive tumor behavior. For additional information in this respect, the interested reader may wish to consider previous reviews where such ideas have been discussed extensively [11, 61]. A corollary to this concept is that Caveolin-1 function as a tumor suppressor is linked to events favoring cell death, while more aggressive tumor behavior is likely to be associated with Caveolin-1-dependent mechanisms that favor cell survival. The following discussion in this article will focus on these aspects of Caveolin-1 function.

**Caveolin-1-Mediated Control in Signaling**

Caveolin-1 is viewed as a negative regulator in signaling, based on observations linking interaction with Caveolin-1 to subsequent inhibition of target protein function. Many of these interactions, such as those with the epidermal growth factor receptor, Src kinases, the Ras/Raf/MAPK pathway, PKCs and endothelial nitric oxide synthase (eNOS), occur via the scaffolding domain of Caveolin-1 (CSD; amino acids 82-101) and the scaffolding domain binding domain (CBD) found in the respective target proteins [3]. However, as highlighted in Fig. (2), several other modes of action are apparent for Caveolin-1 and association with Caveolin-1 does not necessarily block target protein function.

**Other Mechanisms of Post-Transcriptional Control**

Alternative modes of action include enhanced proteasome-mediated degradation of the inducible isoform of nitric oxide synthase (iNOS) via an
interaction that presumably requires the Caveolin-1 segment 101-135 [62-63]. Phosphorylation of Caveolin-1 on Tyr-14 by members of the Src-family kinases, and other tyrosine kinases including the insulin receptor [64-66] permits recruitment of the COOH-terminal Src kinase (Csk), which then phosphorylates Src on residue Y527 favoring intramolecular binding to the SH2 domain and auto-inhibition of the kinase [67-68]. Since this site is phosphorylated in response to a variety of growth factors (insulin, PDGF, EGF) and stress stimuli, including UV irradiation, mechanical and oxidative stress, as well as hyperosmolarity, phosphorylation of Caveolin-1 on Tyr-14 may constitute an important element in cellular stress responses [68-69]. Indeed, although Caveolin-1 knock-out animals are viable and fertile, their ability to respond to specific stress situations, as well as life-span in general is diminished [4-5, 17-18]. Phosphorylation of Caveolin-1 on Tyr-14 is also linked to augmented anchorage-independent growth and cell migration via a Grb7-dependent mechanism [57], as well as association with type-I matrix metalloproteinase [70]. Additionally, phosphorylation at this site is considered a crucial event in integrin-regulated membrane microdomain internalization [71-72], as well as EGF-induced caveolae formation [73]. Moreover, presence or absence of this site may account for functionally non-redundant roles ascribed to the two Caveolin-1 isoforms 1α and 1β in early vertebrate development [74]. Thus, phosphorylation on Tyr-14 is clearly relevant to Caveolin-1 function in a number of settings; however, the responses associated with this event are highly variable.

Mechanisms of Transcriptional Control

Caveolin-1 promotes cell cycle arrest via a p53/p21Waf1Cip1-dependent pathway [75]. Also Caveolin-1 enhances premature senescence in primary murine fibroblasts [76]. Oxidative stress-induced senescence involves augmented Caveolin-1 expression via p38 MAPK activated Sp1-dependent transcription [77]. Caveolin-1 expression and intracellular distribution depend on cell-cell adhesion in a manner related to that observed for β-catenin [78-79]. Indeed, studies have now implicated Caveolin-1 as a negative regulator of β-catenin-Tcf/Lef-dependent transcription [28, 80-81]. Although it remains unclear whether the interaction between Caveolin-1 and β-catenin is direct or indirect, recruitment of β-catenin to caveolae and/or Caveolin-1-containing protein complexes at the cell surface is thought to preclude β-catenin-Tcf/Lef-dependent transcription of target genes [28, 81-82]. Specifically, Caveolin-1 is suggested to promote cell cycle arrest in G0/G1 and decrease the number of cells in S phase by decreasing Cyclin D1 expression [75, 83]. More recently, work from our group has shown that expression of the Inhibitor of Apoptosis (IAP) protein Survivin and also cyclooxygenase-2 (COX-2) are down-regulated by Caveolin-1 in a β-catenin-Tcf/Lef-dependent manner [81-82]. Interestingly, reduction of survivin expression has been associated with enhanced sensitivity to anti-cancer drugs [84].

Moreover, reduction of Survivin expression provides an explanation for several alterations caused by the presence of Caveolin-1, including a decrease in the number of cells in G0/M and an increment in the susceptibility to apoptosis [81]. Consistent with these observations, the absence of Caveolin-1 in vivo in knock-out mice leads to hyper-proliferation and enhanced β-catenin-Tcf/Lef signaling in both intestinal crypts and mammary gland stem cells [85-86].

Caveolin-1-Dependent Mechanisms that Modulate Cell Proliferation and Survival

Caveolin-1 has long been implicated in cell death, either by sensitizing to or directly inducing apoptosis. A variety of possible mechanisms have been associated with such Caveolin-1 functions in cells. Initially, many were linked to the idea that Caveolin-1 binds to and inhibits crucial constituents of cell survival pathways, thereby favoring mitochondrial permeability and caspase activation. Some examples involving CSD-CBD interactions, as well as others are summarized below with a focus on the pathways Ras/Raf/ERK, PI3K/Akt, and Wnt/β-catenin and their role in cell death or survival.

The Ras/Raf/ERK Connection

Strong links between Caveolin-1 and the MAPK/ERK pathway were established early on in oncogenically transformed fibroblasts, where Caveolin-1 expression is lost or diminished [26] and upon re-expression of Caveolin-1 cell transformation is reversed. In Ras-transformed fibroblasts, this correlates with substantially reduced MAPK/ERK signaling and augmented apoptotic cell death [27]. In NIH3T3 fibroblasts, down-regulation of Caveolin-1 using specific siRNA is sufficient to hyperactivate the MAPK/ERK pathway and induce cell transformation [78]. Also, in Caveolin-1 knock-out mice, signaling via the MAPK/ERK pathway is increased and associated with increased sensitivity to topically applied carcinogens, cardiac hypertrophy and neointimal hyperplasia [33, 87-88]. Moreover, in human head and neck squamous cell cancer, Caveolin-1 inhibits the ERK pathway and cell growth [89], and in human laryngeal carcinoma cell lines, Caveolin-1 interaction with the EGFR is associated with reduced MAPK/ERK phosphorylation and increased apoptotic cell death [90].

Alternatively, chronic airway diseases, including asthma, are associated with increased airway smooth muscle (ASM) mass, likely due to enhanced proliferation. In ASM cells, down-regulation of Caveolin-1 using siRNA leads to spontaneous MAPK/ERK activation and increased proliferation in the absence of mitogens. Moreover, PDGF stimulation reversed the ability of Caveolin-1 to inhibit MAPK/ERK signaling [91]. Taken together, Caveolin-1-mediated inhibition of the MAPK/ERK pathway appears to preclude inappropriate cell proliferation and also promote cell death.
The PI3K/Akt Connection

The Phosphatidylinositol 3-kinase (PI3K)/Akt pathway is an important signaling pathway activated by growth factors that is involved in growth control and cell survival [92-95]. Interestingly, PI3K has been found in caveolae fractions in different cells, including fibroblasts, endothelial cells, and myeloid-derived cells [96] and, consistent with a role as a tumor suppressor, Caveolin-1 has been suggested to inhibit PI3K activity [97]. In a cellular context, this may also involve stabilizing the tumor suppressor phosphatase PTEN [98].

Strangely, however, Caveolin-1 reportedly sensitizes L929 fibrosarcoma, HEK293 and HeLa cells to TNFα, staurosporine, H2O2 and arsenite [99-100] via PI3K/Akt activation, possibly via a ceramide-mediated mechanism [100]. The latter finding is unexpected since Caveolin-1 has also been shown to promote ceramide-dependent cell death via PI3K/Akt activation [101]. Moreover, upon inhibition of PI3K/Akt with inhibitors, like LY-294002 or wortmannin, survival of TNF-α-treated L929 cells is substantially improved. Similar effects are also seen in HEK293 and HeLa cells. Thus contrary to the general view, Caveolin-1α is required for TNF-α-induced cell death in L929 cells, and this effect is dependent on activation of a PI3K/Akt signaling pathway [99]. See data summarized in the Table 1.

These examples suggest that Caveolin-1-dependent regulation of the PI3K/Akt pathway and also PTEN play a significant role in modulating cell survival, although the precise consequences of Caveolin-1 interaction with this pathway appear to vary quite dramatically.

The β-Catenin/Tcf-Lef Connection

As mentioned, results from several laboratories including our own, implicate Caveolin-1 in the regulation of a significant number of β-catenin/Tcf-Lef target genes, including Cyclin D1, Survivin and COX-2. In doing so, the presence of Caveolin-1 modulates parameters associated with cell proliferation and cell death. Interestingly, however, while Caveolin-1-mediated suppression of Survivin was observed in a variety of different cell lines available in the laboratory [81], there were notable exceptions. Specifically, expression of Caveolin-1 in a sub-line derived from the human adenocarcinoma cell line HT29, termed HT29(US), that was obtained by selection for higher metastatic potential, did not alter Survivin expression or cell proliferation. Since loss of E-cadherin is often associated with metastasis, we asked whether the absence of E-cadherin might be linked to the inability of Caveolin-1 to regulate Survivin. Indeed, E-cadherin levels are reduced in HT29(US) cells, as compared to HT29 cells obtained from ATCC, referred to as HT29(ATCC) cells. Furthermore, re-expression of E-cadherin is sufficient to restore the ability of Caveolin-1 in HT29(US) cells to sequester β-catenin to the plasma membrane, inhibit Survivin expression and control cell proliferation [82, 102]. Similar results were obtained in metastatic murine melanoma B16-F10 cells, where the simultaneous expression of Caveolin-1 with E-cadherin not only reduced significantly proliferation but also enhanced cell death [102]. Taken together, these results indicate that loss of E-cadherin, as is frequently observed during metastasis, provides a molecular understanding of how Caveolin-1 function can switch in a cell context-dependent fashion from functioning as a tumor suppressor to promoting characteristics associated with more malignant tumor cell behavior (see Fig. 1).

Enhanced expression of COX-2 is also frequently observed in human cancers and, as for Survivin, augmented presence is associated with increased tumor cell survival. Indeed, due to its known role in carcinogenesis, angiogenesis and apoptosis, COX-2 has been proposed as a good target for the development of chemopreventive and anti-cancer drugs [103]. Our studies also revealed that Caveolin-1 reduces COX-2 expression via a β-catenin/Tcf-Lef-dependent transcriptional mechanism. Interestingly, accumulation of prostaglandin E2 (PGE2) in the medium of cancer cells is reduced by Caveolin-1 expression and exogenous addition of PGE2 to cells is sufficient to revert Caveolin-1-mediated effects. Thus, on the one hand Caveolin-1 presence interrupts a potent feed-forward amplification loop involving the COX-2-PGE2 axis and downstream activation of β-catenin/Tcf-Lef-dependent transcription of genes, including COX-2 itself, as well as Survivin, which promote cell survival and proliferation. Alternatively, the observation that exogenous PGE2 reverts Caveolin-1 mediated suppression of β-catenin/Tcf-Lef-dependent transcription, even in the presence of E-cadherin, indicates that Caveolin-1-functions associated with its potential role as a tumor suppressor are “conditional” and depend on the cellular environment. In a pro-inflammatory context, where molecules like PGE2 are present, the ability of Caveolin-1 to function in this sense is limited. Finally, the results indicate that Caveolin-1-function in any given cell is not only determined by existing constraints within the same cell, but is also subject to modulation by ongoing processes in neighboring cells.

Caveolin-1 and Apoptosis

As discussed in previous sections, Caveolin-1 impacts on cell survival pathways in a number of ways that ultimately may predispose to or even directly promote cell death. In this section, we will focus on a few select examples where direct connections to either the extrinsic or intrinsic cell death pathways are apparent.

Binding of ligands to the appropriate death receptors, induces receptors aggregation and caspase-8-, followed by caspase-3/7 activation, leading to cell death via the extrinsic pathway [104]. A potential Caveolin-1 binding motif (G53LHHDGQFCH) was identified in the human death receptor Fas sequence and, in a model of lung epithelial apoptosis induced by hyperoxia, Caveolin-1 and Fas colocalization as well as interaction were followed by Fas multimerization and
Death-Induced Signaling Complex (DISC) formation. In this context, Caveolin-1-dependent Fas receptor aggregation and the efficiency of BID cleavage required Fas palmitoylation. The absence of Caveolin-1 in deficient cells (Cav-1−/−) disrupted DISC formation. Moreover, mutation of Tyrosine-14 (Y14F) disrupted hyperoxia-induced interaction between BID and Caveolin-1, decreased tBID formation and increased resistance to hyperoxia-induced apoptosis [105].

Recently, Autophagic microtubule-associated protein 1 light chain 3B (LC3B) has been studied as a regulator of lung cell death. In epithelial cells, LC3B forms a complex with the death receptor Fas in lipid rafts, which requires the presence of Caveolin-1. The different complexes, Fas-LC3B, Fas-Caveolin-1 and the Caveolin-1-LC3B were observed in epithelial cells under basal conditions; however, these complexes dissociated rapidly after cellular treatment with cigarette smoke. LC3B knockdown reduces DISC

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The table summarizes available evidence linking Caveolin-1 presence to reduced proliferation and/or increased cell death. The cell type studied, the experimental approach used to manipulate Caveolin-1 levels, the effects observed, the signaling pathways involved and the corresponding references are indicated (see text for details).
formation, in epithelial cells. Therefore, in this model, Fas is sequestered by Caveolin-1 and thus regulates the extrinsic apoptosis pathway. Additionally, LC3B is proposed also to sequester Fas in the basal state. Hence, the net effect of LC3B expression is pro-apoptotic during cigarette smoke exposure [106-107].

Caveolin-1 is also implicated in regulating the intrinsic apoptosis pathway via studies that establish a connection with acetylcholinesterase (AChE). Previously, AChE activity was found to increase in various types of apoptotic cells [108] and pharmacological inhibition of AChE, as well as anti-sense RNA-mediated down-regulation of AChE prevented apoptosis. At the onset of apoptosis, AChE was found in the cytoplasm and then, upon commitment to cell death, the enzyme accumulated in the nucleus and in apoptotic bodies [108-109]. Moreover, AChE interacts with Caveolin-1 during apoptosis in events that precede apoptosis formation. While AChE plays a crucial role in promoting oligomerization of Apaf-1, Caveolin-1 appears neither to interact with cytochrome C nor with Apaf-1 [110].

Apoptosis of macrophages is considered important for determining the efficiency of immune responses. Treatment of isolated macrophages activated in vivo in mice with apoptosis-inducing agents lead to a dramatic increase in Caveolin-1 levels while Caveolin-2 is not affected. Phosphatidylserine (PS) externalization is considered a defining feature associated with apoptosis [111]. Interestingly, Caveolin-1 is present in lipid rafts and colocalizes with PS at the cell surface of apoptotic macrophages, where it is suggested to be involved in the efficient externalization of PS [112]. Taken together, these observations link Caveolin-1 directly to the regulation of mechanisms that are relevant to the execution of both the extrinsic and intrinsic apoptosis pathways.

**Caveolin-1 – Mediated Survival Mechanisms**

As mentioned, Caveolin-1 was initially implicated as an “oncosuppressor” that blocks pathways relevant to cell transformation. Meanwhile, however, it has become clear that Caveolin-1 may also promote signaling events that favor cell survival [113-114]. In this section, we will focus on discussing such events.

The down-regulation of Caveolin-1 in H9C2 rat cardiomyoblasts with Cav-1-siRNA reduces significantly Insulin-like Growth Factor-I Receptor (IGF-IR) tyrosine phosphorylation and Akt activation after IGF-I stimulation and, in these cells, IGF-I was unable to prevent serum withdrawal-induced apoptosis [115]. In endothelial HUVECs, Caveolin-1 down-regulation inhibits IGF-1 and insulin-induced activation of eNOS (endothelial nitric oxide synthase), an anti-apoptotic factor in these cells [116]. Moreover, Caveolin-1 seems to play a pro-survival role in prostate cancer cells by promoting PI3K/Akt signaling. Caveolin-1 binds to and inhibits the serine/threonine protein phosphatases PP1 and PP2A, leading to higher PDKI, Akt and ERK1/2 activities and a decrease in thapsigargin-induced apoptosis in the human prostate cancer cell line LNCaP [117]. Also, the over-expression of Caveolin-1 protects against c-myc-stimulated apoptosis in LNCaP cells [118] and loss of Caveolin-1 favors apoptosis of prostate tumor cells in a transgenic adenocarcinoma mouse prostate (TRAMP) model [119]. Moreover, physical interaction between Caveolin-1 and the putative oncogene Inhibitor of differentiation/DNA binding (ID-1) plays an essential role in the epithelial-mesenchymal transition, cell migration and resistance to taxol-induced apoptosis in the human prostate cancer cell lines LNCaP and 22RV1. Again, the observed anti-apoptotic effects depend on the PI3K/Akt pathway [120].

Anti-apoptotic functions of Caveolin-1 also have been reported in others cell types. In primary cortical neurons from neonatal rats, the expression of Caveolin-1 protects from ischemic cell death induced via stimulation of the N-methyl-D-aspartate receptor (NMDAR). In these cells, Caveolin-1 is thought to favor the correct localization of the NMDAR/Src tyrosine kinase family/ERK signaling components [121]. In lymphoblastoid TK6 cells, expression of Caveolin-1 protected against UV irradiation-induced apoptosis, as well as promoted proliferation after this insult [122] and knock-down of Caveolin-1 with siRNA sensitized human ducal adenocarcinoma cells to ionizing radiation [123]. Besides, NO-induced resistance to anoikis mediated by Caveolin-1 in human lung carcinoma NCI-H460 cells and over-expression of Caveolin-1 protects against detachment-induced apoptosis [124]. Over-expression of Caveolin-1 in HepG2, a hepatocellular carcinoma cell line, protects from serum deprivation-induced apoptosis, and also enhances migration and invasion by up-regulating MMP-2, MMP-9 and VEGF expression, suggesting that Caveolin-1 could be a critical pro-survival factor in hepatocellular cancer [125]. High glucose levels induce apoptosis in HLE-B3, a lens epithelial cell line, and this effect is observed concomitant with a decrease in Caveolin-1 expression. Upon simvastatin (3-hydroxy-3-methylglutaryl coenzyme A inhibitor) or EGF addition to HLE-B3 cells cultured to high glucose-medium, expression of Caveolin-1 increases while apoptosis decreases [126]. Interestingly, Caveolin-1 has been found to prevent oxidative damage in human SK-N-MC neuroblastoma cells. The populations of DAF-2DA-positive (NO producers) and Annexin V-positive cells were remarkably reduced by cell treatment with the CSD (Caveolin-1 scaffolding domain) peptide and Caveolin-1 transfection, but not by CSC, scrambled control peptide, or transfection with an empty vector. Indeed, in this study hypoxia activated iNOS and promoted NO production, resulting in an up-regulation of Caveolin-1 expression. This increase protected neuroblastoma cells against oxidative injury by inhibiting iNOS expression and NO production. The results suggest that up-regulation of Caveolin-1 in response to hypoxia may serve to prevent oxidative injury in neuroblastoma cells [127].

Here it is important to note that Caveolin-1 not only protects from apoptosis by enhancing anti-apoptotic signaling in cell lines, but reportedly also plays a similar...
role in normal cell physiology. Indeed, the absence of Caveolin-1 in knock-out mice induces cell damage and apoptosis in thyrocytes. In this case, the absence of Caveolin-1 leads to thyrocyte dysfunction, excessive oxidative stress and then finally cell death [128]. Also, genetic ablation of Caveolin-1 in mice increases the volume of cerebral ischemia due to impaired angiogenesis of vascular endothelial cells, whereby the expression of Caveolin-1 appears to be necessary to increase the protein levels of eNOS after an ischemic insult [129].

In summary, these reports suggest that besides its well documented pro-apoptotic role, Caveolin-1 also acts as an anti-apoptotic and pro-survival factor in various cell types, whereby several possible mechanisms appear to be involved. Thus, as already mentioned, Caveolin-1 plays a highly ambiguous role in the regulation of cell survival and proliferation pathways, whereby the observed outcomes appear to depend largely on the cell context.

**Caveolin-1 and Drug-Resistance**

Chemotherapy is one of the most frequently used treatments against cancer. Unfortunately, cancer cells often adapt to this challenge by becoming resistant, thereby avoiding drug-induced cell death [130]. Several reports suggest that Caveolin-1 participates as an important mediator of drug-resistance in cancer cells. In patients, up-regulation of Caveolin-1 levels is frequently observed in advanced stages of lung [51, 131], prostate [42, 44], breast [44], pancreas [132] and renal cancer [133]. In these cases, Caveolin-1 is associated with poor patient prognosis and reduced patient survival. Moreover, in lung cancer patients, Caveolin-1 expression is inversely correlated with responses to gemcitabine, since absence of Caveolin-1 expression is associated with increased responsiveness to therapy and patient survival. These observations provide strong evidence favoring the notion that Caveolin-1 presence is associated with the development of drug-resistance [51].

These clinical data are complemented by findings in cell lines that correlate enhanced Caveolin-1 with the development of drug resistance. In colon cancer cells, knock-down of methotrexate resistance is associated with increased Caveolin-1 expression [31, 134]. Interestingly, in HT29 cells siRNA-mediated Caveolin-1 down-regulation reduces cell viability after methotrexate exposure [134]. Similar increases in Caveolin-1 levels are observed in colchicine-resistant HT29 colon cancer and adriamycin-resistant MCF7 breast cancer cells. In these cell lines, Caveolin-1 expression increased together with Caveolin-2 and glucosylceramide cell content. These changes were independent of P-glycoprotein expression, indicating that the observed changes in Caveolin-1 are not the consequence of P-glycoprotein induction [47]. Furthermore, in lung cancer cells augmented Caveolin-1 expression is detected after chronic etoposide exposure [135] and acute bleomycin treatment [136]. In both cases, augmented Caveolin-1 expression correlated with cell survival [135-136]. In addition, augmented Caveolin-1 expression is observed in taxol and epothilone-resistant A549 cancer cells [43]. In this case, Caveolin-1 upregulation occurred in the absence of changes in P-glycoprotein [43]. Furthermore, in Ewing’s sarcoma cells incubated with doxorubicin an increase in Caveolin-1 levels is detected. In this case augmented Caveolin-1 expression is related to reduced doxorubicin-induced cell death [137]. In metastatic prostate cancer cells, unlike other cancers, higher Caveolin-1 protein levels are frequently observed. In this case, Caveolin-1 has been proposed as a metastasis gene, which participates in androgen resistance [59, 138]. As mentioned, in prostate cancer cells, Caveolin-1 mediated inhibition of apoptosis is associated with the transcription factor Id-1 (for inhibitor of differentiation and DNA binding). Caveolin-1 interaction with Id-1 increased Bcl-2 and prevented taxol-mediated induction of apoptosis by decreasing caspase-3 and PARP cleavage [120]. Taken together, these data strongly suggest that increased Caveolin-1 levels in cancer cell lines favors the development of the multidrug-resistant phenotype in a manner apparently unrelated to the presence of P-glycoprotein.

Given the significance of augmented Caveolin-1 expression in advanced stages of cancer and the association there with multidrug resistance, it is tempting to speculate that Caveolin-1 presence favors mechanisms which help avoiding cell death. Indeed, in a mouse model of metastatic prostate cancer, antisense mediated Caveolin-1 knock-down, enhanced sensitivity to androgen withdrawal. Interestingly, antisense mediated decreases in Caveolin-1 levels also reduced prostate tumor volume and increased cell death and this effect was lost when mice were injected with testosterone. In vitro, in prostate cancer cells, Caveolin-1 specific anti-sense constructs induce cell death after testosterone removal. This effect was abrogated, when the cells were treated with the general caspase inhibitor Z-VAD-FMK [139]. Additionally, in human prostate cancer cells, Caveolin-1 presence favors phenylephrine-induced resistance to thapsigargin mediated cell death. This Caveolin-1-dependent effect is characterized by reduced caspase-3 activation and PARP cleavage in a Bax dependent fashion [140]. In addition, in renal cancer cells, Caveolin-1 is up-regulated after chronic treatment with doxorubicin. siRNA treatment against Caveolin-1 reduces cell survival and activates the proapoptotic proteins PARP and Bax and reduces anti-apoptotic Bcl-2 after doxorubicin treatment. These results point towards an anti-apoptotic role for Caveolin-1 in these cells. Also, pulmonary metastasis was reduced in SCID-mice injected with Caveolin-1 siRNA-transfected cells treated with doxorubicin, suggesting again that Caveolin-1 reduces sensitivity to chemotherapeutic agents both in vitro and in vivo [141]. Finally, Caveolin-1 knock-down in MDCK cells over-expressing the drug transporter protein BCRP (for breast cancer resistance protein) sensitizes the cells to the chemotherapeutic agent mitoxantrone, thus reducing cell proliferation [142]. Altogether, these results indicate that Caveolin-1
participates significantly in facilitating the development of multidrug resistance. Thus, drugs that eliminate or reduce Caveolin-1 levels are expected to sensitize cells to drug-induced death.

Mechanisms of Caveolin-1-Mediated Drug Resistance

The main transporters involved in the development of drug-resistance, predominantly as a consequence of over-expression, are P-glycoprotein and BCRP. Both belong to the ABC transmembrane transporter family that, in an energy-dependent fashion, transport drugs to the cell exterior, thereby reducing the effective intracellular concentration. Some anticancer-drugs that are known substrates for P-glycoprotein and BCRP include anthracyclines, topoisomerase inhibitors, taxanes and mitoxantrone among others [130]. Interestingly, a tight association has been noted between Caveolin-1 and P-glycoprotein. Indeed, both proteins co-distribute in the same detergent-resistant membrane fractions [47, 135, 143], and co-immunoprecipitate in brain capillaries, rat brain endothelial, Chinese hamster ovary and breast cancer cells [143-145]. This interaction appears to be mediated by the presence of a Caveolin-1-binding motif in P-glycoprotein [143]. In addition, both Caveolin-1 and the MDR gene are co-expressed in normal and leukemia cells obtained from human patients [146]. However, despite these findings some groups have obtained evidence showing that Caveolin-1 represses P-glycoprotein function in brain-derived endothelial cells and breast cancer cells [145, 147]. Therefore, the role of Caveolin-1 interactions with P-glycoprotein and their consequences for P-glycoprotein activity remain controversial. However, as suggested in the previous sections, the ability of Caveolin-1 to promote drug-resistance does not appear to be linked to P-glycoprotein expression.

Additionally, Caveolin-1 function in this context has been linked to another ABC transporter, the BCRP protein, since it was shown that Caveolin-1 co-distributes with BCRP in detergent-resistant membrane fractions and interacts there with BCRP [142, 146]. Interestingly, in Caveolin-1 knock-down cells, BCRP activity was reduced and the cells became more sensitive to mitoxantrone-induced reduction in cell proliferation [142]. These results clearly suggest that Caveolin-1 presence promotes BCRP function, although, at the molecular level, it remains unclear how this occurs.

Recently, an alternative mechanism was put forward to explain how Caveolin-1 presence may facilitate multi-drug resistance and protect against cell death. In sarcoma cells, Caveolin-1 expression is associated with protection against doxorubicin-induced cell death. Indeed, re-expression of Caveolin-1 in cells in which Caveolin-1 had previously been silenced lead to a reduction in apoptosis after doxorubicin treatment. Importantly, loss of Caveolin-1 correlated with a reduction in the active, phosphorylated form of protein kinase Ca (PKCa). Interestingly, drug-sensitization after Caveolin-1 knock-down was abrogated when PKCa was overexpressed, suggesting that PKCa may act downstream of Caveolin-1 to protect against cell death in drug-resistant cells [137]. Whether PKCa acts in a similar fashion as a downstream effector of Caveolin-1 in other cellular systems remains to be shown. See data summarized in the Table 2.

Taken together, the data discussed strongly suggest that up-regulation of Caveolin-1 is observed in late stages of cancer and in drug-resistant cancer cell lines. Moreover, increased Caveolin-1 expression appears to favor cancer cell survival by preventing apoptotic cell death after exposure to chemotherapeutics agents. Additionally, there is substantial evidence linking Caveolin-1 function to the ABC transporters, P-glycoprotein and BCRP, although the data remain controversial in this respect. Additional experiments are required to clarify this point. Finally, PKCa has emerged as a potential effector molecule that mediates Caveolin-1-dependent protection against cell death in drug-resistant cells. Again, additional experiments are required to confirm the relevance of these observations in other experimental models.

The Two Sides to Caveolin-1: Summary and Outlook

The literature revisited in this review highlights Caveolin-1 as a protein, which plays a highly ambiguous role in cancer. As depicted in the Fig. (1), Caveolin-1 expression is frequently reduced or suppressed in early stages of cancer, by mechanisms that are not entirely clear, although methylation of CpG-rich islands in the promotor region has been suggested. As might be expected for a tumor suppressor, re-expression of the protein frequently reduces tumor growth in vivo observed for a number of different tumor cell lines. Despite such evidence, Caveolin-1 is also implicated in tumor progression, the development of multi-drug resistance and metastasis. Moreover, presence of the protein in tumors has been associated with poorer patient prognosis. Consistent with such ambiguity in function, this review summarized a considerable amount of data showing that Caveolin-1 can both favor cell proliferation and survival, as well as enhance processes that lead to cell death. While such distinct results may be attributed to use of different experimental systems, some reports suggest that this “switch” in function can occur within the same cell. To resolve this apparent dichotomy, our model proposes that both intracellular and extracellular changes help create a permissive environment. Loss of E-cadherin is highlighted as one possibility, but others include exposure to a pro-inflammatory environment, as was discussed. Hence, when Caveolin-1 is re-expressed, by again poorly defined mechanisms, restraints initially present in the non-transformed cells, no longer exist such that the protein now favors activities associated with more malignant tumor cell behavior. One possibility depicted here is phosphorylation on Tyrosine-14, a modification that is implicated in promoting cell migration and metastasis. To what extent this may contribute to other characteristics, such as multi-drug resistance remains to be defined. Thus, studies related to Caveolin-1 (and a few other select molecules not discussed here) are beginning
to alter the classic view suggesting that cancer originates as the consequence of mutations in either oncogenes or tumor suppressors. In doing so, they are likely also to alter how we go about treating the disease. As a corollary, a better understanding of Caveolin-1 biology and how function of the molecule changes throughout tumor development can be expected to help in the development of therapeutic strategies that harness its ability to promote cell death in tumor cells without undesired side effects.

### ABBREVIATIONS

- APC = Adenomatous polyposis coli
- COX-2 = Cyclooxygenase-2
- GSK-3 = Glycogen synthase kinase 3
- CSD = Caveolin scaffolding domain
- CBD = Caveolin binding domain

### Table 2. Caveolin-1 Expression Favors Cell Survival and/or Proliferation

<table>
<thead>
<tr>
<th>Model</th>
<th>Manipulation</th>
<th>Effects</th>
<th>Implicated Signaling Pathway</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H9C2 (rat heart muscle)</td>
<td>Down-regulation of Caveolin-1 with siRNA</td>
<td>Inhibition of protection against serum withdrawal-induced apoptosis by IGF</td>
<td>IGFR/Akt</td>
<td>[115]</td>
</tr>
<tr>
<td>HUVEC (human endothelium)</td>
<td>Down-regulation of Caveolin-1 with siRNA</td>
<td>Inhibition of IGF and Insulin-induced activation of eNOS as a pro-survival factor</td>
<td>IGFR and IR</td>
<td>[116]</td>
</tr>
<tr>
<td>LNCaP (human prostate)</td>
<td>Over-expression of Caveolin-1</td>
<td>Inhibition of thapsigargin-induced apoptosis</td>
<td>PI3K/Akt/Erk 1/2</td>
<td>[117]</td>
</tr>
<tr>
<td>LNCaP (human prostate)</td>
<td>Over-expression of Caveolin-1</td>
<td>Inhibition of c-myc-induced apoptosis</td>
<td>c-myc-induced apoptosis</td>
<td>[118]</td>
</tr>
<tr>
<td>LNCaP (human prostate)</td>
<td>Over-expression of Caveolin-1</td>
<td>Resistance to taxol-induced cell death</td>
<td>ID-1/PI3K/Akt</td>
<td>[120]</td>
</tr>
<tr>
<td>Cross between Cav1 null mouse and TRAMP (transgenic adenocarcinoma of mouse prostate) mouse</td>
<td>Generation of Cav1 (-/-) prostate tumors</td>
<td>Inhibition of tumor progression</td>
<td>Par4 and PTEN</td>
<td>[119]</td>
</tr>
<tr>
<td>Primary cortical neurons (neonatal rat neocortex)</td>
<td>Down-regulation or knock-out of Caveolin-1</td>
<td>Enhanced ischemic cell death</td>
<td>N-methyl D-aspartate receptor/Src/ERK</td>
<td>[121]</td>
</tr>
<tr>
<td>TK6 cells (human spleen)</td>
<td>Over-expression of Caveolin-1</td>
<td>Enhanced proliferation after UV irradiation</td>
<td>-</td>
<td>[122]</td>
</tr>
<tr>
<td>PATU8902, MiaPaCa2, Panc1 (human pancreatic carcinoma)</td>
<td>Knock-down of Caveolin-1</td>
<td>Sensitization to ionizing radiation</td>
<td>β1-integrin/FAK</td>
<td>[123]</td>
</tr>
<tr>
<td>NCI-H4060 (human lung carcinoma)</td>
<td>Over-expression of Caveolin-1</td>
<td>NO-induced resistance to anoikis</td>
<td>PI3K/Akt</td>
<td>[124]</td>
</tr>
<tr>
<td>HepG2 (human hepatocellular carcinoma)</td>
<td>Over-expression of Caveolin-1</td>
<td>Inhibition of serum withdrawal-induced apoptosis</td>
<td>Survivin</td>
<td>[125]</td>
</tr>
<tr>
<td>HLE-B3 (human lens)</td>
<td>Decreased Caveolin-1 expression</td>
<td>Increased high glucose-induced apoptosis</td>
<td>-</td>
<td>[150]</td>
</tr>
<tr>
<td>SK-N-MC (human neuroblastoma)</td>
<td>Up-regulation of Caveolin-1</td>
<td>Protection against oxidative damage in hypoxia</td>
<td>iNOS</td>
<td>[127]</td>
</tr>
<tr>
<td>Thyrocytes (mouse thyroid gland)</td>
<td>Knock-out mouse Caveolin-1</td>
<td>Cell damage and apoptosis in thyrocytes</td>
<td>ROS production</td>
<td>[128]</td>
</tr>
<tr>
<td>Vascular endothelial cells (from mouse brain)</td>
<td>Knock-out mouse Caveolin-1</td>
<td>Enhanced cerebral ischemia by impaired angiogenesis</td>
<td>eNOS</td>
<td>[129]</td>
</tr>
</tbody>
</table>

The table summarizes available evidence linking the presence of Caveolin-1 to cell survival and/or proliferation. The cell type or animal models studied, experimental approach used to manipulate Caveolin-1 levels, the signaling pathway involved and the corresponding references are indicated. Information concerning the signaling pathways involved was not always available (see the text for details).
The Caveolin-1 Connection to Cell Death and Survival

IAP = Inhibitor of Apoptosis

eNOS = Endothelial oxide nitric synthase

iNOS = Inducible oxide nitric synthase

MAPK = Mitogen activated protein kinase

PGE2 = Prostaglandin E2

TNFα = Tumor necrosis factor alpha

ASM = Airway smooth muscle

PI3K = Phosphatidylinositol 3-kinase

PTEN = Phosphatase and tensin homolog

Tcf/Lef = Binding element

DISC = Death-induced signaling complex

LC3B = Protein 1 light chain 3B

AChE = Acetylcholinesterase

PS = Phosphatidylserine

IGF-1R = Insulin-like growth factor-I receptor

PP1 and = Serine/threonine protein phosphatases 1 and 2, respectively

TRAMP = Transgenic adenocarcinoma mouse prostate model

NMDAR = N-methyl-D-aspartate receptor

MMP-2 and = Metalloproteinase 2 and 9, respectively

MMP-9

Z-VAD-FMK = Z-Val-Ala-Asp-fluoromethylketone

PARPs = Poly ADP-ribose polymerases

MDR = Multidrug resistance

BCRP = ATP-binding cassette transporters

PKCα = Protein kinase Ca

VEGF = Vascular endothelial growth factor

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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