

## Chapter 2

# Caveolin-1 in Colon Cancer: The Flexible Connection to Wnt Signaling

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### Abbreviations

AA	Arachidonic acid
APC	Adenomatous polyposis coli
CK1	Casein kinase 1
CK2	Casein kinase 2
COX-2	Cyclooxygenase-2
CSD	Caveolin scaffolding domain
Dvl	Disheveled
FAP	Familial adenomatous polyposis
GSK3 $\beta$	Glycogen synthase kinase 3 $\beta$
HNPCC	Hereditary non-polyposis colorectal cancer
IAP	Inhibitor of apoptosis
LRP	Low-density lipoprotein receptor-related protein
MDR	Multidrug resistance
NSAIDs	Nonsteroidal anti-inflammatory drugs
PCP	Planar cell polarity
PGE <sub>2</sub>	Prostaglandin E <sub>2</sub>
PGH <sub>2</sub>	Prostaglandin H <sub>2</sub>
SCF	Skp1-Cul1-F-box-protein
Tcf/Lef	T cell factor/lymphoid enhancer binding factor
$\beta$ TrCP	$\beta$ -Transducin repeat containing protein

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## Introduction

Caveolins are a family of membrane-associated scaffolding proteins implicated in a variety of functions in cells including vesicle trafficking, cholesterol transport, and regulation of signal transduction processes [2, 102, 112]. To date, three major isoforms have been described in mammals, namely caveolin-1, -2, and -3. Caveolin-1 and -2 are fairly generically expressed, while caveolin-3 presence is limited to muscle and glial cells [102, 116, 148]. All three isoforms are encoded by distinct genes [148]. Different variants have been described for caveolin-1 and -2. In the case of caveolin-2, function remains poorly defined [117, 140]. Since evidence available to date has predominantly linked changes in caveolin-1 to cancer, we will focus the discussion here on this isoform.

For caveolin-1, two variants referred to as caveolin-1 $\alpha$  and -1 $\beta$  have been described that are generated by alternative initiation or splicing [72, 73, 124]. Caveolin-1 $\beta$  lacks the first 31 amino acids present in caveolin-1 $\alpha$ , which also contains the amino acid tyrosine 14 that is phosphorylated by src family kinases [18, 77] in response to growth factors like insulin [71, 82, 97, 98] or EGF [82, 103] and by extracellular stimuli including, UV, oxidative stress, or hyperosmolarity [19, 89, 121, 141]. The latter observations have implicated caveolin-1 and phosphorylation on tyrosine 14 in cellular stress responses. Consistently with this notion, caveolin-1 knockout mice have a reduced lifespan and are less resistant to partial hepatectomy [35, 105].

Caveolin-1 and its phosphorylated form are also implicated in cell migration. A specific sequence (amino acids 46–55) is required for the localization to the rear of migrating cells [132, 133]. These events are important for polarized distribution of cell signaling elements and directional cell migration [8, 63, 104]. Although phosphorylation of caveolin-1 on tyrosine 14 has been shown to favor migration via a process involving recruitment of the adaptor protein Grb7 [82], the precise role of caveolin-1 in these events remains an issue of controversy due to technical problems associated with the definition of phospho-caveolin-1 localization in migrating cells [58].

Despite these issues, a large body of literature is available linking the expression of caveolin-1 not only to enhanced migration but also to metastasis of cancer cells. Likewise, caveolin-1 is implicated in development of the multidrug resistance (MDR) phenotype of aggressive cancer cells. All three characteristics of caveolin-1 mentioned, namely its participation in cellular stress responses and regeneration, migration and metastasis, as well as MDR tend to favor the interpretation that caveolin-1 represents a protein whose presence favors tumor development. Such evidence, however, has generated an intense discussion concerning the precise role of caveolin-1 in cancer, since also a large body of data is available in the literature suggesting that caveolin-1 functions as a tumor suppressor (see subsequent sections). A key objective of this chapter will be to highlight important aspects of this ongoing discussion and reconcile in a working model (see Fig. 2.3) these different and opposing functions of caveolin-1. In doing so, we will focus our attention mostly on studies dealing with the role of caveolin-1 in colorectal cancer. There, as will be eluded to in the next section, alterations in the so-called canonical Wnt signaling pathway are particularly important.

## Canonical Wnt Signaling in Colorectal Cancer: The Role of $\beta$ -Catenin

Colorectal cancer is one of the most common cancers and a leading cause of cancer death worldwide. By the age of 70, roughly 50% of the Western population develops polyps, some of which will progress to cancer. The lifetime risk of developing cancer in this population is estimated to be 5% [65]. Despite the fact that the incidence of this cancer has decreased in recent years as a result of the introduction of preventive measures, including the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and changes in life-style and nutrition, the disease still remains a major threat. Every year, some 550,000 patients worldwide continue to succumb to the disease [49].

In molecular and genetic terms, colorectal cancer is likely to be one of the best-understood solid malignancies. The earliest detectable microscopic lesions are aberrant crypt foci, which progress over time to macroscopically detectable polyps. The transition to benign adenomas and then to malignant carcinomas is thought to be progressive. Our current molecular understanding of these events is strongly based on insights gained from hereditary forms of the disease that either involve mutations in the tumor suppressor protein *adenomatous polyposis coli* (APC, familial adenomatous polyposis (FAP) patients) or mismatch repair genes (hereditary non-polyposis colorectal cancer (HNPCC) patients). In the latter case, mutations in cancer causing genes, such as APC, are observed. Indeed, mutations in APC appear to represent a common event in a large majority of sporadic colon cancers, although the timing might vary considerably (reviewed in [114]). Despite such variations, the following sequence of events is invoked for the adenoma-carcinoma progression in colorectal cancer: First, colon tumors are thought to result from mutational activation of oncogenes (*K-ras*,  $\beta$ -catenin) and inactivation of tumor suppressor genes (APC and *P53* (*TP53*)), whereby APC mutation is often an early event; second, the accumulation of several mutations is required to generate the disease; third mutations may occur in a preferential order. However, this is not required and it is the accumulation of specific mutations together with the associated survival-enhancing characteristics that are most relevant [51, 114]. Given the aforementioned importance of APC mutations in the genesis of colon cancer, it is perhaps not surprising that the canonical Wnt signaling pathway represents an important mechanism implicated in the etiology of both, inherited and sporadic colorectal cancers.

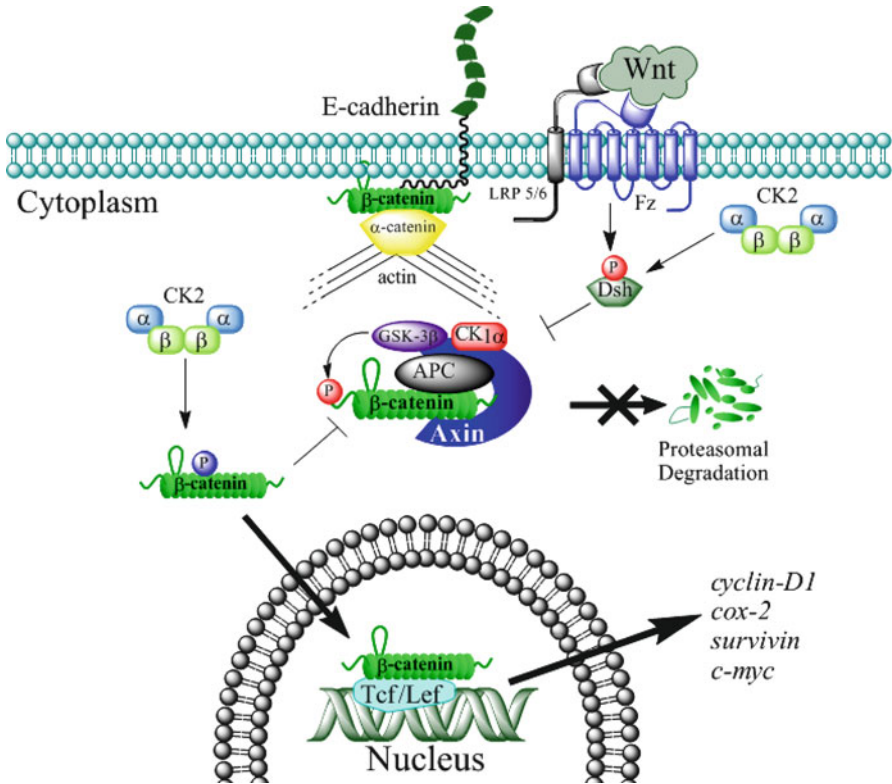
Wnt morphogens were originally described as factors involved in *Drosophila* development, and thereafter they became the focus of interest in other areas of research due to their implication in the development of human diseases like cancer. Two principle Wnt signaling pathways exist, referred to as the canonical and non-canonical pathways. For the non-canonical Wnt pathway, two variants have been described, the “Planar Cell Polarity” (PCP) pathway, which is important in the regulation of cytoskeletal changes associated with the development of the embryonic axis, and the “Calcium pathway,” which regulates cell adhesion [144]. Alterations in all signaling pathways (canonical and non-canonical) have been associated with the development of cancer [6, 9, 12]. However, to date, caveolin-1 interactions

predominantly with the canonical pathway have been reported. Thus, due to the focus of this book chapter, we will limit our discussion here to establishing connections between caveolin-1 and the canonical pathway, which still represents the best-characterized Wnt signaling pathway.

The canonical Wnt pathway is involved in the control of a large variety of processes, including cell proliferation, morphology, migration, and differentiation, all key events in the genesis and progression of cancer. A crucial molecular component in this pathway is the protein  $\beta$ -catenin [12, 109, 144]. A large number of studies in flies, frogs, and mammals have contributed to our current understanding of the importance of  $\beta$ -catenin turnover and localization for signaling via the canonical Wnt pathway (see Fig. 2.1). In non-stimulated cells, cytoplasmic free  $\beta$ -catenin is destabilized by the action of a multiprotein complex containing Axin/Conductin, glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ /Shaggy), and the tumor suppressor APC [12, 54, 56, 100, 109]. In this complex, Axin/Conductin acts as a scaffolding protein that binds APC, GSK3 $\beta$ , and  $\beta$ -catenin, thereby promoting the phosphorylation of APC and  $\beta$ -catenin, the latter being at specific serine and threonine residues located at the N-terminal end. Presence of the tumor suppressor p53 favors integration of Axin into this complex and hence phosphorylation of  $\beta$ -catenin [84].

Axin also associates with the protein kinase casein kinase 1 (CK1 $\alpha$ ), which phosphorylates  $\beta$ -catenin prior to GSK3 $\beta$  engagement and thereby promotes subsequent GSK3 $\beta$ -dependent phosphorylation, in a process referred to as hierarchical phosphorylation [54]. The importance of this sequence is substantiated by experiments showing that CK1 $\alpha$  silencing causes abnormal embryogenesis due to excessive canonical Wnt signaling as the result of reduced  $\beta$ -catenin degradation [92]. Subsequent phosphorylation of  $\beta$ -catenin by GSK3 $\beta$  drives ubiquitination by the Skp1-Cul1-F-box-protein (SCF) complex, which contains the F-box protein  $\beta$ TrCP/Slimb that contacts the phosphorylated N-terminus of  $\beta$ -catenin and promotes its ubiquitination via an E3 ubiquitin ligase and subsequent proteasome-mediated degradation [70]. The exact role of APC in the complex remains unclear, although the C-terminal region of APC reportedly regulates  $\beta$ -catenin phosphorylation by GSK3 $\beta$  [120]. Also APC phosphorylation favors interactions with  $\beta$ -catenin that enhance its subsequent degradation by favoring nuclear export [50, 55, 56, 151].

Wnt-dependent activation of the pathway requires two transmembrane receptors, Frizzled and LRP5/6 (low-density lipoprotein receptor-related protein 5/6), which form a complex that triggers signaling to the cytoplasm and precludes  $\beta$ -catenin degradation [101]. The LRP5/6 co-receptor is sequentially phosphorylated at several PPPSP sites by CK1 $\gamma$  and GSK3 $\beta$  [155]. CK1 $\gamma$  association with LRP5/6 at the membrane is necessary and sufficient to transduce the signal in vertebrates [27]. Phosphorylation of LRP5/6 promotes recruitment of Axin and Disheveled (Dvl/Dsh), whereby the latter inhibits GSK3 $\beta$  in the complex and prevents phosphorylation of  $\beta$ -catenin, APC, and Axin. Nonphosphorylated  $\beta$ -catenin does not bind to  $\beta$ TrCP/Slimb and translocates to the nucleus, where it displaces Groucho, a repressor of T cell factor/lymphoid enhancer binding factor (Tcf/Lef) family of transcription factors. In doing so, the expression of many target genes involved in cell progression, viability, and resistance to apoptosis, such as *myc*, *cyclin D1*, *cox-2*, and *survivin*, is



**Fig. 2.1** Scheme summarizing key events in the Wnt signaling pathway. The key molecular component of this pathway is the protein  $\beta$ -catenin. In cells,  $\beta$ -catenin is found in three subcellular locations, the plasma membrane, the cytosol and the nucleus. At the plasma membrane,  $\beta$ -catenin is present in complexes with  $\alpha$ -catenin and E-cadherin that are important for the regulation of cell-cell interactions and organization of the actin cytoskeleton. In the cytoplasm,  $\beta$ -catenin is part of a multiprotein complex containing Axin, adenomatous polyposis coli (APC), glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ), and casein kinase (CK1 $\alpha$ ). There, GSK3 $\beta$  phosphorylates  $\beta$ -catenin, which results in its ubiquitination and subsequent proteasome-mediated degradation. Wnt binding to Frizzled receptors (Fz) in association with co-receptors of the low-density lipoprotein receptor-related protein (LRP) family (LRP5/6) promotes Disheveled (Dvl) phosphorylation and thereby precludes  $\beta$ -catenin degradation. Additionally, CK2 can either phosphorylate and activate Dsh or directly phosphorylate  $\beta$ -catenin. Both canonical Wnt signaling and CK2-mediated events preclude  $\beta$ -catenin degradation and promote translocation to the nucleus. There,  $\beta$ -catenin acts as a transcriptional co-activator by associating with transcription factors of the T cell factor/lymphoid enhancer binding factor (Tcf/Lef) family and promotes the expression of a large number of genes, many of which are directly implicated in cancer, such as *cyclin-D1*, *cox-2*, *survivin* and *c-myc*. According to this model, both sequestration of  $\beta$ -catenin at the plasma membrane and degradation in the cytosol limit the amount of  $\beta$ -catenin available for translocation to the nucleus

enhanced [69, 75, 76, 96, 110, 134, 137, 138, 157]. More recently,  $\beta$ -catenin has also been suggested to function as a platform for the formation of chromatin-remodeling complexes [99].

Mutations in the N-terminus of  $\beta$ -catenin make it refractory to regulation by APC, decreasing phosphorylation of serine and threonine residues essential for degradation of  $\beta$ -catenin and thereby eliminating the phosphorylation-dependent interaction with  $\beta$ -transducin repeat containing protein ( $\beta$ TrCP). Mutations of the  $\beta$ -catenin N-terminus have been described in a number of human cancers, as well as in chemically- or genetically-induced animal tumor models. However, most tumors in colon cancer are associated with deletions at the C-terminal end of APC, while the frequency of mutations in  $\beta$ -catenin is surprisingly low [109].

In addition to the APC/axin complex that favors  $\beta$ -catenin degradation, another cytoplasmic complex exists that promotes the stabilization of  $\beta$ -catenin. This complex is thought to be activated by Wnt ligands and includes amongst others Dvl and the protein kinase CK2 as a central element [131]. CK2 is also suggested to participate as a critical component of the canonical Wnt pathway, since overexpression of this kinase mimics the dorsal axis development in *Xenopus* embryos probably by acting downstream of  $G\alpha_q$  and  $G\alpha_o$  and Dvl [29, 41]. By using immunoprecipitation, pull-down and in vitro activity assays, CK2 was shown to associate with and phosphorylate APC [131]. Notably, the same region of APC that is frequently deleted in colorectal cancers contains a sequence rich in basic residues that presumably inhibit the catalytic activity of CK2 [61]. CK2 inhibition by APC is thought to destabilize  $\beta$ -catenin, as well as Dvl and thereby block cell proliferation [131]. Protein kinase CK2 also interacts with and phosphorylates  $\beta$ -catenin, thereby increasing cytoplasmic stability [125, 130]. Consistent with these observations, CK2 overexpression promotes expression of the inhibitor of apoptosis protein (IAP) survivin, a known canonical Wnt target gene, while pharmacological CK2 inhibition decreases survivin expression [137]. Site-directed mutagenesis showed that phosphorylation of  $\beta$ -catenin by CK2 occurs mainly at threonine-393, where the proteins Axin and APC interact to promote its degradation [130]. Thus, CK2-phosphorylated  $\beta$ -catenin at residue 393 is thought to be protected from Axin and APC-dependent degradation, hence enhancing transcriptional activation [125].

Finally, ectopic expression of Wnt1 in the mammary gland cell line C57MG, as well as ectopic expression of CK2 $\alpha$  in the same tissue from transgenic mice, revealed that this kinase associates with and phosphorylates Dvl, as well as stabilizes  $\beta$ -catenin. Thus, elevated CK2 levels are associated with increased proliferation and hyperplasia in vitro and in vivo [78, 79, 131]. Despite this evidence, several aspects concerning the mechanism by which CK2 positively regulates  $\beta$ -catenin are controversial. For instance, it remains unclear whether the regulatory effects require only the CK2 $\alpha$  catalytic subunit- or the holoenzyme or whether all effects are associated exclusively with  $\beta$ -catenin phosphorylation. However, it is beyond the scope of this book chapter to discuss such aspects. The interested reader is referred to other studies which deal in more detail with these aspect [41, 125, 130, 131, 137, 142].

As outlined, the protein  $\beta$ -catenin is found at three principle intracellular locations: the membrane, the cytoplasm, and the nucleus. Association with protein complexes in

the cytoplasm modulates the turnover of the protein, while presence in the nucleus is associated with transcription. An alternative mode to restrict translocation to the nucleus is by sequestration at the plasma membrane. There  $\beta$ -catenin is bound to cadherins (i.e., E-cadherin in epithelial cells) in a multiprotein complex that links the membrane to the actin cytoskeleton and is thought to stabilize  $\beta$ -catenin. E-cadherin is a transmembrane protein with an extracellular domain involved in the  $\text{Ca}^{2+}$ -dependent homophilic interactions between molecules on adjacent cells. The cytoplasmic domain binds the proteins  $\alpha$ - and  $\beta$ -catenin (or plakoglobin), as well as p120-catenin in a multiprotein complex that connects to the actin cytoskeleton. In doing so, cadherins physically link neighboring cells to one another [44]. The complex also is involved in the formation and organization of functionally distinct cell junctions, such as tight and gap junctions, as well as desmosomes [48, 143]. All these macromolecular structures are mediators of signaling events between adjacent cells that contribute to phenomena important for epithelial homeostasis, such as contact inhibition [33]. Here, it is perhaps worth mentioning that although cadherin–catenin adhesive complexes are generally associated with  $\beta$ -catenin sequestration and stabilization, recent evidence suggests alternative,  $\beta$ -catenin phospho-destruction complexes exist at cell–cell contact sites that may also be relevant to tissue morphogenesis [95].

In summary, enhanced signaling via the canonical Wnt pathway due to genetic and epigenetic changes is considered a major factor contributing to the development of colon cancer. A central player in this pathway is  $\beta$ -catenin that, once in the nucleus, promotes transcription of cancer-related genes in association with the Tcf/Lef family of transcription factors. Of particular interest in the subsequent discussion will be *cox-2* and *survivin* as target genes. Limiting  $\beta$ -catenin access to the nucleus is hence crucial to controlling such activities. Essentially two different mechanisms have been described: one involving proteasome-mediated turnover and other by sequestration to the plasma membrane. Available evidence indicates that perturbations in any one of these two pathways favor development and progression of colon cancer. Hence, the following sections will center on the discussion of our current understanding of how caveolin-1 participates in this scenario.

## **Role of Caveolin-1 as Tumor Suppressor in Colorectal Cancer: Inhibition of $\beta$ -Catenin-Tcf/Lef-Dependent Gene Expression**

Over the previous 15 years, a large amount of data has become available associating the presence of caveolin-1 with tumor suppression. However, as will be discussed later on, the ability of caveolin-1 to act in this fashion depends on the cellular context. Thus, caveolin-1 can be considered a “conditional” tumor suppressor. In the following paragraphs, data favoring a role for caveolin-1 as a tumor suppressor will be briefly summarized before focusing the discussion particularly on linking this ability to control of Wnt signaling pathways.

Initially, oncogene-mediated transformation of NIH3T3 fibroblasts was correlated with reduced caveolin-1 mRNA and protein levels, and re-expression of the protein

was sufficient to revert cell transformation [32, 74]. Likewise, selective loss of caveolin-1 expression using a siRNA approach was sufficient to transform NIH3T3 fibroblasts [40]. Furthermore, caveolin-1 expression is reduced in a number of human tumors, including lung, mammary, colon, and ovarian carcinomas, as well as ovarian sarcomas and osteosarcomas [10, 11, 17, 59, 83, 113, 145, 146]. Here too, re-expression of caveolin-1 frequently, but not always, reverts characteristics associated with the transformed phenotype [7, 67, 88, 136, 153, 154]. More recently, decreased caveolin-1 level has been reported for lymph node metastases from head and neck squamous cell carcinoma and restoration of caveolin-1 expression suppressed growth and metastasis [156].

Despite the fact that caveolin-1 depletion in mice knockout models does not affect overall viability, it is now clear that caveolin-1 absence increases lung and mammary hyperplasia, angiogenesis, as well as carcinogen-induced tumor formation in skin tissue [20, 30, 115, 147]. Also, increased mammary and intestinal stem cell proliferation is observed in caveolin-1 knockout mice and caveolin-1 was also recently shown to control neural stem cell proliferation [64]. Finally, stromal expression of caveolin-1 in breast cancer predicts outcome, recurrence, and survival, further highlighting its relevance as a potential therapeutic target [129, 150]. Indeed, caveolin-1 mutation on P132L, which was previously linked to breast cancer [53], was recently demonstrated to predict recurrence and metastasis in a mouse orthotopic model [13]. Taken together, these reports demonstrate that caveolin-1 displays traits consistent with a role as a tumor suppressor. This ability of caveolin-1 has often been linked to inhibition of signaling events associated with cell survival and proliferation. However, it is important to note that alternative mechanisms have also been proposed. For a more detailed discussion of literature related to the tumor suppressor hypothesis, the interested reader is referred to additional reviews [111, 149].

Initially, our entrance to the caveolin field came with the demonstration that caveolin-1 protein levels are reduced both in the mucosa and stroma of tumors from patients with colon cancer, as well as in colon adenocarcinoma cells and that caveolin-1 functions as a tumor suppressor *in vivo* upon re-expression in different colon adenocarcinoma cells [10, 11]. Despite the ever-increasing abundance of signaling molecules available in the literature for regulation by caveolin-1 at the time, relatively few were linked to specific transcriptional events. Thus, as one approach, we set out to compare, by microarray analysis, colon cancer cell lines expressing or not caveolin-1. Rather intriguingly, those studies identified in an initial screen the IAP protein survivin as one of the most strongly down-regulated targets at the transcriptional level [138]. This protein is of tremendous interest, since it is abundantly expressed in a variety of human tumors including lung, colon, breast, prostate, pancreatic, and gastric carcinoma, but is essentially absent in most normal tissues. Importantly, survivin expression in cancer cells is linked to tumor survival. These characteristics define survivin as a tumor-specific antigen [1, 85, 118].

The difficulty, at the time, consisted in linking the expression of what was generally considered a plasma membrane bound scaffolding protein (caveolin-1) to specific transcriptional regulation. Suggestive hints in that respect came from two reports showing that caveolin-1 inhibits canonical Wnt signaling pathway by sequestering  $\beta$ -catenin to the plasma membrane and preventing the transcription of genes, such

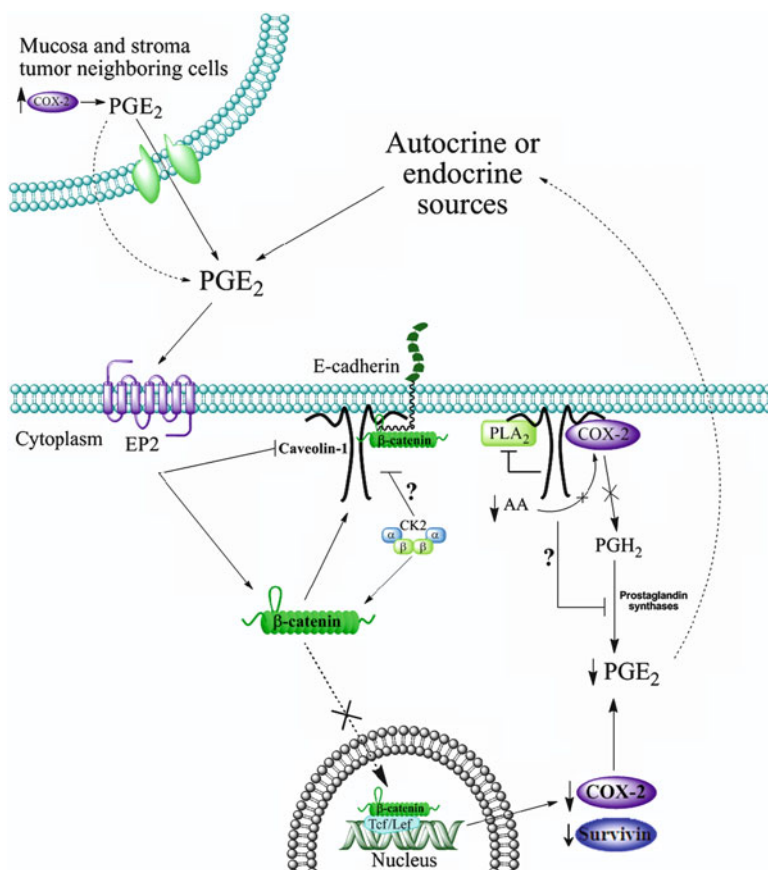
as *cyclin-D1* [39, 62]. Furthermore, the possibility that caveolin-1 might regulate *survivin* expression via the  $\beta$ -catenin pathway became all the more likely when *survivin* was identified as a  $\beta$ -catenin-Tcf/Lef target gene [69, 157]. Given the relevance of this pathway to the genesis of colon cancer, these results inspired the experiments that are summarized in a working model (see Fig. 2.2).

The following studies in a number of different cell lines, including human embryonic kidney cells (HEK293T), breast (ZR75), and colon (DLD-1) cancer cell lines, as well as mouse NIH3T3 fibroblasts confirmed the suspicion that caveolin-1 limited  $\beta$ -catenin-Tcf/Lef-dependent transcription of the *survivin* gene by a mechanism involving formation of a multiprotein complex and sequestration to the plasma membrane. Interestingly, limitations imposed on cells by the presence of caveolin-1 in terms of viability and proliferation were overcome by the re-expression of *survivin* [138]. These observations were subsequently confirmed in HT29 colon adenocarcinoma cells. Furthermore, the HT29 studies revealed that formation of caveolin-1/ $\beta$ -catenin multiprotein complexes at the cell surface required the presence of E-cadherin. In the absence of this protein, the ability of caveolin-1 to limit  $\beta$ -catenin-Tcf/Lef-dependent transcription of the *survivin* gene was lost. These findings were also shown to be valid in metastatic B16-F10 murine melanoma cells [139].

Given that many genes are regulated by the Wnt pathway, studies were initiated to identify other potentially interesting cancer-related genes. In this context, the analysis focused on Cyclooxygenase-2 (COX-2), a protein that is frequently up-regulated in cancer. Increased levels of COX-2 augment prostaglandin  $E_2$  (PGE<sub>2</sub>) production enhance  $\beta$ -catenin-Tcf/Lef-dependent transcription, cellular proliferation, and reduce apoptosis [21, 127, 128]. In human colorectal cancer cells, increased expression of COX-2 is also associated with cancer progression and phenotypic changes that promote metastasis. Interestingly, NSAIDs that specifically inhibit COX-2 activity have been shown to be quite effective in chemoprevention of FAP patients. Thus, COX-2 is of great interest as a target in cancer therapy [49].

As suspected, ectopic expression of caveolin-1 down-regulates also *cox-2* expression by suppression of  $\beta$ -catenin-Tcf/Lef-dependent transcription via sequestration of  $\beta$ -catenin to the plasma membrane. Interestingly, the presence of E-cadherin is also required here [119]. Several previous studies linked COX-2 and *survivin* expression, not only because they are both  $\beta$ -catenin-Tcf/Lef-dependent genes, but also because COX-2-dependent mechanisms involving PGE<sub>2</sub> are part of a positive feedback loop that potentiates signaling events linked to enhancing *survivin* levels (see Fig. 2.2). Regulation of *survivin* in this manner may also implicate post-transcriptional mechanisms [76]. Since loss of E-cadherin is frequently observed in human epithelial tumors [22], these studies suggested that the combined loss of caveolin-1 and E-cadherin in epithelial cells promotes increased expression of genes relevant to epithelial–mesenchymal transition, loss of cell–cell contacts, and cell transformation.

Perhaps even more importantly, they provide mechanistic insights to how caveolin-1-specific suppression of genes associated with its role as a tumor suppressor becomes “conditional,” that is dependent on the cellular context [111, 139]. Interestingly, this ability of caveolin-1 is not only limited by the proteins present within cells expressing caveolin-1, but also by factors present in the cellular medium.



**Fig. 2.2** Caveolin-1-mediated inhibition of the canonical Wnt and cyclooxygenase-2 (COX-2)/prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) signaling pathways. Caveolin-1 presence promotes recruitment of  $\beta$ -catenin to the plasma membrane in association with E-cadherin, thereby decreasing  $\beta$ -catenin-Tcf/Lef-dependent transcriptional activity and the expression of genes like *cox-2* and *survivin*. Alternatively, caveolin-1 may inhibit phospholipase A<sub>2</sub> (PLA<sub>2</sub>) and reduce the levels of arachidonic acid (AA), thereby limiting the ability of COX-2 to produce prostaglandin H<sub>2</sub> (PGH<sub>2</sub>), or caveolin-1 may reduce the activity of prostaglandin synthases that convert PGH<sub>2</sub> to PGE<sub>2</sub>. PGE<sub>2</sub> is depicted as acting in an autocrine or paracrine/endocrine fashion when derived from neighboring mucosa and/or stroma cells. Subsequently, PGE<sub>2</sub> can bind to receptors of the EP family (specifically depicted EP2) and thereby trigger signaling events that disrupt both the cytosolic complex that promotes  $\beta$ -catenin degradation and the caveolin-1-containing complex that sequesters  $\beta$ -catenin to the membrane. Both mechanisms enhance  $\beta$ -catenin-Tcf/Lef-dependent transcriptional activity and target gene expression. CK2 activity can also increase  $\beta$ -catenin-Tcf/Lef-dependent transcription. However, whether this ability is associated exclusively with regulation of the  $\beta$ -catenin degradation complex remains an open question. According to our model, reduced presence of caveolin-1 in tumor cells and/or the stroma compartment will generate an environment that facilitates COX-2 expression, PGE<sub>2</sub> production and  $\beta$ -catenin-Tcf/Lef-dependent transcription of cancer-related genes

In particular, caveolin-1 expression was shown to limit  $\text{PGE}_2$  accumulation in the culture media of HEK293T, DLD-1, and HT29 cells. Moreover, supplementation of media with  $\text{PGE}_2$  disrupted caveolin-1-complexes responsible for sequestration of  $\beta$ -catenin to the plasma membrane [119].

Although our recent findings suggested that caveolin-1 presence decreased COX-2 expression and  $\text{PGE}_2$  levels via a transcriptional mechanism [119], other possible scenarios by which caveolin-1 may decrease  $\text{PGE}_2$  levels must be considered, given that  $\text{PGE}_2$  is produced by the concerted action of several enzymes. Initially, arachidonic acid (AA) is generated by phospholipase  $\text{A}_2$  ( $\text{PLA}_2$ ) and converted to prostaglandin  $\text{H}_2$  ( $\text{PGH}_2$ ) by COX-2.  $\text{PGH}_2$  is then specifically converted to  $\text{PGE}_2$  by the prostaglandin synthase  $\text{E}_2$  [106]. Thus, caveolin-1 may also interfere with any of these intermediate steps. Interestingly, in this context, caveolin-1 co-localizes both with  $\text{PLA}_2$  [47] and COX-2 [91, 108] in caveolae [47, 108]. Moreover, caveolin-1 co-fractionates and co-immunoprecipitates with both proteins [43, 91]. Importantly, caveolin-1 inhibits the enzymatic activity of  $\text{PLA}_2$  and decreases AA production via an interaction with the “caveolin-1 scaffolding domain (CSD)” [43], although the enzymatic activity of COX-2 appears not to be affected [91]. Thus, in addition to the aforementioned process of transcriptional regulation, one may envisage a scenario in which association of caveolin-1 with  $\text{PLA}_2$  and/or COX-2, possibly in a common complex, will reduce  $\text{PGH}_2$  availability and  $\text{PGE}_2$  production. Hence, our model (Fig. 2.2) depicts both these mechanisms as possibilities by which caveolin-1 may inhibit  $\text{PGE}_2$  production.

Additionally,  $\text{PGE}_2$  is exported through the plasma membrane, either by passive diffusion or by active transport, for example via the multidrug resistant protein 4 (MDR-4) [106], which is overexpressed in some colon cancer cell lines [60]. Thus, we cannot rule out the possibility that caveolin-1 may also modulate  $\text{PGE}_2$  transport from the cytosol to the extracellular space (see Fig. 2.2).

In summary, loss of caveolin-1 is associated, at least early on, with the development of some tumors. A majority of the data available suggests that this is the result of transcriptional silencing of caveolin-1 gene by epigenetic mechanisms (reviewed in [111]). The findings related to E-cadherin and  $\text{PGE}_2$  highlight the existence of alternative modes of restricting caveolin-1 function that do not rely on gene silencing. Instead, the ability of caveolin-1 to function as a tumor suppressor appears limited by both intracellular and environmental factors [111, 119]. The latter observations suggest that inflammatory processes and events occurring in adjacent stroma cells are likely to be highly relevant to the role caveolin-1 plays in epithelial cells, both in early and later stages of tumor development. In this context, it is important to note that caveolin-1 protein levels are reduced in both the mucosa and stroma from tumors when compared with the same samples from normal colon tissue [11]. In view of these observations, it is intriguing to speculate that alterations in caveolin-1, not only in the epithelial compartment, are likely to be relevant to the genesis of colon and other cancers. Furthermore, once liberated from complexes, for instance with E-cadherin, caveolin-1 would be free to engage in other activities not necessarily related to tumor suppression (see following sections).

## Caveolin-1 Expression in Colon Cancer: Tissue Analysis

The human intestine is divided anatomically into two segments, the small and the large intestine, whereby the first is considerably longer (6–7 m in an adult) than the second (roughly 1.5 m). Both segments are composed of several layers, including the mucosa (glandular epithelium and muscularis mucosa), submucosa, muscularis externa (inner circular and outer longitudinal), and lastly the serosa. As might be expected based on the presence of a considerable variety of cells in this tissue, including epithelial and muscle cells (see section “Introduction”), all three isoforms (caveolin-1, -2, and -3) have been detected in both intestinal segments [90]. Results from the literature suggest that caveolin-1 and -2 are expressed in epithelial cells of the small intestine and colon (Table 2.1).

Most available studies have focused on the analysis of caveolin-1 in the human colon; however, data are controversial. On the one hand, caveolin-1 is reportedly present in normal colon mucosa, as well as stroma and expression is reduced in tumors of different stages [11]. On the other hand, data arguing that caveolin-1 levels are elevated in colon tumor samples has also been provided [37, 107]. Specifically, caveolin-1 expression was increased in samples of adenocarcinomas, but not adenomas and normal mucosa [37]. Studies in rodents investigating the role of caveolin-1 in colon carcinogenesis are generally scarce. In one such study, caveolin-1, but not caveolin-2, expression increased in a rat model of adenocarcinoma induced by azoxymethane [107]. To the contrary, however, another study using caveolin-1 knock-out mice points to a role for caveolin-1 in controlling proliferation of intestinal crypt stem cells [86]. Clearly more experiments are required to clarify these discrepancies concerning caveolin-1 expression and function in humans and rodent models.

A review of the literature summarizing data available concerning caveolin expression in human, mouse, and rat intestine is shown in Table 2.1. In the majority of these studies, caveolin-1 mRNA and protein were detected in the mucosa of the intestine, specifically in epithelial cells [4, 5, 11, 36, 94]. Studies in tumors also offer controversial data, indicating that caveolin-1 may decrease in mucosa and stromal cells [11] or increase in epithelial cells [37] and in distant metastases [66].

## Caveolin-1 Expression in Colon Cancer: Human Colon Cancer Cell Lines

The aforementioned controversy concerning caveolin-1 expression is further highlighted by the situation in cell lines (see Table 2.2). For a number of colon adenocarcinoma cells (HT29, DLD-1, Lovo, Co112, SW480, SW620), low caveolin-1 expression levels have been reported [11, 15, 107], while for others (T84, HCT116) caveolin-1 levels are readily detectable [5, 23, 36, 107]. A number of possible

**Table 2.1** Expression of caveolin-1 and caveolin-2 in intestinal tissues

Pathological status	Species	Segment	Cell type or tissue analyzed	Caveolin isoform	Detection method	References
Normal	H	SI	EpiC	Cav-1	WB, IHC, RT-PCR	[5]
Normal	H	SI	EpiC	Cav-2	RT-PCR	[5]
Normal	H	SI, CR	Whole tissue	Cav-1	NB	[11]
Normal	H	SI		Cav-1	WB, RT-PCR	[36]
Normal	H	CR	SMC, EnC	Cav-1	IHC	[4]
Normal	H	CR	N.d.	Cav-2	IHC	[4]
Normal	H	CR	Mucosa/Stroma	Cav-1	WB	[11]
Normal	H	CR	EpiC	↓ Cav-1	IHC	[37]
Normal	H	CR	EnC	Cav-1	IHC	[37]
Normal	M	CR	EpiC	Cav-1	WB	[94]
Inflammation	H	CR	SMC, EnC	Cav-1	IHC	[4]
Inflammation	H	CR	EpiC	↑ Cav-2	IHC	[4]
Adenoma	H	CR	EpiC	↓ Cav-1	IHC	[37]
Carcinoma	H	CR	Mucosa	↓ Cav-1	WB	[11]
		CR	Stroma	↓ Cav-1	WB	[11]
		CR	Glands	↑ Cav-1	IHC	[37]
Carcinoma	H	CR		↑ Cav-1	IHC	[66]
Carcinoma	H	CR		↑ Cav-1	IHC	[66]
Carcinoma	H	CR	Tumor	↑ Cav-1	RT-PCR	[68]
Experimental carcinoma	R	CR	Mucosa	↑ Cav-1	WB, RT-PCR	[107]
Distant metastasis	H	CR		↑ Cav-1	IHC	[66]

Species: *H* human; *M* mouse; *R* rat  
Segment: *SI* small intestine; *CR* colorectum  
Cell type: *SMC* smooth muscle cell; *EnC* endothelial cell; *EpiC* epithelial cell  
Detection method: *WB* Western blotting; *IHC* immunohistochemistry; *RT-PCR* reverse transcription-polymerase chain reaction; *NB* Northern blot  
*N.d.* Analyzed but not detected

**Table 2.2** Expression of caveolin-1 and caveolin-2 in human colorectal carcinoma cell lines

Cell line	Source <sup>a</sup>	Caveolin isoform	Detection method	References
T84	Colorectal carcinoma derived from lung	Cav-1	WB/RT-PCR	[5]
		Cav-2	RT-PCR	[5]
Caco-2	Colorectal adenocarcinoma	↓ Cav-1	WB/NB	[11, 15]
		↓ Cav-1	WB	[107]
Caco-2E	Colorectal adenocarcinoma	Cav-1	WB, IHC, RT-PCR	[36]
		↓ Cav-2	WB	[15]
		Cav-1	WB/RT-PCR	[5]
HCT116	Colorectal adenocarcinoma	Cav-2	RT-PCR	[5]
		Cav-1	WB	[23]
HT29	Colorectal adenocarcinoma	Cav-1	WB	[57]
		Cav-1	WB, RT-PCR	[107]
		↓ Cav-1	WB/NB	[11, 15, 16]
HT29-MDR	Colorectal adenocarcinoma	Cav-1	WB, RT-PCR	[107]
		↑ Cav-1	WB	[80]
SW480	Colorectal adenocarcinoma (Dukes' type B)	↑ Cav-2	WB	[80]
		↓ Cav-1	WB/NB	[11, 25]
SW620	Colorectal adenocarcinoma derived from lymph node (Dukes' type C)	↓ Cav-1	WB/NB	[11]
Col12	Colorectal adenocarcinoma (Dukes' type C)	↓ Cav-1	WB/NB	[11]
DLD-1		↓ Cav-1	WB/NB	[11]

<sup>a</sup>Data obtained from ATCC web site (<http://www.atcc.org>)  
Tumor stage in brackets

explanations may help explain these often contradictory observations. For instance, Caco-2 cells have been observed both to express or not caveolin-1 (Table 2.2). These variations may be linked to cell passaging, since differences in caveolin-1 expression have been reported for Caco-2 with low (Caco-2E) and high passage numbers (Caco-2L) [93]. Also, augmented caveolin-1 levels in colon cancer cell lines have been associated with MDR and elevated metastatic potential. For instance, HT29-MDR cells obtained by selecting HT29 cells for growth in increasing concentrations of colchicine [14] or HT29-5M21 and M12 cells obtained from HT29 cells by selection in the presence of methotrexate [11] all have elevated caveolin-1 levels with respect to HT29 cells. Alternatively, cells with elevated metastatic potential, such as Lovo E2 and C5 as well as HT29(US), express higher caveolin-1 levels than the reference lines, Lovo and HT29(ATCC), respectively [11, 139]. Finally, caveolin-1 expression levels may vary quite dramatically upon exposure of colon and other cancer cells to different stress situations, including the addition of hydrogen peroxide (Gutierrez-Pajares and Quest, unpublished data).

Indeed, similar variations in caveolin-1 expression linked to MDR and metastasis have also been observed in other cancer cell lines. Likewise, a significant amount of data is available in the literature associating elevated caveolin-1 levels in prostate, breast, and other cancers with angiogenesis, aggressive cancer recurrence, enhanced metastasis and generally reduced patient survival (reviewed in [111]). More recently, caveolin-1 was found to represent an independent predictor of decreased survival and higher metastatic potential, not only in colon, but also in breast cancer [66]. Moreover, gene expression profiling identified caveolin-1, together with PKC $\alpha$  and Enolase 2 as the main targets up-regulated in HT29 cells resistant to methotrexate, while E-cadherin was repressed in resistant cells [126]. This result is remarkably similar to the aforementioned situation in HT29 cells, where HT29(US) with elevated metastatic potential, unlike the original HT29(ATCC) cells, essentially lack E-cadherin, but have modestly increased (roughly fivefold) caveolin-1 levels [139]. Interestingly, siRNA-mediated targeting of caveolin-1 decreased viability of resistant cells in the presence of methotrexate and reconstitution of E-cadherin in addition to caveolin-1 depletion further sensitized these cells to the chemotherapeutic drugs [126].

In summary, these observations may be taken to indicate that caveolin-1 levels can fluctuate considerably depending on the circumstances. Consistent with this possibility, a large number of mechanisms have been described that may either promote or suppress caveolin-1 expression in both non-transformed and cancer cell lines (reviewed in [111]).

## The Ambiguous Role of Caveolin-1 in Cancer

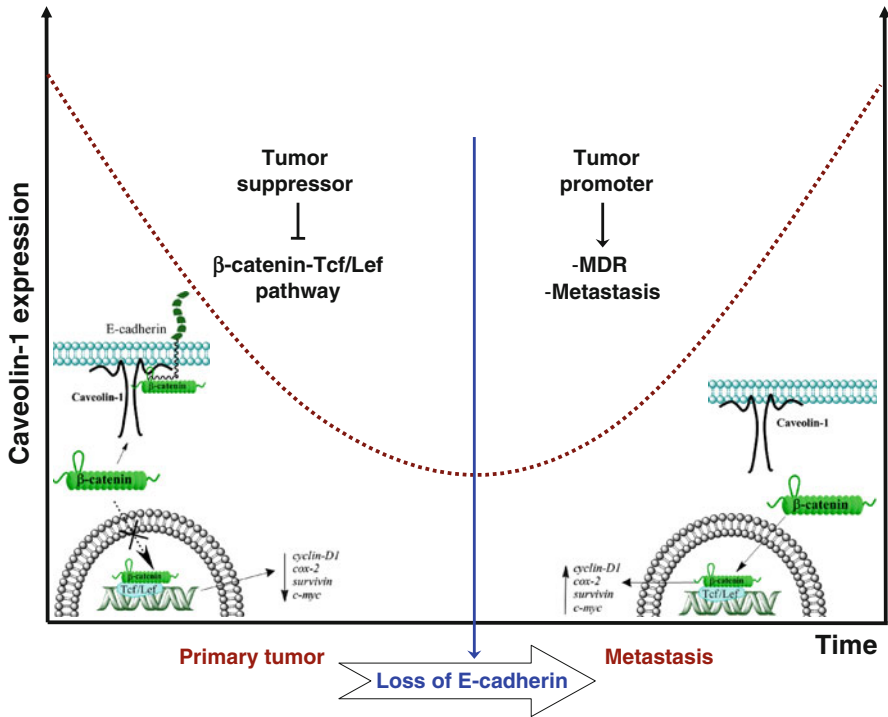
Despite the abundance of evidence summarized previously indicating that caveolin-1 functions as a tumor suppressor, there is also evidence suggesting a radically different, even opposite role for caveolin-1. This potentially conflicting interpretation of data in the literature already became apparent from the summary provided concerning

the expression of caveolin-1 in colon tissue and cancer cell lines (see previous section). Furthermore, caveolin-1 is known to promote tumor formation and its presence is correlated with poor prognosis and survival in prostate cancer. Indeed, the expression of caveolin-1 reportedly increases in primary tumors from prostate [154] and certain leukemia-derived cell lines [52]. Also, in prostate cancer cells, caveolin-1 presence increases tumor growth and the incidence of metastasis [7, 67, 88, 136]. Increased caveolin-1 expression in tumor samples is not restricted to cases, like the prostate, where normal tissues have low relative caveolin-1 levels, since increased expression was also reported in tumor models where initial caveolin-1 loss is observed, such as colon [11] and breast cancer [38, 42, 123]. In most of these cases, the available data argue for a strong positive correlation between expression of caveolin-1, metastasis, and MDR [42, 80, 81]. Moreover, studies in samples derived from esophageal squamous cell carcinoma [3], small cell lung carcinomas [59], colon cancer cells with high metastatic potential ([11], see below) and gastric cancer [16], revealed that caveolin-1 expression correlates with poor patient prognosis. Furthermore, caveolin-1 is also overexpressed in nasopharyngeal carcinoma and protein levels correlate there with poor prognosis, enhanced tumor cell migration, and metastasis [31]. Finally, caveolin-1 was recently associated with tumor promotion in a panel of melanoma cell lines, since increased expression correlated with enhanced proliferation, cell migration, and tumorigenicity [34].

A variety of mechanisms have been proposed to explain how caveolin-1 may promote tumorigenesis. As so often, these depend on the tumor model under study. For example, in prostate cancer cells, increased caveolin-1 levels were found to favor growth factor release and regulation by a positive feedback loop that enhances tumor cell invasiveness [87] and VEGF-associated angiogenic signaling [135]. In breast cancer cells, caveolin-1 was recently shown to associate with type 1 matrix metalloproteinase, both promoting invadopodia formation and matrix degradation, thereby providing a mechanism explaining increased invasiveness [152]. Indeed, caveolin-1 increased hepatocellular carcinoma cell motility and invasiveness was associated with augmented metalloproteinase expression and secretion together with down-regulation of E-cadherin [26]. Successful tumor cell migration requires proper cell polarization, directionality, and the ability to invade new surrounding matrices. Importantly, caveolin-1 is known to promote cell polarization and directional migration in different experimental settings [8, 104]. Indeed, in transmigrating endothelial cells, caveolin-1 was shown to interact with intermediate filaments [122]. In support of this, a body of evidence involves caveolin-1 in regulating the small GTPases Rho and Rac, which are required for actin dynamics, cell polarization, and directional migration [28, 45, 46].

The role of caveolin-1 in tumorigenesis has not only focused on mechanisms of migration and invasiveness. It was recently suggested that in human lung carcinoma cells, caveolin-1 undergoes proteasome-dependent degradation during anoikis, and resistance induced by nitric oxide involves decreased caveolin-1 ubiquitination and impairment of apoptotic responses [24].

Taken together, the data summarized in this section collectively support the view that caveolin-1 expression is linked to the acquisition of traits associated with malignant cell behavior, including MDR and metastasis, as well as poor patient prognosis in the clinic (see Fig. 2.3).



**Fig. 2.3** Dual role of caveolin-1 in tumorigenesis. In colon cancer, loss of caveolin-1 is depicted as correlating initially with enhanced  $\beta$ -catenin-dependent transcription and the acquisition of traits associated with tumor development, including increased proliferation and decreased apoptosis. Re-introduction of caveolin-1 into tumor cells that still express E-cadherin (early stages of tumor development) leads to the repression of  $\beta$ -catenin-Tcf/Lef-dependent transcription of genes, such as *cyclin D1*, *cox-2*, *survivin* and *c-myc*. However, during tumor progression multiple changes occur at the molecular level (i.e., genome instability, genetic mutations and/or epigenetic alterations). One such possibility is the loss of E-cadherin. In this now “permissive” cellular environment, caveolin-1 can no longer repress pathways associated with its role as a tumor suppressor, including the canonical Wnt signaling pathway. Instead, traits of the molecule prevail that favor the development of multi-drug resistance (MDR) and metastasis. This view is consistent with data in the literature associating caveolin-1 expression at later stages of tumor development with higher metastatic potential, MDR and poor patient survival. Finally, our model reinforces the view that caveolin-1 is a “conditional” tumor suppressor and that its ability to promote or suppress tumor development depend both on the cellular context and environmental conditions

## The Caveolin-1 Conundrum: Summary and Outlook

The data summarized here reinforce the notion that caveolin-1 plays a dual role in cancer (reviewed in [111, 112]). The ambiguity of caveolin-1 function is perhaps best reconciled by the view portrayed for colon cancer in Fig. 2.3. An initial loss of caveolin-1 is depicted as being followed by re-expression at later stages. Early on the cellular environment is such that if caveolin-1 is re-expressed, it develops traits consistent with a role as a tumor suppressor. In our model, regulation of the Wnt

signaling pathway is depicted as one possibility. Surely, many more are likely to exist. During tumor progression, the cellular context changes, since expression of a large number of proteins is altered. One such possibility highlighted here is the loss of E-cadherin. Bearing in mind the effects of the  $\text{PGE}_2$  that were discussed, it is important to note that not only “intracellular” but also “extracellular” changes need to be considered. The latter may represent the consequence of events occurring within the tumor cell itself, the stroma compartment or both. Later, if caveolin-1 expression is triggered by events that remain as yet poorly defined, the protein will no longer encounter a cellular environment conducive to its role as a tumor suppressor, indicated here as the loss of its ability to suppress  $\beta$ -catenin-dependent transcription. Instead, other characteristics of the protein prevail, favoring the acquisition of characteristics associated with malignant cell behavior.

Although complex, the emerging picture is beginning to reconcile a large amount of data that at first sight appear contradictory. In doing so, the traditional view of cancer as a disease dominated by the interplay between oncogenes and tumor suppressors is blurring. Clearly, this image in black and white needs refining. Hence, learning more about such details by investigating caveolin-1 is likely to bring a great deal of insight to cancer biology per se. Two immediate needs in caveolin-1 research have become apparent. First, we need to improve our knowledge of what “environmental” and “cellular” components determine whether caveolin-1 functions one way or another. Second, a specific understanding of the elements within the protein that are required in vivo for the molecule to act as a tumor suppressor or promote opposing characteristics in a tumor cell is essential. With these insights at hand, we can expect to initiate the design and use of successful caveolin-1-based strategies in the treatment of cancer.

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