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Caveola-forming proteins and prostate cancer

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Abstract

Caveolae are specialised and dynamic plasma membrane subdomains, involved in many cellular functions including endocytosis, signal transduction, mechanosensing and lipid storage, trafficking, and metabolism. Two protein families are indispensable for caveola formation and function, namely caveolins and cavins. Mutations of genes encoding these caveolar proteins cause serious pathological conditions such as cardiomyopathies, skeletal muscle diseases, and lipodystrophies. Deregulation of caveola-forming protein expression is associated with many types of cancers including prostate cancer. The distinct function of secretion of the prostatic fluid, and the unique metabolic phenotype of prostate cells relying on lipid metabolism as a main bioenergetic pathway further suggest a significant role of caveolae and caveolar proteins in prostate malignancy. Accumulating *in vitro*, *in vivo*, and clinical evidence showed the association of caveolin-1 with prostate cancer grade, stage, metastasis, and drug resistance. In contrast, cavin-1 was found to exhibit tumour suppressive roles. Studies on prostate cancer were the first to show the distinct function of the caveolar proteins depending on their localisation within the caveolar compartment or as cytoplasmic or secreted proteins. In this review, we summarise the roles of caveola-forming proteins in prostate cancer and the potential of exploiting them as therapeutic targets or biological markers.

Keywords Caveolae · Caveolin-1 · Cavin-1 · Prostate cancer

1 Introduction

Prostate cancer (PCa) is the most diagnosed cancer and the second leading cause of cancer-related death in men in Western countries [1]. Introducing the PSA test in the early 1990s has facilitated the disease diagnosis at very early stages, giving patients the opportunity to opt for active surveillance and to avoid the side effects of treatment. However, a subset of those patients have a high risk to develop aggressive tumours and would have benefited from a prompt treatment at the time of diagnosis. Since the 1940s, androgen deprivation therapy has been established as a main strategy to manage PCa, yet it impacts patient quality of life and inevitably all patients develop resistance against therapy and progress to the deadly incurable castrate-resistant prostate cancer (CRPC) stage. Discovering biomarkers that can identify patients with a high risk of developing aggressive disease and new therapeutic targets that can delay and treat CRPC is necessary to improve patient quality of life and survival rates. In this review, we discuss the involvement of small plasma membrane structures, called caveolae, and the proteins necessary to their formation and function, in PCa oncogenesis, and the potential of using these proteins as biomarkers and therapeutic targets. Caveolae (little caves) were first described in 1953 and defined as smooth plasma membrane invaginations devoid of clathrin coat [2]. Advances in microscopy imaging further characterised caveolae as 60- to 80-nm flask-shaped specialised subdomains. The coat of caveolae displays a striped structure under platinum-replica electron microscopy (PREM). They differ from the clathrin-coated pits that are wider in diameter (~ 100 nm) and whose coat is more evident and uniform and shows a network of hexagons under PREM [3–5].

Structurally, caveolae consist of sphingolipids, cholesterol, glycosylphosphatidylinositol-anchored proteins, and integral membrane proteins [5, 6]. Two proteins were thought to be

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essential and sufficient for caveola formation and have been studied thoroughly, namely caveolin-1 (CAV1) in most cell types (caveolin-3 in muscles) and CAVIN1 or polymerase I and transcript release factor (PTRF) [7–11]. However, recent reports found that pacsin2/syndapin2 is indispensable for caveola formation [12, 13]. Other proteins can be found in the caveolae that are not essential for caveola formation but can alter the shape, size, or function of caveolae, including caveolin-2 (CAV2), cavins (CAVIN2 or serum deprivation protein response (SDPR), CAVIN3 or serum deprivation response–related gene product that binds to c-kinase (SRBC), and CAVIN4 or muscle-restricted coiled–coiled protein (MURC), EH-domain containing 2 (EHD 2), and receptor tyrosine kinase–like orphan receptor 1 (ROR1) [6, 14–19].

Caveolae are implicated in many cellular functions including endocytosis, signal transduction, mechanosensing/mechanoprotection, and lipid homeostasis [20, 21]. In contrast to clathrin-coated pits which exhibit a similar density in all tissues, caveolae show a large variation in their density in different tissues, reflecting a wide disparity in expression of caveolar proteins. Caveolae are most abundant in endothelial cells, skeletal muscles, and adipocytes where they cover up to 50% of the total cell surface area, but are barely noticeable in the kidney proximal tubule, liver, and neurons [16]. The low density of caveolae in these tissues is not a reflection of their lack of function but reveals distinct roles of caveolae in different tissues. For instance, caveolae are highly expressed in tissues that are under constant physical pressure such as skeletal and endothelial cells, where they work as mechanoprotectors, but serve distinct crucial functions in liver and macrophages where their expression is low [5, 22–25].

The expression of caveola-forming proteins is deregulated in cancer, and they are reported to serve both tumour-repressing and tumour-promoting functions not only in a tumour-type-specific way, but also in a stage-specific way within the same type of tumour [26]. In addition, the deregulated expression of caveolar proteins in the stroma impacts tumour progression [27]. In this review, we summarise the role of caveola-forming proteins in prostate cancer (PCa) progression and the potential of caveola-forming protein clinical translation as biomarkers or therapeutic targets.

2 Caveolae and caveola-forming protein expression in prostate tissues

Transmission electron microscopy revealed the presence of caveola-like structures in stromal and basal epithelial cells in rat and dog prostate tissue samples, respectively [28, 29]. Caveola-like structures were also detected in both cultured human normal prostate epithelial (PrEC) and stromal cells (PrSC) [30]. Caveola formation requires the expression of both CAV1 and CAVIN1, both of which are expressed at mRNA level in PCa (Fig. 1a–c). However, prostate cancer is characterised by a loss of co-regulation of expression of the two proteins. Several independent immunohistochemistry (IHC) analyses reported a significant increase in CAV1 expression positivity in PCa tissues compared with normal or benign prostatic hyperplasia tissues [30, 46–51]. Fewer studies investigated CAVIN1 expression in PCa. CAVIN1 mRNA expression is strongly correlated with CAV1 expression in primary and metastatic PCa tissues (Fig. 2a), and in normal and cancer cell lines with the exception of PC3 cells (which express CAV1 but lack CAVIN1 at both mRNA and protein levels) (Fig. 2b). This has been confirmed at protein level for several cell lines in multiple independent reports. https://www.ncbi.nlm.nih.gov/pubmed/27213551 [73, 76, 77]. However, immunostaining studies of human PCa tissues revealed the overexpression of CAV1 (Table 1) and the absence of CAVIN1 protein expression [30], a phenotype recapitulated in PC3 cell lines. This suggests that CAVIN1 mRNA expression is not correlated with the protein expression and results in a loss of caveola structures in human prostate tumours. There is yet no study investigating the presence of caveolae in clinical PCa tissues, and, if any, whether the number of caveolae is correlated with the disease progression.

The molecular basis for altered CAV1 expression in PCa is still unclear and may reflect the high disease heterogeneity. The *CAV1* gene is co-localised to 7q31.1, a fragile site region that is commonly deleted in several types of cancer. In contrast to breast, ovarian, renal, colorectal, head and neck, ovarian adenocarcinoma or squamous cell carcinomas where FRA7G is often deleted, the genetic changes in the chromosome 7q in PCa are unclear. Many studies reported loss of portions of chromosome 7q in PCa [53–56]. For instance, Zenklusen et al. found that 75% of prostate tumour specimens exhibit a loss of 7q markers with peak loss at the 7q31.1 region. In contrast, studies described a chromosome 7 gain in 35–56% of cases [57–61] and reported associations between 7q gain and advanced stages [62, 63], metastasis [64], or poor prognosis of PCa [65, 66]. It is worth mentioning that no mutations have been observed in caveolin-encoding genes in PCa cells or pathological specimens [67, 68]. Cui et al. observed CAV1 promoter hypermethylation in 90.9% of cases in PCa cells compared with normal adjacent cells [69]; however, Bachmann et al. have not found a consistent correlation between CAV1 protein expression level and genetic changes or promoter hypermethylation [70]. In contrast, Woodson et al. using 90 tumours reported a complete absence of CAV1 promoter methylation [71]. Regardless of these inconclusive studies on the genetic alterations, an accumulating body of IHC studies reveals the overexpression of CAV1 in malignant prostate tissues compared with normal tissues, and shows that expression is further increased with the disease progression (Table 1). It is proposed that CAV1 is one of the "progression-related proteins" that functions in advanced

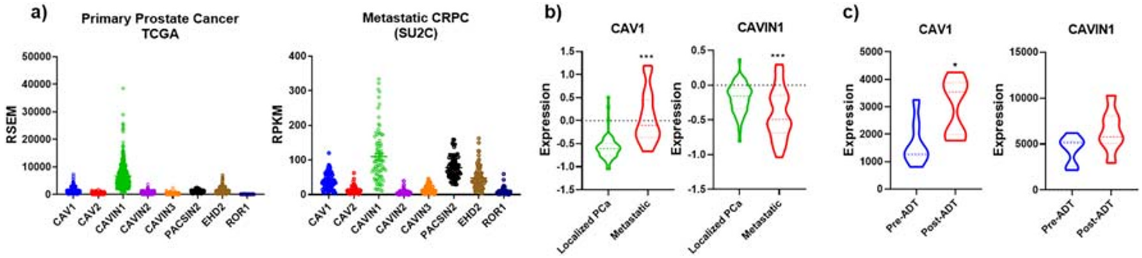

Fig. 1 **a** RNA-Seq analysis of caveolar protein expression in primary prostate tumours (TCGA) and metastatic castration-resistant prostate tumours (SU2C). Data were obtained from CbioPortal [193, 194]. **b** CAV1 and CAVIN1 mRNA expression in metastatic *versus* localised PCa tissues; data were obtained from GSE35988. **c** RNA-Seq analysis of CAV1 and CAVIN1 expression in PCa patient material pre- and post-treatment with androgen deprivation therapy. Data were obtained from [120]. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ t-test

stages rather than a protein that significantly impacts localised tumour growth [72]. In agreement, mRNA expression of CAV1 mRNA is upregulated in metastatic tissues compared with localised ones (Fig. 1b).

In contrast to CAV1 and CAVIN1 which are expressed in primary and metastatic PCa tissues, the mRNA expression of other caveolar proteins (namely CAV2, CAVIN2 and 3, PACSIN2, EHD2, and ROR1) is weak as revealed by interrogating publicly available datasets (Fig. 1a). Expression of CAV2 mRNA is correlated with the expression of CAV1 mRNA (Fig. 2c), and CAV2 protein expression is reported to increase alongside CAV1 in clinical PCa tumours [30] [52]. In addition, a correlation between plasma CAV1 and CAV2 levels and with the PCa progression is reported [78]. The cavin2 and cavin3 expression profile is consistent with previous studies that suggested their tumour-suppression properties in various types of tumours including breast and ovarian cancers. In clinical samples, Cavin2 expression is reduced in kidney, breast, and prostate tumour tissues compared with that in adjacent normal epithelium [31, 32]. Recent studies revealed cavin2 inhibits breast cancer cell proliferation, invasion, and metastasis [33, 34]. Cavin3 was reported to be downregulated in 70% of 43 tested cancer cell lines derived from breast, ovarian, and lung tumours, and cavin3 promoter to be hypermethylated in several cancer cell lines and human cancer tissues (reviewed in [6]). Similarly, EHD2 expression is decreased in malignant breast tissues compared with that in adjacent normal ones, and this decreased expression is reported to promote cell migration and invasion [35, 36]. ROR1 is exclusively expressed in embryonic tissue and in some malignant tissues but essentially absent in normal adult tissues. ROR1 expression is associated with poor clinical outcomes and its expression promotes cell tumourigenesis in breast [37–39], ovarian [40–44], and endometrial [45] cancer. Interestingly, interrogating publicly available databases unveils that the mRNA expressions of PASCIN2 and EHD2 seem increased in PCa metastatic tissues compared with primary ones (Fig. 1a). Further studies investigating the expression of PASCIN2 and EHD2 proteins and their implication in the metastatic disease are warranted.

3 Caveolins as a bio- and prognostic marker for PCa

CAV1 and CAV2 are secreted from PCa cells and can be found in the circulation of PCa patients. Early studies showed that CAV1 is secreted by pancreatic acinar cells in a complex with lipids in HDL-like particles [79]. Later, CAV1 was confirmed to be secreted by cultured mouse and human PCa cells in a process stimulated by androgen in androgen receptor (AR)–expressing cells [73]. Of note, expressing CAV1 does not equate with the ability of cells to secrete the protein; for example, endothelial cells, fibroblasts, lung epithelial cells,

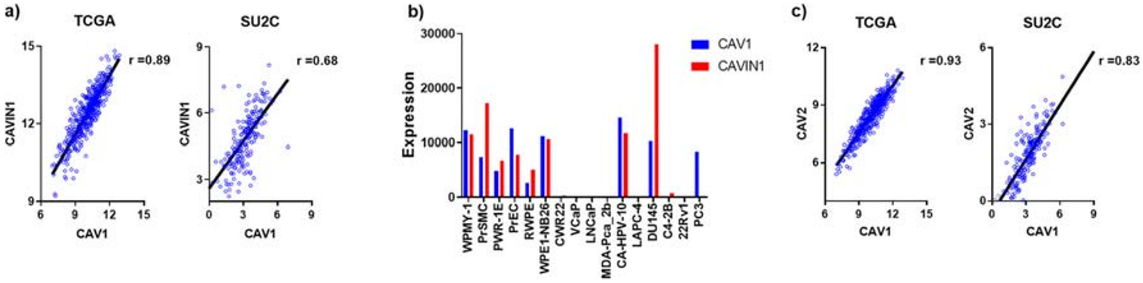

Fig. 2 **a** mRNA expression correlation between CAV1 and CAVIN1 in primary prostate tumours (TCGA) and metastatic castration-resistant prostate tumours (SU2C). **b** mRNA expression of CAV1 and CAVIN1 in several normal, stromal, and PCa cell lines. **c** mRNA expression correlation between CAV1 and CAV2 in primary prostate tumours (TCGA) and metastatic castration-resistant prostate tumours (SU2C). Data in **a** and **c** were obtained from CbioPortal. Data in **b** were derived from [195] and obtained from Betastasis platform

Table 1 Clinical studies investigating the expression of caveolar proteins in prostate cancer

# of cases	Ref.	Key findings
93	[91]	CAV1 expression in tumour tissues is higher than in normal tissues and is increased in metastatic tissues.
189	[92]	CAV1 is an independent prognostic marker for clinically confined PCa.
		CAV1 expression is positively correlated with histological grade, lymph node metastasis, and positive surgical margin.
142	[196]	Incidence of CAV1 staining is significantly higher in PCa specimens of African Americans, who are known to exhibit a more aggressive form of the disease, than in samples of Caucasian patients.
61	[73]	CAV1 positivity is associated with the androgen refractory phase of PCa.
		CAV1 expression is increased in both primary and metastatic tissues after hormone therapy.
152	[74]	Increased CAV1 expression is associated with PCa progression and predicts poor clinical outcome after surgery.
104	[75]	The co-expression of CAV1 and c-myc is associated with Gleason score and positive surgical margin.
56	[89]	CAV1-positive tumours have higher microvessel density compared with negative samples.
		Microvessels in CAV1-positive tumours have more VEGFR2 than those in CAV1-negative specimens.
232	[47]	Overexpression of CAV1 is associated with Gleason score, high preoperative PSA, and risk of aggressive recurrence.
38	[30]	CAV1 and CAV2 expression is associated with PCa progression.
		CAVIN1 expression is decreased with PCa progression.
36	[52]	Overexpression of CAV1 in human high-grade prostatic intraepithelial neoplasia is potentially a biomarker for early recognition of patients who tend to develop CAV1-positive primary PCa.
258	[76]	CAV1 expression is increased in PCa tissues compared with that in normal or benign prostatic hyperplasia tissues.
		CAVIN1 is absent in normal and malignant tissues.
50	[152]	CAV1 is associated with ACC1 in human tumours and is increased in metastatic PCa compared with that in primary tumours and normal prostate epithelium.
3 117	[90]	CAV1 is associated with higher pathological Gleason score and lymph node metastasis, and independently predicts biochemical recurrence after radical prostatectomy.
67	[46]	CAV1 expression is higher in PCa samples than in benign prostatic hyperplasia samples and correlated with the disease pathological grades.
435	[51]	CAV1 expression is higher in PCa tissues compared with that in benign tissue.
81	[118]	CAV1 is overexpressed in CRPC and is associated with Ras signalling pathway genes, and bone metastasis.
		CAV1 expression is an independent risk factor for CRPC and is associated with a shorter recurrence-free survival time in CRPC patients.

PCa, prostate cancer; *VEGFR2*, vascular endothelial growth factor receptor 2; *PSA*, prostate-specific antigen; *ACC1*, acetyl-CoA carboxylase 1; *CRPC*, castrate-resistant prostate cancer

Chinese hamster ovary, and smooth muscle cells express CAV1 but do not secrete it [73]. This enigma could be explained by the presence in PCa cells of specialised secretory pathways mediating CAV1 secretion. Secretion is one of the main epithelium prostate cell functions, which may explain this ability to secrete CAV1. CAV1 is secreted in the form of lipoprotein-like particles and prostasomes. Prostasomes are small vesicles (40–500 nm) secreted by the prostate epithelial cells into the seminal fluid that play roles in sperm motility and health [80]. CAV1 was identified as a component of prostasomes secreted by the PCa PC3 cell line [81]. Biochemical fractionation of conditioned medium of CAV1-transfected LNCaP cells revealed that it is secreted in association with lipoprotein particles with a slightly higher density than HDL particles (15–30 nm) [82]. CAV1 is exported within large oncosomes (1–10-μm-diameter tumour-derived macrovesicles) derived from bulky cellular protrusions [83]. Ectopic expression of CAV1 in LNCaP cells increased membrane blebbing and shedding, suggesting a role of CAV1 in oncosome secretion [83]. However, a recent study found that ectopically expressing CAV1 in LNCaP cells or decreasing its expression in DU145 cells did not alter the exosome size or number, but resulted in exosomes exhibiting distinct oncogenic properties [84]. CAV1 was detected in human serum and plasma and measured using enzyme-linked immunosorbent assay (ELISA) [72, 78, 85–88]. One study reported CAV2 secretion and measurement in patient plasma and its correlation with CAV1 levels [78]. Secreted CAV1 is proposed to be a biomarker of PCa, and its autocrine and paracrine functions impact the tumour and tumour microenvironment biology.

In PCa clinical samples, CAV1 protein expression and serum level increase with the disease stage, grade, features of tumour aggressiveness, angiogenesis, and resistance to androgen ablation, overall predicting poor clinical outcome (Tables 1 and 2). CAV1 immunoreactivity was shown to increase with Gleason score [47, 75, 76], pathological grade, clinical stage [46], positive surgical margin [75], preoperative PSA level [46, 47], and tumour microvessel density [89]. In a multicentric study ($n = 3117$ patients), CAV1 expression was associated with Gleason score and lymph node metastases [90]. CAV1 expression was found to increase in metastatic tissues compared with that in localised tumours [91]. In a clinically feasible, non-invasive approach, ELISA assays to measure CAV1 levels in serum or plasma were developed and CAV1 levels were proven to differentiate patients with clinically localised disease (0.463 ng/ml) from healthy control men (0.324 ng/ml, $p = 0.0446$) or men with BPH (0.172 ng/ml, $p = 0.0317$) [85]. More importantly, CAV1 expression detected by IHC proved to predict a shorter time to disease progression in several independent studies [47, 48, 74, 75, 90, 92]. Patients with higher preoperative serum CAV1 levels had a 2.7-fold greater risk of developing biochemical recurrence compared with those with low serum CAV1 [87]. A single meta-analysis involving four IHC studies ($n = 677$) and two studies with ELISA-measured CAV1 levels in serum ($n = 621$) was conducted to investigate the prognostic value of CAV1 in PCa. The IHC studies of CAV1 expression and the association with the recurrence-free survival revealed a combined hazard ratio of 1.83 (95% CI 1.36 to 2.47), while the serum ELISA studies combined hazard ratio was 1.25 (95% CI 0.36 to 4.36) [93]. However, despite this coherent evidence of increased CAV1 expression in PCa tissues and its levels in circulation, the addition of CAV1 in a model for biochemical recurrence (BCR) prediction based on standard prognostic factors failed to add significant prediction value which limits its clinical use [90].

More interestingly, CAV1 is suggested to help identify high-risk patients and guide clinical decision-making at early stages. CAV1 plasma level in patients with early PCa undergoing active surveillance was an independent predictor for the disease classification (odds ratio 1.82, 95% CI 1.24–5.65, $p = 0.02$) [94]. An *in vivo* study revealed the utility of CAV1 as a biomarker of response to drug treatment. Mouse serum CAV1 levels were lower in dasatinib- and sunitinib-treated mice than in untreated mice [86]; however, this yet needs to be confirmed in human clinical trials especially with established and common therapeutics used for PCa management. Collectively, CAV1 is associated with the risk of aggressive PCa, and poor clinical outcomes. However, its clinical use as a tumour marker is limited since it does not add more relevant information beyond the standard established tests.

4 Stromal expression of caveola-forming proteins

The tumour stroma plays essential roles in various stages of cancer development. The stroma evolves as the tumours develop [95–98]. Stroma consists of fibroblasts, immune cells, basement

Table 2 Clinical studies investigating secreted caveolar proteins in prostate cancer

# of cases	Ref.	Key findings
290	[85]	Median serum CAV1 level is significantly higher in PCa patients than in patients with benign prostatic hyperplasia or healthy men.
419	[87]	The risk of developing BCR is higher in PCa patients with high preoperative serum CAV1.
97	[197]	CAV1 is overexpressed in high stages *versus* lower stages of PCa and is correlated significantly with histological grading. The anti-oxidant capacity of the body is reduced in patients with high CAV1 serum concentrations.
58	[78, 88]	Plasma levels of CAV1 and CAV2 are significantly correlated and higher in CRPC patients than in non-CRPC patients.
542	[94]	Baseline plasma CAV1 level is an independent predictor of disease classification.
126	[118]	CAV1 serum level in CRPC patients is higher than in primary PCa patients. CAV1 could be employed for the accurate diagnosis of CRPC.

PCa, prostate cancer; *BCR*, biochemical recurrence; *CRPC*, castrate-resistant prostate cancer membrane, extracellular matrix, and blood and lymphatic vessels. Stromal cells exhibit tumour-suppressing activities; however, stroma is altered during malignancy and supports tumour cell growth, invasion, and metastasis [99]. Caveola-forming proteins CAV1 and CAVIN1 are strongly expressed in normal prostate and BPH stromal compartment [76]. However, the expression of both proteins was reported to decrease with the disease progression [76, 100–103], and to be totally absent in metastatic tumours [100], but not in the vascular compartment [50] (Table 3). CAV1 stromal expression is inversely correlated with Gleason score and predicts worse prognosis and clinical outcome [100, 101, 104, 105], and low CAV1 expression is associated with reduced BCR (HR 0.75, 95% CI 0.61 to 0.93, $p = 0.009$) [104]. Loss of CAV1 in the stromal compartment was suggested to take place because of cancer cell induction of a pseudo-hypoxic cell environment involving HIF-1α stabilisation, NFκB activation [106], increased oxidative stress, and a metabolism switch from mitochondrial respiration to glycolysis, autophagy, and catabolism in cancer-associated fibroblasts [106–108]. Loss of CAV1 in stromal cells increased their proliferation [104], clonogenic survival [109], and AKT activation and increased the expression and secretion of angiogenesis, anti-apoptosis, invasion, and metastasis proteins such as TGF-β1 [104] and TRIAP1 (TP53 regulated inhibitor of apoptosis 1) [109]. CAV1 downregulation in WPMY-1 prostate fibroblasts increased their ability to chemoattract PCa cells [104], and their supernatant enhanced *in vitro* PCa cell radiation resistance [49, 109]. Loss of CAV1 in stroma is suggested to maintain intratumoural androgen levels in CRPC [104]. CAV1 downregulation in cultured prostate fibroblasts resulted in increased mRNA expression of CYP17A1, a cytochrome P450 involved in androgen synthesis in CRPC, and increased testosterone production and secretion in CAV1-silenced stromal cell [104]. Pharmacological inhibition of CYP17A1 abolished PCa cell–induced proliferation by stromal cells [104]. Most of CPRC maintain AR activity and one mechanism is preserving high intratumoural androgen levels [110]. Increased testosterone levels in CAV1 downregulated cells can maintain high testosterone levels despite undetectable plasma levels.

These observations reveal a dynamic interaction between the stromal and epithelial cells and suggest a role of stromal cells in mediating CRPC. Furthermore, therapeutic interventions altering the stromal-epithelial communication may inhibit tumour progression and drug resistance and delay evolution of the disease to CRPC.

5 Caveolin-1, androgen receptor, and CRPC

Although CAV1 expression and its association with PCa progression are supported by strong evidence, the relationship between CAV1 and androgen receptors (AR) is less clear. While some studies reported an increase in CAV1 expression in response to androgens and CAV1 functions as a co-activator for AR, other studies reported the overexpression of CAV1 after androgen ablation. On the one hand, an intimate relationship between the two proteins was reported; AR were found to co-localise with caveolin-rich low-density membrane fraction and co-immunoprecipitated with CAV1 [111, 112]. In addition, CAV1 expression decreased following androgen deprivation [113] and increased at the transcriptional level in response to testosterone treatment [114]. In turn, CAV1 works as an AR co-activator and mediates androgen-stimulated prostate cell proliferation and survival [114, 115], and increases AR phosphorylation and nuclear translocation *in vitro* and *in vivo* [116]. CAV1 downregulation inhibited AR expression

Table 3 Clinical studies investigating the expression of caveolar proteins in PCa stroma

# of cases	Ref.	Key findings
258	[76]	The expression of CAV1 and CAVIN1 decreased significantly in PCa stromal tissues compared with that in normal prostate stroma, and the loss of expression of the two proteins in the stroma is significantly correlated with Gleason score.
97	[100]	CAV1 is absent in stroma of metastatic PCa and its expression decreased in stroma of primary PCa tissues compared with BPH which express abundantly CAV1. The decrease of stromal CAV1 expression is correlated with a high Gleason score.
96	[101]	Loss of CAV1 expression in the stroma is associated with high Gleason score.
724	[104]	Loss of stromal CAV1 is correlated with high Gleason score, with clinical stage, and with reduced relapse-free survival.
492	[105]	Stromal CAV1 expression is weakly inversely correlated with Gleason score, tumour size, tumour stage, tumour cell proliferation, and metastasis, and is weakly positively correlated with androgen receptor expression in the stroma. Stromal CAV1 expression is associated with a favourable prognosis in PCa patients managed by watchful waiting.

PCa, prostate cancer; *BPH*, benign prostatic hyperplasia and genomic activity [112], and its overexpression increased AR expression [76]. On the other hand, cultured non-malignant and PCa cells exhibit an inverse relationship between AR and CAV1 expression [112]. Nasu et al. demonstrated a link between CAV1 expression and castrate resistance as they found that CAV1 downregulation sensitises PCa cell to androgen withdrawal *in vitro* and *in vivo*, and restoration of CAV1 expression rescued the cells [117]. This has been further confirmed in clinical prostate tumours where the frequency of CAV1 positivity in primary PCa increased significantly from 38% in hormone-naïve patients to 73% in hormone refractory patients [73]. Data derived from [120] showed that CAV1 mRNA expression in PCa patient increased in PCa tissues after 22 weeks of treatment with androgen deprivation therapy (Fig. 1c). IHC for CAV1 study revealed that CAV1 expression is higher in CRPC tissues compared with that in the primary PCa tissues (72.2% *vs* 31.1%; $p = 0.002$) [118]. Plasma or serum CAV1 levels were significantly higher in CRPC *versus* non-CRPC in independent studies (1.46 ± 1.37 ng/ml *vs* 0.56 ± 0.32 ng; $p < 0.004$ [88], and 1.57 ± 0.83 ng/ml *vs* 0.64 ± 0.25 ng/ml; $p < 0.001$ [118]). CAV1 immunostaining positivity is associated with recurrence after androgen deprivation therapy (HR = 2.65, 95% CI = 1.162–6.029; $p < 0.02$) [118], suggesting that CAV1 is an independent risk factor for CRPC. In addition, serum CAV1 levels could be used for CRPC diagnosis (AUC = 0.876, 95% CI = 0.831–0.939) [118].

A model for AR and CAV1 relationship was suggested to explain these observations, in which AR induces the expression of CAV1 at early stages of the disease and CAV1 then supports cell survival after androgen ablation [119]. Further studies using more clinically relevant models such as patient-derived explants or organoids are needed to expose the relationship between the two proteins and confirm this model.

6 Caveolin-1 autocrine and paracrine oncogenic functions

An accumulating body of evidence shows that CAV1 exhibits oncogenic properties *via* autocrine, paracrine, and endocrine actions. CAV1 increases PCa cell growth, migration, angiogenesis, metastasis, and resistance to apoptosis *in vitro* and *in vivo* (*in vivo* studies are summarised in Table 4). For instance, ectopic CAV1 expression maintains activation of the AKT pathway [116], increases *in vitro* cell viability [82], and inhibits apoptosis mediated by thapsigargin [116], c-myc overexpression [125], and androgen withdrawal [114]. *In vivo*, interbreeding TRAMP (transgenic adenocarcinoma of mouse prostate) mice with $cav1^{(-/-)}$ or $cav1^{(+/-)}$ mice reduced significantly the tumour burden and metastasis [126]. In a subcutaneous model, CAV1-devoid cells did not form tumours, and the tumour size positively correlated with the CAV1 expression level of the inoculated cells [126]. In an orthotopic model where mice were implanted with antisense CAV1 cells, lymph node metastasis was reduced and sensitivity to castration increased compared with control cells [114]. This is strong evidence of the oncogenic role of CAV1 in PCa.

A number of studies have investigated the mechanisms by which CAV1 promotes PCa progression (Fig. 3). CAV1 modulates growth factor expression and cell motility. An AKT-mediated autoregulatory feedback loop between CAV1 and VEGF, TGF-β1, and FGF2 was identified, in which these growth factors upregulated CAV1, and in turn CAV1 increased these growth factor mRNA and protein levels, and enhanced cell migration [127]. CAV1 interacts with ID-1 (inhibitor of differentiation/DNA binding) protein and induces epithelial–mesenchymal transition (EMT) and cell migration through the AKT pathway [128]. Microarray analysis of independent datasets for many cell lines showed an association of CAV1 expression with an EMT gene signature [51]. CAV1 overexpression in LNCaP cells increased vimentin and reduced E-cadherin expression and promoted cell motility and invasion [84], and its downregulation decreased expression of vimentin and N-cadherin, and increased E-cadherin expression and decreased cell motility and invasion [51, 84, 129]. In clinical human PCa tissues, CAV1 expression is inversely correlated with E-cadherin expression [51].

In addition to CAV1 autocrine functions, secreted CAV1 exhibits paracrine and endocrine functions. The effect of CAV1 expression on PCa function resembles adding purified recombinant CAV1, and anti-CAV1 antibodies abolish the CAV1 effects [73, 121]. CAV1 is taken up by close or distant PCa cells and endothelial cells *in vitro* and *in vivo*, which promotes tumour growth, angiogenesis, and metastasis [73, 82, 84, 89, 122–124]. Secreted CAV1 from CAV1-expressing cells enhanced CAV1-devoid PCa cell viability and colony formation [114] and sphere formation [84]. *In vivo*, CAV1-secreting cells injected into one side of a mouse stimulated tumour growth of CAV1-negative cells injected on the other side of the same animal [82].

As a result of the autocrine and paracrine roles described above and the involvement of AKT signalling as well as pro-angiogenic growth factors, CAV1 expression in PCa is likely to regulate angiogenesis and lymphangiogenesis. In agreement with this suggestion, in human PCa specimens, CAV1-positive tumours have higher microvessel density compared with negative samples and the microvessels in CAV1-positive tumours have more VEGFR2 than those in CAV1-negative ones [89]. CAV1 ectopic expression or recombinant CAV1 protein treatment heightened VEGF-stimulated angiogenic signalling, differentiation, and migration of $cav1^{(-/-)}$ endothelial cells [122, 124]. Conditioned medium from LNCaP and PC3 cells induced lymphatic endothelial cell proliferation, migration, and differentiation [130]. CAV1-expressing cells inoculated subcutaneously resulted in bigger tumours and higher blood vessel density than CAV1-

Table 4 *In vivo* preclinical studies of CAV1 involvement in prostate cancer growth and metastasis

Method	Tested group	Control group	Size	Findings	Ref.
Syngeneic 129/SV mice Orthotopic injection Castration	CAV1-expressing lung metastatic cell lines. Mouse stable antisense CAV1 clones.	Mouse cell line clones transfected with control vector.	$n = 8$–10 animals for each cell line	CAV1 suppression induced androgen sensitivity. Tumour volume was reduced in antisense CAV1 tumour-bearing animals upon castration.	[117]
Syngeneic 129/SV mice Orthotopic injection Castration	Animals treated with polyclonal CAV1 Ab (I.P).	Mice treated with control rabbit IgG.	–	Anti-CAV1 Ab decreased tumour weight and metastases.	[73]
Syngeneic 129/SV mice Orthotopic injection and tail vein injection Castration	A panel of mouse stable antisense CAV1 clones.	A panel of mouse stable control vector clones.	$n = 8$–9 animals for each cell line	CAV1 downregulation reduced lymph node and lung metastasis in the orthotopic and tail vein models, respectively. Castration further reduced metastasis in animals inoculated with antisense clones.	[114]
Crossed TRAMP and cav1$^{(-/-)}$ mice	Tramp cav1$^{(-/-)}$ mice, TRAMP cav1$^{(+/-)}$ mice.	Tramp cav1$^{(+/+)}$ mice.	$n = 38$	Inactivation of one or both of cav1 alleles decreased tumour burden, and metastasis.	[126]
C57Bl/6 mice S.C mouse PCa model	TRAMP cell lines (C1, C2) expressing CAV1 in high and moderate levels, respectively. C1 cells retrovirally infected with ShCAV1. C3 cells retrovirally infected to overexpress CAV1.	Non-CAV1-expressing cells (C3). TRAMP C1 and C3 cells infected with empty vectors.	$n = 5$ for each cell line	The tumour size correlates with CAV1 expression. Non-CAV1-expressing cells did not form tumours. CAV1 downregulated cells showed less lung metastasis.	[126]
Crossed TRAMP and cav1$^{(-/-)}$ mice	TRAMP/cav1$^{(+/+)}$.	TRAMP/cav1$^{(-/-)}$.	–	CAV1 expression is required for fatty acid synthase (FASN) upregulation.	[151]
cav1$^{(+/+)}$, cav1$^{(-/-)}$ mice Orthotopic mouse PCa model	CAV1-secreting RM-9 PCa cells injected into the dorsolateral prostate of cav1$^{(+/+)}$ mice.	CAV1-secreting RM-9 PCa cells injected into the dorsolateral prostate of cav1$^{(-/-)}$ mice.	$n = 7$ for each group	Tumour weight and BVD were higher in cav1$^{(+/+)}$ mice *versus* Cav1$^{(-/-)}$ mice. Endothelial cells took up CAV1; > 70% of the CD31^{+} microvessels in the cav1$^{(-/-)}$ tumour sections were CAV1 positive.	[122]
Nude mice S.C mouse PCa model	LNTB25cav cells (doxycycline regulated CAV1 expression). Tumour-bearing mice received doxycycline.	LNTB25cav tumour-bearing mice received sucrose solution.	$n = 8$ for each group	Tumour volume and BVD in the doxycycline-treated group was significantly greater than those in the control group.	[122]
Nude mice Tail vein injection	LNTB25cav cells (doxycycline regulated CAV1 expression). Mice were treated with doxycycline.	LNTB25cav cells. Mice received sucrose solution.	Tested group = 7 Control group = 8	CAV1 induction increased number, average size, and frequency of lung metastases.	[122]
Nude mice S.C. mouse PCa model	LNCaP cells transfected with CAV1 construct.	CAV1-negative LNCaP cells.	$n = 15$ for each cell line	CAV1 expression increased tumour incidence.	[82]
Nude mice S.C mouse PCa model	Double injections for each mouse: in one side CAV1-negative LNCaP cells and on the contralateral side CAV1-positive LNCaP cells.	Double injections of CAV1-negative LNCaP cells in both sides for each mouse.	$n = 18$	CAV1-secreting cells injected into one side of a mouse stimulated tumour growth of CAV1-negative cells injected on the other side of the same animal.	[82]
PBCAV1 transgenic mice	PBCAV1 transgenic mice: transgenic mice with targeted overexpression of cav1 in the prostate.	Non-transgenic littermates.	Tested group = 28 Control group = 29	PBCAV1 animals showed significantly greater prostate weight, higher epithelial hyperplasia incidence, more resistance to castration, and higher serum CAV1 levels.	[121]
PBCAV1 transgenic mice Orthotopic mouse PCa model	CAV1-secreting RM-9 PCa cells injected into adult male PBCAV1 mice.	CAV1-secreting RM-9 PCa cells injected into adult male non-transgenic littermates.	–	Tumour size was significantly larger in PBCAV1 mice than in non-transgenic littermates.	[121]

Table 4 (continued)

Method	Tested group	Control group	Size	Findings	Ref.
PBCAV1 transgenic mice Tail vein injection	CAV1-secreting RM-9 PCa cells injected into the tail vein of PBCAV1 and cav1$^{(+/+)}$ mice.	CAV1-secreting RM-9 PCa cells injected into the tail vein of non-transgenic littermates and cav1$^{(-/-)}$ mice.	–	PBCAV1 and cav1$^{(+/+)}$ mice showed more lung metastases than in control, with upregulation of CAV1, P-Akt, and VEGF in PBCAV1 lung tumour nodules.	[121]
PBCAV1 transgenic mice Tail vein injection	PBCAV1^{+} and cav1$^{(+/+)}$ mice injected in the tail vein with RM-9 mouse PCa cells and divided into 5 treatment groups: sham surgery group received HBSS, castrated animals received HBSS, mice treated with control rabbit IgG, mice treated with CAV1 Ab, or mice castrated and treated with CAV1 Ab.	PBCAV1^{-} (non-transgenic) littermates, Cav-1$^{(-/-)}$ mice received a tail vein injection of RM-9 mouse PCa cells and were divided into the same five treatment groups.	–	Castration treatment was most effective in cav1$^{(-/-)}$ mice. CAV1 AB administration was more efficient than castration to prevent lung metastasis in all genotypes except cav1$^{(-/-)}$ mice. A similar inhibition of lung metastasis was detected between mice treated with CAV1 Ab alone and mice treated with both CAV1 Ab and castration in all genotypes.	[121]
Nude mice S.C mouse PCa model	LNTB25cav cells (doxycycline regulated CAV1 expression). Tumour-bearing mice received doxycycline.	LNTB25cav cells, tumour-bearing mice received sucrose solution.	Tested group = 10 Control group = 11	Induction of CAV1 in the LNTB25cav xenografts resulted in a significant increase in the expression of VEGF and TGF–β1.	[127]
ARR2PB–c-myc transgenic mice	Transgenic mice with c-myc overexpression driven by the prostate-specific ARR2PB promoter.	Wild-type mice.	Tested group = 41 Control group = 26	CAV1 was overexpressed in PCa cells and prostatic intraepithelial neoplasia (mPIN) lesions and was associated with increased levels of P-Akt and VEGF-A, and with a higher ratio of proliferative to apoptotic labelling in mPIN lesions.	[52]
NOD/SCID S.C mouse PCa model	DU145 shCAV1 cells subcutaneously injected in mice and treated with tumour-derived exosomes purified from DU145 (CAV1-positive).	DU145 shCAV1 cells subcutaneously injected in mice and treated with PBS or tumour-derived exosomes from shCAV1 DU145 cells.	Tested group = 10 Control group = 18	Tumour-derived exosome-containing CAV1 increased the tumour incidence of DU145 shCAV1 cells.	[84]
Nude mice S.C mouse PCa model	Mice bearing PC3 or DU145 tumours received anti-CAV1 Ab (dasatinib or sunitinib) and combined (dasatinib or sunitinib) plus anti-CAV1 Ab.	Mice bearing PC3 or DU145 tumours received vehicle alone or immunoglobulin G	8–10 mice each treatment group	Serum CAV1 concentration correlates with PC3 and DU145 tumour growth and suppression induced by drug treatment dasatinib or sunitinib, each in combination with anti-CAV1 Ab, suppresses the tumour growth of PC3 or DU145 xenografts.	[86]
PBCre^{+};Ptenloxp/loxp;PBCav-1^{+} mouse model Castration	PBCav1^{+}	PBCav1^{-}	PBCav1^{+} = 25 PBCav1^{-} = 25	CAV1 induction increased cancer incidence and growth, and ACC1-FASN expression in intact and castrated mice.	[152]
NOD/SCID mice Orthotopic PCa model	PC3 cells orthotopically injected into the prostate gland. Mice received hypercholesterolemic diet.	PC3 cells orthotopically injected into the prostate gland. Mice received low-cholesterol normal diet.	Low-cholesterol normal diet = 14 Hypercholesterolemic diet = 15	Diet-induced hypercholesterolemia promotes tumour metastasis, concomitant with elevated expression of CAV1.	[184]
NOD/SCID mice Orthotopic PCa model	PC3-CAVIN1 cells orthotopically injected into the prostate gland.	PC3 cells orthotopically injected into the prostate gland.	Control PC3 = 11 PC3-CAVIN1 = 12	CAVIN1 expression suppressed PC3 tumour progression, angiogenesis, lymphangiogenesis, and metastasis.	[76, 77]

TRAMP, transgenic adenocarcinoma of mouse prostate; *Ab*, antibody; *IP*, intra-peritoneal injection; *HBSS*, Hank's Balanced Salt Solution; *BVD*, blood vessel density

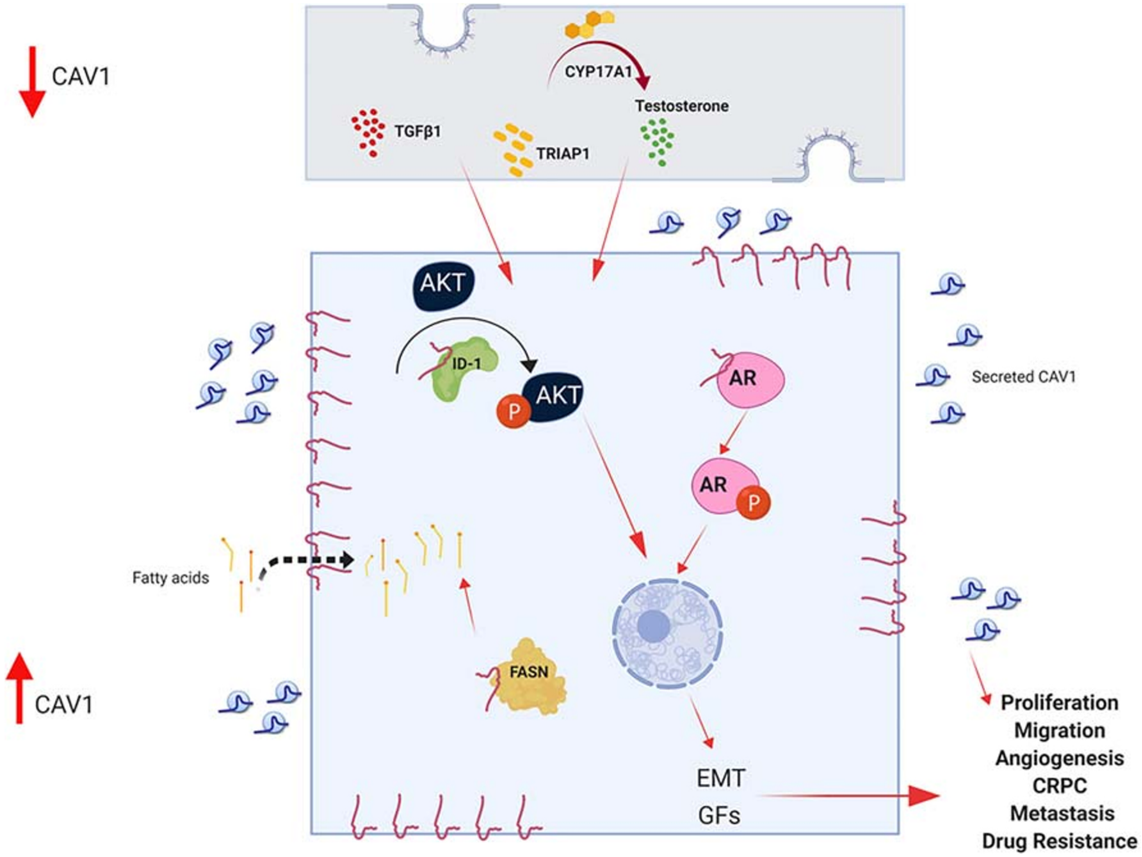

Fig. 3 PCa is characterised by CAV1 overexpression in epithelial cells and CAV1 downregulation in the stroma compartment. CAV1 interacts with many intracellular and signalling proteins and maintains phosphorylation of AKT and androgen receptor (AR); these lead to increased expression of growth factors (GFs) and induce cell proliferation, epithelial–mesenchymal transition, migration, drug resistance, and angiogenesis. CAV1 modulates cell metabolism, increases fatty acid uptake, and binds and activates FASN to increase cell lipid biomass and mediate CRPC. CAV1 is secreted and exerts endocrine and paracrine functions to support tumour growth and metastasis. Secreted CAV1 modulates the tumour microenvironment by inducing angiogenesis. Loss of CAV1 expression in stroma increases TGFβ and TRIAP1 production and increases CYP17A1 expression resulting in increased androgen production which maintains androgen level and androgen signalling in tumour tissues regardless of androgen levels in the circulation

devoid cells. When CAV1-expressing cells were inoculated orthotopically in *cav1*$^{(+/+)}$ mice, they generated tumours of higher weight and blood vessel density compared with cells inoculated in *cav1*$^{(-/-)}$ mice [122]. The effect of secreted CAV1, by using recombinant CAV1 or conditioned medium from CAV1-secreting cells, on downstream signalling pathways in the recipient cells has not been well characterised; however, recombinant CAV1 promotes angiogenic properties of *cav1*$^{(-/-)}$ endothelial cells *via* activation of PI3K Akt and eNOS signalling [122], emphasising the AKT pathway as a key mediating pathway for autocrine and endocrine functions of CAV1.

7 Caveolin-1 and PCa metabolism

Increasing evidence supports the critical roles of caveolar proteins in lipid metabolism, storage, and trafficking [8, 131–133]. This was clearly demonstrated in humans with mutations in CAV1 or CAVIN1 who exhibit severe lipodystrophy [134–137]. In addition, CAV1 loss is associated with mitochondrial impairment [138–140] indicating a functional implication of caveolar proteins in cellular metabolism. This is relevant to the role of caveola-forming proteins in PCa, because fatty acid metabolism is suggested to be the dominant bioenergetic pathway in PCa [141, 142] and the disease is characterised by overexpression of *de novo* fatty acid synthesis pathways' key players [143]. Overexpression of fatty acid synthase (FASN) takes place at early stages of PCa and is associated with metastasis and poor clinical outcomes [144–146]. Transcriptional expression of the lipogenesis enzymes FASN, ATP citrate lyase (ACLY), and acetyl-CoA carboxylase-1 (ACC) is regulated by the sterol response element-binding protein-1 (SREBP-1) [143]. Interestingly, the CAV1 promoter contains sterol response element (SRE) sites where SREBP-1 binds [147–149], and a close relationship between CAV1 and FASN was disclosed; both proteins are coordinately expressed in PCa tissues and co-immunoprecipitated from human and mouse PCa cells [150]. A crossbreeding study between TRAMP and *cav1*$^{(-/-)}$ revealed that CAV1 is essential for FASN upregulation [151]. CAV1 expression induction in prostate tissues increased the expression of ACC1 and FASN expression in intact and castrated mice. CAV1 overexpression increased palmitate levels in LNCaP cells, while CAV1 downregulation in PC3 decreased it [152]. CAV1 induction of fatty acid synthesis in an androgen-independent manner was suggested to underline the increased levels of fatty acids palmitoleate and oleate in mCRPC and poor response to anti-androgen treatment [152]. Recently, fatty acid uptake was found to increase in PCa and targeting the process slowed cancer progression [153]. CAV1 binds to and increases uptake of fatty acids [154–158]; however, this needs to be confirmed in PCa cells and tissues.

In addition to activating fatty acid metabolism, CAV1 was reported to stimulate aerobic glycolysis by interacting with low-density lipoprotein receptor–related protein 6 (LRP6) which results in activation of insulin and insulin-like growth factor 1, AKT signalling, and aerobic glycolysis [159]. Activation of aerobic glycolysis has been associated with cancer cell growth, acetyl Co-A production, and NADPH needed for fatty acid synthesis [160, 161]. Ectopic expression of CAV1 in LNCaP cells made them more sensitive to FASN inhibitors [152], which suggests that deciphering the molecular basis of metabolism regulation by CAV1 in PCa could help to expose new metabolic targets for PCa therapy. Collectively, these studies show that CAV1 modulates cell metabolism and suggest that its activities in PCa can promote cell proliferation and hormone resistance by increasing cell lipid biomass.

8 Caveola-dependent and caveola-independent functions of CAVIN1 in PCa

PCa studies focused on CAVIN1 as it is indispensable for caveola formation in all cells including prostate cells. CAVIN1 expression is lost in PCa tissues suggesting it functions as a tumour suppressor protein. The absence of CAVIN1 expression leads to loss of caveolae and the redistribution of CAV1 on the plasma membrane (non-caveolar CAV1), a phenotype observed in PCa PC3 cells [7]. Ectopic expression of CAVIN1 in PC3 cells was sufficient to sequester CAV1 and form caveolae [7]. Ectopic CAVIN1 expression in PCa cells expressing CAV1 endogenously (PC3) or exogenously (LNCaP) decreased cell anchorage-independent growth, AKT activation, and CAV1-induced AR expression, and orthotopic *in vivo* tumour growth, angiogenesis, lymphangiogenesis, and metastasis [76, 77].

Using both CAV1-negative and CAV1-positive PCa cells, we showed that CAVIN1 exhibits both caveola-independent and caveola-dependent tumour suppressor properties. For instance, CAVIN1 expression in PC3 altered cholesterol distribution and the abundance of many cytoskeletal proteins such as actin, myosin 9 and 11, and filamin A in the detergent-resistant membrane fraction, leading to cytoskeletal rearrangement and altering the link between cytoskeleton and lipid raft microdomains. In addition, CAVIN1 expression altered the expression and/or recruitment of many proteins linked to secretion in the lysosomes, Golgi, and ER compartments. These changes in cholesterol distribution, cytoskeletal/lipid raft interaction, and secretory pathways led to decreased secreted and prostasome proteins including proteases, growth regulatory proteins, and cytokines [173]. Another study showed that CAVIN1 expression in PC3 reduced the abundance of a subset of extracellular vesicle proteins without altering the extracellular vesicle quantity, size, or shape, suggesting that CAVIN1 does not affect extracellular vesicle release but their content recruitment. In addition, CAVIN1 reduces extracellular vesicle uptake by primary human osteoblast and osteoclast precursor RAW264.7 macrophages, lessening the extracellular vesicle induction effect on osteoblast proliferation and RAW264.7 osteoclastogenesis [174]. Similarly, we showed that conditioned medium derived from CAVIN1-expressing cells had a decreased ability to elicit *in vitro* angiogenesis and lymphangiogenesis compared with the conditioned medium produced by CAVIN1-devoid control cells, and this effect was demonstrated in both CAV1-expressing cells and CAV1-devoid cells implying that CAVIN1 exert both caveolar and non-caveolar functions [77]. In addition, we showed that CAVIN1 in PC3 cells decreased PC3 migration, mesenchymal epithelial transition, and MMP9 expression in a caveola-independent fashion [171, 172].

Further suggesting non-caveolar functions for CAVIN1 is the fact that it can be localised in different intracellular locations including the nucleus [167, 175, 176]. CAVIN1 possesses two nuclear localization signals facilitating its translocation to the nucleus [177, 178] and was first identified as a protein involved in transcriptional regulation by termination of RNA polymerase I–catalysed transcription [162–164]. Later, its presence and essential function in caveolae were revealed [7, 165, 166]. This ability of CAVIN1 to localise both at the plasma membrane and into the nucleus suggests it could function as a signalling molecule, mediating the transfer of information between plasma membrane (caveolae) and nucleus. Indeed, CAVINs were proven to be released from caveolae as a response to cellular stressors or insulin treatment, interact with other intracellular targets, and act as signalling molecules [167–170]. For instance, insulin phosphorylates CAVIN1 associated with caveolae in adipocytes, stimulating its translocation to the nucleus and leading to the upregulation of ribosomal RNA transcription [167]. In their recent elegant study, McMahon et al. revealed the proteomic cavin interaction network, demonstrating the involvement of cavins in several cellular possesses such as metabolism, stress signalling, and apoptosis [168]. Prostate cancer is characterised by a dysregulation of the co-expression of CAV1 and CAVIN1, and studies have reported caveola-independent functions of CAVIN1 in PCa; however, the exact mechanisms by which CAVIN1 operates in PCa in its caveola-independent function are not elucidated yet.

9 Targeting CAV1 for PCa management

In light of the significant oncogenic functions of CAV1 in PCa, targeting CAV1 has attracted interest. The fact that CAV1 is secreted from PCa cells and exerts paracrine and endocrine functions led to the development of neutralising anti-CAV1 antibodies for PCa therapy. Neutralising anti-CAV1 antibody decreased tumour burden and metastasis in an orthotopic tumour model [73], and was more efficient than castration to prevent lung metastasis in a tail vein injection model [121]. However, such an antibody for human use has not been developed or tested clinically yet. Another approach suggested to neutralise CAV1 oncogenic properties is to overexpress or restore expression of CAVIN1 [76, 77, 174]. Identifying the molecular basis for the loss of CAVIN1 expression and discovering and developing molecules to promote CAVIN1 expression would be an interesting strategy targeting the harmful effects of CAV1 in PCa.

The second major axis of research to translate basic research about CAV1 in PCa into the clinic involves modulation of the available cholesterol. CAV1 binds cholesterol, and the presence of cholesterol is essential for caveola formation; accordingly, cholesterol-depleting agents result in loss of caveolae and decreased CAV1 expression, while cholesterol replenishment increases it [179–182]. In PCa, cell treatment with cholesterol-lowering agents such as simvastatin decreased CAV1 expression. CAV1 was reduced in abdominal aortic aneurysm in patients treated with statins [183], providing preliminary evidence of the ability of statins to lower CAV1 clinically. Whether the expression of CAV1 in PCa tissues will be decreased after statin administration remains to be investigated. We showed previously that diet-induced hypercholesterolemia induces androgen-independent metastasis partly via upregulation of CAV1 [184], suggesting that patients with PCa could benefit from a low cholesterol diet.

Aside from sequestering CAV1 or lowering cholesterol, a number of molecules have been investigated for their potential to decrease CAV1 expression. *In vitro* studies showed that angiotensin receptor blockade decreased CAV1 expression at both mRNA and protein levels [185]. The therapeutic efficacy of angiotensin receptor antagonists in the context of PCa needs to be confirmed using more preclinical *in vivo* models. Angiotensin receptor antagonists are available on the market for blood pressure management, and thus, drug repurposing is feasible.

Other agents such as incadronate, a third-generation bisphosphonate [186]; phenylbutyrate, a histone deacetylase inhibitor [187]; baicalein [188]; γ-oryzanol [189]; triptolide [190]; and β-carotene [191] were reported to lower transcriptional CAV1 expression in PCa cells. However, the effect of these drugs on CAV1 was weak to modest. Future directions to exploit CAV1 as a target in PCa include screening libraries of hundreds of thousands of compounds that could identify interesting therapeutic candidates to lower CAV1 levels in PCa cells more effectively. Furthermore, deciphering CAV1 druggable downstream effectors might facilitate the introduction of new therapeutics for CAV1-positive PCa patients. For instance, FASN inhibitors were more effective in highly CAV1-expressing cells [152]. Several reports indicated that CAV1 functions are mediated by AKT activation [52, 72, 76, 116, 121, 122, 124, 127, 150, 159, 188]. Thus, using AKT inhibitors might interrupt CAV1 oncogenic activities and be exploited in patients with CAV1-expressing PCa. Interestingly, the AKT inhibitor alpelisib was FDA-approved recently [192] and therefore can be integrated easily in PCa clinical trials for CAV1-positive patients.

10 Conclusion

Although caveola-like structures have been detected early in the 1950s, we are still discovering new facets of their biology and functions. The implication of caveolae in many human diseases is thoroughly studied, including lipodystrophies, cardiomyopathies, and cancer. Particularly, caveola-forming proteins play essential roles in prostate tumourigenesis, presumably due to prostate cells' unique secretory functions and metabolic phenotype. An accumulating body of evidence reported tumour-promoting functions of CAV1, in contrast with tumour-suppressing properties of cavins. When secreted, circulating CAV1 is correlated with the disease grade and stage; CAV1 plasma/serum levels failed to add more diagnostic value to the established clinical tests. However, secreted CAV1 was proven to promote tumourigenesis, angiogenesis, and metastasis. Targeting CAV1 (e.g. using neutralising antibodies, statins, or CAVIN1) are promising approaches warranting translation.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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