

Role of Bile Acid Receptors in the Development and Function of Diabetic Nephropathy



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Diabetic nephropathy (DN) is a prevalent microvascular complication that occurs often in individuals with diabetes. It significantly raises the mortality rate of affected patients. Therefore, there is an urgent need to identify therapeutic targets for controlling and preventing the occurrence and development of DN. Bile acids (BAs) are now recognized as intricate metabolic integrators and signaling molecules. The activation of BAs has great promise as a therapeutic approach for preventing DN, renal damage caused by obesity, and nephrosclerosis. The nuclear receptors (NRs), farnesoid X receptor (FXR), pregnane X receptor (PXR), vitamin D receptor (VDR); and the G protein-coupled BA receptor, Takeda G-protein-coupled receptor 5 (TGR5) have important functions in controlling lipid, glucose, and energy metabolism, inflammation, as well as drug metabolism and detoxification. Over the past 10 years, there has been advancement in comprehending the biology and processes of BA receptors in the kidney, as well as in the creation of targeted BA receptor agonists. In this review, we discuss the role of BA receptors, FXR, PXR, VDR, and TGR5 in DN and their role in renal physiology, as well as the development and application of agonists that activate BA receptors for the treatment of kidney diseases.

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KEYWORDS: bile acids; diabetic nephropathy; membrane receptor TGR5; nuclear receptor FXR PXR VDR

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The increase in sugar and fat-rich diets due to economic progress and improved quality of life has led to a rise in obesity and diabetes mellitus, a significant global public health concern.¹ The International Diabetes Federation predicts that diabetes mellitus will reach 10.5% in 2021 and 12.2% by 2045.² In addition, 30% to 40% of individuals with diabetes will develop DN,³ a prevalent microvascular complication, contributing to end-stage renal disease.^{4,5} DN is characterized by structural alterations in the kidney, such as glomerulosclerosis, tubule interstitial fibrosis, thickening of the glomerular basement membrane, loss of podocytes, glomerular hypertrophy, and expansion of the mesangial matrix. The pathogenesis and progression of DN involve several key factors, including hypertension, abnormal carbohydrate and fat

metabolism, lipid accumulation, increased glycation end product, increased oxidative stress, and upregulation of profibrotic growth factors.⁶ The development of albuminuria and a decrease in glomerular filtration rate are the results of these alterations taken together.⁷

The kidney is a crucial organ in the context of DN,⁸ and a potential therapeutic strategy for kidney illness could involve targeting the expression and activation of BA receptors. BA receptors play a vital role in renal physiology and disease,⁹ activating various BA receptors such as FXR, G-protein-coupled receptor-1 / TGR5, PXR, and VDR.^{10,11} The kidney shows a high expression level of FXR and TGR5 and their target genes. BAs also regulate metabolism by activating NRs and G-protein-coupled receptor signaling pathways,^{12,13} regulating kidney lipid, glucose, and energy balance.^{14–16} Disruptions in BA metabolism can lead to cholestatic liver disorders, dyslipidemia, fatty liver illnesses, cardiovascular diseases, and diabetes.¹⁷ Activating these receptors has great potential for treating acute and chronic kidney illnesses by reducing lipid buildup, inflammation, oxidative stress, and fibrosis in the kidneys.¹⁸

In recent times, the significance of BAs in renal pathophysiology has grown due to their activation of

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FXR and TGR5, as well as transcription factors associated with lipid, cholesterol, and glucose metabolism. In addition, BAs have been found to influence genes implicated in inflammation and renal fibrosis.^{19,20} Therefore, the activation of BA receptors potentially contribute to the therapeutic management of renal disease. This study aims to examine the existing knowledge on the role and functionality of BAs and BA receptors, namely FXR and TGR5, in the context of kidney disease. Specifically, we will emphasize their involvement in diabetic kidney-related inflammation, lipid buildup, and fibrosis.

Furthermore, this review examines different agents that activate BA receptors and their impact on DN upon activation. It also discusses the current utilization and prospects of these agents, offering novel targets and therapeutic approaches for the clinical management and successful regulation of DN.

DN

DN is a common microvascular consequence in individuals with diabetes, leading to kidney cell dysfunction and renal failure.²¹⁻²⁵ It is the primary

contributor to end-stage nephropathy²⁶ and is responsible for most cases of chronic and end-stage renal disease globally.^{27,28} DN represents a renal manifestation of the same glucose-driven pathological process,^{29,30} which also occurs in other susceptible areas of the body.³¹

The pathological characteristics of DN encompass many changes, such as the thickening of basement membranes in glomeruli and tubules, mesangial dilatation, interstitial inflammation, hypertrophy of glomeruli and tubules, glomerular sclerosis, and fibrosis in the tubule interstitium^{28,32} (Figure 1). During the initial phase of DN, there is a presence of subtle pathological alterations, and the manifestation of clinical symptoms is challenging to identify. The observed manifestations mostly consist of glomerular mesangial hyperplasia, basal membrane thickening, and glomerular sclerosis.³³ As the disease advances, glomerular nodular degeneration undergoes a slow transition into diffuse lesions, encompassing interstitial fibrosis, renal tubule atrophy, and hyaline degeneration of the arterioles within and outside the bulb. These lesions exhibit a limited capacity for reversal. Ultimately, they advance to the terminal stage of renal disease, occurring approximately 20 to 25

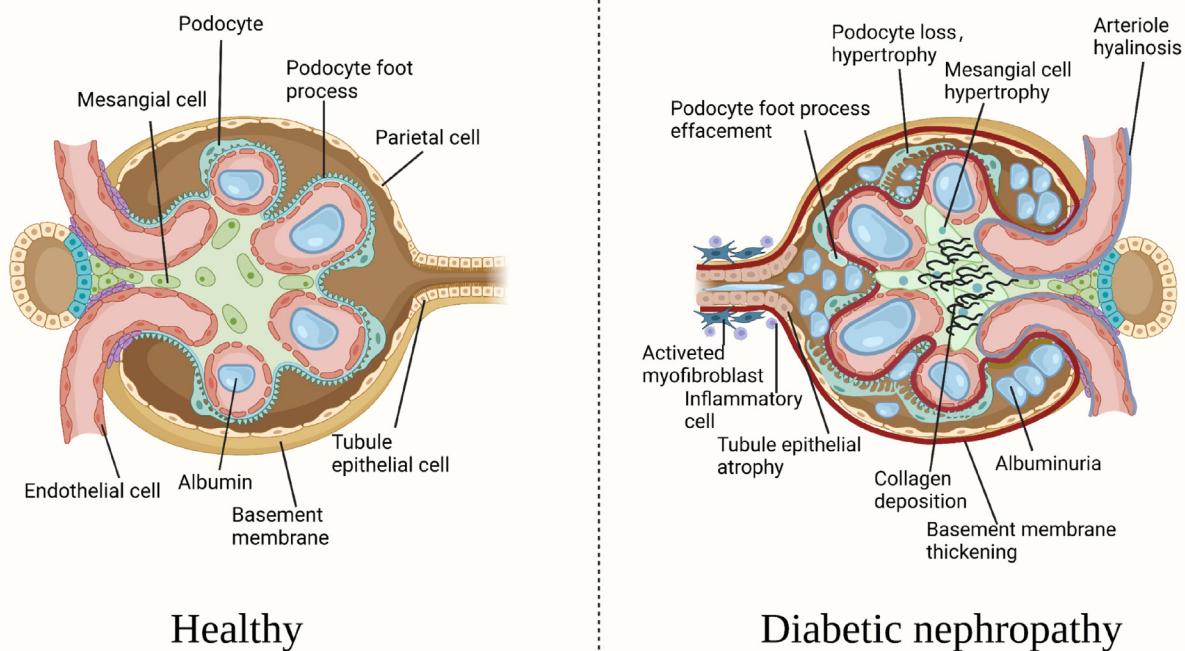


Figure 1. Pathological lesions of DN. The normal healthy glomerulus includes afferent arterioles, capillary loops, endothelial cells, basement membrane, podocytes, parietal epithelial cells, and tubule epithelial cells and is impermeable to albumin. In contrast, the diabetic glomerulus displays arterial hyalinosis, mesangial expansion, collagen deposition, basement membrane thickening, podocyte loss and hypertrophy, albuminuria, tubular epithelial atrophy, accumulation of activated myofibroblasts and matrix, influx of inflammatory cells, and capillary rarefaction. DN, diabetic nephropathy.

years after the first signs of diabetes. This stage is characterized by reduced glomerular filtration rate, arterial hypertension, low serum renin levels, decreased protein excretion, and gradual renal function decline.³⁴ The etiology of DN is intricate and encompasses the activation of various pathways that result in renal damage. These pathways include the polyol pathways, advanced glycosylation end products, oxidative stress, proinflammatory cytokines, and profibrotic growth factors. The dysregulation of the signaling cascade is a consequence of these pathways, ultimately leading to the development of DN.

Strict glycemic control, blood pressure management, and the use of renin-angiotensin system (RAS) blockers have all been shown in clinical studies to prevent the development and progression of diabetic neuropathy. Regrettably, a sizable portion of patients continue to be uncontrolled. Therefore, we need novel strategies for better therapies.

BA ANABOLISM AND ITS RECEPTORS

BA, a class of steroid acids, are crucial signaling molecules that facilitate precise intratissue communication. They are primarily synthesized in the liver and undergo metabolic transformations in the intestine by the gut microbiota.³⁵ These transformations include deconjugation, dehydroxylation, oxidation, epimerization, and re-conjugation.^{36,37} BAs play a vital role in maintaining a healthy gut microbiome, regulating lipid and carbohydrate metabolism, enhancing insulin sensitivity, and supporting innate immunity.³⁸

The composition of the human BA pool comprises the principal Bas, cholic acid (CA) and chenodeoxycholic acid (CDCA), along with the secondary BA, deoxycholic acid and a minimal quantity of lithocholic acid. The synthesis of primary BAs occurs in the liver through the conversion of cholesterol. Enzymatic processes facilitated by gut bacteria lead to the conversion of certain primary BAs into secondary BAs. *Firmicutes*, *Bacteroides*, *Lactobacillus*, *Bifidobacterium*, and *Clostridium* all contribute significantly to the production of secondary BAs.³⁹ Within the hepatic organ, the synthesis of primary BAs occurs via 2 prominent pathways: the conventional pathway (often referred to as the neutral pathway) and the alternate pathway (known as the acidic pathway owing to the generation of acidic intermediates). The classical pathway involves the conversion of cholesterol into the primary BAs, CA and CDCA through the actions of cholesterol 7 α -hydroxylase and sterol 12 α -hydroxylase. In contrast, the alternative pathway is initiated by sterol 27-hydroxylase and primarily results in the production of CDCA.⁴⁰ In humans, the primary BAs consist of CA

and CDCA; however, in mice, the primary BAs are CA, CDCA, ursodeoxycholic acid (UDCA), and muricholic acid (MCA).⁴¹ Within the gastrointestinal tract, the process of deconjugation occurs, whereby conjugated CA and CDCA are enzymatically modified by the bile salt hydrolase (BSH) enzyme produced by gut bacteria. Subsequently, the deconjugated CA and CDCA undergo a transformation mediated by the 7 α -dehydroxylase enzyme in humans, resulting in the production of secondary BAs such as deoxycholic acid, lithocholic acid, and ursodeoxycholic acid.^{42,43} (Figure 2).

Abnormalities in the gut flora can cause metabolic abnormalities in people with DN.^{39,44,45} Metabolites produced by gut microorganisms facilitate many interactions between the gut microbiota and the human body are facilitated by metabolites produced by gut microorganisms. Gut microorganisms' metabolic products mostly consist of SCFAs (formic acid, acetic acid, propionic acid, isobutyric acid, butyric acid, isovaleric acid, and valeric acid), BAs, TMAO (a metabolite of choline, L-carnitine), and betaine, uremic toxins, and hydrogen sulfide.^{46,47} These metabolites alter the intestinal epithelium's barrier function by modulating receptor expression or activating transcription factors, playing an important role in the onset and progression of DN. This study focuses on the relationship between DN and receptors for metabolites of gut bacteria, BAs.

BA ligands are endogenous ligands that activate NRs and a G-protein-coupled receptor, allowing them to modulate metabolic pathways in various tissues.⁴⁸ They can act as agonists or antagonists of signaling molecules on FXR and G protein-coupled BA receptor 1.^{10,48} Abnormal BA metabolism and receptor expression have been linked to liver injury,⁴⁹ metabolic disorders, cardiovascular diseases, digestive system diseases,⁵⁰ colorectal cancer,⁵¹ and kidney disease.^{52,53} Using synthetic and natural receptor agonists or antagonists has shown potential in managing metabolic disturbances and inflammation.

BA Receptors in DN

BA receptors, FXR, PXR, VDR, and TGR5 play an important role in the pathophysiology of the kidney. BA receptors are important targets for the treatment and control of DN. Many studies have shown the importance of BA receptors in DN.

The Function of NRs in the Kidney

NRs are crucial regulators of systemic homeostasis and play a significant role in various illnesses. They regulate various metabolic processes, including renal lipid metabolism, medication clearance, inflammation, fibrosis, cell differentiation, and oxidative stress. Dysregulation of NRs, often caused by obesity, can lead to metabolic syndrome, end-stage renal disease, and

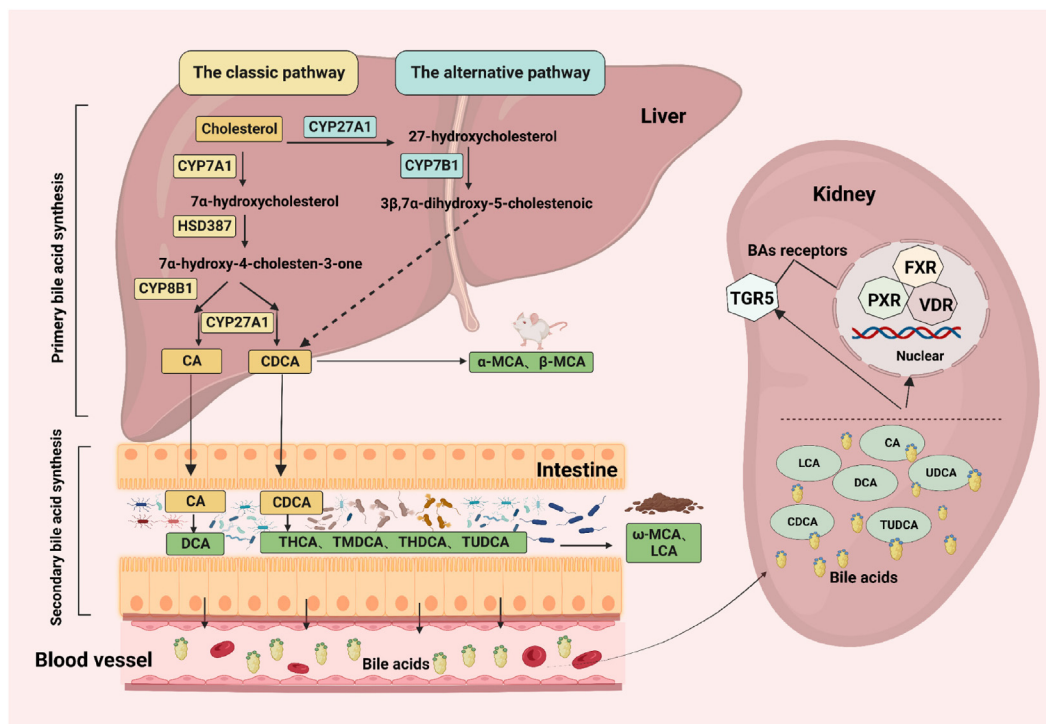


Figure 2. Bile acid synthesis and bile acids receptors. In the classic bile acid synthesis pathway, cholesterol is converted to cholic acid (CA, 3α , 7α , 12α) and chenodeoxycholic acid (CDCA, 3α , 7α). CYP7A1 is the rate-limiting enzyme and CYP8B1 catalyzes the synthesis of CA. In mouse liver, CDCA is converted to α -muricholic acid (α -MCA, 3α , 6β , 7α) and β -MCA (3α , 6β , 7β). Most bile acids in mice are taurine (T)-conjugated and secreted into bile. In the intestine, gut bacteria de-conjugate bile acids and then remove the 7α -hydroxyl group from CA and CDCA to form secondary bile acids deoxycholic acid (3α , 12α) and lithocholic acid (3α), respectively. T- α -MCA and T- β -MCA are converted to T-hyodeoxycholic acid (THDCA, 3α , 6α), T-ursodeoxycholic acid (TUDCA, 3α , 7β), T-hyocholic acid (THCA, 3α , 6α , 7α) and T-murideoxycholic acid (TMDCA, 3α , 6β).

chronic renal disease progression. NRs are at the forefront of innovative therapeutic approaches for kidney diseases such as glomerulosclerosis, tubulointerstitial disease, renal lipotoxicity, kidney fibrosis, and hypertension. The kidney expresses NRs, FXR, PXR, and VDR, which are essential in renal disease.

The Role of FXR in DN

The NR, FXR was discovered in 1995^{54,55} and plays a crucial role as the primary detector of BAs and regulator of their synthesis, secretion, and metabolism in the liver, ileum, and colon.⁵⁶ It is a member of the NRs superfamily, which regulates the transcription of specific target genes. FXR maintains BAs, glucose, and lipid equilibrium by regulating various target genes. It is highly expressed in various organs, including the liver,⁵⁷ gallbladder,⁵⁸ kidney,⁵⁹ heart,⁶⁰ intestine, vasculature, atherosclerotic plaque,^{61,62} and adrenal glands.⁶³ It is involved in inflammation, immunological responses, and fibrosis. The kidney is vital for regulating water and solute balance, and any impairment or malfunction is linked to increased illness and death rates.⁶⁴ FXR plays a significant role in renal water reabsorption and is believed to have protective activities in cases of acute kidney disease, chronic kidney disease, and diabetic kidney disease.¹⁸

Inhibiting increasing proteinuria, podocyte loss, mesangial expansion, and renal lipid accumulation, the renoprotective impact of FXR is primarily mediated by modulating lipid metabolism, oxidative stress, proinflammatory cytokines, and profibrotic factors.⁶⁵ In STZ-induced diabetic mice, FXR deletion accelerated fibrosis, increased plasma lipid levels, and worsened diabetic kidney injury compared to diabetic wild-type (WT) mice.⁶⁶ The FXR agonist, GW4064, in contrast, decreased visfatin in HG-induced HMCs. This stopped inflammation, fibrosis, and cell division. In animal models of type 2 diabetes,⁶⁶ OCA and GW4064 were effective in preventing the progression of DN by ameliorating proteinuria, podocyte injury, profibrotic and proinflammatory gene expression, and mesangial cell proliferation.⁶⁷⁻⁶⁹ In db/db mice, GW4064 reduced glomerular damage and fibrosis, as well as blood glucose, albuminuria, blood urea nitrogen, and serum creatinine. This suggested that FXR activation stopped the progression of DN.⁶⁹

FXR Regulates Glucose Metabolism

FXR is a key player in glucose metabolism, controlling glucose levels⁷⁰⁻⁷⁴ and increasing glycogen synthesis.^{75,76} It inhibits the expression of glycogen synthase kinase-3 beta, a transcription factor that

phosphorylates and inactivates glycogen synthase, leading to increased glycogen synthesis. FXR reduces glycolysis⁷⁷ by suppressing the transcriptional activity of carbohydrate response element-binding protein, a transcription factor that promotes glycolysis. This inhibits the expression of glycolytic enzymes and reduces glycolysis. FXR downregulates genes involved in gluconeogenesis, such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, which are key enzymes in the gluconeogenic pathway. These down-regulations lead to a decrease in gluconeogenesis and serum glucose levels.^{75,78}

Insulin resistance and hyperglycemia were observed in FXR-null mice, indicating disruption of normal glucose homeostasis.⁷⁹ Elevated fatty acid levels likely caused these issues. When activated by an agonist, FXR repressed gluconeogenic genes, phosphoenolpyruvate carboxykinase, and glucose-6-phosphatase, indicating that the FXR/SHP system regulates glucose synthesis in the liver.⁷⁹ Activating FXR enhanced insulin sensitivity and tolerance in diabetic obese mice. When FXR-VP16 or FXR agonists were administered to diabetic mice, plasma glucose levels were significantly lowered and insulin sensitivity increased.⁷⁶ In summary, FXR activation modulates glucose metabolism by increasing glycogen synthesis, reducing glycolysis, and decreasing gluconeogenesis, ultimately reducing serum glucose levels.

FXR Regulates Lipid Metabolism

FXR is recognized as a crucial controller of cholesterol and lipid balance in the body. Numerous studies have established a link between kidney dysfunction and the buildup of lipids in the kidneys in different disease models, such as metabolic disease (obesity, metabolic syndrome, and diabetes mellitus), acute kidney injury, and chronic kidney disease.⁸⁰

In mice models of diabetes and diet-induced obesity, there is an elevation in triglyceride and cholesterol levels as compared to healthy controls. The elevated levels of triglycerides in the kidneys are linked to an increase in the levels of 2 transcription factors, sterol regulatory element-binding protein 1c and carbohydrate response element-binding protein. These transcription factors are known to enhance the synthesis of fatty acids.⁸¹ Sterol regulatory element-binding protein 1c is a crucial factor that promotes the synthesis of fatty acids⁸² and the accumulation of lipids in the kidneys. In these 2 models, treatment with FXR agonists demonstrates a protective effect on the kidneys by reducing the expression of genes involved in the fatty acid synthesis, such as sterol regulatory element-binding protein 1c, stearoyl CoA desaturase-1, and acetyl CoA carboxylase, and increasing the expression

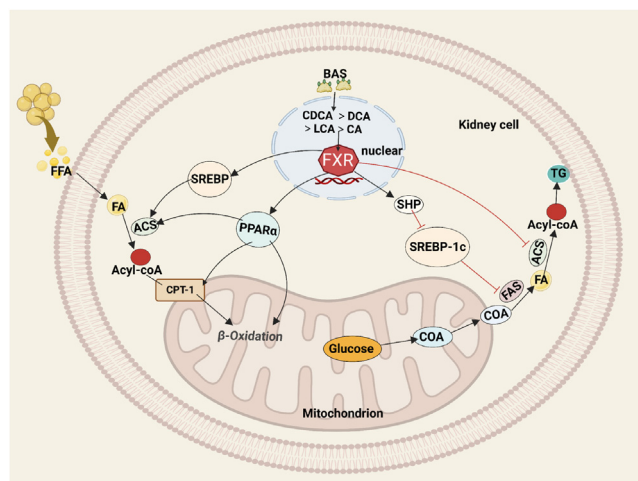


Figure 3. FXR inhibits the synthesis of FA and TG, promotes the oxidative decomposition of FA, and plays a role in lipid lowering through various pathways. ACSL, long chain fatty acyl CoA synthetase; CoA, coenzyme A; CPT1, carnitine palmitoyl transferase 1; FA, fatty acid; FAS, fatty acid synthase; FFA, free fatty acids; FXR, farnesol X receptor; Glu, glucose; PPAR alpha, peroxisome proliferator activates receptor alpha; SHP, small molecule heterodimer; SREBP-1c, sterol element-binding protein-1c; TG, triglyceride.

of genes involved in fatty acid oxidation and lipid breakdown, such as PPAR α , CPT1a, UCP-2, PGC-1 α , and LPL. FXR suppresses the production of fatty acids and triglycerides, enhances the breakdown of fatty acids by oxidation, and contributes to the reduction of lipid levels by engaging a variety of pathways (Figure 3).

FXR reduces the concentration of low-density lipoprotein cholesterol in the blood plasma⁸³ by promoting the uptake and breakdown of low-density lipoprotein particles.⁷⁶ FXR knockout mice show increased levels of high-density lipoprotein cholesterol due to a decrease in the expression of genes involved in reverse cholesterol transport, such as SCARB1 and ATP-binding cassette transporters G5 and G8, which remove high-density lipoprotein cholesterol from the bloodstream.⁸⁴ FXR can also decrease cholesterol buildup in hepatocytes and renal epithelial cells by suppressing cholesterol production⁸⁵ and increasing ATP-binding cassette transporter A1 expression.⁸⁶ In models of insulin resistance, FXR can decrease triglyceride buildup in the liver and kidneys by lowering the expression of fatty acid synthase and acetyl CoA carboxylase, inhibiting the activity of sterol regulatory element-binding protein 1c and carbohydrate response element-binding protein, which regulate the response to carbohydrates.⁸⁷ This inhibition promotes the clearance of triglycerides by increasing the oxidation of fatty acids through the PPAR α / γ -CPT1 pathway^{88,89} and reduces the uptake of fatty acids by decreasing CD36 expression. FXR also causes the whitening of

brown adipose tissue in adipocytes by activating SCD expression through PPAR γ activation.^{90,91}

FXR Regulates Inflammation

In the course of diabetes and renal disease, inflammatory infiltrates are a key characteristic of DN development.⁹² NF- κ B serves as a crucial signaling pathway for initiating the inflammatory response, facilitating the release of inflammatory mediators such as leukin and tumor necrosis factors such as MCP-1, TNF- α , and IL-6,^{93,94} thereby inducing inflammation,⁹⁵ which are closely associated with DN development. Consequently, effectively controlling the duration of the inflammatory response can significantly prevent DN (Figure 4).

BAs treatment in diabetic mice reduced proinflammatory factors in their kidneys.⁹⁶ FXR activation has been shown to inhibit inflammation in various diseases, including nonalcoholic fatty liver disease, pulmonary fibrosis,⁹⁷ atherosclerosis, inflammatory bowel disease, chronic pancreatitis, and DN. Macrophages are key mediators of renal vascular inflammation, and DN is characterized by an increase in these cells. High glucose, AGEs (are stable covalent compounds that are derived from the amino groups of proteins, fats and nucleic acids and reducing sugars [glucose, fructose, pentose, etc.] in physiological environments through non-enzymatic catalyzed reactions), and oxidized low-density lipoprotein contribute to

macrophage accumulation and activation. When FXR deficiency is treated, NF- κ B activity is linked to increased macrophage infiltration. However, when FXR agonist INT-747 is administered, this trend reverses.^{98,99} INT-747 reduces inflammatory response in hepatocytes and vascular smooth muscle cells by blocking the NF- κ B signaling pathway. These findings suggest that FXR activation suppresses inflammatory characteristics in diabetic kidneys and macrophages.

FXR Regulates Oxidative Stress

Oxidative stress, the excessive production of reactive oxygen species and weakening of antioxidant capacity, is a significant factor in the development of DN. Redox homeostasis is crucial for cellular functionality and survival,¹⁰⁰ whereas oxidative stress is a state of imbalance between oxidizing agents and antioxidant substances in the human body. Oxidative stress is a major cause of kidney damage, because it leads to the production of reactive oxygen species in mesangial cells of the glomerulus when exposed to high glucose levels. This intensifies oxidative stress, exacerbating kidney injury. However, mitigating the excessive production of reactive oxygen species can alleviate the negative effects of oxidative stress.¹⁰¹

Treatment with GW4064 and cholic acid can induce the glutathione metabolism gene to increase, eliminate excess reactive oxygen species, reduce oxidative stress, restore mitochondrial and endoplasmic reticulum

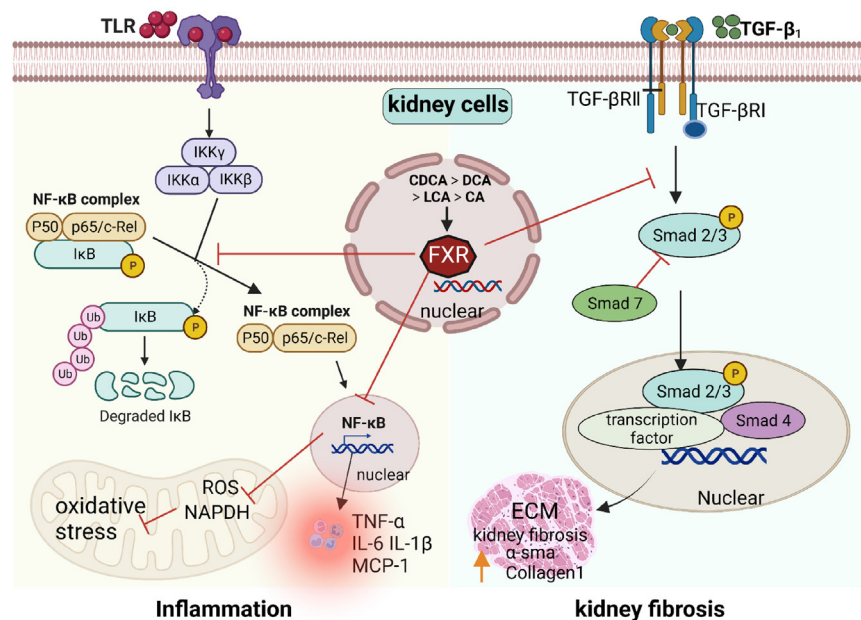


Figure 4. FXR regulates inflammation as well as the kidney fibrosis. The activation of FXR by bile acids can inhibit the NF- κ B pathway to reduce inflammation, thereby reducing the production of mitochondrial ROS and alleviating oxidative stress. FXR activation also reduces renal fibrosis by inhibiting the TGF- β pathway. α -sma, alpha-smooth muscle actin; ECM, extra cellular matrix; IKK, inhibitor of KappaB kinase; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; MCP-1, monocyte chemotactic protein-1; NAPDH, nicotinamide adenine dinucleotide phosphate; NF- κ B, nuclear factor-k-gene binding; ROS, reactive oxygen species; TGF- β 1, transforming growth factor- β ; TLR, toll-like receptor; TNF- α , tumor necrosis factor.

function, and prevent apoptosis, thus protecting proximal renal tubule cells. Activation of FXR can reduce inflammatory factors, alleviate apoptosis, downregulate reactive oxygen species levels, and prevent oxidative stress induced mitochondrial damage. NADPH oxidase 2 is a major source of reactive oxygen species *in vivo*. CDCA can activate FXR, downregulate NADPH oxidase 2 expression and alleviate oxidative stress in rats fed high fructose. Changes in the protein folding pathway regulated by the endoplasmic reticulum can cause imbalance of reactive oxygen species and increase the production of active oxides, potentially leading to kidney injury by mediating oxidative stress. FXR agonist, Tauro ursodeoxycholic acid can protect renal tubular epithelial cells from hyperglycemia damage and improve endoplasmic reticulum stress signal transduction.

FXR Regulates Renal Fibrosis

Renal fibrosis is a significant characteristic of chronic kidney disease,⁹⁶ involving DN, and is a crucial phase in the progression of all renal diseases toward end-stage renal disease.¹⁰² It is primarily caused by the activation of renal fibroblasts and myofibroblasts in response to factors such as inflammation, hypoxia, and hyperglycemia. The main harmful effects of increasing renal fibrosis include the gathering of fibroblasts, increased expression of extracellular matrix (ECM) proteins, and issues with nephron function. TGF- β is a crucial player in the development of renal fibrosis, because it both increases the expression of ECM proteins and stops them from breaking down, leading to the buildup of ECM.

In animal models of obesity and insulin resistance induced by high-fat diet,¹⁰³ type 1¹⁰⁴ or type 2 diabetes, and aging models,¹² the downregulation of FXR and its target genes in the kidney is closely related to renal fibrosis and the degree of renal insufficiency.¹⁰⁵ FXR agonists can regulate ECM production through the TGF- β -Smad pathway and FXR-SHP pathway, improving liver, myocardial, and kidney fibrosis. When FXR is turned on, many markers related to ECM, myofibroblast activation, profiber signaling proteins, and histochemical fibrosis go down.¹⁰⁶ The FXR protein controls the TGF- β pathway by decreasing the expression of SREBP-1, which can enhance the expression of TGF- β . When FXR is turned on, it activates the α/β hydrolase NDRG2, stopping the production of TGF- β .¹⁰⁷

The downregulation of FXR prevents renal fibrosis. It is important to note that inflammatory mediators can induce organ fibrosis by promoting inflammatory response; and FXR, as an anti-inflammatory NR, can delay the progression of renal fibrosis by inhibiting inflammation.

FXR Reduces Proteinuria

Proteinuria is a key indicator of DN, with microalbuminuria being a key predictor of disease progression.⁵⁹ Hemodynamic abnormalities, podocyte dysfunction, and renal tubular reabsorption damage contribute to the progression of nephropathy.¹⁰⁸⁻¹¹⁰ Wang *et al.*⁶⁶ treated DBA/2J mice fed with a Western diet by daily gavage of INT-747, which significantly reduced urinary protein, improved podocyte loss and mesangial expansion, and considered that activation of FXR could regulate fatty acid synthesis and oxidation, improve triglyceride accumulation and kidney structure. In Wistar rats,¹¹¹ intragastric administration of CDCA alleviated kidney damage, and urine protein was significantly reduced. FXR KO diabetic mice exhibited typical DN pathological changes, including podocyte loss,⁶⁶ glomerular lobulation, mesangial matrix expansion, tubular injury, and protein cast. Treatment with CA for 12 weeks improved proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis,⁸¹ further confirming FXR's role in reducing urinary protein in DN. Urinary microalbumin is a clinically recognized early biomarker of DN. The combination of oral enalapril and intraperitoneal Tauro ursodeoxycholic acid can effectively reduce urinary albumin in 16-week-old db/db mice, and Tauro ursodeoxycholic acid only can improve renal tubular damage. FXR activation can protect podocytes, tubular cells, and mesangial cells, thus reducing DN urinary protein.

The Role of PXR in DN

PXR, a NR, is highly expressed in the human liver, intestinal tissues, and kidneys.¹¹² It regulates various physiological and pathological processes, including metabolism, transport, combination, excretion, and exogenous and endogenous substances.¹¹³ PXR also regulates glucose,¹¹⁴ lipids, steroids, CA, bilirubin, and bone minerals, and immune response.^{115,116} It affects liver, gastrointestinal, and tumor development and plays a crucial role in renal physiology and pathology.¹¹⁷⁻¹¹⁹ This study demonstrates that xenobiotic NR, PXR is activated and epigenetically changed, potentially playing a role in diabetic kidneys.¹²⁰ PXR is essential in metabolic alterations associated with diabetes and obesity.¹²¹

PXR Regulates Cholesterol Homeostasis

Endogenous cholesterol metabolites can activate PXR, suggesting that PXR plays a role in the removal of potentially hazardous intermediates. Cholesterol catabolism is known to be inhibited by the signaling molecule known as cholecalciferol acid. When mice lacking PXR were given a diet supplemented with CA in research by Sonoda *et al.*,¹²² adding cholesterol to their food caused rapid mortality accompanied by symptoms

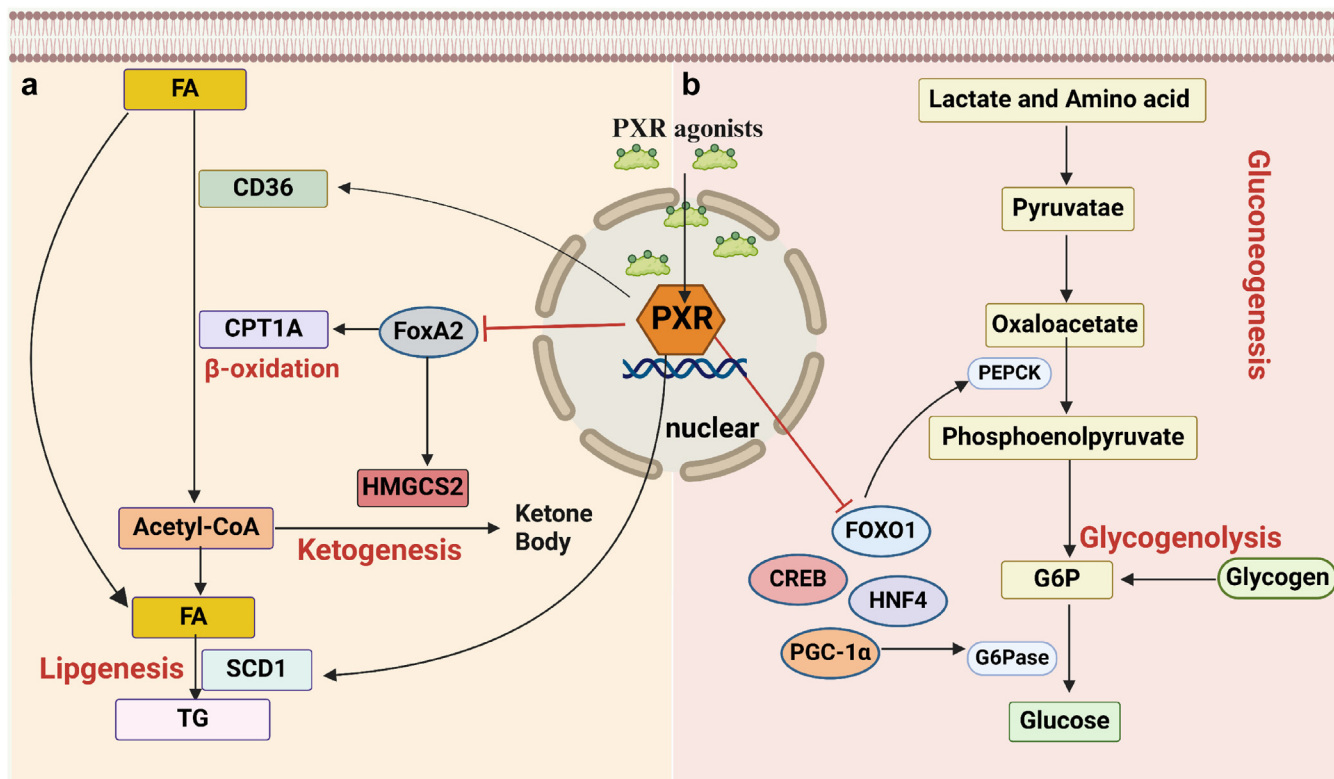


Figure 5. PXR regulates glucose and cholesterol metabolism. (a) PXR, a xenobiotic sensing regulator, is critical for glucose metabolism. (b) PXR regulates cholesterol metabolism. CD36, cluster determinant 36; CPT1A, carnitine palmitoyl transferase 1A; CREB, cAMP -response element binding protein; FA, fatty acid; FAT, fatty acid translocase; FFA, free fatty acid; FoxA2, forkhead box A2; FOXO1, forkhead box O1; G6Pase, glucose-6-phosphatase; HNF4, hepatocyte nuclear factor 4; PEPCK, phosphoenol pyruvate; carboxykinase; PGC-1 α , peroxisome proliferators-activated receptor γ coactivator I alpha; PXR, pregnane X receptor; SCD1, stearoyl-CoA desaturase-1; TG, triglyceride.

of hepatorenal failure. Renal failure was suggested as the possible direct cause of death. These findings highlight the special and vital role that PXR plays in defending against cholesterol and its metabolites.

Carnitine palmitoyltransferase 1A (CPT1A) and mitochondrial 3-hydroxy-3-methylglutaryl-coenzyme A synthase 2 (HMGCS2) are key enzymes for β -oxidation and ketogenesis. FoxA2, a winged helix/forkhead transcription factor, speeds up the transcription of CPT1A and HMGCS2 when insulin is not present.¹²³ Insulin stimulates FoxA2 by phosphorylating and exonucleating it while suppressing the transcription of CPT1A and HMGCS2.¹²⁴ Nakamura *et al.*¹²⁵ discovered that pregnenolone-16 α -carbonitrile suppresses transcription of CPT1A and HMGCS2 in WT mice but not in Pxr knockout mice. PXR may bind directly to FoxA2, inhibiting the activation of the CPT1A and HMGCS2 genes. In Figure 5a, we depict PXR's entire mechanism in cholesterol metabolism.

PXR Regulates Glucose Metabolism

PXR regulates gluconeogenesis by modulating the expression of key enzymes; and is involved in the oxidative uptake of glucose by regulating glucose transporter 2 and glucokinase. PXR also regulates

cellular processes such as sterol regulatory element binding protein 1c, fatty acid translocation enzyme CD36, carnitine palmitoyl transferase 1A, mitochondrial hydroxyl-3-methylglutaryl CoA synthetase 2, mitochondrial sterol 27 hydroxylase, and cholesterol effluent transporter A1, G1.

Increasing evidence suggests that PXR activation has a function in glucose homeostasis. Hormones (insulin, glucagon, glucocorticoids, etc.) regulate the activity of key enzymes involved in various glucose metabolism processes, allowing blood glucose concentrations to remain relatively constant. When PXR is turned on, it lowers the amounts of 2 important enzymes that control gluconeogenesis.^{126,127} These are glucose-6-phosphatase and phosphoenolpyruvate carboxy kinase. Kodama *et al.*¹²⁷ discovered that PXR regulates gluconeogenesis by interacting with FOXO1, CREB, and HNF4. HNF4, together with PGC-1 α , stimulates gluconeogenesis. Bhalla *et al.*¹²⁶ found that PXR competes with HNF4 for PGC-1 α and suppresses gluconeogenesis. *In vivo* studies confirmed the validity of these findings. When insulin levels are low, FOXO1 activates glucose-6-phosphatase and phosphoenolpyruvate carboxykinase. In contrast, PXR stops CREB from attaching to similar sites, which stops the transcription

of glucagon-activated glucose-6-phosphatase and stops the process of making glucose.¹²⁸ In a nutshell, PXR is an important xenobiotic sensing regulator in glucose metabolism (Figure 5b).

PXR Regulates Renal Fibrosis

PXR is expressed in many parts of the kidney, indicating that it plays an important role in regulating kidney function. In the mouse model of cisplatin-induced acute kidney injury, the expression of PXR in the kidney also decreased with the aggravation of acute kidney injury. When pregnenolone-16 α -carbonitrile, a specific PXR agonist, was used, renal tissue damage and functional decline got a lot better. This protective mechanism may have something to do with PI3K being turned on. Renal fibrosis is the common pathological feature and final manifestation of DN, and PXR plays an important role in renal fibrosis.^{129,130} Pregnenolone-16 α -carbonitrile treated a mouse model of chronic kidney disease, and they found significant improvements in renal function decline and kidney fibrosis. On the contrary, when the PXR gene is knocked out, the degree of renal fibrosis is significantly aggravated.¹³¹ By stopping the Smad3 signaling pathway and the Wnt7a/ β -catenin signaling pathway from working, PXR helps treat renal fibrosis. PXR controls Wnt7a, which is linked to p53. PXR can bind to p53 and stop p53 from increasing Wnt7a gene transcription, which lowers ECM production.¹³²

The role of VDR in DN

VDRs are nucleophilic proteins within the thyroid hormone superfamily.¹³³ VDRs form a heterodimer with retinoid receptors, necessary for high-affinity DNA binding. They are part of the ligand-activated transcription factor family. 1,25-(OH)₂D₃ is the primary ligand that activates VDRs, binding to the VDR-retinoid X receptor complex and a specific cis-DNA sequence of VDRE.⁵³ This modulates transcription by activating the target motif. 1,25-(OH)₂D₃ has both active and inhibitory sexual properties and has a wide range of physiological effects,¹³⁴ including maintaining calcium and phosphorus homeostasis, regulating the immune response, participating in inflammatory responses, inhibiting cell proliferation, causing cell apoptosis, and promoting differentiation.¹³⁵

VDRs are found in various cells, including skin, vascular, immunological, colon, pancreatic, and kidney cells.¹³⁶ In kidney tissues, they produce the highest 1,25-(OH)₂D₃ due to high selectivity and affinity binding.¹³⁷ This results in a heterodimer between VDR and retinoid X receptor, facilitating transcription of VDR-targeted genes. VDRs are involved in mineral metabolism, renal and cardiovascular control,¹³⁷ and have various implications in renal illness.

Recent studies have shown that VDRs play a crucial role in the development of DN by controlling inflammatory reactions, reducing proteinuria, stopping renal fibrosis, and inhibiting the RAS.^{138,139} Treatment with a VDR agonist can reduce proteinuria, podocyte damage, mesangial enlargement, and ECM protein buildup in a mouse model of diet-induced obesity. The VDR agonist also decreases macrophage infiltration, oxidative stress, proinflammatory cytokines, and profibrotic growth factors. In addition, VDR activation reduces the accumulation of neutral lipids and adipophilin in the kidney, inhibiting renal diet-induced obesity symptoms.

VDR and RAS

The RAS is a regulatory process where angiotensin (Ang) II acts as the main mediator. Ang II is produced through 2 enzymatic cleavages. The first step involves the cleavage of angiotensinogen by renin, resulting in the formation of Ang I. This is then converted to Ang II by the angiotensin-converting enzyme.¹⁴⁰ Clinical research¹⁴¹ shows that Ang II type 1 receptor blockers or angiotensin-converting enzyme inhibitors slow the development of tubulointerstitial fibrosis, glomerulosclerosis, and proteinuria in diabetic patients. This suggests that the RAS plays a key role in the progressive renal injury seen in DN.¹⁴²

According to a study by Zhang *et al.*,¹⁴³ diabetic VDR KO mice experienced more severe nephropathy than WT mice because of increased RAS activation in the kidney. This finding confirms that VDR protects against renal injury caused by hyperglycemia by suppressing RAS. A model of type 1 diabetes produced by STZ was employed in this investigation. Diabetes was established in VDR KO mice and WT mice by administering a low-dose injection of STZ. The mice were then observed for 19 weeks. Both diabetic WT and VDR KO mice had a similar level of increasing hyperglycemia. VDR KO animals exhibited accelerated and more pronounced albuminuria compared to WT mice. The electron microscopy analysis of VDR KO mice indicates that there is a notable thickening of the glomerular basement membrane and an increase in podocyte foot process effacement, which is consistent with the more severe albumin uric phenotype. In mice that do not have the VDR gene, the production of renin in the kidney was significantly increased. This resulted in a significant increase in plasma renin and Ang II levels, leading to hypertension and cardiac hypertrophy. However, when the human VDR gene was specifically expressed in the juxtaglomerular cells of transgenic mice using the renin gene promoter, the expression of renin was suppressed. This inhibitory effect was not influenced by parathyroid hormone or

calcium levels, indicating that the VDR receptor directly regulates renin production.¹⁴⁴

VDR is Involved in Inflammation and Fibrosis

NF- κ B is a key regulator of genes involved in inflammation and fibrogenesis, including TNF- α , TGF- β 1, monocyte chemoattractant protein-1, and plasminogen activator inhibitor-1. These genes are crucial in the progression of kidney disease and are linked to the functioning of endothelium. TNF- α activates the c-Jun N-terminal kinase pathway, which hinders the activity of endothelial NO synthase (eNOS), reducing the availability of nitric oxide. This leads to the formation of the superoxide anion O_2^- by upregulating xanthine oxidase activity, further impacting endothelial function. TNF- α -bound TNFR triggers NF- κ B translocation to the nucleus, promoting the expression of pro-inflammatory mediators (Figure 6).

NF- κ B activation has been reported in patients with DN.¹⁴⁵ In a mouse model, TNF- α stimulates renal tubular cells to produce the RANTES chemokine, facilitating the infiltration of monocytes and T cells into the kidneys, contributing to kidney damage. Paricalcitol injection disrupts this harmful cycle by increasing the expression of VDR in renal tubule cells,

which binds to NF- κ B and inhibits the transcription of RANTES.

TGF- β 1 is synthesized in an inactive state and stored in the endothelium.¹⁴⁶ When activated, it attaches to its receptor and enters the nucleus to initiate the transcription of genes necessary for myofibroblast development, ECM components, and connective tissue growth factor.¹⁴⁷ In addition to the aforementioned traditional TGF- β 1 signal pathways, numerous additional routes exist.¹⁴⁸ Monocyte chemoattractant protein-1 promotes macrophage infiltration in the kidney, a problem seen in a number of kidney diseases. Macrophages release many factors that promote kidney disease progression.¹⁴⁹ By inhibiting the activation of NF- κ B, 1,25-(OH) $_2$ D $_3$ at the molecular level reduces the expressions of angiotensinogen and monocyte chemoattractant protein-1, as well as plasminogen activator inhibitor-1, which is generated by inflammation and high hyperglycemia.

VDR Reduces Proteinuria

Podocytes are essential for controlling the kidney's glomerular filtration rate. The glomerular filtration barrier, which keeps proteins and other big molecules from being filtered into the urine, is largely composed

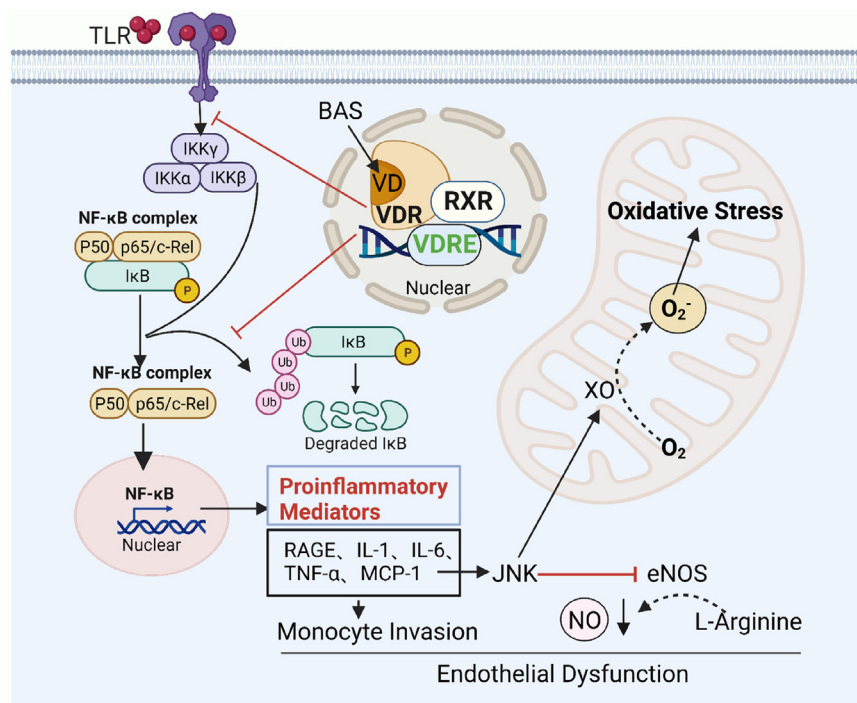


Figure 6. VDR regulates inflammation and oxidative stress. Ligand bound vitamin D receptor (VDR) activation suppresses gene expression of nuclear factor- κ B (NF- κ B) and tumor necrosis factor (TNF)- α receptors 2 and 4 (TNFRs). Among these proinflammatory cytokines, TNF- α activates the c-Jun N-terminal kinase (JNK) pathway that inhibits endothelial NO synthase activity, consequently resulting in reduction of nitric oxide (NO) bioavailability. In addition, the upregulated JNK pathway induces the formation of superoxide anion O_2^- from oxygen (O_2) through upregulating xanthine oxidase (XO) activity, which further impairs endothelial function via inducing oxidative stress in the cell. Furthermore, TNF- α bound TNFRs trigger the translocation of NF- κ B to the nucleus to promote the expression of pro-inflammatory mediators.

of the foot processes of podocytes. Strong evidence from Wang's work¹⁵⁰ suggests that vitamin D/VDR signaling in podocytes is essential for protecting the kidney from diabetic damage. In this work, DBA/2J mice that overexpress the human VDR were employed. Following streptozotocin-induced diabetes development, transgenic mice exhibited reduced levels of albuminuria in comparison to WT controls. A low dosage of the vitamin D analog doxercalciferol inhibited podocyte loss and death, decreased glomerular fibrosis, and avoided the development of albuminuria in transgenic mice. However, in WT mice, the same dosage of vitamin D had minimal impact on the development of DN. Furthermore, significant diabetes-related kidney damage was prevented in VDR-null mice by restoration of the mice using the human VDR transgene in podocytes.¹⁵¹

The Function of Membrane Receptor in the Kidney

The G-protein-coupled receptor, TGR5, abundantly expressed on eukaryotic cell membranes, serves as a highly prominent membrane receptor in the kidney. It exerts its cellular functions by binding to agonists such as hormones, neurotransmitters, or external stimuli upon activation. The activation of G-protein-coupled receptors subsequently triggers the activation of G proteins located on the cell membrane. These activated G proteins then bind to effector enzymes present on the cell membrane, leading to the generation of second messengers that initiate cytoplasmic cellular responses. Research has demonstrated that TGR5 plays a crucial role in kidney pathophysiology.

The Role of TGR5 in DN

TGR5 serves as a cell membrane receptor for BAs and belongs to the G-protein-coupled receptor family.^{11,152} It is composed of 7 transmembrane domains and facilitates the transmission of extracellular signals by interacting with a heterotrimeric G protein structure. In contrast to other BA receptors, TGR5 exhibits selectivity toward the structural characteristics of BAs, remaining unaffected by the derivation pattern and binding state of BAs. Different BAs can be ranked by how well they activate TGR5. Lithocholic acid is the most effective, followed by deoxycholic acid, CDCA, CA, and UDCA. The TGR5 receptor exhibits broad expression patterns in various human and animal tissues, including but not limited to the spleen, kidney, lung, liver, gallbladder, intestine, and skeletal muscle. In the kidney, TGR5 is highly expressed in tubular cells but also in glomerular cells including podocytes and mesangial cells.^{153,154} Possible mechanisms by which TGR5 activation is beneficial to the kidney

include increased mitochondrial oxidative phosphorylation, mitochondrial fatty acid β -oxidation and mitochondrial superoxide dismutase activity, inhibition of mitochondrial ROS production, and anti-inflammatory effects.

TGR5 Improves the Lesion of DN

On an HFD, TGR5 knockout mice gain weight. In standard rodent chow diet, TGR5 knockout mice do not exhibit any kidney disease phenotype and remain viable. In contrast to their male WT littermates or female TGR5 knockout mice, TGR5 knockout mice exhibited more obvious hepatic steatosis when subjected to an HFD or diabetes. When INT-777 or another TGR5 agonist, oleanolic acid, is administered to WT mice, it also increases fat burning and energy expenditure, which mitigates HFD-induced kidney impairment.¹⁵⁵

TGR5, a membrane sensor that is turned on by BAs, can directly control how podocytes work. In addition, activating TGR5 led to the release of ileac glucagon-like peptide-1,¹⁵⁶ which suggests that BAs might be useful as a treatment for DN. To treat diabetic db/db mice with the TGR5 agonist INT-777,^{152,157,158} proteinuria, glomerular mesangial expansion, glomerular podocyte damage, and the buildup of ECM proteins and macrophages were all greatly reduced.¹³ Consistently, Xiao *et al.*¹⁵⁹ revealed that activating TGR5 stopped the disease from getting worse by reducing inflammation through the NF- κ B pathway. Studies done in the laboratory also revealed that turning on TGR5 greatly reduced the levels of TGF- β 1 and fibronectin in HG-induced GMCs, both of which can help cause kidney fibrosis.^{153,154} Studies¹³ show that lowering the high levels of acetylation of SOD2 and isocitrate dehydrogenase 2 in mitochondria from db/db animals that had not been treated exhibited higher SIRT3 activity. Therefore, INT-777 increased SOD2 activity and decreased the production of H₂O₂ in mitochondria. This was connected to a decrease in H₂O₂ and thio-barbituric acid reactive chemicals in the urine. TGR5 activation leads to increased energy metabolism, mitochondrial biogenesis, and fatty acid oxidation in the kidneys by activating AMPK, SIRT1, PGC-1 α , ERR α , and SIRT3.¹³ This is in line with several studies in humans and animal models that link impaired mitochondrial function and oxidative phosphorylation to the development of type 2 diabetes.^{160,161} This stops oxidative stress and lipid buildup, firmly establishing TGR5's important role in preventing kidney disease in people with diabetes and obesity. Overall, TGR5 has a significant impact on controlling the formation and function of kidney mitochondria, the breakdown of fatty acids by beta-oxidation, the reduction of

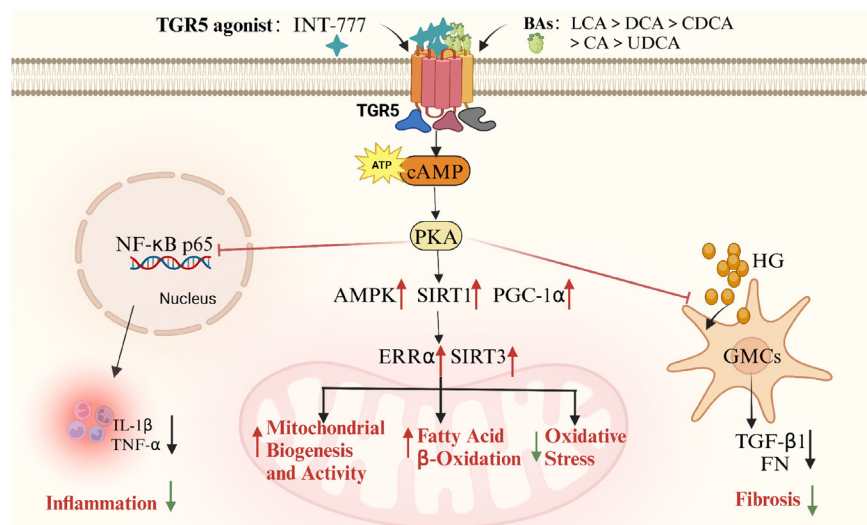


Figure 7. TGR5 regulates renal mitochondrial biogenesis, fatty acid β -oxidation and oxidative stress, alleviates renal inflammation and fibrosis. Activation of TGR5 by bile acids or TGR5 agonists leads to rapid intracellular cAMP production and activation of PKA, which affects downstream cellular events. TGR5 activation in inducing energy metabolism, mitochondrial biogenesis, and fatty acid oxidation in the kidney by activating AMPK, SIRT1, PGC-1 α , ERR α , and SIRT3, which lead to prevention of oxidative stress and lipid accumulation. TGR5 activation inhibits NF- κ B signaling pathway to reduce renal inflammation and inhibits HG-induced up-regulation of GMCs fibrosis markers, thereby alleviating fibrosis. Activation of TGR5 can regulate glycolipid metabolism through downstream cAMP and inhibit inflammatory response through PKA pathway. AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; cAMP, Cyclic adenosine monophosphate; ERR α , estrogen-related receptor alpha; GMCs, glomerular mesangial cell; HG, high glucose; PGC-1 α , peroxisome proliferators-activated receptor γ coactivator I alpha; PKA, protein kinase A; SIRT1, Silent information regulator 1; SIRT3, Silent information regulator 1; TGR5, G protein-coupled receptor.

oxidative stress, and the prevention of kidney inflammation and fibrosis (Figure 7).

CONCLUSION

Kidney diseases, particularly DN, are a major global health issue with increasing morbidity and mortality. DN is a microvascular complication, particularly prevalent in patients with diabetes, and significantly increases mortality rates. It poses a threat to public health, peripheral vascular disease, and cerebrovascular disease. BA receptors play a crucial role in renal pathophysiology, activating transcription factors for lipid, cholesterol, and glucose metabolism, as well as genes linked to inflammation and renal fibrosis. Advances in understanding kidney BA receptor biology and creating agonists have shown promising therapeutic potential for preventing DN and obesity-induced kidney damage.

Studies suggest that FXR, PXR, VDR, and TGR5 play a role in the pathogenesis of kidney disease (e.g., DN), suggesting that manipulating these receptors may offer new treatments. FXR activation reduces proteinuria, podocellular loss, mesangial dilation, fibrosis, and glomerular basement membrane thickening in patients with DN. PXR activation inhibits inflammation and liver fibrosis, plays a crucial role in cholesterol and lipid homeostasis, and shows promise in slowing DN progression. VDR activation has numerous positive

effects on RAS, inflammation, fibrosis, proteinuria, and lipid metabolism. TGR5 activation increases mitochondrial oxidative phosphorylation, fatty acid β oxidation, mitochondrial superoxide dismutase activity, inhibits mitochondrial ROS production, reduces proteinuria, and inhibits inflammation and liver fibrosis, making it an important target for DN treatment.

Nuclear hormone receptors have been understudied in the context of DN; however, ongoing clinical trials^{69,162,163} and animal research¹⁶⁴⁻¹⁶⁶ are exploring the development of drugs that specifically alter the activity of these receptors. This could lead to increased application of nuclear hormone receptors modification for DN treatment and prevention. TGR5 modulators, which release glucagon-like peptide-1 and impact metabolic pathways, are expected to be helpful in treating diabetes and obesity.¹⁶⁷⁻¹⁶⁹ The combined action of both FXR and TGR5 can reduce inflammation, lipid buildup, and fibrosis. Dual agonists such as INT-767, which activate both FXR and TGR5, can provide additional protective effects in the kidney and for injuries related to diabetes and obesity.^{12,61} BA receptors FXR and TGR5 are prominent subjects of investigation in translational and therapeutic studies related to metabolic illnesses. Understanding the effects of BA metabolism and their interactions could provide a solid foundation for understanding preclinical data.

DISCLOSURE

All the authors declared no conflict of interests.

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AUTHOR CONTRIBUTIONS

YYF and MJQ are the primary writers of this manuscript. QTZ, KLW, XH, and QY participated in the writing of this manuscript. XNS and GC designed and revised the whole manuscript and wrote the manuscript.

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