# Membrane tension buffering by caveolae: a role in cancer?

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**Abstract**

Caveolae are bulb-like invaginations made up of two essential structural proteins, caveolin-1 and cavins, which are abundantly present at the plasma membrane of vertebrate cells. Since their discovery more than 60 years ago, the function of caveolae has been mired in controversy. The last decade has seen the characterization of new caveolae components and regulators together with the discovery of additional cellular functions that have shed new light on these enigmatic structures. Early on, caveolae and/ or caveolin-1 have been involved in the regulation of several parameters associated with cancer progression such as cell migration, metastasis, angiogenesis, or cell growth. These studies have revealed that caveolin-1 and more recently cavin-1 have a dual role with either a negative or a positive effect on most of these parameters. The recent discovery that caveolae can act as mechanosensors has sparked an array of new studies that have addressed the mechanobiology of caveolae in various cellular functions. This review summarizes the current knowledge on caveolae and their role in cancer development through their activity in membrane tension buffering. We propose that the role of caveolae in cancer has to be revisited through their response to the mechanical forces encountered by cancer cells during tumor mass development.

**Keywords** Caveolae · Cancer · Mechanosensing · Mechanotransdcution · Membrane tension · EHD2

## 1 Introduction

The cell membrane of eukaryotic cells is compartmentalized into microdomains with distinct functions. One such kind of specialized microdomains is called caveolae, and is present in many mammalian cell types. Structurally and biochemically caveolae differ from the other invaginations of the plasma membrane (PM), as they have a characteristic bulb-like shape (size around ~ 70 nm) and are enriched in sphingolipids and cholesterol. Caveolae were first described in 1953 as non-clathrin-coated "*plasmalemmal vesicles*" [1], and subsequently in 1955 as "*caveola intracellularis*" as they displayed a "cave-like shape" [2]. Caveolae have been reported in many different cell types, with the exception of neuronal and lymphoid cells, and are prominently abundant in adipocytes, endothelial, and muscle cells. Caveolin-1 (Cav1), the main structural protein of caveolae, was initially characterized as a substrate of the v-Src tyrosine kinase, almost 40 years after the discovery of caveolae [3]. If the characterization of Cav1

allowed a stream of cell biology and biochemistry experiments, which led to the discovery of several cellular functions regulated by caveolae, the role of caveolae has been constantly mired with controversy. The last decade has seen a new understanding of this fascinating organelle through a combination of new techniques, tools, and *in vitro* reconstitutions. In this chapter, we will more particularly address the recently discovered function of caveolae in cell mechanics and how this new aspect could be related to the long known but still enigmatic role of caveolae in cancer.

## 2 Caveolae components

The two core families of proteins that represent the structural components of caveolae are caveolins and cavins. Caveolin has three isoforms. Caveolin-1 (Cav1) is a 24-kDa protein identified almost 30 years ago [3, 4], expressed in most cell types, except muscle cells, and mainly localized at the plasma membrane and the trans-Golgi network [4, 5]. Caveolin-2 (Cav-2) is a 20-kDa protein with similarity to Cav-1 in many aspects, but differs in its functional interaction with signaling molecules [6]. The third isoform caveolin-3 (Cav3) is restricted to vascular smooth muscle, skeletal muscles, and cardiac cells [7, 8]. All caveolin isoforms have an N-terminal caveolin

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scaffolding domain (CSD), a transmembrane domain, and a C-terminal domain [5]. Cav1 and Cav3, but not Cav2, are indispensable for caveolae formation.

The role and importance of the second core family of protein, cavins, were discovered much later since the first member, cavin-1, was identified initially as PTRF (polymerase I and transcript release factor) in 2004 [9]. The cavin family encompasses four members, cavin-1 (PTRF), cavin-2 or SDPR (serum deprivation response protein), cavin-3 or SBRC (serum deprivation response factor-related gene product that binds to C-kinase), and muscle-specific cavin-4 or MURC (muscle-restricted coiled coil) [10, 11]. While each cavin isoform has a specific role in caveolae function, only cavin-1 is indispensable for caveolae formation [12]. In addition to caveolins and cavins, several accessory proteins have been reported to modulate various aspects of caveolae biogenesis, stability, and function, by mechanisms that are often not fully characterized. Pacsin2/Syndapin2 belongs to the F-BAR domain containing protein family which is instrumental to membrane curvature. Pacsin2 appears to control caveolae morphogenesis and mobility in concert with the membrane scission GTPase dynamin 2 [13, 14]. EHD2 is a dynamin-like ATPase that oligomerizes in a ring-like structure at the neck of caveolae [15]. EHD2 stabilizes caveolae at the plasma membrane and regulates their dynamics [16] through association with the actin cytoskeleton [16–20]. Whereas the three other members of the family do not normally localize to caveolae, in the absence of EHD1, EHD2 and EHD4 can be recruited to the neck of caveolae under repeated mechanical stress, revealing a certain redundancy within the family [16]. It is noteworthy that accessory proteins only partly colocalize with caveolae suggesting a transient association or the existence of caveolae subpopulations.

Lipids represent another class of important players involved in different aspects of caveolae biology. Early on, it has been reported that membrane lipids such as phosphatidylserine [21], glycosphingolipids [21], and cholesterol [22] are required for caveolae formation, dynamics, and integrity. Caveolin-1 localizes in the inner leaflet of plasma membrane where it interacts with cholesterol through its CSD, and this interaction brings about the unique shape of caveolae [23]. Caveolae are also a hub for important signaling lipids such as ceramide, phosphatidic acid, and glycosphingolipids [21, 24, 25].

If caveolin-1 and cavin-1 are established as the minimal structural proteins required for the formation of the caveolar invagination, the coordination of their likely complex stepwise assembly is far from being fully understood. Caveolin-1 is synthesized in the endoplasmic reticulum (ER) where it forms hetero-oligomers that assembles into 8S complexes [26]. The 8S complex is transported to the Golgi apparatus, where it associates with cholesterol and is subsequently trafficked en route to PM [26]. Once at the plasma membrane, the caveolin-1/cholesterol complex associates with lipids such as phosphatidylserine (PtdSer/PS) to generate nanodomains [25]. Cavin-1 is synthesized in the cytosol and trafficked to the plasma membrane where it has affinity for PS clusters [11, 12]. Accessory proteins such as Pacsin2 [13] and EHD2 [20, 27] are recruited to the caveolin-1 complex where they contribute to caveolae morphogenesis. It was therefore unexpected that the expression of Cav1 alone in bacteria was sufficient to drive the formation of caveolae-like structures without the aid of accessory proteins [28].

The very existence of caveolae was unveiled in the fifties by their typical shape in electron microscopy. Although the general morphology of caveolae has been known for decades, the field has awaited the high-resolution architecture of the caveolae protein subunits for more than five decades, a delay attributed to the unusual topology of Cav1 and the peculiarity of its interaction with the other caveolae constituents. The study of the ultrastructure of caveolae by high-resolution scanning and frozen deep-etch transmission electron microscopy, first revealed the presence of organized striations or spike-like structures on the inner surface of the caveolar bulb [29, 30]. Caveolae were defined as uncoated invaginations to distinguish them from the well-studied and better described clathrin-coated pits [31]. Recent ultrastructural studies on cavin-1 have however refuted this long believed postulate. Thus, the crystal structure of cavin-1 revealed that cavin-1 oligomers are assembled as trimeric coiled coil structures that organize a striated coat made up of cavin polymers [11, 32]. Recently, a model using cryoEM and 3D electron tomography was proposed, where cavin1 HR1 domain results in trimeric coiled coil structures, which eventually forms cavin oligomers. This has become highly appreciated model in recent time, where cavin-1 trimers decorate the membrane surface, and cavin-caveolin-lipid interaction stimulates invagination to provide the peculiar caveola shape [27]. As crystallization methods are continually improving, crystal structure of caveolin-1 (alone or in complex with associated lipids and/or proteins) will definitely enhance our understanding of caveola formation and function to a much greater depth.

## 3 Caveolae functions

Over the years, many functions have been attributed to caveolae and/or caveolin-1 ranging from plasma membrane organizers [33], lipid trafficking [34], endocytosis [35], signaling [36], and more recently mechanosensors [37, 38]. Some of these functions have been recently revisited and the consensus today is that caveolae play important roles in membrane bioactivity through the organization of signaling nanodomains and their interaction with lipids. The role of caveolae in endocytosis is certainly more modest than initially proposed [39]. It has been hypothesized that the membrane mechanosensing and mechanoprotective roles of caveolae could represent a unifying principle encompassing their different functions [40]. In the following sections, we will present the arguments

in favor of such a role in cancer. We will describe how the classical functions of caveolae that have long been associated with tumorigenesis could indeed be related to the recently described mechanical function of caveolae.

## 4 Caveolae and cancer: oncogenic or tumor suppressor?

Cancer is a complex condition involving many steps with either the activation of oncogenes or the inactivation of tumor suppressor genes. Over the years, numerous studies have associated caveolin-1 with various processes involved in tumor growth and cancer growth [41–43]. Today, more than 2000 PubMed studies in epidemiology, genetics, clinics, and molecular and cell biology converge to implicate caveolae and/or caveolins in several processes associated with cancer. This role remains nevertheless poorly understood and mired in controversy as most studies have reported a dual role for caveolin with either a positive or a negative effect on tumor growth [44, 45]. The role of tumor suppressor has been particularly well documented in breast cancers. For instance, *CAV1* knockout mice have provided evidence that Cav1 plays a dynamic role in the pathogenesis of mammary epithelial cell hyperplasia, tumorigenesis, and metastasis [46]. Expression of Cav1 RNAs is often reduced in primary breast tumors and in tumor-derived cell lines [47]. Reintroduction of *CAV1 in vitro* is sufficient to inhibit the tumorigenic traits of these cells. Interestingly, the human gene *CAV1* is present at a locus (D7S522/7q31.1) that is frequently deleted in human breast carcinomas. In this context, it is interesting that several studies from the Lisanti's group showed that the expression of Cav1 in epithelial and stromal cells (adipocytes, fat pads, fibroblasts) provides a protective effect against mammary tumorigenesis [48]. In contrast, another study shows that stromal Cav1 remodels peri- and intratumoral microenvironments *in vivo* to facilitate tumor invasion, correlating with increased metastatic potency [49]. Altogether, these data support Cav1 as a tumor suppressor that inhibits development of mammary tumors and metastases *in vivo*, as well as growth and transformation *in vitro* [50]. Reduced mRNA and protein levels of Cav1 were also associated with different stages and types of cancer including the lung [51], colon [52], ovarian carcinoma [53], or sarcomas [54].

In apparent discrepancy, several other studies show that Cav1 can also have an oncogenic function [50]. For instance, the migration and invasion of breast cancer cell lines are often positively correlated with Cav1 expression [55, 56]. Cav1 and Cav2 are expressed in myoepithelial cells in normal breast, upregulated in triple negative breast cancers, and associated with poor prognostic factors [57]. High expression of Cav1 was found in clinical tumor samples from renal [58], brain [59], and lung cancer [60]. More recently, cavin-1, the other key structural component of caveolae, has been studied for its role in cancer progression and has been reported to behave like caveolin-1 with a dual role as well [61]. Thus, cavin-1 is downregulated in breast cancer cell lines and breast tumor tissues [62] and prostate cancer [63]. Nevertheless, cavin-1 expression also enhances the tumor promoter role of Cav1 in pancreatic cancer, as it stabilizes Cav1 [64]. These studies therefore reinforce the notion that cavin-1 and Cav1, which often display the same properties, both have dual roles in cancer.

It has been proposed that this duality could result from a shift of the intrinsic growth inhibitory function of Cav1 towards oncogenicity. It was shown that this shift of activity could be controlled by the phosphorylation of caveolin-1 on tyrosine 14 or serine 80, and some dominant negative mutations [61]. Additionally, a variety of factors, alone or in combination, including cell transformation, physiological context, tumor stage, and nature of tumor stroma could contribute to the dual role of Cav1 [44, 65]. The fact that the expression of Cav1 in human cancer cell lines and tumor samples seems to depend on tumor type and stage may explain these apparent contradictions [66]. Thus, the role of Cav1 in tumorigenesis would clearly depend on the stage of the tumor with a tumor suppressor role in non-neoplastic tissues, a loss of expression during transformation and a re-expression in advanced tumor stages (metastases and multidrug resistance) [67]. If this model corroborates with most animal models and patient data, the molecular mechanisms controlling Cav1 levels with respect to tumor evolution still remain unknown.

## 5 The new role of caveolae in cell mechanics

Tissues and cells are constantly submitted to external mechanical stresses, both in normal and disease conditions, which they must withstand and respond to. Cells perceive their microenvironment not only through soluble signals and receptors, but also through physical and mechanical cues, such as extracellular matrix (ECM) stiffness, confined adhesiveness, and shear pressure. The plasma membrane of mammalian cells has evolved to be plastic, an essential quality to sense and transmit the various forces that cells experience *in vivo*. Cells translate these stimuli by mechanotransduction into biochemical signals controlling multiple cellular aspects such as cell growth and differentiation, and modulation of cell and tissue homeostasis [68]. It is noteworthy that caveolae are particularly abundant in muscle, endothelial, fibroblast, and adipocytes cells, all cells that constantly experience various types of mechanical stress. Early on, it was observed by electron microscopy that caveolae were reacting to mechanical stress by changing their morphology in muscle cells [69–71]. These studies were the first ones to suggest a possible role of caveolae in cell mechanics.

In 2011, the mechanical function of caveolae was revisited with new imaging tools and micromechanical devices. By combining cell biology with biophysics, the Lamaze and Nassoy laboratories could establish that the budded profile of caveolae constitutes a reservoir of membrane which buffers against instantaneous changes in membrane tension, thereby acting as key mechanosensors and mechanoprotectors [37]. Caveolae respond in a two-step mechanism consisting of the rapid flattening of the caveolar invagination, which is followed by its disassembly and the release of caveolin-1 and cavin-1, a passive process that is solely driven by the mechanical force. Upon stress release, caveolae reform immediately in a process that, in contrast to disassembly, is active and requires ATP. In the absence of functional caveolae, cells were unable to buffer changes in membrane area resulting in increased membrane tension and cell death by membrane rupture. The central role of caveolae in cell mechanics has since been confirmed in many different cell types and extended to living organisms [32]. Today, there is consensus that the classical functions of caveolae (trafficking, signaling, lipid metabolism) and their role in associated diseases (fibrosis, cancer, lipodystrophy, muscle dystrophies…) should be revisited through this new mechanical perspective (reviewed in [39]). Indeed, many of these diseases can be associated with defects of the mechanical response [72].

The role of caveolae mechanics in cancer has been less investigated. Nevertheless, recent studies suggest the possibility that some aspects of cancer progression could be controlled by caveolae mechanics. We will focus here on the role that caveolae mechanics could play in mechanosignaling and mechanotransduction and how this could be related to tumorigenesis.

# 6 Mechanical forces in cancer

Cells in multicellular tissues are subjected to a myriad of forces, including compressive, tensile, fluid shear stress, and hydrostatic pressure, each of which plays an intricate part in the shaping, development, and maintenance of the tissue. The manner in which cells interact with these forces, and hence respond to them, is largely dictated by the physical properties of the cells, their adjacent cells, and the extracellular matrix, which is the principal extracellular component of all tissues and organs. Matrix mechanical properties have been shown to modulate cell adhesion machineries [73], cell shape [74], and membrane tension [75] through changes in cell-generated forces, cytoskeleton contractility, and mechanosensitive channels. Furthermore, substrate topography and stiffness lead to drastic changes in focal adhesion (FA) distribution and dynamics as well as cytoskeletal tension [76, 77].

Also of paramount importance, tissue biomechanics can critically influence cancer progression through ECM composition, collagen network density, and tissue biomechanics [78]. In breast cancer management, increased mammographic density in relation with elevated collagen deposition, fiber alignment, and tissue stiffening are predictive of tumor progression and higher metastatic risk [79, 80]. Cancer cells exist in a constantly evolving tissue microenvironment of diverse cell types within a proteinaceous extracellular matrix. As tumors evolve, the physical forces within this complex microenvironment change, with pleiotropic effects on both cell- and tissue-level behaviors. Tumors are often characterized by an enhanced rigidity of their structure in comparison to the surrounding tissue [81]. While this aspect is well known to pathologists, it has been poorly explored at the molecular level and whether tissue stiffness could actively promote malignant transformation has yet to be demonstrated.

Several recent studies point to the emerging idea that the mechanical microenvironment of tumors may have an important role in the control of their evolution [82–84]. It was recently shown that magnetically induced pressure on non-tumorous tissues could activate the tumorigenic beta-catenin pathway and lead to malignant transformation [85]. In breast cancer cell lines, the degree of tumor rigidity and fibrosis may influence the first stage of cancer leading to the invasive stage when cells metastasize to other parts of the organism [86] and fibrotic "stiff" lesions have a poor prognosis [87]. In a study examining tissue rigidity and tumor behavior, matrix stiffness could be directly related to tissue growth and was suggested to be a key factor in tumorigenesis [88]. It was further shown that tumor rigidity reflected an increase in stromal stiffness and tumor cell tension, and that these two processes were linked through Rho and growth factor-dependent ERK activation, and involved integrins [89]. *In situ* biomechanical characterization of mouse mammary gland with atomic force microscopy revealed that mammary tissue stiffness increases as they transformed and that the epithelium, tumor-associated vasculature and the extracellular matrix each contribute to the mechanical landscape of the evolving tumor [90]. Importantly, isolated tumor cells also show an intrinsic higher membrane tension value than their normal counterparts [88].

It is likely that the caveolae disassembly/reassembly cycle will be affected in cellular microenvironments with increased membrane tension and rigidity such as those experienced by cancer and stroma cells during tumor mass progression. In support of this, cavin-1, -2, and -3, which are required to assemble a functional caveolae at the plasma membrane, are downregulated in breast cancer cell lines and breast tumor tissues [62]. Similarly, several studies revealed that breast tumors expressing a Cav1 P132L mutated form were more invasive [91, 92]. Although other studies have failed to identify this mutation [93], it is interesting that a similar mutation in the Cav3 muscle isoform results in lack of cell adaptation to increased membrane tension [37].

It is therefore plausible that the role of caveolae in tumor progression may involve, at least in part, the alteration of their mechanical function. The significance of caveolae in mechanical force buffering and mechanotransduction of breast cancer cells and breast tumors has not been investigated.

# 7 A new role for caveolae in mechanotransduction

A central function of caveolae that is likely to be controlled by mechanical forces associated with tumor mass growth is signaling. Indeed, earlier studies have postulated that caveolae and/or caveolins could act as a scaffold to facilitate the interaction with signaling molecules and organize specific signaling platforms at the plasma membrane [94]. This assumption relied on putative Cav1 interactions with many signaling effectors, and the impact of caveolae/Cav1 modulation on signaling outputs. Caveolae and/or Cav1 have been associated with a broad range of signaling pathways by organizing/recruiting many growth factor and receptor molecules such as eNOS, EGF-R, insulin-R, TGF-R, PDGF-R, and the small GTPase HRas... [95]. These signaling effectors can affect various gene profiles, cell proliferation and migration, anchorage dependence, or extracellular matrix remodeling [43]. It is worth noting that caveolae have been associated with *bona fide* mechanosignaling pathways including MAP kinase, Akt, Src kinases, and Rho GTPases [96]. Noticeably, the distribution of integrins at the plasma membrane in cells under mechanical stress is controlled by caveolae [97].

How caveolae and/or Cav1 control intracellular signaling remains poorly understood [32]. The N-terminus part of Cav1 contains a caveolin scaffolding domain (CSD), a conserved peptide sequence (82-DGIWKASFTTFTVTKYWFYR-101) that is required for Cav1 and Cav3 oligomerization. Interactions between Cav1 and downstream signaling molecules would occur through the CSD and a corresponding hydrophobic caveolin binding motif (CBM) identified in several effector proteins [98, 99]. The CSD-CBM interaction has been shown to be inhibitory in nature as initially reported for eNOS [36] and the heme-oxygenase-1 [98], and confirmed by following studies [100]. It is interesting that the tumor suppressor role of Cav1 has been shown to depend on the Cav1 CSD [50]. Recent structural and bioinformatics analyses however have casted doubts on this interaction [101]. The Cav1 CSD would be unlikely to physically interact with signaling molecules in fully assembled caveolae as it forms an in-plane amphipathic helix, which is buried in the plasma membrane [102]. In this context, a recent study showed that the function of caveolae in arteriolar endothelial cells was independent of the eNOS-mediated NO pathway [103].

It is therefore likely that the Cav1 CSD is unable to interact with signaling molecules in budded caveolae. Whether the Cav1 CSD could interact within the non-caveolar pool of Cav1 at the plasma membrane is an interesting possibility that should be tested. Indeed, it has long been suspected in the caveolae field that in addition to caveolae, Cav1 itself could also play a role in signaling. A few reports had suggested that intracellular signaling could be mediated by free Cav1, i.e., the pool of non-caveolar Cav1 present at the plasma membrane outside caveolae [32, 33]. Thus, expression of Cav1 at levels below the threshold for caveolae formation resulted in the assembly of stable oligomerized Cav1 microdomains, or scaffolds, which can inactivate signaling as shown for EGF-R signaling [104]. A possible bias in these studies comes from overexpression or transient knockdown of Cav1 that may not faithfully reproduce the endogenous levels of free Cav1 that is known to be barely detectable at the plasma membrane.

The function of non-caveolar Cav1 has long remained elusive [32] but recent studies have opened new perspectives. A first study combining proteomics with subdiffraction-limit microscopy indicated that Cav1 scaffolds are structurally and functionally distinct from caveolae [105]. More recently, super resolution microscopy analysis with 3D machine learning allowed to propose the existence of several distinct small scaffolds that can combine to form larger scaffolds and caveolae in HeLa cells [106, 107]. The plasma membrane would therefore present three distinct Cav1 assemblies with oligomerized caveolar Cav1, non-caveolar Cav1 scaffolds, and single Cav1 molecules. How these scaffolds are formed, their regulation, and function remain open but exciting questions. In the context of mechanical forces, it is intriguing that under hypo-osmotic shock, the amount of free Cav1 released from disassembled caveolae increased by three fold at the plasma membrane [37, 108, 109]. It is therefore possible to envisage that the ON/OFF cycle of caveola disassembly/reassembly induced by mechanical stress variations should have a major impact on the activation/inactivation cycle of signaling molecules either through their binding to the Cav1 CSD that would then be exposed or hidden accordingly. Thus, the changing mechanical environment associated with the evolution of the tumor mass in solid cancers would impinge the mechanodependent cycle of caveolae disassembly/reassembly, resulting in altered mechanosignaling, abnormal cancer cell proliferation, and increased invasion. In support of this, Src-dependent signaling was reported to be modulated by mechanical stress in a caveolae-dependent manner [110]. The activity of the Src kinase, the first kinase identified in Cav1 tyrosine phosphorylation [111], is involved in many processes related to cancer invasion [112]. For instance, Src activity is critical for invadopodia formation by phosphorylating and activating several essential invadopodia components [113, 114]. Thus, caveolae mechanosignaling could affect invadopodia formation and therefore cancer cell invasion through the control of c-Src activity.

In this context, a recent study has for the first time linked caveolae mechanosensing and mechanosignaling in the pathogenesis of human muscular dystrophies. Muscle cells of patients bearing the P28L and R26Q Cav3 mutations that are found in several types of human muscular dystrophies are devoid of functional caveolae at PM, and as a result defective in mechanoprotection. As a consequence, the IL6/STAT signaling axis, which is normally downregulated in response to caveolae flattening induced by myotube stretching, is constitutively hyperactivated leading to the upregulation expression of genes involved in muscle catabolism [115]. It will be therefore interesting to investigate whether the signaling of IL-6, a known pro-inflammatory cytokine in cancer, can be controlled by caveolae mechanical buffering in carcinomas.

In addition to the control of mechanosignaling by the release of non-caveolar Cav1 at the plasma membrane, other mechanotransducing mechanisms could be at play. Several recently discovered Cav1 partners (such as cavins, Pacsin2, EHD2) are good candidates for regulating caveolae disassembly/reassembly cycle under mechanical stress. Indeed, the mechanical disassembly of the caveolae structure leads also to the cytosolic release of peripheral proteins such as EHD2 and cavins [37, 108, 116, 117]. Particularly noteworthy is that cavin-1 and the EHD2 ATPase bear a nuclear localization sequence (NLS) and were initially identified as transcription factors [118, 119]. A recent study showed however that EHD2 but not cavin-1 was efficently translocated in the nucleus upon mechanical stress [116]. That cavin-1 is not translocated to the nucleus in response to mechanical stress [116] was unexpected since it is the only cavin family member that presents a nuclear localization signal. It was shown however that cavins can interact with cytosolic targets upon their mechanical release from disassembled caveolae. Biotin affinity proteomics revealed several cavin-interactor intracellular candidates involved in metabolism and stress signaling [117]. Furthermore, upon UV exposure, the release of cavin-1 and cavin-3 from caveolae led to their interaction with protein phosphatase 1 alpha, thereby increasing H2AX histone phosphorylation to stimulate apoptosis. Under cyclic stretch, EHD2 performed two essential functions: first, regulating the transcriptional program of several genes including but not limited to caveolae constituents as well as invasion and migration genes; second, EHD2 was required for the reconstitution of a stable pool of caveolae at the plasma membrane under mechanical stress in agreement with a recent study in mouse NIH3T3 cells [16].

In the context of cancer, several cell lines derived from triple negative breast cancer (TNBC) had low or no expression of EHD2 and lacked caveolae at their cell surface even though they expressed Cav1 and cavin-1 (Fig. 1). In these cells, gene transcription was not regulated by mechanical stress, and cell migration and invasion were strongly enhanced. Re-expression of EHD2 in EHD2-deficient TNBC cells was

sufficient to restore a pool of functional caveolae and decrease cell invasion and migration [116]. EHD2 appears therefore as a key mechanotransducer connecting mechanosensing with gene transcription. The role of EHD2 in breast cancer was further confirmed by the immunohistochemistry analysis of patient biopsies of the different subtypes of breast cancers that revealed that EHD2 was low in TNBC tissues and in TNBC-derived cell lines [120]. Remarkably, EHD2 was recently associated with tumor progression and reduced survival in several cancers including ovarian serous papillary carcinoma, hepatocellular carcinoma, and esophageal squamous cell carcinoma [121–123]. As for Cav1 and cavin-1, EHD2 expression can be correlated with either a bad or a good prognosis. Whether the role of EHD2 in these cancers is also connected with caveolae mechanics is unknown.

## 8 Caveolae and cell migration

Cell morphogenesis and motility are crucial processes at all stages of cellular life, from physiological events like embryogenesis and development to pathological conditions like cancer. Cell migration programs are central to cancer cell invasion and metastasis [124]. During their migration, cells continuously experience dynamic biochemical and mechanical interactions when they move through 3D interstitial matrix, guided by chemical and physical cues. Motile cells quickly adapt their morphogenetic programs to changing microenvironments, which requires the spatiotemporal integration of many mechanical and biochemical clues. Understanding how migrating cells read and interpret those mechanochemical stimuli remains an outstanding challenge in cell biology. Over the past 10 years, several studies pointed to a role of caveolae and/or caveolin-1 in cell migration. This role remains poorly understood with caveolae described as either promoting or inhibiting cell migration. For example, it has been reported that Cav1 knockdown results in decreased chemotaxis of endothelial cells, astrocytes, and multiple myeloma cells [125, 126]. On the other hand, other studies suggest that Cav-1 could be a negative regulator. For instance, forced expression of Cav1 in MTLn3 cells impairs lamellipodia formation and migration [127]. Furthermore, it is yet unclear whether the defects in global cellular translocation result from reduced velocity and/or reduced persistent migration.

These contradictory results may arise from differences not only in the cellular systems used, but also in the experimental setups that may not affect or challenge membrane tension in the same way. Caveolae are asymmetrically distributed in migrating cells with opposite polarity in 2D and 3D systems, raising the possibility that they could steer cell migration by locally regulating membrane tension [128]. Moreover, EGF-dependent Cav1 tyrosine phosphorylation promotes actin and matrix remodeling and tumor cell migration in metastatic breast cancer cells, a
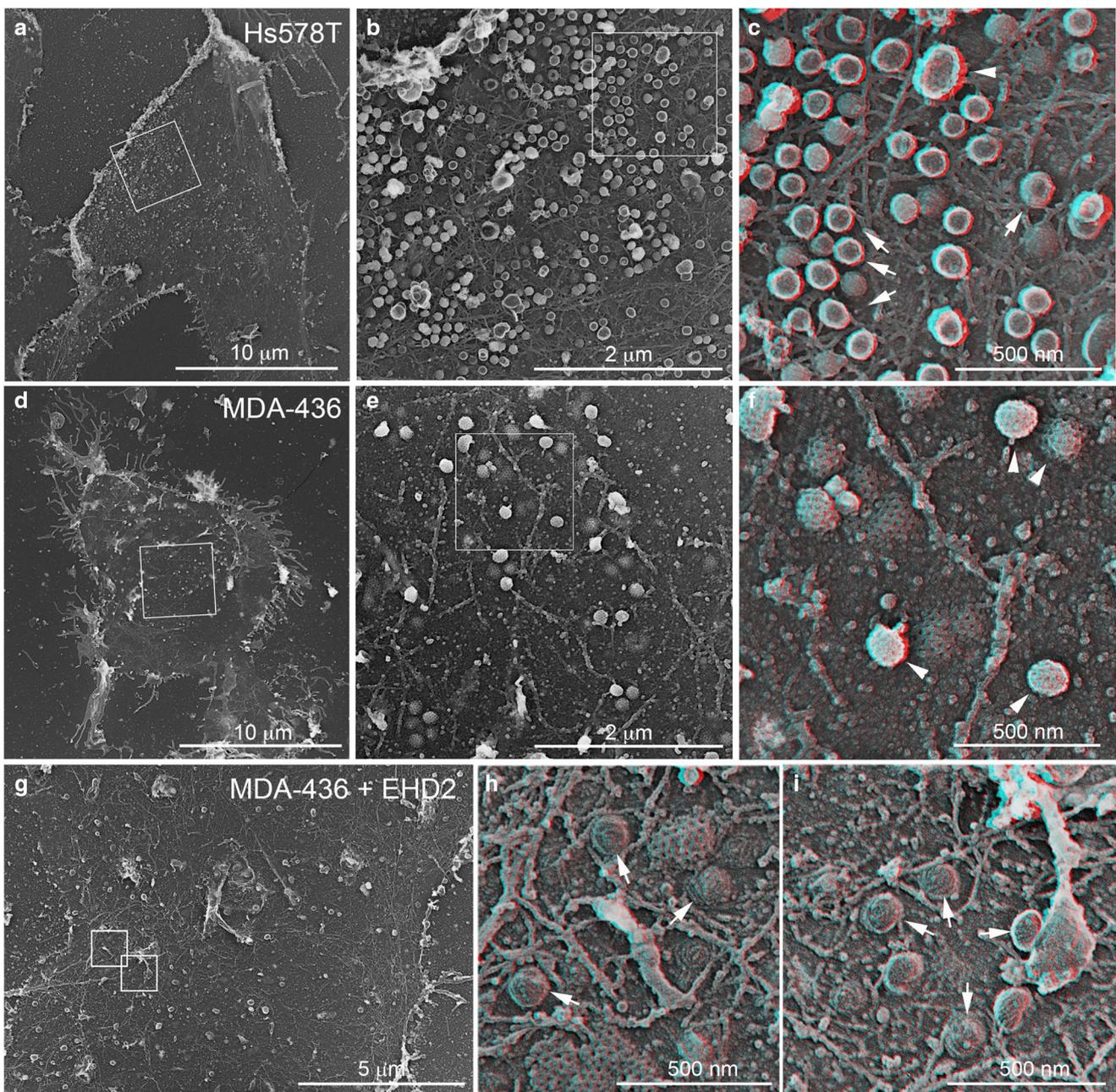
**Fig. 1** EHD2 expression is required for the presence of caveolae at the plasma membrane of breast cancer cells. **a–i** Survey view of the cytoplasmic surface of the plasma membrane in unroofed Hs578T (**a–c**), MDA-MB-436 (**d–f**) cells, and MDA-MB-436 cells transfected by EHD2-EGFP (**g–i**). For second inset (**c**, **f**, **h**, **i**) use view glasses for 3D viewing of anaglyphs (left eye = red). Arrows indicate caveolae. Arrowheads indicate clathrin-coated pits. Adapted from [116]

process involving fibronectin fibrillogenesis *via* Src and integrin-linked kinase (ILK)-dependent signaling [129]. Whether matrix remodeling and tumor cell migration depend on caveolae mechanosensing and mechanosignaling has not been addressed particularly in 3D environment and *in vivo* mimicking systems, but it is quite remarkable that mechanical stress results in Cav1 phosphorylation on tyrosine-14 (Y14) [110]. In this context, it is interesting that pY14-Cav1 binds to vinculin to enhance tension in focal adhesions, dampening force fluctuation and

synchronously stabilizing cellular focal adhesions in a high-tension mode, paralleling effects of actin stabilization. This identifies pY14Cav1 as a molecular regulator of focal adhesion tension to promote focal adhesion traction and, thereby, cancer cell motility [130].

The engine of cell locomotion is the acto-myosin machinery which, by pushing and/or pulling on the plasma membrane, enables membrane protrusions to extend, new adhesion sites to form at the cell front, and the detachment of the cell

rear. These processes not only depend upon, but also modulate membrane tension. In addition, obstacles and geometrical cues encountered during migration may also locally perturb membrane tension. Thus, membrane tension is a key mediator of mechanical cues and it has been implicated in the regulation of cell migration [131–133]. For instance, increase in membrane tension controlled by actin polymerization at the lamellipodium may prevent the formation of other lamellipodia at distal sites, thus reinforcing the persistence of migration in a given direction. In this context, a recent study reported that cells moving in cell-derived matrix established a positive feedback control of rear retraction by sensing membrane tension through caveolae. Thus, in response of low membrane tension, the formation of caveolae is favored at the cell rear. Caveolae can then activate the RhoA-ROCK1/PKN2 axis to regulate acto-myosin contractility and to support rear retraction and persistent migration [134]. These results are in agreement with the role of EHD2 in migrating cells [116].

Like caveolin-1, several studies report a role for cavin-1 in cell migration [135–138]. Cavin-1 knockdown promoted proliferation and migration of cultured vascular smooth muscle cells, and thus could be a potential target for the treatment of post injury vascular remodeling [135]. Contrary, in embryonal alveolar rhabdomyosarcoma RH30 cells, cavin-1 knockdown reduced cell proliferation and migration [137]. In the PC3 prostate cancer cells, which lack cavin-1, re-expression of cavin-1 resulted in decreased cell migration, a consequence of reduced matrix metalloprotease MMP9 production [136]. In DU145 prostate cancer cells and NIH3T3 fibroblasts, knockdown of cavin-1 increased cell migration [138]. Taken together, these studies suggest a dual role of cavin-1 in promoting/inhibiting cell migration, similar to caveolin-1.

## 9 Caveolae and chemoresistance

The efficiency of chemotherapy and radiotherapy is most often compromised by the development of resistance in tumor cells, which results in metastasis and cancer relapse in many patients. Multidrug resistance (MDR) in late cancer stages is generally associated with poor prognosis [139]. Cav1 has emerged as a promising target to study multidrug resistance (MDR) in several cancers, especially TNBC patients. Interestingly, caveolae are abundant in MDR cancer cells and short exposure to cytotoxic drugs induced Cav1 upregulation in several cancer cells including triple negative breast cancer (TNBC) cells [140–142]. Furthermore, Cav1 silencing re-sensitizes cancer cells to drug/radiation therapy and reduces chemoresistance in renal carcinoma, pancreatic cancer [143], and breast cancer stem cells [144]. Cav1 overexpression could aid cancer cells escape death, making it drug resistant and metastatic during advanced stage or on treatment with cytotoxic agents [45].

In this context, it is interesting that a recent study associated low EHD2 transcripts and protein expression levels in TNBC-derived cell lines and patient biopsies with enhanced proliferation, migration, and invasion [120]. Furthermore, the multivariate analysis of breast cancer patients followed for 30 years revealed that TNBC patients with low EHD2 expression showed a better response to chemotherapy. EHD2 acts therefore as a tumor suppressor in breast cancer and could be used as a prognostic marker for TNBC patients and as a biomarker to predict chemotherapy efficacy.

## 10 Conclusion and perspectives

If it is now well accepted that caveolae and/or Cav1 play an important role in tumor progression, the underlying molecular mechanisms remain poorly described. Whether caveolin-1 has a pro- or anti-tumoral function has been debated since the first description of its association with cancers, more than 30 years ago. While previous studies have simply focused on Cav1 transcriptomic changes in tumors, recent findings emphasize the need to investigate caveolae mechanobiology in the fluctuating membrane environment met during the different stages of tumor progression. In the future, it will be critical to address the potential crosstalk between caveolae mechanosensing and mechanotransduction, and other processes involved in tumor progression such as cell migration and invasion during metastasis. It is likely that the plasticity of the caveolar machinery and its impact on mechanosignaling and mechanotransduction are to be triggered by mechanically tensed intra- and extracellular tumoral environments. In this context, the design of new and improved methods of investigation enabling studies in three-dimensional (3D) environments is likely to significantly improve our understanding of these phenomena within complex tissue structures. 3D organoids have emerged as a powerful technology to culture tumoral and non-tumoral tissues in conditions preserving their initial characteristics [145, 146]. A few studies have started to investigate the role of Cav1 in organoid tumors. Thus, knocking down Cav1 in a 3D renal cell carcinoma chimera organoid model led to inhibition of the nephrogenesis program during epithelial tubule formation [147]. In a 3D prostate cancer model, Cav1 was found in tumor-derived exosomes and drove the induction of cancer stem cell phenotypes [148].

Targeting mechanosensing and mechanotransducing biochemical molecules is emerging as a new approach of cancer therapy. Current candidates include integrins, FAK, Src, and Rho/ROCK [149, 150]. In future, the identification of new factors involved in caveolae mechanotransduction and of possible abnormalities during the different stages of tumor progression could constitute an array of markers for cancer prognosis and may open new therapeutic strategies.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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