Caveola-forming proteins caveolin-1 and PTRF in prostate cancer

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Abstract | The expression of caveola-forming proteins is dysregulated in prostate cancer. Caveolae are flask-shaped invaginations of the plasma membrane that have roles in membrane trafficking and cell signalling. Members of two families of proteins—caveolins and cavins—are known to be required for the formation and functions of caveolae. Caveolin-1, the major structural protein of caveolae, is overexpresssed in prostate cancer and has been demonstrated to be involved in prostate cancer angiogenesis, growth and metastasis. Polymerase I and transcript release factor (PTRF) is the only cavin family member necessary for caveola formation. When exogenously expressed in prostate cancer cells, PTRF reduces aggressive potential, probably via both caveola-mediated and caveola-independent mechanisms. In addition, stromal PTRF expression decreases with progression of the disease. Evaluation of caveolin-1 antibodies in the clinical setting is underway and it is hoped that future studies will reveal the mechanisms of PTRF action, allowing its targeting for therapeutic purposes.

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Introduction

Caveolae are invaginations of the plasma membrane that measure 60–80 nm in diameter and have been observed in most cell types but are particularly abundant in terminally differentiated cells, such as adipocytes, endothelial cells, fibroblasts and muscle cells (both smooth and striated).[1] Caveolae have membrane trafficking, mechanotransducing and signalling functions.[1] Like other lipid rafts, caveolae are enriched in cholesterol, glycosphingolipids and lipid-anchored proteins, but their discrete morphology and signature proteins—caveolin-1 and polymerase I and transcript release factor (PTRF)—are unique (Figure 1).[2]

Electron microscopy has revealed that caveolae are present in prostate tissue, in both stromal cells (smooth muscle cells of normal rat prostate tissue)[3,4] and epithelial cells (basal but not luminal epithelial cells of dog prostate tissue).[5] Analysis of caveola content in cultured primary human prostate stromal and epithelial cells has shown that prostatic stromal cells have about twice as many caveolae per micron of the cell membrane as prostatic epithelial cells.[6]

Caveolin-1-null mice have cardiovascular[7–17] and metabolic[18–21] abnormalities. Metabolic disorders have also been characterized in PTRF-null mice.[22] Urogenital abnormalities observed in male caveolin-1-null mice include urolithiasis,[23] bladder hypertrophy[24] and enlarged seminal vesicles.[25] Both mutated mouse models have impaired detrusor contractility.[26,27]

Caveolin-1 is aberrantly overexpressed in prostate cancer and associated with disease progression.[28] By contrast, despite PTRF expression being proportional to caveolin-1 expression in most normal tissues,[22,29] PTRF is not expressed in prostate cancer[6] and its expression can attenuate prostate cancer aggressiveness.[30–32] In this Review we discuss the roles of caveolin-1 and PTRF in prostate cancer. We summarize the available data on the expression and function of these caveola-forming proteins in prostate cancer and analyse whether they might be targeted for future therapeutic strategies.

Caveolin-1

Caveolins are a family of membrane-embedded proteins that oligomerize to form caveolae (around 144 monomers are found per invagination; Figure 1).[33] Ablation of caveolin-1 in nonmuscle cells or caveolin-3 in muscle cells (but not caveolin-2, which is co-expressed with caveolin-1 in most cell types) causes loss of caveolae.[9,34,35] Caveolins have an unusual membrane topology with both the N-terminal and C-terminal extending into the cytosol. Molecular dissection studies have revealed the presence of a scaffolding domain in the N-terminus of caveolins. In caveolin-1 and caveolin-3 this scaffolding domain can bind a multitude of signalling proteins, resulting in both their direct regulation and their compartmentalization into discrete subdomains.[36,37] Although the validity of regulation via direct interaction has been questioned,[38,39] there is no doubt that disruption of caveolae has widespread consequences on cellular signalling, by disturbance of the segregation of signalling components.[1]

Caveolin-1 in prostate cancer

Cellular, preclinical and clinical studies have shown that caveolin-1 can either promote or suppress tumour

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Key points

- Caveolae are flask-shaped plasma membrane invaginations, the formation of which requires two families of proteins, the membrane-inserted caveolins and cytoplasmic cavins
- Caveolin-1, the major caveolin family member, is overexpressed in prostate cancer and promotes tumour growth, angiogenesis and insensitivity to androgen deprivation
- Caveolin-1 can be secreted and exert paracrine and endocrine effects that contribute to prostate tumour growth and metastasis
- Expression of polymerase I and transcript release factor (PTRF) is reported to be absent in prostate cancer
- Exogenous expression of PTRF reduces prostate cancer aggressiveness probably via both caveola-mediated and caveola-independent mechanisms

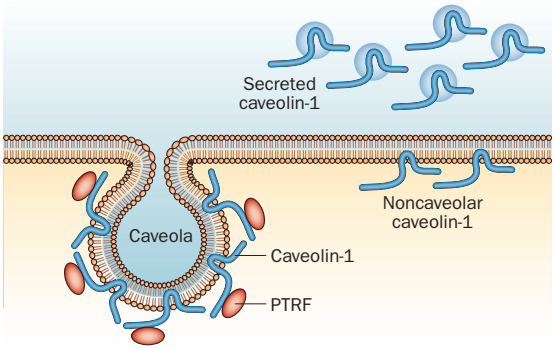

Figure 1 | Caveola formation requires membrane-inserted caveolin-1 and cytoplasmic PTRF. Caveolae are invaginations of the plasma membrane that measure 60–80 nm in diameter. In the absence of PTRF, caveola formation is lost and caveolin-1 is found on noncaveolar plasma membrane. Prostate cancer cells secrete caveolin-1, which is found in the circulatory system in lipoprotein-like particles. Abbreviation: PTRF, polymerase I and transcript release factor.

growth. Early observations suggested that caveolin-1 has a tumour-suppressor role[40] inhibiting both cell proliferation[41] and anchorage-independent growth.[42] Moreover, genetically engineered mice with disruptions in the caveolin-1 gene (*Cav1*) are more susceptible to carcinogen-induced epidermal tumour formation than wild type mice.[43] The progeny of *Cav1* mutant mice crossed with mouse mammary tumor virus-polyoma middle T antigen (MMTV-PyMT) mice, demonstrate an accelerated onset of mammary tumours and lung metastasis.[44,45] The genes encoding caveolin-1 and caveolin-2 have been mapped to 7q31.1, a locus frequently deleted in human cancers, including prostate cancer.[46]

Expression of caveolin-1 is thought to be tumour-type specific. Clinical studies have indicated downregulation or mutation of caveolin-1 in cancers including breast, ovarian, small cell lung, small cell bladder and colorectal carcinomas.[47] However, in other cancers including prostate cancer, caveolin-1 is overexpressed and has been proposed to be stage specific, such that at early stages of the disease loss of caveolin-1 promotes proliferation and survival, whereas upregulated expression at later stages correlates with invasiveness, metastasis and multidrug resistance.[48]

Few studies have explored the correlation between caveolin-2 and cancer. The overexpression of caveolin-2 was found to correlate with tumour progression and poor prognosis of oesophageal squamous cell carcinoma,[49] lung cancer,[50] urothelial carcinoma of the urinary bladder[51] and prostate cancer.[6] In breast cancer, both overexpression[52–54] and downregulation[55] of caveolin-2 have been reported in human tumour specimens.

In prostate cancer, evidence from *in vitro*, animal and clinical studies suggests that caveolin-1 mediates the development of aggressive disease. Expression of caveolin-1 was shown to be upregulated in mouse prostate cancer cells derived from metastasis compared with cells isolated from the primary cancer.[56] Moreover, the overexpression of caveolin-1 in DU145, PC3 and ND-1 human prostate cancer cell lines, as well as in mouse and human cancer tissues, has been reported, with further increased expression in metastatic samples.[56] Consistent with these findings, an immunohistochemical study of 61 patients revealed that caveolin-1 expression increases with disease stage; caveolin-1 positivity staining was 8%, 14%, 38% and 62% in normal epithelium, localized tumour, primary adenocarcinoma with metastasis and in metastatic tissues derived from lymph node, respectively.[57] Overall, evidence has demonstrated that caveolin-1 protein expression increases with prostate cancer stage and grade,[58–60] with features of tumour aggressiveness,[61] angiogenesis[62] and resistance to androgen ablation,[57] and predicts poor clinical outcome.[58,63,64]

In addition to the abundant literature showing increased caveolin-1 in prostate cancer, a few studies have reported decreased expression of caveolin-1 mRNA in prostate cancer.[65,66] Genetic studies have so far failed to demonstrate an association between prostate cancer and coding mutations of caveolin-1, but intronic polymorphisms, downstream gene variants and hypermethylation of the gene promoter have been reported in patients with prostate cancer.[65,67–70] Whether increased caveolin-1 expression is associated with changes in the number of caveolae in clinical prostate cancer tissues remains unknown. In dogs, however, the number of basolateral caveolae in basal epithelial cells was shown to increase prominently upon androgen-induced prostate hyperplasia.[5]

Multiple studies have demonstrated that increasing caveolin-1 expression promotes prostate cancer aggressiveness. *In vitro*, caveolin-1 increases viability,[71] colony formation,[71,72] invasive potential[73] and angiogenic potential[74] and promotes resistance to androgen deprivation.[71,75] *In vivo* studies further support these findings; caveolin-1 suppression via antisense cDNA vector in mouse prostate tumour cells leads to reduced metastasis[71] and increased androgen sensitivity.[71,75] Inactivation of one or both alleles of the *Cav1* gene in the TRAMP (transgenic adenocarcinoma of mouse prostate) mouse reduced prostate tumour burden and metastasis.[76] Conversely, prostate-specific transgenic expression of caveolin-1 in mice led to hyperplasia and resistance to castration-induced prostatic regression.[77]

Inducible expression of caveolin-1 in LNCaP cells has been shown to increase tumour volume, metastasis and angiogenesis.[73,78]

Paracrine and endocrine effects of caveolin-1

Even though caveolin-1 is primarily a membrane-embedded protein, evidence has accumulated that it can be secreted in two different forms—lipoprotein-like particles and prostasomes—both of which can act on neighbouring or distant cells.

Differential centrifugation and negative staining electron microscopy have demonstrated the presence of caveolin-1 in lipoprotein-like particles that co-separate with apolipoprotein A-1.[79] Furthermore, caveolin-1 is present in the conditioned medium of cultured GH3 pituitary cells, in the lumen of vesicles of exocrine cells from mouse tissues[80] and in the secretions of secretagogue-stimulated pancreas.[79,81] The secretion of caveolin-1 by prostate cancer cells (LNCaP cells transfected to express caveolin-1) in the form of soluble 15–30 nm lipoprotein particles has been demonstrated *in vivo* and *in vitro*.[82] Most notably, caveolin-1 has been detected by western blot analysis in the high density lipoprotein 3 subfraction of serum from patients with prostate cancer.[57]

In addition, normal and malignant prostate epithelial cells produce secretory vesicles termed prostasomes that are found in prostatic fluid and seminal plasma and have physiological roles in reproductive health.[83] These membrane-bound structures measure approximately 150 nm in diameter and are secreted from a multivesicular compartment.[84] Prostasome levels are not only significantly elevated in blood samples taken from men with prostate cancer compared with healthy controls and men with benign biopsy results, but also reflect disease aggressiveness.[85] Proteomic analysis of prostasomes derived from vertebral metastases of men with prostate cancer revealed proteins involved in prostate cancer growth and development.[86] Prostasomes derived from PC3 cells contain caveolin-1[84] and PC3 cells induced to form caveolae by exogenous PTRF expression secrete prostasomes with a different composition to uninduced PC3 cells.[30] Caveolin-1-positive vesicles of a larger size than prostasomes (1–10 μm in diameter) have been identified in the conditioned medium of LNCaP cells expressing the MyrAkt1 oncogene, DU145 cells and in the serum of TRAMP mice.[87]

Compelling evidence suggests that caveolin-1 secreted by prostate cancer cells has both paracrine and endocrine effects. Secreted or purified recombinant caveolin-1 can be taken up by neighbouring or distant caveolin-1-negative prostate cancer cells and endothelial cells, both *in vitro* and *in vivo,* and promote tumour growth and angiogenesis.[57,78,82,88] For example, caveolin-1-expressing LNCaP cells injected into one side of a nude mouse promote the growth of caveolin-1-negative LNCaP cells injected in the contralateral side.[82] Furthermore, a polyclonal anti-caveolin-1 antibody added to cell culture or injected intraperitoneally in mice can antagonize the tumour-promoting effects of secreted caveolin-1.[57,77] Monoclonal anti-caveolin-1 antibodies are, therefore, being generated for evaluation as prostate cancer therapies.[89]

Stromal cell caveolin-1 expression

Tumour-associated stroma is not merely a scaffold that supports the tumour. Infiltrating cells, such as fibroblasts, immune cells and endothelial cells, contribute actively to tumour progression via extensive crosstalk with cancer cells in the tumour microenvironment. Loss of stromal caveolin-1 has been reported in patients with prostate cancer[90,91] and was associated with high Gleason score (7[4 + 3]–10), which suggests that low levels of stromal caveolin-1 are associated with prostate cancer. This finding was confirmed in a study of the periepithelial stroma, which was found to be positive for caveolin-1 in all samples from patients without prostate cancer but negative in 39.6% of samples from men with prostate cancer of Gleason score of ≥7.[92] However, experiments in animal models have shown that injection of caveolin-1-expressing RM-9 prostate cancer cells into the prostate of caveolin-1-null mice produced smaller and less vascularized tumours than injection of the same cells into caveolin-1-expressing mice.[78] Future studies of the role of stromal caveolin-1 in prostate cancer might clarify whether low expression of caveolin-1 in this compartment is a consequence of tumour growth or stage, and whether it has any effect on tumour growth in humans.

Caveolin-1 as a biomarker for prostate cancer

Caveolin-1 levels in prostate tissue or serum have been proposed to serve as diagnostic, prognostic or therapeutic efficacy markers for patients with prostate cancer. Immunohistochemical detection of caveolin-1 overexpression in high-grade prostatic intraepithelial neoplasia has been suggested to be a biomarker for the early identification of patients who will develop caveolin-1-positive primary prostate cancer.[93] For patients with lymph-node-negative prostate cancer, caveolin-1 immunoreactivity in the prostate predicts a shorter time to disease progression after surgery than for those without immunoreactivity.[58,63] Because caveolin-1 overexpression is associated with biochemical recurrence, its detection might be used to identify patients at high risk of recurrence for early systemic therapeutic intervention.[61]

Secreted caveolin-1 can be measured in the serum of patients using ELISA and is significantly higher in patients with prostate cancer than in men with BPH or healthy controls.[94] High preoperative serum caveolin-1 indicates a greater risk of PSA recurrence, and serum caveolin-1 can be used clinically to predict time to recurrence when combined with biopsy Gleason score.[64]

Lastly, preclinical data indicate that decreased levels of serum caveolin-1 might be an indicator of therapeutic efficacy; in a mouse model of prostate cancer, serum caveolin-1 levels were lower in dasatinib-treated and sunitinib-treated mice than they were in vehicle-treated mice.[95] Moreover, serum caveolin-1 levels correlated positively with tumour growth, suggesting a role for caveolin-1 as a biomarker of response to prostate cancer treatment.[95]

PTRF

The cavin family of cytoplasmic proteins is essential for the formation and functions of caveolae.[29,96,97] Four members exist, namely PTRF (or cavin-1), which is essential for caveola stabilization at the plasma membrane; serum deprivation-response protein (SDPR or cavin-2), which regulates membrane tubulation;[98] protein kinase C delta-binding protein (hSRBC or cavin-3), which regulates caveola endocytosis;[99] and muscle-related coiled-coil protein (MURC or cavin-4).[96] Cavins form a multiprotein complex of 60–80 individual molecules, which is recruited to the plasma membrane by caveolin-1 in a PTRF-dependent fashion.[100]

PTRF was originally discovered as a cytoplasmic factor that interacts with RNA polymerase I and dissociates paused transcription complexes, thereby facilitating re-initiation of the polymerase.[101–103] PTRF was later revealed to associate with caveolae[104] and participate in caveola formation and function.[29,97] PTRF has roles in processes as diverse as senescence,[105,106] muscle membrane repair,[107] lipolysis,[108] obesity[109] and metabolic regulation.[22] Accordingly, PTRF mutations in humans have been associated with lipodystrophies and muscular dystrophies,[110–113] some of which are closely linked to caveolin-1 expression.[110]

A role in immunity has also been proposed for PTRF. Endothelial cells express high levels of PTRF that is processed into an abundant PTRF-derived self-peptide that, when presented on the cell surface with major histocompatibility complex class I molecules, protects endothelial cells from cytotoxic T lymphocyte-mediated lysis in the course of immune responses.[114] Taken together, these findings suggest that PTRF possesses cellular functions that are related to the formation of caveola in combination with caveolins, as well as caveola-independent roles.

PTRF is a phosphorylated protein, and site-directed mutagenesis has shown that mutation of the phosphorylation sites serine-42, threonine-304 or serine-368 impairs PTRF-induced fat mobilization.[108] Although it has been revealed in a phosphoproteomic study that PTRF phosphorylation is increased in cells expressing constitutively active EGFR,[115] the role of PTRF phosphorylation in cancer is currently unknown.

PTRF has been documented to be downregulated, together with hSRBC and SDPR, in breast cancer cell lines and tissues, and this downregulation was accompanied by PTRF promoter hypermethylation.[116] Proteomic analysis, western blotting and immunohistochemistry have demonstrated the loss of PTRF expression in non-small-cell lung cancer samples[117] and in malignant human bronchial epithelial cells.[118] PTRF might participate, in concert with caveolin-1, in the regulation of multidrug resistance in breast cancer cells via drug efflux,[119] although this was not confirmed in a subsequent study of colorectal cancer cell lines.[120]

Co-regulation of caveolin-1 and PTRF expression

The expression patterns of caveolin-1 and PTRF closely match in normal tissues in mice[22,29] and this correlation remains upon physiopathological or environmental stimulation. For example, expression levels of both caveolin-1 and PTRF increase upon nutrition-induced fat expansion.[109] Furthermore, PTRF downregulation results in reduced expression of caveolin-1 in various cell lines.[29,97] One proposed mechanism for this co-regulation is that in the absence of PTRF, caveolae do not form and noncaveolar caveolin-1 is internalized and undergoes lysosomal degradation.[29]

Caveolin-1 and PTRF are co-regulated at the transcriptional level by the transcription factor early growth response-1 (EGR1). EGR1 was shown to inhibit the transcription of both *CAV1* and *PTRF* genes, probably by competing with transcription factor SP1 for overlapping binding sites.[121] When phosphorylated upon cellular stimuli, EGR1 failed to bind target promoter DNA and expression of both caveolin-1 and PTRF increased in a process that required endogenous caveolin-1.[121] Like caveolin-1, *EGR1* is overexpressed in prostate cancer and expression level correlates with Gleason score.[122] However, increased caveolin-1 expression has been reported without concomitant increase of PTRF expression in prostate cancer tissue samples, suggesting that co-regulation of the expression of caveolin-1 and PTRF is lost in prostate cancer.[6,92]

PTRF in prostate cancer

The spatial and functional associations of PTRF with caveolin-1 have led to the suggestion that PTRF might also be involved in prostate cancer. Immunohistochemical analysis of prostate specimens from men with BPH, prostate cancer and healthy controls revealed a lack of PTRF expression associated with an elevated caveolin-1 expression in prostate cancer and with slight elevation in BPH.[6,92] These two studies are the only ones to date that report immunohistochemical staining of PTRF in prostate cancer samples, and their findings are slightly different. Gould *et al.*[6] found PTRF expression in normal prostate epithelia, whereas Moon *et al.*[92] did not, but they both found high expression levels of caveolin-1 and no expression of PTRF in prostate cancer epithelium. Furthermore, both studies report that stromal PTRF is expressed in normal prostate but lost as cancer progresses, for example Moon *et al.*[92] found that 52.9% of specimens with a Gleason score of ≥8 were negative for PTRF in the periepithelial stroma.

Similarly to human prostate cancer specimens, the prostate cancer cell line PC3 expresses high levels of caveolin-1 but does not express PTRF.[29] In this cell line, exogenous expression of PTRF restores caveola formation and induces caveolin-1 localization to morphologically identifiable caveolae. In addition, PTRF-expressing PC3 cells exhibit reduced cell migration[31] and lower expression levels of matrix-degrading enzymes than normal PC3 cells.[30,31] Proteomic analysis revealed that PTRF modulates the secretion of other factors involved in cell migration, such as extracellular matrix components and cytokines.[30] In DU145 prostate cancer cells, small-hairpin-RNA-mediated downregulation of PTRF expression led to increased migration.[32] Thus, current

evidence suggests a suppressive role for PTRF in prostate cancer, in contrast to that of caveolin-1.

Both caveola-dependent and caveola-independent mechanisms of action have been documented for PTRF in prostate cancer cells. In order to differentiate between caveola-mediated and caveola-independent mechanisms of action for PTRF, we studied the effect of PTRF expression on prostate cancer cell migration in PC3 cells engineered to express all possible combinations of caveolin-1 and PTRF.[32] We found that caveolae only formed when both proteins were present, and PTRF had a different effect on migration depending on whether or not caveolin-1 was expressed.[32] Analysis of secretomes (concentrated conditioned medium) and prostasomes (conditioned medium sequentially centrifuged to isolate vesicles) from PC3 cells suggested that PTRF modulates secretory pathways by sequestration of caveolin-1 to form caveolae.[30] On the other hand, the downregulation of MMP-9 production upon PTRF expression in PC3 cells was demonstrated to be the same whether or not the cells expressed caveolin-1.[31] Also in favour of a caveola-independent function, the subceullar localization of PTRF in migrating prostate cancer cells is distinct from that of caveolin-1.[32] Lastly, PTRF seems to regulate gene expression independently of caveolin-1 via indirect binding to promoters; for example, PTRF associates with BFCOL1 (zinc finger protein 148) to enhance its binding to, and suppress activity of, the type I collagen promoter.[123]

The mechanisms by which PTRF might suppress prostate cancer are multiple. By enabling caveola formation, PTRF expression might trap caveolin-1 in caveolae, thereby affecting the activities of the different pools of caveolin-1; noncaveolar caveolin-1 might exert its tumour-promoting effects within the cell or might exit the cell via incorporation into prostasomes or direct secretion. Theoretically, PTRF might restore caveola function in stromal or prostate cancer cells, which has the potential to exert metabolic changes[124] in the tumour microenvironment, to affect cancer cell signalling and to influence cholesterol transport,[125] all of which might regulate prostate cancer aggressiveness.[126] At the moment, however, these mechanisms are entirely speculative.

Independent of caveola formation and caveolin-1, PTRF might also modulate the expression of genes encoding proteins that have key roles in prostate cancer, including matrix-building or matrix-degrading enzymes such as collagen[123] or MMP-9.[31] Further studies evaluating differential gene expression in prostate cancer cells upon PTRF expression might reveal new target genes of PTRF.

Conclusions

The expression of caveola-forming proteins is dysregulated in prostate cancer. Caveolin-1 is overexpressed without concomitant expression of PTRF,[6,92] leading to the possibility that noncaveolar caveolin-1 has a role in the aggressiveness of prostate tumours. PTRF emerges from recent literature[30–32,92] as a protein that, when exogenously expressed in prostate cancer cells, reduces their aggressive potential, probably via both caveola-mediated and caveola-independent mechanisms.

Several questions arise from the current data on caveola-forming proteins in prostate cancer. Although studies investigating caveolin-1 in this context are concordant—showing that caveolin-1 overexpression promotes prostate cancer growth, angiogenesis and resistance to androgen deprivation—a role for PTRF in prostate cancer remains to be demonstrated. The only two existing reports on PTRF expression in prostate cancer tissue demonstrate that prostate cancer cells express increased caveolin-1 without concomitant increase in PTRF.[6,92] Further studies are awaited to confirm this finding and to elucidate whether normal prostate epithelium expresses PTRF. In addition, stromal PTRF decreases with progression of the disease.[6,92] Experimental animal models with PTRF expression ablated from either the prostate cancer cells or the host cells should confirm whether or not epithelial and stromal PTRF has a suppressive role in prostate cancer.

Given the ability of caveolin-1 antibodies to antagonize the tumour-promoting effects of caveolin-1 *in vitro* and in animal prostate cancer models[57,77]—and the upcoming evaluation of caveolin-1 antibodies in the clinical setting[89]—the putative PTRF-mediated prevention of caveolin-1 secretion might limit prostate cancer growth *in vivo*. Experimental data supporting this possibility are awaited. Studies using genetically modified cells or mice will shed more light on PTRF mechanisms of action in the context of this disease. Until more is known about its transcriptional regulation, the overexpression of PTRF for therapeutic purposes would have to be achieved via targeted gene therapy.

Review criteria

Search engines used were PubMed and Google Scholar. Search terms used were "caveolae", "caveolin", "PTRF", "cavin", "prostate", and "cancer" in various combinations. There was no limitation on the year of publication. The reference lists of identified publications were searched for additional material.

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Author contributions

Z. D. Nessar and M.-O. Parat researched data for the article and wrote the article. All authors contributed to discussion of content. M.-O. Parat, M. M. Hill and R. G. Parton reviewed the manuscript before submission.