CD36 in chronic kidney disease: novel insights and therapeutic opportunities

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Abstract | CD36 (also known as scavenger receptor B2) is a multifunctional receptor that mediates the binding and cellular uptake of long chain fatty acids, oxidized lipids and phospholipids, advanced oxidation protein products, thrombospondin and advanced glycation end products, and has roles in lipid accumulation, inflammatory signalling, energy reprograming, apoptosis and kidney fibrosis. Renal CD36 is mainly expressed in tubular

epithelial cells, podocytes and mesangial cells, and is markedly upregulated in the setting of chronic kidney disease (CKD). As fatty acids are the preferred energy source for proximal tubule cells, a reduction in fatty acid oxidation in CKD affects kidney lipid metabolism by disrupting the balance between fatty acid synthesis, uptake and consumption. The outcome is intracellular lipid accumulation, which has an important role in the pathogenesis of kidney fibrosis. In experimental models, antagonist blocking or genetic knockout of CD36 could prevent kidney injury, suggesting that CD36 could be a novel target for therapy. Here, we discuss the regulation and post-translational modification of CD36, its role in renal pathophysiology and its potential as a biomarker and as a therapeutic target for the prevention of kidney fibrosis.

[H1] Introduction

The transmembrane protein CD36 (also known as scavenger receptor B2) has important roles in metabolic diseases, including atherosclerosis,[1] non-alcholic fatty liver disease[2] and diabetes melitus[3], as well as in metastatic colonization in cancer[4]. CD36 is ubiquitously expressed on the surface of many cell types, including monocytes,[5] macrophages,[6] adipocytes,[7] myocytes,[8] enterocytes[9] and hepatocytes[2]. In the kidney, CD36 is expressed in the proximal[10] and distal tubular epithelium[11], podocytes,[12] mesangial cells,[13,14] microvascular endothelial cells and interstitial macrophages[15,16]. Renal CD36 expression is upregulated by hyperlipidaemia and hyperglycaemia, and patients with chronic kidney disease (CKD), particularly those with diabetic nephropathy, show increased expression of the protein.[12,17]

CD36 has multiple ligands, which can be classified as lipid-related ligands, such as (long-chain) fatty acids,[18] oxidized LDL (Ox-LDL),[19,20] and oxidized phospholipids[21]; and as protein-related ligands, including advanced oxidation protein products (AOPPs),[22] advanced glycation end products (AGEs),[23] thrombospondin-1 (TSP1), TSP2,[24,25] S100 family proteins (S100-A8, S100-A9[26] and S100-A12[27]), amyloid proteins[28,29], and the synthetic

growth-hormone-releasing peptide family members hexarelin[30] and EP 80317[31]. Apoptotic cells can also act as a ligand for CD36[32] (Table 1). Many of these ligands have important roles in kidney injury.

The findings of several studies suggest that CD36 serves as a signalling hub for lipid homeostasis[33,34], immunological responses[35], and programming of energy availability[36,37]. CD36 also mediates crosstalk between different cell types — for example between macrophages and endothelial cells or between tubular cells and macrophages or myofibroblasts — in response to oxidized ligands such as Ox-LDL, oxidized phospholipids, apoptotic cells and AOPPs.[38] In proximal tubular epithelial cells (PTECs), CD36 is involved in energy source regulation via mitochondrial β-oxidation of fatty acids, which are a major source of renal ATP production.[39]

Disruption of any of the above mentioned CD36-dependent pathways, such as defective fatty oxidation in PTECs, has a critical role in the development of kidney fibrosis.[40] In mice, blocking CD36 prevents CKD progression,[41] demonstrating an important role of CD36 in renal injury and its potential as a therapeutic target. In this Review, we focus on the biological, physiological, and pathological roles of CD36 that might promote CKD progression, namely roles in lipid homeostasis, metabolic inflammation, apoptosis, and reprogramming of energy metabolism.

[H1] The CD36 gene

The human CD36 gene is ~46 kb in length and is located on chromosome 7q11.2. The gene has 15 exons; exons 4 to 13 and part of exons 3 and 14 encode the CD36 protein.[42] Mutations in the CD36 gene are linked to abnormalities of plasma fatty acids and triglycerides, which are risk factors for metabolic diseases involving insulin resistance.[43]

[H2] Transcriptional regulation

The CD36 gene promoter contains CCAAT/enhancer-binding protein (C/EBP) responsive elements, which enable C/EBP to bind and regulate CD36 expression in various cell types.[7] Nuclear receptors also have important roles in the transcription of the CD36 gene. For example, peroxisome proliferator-activated receptor α (PPAR-α) and PPAR-γ have been shown to regulate CD36 expression in human macrophages[44] and cardiac microvascular endothelial cells[45]. In addition, study have shown that PPARγ dependent pathway increase CD36 expression can be activated by high glucose in the human HK-2 proximal tubular cell line.[46,47] Whether or not the CD36 promoter contains a PPAR responsive element, however, remains unclear. Response element binding sites for Pregnane X receptor (PXR) and liver X receptor (LXR) have been identified in the CD36 promoter, and activation these receptors could upregulate CD36 expression and promote hepatic steatosis .[33] However, LXR activation in diabetic kidney models was determined to be renoprotective through mechanisms independent of CD36 but expression levels were not examined in all studies.[48-50]

Lipids including fatty acids[12], and Ox-LDL[51] can upregulate CD36 expression. Following CD36-mediated uptake in macrophages, Ox-LDL is metabolized to produce 9-hydroxy octade-cadienoic acid and 13-octade-cadienoic acid. These metabolites are PPAR agonists that activate PPAR through protein kinase C (PKC), protein kinase B and p38 mitogen-activated protein kinase (MAPK) pathways. Following activation, PPAR and retinoid X receptor form a heterodimer that binds to the CD36 promoter and increases CD36 transcription.[52] In turn, increased expression of CD36 leads to an increase in Ox-LDL uptake in macrophages and promotes foam cell formation.[53] In contrast to Ox-LDL, oxidized HDL (Ox-HDL) inhibits macrophage CD36 expression via PPAR-dependent mechanisms.[54]

Lysophosphatidic acid (LPA) is a central component of cellular phospholipid metabolism and an important regulator of vascular remodelling and inflammation.[55] LPA downregulates CD36 transcription in microvascular endothelial cells via a protein kinase D1 (PKD1)-dependent pathway.[56] LPA/PKD1-induced downregulation of CD36 in these cells is mediated by nuclear accumulation of histone deacetylase 7, which interacts with forkhead

box protein O1 to suppress CD36 transcription[57]. In microvascular endothelial cells, LPA/PKD-1 signalling activated a transcriptional proangiogenic switch involving ephrin B2, which is a critical mediator of angiogenesis and arteriogenesis.[57]

In addition to lipids, high glucose levels and insulin have been reported to induce the expression of CD36 in mesangial cells[58] and cardiac myocytes[59], respectively. Monocyte-colony stimulating factor[60], phorbol ester[61], tumour necrosis factor (TNF) [62], IL-4[63] and thiazolidinediones[64,65] can also promote CD36 expression in monocyte/macropahges. By contrast, lipopolysaccharide[66], dexamethasone[60], interferon[67], transforming growth factor (TGF)-β1/2[68], tamoxifen[69], and HDL[70] inhibit macrophage CD36 expression, whereas statin treatment has been reported to substantially reduce platelet CD36 expression.[71]

[H1] The CD36 protein

Full-length human CD36 comprises around 472 amino acids and has a predicted molecular mass of 53 kDa.[72] The protein has two transmembrane domains with a huge extracellular region, which contains the ligand-binding region, and two short cytoplasmic tails at the N-terminus and C-terminus.[42,73] The extracellular loop contains a large hydrophobic cavity that traverses the entire length of the molecule. This cavity is thought to serve as a tunnel through which hydrophobic ligands (including cholesterol and fatty acids) are delivered from the extracellular space to the outer leaflet of the plasma membrane[74] (FIG. 1).

CD36 also has a positively charged domain (155–183 amino acids contain lysine cluster) that binds negatively charged ligands.[75] Almost all end-stage biological oxidation products are negatively charged, including Ox-LDL, AOPPs, AGEs, and apoptotic cells. Binding of these ligands, which are markers of cellular oxidative stress and denaturation of lipids or proteins, to CD36 triggers pathophysiological responses such as inflammatory and proatherogenic processes.[15,23,53] CD36 has been shown to interact with TSP1 through electrostatic forces mediated by the multiple negatively charged CD36, LIMP-2, Emp sequence homology domain (CLESH) residues of CD36 and the positively charged surface of the thrombospondin

type I repeat 2 domain of TSP1[76]. This interaction is required for the CD36 CLESH-dependent anti-angiogenic activity of TSP1.

Previous studies indicated that circulating soluble CD36 (sCD36) consists of part of the extracellular segment of CD36.[77,78] The huge CD36 extracellular segment might undergo a 'cut-down' process by a plasma protease, resulting in release of sCD36 into the circulation.[78] Driscoll and colleagues demonstrated that ADAM17 mediates proteolytic cleavage of the CD36 extracellular domain, which might be a mechanism to regulate efferocytosis or clearance of apoptotic cells.[79] However, another group reported that sCD36 is not a 'cut-down' product from extracellular domain, more likely is a specific subset of circulating microparticles.[80] Thus, the mechanism by which sCD36 is formed is not clear and more studies are need for this confusion.

[H2] Post-translational modifications

Post-translational modifications might have an important role in regulating CD36 location and function. In general, glycosylation, ubiquitination, and palmitoylation are involved in regulating CD36 stability, protein folding, and trafficking, whereas phosphorylation at extracellular sites affects the rate of ligand (such as fatty acid) uptake.[81] Acetylation of CD36 has also been reported,[82,83] but the effects of this modification on CD36 expression and function have not yet been elucidated.

[H3] Phosphorylation. CD36 has two phosphorylation sites at Thr92 and Ser237, both of which modulate ligand binding within the extracellular loop. The Thr92 site is a putative PKC bindingsite, whereas the Ser237 site is recognized by PKA.[84,85] Phosphorylation of these sites is positively linked to CD36 function possibly through the modulation of ligand binding.

In platelets, phosphorylation and dephosphorylation of CD36 on the cell membrane affects TSP binding and controls collagen adhesion.[85] *In vitro* cell free condition, inhibition of TSP binding to CD36 was correlated with level of Thr92 phosphorylation of CD36.[86]In addition, this site phosphorylation occurred during the process of new protein synthesis and

trafficking through the Golgi.[86] Phosphorylation of CD36 at Thr92 is also necessary for binding of CD36 to erythrocytes that are infected by *Plasmodium falciparum*.[87] Phosphorylation of CD36 at Ser237 has been reported to inhibit fatty acid uptake in platelets and enterocytes[88,89]. Whether such CD36 phosphorylation also leads to inhibition of fatty acid uptake in the kidney has not yet been investigated.

[H3] Glycosylation. The process of glycosylation occurs within the endoplasmic reticulum (ER) and the Golgi, where it provides stable coupling of complex oligosaccharide structures to proteins.[90] The majority of glycosylation is N-linked at asparagine residues.[91] CD36 has 10 potential glycosylation sites, all of which are located within the extracellular loop, and fully glycosylated CD36 is an approximately 88 kDa transmembrane glycoprotein receptor[72]. Glycosylation of CD36 is a hydrophilic modification, which is very important for protein folding, stability, and trafficking, but does not affect ligand binding.[91] In intestinal enterocytes, enhanced CD36 glycosylation reportedly results in an increase in the absorption of fatty acids by unknown mechanisms.[9]

In spontaneously hypertensive (SHR) rats, CD36 is mutated at multiple sites including Asp102, which is located within the fatty acid binding pocket and is a potential *N*-glycosylation site.[92] In the hearts of these rats, both total CD36 protein expression and fatty acid utilization were significantly reduced, perhaps owing to a decrease in CD36 stability as a result of the mutation at Asp102.[92] Further studies are needed to investigate the role of glycosylation in altered fatty acid uptake in CKD.

[H3] Palmitoylation. Palmitoylation regulates the subcellular localization, membrane interactions, and subcellular trafficking of proteins. CD36 has four palmitoylation sites, which are located in the third, seventh, 464th and 466th cysteine residues in the cytoplasmic segment of the N-terminal and C-terminal.[93] Palmitoylation of CD36 is a reversible catalytic process. In most cases the reversible covalent bond occurs between palmitate and cysteine residues via a thioester linkage. Protein palmitoylation requires palmitoyl-transferases (PATs) and palmitoyl-protein thioesterases (PPTs) for palmitoylation

and depalmitoylation, respectively.[94] Under palmitic acid stimulation, PATs cause CD36 palmitoylation in the ER.[93,95]

Palmitoylated CD36 is located in the lipid rafts of the cell membrane where it mediates adsorption and transport of fatty acids.[96] Inhibition of palmitoylation stops the maturation of CD36 and causes CD36 precursor proteins to remain in the ER.[95] Non-palmitoylated CD36 has a short half-life as it is more likely to be degraded than palmitoylated CD36.[95] Palmitoylation of CD36 might, therefore, have a role in lipid accumulation. Inhibition of CD36 palmitoylation might be a potential strategy to reduce CD36-mediated lipid accumulation and inflammatory signalling; however, whether such palmitoylation occurs in renal cells has not been determined.

[H3] Ubiquitination. The polyubiquitination pathway targets proteins for proteasomal degradation. CD36 has two ubiquitination sites in the C-terminus at Lys469 and Lys472 that are responsible for its regulation by polyubiquitination.[97] In C2C12 myotubes, the degree of polyubiquitination of CD36 did not affect the relative distribution of the protein between the intracellular storage compartments and thecell surface, but down-regulate protein expression level[97].

Platelet-derived exosomes increase the polyubiquitination of CD36 and enhance proteasome degradation.[98] In a mouse muscle cell line (C2C12), oleic acid increased, whereas insulin decreased the polyubiquitination of CD36.[97] Concomitantly, fatty acids reduce CD36 protein levels and decrease cellular fatty acid uptake, whereas insulin has the opposite effect.[97]

In contrast to polyubiquitination, mono-ubiquitination is considered to be non-degradative and has other functions such as protein complex formation. The intracellular C-terminal lysines in CD36 can be targeted by parkin, which has E3 ubiquitin-protein ligase activity and participates in the process of protein ubiquitination. [99] In mice, a high-fat diet increased hepatic parkin and CD36 levels, which contributed to increased lipid accumulation and insulin resistance.[100] Parkin-knockout mice on a high fat diet had reduced hepatic CD36

levels that blunted the maladaptive response to lipid metabolism and insulin signalling compared with controls.

High-fat diet increased Parkin levels and CD36 levels in liver of mice, suggesting that fatty acids should stabilize or increase the CD36 protein level via Parkin-mediated mono-ubiquitination.[100] Indeed, fatty-acid-mediated polyubiquitination and degradation of CD36 in C2C12 myotubes cell lines.[97,100] and can be explained by the fact that parkin exhibits both mono-ubiquitination and polyubiquitination functions.[101] Hence, the downstream effects of parkin can be both dependent and independent of the proteasome. The function of parkin might vary between different tissues and conditions such that it operates as a mono-ubiquitinase in some settings and as a polyubiquitinase in others. The role of fatty acids in CD36 degradation in the kidney remains unclear.

[H3] Acetylation. Protein acetylation has roles in cell apoptosis[102], subcellular protein localization[103], glucose and FA metabolism[82] DNA and protein interactions, DNA replication and repair, DNA transcriptional activity and protein stability[104]. Acetylation of CD36 at Lys52, Lys166, Lys231 and Lys403 has been shown using mass spectrometry[82,83], but the biological effects of this acetylation remain unclear.

[H2] Cellular location

CD36 is not only present at the cell surface but also in endosomes, the ER and mitochondria.[105] The protein can migrate between these locations via vesicular transport along exocytotic and endocytotic pathways to control lipid homeostasis and energy reprogramming[2,59,106-108](FIG. 3). A net translocation of CD36 to the plasma membrane is induced by several physiological stimuli, most notably elevated circulating insulin levels[106], muscle contraction[109].

Insulin-induced CD36 translocation requires activation of the phosphatidylinositol-3-kinase–Akt2 signalling axis,[59,106] whereas muscle-contraction-induced CD36 translocation is dependent on activation of AMP-activated kinase (AMPK).[109,110] Inflammation increases

CD36 transcription, translation, and translocation to the cell surface.[96] Post-translational modifications could be major factors that determine the cellular location and function of CD36.

High molecular weight CD36 homodimers and oligomers have been detected in human platelets and in COS-7 cells transfected with human CD36.[24,111] G12xxxG16xxxA20 and A20xxG23 motifs in the N-terminal transmembrane domain of CD36 are responsible for its dimerization[112]. Whether homodimerization of CD36 and palmitoylation of cysteine residues close to the N-terminal region affects its function, cellular location, ligand binding and signal transduction remains unclear.

[H1] Roles of CD36 in renal pathophysiology

CD36 modulates multiple pathways that have important roles in acute kidney injury(AKI) and CKD.

[H2] Fatty acid accumulation

The lipid nephrotoxicity hypothesis, which was first proposed by Moorhead *et al*. in 1982[113] and updated by Ruan *et al*. in 2009[114], suggests that. This concept has led to a large number of studies focusing on the relationship between lipids and renal disease. Evidence from experimental animals and from humans suggests a direct role of lipids, including non-esterified fatty acids, triacylglycerols and cholesterol, in the initiation and progression of CKD.[115]

The total lipid content of the healthy human kidney is estimated to comprise approximately 3% of the wet weight.[116] More than half of this lipid content is phospholipids, approximately one-fifth is triglycerides, and about one-tenth is non-esterified fatty acids (NEFAs).[117] *In vivo* studies using radiolabelled fatty acids in dogs[118], as well as analysis of differences in substrate (including fatty acids, lactate, citrate and pyruvate) levels between human arterial and renal venous blood[116], have indicated that the kidney extracts fatty acids from the circulation, and that fatty-acid oxidation could account for more than half of renal

oxygen consumption. Importantly, fatty acid extraction by the human kidney *in vivo* was linearly dependent on plasma fatty acid concentrations.[116]

Kidney uptake of circulating fatty acids requires dissociation from albumin, which is mediated by specific membrane proteins such as CD36.[119] The renal proximal tubule retrieves albumin-bound fatty acids from the filtrate by CD36 or receptor-mediated albumin endocytosis.[120] In mice, the kidney takes up NEFAs and increases fatty acid oxidation (FAO) during fasting states, whereas *de novo* lipid synthesis pathways are downregulated[121]. Similar to the liver and in contrast to muscle, CD36 and lipoprotein lipase are not required for uptake of NEFAs in the normal murine kidney[121]. These findings do not, however, rule out a role of CD36 in fatty acid transport in the kidney as CD36 does not have a role in the passive transmembrane movement of fatty acids,[105] which might be an important mode of fatty acid uptake during fasting.

As fatty acids are the preferred energy source for PTECs, a reduction in FAO in CKD affects kidney lipid metabolism by disrupting the balance between fatty acid synthesis, uptake and consumption.[40] The outcome is intracellular lipid accumulation, which has an important role in the pathogenesis of kidney fibrosis.[40]

In the settings of murine and human CKD, genes that are associated with FAO are downregulated in the kidney.[40] Kidney biopsy samples from patients with diabetic nephropathy showed lipid accumulation in the glomeruli and tubulointerstitium together with upregulation of CD36 compared to normal control samples.[12,17] Transgenic overexpression of tubular CD36 lead to increase intrarenal lipid accumulation but only a slight increase in profibrotic genes in the absence of kidney injury and did not show any difference in fibrosis.[40,122] In podocytes, CD36-dependent uptake of palmitic acid led to a dose-dependent increase in the levels of mitochondrial reactive oxygen species (ROS), depolarization of mitochondria, ATP depletion, and apoptosis.[12,28] Moreover, studies in mouse models have shown that in the setting of CKD, CD36 promotes fibrogenesis by

increasing oxidative stress and activating proinflammatory pathways, although the role of CD36 in FAO was not investigated.[123]

Further research is required to identify the differential roles of passive and active fatty acid transport in kidney disease as well as the major receptors that are involved in fatty acid uptake in the kidney. Such studies will enable greater insight into the mechanisms of fatty acid metabolic dysfunction in kidney disease.

[H2] Interactions with oxidized lipids

Accumulation of Ox-LDL in the circulation and renal interstitium has been reported in experimental models and in patients with CKD and end-stage renal disease (ESRD).[124,125] Macrophage CD36 can bind large amounts of Ox-LDL and mediates the endocytosis and degradation of Ox-LDL *in vivo*; some studies have reported that CD36 is responsible for more than half of Ox-LDL uptake in macropahges[126]

In hypercholesterolemic mice with kidney injury (as a result of unilateral ureteral obstruction), Ox-LDL deposition was evident in the renal tubules and interstitial compartment and correlated with fibrosis.[11] CD36 deficiency in the same model reduced the activation of proinflammatory and oxidative pathways, resulting in a substantial reduction in the number of interstitial myofibroblasts compared with wild-type controls.[123] Even in normocholesterolemic states, however, chronic kidney injury results in the *de novo* generation of intracellular oxidized lipids in macrophages.[126]

In a mouse model of renal fibrosis induced by unilateral ureteral obstruction, lipid metabolism led to a twofold to sixfold increase in the levels of the intracellular lipid peroxides hydroxyoctadecadienoic acid (HODE) and hydroxyeicosatetraenoic acid (HETE) in $CD36^{+}$renal macrophages.[126] The absence of macrophage CD36 expression in this model led to a 50% reduction in the intracellular levels of HODE and HETE, reduced fibrosis and preservation of kidney function. In this nonproteinuric model of CKD, macrophage CD36

formed a heterodimer with Lyn kinase at its C-terminus to activate a NF-κB p50p65-dependent proinflammatory pathway.[126]

Activation of NF-κB increases the production of proinflammatory cytokines and chemokines, which might trigger an influx of monocytes and accumulation of macrophages in the kidney.[41] In proximal tubular cells, CD36 heterodimerizes with the Na^+/K^+-ATPase α-1 subunit in response to Ox-LDL or ouabain[15]. This heterodimer activates Src and Lyn kinases and can potentiate a proinflammatory signaling loop involving TNF, CC motif chemokine 2 and IL-6.[15] Moreover, Ox-LDL or ouabain induced ROS production in proximal tubular cells was significantly attenuated by knockdown of the Na^+/K^+-ATPase α-1 subunit or N-acetyl-cysteine. These facts suggsting that CD36 and the Na^+/K^+-ATPase share ligands and downstream molecular cross-talk in kidney and they act synergistically to promote inflammation in hyperlipidemic states.[15] Sheedy et al. found that sustaining uptake of Ox-LDL by CD36 causes the nucleation and accrual NLRP3-activating crystals within the macrophage, and induced the release of IL-1β.[127]

HDL is susceptible to structural modifications, including oxidation, in the setting of metabolic disorders.[128,129] Oxidative modification of HDL (Ox-HDL) has been reported in patients with advanced-stage renal disease, particularly in those with diabetic nephropathy.[130] The levels of oxidized phospholipids was also significantly increased in apoptotic cells in an experimental CKD model.[126] In human renal tubular (HK-2) and mesangial cells, binding of Ox-HDL to CD36 enhanced ROS production and upregulated the expression of proinflammatory factors via activation of p38/MAPK, extracellular-regulated kinase (ERK)/MAPK and NF-κB.[131] Src family kinase was also activated in HK-2 cells following stimulation with Ox-HDL, and apoptosis was increased.[131]

[H2] Endocytosis of AOPPs

AOPPs are a family of oxidized, dityrosine-containing, cross-linked protein compounds that are formed by the reaction of plasma proteins with chlorinated oxidants. Studies suggest

that AOPPs are important renal pathogenic mediators in the progression of CKD and associated cardiovascular disease.[132,133] CD36 is a receptor for AOPP-modified albumin in proximal tubular cells.[22] Moreover, anti-CD36 antibody treatment has been shown to inhibit oxidant-damaged human serum albumin (AOPPs-HSA)-induced endocytic association and degradation of AOPPs in HK-2 cells[22]. AOPPs-HSA increased intracellular ROS generation and TGF-β1 secretion in these cells, whereas anti-CD36 antibody abrogated AOPPs-HSA-induced up-regulation of TGF-β1.[22]

CD36 binding of AOPPs activates the renin–angiotensin system in proximal tubular NRK52E cells via PKCα/NADPH-dependent activation of NF-kB.[134] Blocking CD36, PKCα or NADPH oxidase dramatically abolished AOPP-augmented activation of AP-1 and NF-kB in these cells, suggesting that AOPPs activate NF-kB and AP-1 through the CD36-PKCα-NADPH oxidase pathway.[134]

[H2] Interactions with thrombospondin 1

TSP1 is a matricellular protein that inhibits angiogenesis and causes apoptosis *in vivo* and *in vitro* in several cells and tissues. Interaction of TSP1 with CD36 is critical for activation of latent TGF-β and might be involved in initiating and regulating cellular fibrosis.[135] TSP1 and CD36 are induced early in renal ischaemic-reperfusion injury (IRI) and TSP1-null mice showed substantial preservation of kidney function after IRI.[136] In rodent kidneys subjected to IRI, formation of the TSP1–CD36 complex in proximal tubular cells led to cleavage of caspase 3 and apoptosis.[136] Similarly, in an adriamycin-induced nephropathy mouse model of focal segmental glomerulosclerosis, TSP1 expression increased in injured podocytes and led to CD36-dependent apoptosis via activation of the p38MAPK pathway.[137]

In a model of diet-induced obesity, podocyte apoptosis and dysfunction were attenuated in TSP1-deficient and in CD36-deficient mice, suggesting that the interaction of TSP1 with CD36 contributes to obesity-associated podocytopathy[138]. Moreover, blocking TSP1 binding to CD36 using peptide treatment attenuated fatty-acid-induced podocyte apoptosis,

suggesting that the TSP1/CD36 interaction mediates this process.

The antiangiogenic effects of TSP1 and TSP2 are mediated through binding to microvascular CD36 as evidenced by the finding that TSP1 and TSP2 do not inhibit neoangiogenesis in $CD36^{-/-}$ mice.[139,140] LPA has been shown to downregulate CD36 transcription via protein kinase D1 (PKD1) and antagonize the antiangiogenics effect of TSP1 and TSP2.[56]

[H2] Endocytosis of AGEs

AGEs are a heterogeneous and complex group of compounds that have an important role in the development of diabetic nephropathy. Using Chinese hamster ovary cells that overexpressed CD36, Ohgami *et al*. made the interesting discovery that AGEs are recognized by CD36, endocytosed in a dose-dependent fashion and undergo lysosomal degradation.[6]

AGE–BSA **[Au: bovine serum albumin? Yes]** upregulated CD36 expression and lipid uptake in monocytes from patients with diabetes and in aortic vascular smooth muscle cells from diabetic rats.[141-143] AGE-LDL has been shown to potentially induce production of proinflammatory cytokines by interacting with CD36 in mouse monocytes.[144] Moreover, early work from Suztak and colleagues demonstrated that CD36 expression is necessary and sufficient to mediate apoptosis of PTECs induced by AGEs and fatty acids through sequential activation of Src kinase, p38MAPK and caspase 3.[10]

[H2] Amyloid deposition

Deposition of amyloid fibrils derived from serum amyloid A protein (SAA) causes systemic amyloid A (AA) amyloidosis, which is a serious complication of chronic inflammatory conditions. The kidney is one of the organs that is most often affected by AA amyloidosis. Renal AA amyloidosis leads to progressive deterioration of renal function and is considered to be intractable.[145] CD36 is a receptor for SAA[23] and has been reported to have a role in SAA-induced proinflammatory activation through JNK and ERK1/2-mediated signalling in the HEK293 human embryonic kidney cell line.[108] This finding suggests that CD36 has an

important role in the initiation of inflammatory reactions and oxidative stress in renal AA amyloidosis. Further exploration of the role of CD36 in this disease would, therefore, be of interest.

[H2] Other activators of CD36

In HK-2 cells, high glucose levels increased CD36 expression in a time-dependent manner and induced epithelial-to-mesenchymal transition at 72 h.[146] This effect could be prevented either by knockdown of CD36 or by treatment with the CD36 antagonist sulfosuccinimidyl-oleate.[146] Studies using a proximal tubular cell line (LLC-PK1 cells) showed that albuminuria enhanced the secretion of bioactive TGF-β and fibronectin and upregulated CD36[122]. Treatment with CD36 siRNA abrogated these increases, suggesting potential anti-fibrotic effects.

[H2] CD36 signalling and kidney injury

CD36 is able to generate cell-specific responses to multiple ligands through the binding of context-specific binding partners (such as toll-like receptor 2 (TLR2),[147] TLR4, TLR6,[148] [149] [13] [150] [131] tetraspanin CD9, [151] integrin[152,153] and Na^+/K^+ATPase) and to activate NF-kB[154], NLRP3[127], PKC-NAPDH oxidase,[134] Src/Lyn/Fyn and MAPK kinases[131], and TGF-β[22] signalling pathways (FIG. 2). These effects result in metabolic inflammation, energy reprogramming, apoptosis and fibrosis, which contribute to the development of renal injury.

Fatty acids and Ox-LDL increase the apoptosis of human macrophages.[19,155] In ER-stressed murine macrophages, oxidized phospholipids, Ox-LDL, saturated fatty acids, and lipoprotein(a) have been shown to trigger apoptosis via an interaction between CD36 and TLR2/TLR6 heterodimers.[21] When exposed to Ox-LDL and amyloid β, CD36 forms heterodimers with TLR4 and TLR6 via its C-terminus Tyr463, and CD36-Lyn kinase interaction, causing inflammatory responses.[149] The interactions of CD36 with TLR2,[147] tetraspanin[151] and integrins[152,153] contribute to Ox-LDL uptake and foam cell formation in atherosclerosis.

Whether all CD36 ligands have similar effects on binding partners, downstream signal transduction pathways and their biological effects in the kidney is unclear as are the mechanisms by which CD36 senses different ligands and exerts specific responses. The specific effects of crosstalk between CD36 ligands, binding partners and signal pathways on inflammation, apoptosis, and especially energy reprogramming in the kidney, warrant further investigation.

Macrophage infiltration into the kidney has an important role in CKD. Increased CD36 expression has been observed in the kidneys and peripheral blood monocytes of patients and mice with chronic renal failure.[156,157] [5] [158] Moreover, in mouse models of unilateral ureteral obstruction and ischaemia reperfusion, knockout of CD36 in monocytes decreased the severity of fibrosis and improved kidney function.[126] The role of CD36 in crosstalk between macrophages and kidney cells and in the initiation and amplification of inflammation, apoptosis and fibrosis required further investigation.

[H2] Energy reprogramming

Mitochondrial β-oxidation of fatty acids is a primary source of renal ATP production, particularly in the proximal tubule, which has a high-energy demand and relatively low glycolytic capacity, suggesting that fatty acids are the preferred energy source for proximal tubule cells.[39] A reduction in fatty acid oxidation in CKD would affect lipid metabolism by disrupting the balance between fatty acid synthesis, uptake, and consumption, leading to dysregulated intracellular lipid accumulation, which has a crucial role in the pathogenesis of kidney fibrosis.[159]

Metabolic reprogramming is characterized by decreased expression of key enzymes and regulators of FAO and increased intracellular lipid deposition. Inhibition of FAO in tubular epithelial cells *in vitro* causes ATP depletion, cell death, de-differentiation, and intracellular lipid deposition.[40]

Diabetic complications have been shown to arise in the context of distinct tissue-specific alterations in metabolism[160]. In the diabetic kidney, substrate utilization progressively increased with simultaneous consumption of glucose and fatty acids, suggesting that metabolic reprogramming with enhanced protein acetylation led to mitochondrial dysfunction.[160] Increasing amounts of fatty acid bound to albumin lead to defects in mitochondrial respiration and to peroxide-mediated apoptosis of tubular cells.[161] Compared to people with normal kidney function, patients with CKD had markedly lower transcriptional levels of genes related to fatty acid metabolism and their key transcriptional regulator complex PPARα–PPARr co-activator 1-α (PGC-1α).[40] Moreover, proximal tubular cells with defective fatty acid oxidation showed fibrosis phenotypes with ATP depletion, increased cell death, dedifferentiation and intracellular lipid deposition.[40] Thus, restoring metabolic defects in fatty acid oxidation might be a potential therapeutic strategy for CKD (FIG. 3).

Mitochondrial transfer of fatty acids is the rate-limiting step in fatty acid oxidation. This transfer requires linking of fatty acid products to carnitine via carnitine palmitoyltransferase 1 (CPT1) and CPT2.[162] The mitochondrial enzyme carnitine O-acetyltransferase (CRAT) complexes excess acyl groups to carnitine, enabling them to exit the mitochondria[163]. The importance of CD36 in FAO has been suggested to relate to its function in mitochondrial transfer of fatty acids, which has been demonstrated in human skeletal muscle cells.[16,162] CD36 was identified in purified mitochondria from these cells and was shown to co-immunoprecipitate with CPT1. In addition, increased mitochondrial CD36 content paralleled up-regulation of fatty acid oxidation in skeletal muscle.[16,162]

CD36 might have a similar function in mitochondrial fatty acid transfer in PTECs, which also have a high energy demand. PTECs express high levels of CPT1A, CPT1B, and CPT2 and CRAT.[164] In contrast to CRAT in the liver and skeletal muscle, which can be both mitochondrial and peroxisomal, renal CRAT is almost exclusively mitochondrial.[165] Any alterations in CPT1 activity will likely affect fatty acid metabolism and oxidation in proximal

tubular cells. Deletion of CPT1B in the heart causes cardiac hypertrophy and death,[166] whereas inhibition of CPT1 in the liver leads to steatosis.[167] These findings suggest that CPT1 control of FAO has profound implications for cellular energy balance. In the kidney, too little CPT1 expression accompanied by decreases in the levels of other enzymes with roles in FAO might lead to an energetic crisis and potentially result in tubulointerstitial fibrosis.

The role of CD36 in FAO seems to be linked to inter-regulation of CD36 and AMPK. In the heart, AMPK functions as an important energy sensor and metabolic regulator that is activated in response to increasing energy demand and upregulates nutrient uptake, and catabolism.[168] AMPK enhances fatty acid oxidation by reducing the levels of malonyl-CoA via phosphorylation and inactivation of acetyl-CoA carboxylase.[169] In cardiac myocytes, CD36 co-ordinates dynamic protein interactions within a molecular complex consisting of CD36, Fyn kinase, LKB1 and AMPK.[36] In the setting of low fatty acid concentrations, CD36 expression maintains AMPK quiescent by enabling Fyn to access and phosphorylate LKB1, promoting its nuclear sequestration away from AMPK, resulting in inhibition of AMPK and consequently of AMPK-mediated FAO.[36] However, high levels of palmitate binding to CD36 activate AMPK within minutes via its ability to dissociate Fyn from the complex as CD36 is internalized into LKB1-rich vesicles.[36] The ensuing enrichment in cytosolic LKB1 levels activates AMPK, which enhances FAO by inactivating acetyl-CoA carboxylase.[36] AMPK activation also induces cell surface CD36 recruitment in myocytes.[170] This dual effect would serve to adjust the capacity for fatty acid oxidation to match fatty acid availability and balance on energy saving and usage.[171]

Dysregulation of AMPK signalling[172] or CD36 deletion in myocytes[173] is associated with metabolic inflexibility evidenced by a diminished capacity to adjust FAO to fatty acid availability. Whether these mechanisms also occur in the proximal tubule during kidney disease is currently unknown. However, targeted deletion of LKB1 in distal tubular cells resulted in renal fibrosis by significantly reduced the levels of key effectors of FAO, such as AMPK, PGC-1α, and PPARα.[174] Moreover, Suztak and colleagues demonstrated that free

palmitic acid leads to CD36-dependent proximal tubule apoptosis via activation of the p38 MAPK pathway.[10] These results could suggest that the CD36–LKB1 pathways are important in promoting metabolic dysfunction in tubular cells during CKD.

[H1] Soluble CD36 —a potential biomarker

Evidence suggests that sCD36 might have a role in modulating the immune response by binding to TLR2.[77] The levels of sCD36 correlate with tissue CD36 expression.[175] Use of HMG-CoA reductase inhibitors (statins) has been reported to affect sCD36 levels by unknown mechanisms.[176]

Several studies have suggested that sCD36 might be a valuable biomarker of disease activity in several chronic inflammatory diseases, including diabetes, non-alcoholic steatohepatitis and atherosclerosis.[177-181] In some clinical studies, serum levels of sCD36 positively and significantly correlated with body weight, BMI, waist circumference, monocyte counts and the levels of cholesterol and LDL.[182,183] In patients with stage 5 CKD (n = 228) on dialysis, serum sCD36 levels were significantly increased and predicted cardiovascular mortality.[176] Several studies have analysed sCD36 levels in plasma samples; however, these samples have to potential to skew interpretation of the results owing to the presence of CD36 in platelets, which could represent a marker of platelet activation.[177,184,185] Furthermore, microparticles that are released upon platelet activation might represent an important source of CD36.

The available evidence indicates a close relationship between CD36 and kidney disease progression. However, the various commercial assays for sCD36 provide inconsistent results.[186] Further studies are needed with standardized and appropriate methods to validate the use of sCD36 as a biomarker in diabetes and CKD.

[H1] CD36 as a potential therapeutic target

CKD is a global health problem with no therapeutic options beyond angiotensin-converting-enzyme inhibitors to slow its relentless progression.[187,188] The

multi-ligand potential and multi-functionality of CD36 make it an attractive target for blocking kidney injury and subsequent progressive loss of kidney function. Several studies have demonstrated that blockade or deficiency of CD36 can block fibrosis pathways, metabolic dysfunction and proteinuria.[41,122,123,126]

[H2] CD36 blockade

CD36-deficient mice develop low-grade proteinuria owing to loss of CD36-mediated albumin and other protein uptake in proximal tubules,[189] without the formation of fibrosis in aged mice. Furthermore, silencing or antibody blockade of CD36 in PTECs exposed to AOPPs *in vitro* blocked TGF-β production,[22] and suggests that CD36 is an important mediator of proteinuric injury. In addition to tubules, CD36 is also upregulated in podocytes during proteinuric injury in experimental models and human podocytes, and blockade of CD36 on podocytes *in vitro* led to an improvement in health with less apoptosis and oxidative stress.[12,22,137,138,190] Blockade of CD36-dependent pathways, therefore, holds great promise as a therapeutic strategy for a variety of kidney diseases.

Apolipoproteins are important for the formation of protein–lipid complexes and have a key role in transporting otherwise insoluble lipids within the body. A common feature of apolipoproteins is the presence of tandem 22-mer repeating domains in exon 4.[191] When these sequences are folded into an alpha-helix, they produce a structure with opposing polar and nonpolar faces.[192] Synthetic amphipathic helical peptides (SAHPs) are able to replicate structural motifs of apolipoproteins that are also able to modulate interactions with scavenger receptors such as CD36.[28,193] In a mouse model of 5/6 nephrectomy with continuous angiotensin II infusion, treatment with the SAHP 5A resulted in preservation of kidney function with reduced glomerulosclerosis, interstitial fibrosis, and albuminuria compared to controls[41]. Although the 5A peptide affects other scavenger receptors (SR-BI/II) in addition to CD36, no benefit of 5A administration in the injury model was seen in CD36-deficient mice, suggesting a dominant role of CD36 in disease progression.[41] SAHPs with more targeted activity against CD36 (ELK-SAHPs) have also been developed. Of these,

ELK-B has been shown to inhibit pulmonary inflammation and dysfunction in a sepsis model.[194] Although blockade of CD36-dependent pathways in the kidney and lung might be beneficial, the effect of this blockade on other tissues that express CD36 remains unclear.

Cyclic azopeptides are another class of peptidomimetic therapeutics that can be to target CD36.[195] The azapeptide EP80317 targets the residues Gln155–Lys183 and has shown impressive efficacy in reducing disease and altering pathogenic mechanisms in experimental models of atherosclerosis and myocardial infarction.[31,196] The efficacy of EP80317 in kidney injury is currently under investigation.

[H2] Activating mitochondrial CD36

Evidence suggests that fully modified CD36 translocates to the cytoplasmic membrane and mediates fatty acid uptake and inflammatory responses.[81,197] In proximal tubular cells, increased levels of fatty acids lead to defects in mitochondrial respiration, reduced FAO and intracellular lipid deposition, causing renal fibrosis.[40,164,198] Thus, activation of mitochondrial CD36, which enhances FAO, might restore these metabolic defects (FIG. 3). Inhibition of CD36 protein modifications by genetic or pharmacologic approaches could potentially result in increased levels of mitochondrial CD36 and, therefore increased shuttling of fatty acids towards oxidation, which might switch fatty acids from an accumulation to a consumption phenotype and protect against kidney fibrosis.

[H1] Conclusions

CD36 has important roles in lipid homeostasis, metabolic inflammation, reprogramming of energy metabolism, apoptosis and kidney fibrosis. The expression and intracellular location of CD36 is regulated by its multiple ligands in transcription and post-translational modifications. Cross-talk between CD36 ligands, binding partners and signalling pathways; and between macrophages and kidney cells; leads to inflammation, apoptosis and/or energy reprogramming. These effects represent important molecular mechanisms for the development of CKD that warrant further investigation. The development of novel CD36

peptides have demonstrated efficacy in slowing the progression of CKD. Given the cell specific effects of CD36 and its ubiquitous expression in several tissues, future development of new CD36 peptides to target specific sites on the receptor and in select cell populations will limit off target effects and improve its efficacy in different kidney diseases.

Competing Interests

The authors declare no competing interests.

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Contributions

X.Y., D.O., X.L. and Y.C. researched the data and wrote the manuscript. X.Z.R. contributed to the writing, reviewing and editing of the manuscript. J.M. and Z.V. critically read and revised the manuscript before submission.

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Key Points

- CD36 is a multifunctional receptor for long-chain fatty acids, oxidized lipids, advanced oxidation protein products, thrombospondin and advanced glycation end products
- CD36 is expressed in a wide variety of kidney cells such as PTECs, mesangial cells, podocytes and monocytes/macrophages
- The expression and intracellular location of CD36 is regulated by multiple ligands with roles in gene transcription and post-translational modifications

- CD36 is involved in lipid accumulation, inflammation, energy reprograming, apoptosis and kidney fibrosis through activation of Toll-like receptors, Na^+/K^+ATPase, the NLRP3 inflammasome, PKC-NAPDH oxidase, Scr/Lyn/Fyn and MAPK kinases, and TGF-β signalling pathways
- Circulating soluble CD36 correlates with tissue CD36 expression and could be a biomarker for progression of chronic kidney disease
- Experimental studies have demonstrated that blockade or knockout of CD36 can prevent kidney injury, suggesting that CD36 could be a novel therapeutic target for the prevention of kidney fibrosis

Figure 1 | CD36 structure and post-translational modifications. CD36 has two transmembrane domains and two small cytoplasmic tails that contain four palmitoylation sites. The C-terminus contains two ubiquitination sites and the N-terminal transmembrane domain contains two motifs that are responsible for dimerization. The large extracellular loop contains ten N-linked glycosylation sites and two phosphorylation sites. A variety of ligands bind to CD36 via the hydrophobic binding pocket (entrance 1). Crystal structure studies also suggest that CD36 might have a second entrance (entrance 2) for fatty acid transport. CLESH, CD36, LIMP-2, Emp sequence homology domain.

Fig 1

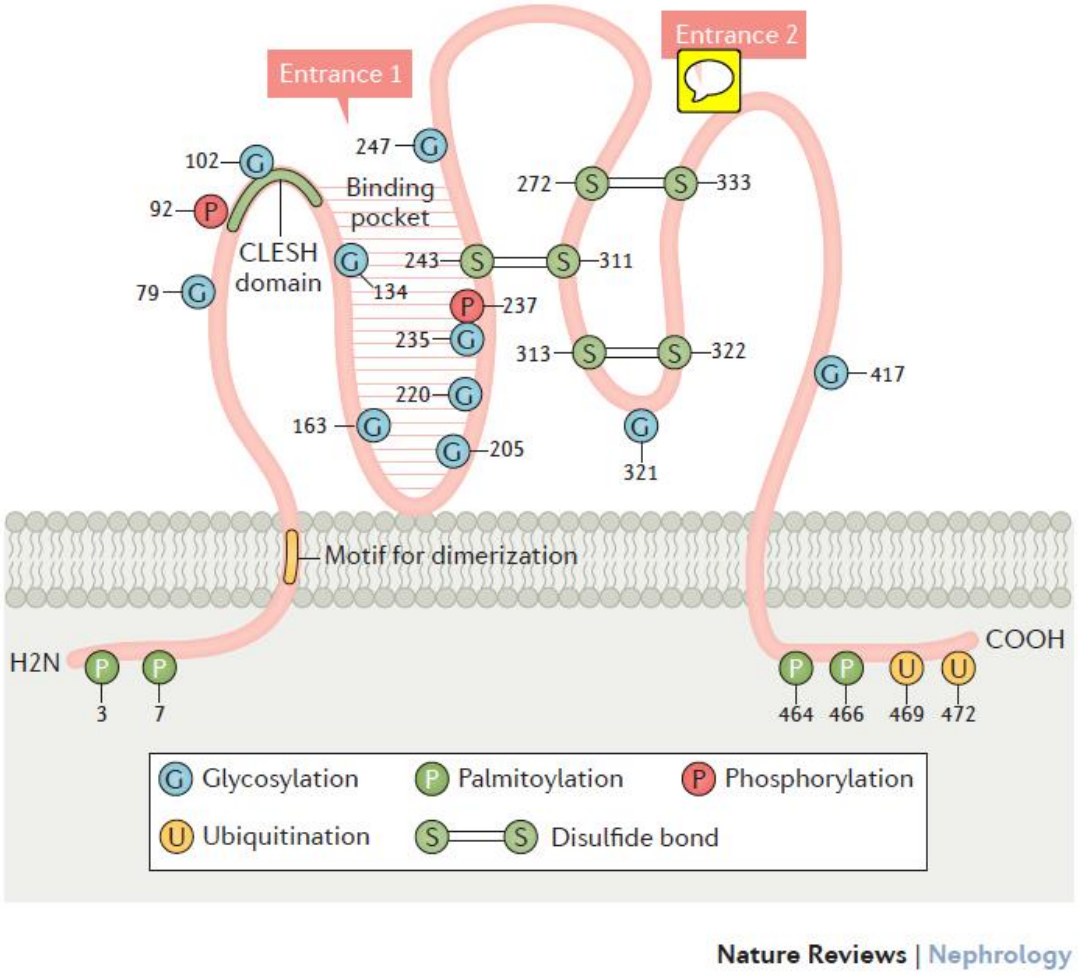

Figure 2 | CD36 ligand and signal transduction pathways with roles in chronic kidney disease progression. Binding of a variety of ligands to CD36 on the plasma membrane initiates assembly of a complex of CD36 and Toll-like receptor 4 (TLR4) and TLR6; TLR2 and TLR6; or Na^+/K^+-ATPase. This complex activates NF-κB, the

NLRP3 inflammasome, protein kinase c (PKC)-NAPDH oxidase, Scr/Lyn/Fyn and mitogen-activated protein kinases (MAPK), and transforming growth factor-β (TGF-β)-specific cell signalling pathways. Activation of these pathways has been shown in kidney reanl cells (green), macrophages (red) or both cell types (yellow). These processes result in lipid accumulation, metabolic inflammation, apoptosis, energy metabolism reprogramming and renal fibrosis. ACE, angiotensin-converting enzyme; AGEs, advanced glycation end-products; AGT, angiotensinogen; Ang ll, angiotensin ll; AOPPs, advanced oxidation protein products; AT1, angiotensin II type 1 receptor; ERK, extracellular-regulated kinase; CCL5, C-C omotif chemokine 5; CPT1, carnitine palmitoyl transferase; FAO, fatty acid oxidation; IL, interleukin; ox, oxidized; MCP-1, monocyte chemoattractant protein-1; NF-kB, nuclear factor-kB; RAS, renin–angiotensin system; TNF, tumour necrosis factor; PPARα, peroxisome proliferator-activated receptor ; PPARGC1α, PPAR γ coactivator 1 α ; ox-HDL, oxidized high density lipoprotein; ox-LDL, oxidized low density lipoprotein; ROS, reactive oxygen species; $\mathrm{TGF}-\beta$, transforming growth factor β.

Fig 2

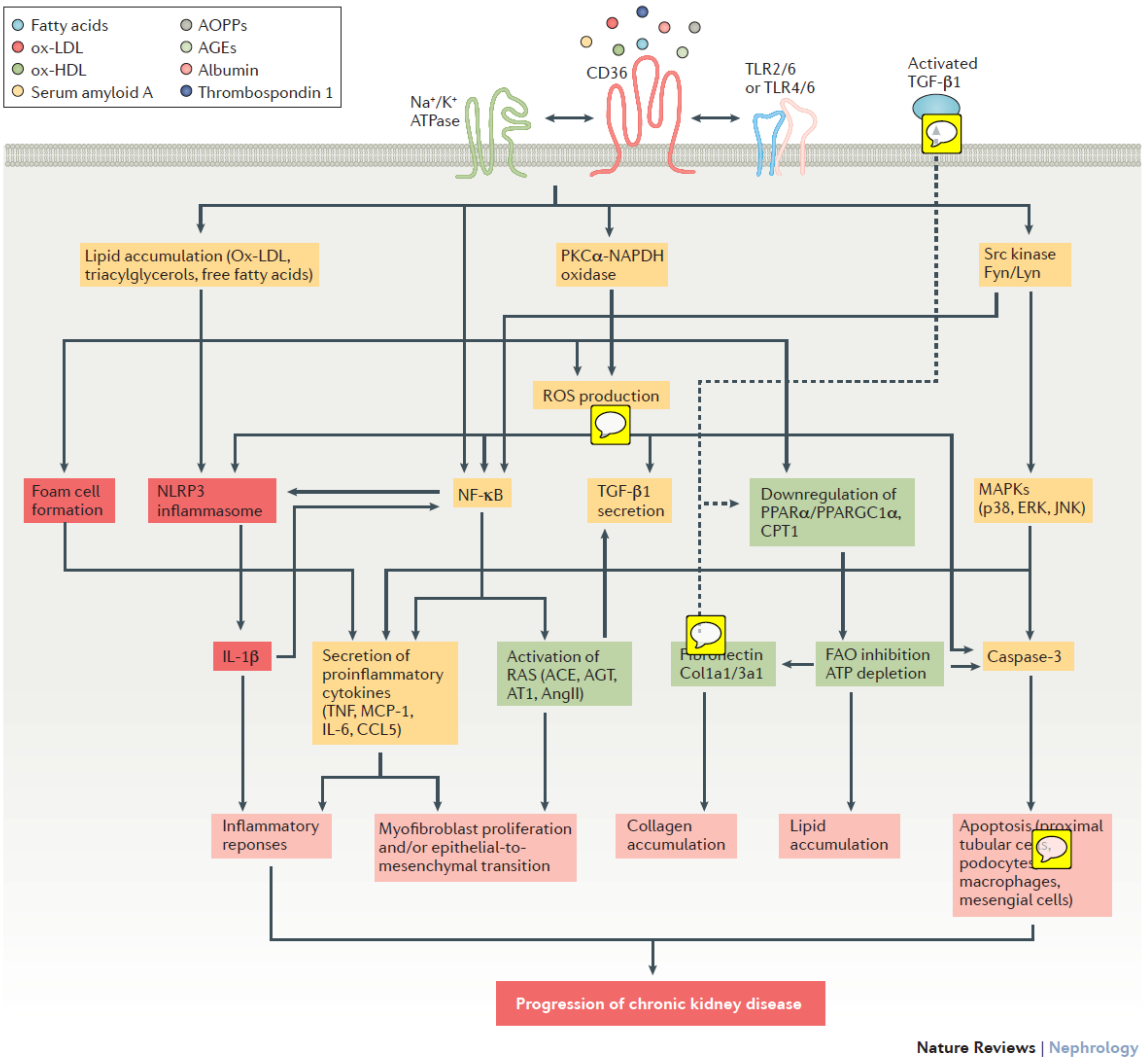

Figure 3 | Post-translational modifications regulate CD36 distribution and function. Fully-modified CD36 translocates to the plasma membrane and mediates fatty acid uptake, oxidative stress and inflammatory responses by triggering inflammatory signalling (not shown). Post-translational modifications may promote dimerization of CD36 and then increase fatty acid load. Increased amounts of intracellular fatty acids lead to defects in mitochondrial respiration in proximal tubule cells with reduced fatty acid oxidation (FAO) and increased intracellular lipid deposition, resulting in renal fibrosis. Metabolic defects in FAO might be restored by

activating mitochondrial CD36, which enhances fatty acid oxidation.

Fig 3

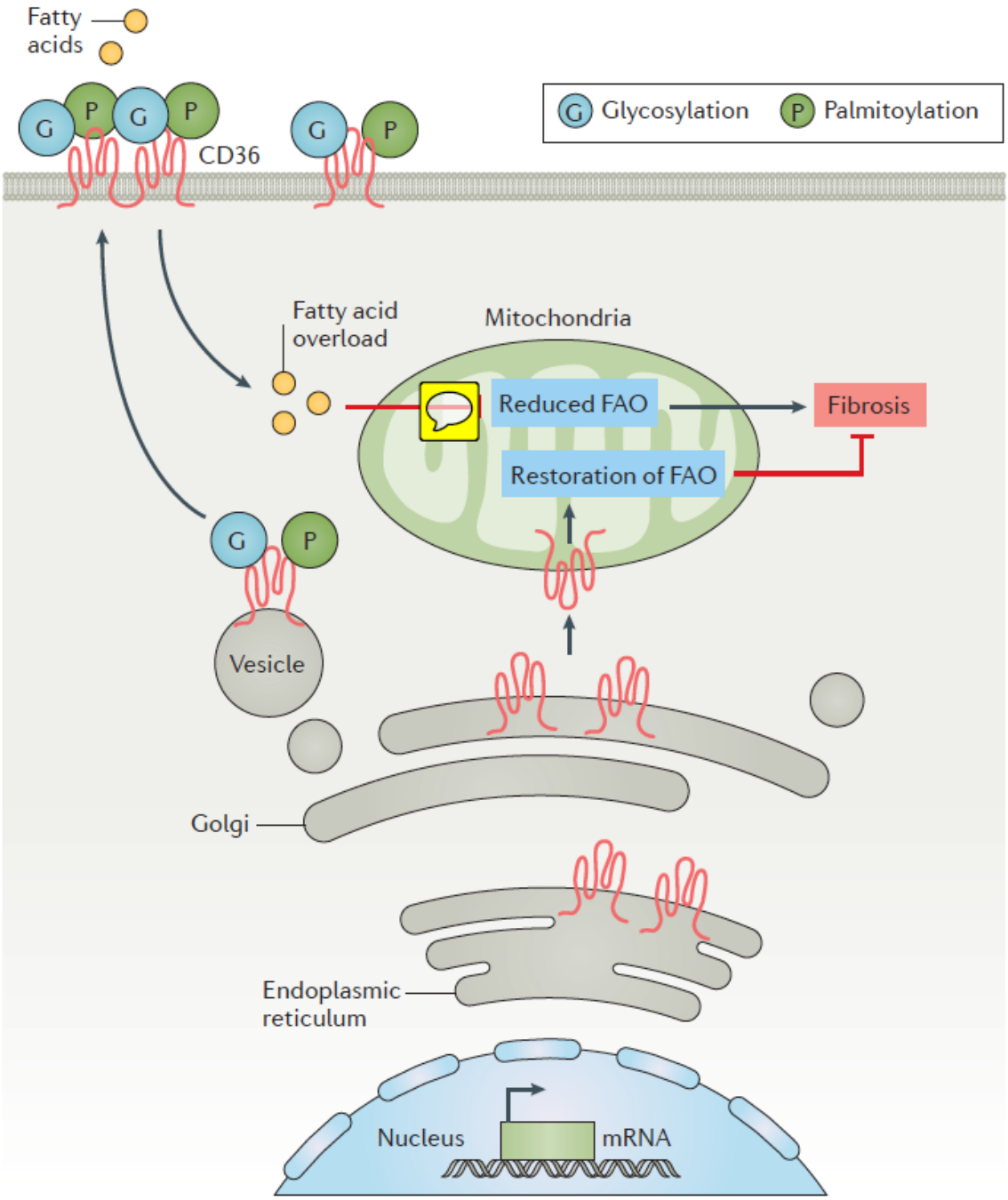

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Table 1 | Ligands and roles of CD36 in kidney and other tissues

Cell type	CD36 ligand	Roles	Refs.
Proximal tubule epithelial cells	Fatty acids	ATP production, lipid accumulation,apoptosis	10,161
	albumin	Fibrosis	122
	AGEs	Apoptosis	10
	AOPPs	Inflammation, apoptosis	134
	Ox-LDL	Inflammation, apoptosis, ROS production	11,15
	Ox-HDL	Inflammation, apoptosis, ROS production	131
Monocytes and/or macrophages	Ox-LDL	Foam cell formation, ROS production, lipid accumulation,apoptosis	15,19,20,199
	Serum amyloid A	Inflammation	29
	AGEs	Inflammation, ROS production, lipid accumulation	143,144
	Thrombospondin 1	Inflammation, apoptosis	148
	Porphyromonas gingivalis	Foam cell formation	147
	Oxidized phospholipids	Apoptosis	21
Podocytes	Fatty acids	lipid accumulation, apoptosis, ROS production	12,138,190
Mesangial cells	Ox-HDL	Inflammation, apoptosis	154
Cardiomyocytes	Fatty acids	ATP production	37
Vascular endothelial cells	Fatty acids	ATP production	45
	Ox-LDL	Foam cell formation, lipid accumulation, inflammation	200

Author biographies

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Xifeng Lu obtained his PhD from Erasmus Medical Centre, Netherlands, and joined the Centre for Nephrology & Urology, Shenzhen University Health Science Centre, China, as a lecturer in 2014. His research focus is the novel functions of the vacuolar H+-ATPase in lipid metabolism, and its interaction with blood pressure regulation.

Professor Yaxi Chen, PhD, has been a principal investigator in the UCL-Chongqing Medical University Joint Centre for Lipid Research, since 2006. Her research interests are the roles of CD36 in lipid homeostasis and metabolic inflammation in fatty liver, obesity-related chronic kidney disease and cancer development.

Professor John Moorhead, FRCP, introduced clinical nephrology to the Royal Free Hospital, London, UK, in 1966. He was Director of Nephrology and Transplantation and of the Renal Laboratory in this hospital. His numerous clinical research publications range across the nephrology spectrum and his lipid nephrotoxicity hypothesis has influenced much research in this area.

Zac Varghese, PhD, FRCPath, was previously the Associate Director of Renal Research at the Royal Free Hospital School of Medicine, London, UK. He was also the director of the Tissue Typing and Clinical Biochemistry laboratories in the Royal Free Hospital. He has published extensively on renal osteodystrophy, lipids, metabolic complications, and transplantation immunobiology.

Xiong Ruan, PhD,MD, leads the renal-oriented lipid research group in the Centre for Nephrology, University College London, UK and Shenzhen University, China. His major goal has been to develop an academic research programme that investigates the mechanisms of crosstalk between lipid disorder and metabolic inflammation in chronic kidney diseases.