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Mechanistic Role of Caveolin-1 in Chronic Renal Disease

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ABSTRACT

An estimated 10–16% of the general population in affluent nations suffers from chronic renal disease (CRD), a severe worldwide public health problem that causes early morbidity and mortality. Since the kidney uses a lot of energy, cellular metabolism is crucial to kidney-related illnesses. The primary component of caveolae on the plasma membrane is the multifunctional membrane protein caveolin-1 (Cav-1). The microscopic invaginations known as caveolae are widely distributed on the plasma membrane and act as a platform to control signal transduction, stress reactions, and cellular endocytosis. Nonetheless, caveolae have drawn more attention as a metabolic platform that contributes to the development of renal disease, facilitates the endocytosis of albumin, cholesterol, and glucose, and takes part in cellular metabolic reprogramming. Because of its widespread dispersion, it has been linked to a number of human disease processes. Altering caveolin-1 might identify novel targets for patients with chronic renal disease, a patient population that has high morbidity and mortality. The structure, signaling, and mechanistic role of the caveolin-1 in chronic renal disease are highlighted in this review.

Keywords: Caveolins, Chronic renal disease, Caveolin-1, Nitric oxide, Cell growth.

INTRODUCTION

The English National Health Service (NHS) was expected to have spent £1.45 billion on chronic renal disease (CRD) in 2009–2010, or 1.3% of all healthcare expenditures in that year. Half or more of these expenditures were attributable to the 2% of CRD patients who needed RRT because of ESRD [1, 2]. Chronic renal disease (CRD) burden results in an excess of hospital periods of stay, inpatient-associated infections, and an excess of 12,000 myocardial infarctions and 7000 cerebral vascular events related to age/gender matched controls [2]. People with CRD must still be identified as soon as possible in order to begin treatment and prevent the progression of end-stage renal disease (ESRD). First detected visually in 1953 using transmission electron microscopy, a subtype on non-clathrin-coated rafts of lipids known as caveolae are 50–100 nanometer-long, cave-like invasions of the plasma membrane [3]. In 1955, Yamada made the first report of caveolae forming in the tubular capillary endothelium of renal mice [4]. Although they are widely dispersed, caveolae are mostly observed in fibroblasts, epithelial cells, endothelial cells, smooth and striated muscle cells, and pneumocytes (type1). In adipocytes, they make up over 20% of the whole plasma membrane [5,6]. The production of caveolae depends on caveolin-1 (CAV1), one of the three primary isoforms of the caveolin protein. According to a 1999 description, caveolin-2 is a 20 kDa protein that co-localizes and forms hetero-dimers with CAV1 [7]. Caveolae containing CAV1 are absent from the apical edges of epithelial cells; however, their localisation occurs on the basolateral surface [8]. Caveolin-3, which resembles caveolin-1 in form, is habitually found in cardiac, smooth, along with skeletal muscle fibres [9].

CAV1 is necessary for the structural integrity of caveolae, which, in contrast to the dispersion of plasma membranes, are mostly composed of lipids with increased glycosphingolipids and sphingomyelin. Caveolae can cause an immediate vesicle production, primarily at the surface of the basolateral region, enlongated (for channel construction), or the typical omega or tiny cave, as illustrated in figure.1 [10]. The presence of proteins known as cavins influences CAV1's mobility, thereby affecting the structural integrity of caveolar structures and facilitating the endocytosis of these structures and their contents. If the proportion of cavin-1 to cavin-2 is high, caveolae will adopt an omega shape; conversely, when cavin-2 expression exceeds that of cavin-1, an elongated morphology will occur, with vesicle production influenced by cavin-3 expression [11]. Reduced CAV1 expression brought on by cholesterol depletion may potentially cause the instability of caveolae architecture to detach from the outermost layer of plasma membrane.

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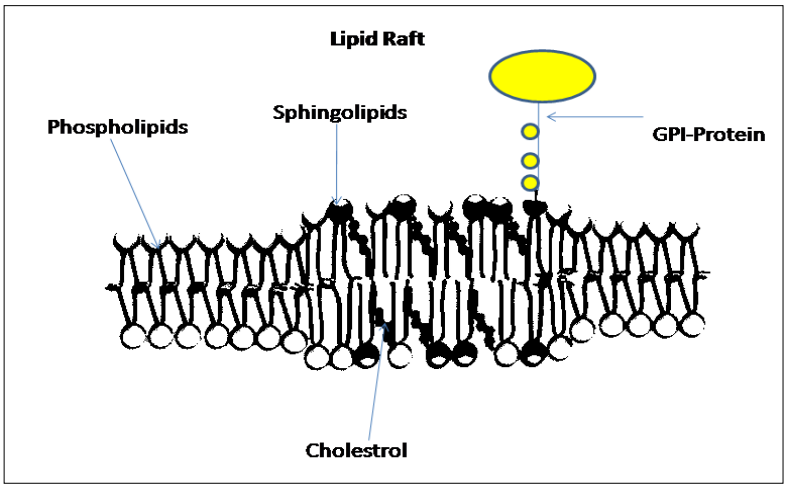

Fig.1 Caveolin Structure

The intracellular protein caveolin-1 is created by the ER, or endoplasmic reticulum, mechanism and then moved from the Golgi structure to the plasma membrane. Increasing cholesterol speeds up CAV1's departure from the Golgi apparatus, while glycosphingolipid depletion inhibits it [12]. CAV1 comes in two isoforms, alpha and beta. Beta is 31 amino acid strands shorter than alpha, which is 178 amino acids long. The plasma membrane is more receptive to the former. Following tyrosine phosphorylation, the N' terminus faces the cytoplasm, while the C' terminus faces palmitoylation. In the space between the two ends, 32 amino acids (residues 102–134) create a hydrophobic domain in the shape of a hairpin. Beta is 31 amino acid strands shorter than alpha, which is 178 amino acids long. The plasma membrane is more receptive to the former. Following tyrosine phosphorylation, the N' terminus faces the cytoplasm, while the C' terminus faces palmitoylation. The 32 amino acids that make up the hairpin-shaped hydrophobic domain (residues 102–134) are produced between the termini. This domain inserts into the plasma membrane and plays a role in the oligomerization of CAV1 and CAV2 [13]. This area is flanked by residues 82-101 and 135-150, The latter has a cis-Golgi targeting region and is referred to as the C' transmembrane attachment domain. The caveolin scaffold domain (residue 82–101), sometimes referred to as the N' transmembrane attachment domain, is crucial for transmembrane localisation, anchoring, and controlling (inhibiting and enhancing) the activity of signaling to various proteins inside caveolae [5]. Moreover residue tyrosine-14 (Y14), which is crucial for cell adhesion with needs to be phosphorylated for caveolar endocytosis, is another significant location.

Genomic Location of CAV-1

CAV-1 gene is situated at genomic location 7q31.1 (7:116540796) on the extended chromosome 7 arm. It has two introns (1.5 and 32 kilobases long) separated by three exons (30 base pairs, 165 base pairs, and 342 base pairs, respectively). The primary component of gene expression of CAV1 in cancer cell lines is believed to be the CpG islands found in the first exons, which are methylated [14]. The third exon contains the membrane, a scaffold, C' transmembrane attachment, and functional oligomerisation domains, which are mostly species-neutral [15].

Signalling role of CAV-1

Caveolae and CAV1 play a number of essential roles in cellular activity. The most prevalent is the transcytosis of macromolecules (such albumin) from the capillary endothelium's luminal side to the interstitial space through membrane-bound vesicles. Transmission electron microscopy shows that the knockout CAV1 mice does not accumulate gold-labeled albumin in the interstitial space like the wild-type mouse does [16]. The second instance of caveolae trafficking vesicular membranes is endocytosis. Similar to the classic clathrin-mediated endocytosis, CAV swap vesicle fusion with docking molecules (dynamin and N-ethylmaleimide-sensitive soluble factor protein receptors, or SNARE). Collections of caveolae are used by pathogens like cholera toxin and simian virus 40 to internalise into the cell. With CAV1 recycled to the plasma membrane, this leads to the creation of a special endoscopic enclave with a pH of neutral, known as a caveosome, which is then transported to the ER as well as Golgi apparatus [5, 17].

Critical to cellular signalling and signal transduction are CAV1 and caveolae, which, upon ligand binding, compartmentalise receptors, shield signalling-molecules and ligand bounded receptor from nuclear translocation, and concentrate these processes in a specific subcellular environment [5]. In response to ligand interactions, caveolae internalise receptors such the transforming growth factor beta (TGFβ) receptor and the epidermal growth factor receptor (EGFR), which occur when the Y14 region of CAV1 is phosphorylated [18]. Protein kinase C and Src kinases are required for this internalisation [19]. Furthermore, the distribution of

insulin, angiotensin II and stress induced channel-related short transient receptor potential channel-1 receptors in the plasma membrane is dependent on CAV1 (golgi-derived) through the syntaxin-6 (SNARE) protein [12].

With the exception of insulin receptors, the majority of CAV1's actions, with the possible exception of insulin receptors, degrade receptors and hinder cellular signalling. Anti-fibrotic and pro-apoptotic effects are the primary results of CAV1 signal connection. The TGFβ and e-NOS (endothelial nitric oxide synthase) pathways are the signalling CAV1 connections that are most frequently reported. By binding eNOS with its CSD, CAV1 renders it inactive and can serve as a store for inactivated eNOS. More calmodulin is recruited and binds to the eNOS enzyme as a result of the calcium inflow, releasing it from the bound CAV1 and restoring Nitric oxide (NO), a vasodilator, synthesised from L-arginine through the action of the heme moiety of eNOS, following the transfer of electrons from NADPH to the flavins in its reductase domain. Signal transduction is stopped when NO is produced because it causes the CAV1 scaffold to dissociate. In situations where the substrate L-arginine is limited, when oxygen comes into contact with the heme moiety during electron transport, reactive oxygen species (ROS) are formed. This results in eNOS operating independently [20]. ROS activates TGFβ-1 by releasing it from its latent TGFβ-binding protein and latency-associated peptide [21]. This ligand interaction results in the formation of a serine/threonine kinase heterotetrameric complex, which phosphorylates the TGFβ type 1 receptor after it binds to the TGFβ type II receptor. Upon internalisation, the early-endosome antigen 1 non-lipid/clathrin raft pathway phosphorylates the downstream SARA/Smad 2/3 complex, which in turn internalises this complex. This process induces a conformational shift that facilitates the heteromerisation of Smad 4, prompting its migration all the way to nucleus. In the nucleus, Smad 4 downregulates CAV1 and Smad 7, thereby regulating the fibrotic gene expression [22]. In instances where the TGFβ receptor I/II complex undergoes internalisation via caveolae, there is a recruitment of SMURF/Smad 7, which negatively influences TGFβ signalling. This happens in CAV1 positive vesicles due to the processes of proteasomal degradation and ubiquitination of the TGFβ receptor complex. Furthermore, CAV1 inhibits the translocation of Smad 2 to the nucleus, reduces Smad 2 phosphorylation, and interferes with its association with Smad 4, thereby diminishing TGFβ signalling [22].

Fibronectin degradation and integrin internalisation are two additional signalling mechanisms linked to caveolae endocytosis [23, 24]. Through CAV1 and the phosphorylation of Y14, fibroblast detachment initiates ganglioside GM1 internalisation; GM1 internalisation results in Rac1 removal from the plasma membrane and decreased activity [12]. Consequently, by localising and emphasising signalling molecules while serving as docking spots for the various cell surface receptors postligand binding, CAV1 is essential in compartmentalising signal transduction within caveolae. Additionally, endothelial cells are supplied with flow sensors and regulating the course of the stretch-induced cell cycle, it also regulates cell adhesion, migration, and interactions with the extracellular matrix (ECM) [12, 24]. The translocation from Golgi complex with plasma membrane, along with the establishment of caveolae, that leads to an increase in CAV1 levels when subjected to prolonged shear stress [25]. Consequently, signalling pathways including eNOS as well as mitogen-activated protein kinase (MAPK) become activated, leading to an enhancement in mechanosensitivity. Observations indicate that there are flaws in the chronic flow mediated remodelling of blood arteries in Cav1-/- mice [26]. Stretch-induced CAV1 downregulation or Cav1-/- smooth muscle cells suppress cell cycle progression via pathways such as PI3 kinase-AKT /protein kinase B, MAPK ERK, c-Src, and integrins [27].

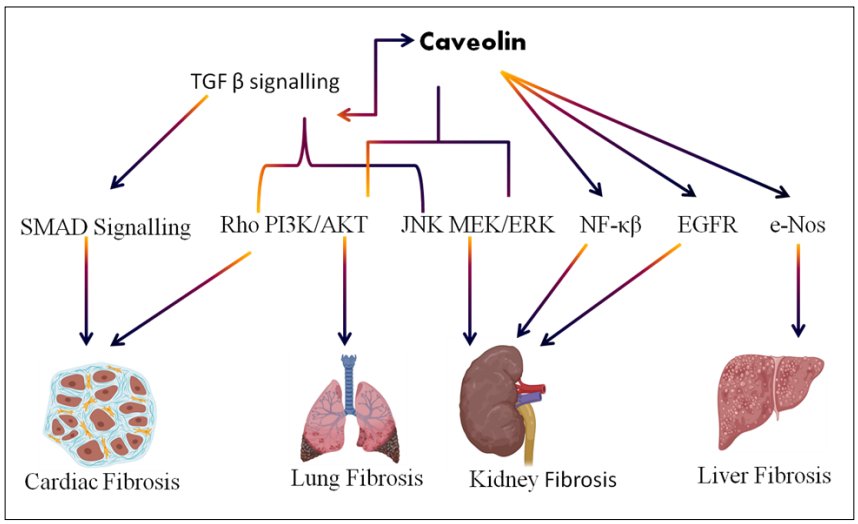

Fig.2 Role of Caveolin-1

Adverse outcomes of renal CAV-1

Caveolin-1 in nephro fibrosis: Patients with CRD, regardless of the underlying aetiology of their disease, have increased interstitial fibrosis as their kidney function declines. As indicated by the effects discussed in the previous section, CAV1 has been a protein of interest for research in the context of organ fibrosis. The research on renal fibrotic CAV1 is summarised in the next section [28].

Numerous studies have examined the connection between CAV1 and TGFβ mediated fibrosis through common mechanism via chronic illnesses, both renal and non-renal, arise. Li et al. used primary murine pulmonary endothelial cells that, when treated with TGFβ-1, developed a myofibroblast phenotype and were able to stimulate αSMA expression in wild-type cells. The elevated spontaneous levels of αSMA observed in Cav1-/- cells, which were normalised through the functional restoration of CAV1 using its CSD peptide, indicate that CAV1 plays a regulatory role in the endothelial-into-mesenchymal transition associated with tissue fibrosis [29]. As demonstrated by Ito et al., hyaluronan and its receptor CD44 improved the internalisation of TGFβ via lipid rafts via MAP kinase from the non-lipid route majority in immortalised renal proximal tubular epithelial cells (HK2) [30]. The researchers inhibited multiple components, such as CD44 mediated interaction with hyaluronan, along this pathway and co-cultured HK2 cells as well as cells that had been transfected with a Smad receptive promoter to validate their findings. The researchers indicate that this contradicts earlier studies on metastatic breast tumour cells, which cause the hyaluronan mediated activation of the non-lipid pathway; thereby the results may be influenced by particular tissue micro-environments. Zhang and associates [31] demonstrated that IL-6 stimulation led to a diminution in the connotation of the IL-6 receptor with CAV1 following co-immunoprecipitation, while simultaneously enhancing the dominance of the TGFβ receptor in the non-lipid raft pathway within HK2 cells. This observation emerged following the discovery that in the context of renal disease, IL-6 is exclusively articulated by proximal tubular epithelial cells. Although the affinity labelling results were observed, with stimulation and IL-6 as well as TGFβ-1 did not lead to an increase in the production of Smad 2, 3, or 7 proteins. Notably, only the luciferase test indicated an increase in Smad activity.

CAV1 has been linked to several other signalling pathways in renal fibrosis in addition to TGF. In order to simulate intraglomerular hypertension that leads to glomerulosclerosis, scientists physically stretched mesangial cells using the cyclic vacuum, which resulted in src-mediated phosphorylation of the CAV1 Y14 site, RhoA activation, with the generation of ROS [32]. When CAV1 was reintroduced, the RhoA and ROS activation that was absent in the Cav1 knockout mice was quickly recovered [33].

Bocanegra et al. [34] examined the caring profile of losartan on proximal tubular cells from spontaneously hypertensive rats, and its CAV1 expression was much lower than control, using a different hypertension paradigm. Losartan, an angiotensin-II type-1 receptor antagonist, reduces reactive oxygen species (ROS) by downregulating Nox4 and inactivating NADPH, facilitated by augmented levels of CAV1 and co-localization with Heat Shock Protein 70. CAV1 functions as a molecular chaperone to AT1, facilitating redox signalling events through the development of reactive oxygen species (ROS) via Nox4, which depends on NADPH oxidase [35].

Furthermore, it has been shown that hereditarily obese Zucker rats fed a food consisting primarily of casein had kidneys with structural abnormalities that had higher CAV1 and lower eNOS levels compared to those on a soy diet. Nonetheless, the fluctuations of CAV1 in relation to cholesterol levels complicate the interpretation of these findings [36]. Ureteric obstruction leads to a significant and rapid elevation of intrarenal angiotensin II levels [37], which damages cells through oxidative stress and produces more extracellular matrix proteins, ultimately leading to fibrosis. Interstitial fibrosis can be alleviated by nitric oxide, and when eNOS is absent in the inducible NOS knockout mice, tubulointerstitial fibrosis manifests. CAV1 is expressed by smooth muscle, vascular endothelium, and the cells lining tubules and ducts, whether they are proximal, distal, or convoluted signalling. The study participants aimed to investigate the involvement of CAV1 expression in congenital unilateral ureteropelvic junction obstruction associated grade IV hydronephrosis, necessitating invasive intervention following the exclusion of vesico-ureteral reflux. All 19 children were not on any medication, exhibited normotension, and demonstrated usual age-appropriate renal function. The interstitial volume and CAV1 staining scores are assessed in an oblivious manner. Group 1 was divided into subset A, characterised by blockage of less than one year, and subset B, defined by obstruction exceeding one year. Group 2 showed significantly worse renal function compared to group 1, with 99 mTc- DPTA renal scan results indicating a kidney filtration proportion of 28.8±2% for group 2 and 39.7±2.1% for group 1. The findings indicated that group 2, CAV1 was situated within the proximal tubule and co-localized with the AT1 receptor, differing from the control and group 1 observations. Western Blotting confirmed increased CAV1 expression for protein transcription from the urine of group 2. Unfortunately, the control group consisted of children with renal cell carcinoma, which may not have constituted a valid control due to the known potential alterations in CAV1 expression in these individuals.

In addition to the human study mentioned above that indicates higher CAV1 expression in children who are more chronic and fibrotic, Japanese patients with glomerulus-targeting diseases like membranous nephropathy, diabetic nephropathy and focal glomerulosclerosis have histologically higher glomerular expression of CAV1 [38]. Additionally, it was observed that the usage of steroids decreased CAV1 expression in glomerular endothelial cells. The STZ induced type 1 diabetic nephropathy showed little tubulointerstitial fibrosis, while murine Cav1 deletion resulted in severe glomerulosclerosis and albuminuria [39]. Expression of

CAV1 was similarly raised in streptozotocin-induced diabetic nephropathy rat models with improved VEGF receptor 2 (VEGFR2)/CAV1 interaction in-vivo [40]. Following VEGF stimulation, primary rat mesangial cells in vitro upregulated fibronectin via RhoA activation and increased CAV1/VEGFR2 and CAV1/Src expression. Non-phosphorylatable CAV1 Y14 was overexpressed in mesangial cells, which prevented fibronectin upregulation and VEGF-induced RhoA activation. Human urine free light-chains from individuals with light-chain deposition disease are administered via tail vein injection in rats to induce nodular glomerulosclerosis in both wild-type and Cav1 knockout animals. The outcomes may have been influenced by the mixed genders utilised; nonetheless, the Cav1 deletion exhibited heightened nodular glomerulosclerosis and mesangial matrix formation [41].

As per demonstrated by Yamamoto et al. [42] that de novo caveolae formation transpires into graft glomerulopathy inside glomerular cells (endothelial), as evidenced by their investigation of CAV1 in chronic active antibody interceded rejection and subsequent transplant capillaropathy. Peritubular capillary endothelia, often absent in healthy kidneys, were discovered to be related with CAV1. Pontrelli et al. [43] found that proximal tubular epithelial cells have increased CD40 levels during acute rejection in their investigation of chronic nephropathy (allograft) induced by immune system initiation. Elevated Lyn phosphorylation resulted in NFκB activation. Inhibiting Lyn prevented PAI-1 from inducing profibrosis, as Lyn phosphorylation is exclusively linked to CAV1.

Park et al. [44] employed a unilateral ureteric obstruction (UUO) model in FVB/N mice to examine the increase of stem cells occurring 10 days after left ureter occlusion. Sirius red staining indicated that Cav1 deletion markedly reduced the post-obstructive surge of mesenchymal stem cells, resulting in little parenchymal regeneration and pronounced fibrosis. It's possible that the spike was caused in part by the indigenous renal stem cells' response. In this paradigm, the contralateral kidney of involved mouse was used as the control kidney, and the FVB/N wild-type mice are a different strain from the Cav1 knock-out animals. Because different mouse strains may be more or less prone to fibrosis and because the contralateral reimbursement after ureter ligation may vary, these factors may affect how their results are interpreted.

Chand *et al*. [45] also examined the UUO paradigm on days 3 as well as on 14, utilising sham-operated animals that matched the age, strain, and gender of their Cav1 knockout mice and the mice subjected to UUO. Although the wild-type mice had increased fibrosis on day 3 of the UUO paradigm, the Cav1 knock-out mice demonstrated more extensive fibrosis by day 14. Confocal microscopy of frozen kidney slices revealed that the primary distinction between wild-type and Cav1 knock-out mice was the quantity of F4/80 positive stained cells.

Overall, CAV1 expression seems to adversely affect the renal phenotype, particularly in glomerular illness. This contrasts with the non-renal literature, which has shown that a reduction in CAV1 in patient samples or caveolin-1 deletion in-vitro results in a more fibrotic phenotype. Disorders, like bleomycin-induced lung fibrosis [46], idiopathic pulmonary fibrosis [47], scleroderma/systemic sclerosis[48], cardiac fibrosis [49], and keloid scars [50] may be attributed to TGFβ-dependent processes that depend on fibroblasts' synthesis of CAV1.

Caveolin-1's pleiotropic impact on poor renal outcomes

As their renal condition worsens, patients with CRD frequently have tubulointerstitial fibrosis and other negative effects. Many of these consequences have been linked to CAV1 because of its widespread distribution.

Infection

Bronchoalveolar lavage from individuals with scleroderma-mediated lung disease revealed activated monocytes and polymorphonuclear cells; the expression of CAV1 was diminished in the monocytes, neutrophils, and T cells of these patients [50]. The absence of Cav1 led to diminished expression of CD14 and CD36 throughout macrophage formation, alongside decreased phagocytic ability and compromised bacterial clearance in mice subjected to lipopolysaccharide challenge [51]. Furthermore, sepsis caused by Klebsiella pneumoniae and Pseudomonas aeruginosa was more likely to kill Cav1 deletion animals [52,53]. For an appropriate immune response to eradicate Pseudomonas aeruginosa and other pathogens in cystic fibrosis, they must be efficiently internalised; this internalisation is dependent on CAV1 in type 1 pneumocytes and bladder epithelium [54]. CAV1 must interact with protein kinase-Cα during activation and calcium release to translocate to caveolae and produce infectious enveloped human cytomegalovi [55]. Polyomavirus viremia can induce BK nephropathy in renal transplant patients. Moriyama et al.'s in vitro research demonstrates that co-localization with CAV1 is essential for caveolae to penetrate human proximal tubular epithelial cells [56].

Heart disease

A phenotype of inflammatory macrophages that produce foam cells, which promote atherosclerosis, has been associated with CAV1 [57]. Reduced expression of CAV1 was found by Schwencke et al. in the VSMC of human atheroma [58]. Furthermore, CAV1 affects vascular function by binding eNOS in an inactive state, which results in its release in response to a calcium influx [59]. The

Cav1 mutant mice exhibit cardiac hypertrophy despite elevated levels of caveolin-3, which is considered the prime isoform of caveolin within the heart. Polyomavirus viremia can induce nephropathy in renal transplant patients. Moriyama et al.'s in vitro research demonstrates that co-localization with CAV1 is essential for caveolae to infiltrate human proximal tubular epithelial cells [60].

Cancer

Depending on the kind of cancer, CAV1 may be able to slow tumour development. Research has shown that CAV1 can help bring about cell death. When people with Cav1 mutations have cancer, it spreads and gets worse because the p42/44 MAP kinase cascade is overactive and cyclin D1 is overexpressed in breast cancer [61]. CAV1 has been regarded as a prognostic indicator in several malignancies [62]. Nonetheless, overexpression of CAV1 has been connected to the progression of prostate cancer [63], suggesting that the function of CAV1 differs according on the tissue microenvironment being studied.

The caveolin-1 single nucleotide polymorphism in renal disease was associated with increased carotid arterial intima width (vascular hypertrophy) and cross-sectional area of the common carotid artery (arterial remodelling). The CAV1 rs4730751 and eNOS rs1799983 genotypes showed a significant independent and interactive association with these variables [64]. It's unclear if these associations apply only to haemodialysis patients or if non-dialysis CRD sufferers also experience them. Due to its attachment to CAV1, eNOS requires a calcium influx in order to be liberated and activated.

Unlike atheromatous disease, which is common in the general population, arteriosclerosis and accompanying vascular stiffness are the most common vascular lesions in chronic renal sickness as it advances [65]. Aortic pulse wave velocity (aPWV), the definitive metric for assessing arterial stiffness, has been reliably linked to cardiovascular and overall mortality across several conditions, including chronic kidney disease [66,67]. Chand et al. discovered in their multivariate study that the CAV1 rs4730751 CC genotype correlates with reduced arterial stiffness in individuals with early and late-stage non-dialysis chronic renal disease, irrespective of established clinical factors affecting aPWV [68]. Within the vascular endothelium, a reduction in CAV1 correlates with an increase in eNOS activity, potentially compromising arterial stiffness and endothelial integrity due to the "uncoupling" of eNOS, which generates superoxide anion radicals [69], particularly under oxidative stress, a hallmark of chronic kidney disease [70].

Aortic smooth muscle cells lacking Caveolin-1 exhibit pro-arteriosclerotic characteristics, including enhanced motility, proliferation, and neointimal hyperplasia [71]. These observations may validate the conclusions of the present investigation. In contrast, macrophages with reduced CAV1 levels exhibit anti-inflammatory properties, produce fewer foam cells, and are thus more resilient to atheroma [57]. Testa et al.'s [64] findings indicate that a CC genotype correlates with increased carotid arterial intima media thickness, an indicator of atheroma rather than arteriosclerosis [72]. Conversely, the current study reveals that a CC genotype is linked to reduced aPWV, suggesting a "anti-arteriosclerotic" effect. These contrasting roles of CAV1 in macrophages ("pro-atheromatous") and endothelium ("anti-arteriosclerotic") may provide support for these observations.

A systemic primary autoimmune illness known as anti-neutrophil cytoplasmic antibody (ANCA) related vasculitis mostly affects small to medium-sized arteries. Notwithstanding enhancements in patient life expectancy, the 5-year death rate persists at a high level (up to 28%), and treatment-related comorbidities, including infection, cardiovascular disease, cancer, and the progression of renal disease, lead to considerable morbidity. These difficulties suggest possible impacts of CAV1, with improved outcomes in this patient group linked to the CC genotype of CAV1 rs4739751 [73].

Conclusion

CAV1 is a desirable target for therapy for many human diseases, particularly CRD patients, due to its pleotropic effects and widespread distribution. It can be used as a biomarker to identify high-risk individuals, to regulate renal fibrosis, or to lower associated morbidity and mortality.

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Conflict of Interest None

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