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Review

Caveolin and cavin family members: Dual roles in cancer

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ABSTRACT

Caveolae are specialized plasma membrane subdomains with distinct lipid and protein compositions, which play an essential role in cell physiology through regulation of trafficking and signaling functions. The structure and functions of caveolae have been shown to require the proteins caveolins. Recently, members of the cavin protein family were found to be required, in concert with caveolins, for the formation and function of caveolae. Caveolins have a paradoxical role in the development of cancer formation. They have been involved in both tumor suppression and oncogenesis, depending on tumor type and progress stage. High expression of caveolins and cavins leads to inhibition of cancer-related pathways, such as growth factor signaling pathways. However, certain cancer cells that express caveolins and cavins have been shown to be more aggressive and metastatic because of their increased potential for anchorage-independent growth. Here, we will survey the functional roles of caveolins and of different cavin family members in cancer regulation.

1. Introduction

The plasma membrane is a dynamic multidomain system heavily decorated with small «flask-shaped» invaginations of 60–80 nm diameter, known as caveolae, which were first observed in 1953 [1]. As further demonstrated by electron microscopy in unfixed fast-frozen material, caveolae have been shown to also exhibit an open neck structure [2,3]. These structures are enriched with various signaling molecules including some cell surface receptors which are attached through a lipid anchor. Caveolae occur at different densities in different cell types, being most prominent in fibroblasts, vascular endothelial cells, adipocytes and epithelial cells. The principal membrane components of caveolae are a family of integral membrane proteins known as caveolins, which are intimately involved in caveolar function. Caveolae and caveolins are involved in a variety of cellular processes including endocytosis, lipid homeostasis, signal transduction and tumorigenesis. Approximately 144 individual caveolin molecules have been estimated as being incorporated in a single caveolar structure [4]. Recently, a new family of membrane proteins was discovered, named cavins, and were shown to stabilize the oligodimerization of caveolins as well as caveolae formation (Fig. 1) [5–7]. Both caveolins and cavins play a major role in the formation and function of caveolae, and are involved in several physiological and pathological processes.

The roles of caveolin and of cavin in cancer regulation are now well recognized and known to be dependent on cancer cell types and conditions. Although, under some conditions, Caveolin-1 (Cav-1), a member of the caveolin family protein, may suppress tumorigenesis, it is also known for its association with and contribution to malignant progression through various mechanisms. Among these, Cav-1 expression was found to correlate with resistance to ionizing radiation [8,9]. Cav-1, via its scaffolding domain, interacts with a variety of specific proteins that are localized in lipid rafts and caveolar membranes, such as receptor tyrosine kinases, platelet-derived growth factor receptor (PDGFR), epidermal growth factor receptor (EGFR), endothelial nitric oxide synthase (eNOS), proteins involved in calcium transport, H-Ras, integrins, nerve growth factor, serine/threonine kinases, phospholipases, G protein-coupled receptors and Src family kinases [10–20]. Such interactions subsequently generate compartmentalized signaling platforms which facilitate the signaling cascades that contribute to cancer regulation. A high level of intracellular Cav-1 expression is associated with metastatic progression of many types of cancers, such as

Abbreviations: Cav, caveolin; CRC, colorectal cancer; CSD, caveolin scaffolding domain; PDGFR, platelet-derived growth factor receptor; EGFR, epidermal growth factor receptor; eNOS, endothelial nitric oxide synthase; ETS, erythroblastosis virus transforming protein; PEA3, polyoma-virus enhancer activator; MMP, matrix metalloproteinases; RCC, renal cell carcinoma; ROS, reactive oxygen species; STB, β-subunit of Shiga toxin.

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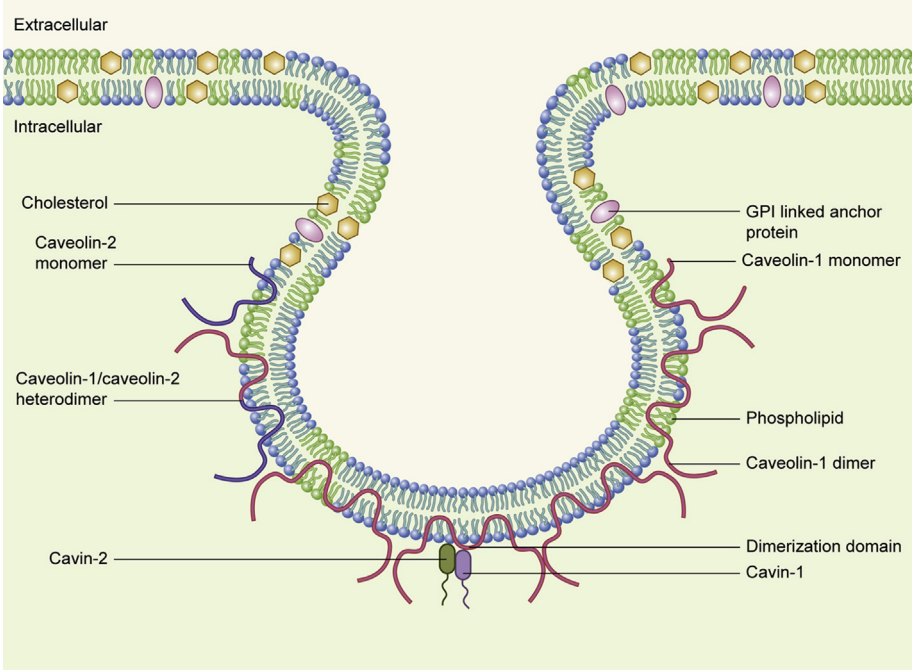

Fig. 1. Caveolin oligomer formation is regulated upon interaction with cavin members. Caveolin-1 and caveolin-2 can exist as monomers, homodimers, or heterodimers. The presence of Cavin-1 and of Cavin-2 allows Caveolin-1/Caveolin-2 to interact within the cell membrane to form heterooligomers in caveolae. In the absence of Cavin-1 or Cavin-2, caveolin oligomers embedded in the cell membrane cannot contribute to caveolae formation.

prostate [21,22], lung [23], renal [24] and esophageal cancers [25]. The expression levels of caveolins and cavins vary in different types of tumor which affects their roles in carcinogenesis (Table 1). In this review, we will discuss the distinctive properties of caveolins and cavins in various cancer types, especially their structures, types, and involvement in cancer regulation. Finally, we will discuss the possibility of biologically targeting these proteins for the development of new and more efficient therapies for cancer cure. Unquestionably, the abilities of caveolins and cavins to modulate signaling has important implications in the process of tumor formation.

2. The caveolin family

The caveolin family is composed of three isoforms of caveolin proteins in mammalian cells: Caveolin-1 (Cav-1), Caveolin-2 (Cav-2) and Caveolin-3 (Cav-3) [26,27]. Most caveolin proteins are expressed in different types of tissues. However, Cav-3 is predominantly expressed in cytoskeletal muscle tissue. All three proteins have an N-terminal Caveolin Scaffolding Domain (CSD), a transmembrane domain and a C-terminal domain. Both the C-terminal and CSD are sufficient for caveolin attachment to the membrane, even without the involvement of the membrane spanning domain [28].

3. Caveolin-1

Caveolin-1 (Cav-1), discovered by immunocytochemistry as a major component of caveolae, is a 178-amino acid protein that is localized in plasma membrane caveolae, Golgi apparatus and trans-Golgi-derived transport vesicles [28–30]. Cav-1 is expressed either as a soluble cytoplasmic form or as a secreted form, depending on the

Table 1
The dual promoting/suppressive roles of cavin and caveolin members in different types of cancer is a consequence of their expression levels.

Type of cancer	Cav-1	Cav-2	Cav-3	Cavin-1	Cavin-2	Cavin-3	Mode of action	References
Thyroid	High	High					Tumor Suppressor/Promoter	[147]
	Low	Low						[231]
Breast	High	High		High			Tumor Promoter	[163,232,203]
	Low	Low		Low	Low	Low	Tumor Suppressor	[164,209]
Prostate	High	High					Tumor Promoter	[219,235]
				Low			Tumor Suppressor	[236]
Hepatocellular carcinoma	High						Tumor Promoter	[234]
Pancreatic	High			High			Tumor Promoter	[198]
Urinary bladder	High	High					Tumor Promoter	[160]
Oesophagous	High	High					Tumor Promoter	[159]
Colon	High						Tumor Promoter	[237]
Mammary			High				Tumor Promoter	[238]
Colorectal						Low	Tumor Suppressor	[249]
Ovarian						Low	Tumor Suppressor	[239]
Lung		Low		Low		Low	Tumor suppressor	[204,233]
Gastric						Low	Tumor Suppressor	[207]

cell type [31]. The first 31 amino acids are believed to be important in the selective targeting of Cav-1 to different subcellular compartments [32]. Cav-1 is expressed at different levels in multiple tissues, with the highest levels found in adipocytes, endothelial cells, fibroblasts, smooth muscle cells, and a variety of epithelial cells [33]. Cav-1 is preferentially targeted to the cytosol of skeletal muscle cells and keratinocytes, to secretory vesicles of endocrine and exocrine cells, to mitochondria of airway epithelial cells and to lipid droplets [34]. Moreover, Cav-1 can also localize away from caveolar regions in the cytoplasm, focal adhesion complexes, the extracellular matrix, and the nucleus, due to its function in a variety of cell signaling activities that may regulate tumor cell behavior [35–37].

Two isoforms of Cav-1 are expressed: Cav-1α, a 24 kDa protein which contains residues 1–178, and Cav-1β, a Cav-1α N-truncated version of a 21 kDa protein which contains residues 32–178. Generation of these isoforms results from either alternative initiation of full-length mRNA or from transcription of a shorter splice variant [38–40]. Both isoforms show distinct but overlapping sub-localization revealing that the N-terminal domain of the protein is not essential for localization in caveolae [40]. *In vitro*, both isoforms were shown to undergo serine phosphorylation. However, only the β-isoform is serine-phosphorylated *in vivo*, suggesting different functions associated with each isoform [41]. Many studies also showed that tyrosine phosphorylation of Cav-1 was dependent on the attachment of the v-Src gene product on the membrane and is associated with different Src tyrosine kinase families. Cav-1 can be phosphorylated by Src at its Tyr14 residue [34,42]. Therefore, only Cav-1α can be tyrosine-phosphorylated upon Src transformation [43]. More recently, other tyrosine kinases such as c-Abl and Fyn have been shown to phosphorylate Cav-1 at its Tyr14 residue [44,45]. Phosphorylation of Cav-1 at Ser80 converts it into a soluble, secreted protein [46]. It has also been observed that palmitoylation of Cav-1 at Cys133, Cys143 and Cys156 is required for its oligomerization [47,48]. The oligomerization of Cav-1, either with other Cav-1 molecules or with other caveolin proteins, is thought to be involved in forming the filamentous structure of the caveolar coat. From the hydrophilicity plots of the primary sequence and from mutational analysis, Cav-1 is predicted to have a membrane-spanning hairpin-like structure, with both amino and carboxyl termini oriented towards the cytoplasm [47]. This membrane-spanning model is supported by findings that antibodies directed against either the Cav-1 amino or carboxyl termini require cell permeabilization prior to immunodetection. Furthermore, a sequence of 10 amino acids located within the amino terminal region of Cav-1 is required for the localization of the protein to the rear of migrating cells as well as for caveolar formation [49–54].

Because of the presence of a high number of aromatic residues, the carboxyl terminal portion of Cav-1 CSD (residues 82–101) can interact with numerous signaling molecules localized within caveolae, including Src family tyrosine kinases, growth factor receptors, eNOS, integrins, and G-protein coupled receptors (GPCR) [34,55–58]. In fact, the signaling of proteins such as c-Neu [59], eNOS [60], EGFR [56], estrogen receptor α [61], Id-1 (inhibitor of differentiation/DNA synthesis) [62], TGF-β1 [63], IGFR1 [64], HGF [65] and others, have been shown to be tightly linked to Cav-1 and to its CSD (Fig. 2). However, recent findings challenge the roles attributed to the caveolin binding motifs in driving direct protein recruitment to the CSD. Therefore, previous work implicating caveolin as a scaffold for direct protein recruitment may need to be re-evaluated to uncover the actual mechanisms by which caveolins modulate specific signaling pathways [66].

4. Caveolin-1 in cancer

Cancer is a multistep process, in which activation of oncogenes or suppression of tumor suppressor genes are phenomena playing critical roles [67]. Cancer is largely characterized by the uncontrolled growth of abnormal cells escaping the immune system, resistance to apoptosis, and the ability to trigger angiogenesis and metastasis. The molecular changes responsible for malignant cell

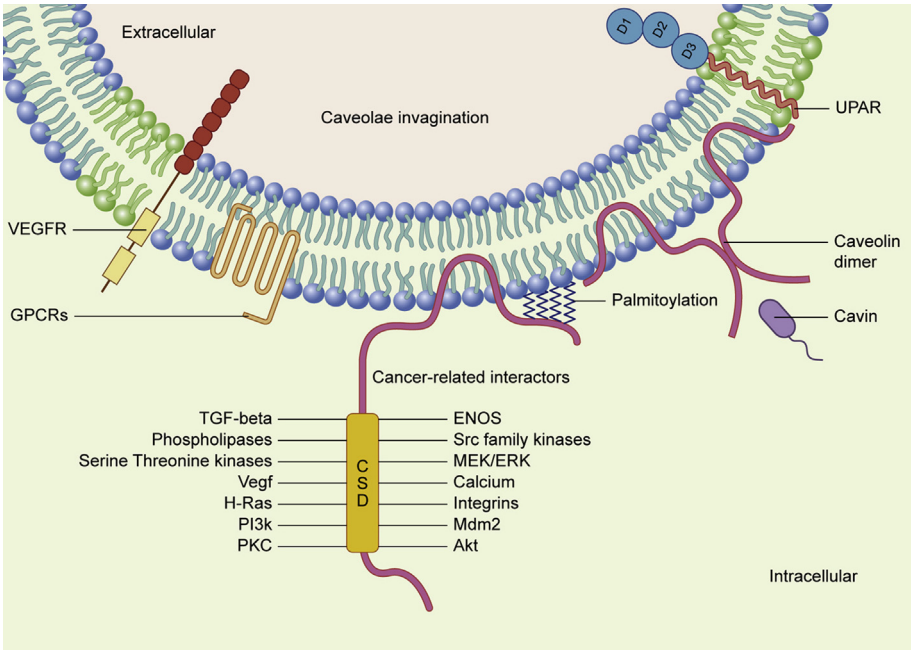

Fig. 2. Compartmentalization of caveolin and cavin proteins in caveolae. Compartmentalization of caveolin and cavin proteins serves as a platform in caveolae to organize various signalling molecules to effectively transduce extracellular stimuli into intracellular signals through the anchoring of a variety of cancer-related signalling interactors to the caveolin scaffolding domain (CSD). However a recent study does not entirely support this hypothesis as explained in the text [66]. ENOS, endothelial nitric oxide synthase; GPCRs, G-protein coupled receptors; TGF, transforming growth factor, VEGFR, vascular endothelial growth factor receptor; uPAR, urokinase plasminogen activator receptor.

function and tumorigenesis are caused by both genetic mutations and epigenetic mechanisms related to changes in gene expression that are primarily mediated by DNA methylation and histone modifications. Disruption of the epigenome is also a fundamental mechanism in cancer where regulation of tumor development is controlled by a balance between oncogenes and tumor suppressors. Several studies have revealed the importance of Cav-1 during the process of tumor progression and its expression was detected in different types of tumors [68]. In several reports, Cav-1 expression was found to be associated with tumor grade, size and stage, which showed its correlation with the evolution of cancers (Table 2). However, it is evident that Cav-1 also acts as a tumor suppressor [69]. The dual role of Cav-1 was shown to depend on tumor types. In the following sections, we will be discussing the role of caveolin as a tumor promoter in tissue invasion and metastasis, and as a tumor suppressor during apoptosis and inflammation.

5. Caveolin-1 as a tumor suppressor

Over the past 10–15 years, a large amount of data has demonstrated that Cav-1 functions as a tumor suppressor. For instance, expression of Cav-1 in transformed NIH-3T3 cells with different oncogenes such as rABI and H-Ras (G12V), resulted in the abrogation of anchorage-independent cell growth [70]. Cav-1 regulates multiple cancer-associated processes including cellular transformation, tumor growth, cell death and survival, multidrug resistance, angiogenesis, cell migration, invasion, apoptosis and metastasis [71]. Cav-1 mRNA and protein levels were down-regulated in oncogene-transformed fibroblasts and re-expression of Cav-1 was sufficient to reverse the transformed phenotype and to prevent anoikis [70,72]. Recently, PI3K/AKT/mTOR was reported to be a suitable target for cancer therapy. Activation of this pathway has, in fact, been associated with breast cancer progression. Interestingly, Cav-1 deficiency has been shown to promote PI3K/AKT, EGFR-MAPK and MAPK signaling in breast cancer [73], pancreatic cancer [74] and in NIH 3T3 cells [75]. Additionally, the presence of single nucleotide polymorphisms in an allele of Cav-1 T29107A was found to be protective against the development of nasopharyngeal carcinoma, while Cav-1 G14713A was shown to enhance tumor progression [76,77]. These results indicate that the loss of Cav-1 is capable of promoting cell transformation in some cell lines [13,27,78]. Furthermore, reduced expression of Cav-1 is seen in several tumors, including lung [21,79,80], mammary [81,82], colon [52,83], ovarian carcinoma [84], breast [85], sarcomas [86] as well as osteosarcomas [87], while re-expression of Cav-1 again reversed the transformed phenotype. Instead of promoting tumor incidence, Cav-1 deficiency promoted susceptibility to tumor formation in knockout mice, and it may be more suitable to consider Cav-1 as a «tumor susceptibility» factor rather than a tumor suppressor gene. A correlation between Cav-1 and cellular differentiation has also been shown where exposure of pre-adipocytes to differentiation-inducing agents dramatically induced Cav-1 expression at both the transcriptional and translational levels [88].

Human genes encoding Cav-1 and Cav-2 were localized to the q31.1–q31.2 region of chromosome 7 at the D7S522 locus as confirmed by FISH analysis. Interestingly, in a variety of human cancer cell types this locus is frequently deleted [60]. Recombinant expression of the Cav-1 P132L mutant or sporadic mutation in Cav-1 at codon 132 (P132L) induced cellular transformation in NIH 3T3 fibroblasts and breast cancer cell lines, respectively, by acting as a negative dominant of wild-type Cav-1 and by exhibiting a defect in intracellular oligomerization and conformation that, in turn, affects its interactions with cellular partners [89–91]. The Cav-1 promoter region was also found to be hypermethylated in prostate cancer

Table 2
Caveolin-1 expression levels in different types of cancer and different cancer stages.

Type of cancer	Number of samples	Grade	High expression of Cav-1 ($n = 3$)	p value	Size (cm)	Expression of Cav-1	Stage	Expression of Cav-1	p value	References
Lobular breast	136	I	14 (61)	0.0001						[240]
		II	21 (55)							
		III	4 (20)							
Basal–like breast cancer	449	I	6 (84)	0.026						[163]
		II	14 (140)							
		III	39 (225)							
Salivary gland	75	I + II	33 (51)	0.011						[241]
		III + IV	8 (24)							
Renal cell carcinoma	114	I	9 (79)	0.0008	<5	4 (31)				[242]
		II	9 (28)		5–7	2 (29)				
		III	3 (7)		>7	15 (53)				
Bladder carcinoma	94	I	0 (6)	<0.001			Ta	0 (20)	<0.001	[160]
		II	0 (25)				T1	3 (14)		
		III	35 (63)				T2	16 (29)		
							T3	13 (23)		
							T4	1 (3)		
NSCLC	115	I	21 (36)	0.07	≤3	13 (32)				[243]
		II	16 (27)		≥3	47 (83)				
		III	19 (41)							
		IV	4 (11)							
Gastrointestinal stromal tumors	108	I	1 (7)	0.334	<2	1 (11)	0.086			[255]
		II	1 (16)		>2–≤5	1 (30)				
		III	0 (27)		>5–≤10	2 (45)				
		IV	4 (58)		>10	2 (22)				
Tongue carcinoma	61						T1	10 (24)	<0.05	[245]
							T2 + T3 + T4	2 (37)		
Upper urinary tract carcinoma	98	I	1 (40)	0.036			Ta + T1	1 (64)	<0.001	[244]
		II + III	9 (58)				T2+T4	9 (34)		
Gastric	405	I	3 (144)	0.027						[244]
		II + III + IV	19 (261)							
Pancreatic cancer	38						1 + 2	3 (19)	<0.0001	[246]
							3 + 4	15 (19)		

[92] and DNA methyltransferase inhibitor was found to induce Cav-1 expression via C-pG Island (CGI) shore demethylation [93] and to suppress breast cancer. Similarly, polymorphisms in Cav-1 were shown to be involved in colorectal cancer (CRC) and may be used as novel and useful genomic markers for early detection of CRC [94]. In one hospital-based case–control study, the association of Cav-1 polymorphisms with oral cancer risk in a central Taiwanese population was investigated. Cav-1 was concluded to be involved in oral cancer where the A allele of the Cav-1 G14713A was risky, the A allele of the Cav-1 T29107A protective, and AA/TT on these two polymorphisms found to be the most risky combined genotype for the development of oral cancer [76]. Recently, it has been shown that mutations (missense and frameshifts) in the gene encoding Cav-1 altered its tumor suppressive functions in breast cancer and found to promote mammary tumorigenesis in a Kashmiri population [95]. Therefore, both expression levels and functional mutations in Cav-1 contribute to the promotion of cancer.

6. Caveolin-1 functions as a tumor promoter

Despite the evidence favoring the tumor suppressive role of Cav-1, several studies also support an opposite role for Cav-1 as a protein that actually promotes tumor growth. The expression of Cav-1 was shown to be increased upon tumor formation in mouse models and human patients [21,96], and thus its presence promoted tumor growth and metastasis of cancer cells via an autocrine/paracrine mechanism [97–99]. Post-translational modifications are also believed to play a role in the function of Cav-1 as a tumor promoter gene such as the phosphorylation of Cav-1 on Tyr14 by Src [100]. These results were confirmed by studies showing that Cav-1 downregulation converted androgen-insensitive metastatic mouse prostate cancer cells into an androgen-sensitive phenotype [101], and could independently promote prostate cancer cell survival and metastatic activities [98].

Similarly, clinicopathological analyses of esophageal [102], breast [103], renal [104], brain [105], lung [23,106], ependymomal [107], and prostate [108] cancers revealed a role for Cav-1 as a tumor promoter. In prostate cancer patients, the presence of Cav-1 was found to be associated with angiogenesis, cancer recurrence, elevated metastasis and poor patient prognosis [68,109–111]. Likewise, upregulation of Cav-1 in MDR colon cancer cells led to a reduced rate of proliferation and thus contributed to their selective growth advantage under chemotherapy [112]. Similarly, Cav-1 expression in MCF-7 human breast cancer cells prevented anoikis [113,114]. Cav-1 also promoted chemoresistance in gastric cancer [115] and in lymph node metastasis of non-small cell lung cancer [116]. Overexpression of Cav-1 has also been associated with metastasis and poor patient prognosis in breast carcinomas [117] and in oesophageal squamous cell carcinoma [94]. Interestingly, Cav-1 upregulates glucose uptake and ATP production through HMGA1-mediated GLUT3 transcription, suggesting that Cav-1 may increase tumor cell growth by enhancing aerobic glycolysis in colorectal cancers [118,119]. In summary, there are equally convincing data which show a dual role for Cav-1 as both tumor promoter and tumor suppressor. Perhaps one way to resolve this discrepancy is by defining Cav-1 as a « conditional tumor suppressor » protein. Along these lines, a recent study demonstrated that Cav-1 expression was increased by an erythroblastosis virus transforming protein (ETS) such as the polyoma-virus enhancer activator (PEA3) in mice epithelial lung cells [120]. It was suggested that PEA3, a pro-metastatic ETS protein involved in breast cancer, was able to increase Cav-1 expression in metastatic lymph node sites [80]. In contrast, the ETS repressor factor Net suppressed Cav-1 transcription in primary lung tumors and PEA3 was found to activate Cav-1 transcription in metastatic lymph nodes in non-small cell lung carcinoma [120]. Similarly, expression of Mgat5/galectin-3 promoted the tumor-enhancing role of Cav-1, and these conditions were associated with poor prognosis in several tumor types [121]. Although we do not know to what extent the absence of Mgat5/galectin-3 regulates other functions of Cav-1, damage to Mgat5/galectin-3 is frequently associated with diminished growth and metastasis of tumor cells, and thus represents an interesting candidate protein for tumor inhibition.

7. Caveolin-1 in invasion and metastasis

As previously mentioned, Cav-1 was first identified as the major tyrosine-phosphorylated protein in Rous sarcoma virus-transformed chicken embryo fibroblasts [30]. It is known that Rho signaling, via Rho kinase (ROCK), is closely associated with stem cells and tumor cell migration and metastasis [122]. Tyrosine-phosphorylated Cav-1 functions as an effector of Rho/ROCK signaling in the regulation of focal adhesion lifetime [100] and, thereby, in tumor cell migration and invasion. This defines a feedback loop between Rho/ROCK, Src, and phosphorylated Cav-1 in tumor cell protrusions, identifying a novel function for Cav-1 in tumor metastasis that may contribute to the poor prognosis associated with some Cav-1-expressing tumors [123]. Moreover, the interaction between Cav-1 and Rho-GTPases (most likely RhoC, but not RhoA) promoted metastasis by stimulating α5-integrin expression and by regulating the Src-dependent activation of the p130 (Cas)/Rac1, FAK/Pyk2 and Ras/Erk1/2 signaling cascades [124]. Furthermore, the association of Cav-1 with invasion, survival, and poor prognosis in hepatocellular cancer was associated with an increased expression of matrix metalloproteinases (MMP) [125].

Export of Cav-1 to secretory vesicles has also been found to be functionally associated with melanoma progression [126]. Consistently, fibroblast expression of Cav-1, through p190RhoGAP, favors directional migration and invasiveness of carcinoma cells *in vitro*. *In vivo*, stromal Cav-1 remodels peritumoral and intratumoral microenvironments to facilitate tumor invasion, correlating with increased metastatic potency. Thus, biomechanical remodeling of the microenvironment by stromal Cav-1 favors tumor invasion and metastasis [127]. In contrast, Cav-1 can inhibit pancreatic carcinoma cell invasion via the Erk-MMP signaling pathway, suggesting that the endogenous expression or re-expression of Cav-1 might help reduce pancreatic carcinoma cells invasive potential [128]. Cav-1 interaction with integrins has also been shown to regulate focal adhesion turnover [19,129,130], and Cav-1 inhibited metastatic potential in melanomas through suppression of the integrin/Src/FAK signaling pathway [131].

8. Caveolin-1 in apoptosis

Cav-1 is believed to regulate apoptosis in different cell lines. Given its dual role as a tumor suppressor or as a tumor promoter gene, it can also regulate either anti- or pro-apoptotic functions. Cav-1 was further demonstrated to promote cell-cycle arrest through a p53/p21-dependent pathway where it was demonstrated that its overexpression induced the cells to exit the S phase and to increase the G0/G1 cell population in mouse embryonic fibroblasts derived from Cav-1 transgenic mice [132].

In cancer therapies, most of the agents used promote apoptosis and result in decreased tumor masses. A defective apoptotic machinery would therefore lead to the failure of treatment, which is commonly observed in most types of cancers these days. Several studies demonstrated an enhanced sensitivity to chemically-induced apoptosis when Cav-1 is expressed. For instance, Cav-1 enhanced resveratrol-mediated transport and cytotoxicity in a hepatocellular carcinoma model [133] and paclitaxel-mediated

apoptosis in MCF-7 breast cancer cells which is regulated via Tyr14 phosphorylation of Cav-1 by inactivating Bcl-2 and increasing mitochondrial permeability [134]. Interaction of multidrug resistance protein with Cav-1 was shown to be increased in bleomycin-induced cell cycle arrest and subsequent cellular senescence [135]. Exposure to sub-toxic concentrations of cisplatin also induced hydrogen peroxide generation, and the subsequent increase of reactive oxygen species (ROS) further up-regulated Cav-1 levels and anoikis resistance which is crucial to the survival of metastatic cancer cells [136,137].

Aside from its pro-apoptotic functions, there is also strong evidence which indicates Cav-1 plays a role as an anti-apoptotic protein. For example, in the case of colon cancer, it was shown that Ku70, a protein identified as part of the Ku70/Ku80 complex that sequesters the pro-apoptotic gene Bax and mediates DNA repair, bound to Cav-1 and led to the inhibition of apoptosis mediated by chemotherapy drugs [138]. Similarly, an inhibition of apoptosis induced by the tumor necrosis factor-related apoptosis-inducing ligand TRAIL was also due to Cav-1 expression in hepatocarcinoma cells [139]. Increased expression of p-Cav-1 was shown to promote cell survival after oxidative stress and to play a role as an anti-apoptotic protein [137]. Cav-1 was shown to play an active role in mediating the transformation and survival of mouse hepatoma cells, and as such might represent a potential target for gene and anti-tumor drug treatment [140]. Furthermore, Cav-1 was demonstrated to inhibit cell detachment-induced p53 activation and anoikis by upregulating insulin-like growth factor-1 receptor's signaling and transcription in breast cancer cells [141,142], to regulate hyperoxia/ROS-induced apoptosis through interactions with Fas and BID [143], and to alter TrkA modification including Tyr490 phosphorylation [144]. These observations suggest that Cav-1 could suppress the TrkA-mediated phenotypic effects by altering TrkA modification via functional interaction. Similarly, RNA interference-directed Cav-1 knockdown sensitized renal carcinoma cells to doxorubicin-induced apoptosis and reduced lung metastasis [145]. In conclusion, the functional role of Cav-1 in apoptosis appears to be linked to tumor type as well as to the nature and the potency of the apoptosis inducers which are used to trigger death signalling.

9. Caveolin-2

Caveolin-2 (Cav-2) was discovered following the micro-sequencing of a 20 kDa protein that co-purified with adipocyte-derived caveolar membranes [146]. Three isoforms, alpha, beta and gamma, exist for Cav-2 which is located on human chromosome 7q31.1, a locus often deleted in breast and prostate cancers [147]. Cav-2 can form stable hetero-oligomeric complexes of 14–16 molecules and can coalesce into large macromolecular complexes that define caveolar architecture at the plasma membrane [148,149]. Similar to Cav-1, Cav-2 is expressed in white adipose tissue, fibroblasts, and epithelial cells, and can be found expressed alone in lungs [149,150]. Caveolar formation can still occur even when Cav-2 is not expressed suggesting a role for Cav-2 as a partner binding to Cav-1 [33]. Otherwise trapped in the Golgi apparatus [151], Cav-2 transport to the plasma membrane is dependent upon Cav-1 expression [152]. Cav-2 differs from Cav-1 in functional domains including a G-protein binding domain and a CSD located at its N-terminal region [153,154]. Additionally, the Cav-1 N-terminal amino acids Lys47-Lys57 are highly conserved in Cav-2, and disruption of this region impedes cell polarity and directional migration [17]. Furthermore, the CSD of Cav-2 is responsible for its localization in the Golgi apparatus of polarized cells derived from colon cancer [155]. Cav-2 also possesses the capacity to modulate several signaling pathways as it has been shown that insulin triggered Tyr19 phosphorylation of Cav-2 which increased the interaction between phospho-Tyr19 and phospho-ERK, indicating that this phosphorylation is required for actin cytoskeleton-dependent ERK nuclear import [156]. Cav-2 expression is also involved in pulmonary defects, lipid metabolism and cancer formation [150]. It has been shown that Cav-2 expression is more frequent in anaplastic carcinoma, papillary thyroid carcinoma and diffuse sclerosing variant of papillary carcinoma. This evidence confirms a role for Cav-2 in the modulation of cancer progression [157,158].

10. Caveolin-2 in cancer

Cav-2 expression was shown not to be altered in oncogenic transformation. Along this evidence, dual roles for Cav-2 have been documented in various cancer cells, as Cav-2 was neither expressed in HepG2 hepatocellular carcinoma cells, nor in SH-SY5Y neuroblastoma cells [158]. However, an increase in Cav-2 expression was documented in esophageal and urothelial carcinomas [159,160], as well as in C6 glioma, HeLa epithelial cervical cancer, A549 lung adenocarcinoma, and MCF7 breast cancer cells [161]. Cav-2 transfection of HepG2 hepatocellular carcinoma cells and Cav-2 knockdown in C6 glioma cells caused reductions in cell proliferation and growth, while Cav-2 re-expression in SH-SY5Y neuroblastoma, and depletion in HeLa epithelial cervical cancer and A549 lung adenocarcinoma cells promoted cancer cell proliferation. Collectively, these data suggest that Cav-2 acts as a modulator of cancer progression. Interestingly, Cav-2 was shown to negatively regulate lung endothelial cell proliferation and cell cycle progression [162], and to be associated with breast cancer basal-like and triple-negative immunophenotypes [163,164]. Cav-2 expression was up-regulated during the late stages of C6 glioma cell differentiation while Cav-3 was gradually down-regulated during this differentiation process [165]. In the case of renal cell carcinoma (RCC), Cav-2 was shown to be a direct target of the specific miRNA miE-218 which is considered to act as a tumor supressor in RCC. Silencing of Cav-2 mRNA and protein produced a high degree of inhibition of cellular proliferation and migration in RCC [166]. These data suggest that, like Cav-1, Cav-2 could be considered as a tumor suppressor or tumor promoter gene.

11. Caveolin-3

Caveolin-3 (Cav-3), the third member of the caveolin family, is more restricted in distribution than are Cav-1 and Cav-2, and has been particularly studied in vascular smooth muscle, cardiac and skeletal muscles [167], in glial cells [165], and in myoepithelial cells within the mammary gland [164]. Cav-3 was identified through database searches and through classical cDNA library screening in an attempt to find Cav-1 homologs. Human Cav-3 proteins contain 151 amino acids and contain specific, separate domains: A N-terminal domain (aa 1–53) which contains a signature sequence (aa 41–48) that is present in all caveolins, a scaffolding segment (aa 54–73) responsible for homo-oligomerization, a transmembrane domain (aa 74–106) and a C-terminal (aa 107–151) domain. The Cav-3 oligomerization process is believed to be initiated in the endoplasmic reticulum and presages the organization of detergent-resistant caveolar complexes of approximately 25–50 nm in diameter. These structures then fuse with the plasma membrane forming the final caveolae. The transmembrane domain forms a hairpin loop in the sarcolemma, allowing both the N- and C-terminal ends to face the cytoplasm. Cav-3 has a small ubiquitin-like modifier (SUMO) consensus motif (ΨKXD/E, where Ψ is a hydrophobic residue) near the scaffolding domain, allowing SUMOylation in a manner that is enhanced by the SUMO E3 ligase PIASy (protein inhibitor of activated STAT-y). Thus, SUMOylation is a

covalent modification of caveolins that influences the regulation of signaling partners [168]. Interestingly, Cav-3 also forms large oligomeric complexes of approximately 350–400 kDa *in vivo*. Cav-3-generated caveolae have been shown to compartmentalize, and to modulate a number of signaling proteins including eNOS, β-adrenergic receptors, protein kinase C isoforms, G proteins, Src-family kinases, multiple components of the dystrophin-glycoprotein complex [169,170], and natriuretic peptide signaling [171]. Additionally, it has been shown that point mutations in Cav-3 (P140L) can attenuate p38, AKT [172] and endoplasmic reticulum stress signaling [173].

In Cav-1-deficient knockout mice, caveolae were only detectable in skeletal and heart muscle cells [174,175], whereas no caveolar formation is observed in skeletal and heart muscle from Cav-3 knockout mice [176]. Tissues from Cav-1/Cav-3 double knockout mice are completely devoid of caveolae [177]. Together with a large body of data in the literature, these results validate the concept that either Cav-1 or Cav-3 is required to form caveolae. Cav-2, therefore, appears less important in this respect although the presence of this isoform does modulate morphological traits and efficacy in caveolar formation. The role of Cav-3 in cancer is still not well established and needs further investigation. In thyroid cancer, Cav-3 was highly expressed in the stroma of anaplastic carcinoma (AC) compared to papillary thyroid carcinoma (PTC) where Cav-1 and Cav-2 were highly expressed [158].

12. The cavins

Evidence for the presence of another protein family responsible for caveolae formation support the role of cavin proteins [178]. These cavins are composed of four types which include Cavin-1 (Polymerase 1 and Transcript Release Factor, PTRF), Cavin-2 (Serum-Deprivation Response Protein, SDPR), Cavin-3 (SDR related gene product that binds to c-kinase, SRBC), and Cavin-4 (Muscle-Restricted Coiled-Coil Protein, MURC), all of which share a role with Cavin-1 in the regulation of caveolae formation.

13. Cavin-1/PTRF

Cavin-1 (PTRF, Cav-p60) was identified by a yeast two hybrid screen as the first caveolin regulatory protein [179]. Originally believed to be a transcript release factor, Cavin-1 is a soluble protein with a putative leucine zipper, nuclear localization sequences and PEST (Proline, Glutamic acid, Serine and Threonine) domains. Studies have shown its colocalization and codistribution with Cav-1 in adipose tissue and in lipid rafts. In particular, Cavin-1 was recently shown to be an abundant caveolar coat protein required for caveolae stabilization and probably for interaction with the cytoskeleton [5,180,181]. Cavin-1 was shown to colocalize with Cav-1 at the plasma membrane but not in the Golgi apparatus [5]. It is recruited by Cav-1 and Cav-3 to plasma membrane domains where it binds to phosphatidylserine, cholesterol and oligomerized caveolins [182]. Binding of Cavin-1 to these domains stabilizes the membrane curvature as evidenced by the flask shape of caveolae. The interaction of Cavin-1 with Cav-1 is not direct, but is possibly mediated through cytoskeletal interactions between microtubules and actin filaments [5]. Live cell imaging demonstrated that the lateral mobility and lysosomal degradation of Cav-1 is enhanced by the loss of Cavin-1 [183]. Therefore, Cavin-1 is a potential caveolar coat protein that regulates caveolar structure and caveolin function.

14. Cavin-2/SDPR

Cavin-2 (SDPR) was purified as a phosphatidylserine-binding protein from human platelets [182] with greater expression in a serum-deprived microenvironment, giving rise to the name of serum deprivation protein [184]. Cavin-2 was also initially shown to potentially bind PKCα and to localize within caveolae [185]. It is now well recognized that biogenesis of caveolae requires both caveolin and Cavin-1 proteins although the identity, function and molecular interaction of other caveolar components remain unresolved. It was demonstrated that Cavin-2 recruited Cavin-1 to the plasma membrane, and was required for stable expression levels of both Cav-1 and Cavin-1 proteins [186]. This interaction leads to the formation of caveolin-containing complexes and to the stabilization of caveolar structures. Interestingly, overexpression of Cavin-2 results in the formation of elongated tubular caveolae, which implies that, unlike Cav-1 or Cavin-1, Cavin-2 does not increase caveolar number but rather induces changes in caveolar morphology [187]. The domains of Cavin-2 responsible for the formation of caveolae curvature comprise a potential helical coiled-coil forming region followed by another conserved domain containing multiple basic amino acids [186]. The membrane tubulations closely resemble those induced by the β-subunit of Shiga toxin (STB). It has been demonstrated that STB induces the formation of membrane tubes even in ATP-depleted cells [188], but whether such tubes arise because of the interaction of the toxin with membrane lipids, or whether additional membrane or cytosolic proteins are required remains unclear. Cavin-2-induced tubes originate from caveolae, and incorporate STB. Loss of Cavin-1, Cavin-2 or Cav-1 reduces the propensity of STB to induce membrane tubulation. Thus, formation of caveolae is not solely dependent on oligomerization of caveolin proteins, but also requires the involvement of other factors [189]. As there is no obvious sequence similarity between Cavin-2 and known curvature-inducing proteins, it is hypothesized that Cavin-2 may induce curvature by a novel mechanism [190]. Further insights into this will necessitate structural information.

15. Cavin-3/SRBC

Cavin-3 (SDR related gene product that binds to c-kinase, SRBC) localizes within caveolae [148] and was initially identified as a phosphatidylserine-binding protein and as a substrate of PKC [191]. Similarly to Cavin-2, its expression was also shown to be induced upon serum deprivation [191,192]. Binding of Cavin-3 to PKCδ depends on the presence of phosphatidylserine, which stabilizes its interaction with PKCδ through bridging. Cavin-3 also binds to PKCα to the same extent as to PKCδ, but it barely binds to PKCζ. Immunofluorescence-based evidence shows that all of the cavin proteins are required for the formation of caveolae, and that an individual caveola can contain more than one member of the cavin family [148]. The ability of these proteins to concentrate in caveolae is believed to be directly or indirectly dependent on the expression of Cav-1. Therefore, all cavins appear to have the properties of a caveolin adaptor molecule that links signal transduction to the regulation of caveolar function. Furthermore, Cavin-3 leads to the formation of caveolar vesicles as it remains associated with caveolae when budding occurs, and its absence impairs intracellular vesicular trafficking [193].

16. Cavin-4/MURC

It has been demonstrated that Cavin-4 (Muscle-Restricted Coiled-Coil Protein, MURC), the fourth member of the cavin family, is an evolutionarily-conserved, muscle-specific component of the cavin complex [194–196] which is associated with the sarcolemmal caveolae complexes. Cavin-4 is also present at low levels in other cell types, such as embryonic fibroblasts [197], and is able to interact with Cavin-2 [194]. Cavin-4 influences skeletal muscle differentiation by activating ERK and RhoA through the Rho-ROCK

pathway, which also modulates cardiac function. Overexpression of Cavin-4 in skeletal and cardiac muscle promotes myogenesis and causes cardiac dysfunction and conduction disturbance. These facts raise the possibility that mutations in Cavin-4 may directly cause muscle disease [197]. Therefore, Cavin-4 is considered to be a new potential candidate for muscle-related caveolinopathies.

17. Cavins in cancer

The role of cavins in caveolae formation is now well recognized. Recently, it has been proposed that Cavin-1 stabilizes Cav-1 expression and promotes its role as a tumor promoter in pancreatic cancer cells [197]. Gene silencing of Cavin-1 decreased cellular invasiveness and metastasis suggesting Cavin-1 as a potential therapeutic target [197]. In contrast, PC3 pancreatic cancer cells that expressed Cavin-1 showed a decrease in invasiveness and migration which correlated with reduced production of the matrix metalloproteinase MMP-9 [198], whose lowered expression associated with reduced angiogenesis and inflammation [199,200]. Cavin-1 and, to a lesser extent, cavins-2, -3, and -4, also decreased MMP-9. Genetic ablation of Cavin-1 also resulted in the loss of caveolae although Cav-1 expression remained albeit at a reduced level [186,201]. Taken together, these observations suggest that Cavin-1 expression alters prostate and pancreatic cancer aggressiveness via two different roles either as tumor suppressor or as tumor promoter respectively. Furthermore, it has been demonstrated that changes occur in cell membranes involving the loss of caveolae and of Cavin-1 expression concurrent with the development of prostate cancer. These changes were also accompanied by an up-regulation of Cav-2 [202]. Cavin-1 and Cavin-2 were shown to be expressed in MDR cell lines, and Cavin-1 was demonstrated to be involved in drug resistance by rendering lipid rafts more rigid [203]. In another study, Cavin-1 was confirmed as a non-small cell lung cancer biomarker by label-free proteomics and was shown to have a relationship with the EGFR pathway [204]. Similarly, Cav-1-induced tubule formation in breast cancer cells was suppressed by the presence of Cavin-1 [205]. Cavin-1 also acts as a novel regulator of oxidative stress-induced premature senescence by linking free radicals to activation of the p53/p21Waf1/Cip1-pathway [206].

In contrast to Cavin-1 and Cavin-2, Cavin-3's function and role in caveolae formation are not well established. The human Cavin-3 gene maps to 11q15.5–15.4 where it is located in a tumor suppressor region and is inactivated in breast and lung cancers [207]. The loss of Cavin-3 in lung cancer appears to be a consequence of DNA methylation and subsequent gene silencing [208], although other studies have suggested that alternate mechanisms could be involved. Targeting of Cavin-3 to caveolae depends on both its LZ domain and the expression of Cav-1. A recent study showed that Cavin-1 and Cavin-3 were down-regulated in breast cancer cell lines and breast tumor tissue [209]. However, given that cavins are required in conjunction with caveolins for caveolae formation, their role in tumor regulation will still require more investigation.

18. Mechanisms involved in the dual role of caveolins and cavins in cancer

Three distinct mechanisms, i.e. tyrosine phosphorylation, serine phosphorylation and P132L dominant negative point mutation, have been shown capable of counteracting the growth inhibitory function of Cav-1. These findings may, in part, explain the dual role of Cav-1; they depend on the tumor type/stage. Cav-1 undergoes tyrosine phosphorylation at its NH_2-terminus and then recruits several SH2-domain containing proteins, such as Grb-7. This, in turn, can increase either the anchorage-independent growth of cells or decrease anoikis [210]. Cav-2 tyrosine phosphorylation at Tyr19 and Tyr27 enables the recruitment of other SH2-domain containing proteins, such as c-Src, Nck, and Ras-GAP. Likewise, Cav-1 serine phosphorylation at Ser80 can serve to convert Cav-1 into a soluble, secreted protein [211]. The secreted form of Cav-1 apparently acts as a growth factor and can enable cells to defend against apoptotic stimuli. It has also been shown that tumor cells which secreted Cav-1 triggered proangiogenic activities in prostate cancer [212]. These are the possible mechanisms by which Cav-1 functions as a growth stimulator in prostate carcinomas and perhaps also in other cancers.

The caveolin scaffolding domain (CSD; residues 82–101) is also believed to inhibit the growth stimulatory activity of several signaling molecules, including receptor tyrosine kinases, Src-family kinases, and members of the Ras-p42/44 MAP kinase cascade. In this regard, the CSD may function as an endogenous kinase inhibitor by recognizing a conserved aromatic amino acid motif that is present within the kinase domain of most known kinases. However, it can also inhibit other signaling molecules, such as eNOS, by recognizing the same aromatic motif within the NOS catalytic domain [57,213]. However, only a limited number of studies have attempted to directly test binding of the CSD peptide to signaling proteins, and in these cases binding was not investigated in the context of an interaction with alleged caveolin binding motifs. Thus, the mechanisms involved in the inhibition of signaling by CSD and, more generally, in the effects of caveolin and/or caveolar loss of function on specific signaling pathways will necessitate reinvestigation, and potentially argues against a role for caveolin binding motifs in driving direct protein recruitment to caveolae via CSD [66].

Caveolin-related cancer research is still finding novel roles for the caveolins. In a recent study, Cav-1 was shown to be important for the endocytosis of E-cadherin and its downregulation resulted in decreased E-cadherin expression, increased β-catenin transcriptional activation, and increased invasiveness in neoplastic cells [214]. Furthermore, loss of Cav-1 function in the tumor microenvironment contributes to the metastatic behavior of prostate tumor cells by a mechanism that involves up-regulation of TGF-β1 and SNCG through Akt activation [215]. Similarly, in follicular thyroid carcinoma, reduced expression of Cav-1 down-regulated PTEN and tumor suppressive functions. Given that PTEN is required for activation of the phospho-Akt apoptotic pathway, down-regulation of its activity consequently leads to increased cell survival and proliferation [147]. In contrast, knockdown of Cav-1 in hepatocellular carcinoma cells strongly reduced TGF-β-mediated AKT phosphorylation, thus sensitizing primary murine hepatocytes for pro-apoptotic TGF-β signaling [216]. Gene expression microarray analyses in glioma cells demonstrated significant enrichment in genes corresponding to downregulation of MAPK, PI3K/AKT and mTOR signaling [217], as well as activation of apoptotic pathways in Cav-1-overexpressing U87-MG cells, as well as upregulation of MAPK/AP1 signaling in Cav-1 knocked-down cutaneous squamous cell carcinoma [218], supporting Cav-1's tumor suppressive role.

Several research groups have shown localization of MT1-MMP and MMP-2 to caveolae and depicted caveolae as being required for proper MT1-MMP localization and function in tumor development [36,219]. Furthermore, recombinant expression of Cav-1 in mammary epithelial cells was reported to suppress their metastatic capacity, to inhibit their invasiveness, and to prevent their ability to secrete MMP-2 and MMP-9. Given the heterogeneity of Cav-1 expression in various tumors, therapies targeting Cav-1 will need to consider the specific roles of this protein within a given specific type of tumor. In one exciting gene therapy strategy, the Cav-1 promoter was used to specifically target prostate cancer cells *in vitro* and *in vivo* with minimal toxicity [220]. Another type of anti-tumor therapy strategy was used to show that Cav-1 was

highly expressed in the vascular endothelium, suggesting that targeting a tumor's blood supply may provide an interesting opportunity for Cav-1-based directed therapies [221].

Cavin-1/PTRF is purported to be an essential component of caveolae, as it has been shown that recruitment of Cavin-1 to membrane domains, enriched in phosphatidylserine, cholesterol and oligomerized caveolins, was responsible for the stabilization of membrane curvature enabling the classic flask shape of caveolae. Loss of Cavin-1 releases caveolar components, including caveolins into the plasma membrane and the level of non-caveolar caveolins is thought to be tightly regulated via endolysosomal degradation [5]. In a recent report, it has been shown that Cavin-1 and Cav-1 can bind IGF-IR and regulate IGF-IR internalization and plasma membrane replacement through mechanisms frequently dysregulated in cancer cells, although the exact roles of Cav-1 and IGF-IR's in human cancer continue to be debated. With the discovery of IGF-IR interaction with Cavin-1 in caveolae, new insight has emerged in understanding the functions of these domains in IGF-I action [222]. Similarly, in metastatic PC3 prostate cancer cells that express abundant Cav-1 but no Cavin-1, heterologous Cavin-1 expression restored caveolae formation and Cav-1 distribution [5]. Recently, it has been shown that Cavin-1-expressing PC3 cells exhibited decreased migration, and that this effect was mediated by reduced MMP-9 production. Cavin-1, and to a lesser extent, Cavin-2, -3, and -4, all decreased MMP-9, suggesting that MMP-9 production may not solely depend on caveolae formation. Taken together, these observations suggest that Cavin-1 expression can inhibit prostate cancer aggressiveness by reducing MMP-9-mediated functions [201]. Interestingly, it was found that Cavin-1 was not expressed in prostate cancer epithelium [202,223,224]. In agreement with a protective role for Cavin-1 in prostate cancer, its down regulation in DU145 cells enhanced cell 3D migration [225]. Fhl1 induced the expression of Cavin-1 in Src-transformed cells, independent of MAPK activity, while Fhl1 and Cavin-1 expression were found to be suppressed in breast, kidney, and prostate tumors [226].

Several lines of evidence suggest that Cavin-3 may function as a tumor suppressor, but the molecular basis of its action remains unknown [227]. Cavin-3 was originally identified in screens looking for PKCδ-binding proteins, and was found to be phosphorylated *in vivo* by PKCδ, a potential tumor suppressor involved in the regulation of cell proliferation, differentiation, and apoptosis [191]. The mRNA for *Cavin-3* is induced in response to serum deprivation and is downregulated during G_0/G_1 transition, suggesting that it may be involved in cell-cycle control [191]. Through a yeast 2-hybrid screen, Cavin-3 was also identified as a BRCA1-interacting protein, raising the possibility that it may participate in DNA-damage response, and that its inactivation may compromise BRCA1-mediated tumor suppression functions [228]. Cavin-3 was also shown to increase p53 protein stability, and its proapoptotic effect stems partially from the p53-enhancing activity suggesting that dysregulation of Cavin-3 may attenuate p53's response to stresses and thus contribute to malignant tumor progression [229].

Cavin-3 is a proapoptotic tumor suppressor which is commonly altered in colorectal cancer by promoter hypermethylation, and whose gene transcription is directly activated by NF-κB in response to TNFα. This suggests that Cavin-3 inactivation may contribute to tumor progression by reducing cellular sensitivity to TNFα and to other stresses such as those due to a chronic inflammatory microenvironment [227]. It was further inferred that Cavin-3 induced G_1 arrest of the cell cycle partially through CDKN1A induction and that this increased the apoptotic response of tumor cells to various stresses including etoposide, 5-FU, γ-irradiation, H_2O_2, and serum deprivation. Consistent with these effects, Cavin-3 significantly decreased the colony-forming ability of tumor cells and delayed the formation and growth of xenograft tumors. It was also found that *Cavin-3* mRNA was strongly elevated in response to genotoxic or nongenotoxic stimuli, raising the possibility that it was controlled by stress signaling and involved in damage response. Moreover, Cavin-3 suppressed both basal and IGF-induced phosphorylation of AKT, without having any detectable effect on ERK and JNK [227]. It was further demonstrated that the p53-enhancing function of Cavin-3 might be associated with its regulatory role on AKT [230]. Therefore, these findings suggest that Cavin-3-mediated tumor suppression might be, in part, attributed to its ability to inhibit the PI3K-AKT signaling pathway which plays a crucial role in the development and progression of a variety of human tumors. Despite several lines of evidence for Cavin-3's tumor suppressive role, the molecular mechanisms underlying these actions in tumorigenesis are not fully understood (Table 3).

19. Concluding remarks

Caveolae formation and function is a crucial phenomenon in several normal or pathological events. Caveolae formation is dependent on the expression and interaction of two protein families, namely caveolins and cavins and current research has clearly

Table 3
The promoting and suppressive roles of cavins 1–3 in different types of cancer.

Tumor	Protein involved	Mechanisms involved	Role in cancer	References
Prostate cancer	Stromal Cav-1	TGF-β, Akt, γ-synuclein (SNCG)	Tumor Suppressor	[215]
Melanoma	Cav-1	Shh heterotypic	Tumor Suppressor	[254]
Thyroid cancer	Cav-1	PTEN, Akt	Tumor Suppressor	[147]
Mammary epithelial cells	Cav-1	p38 MAPK/JNK MAPK activation via TLR4	Tumor Suppressor	[247]
Glioblastoma	Cav-1	Inactivation of MAPK & PI3K/mTOR	Tumor Suppressor	[217]
Cutaneous squamous cell carcinoma	Cav-1	MAPK/AP1	Tumor Suppressor	[218]
Mammary cancer cells	Cav-1	Integrin/EGF	Tumor Promoter	[248]
Hepatocellular cancer	Cav-1	TGF-β	Tumor Promoter	[216]
Prostate cancer	Cav-1	IGF-IR/IR	Tumor Promoter	[220]
Colon cancer	Cav-1	AMPK-TP53/p53	Tumor Promoter	[36]
Breast cancer	Cav-2	MiR-199a-3p	Tumor Suppressor	[250]
Osteosarcoma	Cav-2	NFBD1/Erk	Tumor Suppressor	[251]
Renal cell carcinoma	Cav-2	miR-218	Tumor Promoter	[166]
Mammary tumor	Cav-3	Elf5, Stat5a, c-Myc	Tumor Promoter	[238]
Glioma	Cav-1 & Cav-2	VEGF	Tumor Promoter	[252]
Colon carcinoma	Cav-1 & Cav-2	PPAR-γ	Tumor Promoter	[253]
Prostate cancer	Cavin-1	MMP-9	Tumor Suppressor	[223]
Colorectal cancer	Cavin-3	NF-κB, TNF-α	Tumor Suppressor	[249]
Gastric cancer	Stromal Cav-1, Cavin-3	p53, p21, PUMA, OXA	Tumor Suppressor	[255,207]

established a role for caveolins and cavins as “tumor and metastasis-modifying genes”. Understanding the cross-interactions of these proteins, their structure and their function will in turn give insight into their involvement in diseases such as cancer where the formation or loss of caveolae modulators affects oncogenic functions. Cav-1 and Cav-2 were attributed dual roles in cancer, either as tumor suppressors or tumor promoters depending on the type and stage of cancer. Cav-3, expressed strictly in muscle, has also been documented as an essential protein for caveolae formation but its exact role in cancer remains to be defined. In some types of cancer such as breast cancer, overexpression of Cav-1 inhibits cellular metastasis, cellular adhesion, proliferation and migration whereas in other cancers, Cav-1 was reported to induce these phenomena. Cavin proteins were discovered after caveolin proteins and were also found to be essential components in caveolae formation. Four family members were identified and are thought to interact with caveolin in order to stabilize caveolae. More studies are needed to understand the roles and implications of cavins in cancer although several studies have revealed that expression of Cavin-1 and of Cavin-2 are downregulated in breast cancer cells and tissues. On the other hand, overexpression of cavins in prostate cancer has been shown to be associated with reduced expression of MMPs, which highlights its potential role in tumor suppression. Current research has clearly established roles for caveolins and cavins as «tumor- and metastasis-modifying genes» and, due to the heterogeneity of caveolin and cavin expression in different tumors, these proteins could therefore be targeted in cancer therapies. Future studies will undoubtedly reveal novel relationships between these proteins and their effects on a variety of signaling pathways. This will offer exciting opportunities to develop anti-cancer therapies that target them, both in primary tumors and in metastatic disease.

Authors' contributions

RG, CT and BA contributed to manuscript conception and writing. RG contributed to literature search and manuscript writing. CT and BA contributed to manuscript writing and critically revised the paper. All authors read and approved the final manuscript.

Conflict of interest

All authors declare no conflict of interest on the topics covered by this review.

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