

ISN Forefronts Symposium 2015: Nuclear Receptors and Diabetic Nephropathy



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Diabetic nephropathy (DN) is the major reason for end-stage renal disease in the Western world. Patients with DN developed more severe cardiovascular complications with worse prognosis. In spite of tight blood pressure and glucose control through applying angiotensin II receptor antagonism, angiotensin receptor inhibitors, and even direct renin inhibitors, the progression and development of DN has continued to accelerate. Nuclear receptors are, with few exceptions, ligand-dependent transcription factors, some of which modulate genes involved in the transport and metabolism of carbohydrates or lipids, and in the modulation of inflammation. Considering the diverse biological functions of nuclear receptors, efforts have been made to explore their contributions to the pathogenesis of DN and their potential in therapeutic strategies. This review is mainly focused on the association between various nuclear receptors and the pathogenesis of DN, the potential beneficial effects of targeting these receptors for treating and preventing the progress of DN, and the important role that nuclear receptors may play in future therapeutic strategies for DN.

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There exists a global pandemic in diabetes mellitus.¹ Diabetic nephropathy (DN) develops in as many as 25% to 40% of diabetic patients after 25 years of uncontrolled and even treated diabetes. This makes DN the leading reason for the development of late-stage renal disease especially in the Western world² where it accounts for approximately 22% of patients starting dialysis in Denmark³ and 44% in the USA.⁴ DN is characterized clinically by the increased blood pressure, occurrence of albuminuria, and a continual decrease of kidney function,² and is associated with a remarkable increase in cardiovascular diseases⁵ and mortality.⁶ The annual mortality rate for patients with DN-induced renal disease is around 20%.⁷ During the last decade, there has been an 11-fold increase in spending for the treatment of patients with diabetes mellitus with concomitant DN and chronic kidney disease in the USA.⁸

The diffuse thickening of glomerular basement membrane together with nodular glomerulosclerosis is the major pathological feature of DN. During the initial

stage of diabetic kidney disease, most patients only present modest proteinuria that deteriorates as the disease progresses. More advanced DN leads to primary and secondary pathological changes in the tubulointerstitial and vascular compartments, which is harmful to the maintenance of renal function. In a proportion of patients with clinical symptoms of DN, additional primary renal diseases (e.g., IgA nephropathy and renal arterial disease) may result from the diabetes mellitus-driven pathological abnormalities. Although the pathophysiology of DN is mainly due to hyperglycemia, it is also related to the wider network involving local and systemic processes,^{9,10} some of which have been identified with cell and animal models, tissue samples, and human studies. For instance, in renal parenchymal cells, hyperglycemia induces abnormal activation of protein kinase C together with the increased expression of transforming growth factor β (TGF β), matrix proteins fibronectin and collagen type IV, the dysregulation of nitric oxide, endothelial dysfunction and activation of the nuclear factor kappa B, and mitogen-activated protein kinase signaling.^{10–12} In addition, hyperglycemia can result in the overproduction of advanced glycation end products and induce overexpression of TGF β .¹³ In spite of certain available treatments, the progression of DN continues to increase worldwide and thus novel therapeutic strategies are urgently needed.

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Nuclear receptors are transcription factors that play various roles in embryo development, maintenance of the differentiated cellular phenotype, and manipulation of cell metabolism and death. This review mainly discusses the association between the pathogenesis of DN and nuclear receptors, including peroxisome proliferator-activated receptors (PPARs) α (NR1C1), β/δ (NR1C2), and γ (NR1C3); farnesoid X receptor (FXR, NR1H4); liver X receptors (LXRs, NR1H2, NR1H3); vitamin D receptor (VDR, NR1H1); hepatocyte nuclear factor 4 α (HNF4 α , NR2A1); retinoid X receptors (RXR, NR1F1, NR1F2, NR1F3); retinoid acid receptors (NR1B1, NR1B2, NR1B3); estrogen receptor (ER, NR3A1); and mineralocorticoid receptor (MR, NR3C2). Several studies have suggested that activation or inhibition of specific receptors could prevent the progression of DN, which implies that targeting nuclear receptors may be a potential therapeutic strategy for DN.

Nuclear Receptors

PPAR

PPARs are ligand-activated transcriptional factors and include 3 related forms PPAR α , PPAR β/δ , and PPAR γ . Although they all have different tissue distributions, ligand selectivities, and biological effects, they play an important role in modulating lipid metabolism, adipogenesis, insulin sensitivity, inflammation, and blood pressure. Renal PPAR α and PPAR γ modulate energy utilization in the kidney by regulating fatty acid oxidation.¹⁴ Activated PPAR α can stimulate fatty acid β -oxidation that can reduce the lipid content of tissues and blood, prevent the accumulation of lipid, and ameliorate lipotoxicity.¹⁵ Several kinases, including protein kinase A, protein kinase C, mitogen-activated protein kinases, and adenosine monophosphate kinase, were shown to phosphorylate PPARs resulting in changes in DNA-binding activity, ligand affinity, recruitment of transcriptional cofactors, and proteasome degradation in both a ligand-dependent or -independent manner.¹⁶ Phosphorylation by adenosine monophosphate kinase leads to increased PPAR α and PPAR γ signaling and enhances renal function in a type 2 diabetes mouse model by removing lipid accumulation in the kidney.¹⁵ Furthermore, the activation of PPAR γ suppresses the renal expression of an α (1D)-adrenergic receptor that is overexpressed in the diabetic kidney.¹⁷

Chronic inflammation and oxidative stress play a pivotal role in the pathogenesis of chronic kidney disease. Activated PPAR α can prevent overexpression of proinflammatory molecules.¹⁸ It was shown that the ligand activation of PPAR α will increase the expression of fibroblast growth factor-21 (FGF-21), enhance the

phosphatidylinositol-3 kinase/protein kinase B (AKT)/glycogen synthase kinase 3 β (GSK-3 β)/Fyn-mediated nuclear factor (erythroid-derived 2)-like 2 signal, and prevent the development of DN.¹⁹ PPAR α activation improves lipotoxicity by activating adenosine monophosphate kinase-peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α)-estrogen-related receptor-1 α (ERR-1 α)-forkhead box O3a (FoxO3a) signaling and ameliorating glucose-induced matrix production and mesangial cell proliferation by inhibiting extracellular signal-regulated kinase 1/2 and phosphatidylinositol-3'-kinase/AKT activation, suggesting its potential for the treatment of DN.^{20,21} In the absence of PPAR α , the glomerular lesions displayed enhanced type IV collagen and TGF β levels in DN, indicating that PPAR α agonists can prevent glomerular matrix expansion together with apoptosis and the infiltration of inflammatory cells within the glomerulus.²² A recent study found that Huangkui capsule, an extract from *Abelmoschus manihot* (L.) medic, can ameliorate DN by increasing PPAR α /PPAR γ signaling leading to lowered endoplasmic reticulum (ER) stress in rats.²³ It was reported that fenofibrate, a PPAR α agonist, can dramatically decrease the excretion of urinary albumin and reduce mesangial matrix expansion and glomerular hypertrophy in the *db/db* diabetic mice model.²⁴ Fenofibrate also improved insulin resistance and glomerular lesions in *db/db* mice,²⁴ thus suggesting a renal protective role for fenofibrate in DN via the activation of PPAR α in mesangial cells. A Fenofibrate Intervention and Event Lowering in Diabetes study further suggested that the early use of fenofibrate may prevent or postpone the development of DN.²⁵

The protection provided by activated PPAR γ is partially mediated by downregulating the level of renal disintegrin and metalloprotease-17 (ADAM17) and angiotensin-converting enzyme-2 (ACE2) shedding.²⁶ Increased fibrosis in glomerular microenvironment is a remarkable characteristic of DN. Strong evidence suggests that PPAR γ plays an important role during the pathogenesis of glomerulosclerosis. Treatment with PPAR γ agonist ameliorated the hyperglycemia-mediated cannabinoid receptor type 1 (CB1R) signaling, inflammation, and glomerular fibrosis in diabetic animals.^{27,28} PPAR γ could prevent protein kinase A signaling, the activation of rat intraglomerular mesangial cells, TGF β -induced accumulation of p-cyclic-AMP-responsive element binding protein and collagen-IV.²⁹ PPAR γ also negatively regulates inflammation through binding to the *MIP3A* promoter and downregulating the expression of macrophage inflammatory protein-3 α (MIP-3 α), a pathogenic mediator playing a crucial role in inflammation of DN.³⁰ Other studies showed that PPAR γ provides renoprotective

action by negatively regulating the microsomal prostaglandin E synthase-1 (mPGES-1)/prostaglandin E₂/prostaglandin E₂ receptor 4 (EP4) pathway and restoring expression of the klotho axis in a PPAR γ -dependent manner.^{31,32} PPAR γ may enhance the function of the angiotensin II receptor blocker by downregulating thioredoxin-interacting protein.³³ PPAR γ activated by pigment epithelium-derived factor could suppress the expression of the receptor for advanced glycation end products and decrease the reactive oxygen species (ROS), which subsequently prevents advanced glycation end product-induced apoptotic cell death in podocytes.³⁴ Many studies were performed to separate the insulin sensitizing effects of PPAR γ agonists from the transcriptional activation of genes that result in untoward side effects. This was achieved to some degree by using partial agonists that, compared with a full agonist, only partially activated the transcription of select genes.³⁵

Among patients with type 2 diabetes, the polymorphism within PPAR γ 2 (Pro12Ala) provides protection against nephropathy progression and deterioration of renal function, independent of major confounders.³⁶ However, the PPAR γ 2 (Pro12Ala) polymorphism may not be associated with the progression of DN in patients with type 1 diabetes.³⁷ A meta-analysis showed that the PPAR γ (Pro/Pro) genotype presented close association with DN risk in Caucasians, but the Ala/Ala genotype and Ala allele did not.³⁸ Conversely, another meta-analysis indicated that the polymorphism in PPAR γ (Pro12Ala) gene has no relationship with DN risk in Asians.³⁹ The rs1801282 C>G variant in PPAR γ was closely associated with decreased DN risk.⁴⁰ However, further studies revealed that the PPAR γ 2 Ala12 variant provided renal protection by reducing the occurrence of albuminuria among patients with type 2 diabetes.^{41,42}

PPAR β/δ agonist treatment inhibited glomerular mesangial expansion, albuminuria, and the accumulation of type IV collagen with no effect on blood glucose levels in streptozotocin-treated diabetic mice.⁴³ The activation of PPAR β/δ is necessary for treating DN by preventing inflammation and activating of its downstream receptor for advanced glycation end product or nuclear factor kappa B signals.^{43,44} PPAR β/δ agonist could postpone diabetes-induced nephrin loss, enhance podocyte integrity, and prevent albuminuria subsequently.⁴⁵

LXR

LXRs were first identified as orphan receptors when discovered, and then subsequently found to be targets of oxysterol metabolites of cholesterol.⁴⁶ LXRs include LXR α and LXR β that have different tissue distribution patterns, but have been most extensively studied in the liver. LXRs might have a role in regulating lipid metabolism and

maintaining the function of proximal tubule as well as podocytes by downregulating the expression of nephrin.⁴⁷ The administration of the LXR agonist T0901317 could increase cholesterol efflux via activating the ATP-binding cassette transporter A1 (ABCA1) in cultured glomerular mesangial cells, and enhance the expression of stearoyl-CoA desaturase-1 through increasing the level of sterol regulatory element-binding protein 1c (SREBP-1c) within proximal tubules.^{48,49} LXR α /SREBP-1 signaling also has the capability of regulating the expression of many genes involved in fatty acid and triglyceride synthesis.⁵⁰ Ne-(carboxymethyl) lysine, a member of the advanced glycation end product family, modulates cholesterol metabolism through stimulating LXR and SREBP-2, which resulted in a reduction in ABCA1-mediated cholesterol efflux and the accumulation of lipid in human kidney-2 (HK-2) cells.⁵¹ Bilirubin improved dyslipidemia and renal dysfunction via suppressing the expression of LXR α and SREBP-1 and decreasing ROS.⁵² Furthermore, the activation of LXR may prevent inflammation and the development of DN.^{46,53} T0901317 could prevent the development of albuminuria, glomerular mesangial expansion, and interstitial fibrosis by decreasing osteopontin level, macrophage infiltration, and expression of inflammatory genes, such as monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor α (TNF α), and TGF β , in the diabetic kidney.⁴⁶ Knockdown of LXR α expression resulted in loss of the anti-inflammatory effect of anthocyanins, and further studies demonstrated that LXR α might participate in the anthocyanin-induced action of decreasing intercellular adhesion molecule 1, MCP1, and TGF β 1 via inhibiting the nuclear translocation of nuclear factor kappa B protein.⁵⁴ Expression of LXR α in macrophage of transgenic mice markedly ameliorated hyperlipidemic-hyperglycemic nephropathy by suppressing glycated or acetylated low-density lipoprotein-induced cytokines and ROS in macrophages.⁵⁵ Recently, accelerated mesangial matrix expansion and glomerular lipid accumulation were observed in *Lxra/Lxrb*-null diabetic mice, in coupling with the enrichment of oxidative stress and inflammatory markers. Moreover, treatment with a synthetic oxysterol, *N,N*-dimethyl-3beta-hydroxycholesterol, an LXR agonist, dramatically ameliorated the excretion of albumin and nephrin, the levels of glomerular lipids and plasma triacylglycerol and cholesterol. In addition, the decreased level of kidney inflammatory and oxidative stress markers was observed upon *N,N*-dimethyl-3beta-hydroxycholesterol treatment.⁴⁷ Together, these results indicate that the activity of LXR is necessary for both normal and diabetic kidney.

FXR

FXR was first thought to be an orphan receptor when discovered. However, further studies revealed that

bile acid-induced activation of FXR is important for bile-acid synthesis and transport in the liver and intestine.^{56–58} Endogenous ligands for FXR include the primary bile acids, taurocholic acid, chenodeoxycholic acid, and cholic acid. FXR is expressed at highest levels in the liver and intestine, and at lower levels in adrenal gland and other tissues; it is also highly expressed in the kidney.⁵⁹ It also plays a pivotal role in lipid, glucose, and bile acid homeostasis in the enterohepatic system.^{60,61} Furthermore, FXR agonists may provide protection against liver fibrosis.^{62,63} FXR agonists downregulate renal overexpression of SREBP-1 that could lead to lipid accumulation during the development of nephropathy and regulating renal lipid metabolism. The activation of FXR could prevent the induction of profibrotic growth factors, proinflammatory cytokines, and oxidative stress-related enzymes in the kidney, and thus improve glomerulosclerosis and proteinuria.⁶⁴ Furthermore, the activation of FXR could suppress the development of nephropathy in type 1 diabetes via blocking diabetes-induced dysregulation of lipid metabolism, fibrosis, inflammation, and oxidative stress in the kidney.⁶⁵ Recently, the adipocytokine visfatin was found to have a crucial role in the development of DN, at least partly, through enhancing high glucose-induced human mesangial cell inflammation, fibrosis, and proliferation in the absence of FXR.⁶⁶

VDR

Vitamin D is necessary for the metabolism of calcium and bone. It was reported that vitamin D deficiency was closely associated with increased risk for diabetes development, diabetes complications, and cardiovascular disease.⁶⁷ A meta-analysis including 5 observational studies suggested that children treated with vitamin D are less likely to develop type 1 diabetes mellitus.⁶⁸ The fact that the lack of vitamin D impairs insulin synthesis and secretion suggested its close association with the pathogenesis of type 2 diabetes, although the mechanistic link has not been well established.⁶⁹

The protective activities of VDR may result from the inhibition of the renin-angiotensin system, reduction of proteinuria, and regulation of cell proliferation and differentiation. A recent study suggested that vitamin D and its receptor might modulate the progression of DN via regulating the TGF β levels, the expression of angiotensinogen, and apoptosis of podocytes through the nuclear factor kappa B pathway.⁷⁰ Activated macrophages 1 (M1) and activated macrophages 2 (M2) have opposing roles in inflammation. M1 activation was inhibited by 1,25-dihydroxyvitamin D₃, a VDR agonist, while M2 was activated.⁷¹ Another study reported that vitamin D can switch the M1 phenotype to M2 via activating the VDR-PPAR γ pathway.⁷² Diabetic

Vdr null mice developed more severe nephropathy than wild-type mice as renin-angiotensin system activation was enhanced, suggesting that VDR protects the kidney from hyperglycemia-induced injury through inhibiting renin-angiotensin system activity.⁷³ These data indicated that the combination of renin-angiotensin system inhibitors and a VDR activator might be of value to improve DN-induced albuminuria.⁷⁴ A randomized clinical trial revealed that daily treatment of paricalcitol, a selective VDR agonist, could ameliorate residual albuminuria in ACE inhibitor (ACEI)- or angiotensin II type 1 receptor blockade (ARB)-treated DN patients, especially in those with high dietary sodium intake. These data suggested that the combination of paricalcitol and ACEI or ARBs could effectively reduce residual albuminuria, which may be applied as a new strategy in the treatment of DN.⁷⁵ Wnt/ β -catenin signal-related epithelial-mesenchymal transition was reportedly involved in the pathogenesis of DN.⁷⁶ A recent study documented that VDR could decrease the expression of β -catenin by replacing β -catenin complexing with transcription factor 4 (TCF-4), therefore blocking Wnt/ β -catenin signaling.⁷⁷

Podocyte injury is one of the causes of DN.⁷⁸ VDR activation in podocytes plays an important role in preventing the kidney from diabetic damage.⁷⁹ Calcitriol or a vitamin D analog can improve podocyte damage by inhibiting the expression of transient receptor potential cation channel, subfamily C, member 6 (TRPC6) during the early stage of DN in a rat model.⁷⁸ 1,25-D₃ treatment ameliorated proteinuria in 25-hydroxy-1 α -hydroxylase conventional knockout mice coupled with increasing heparanase expression, suggesting that vitamin D mediated the emergence of proteinuria by reducing heparanase levels in podocytes.⁸⁰ Furthermore, vitamin D analogs provide protection against lesion of renal barrier by maintaining and reactivating the expression of podocalyxin, a specialized component of podocytes.⁸¹

The anti-inflammatory action of vitamin D is due to its influence on the crosstalk between signal transducer and activator of transcription 5 and VDR.⁸² A functional polymorphism of the *VDR* gene may result in individual susceptibility to DN, and a meta-analysis suggested the correlation of a FokI single-nucleotide polymorphism with DN susceptibility in Caucasians.⁸³ Another study showed that a BsmI single-nucleotide polymorphism polymorphism in Han Chinese people was responsible for the type 2 diabetes-related albuminuria.⁸⁴

MR

MR regulates the reabsorption of sodium and water and secretion of potassium via control of the epithelial ion channel. The representative agonist and antagonist of

MR are respectively aldosterone and spironolactone. However, mineralocorticoids could not only regulate the transport of epithelial salt, extracellular volume, and blood pressure, but also inflammation and fibrosis either directly or indirectly. Emerging evidence indicates that aldosterone participates in the pathogenesis of kidney disease in a nonepithelial MR-dependent manner.⁸⁵ Some studies also reported that aldosterone impairs insulin sensitivity through MR activation in adipocytes *in vitro*, which indicates that aldosterone may play an important role in the development of diabetes.^{86,87} Interestingly, leptin, which is upregulated in diabetic obese models, stimulates aldosterone production *in vitro* in human adrenocortical cells and *in vivo* in mice. In addition, aldosterone increases fibrosis by upregulating the production of TGF β 1, ROS, plasminogen activator inhibitor 1 (PAI-1), and the enrichment of collagen protein, which can be blocked by MR antagonist.⁸⁸ Integrin β 1 and β 3 expression in podocytes is essential to the integrity of a glomerular structure. In a high glucose environment, the expression of integrin β 1 in cultured podocytes is markedly decreased, accompanied with an increase of integrin β 3, and a recent study suggested that spironolactone inhibited cell motility and stabilized podocytes cultured in a high glucose environment, in part by normalizing the level of integrin β 1 and β 3.⁸⁹ Treatment with spironolactone provides protection for podocytes and inhibits the development of morphological changes associated with DN, probably by the inhibition of TGF β 1 mRNA expression.⁹⁰ Spironolactone could inhibit MR-induced ROS production and hyperglycemia-mediated podocyte lesions in diabetics.⁹¹ Recent studies revealed a crucial role for aldosterone in the pathogenesis of DN, which has no effect on angiotensin II and blood pressure levels.⁹² Another study enrolling type 2 diabetic patients also demonstrated that patients who developed aldosterone escape, an increase in aldosterone levels during long-term treatment of ACEIs, suffered more severe albuminuria than did patients without aldosterone escape. However, in combination with spironolactone treatment a further decrease in albuminuria was noted in these patients.⁹² Furthermore, the incidence of severe hyperkalemia, which is the major side effect of spironolactone treatment in clinical trials, is low, probably resulting from the monitoring of dietary intake of potassium and diuretics in clinical observation. However, the liberalized usage of spironolactone is strictly forbidden for patients whose kidney function was reduced.⁹² It was suggested that alterations of Na/K ATPase levels might be a new pathophysiological feature for DN. The ability of aldosterone antagonists to decrease Na/K ATPase protein levels and enzyme

mislocation that are increased in diabetes may suggest a new pharmaceutical use in the treatment of DN.⁹³

Other Nuclear Receptors

The sex hormone estrogen has several functions including control of bone growth, modulation of differentiation and function of the reproductive tract, and memory storage.^{94,95} Estrogen exerts its biological activity through the interaction with classic estrogen receptors, ER α and ER β .⁹⁶ It is generally known that females have a lower chance of suffering from nondiabetic chronic kidney disease than males.^{97–100} Although the contribution of gender to the progression of type 1 or type 2 diabetic renal disease is still uncertain,^{100,101} some studies suggested that DN even progresses faster in males than females.^{102–108} However, other results indicated an acceleration of disease progression in females,^{109–112} whereas some studies reported no difference between men and women.^{113–115} Because ER β can regulate cell apoptosis and cycle in tumor cells¹¹⁶ and ER β protein expression is increased in podocytes treated with estrogen,¹¹⁷ estrogens could protect against podocytes apoptosis.¹¹⁷ The fact that podocytes isolated from estrogen-treated diabetic mice showed an increase in the level of AKT phosphorylation indicates that estrogen may achieve such an effect by activating the phosphatidylinositol-3'-kinase-AKT axis.¹¹⁷ The increased ER β protein level in podocytes could manipulate the cell cycle and increase cell survival rates, suggesting that estrogen has the capability of preventing podocyte loss during diabetes-mediated kidney disease.¹¹⁷ Several lines of evidence revealed that TGF β promotes diabetic kidney disease, at least partly through inducing cell apoptosis and podocyte clearance.^{118–121} Relevant data showed that E2 treatment provides protection for podocytes against TGF β or (TNF α)-induced apoptosis *in vitro*. Other studies suggested that treatment with E₂ could be helpful to prevent albuminuria, glomerulosclerosis, and tubulointerstitial fibrosis in the initial stages of diabetes.^{122–124} However, some studies did not support the protective effects of estrogens for the patients with diabetic kidney. A recent study found that elevated serum concentrations of phytoestrogens are positively correlated with the severity of diabetic renal disease, suggesting the potential harmful effect of phytoestrogens.¹²⁵

Retinoic acid is the active metabolite of vitamin A, which plays a pivotal role in many physiological processes including but not limited to energy metabolism. Retinoic acid can facilitate the formation of retinoic acid receptor/RXR heterodimers or RXR/RXR homodimers, which could bind to the retinoic acid response element upstream of retinoic acid target gene promoters and modulate their transcription in the presence of specific

ligands.^{126,127} PPARs or other nuclear receptors can also form heterodimers with RXR, and modulate the biological function of several hormones and drugs.^{128,129} For example, the RXR α :RXR α homodimer and RXR α :PPAR γ are needed to recruit their coactivators to initiate the transcription of target genes¹³⁰ through binding to their response elements.¹³¹ Considering that PPAR γ is a key target in the treatment of DN, RXR α targeting may become a new treatment strategy. Furthermore, RXRs can be used as permissive heterodimers with LXR, FXR, PXR, and constitutive androstane receptor (CAR), or as nonpermissive heterodimer interacting with VDR,

and as conditional heterodimers together with retinoid acid receptor or thyroid receptor (TR).¹³² On the other hand, because of the nature of its partners, the activation state of RXR changes in different heterodimers.¹³³ Three RXR subtypes were identified as RXR α , RXR β , and RXR γ .^{134,135} As compared with the universal distribution of RXR α and RXR β , RXR γ is only detected in some specific tissues.¹³⁶ RXR α also showed antioxidants properties and played an important role in the pathogenesis of diabetic retinopathy.¹³⁷ RXR γ encoded by *RXRG* gene was also involved in the pathogenesis of DN.¹³⁸

Table 1. Systematic and renal effects of nuclear hormone receptor activation in the context of diabetic nephropathy

Nuclear hormone receptor	Affected genes, proteins, and processes	Agonists	Outcomes of receptor activation	Mechanism of action
PPAR α ^{14,15,19–21} (highly expressed in proximal tubule epithelium and medullary thick ascending limbs, with lower levels in glomerular mesangial cells)	Fatty acid oxidation, NF κ B, FGF21, PI3K/Akt/GSK-3 β /Fyn-Nrf2 signaling, AMPK-PGC-1 α -ERR-1 α -FoxO3a signaling, PI3K/AKT, and ERK1/2 signaling	Fibrates	↓ Mesangial expansion, ↓ matrix production, ↓ proteinuria	Systemic: ↓ insulin resistance, ↓ lipid, ↓ hypertension Renal: anti-inflammatory, antifibrotic, antiapoptotic properties
PPAR γ ^{14,15,26,27,29–34} (primarily expressed in the epithelium of distal medullary collecting ducts and to a lesser extent in the glomerular mesangial cells, endothelial cells and podocytes, proximal tubular cells, endothelial cells of renal microvasculature, and interstitial fibroblast cells)	Renal disintegrin, metalloprotease-17, angiotensin-converting enzyme-2, CB1R signaling, protein kinase A, pCREB, collagen-IV, MIP-3 α , mPGES-1/PGE2/EP4 pathway, klotho axis, thioredoxin-interacting protein, RAGE, ROS	Glitazones	↓ Proteinuria; ↓ glomerulosclerosis, ↓ tubulointerstitial fibrosis	Systemic: ↓ insulin resistance, ↓ lipid, ↓ hypertension Renal: anti-inflammatory, antifibrotic, antioxidative, antiapoptotic properties
PPAR δ ^{14,17,43,44} (highly expressed in medullary interstitial and stromal cells)	α (1D)-adrenergic receptor, collagen-IV, RAGE, NF κ B	GW0742	↓ Proteinuria, ↓ mesangial expansion, ↓ tubulointerstitial fibrosis	Renal: anti-inflammatory, antifibrotic
LXR ^{46,48–50,53,55} (expressed in all major renal cells including mesangial cells, endothelial cells, and podocytes)	ABCA1, SREBP-1c, OPN, MCP-1, TNF α , TGF β , ROS	TO901317	↓ Proteinuria, ↓ mesangial expansion, ↓ tubulointerstitial fibrosis, ↓ macrophage infiltration in kidney	Systemic: ↓ lipid Renal: anti-inflammatory, antifibrotic, antioxidative
FXR ^{56–58,64–66} (expressed in isolated glomeruli and proximal tubules, cultured mesangial cells, and podocytes)	SREBP-1, visfatin	Chenodeoxycholic acid, cholic acid	↓ Proteinuria, ↓ glomerulosclerosis, ↓ mesangial cell inflammation, ↓ mesangial expansion, ↓ tubulointerstitial fibrosis	Systemic: ↓ lipid Renal: anti-inflammatory, antifibrotic, antioxidative
VDR ^{69,70,72,73,78,80–82,154–156} (expressed in the proximal and distal tubular epithelial cells, glomerular parietal epithelial cells, collecting duct cells and cultured podocytes, and mesangial cells)	VDR-PPAR γ pathway, TRPC6, heparanase, podocalyxin, STAT5, TGF β , angiotensinogen, NF- κ B	1,25-Dihydroxyvitamin D3, calcitriol	↓ Proteinuria, ↓ glomerulosclerosis, ↓ macrophage infiltration in kidney	Systemic: ↓ insulin resistance, ↓ RAS Renal: anti-inflammatory, antifibrotic, antiapoptotic
MR ^{85–93} (expressed in the orical collecting duct cells of distal nephrons)	TGF β 1, ROS, PAI-1, collagen, integrin β 1, integrin β 3, NKA, ROS	Aldosterone	↑ Proteinuria, ↓ glomerular structural integrity	Systemic: ↑ hypertension, ↑ insulin resistance Renal: inflammation, ↑ fibrosis, ↑ oxidation
Estrogen receptors α and β ^{117,122–124,157–159} (expressed in glomeruli, isolated mesangial cells and podocytes)	PI3K-AKT signaling, TGF β , TNF α	Estrogen	↑ Glomerular structural integrity, ↓ proteinuria, ↓ glomerulosclerosis, ↓ tubulointerstitial fibrosis	Renal: anti-inflammatory, antifibrotic, antiapoptotic properties
RXR ^{131,137} (distribution unknown in kidney)	PPAR, LXR, FXR, VDR	Magnolol	NA	Renal: antioxidative
HNF4 α ^{142–144} (distribution unknown in kidney)	STIM1	NA	↓ Glomerulosclerosis	Renal: antifibrotic

ABCA1, ATP-binding cassette transporter A1; AKT, protein kinase B; AMPK, adenosine monophosphate kinase; CB1R, cannabinoid receptor type 1; ERK, extracellular signal-regulated kinase; ERR, estrogen-related receptor; FGF, fibroblast growth factor; FoxO3, forkhead box O3; FXR, farnesoid X receptor; GSK, glycogen synthase kinase 3 β ; LXR, liver X receptor; MIP, macrophage inflammatory protein; NA, not available; Nrf2, nuclear factor (erythroid-derived 2)-like 2; NKA, Na/K ATPase; NF- κ B, nuclear factor κ B; OPN, osteopontin; pCREB, p-cyclic-AMP-responsive element binding protein; PGC-1 α , peroxisome proliferator-activated receptor γ coactivator-1 α ; PI3K, phosphatidylinositol-3'-kinase; PPAR, peroxisome proliferator-activated receptors; RAGE, receptor for advanced glycation end products; RAS, renin-angiotensin system; ROS, reactive oxygen species; SREBP-1c, sterol regulatory element-binding protein 1c; STAT5, signal transducer and activator of transcription 5; STIM1, stromal interacting molecule-1; TGF β , transforming growth factor β ; TNF α , tumor necrosis factor- α ; TRPC6, transient receptor potential cation channel, subfamily C, member 6; VDR, vitamin D receptor.

Orphan Receptors

HNF4 α is expressed at high levels in the liver, kidney, and intestine, and controls the expression of a large gene set including those involved in glucose and fatty acid metabolism, urea biosynthesis, cholesterol metabolism, blood coagulation, hepatitis B virus infection, and hepatocyte differentiation.¹³⁹ Dysfunction of HNF4 α can lead to metabolic disease. Notably, genetic mutations in HNF4 α result in maturity-onset diabetes of the young-1.¹⁴⁰ The expression of the HNF4 α gene is significantly decreased in the kidney and liver in 2 diabetic rodent models.¹⁴¹ Additionally, HNF4 α is decreased in kidneys of patients with DN. HNF4 α negatively regulates the transcription of stromal interacting molecule-1, which is increased in a high glucose environment in mesangial cells.¹⁴² Blockage of HNF4 α in mesangial cells might be a candidate therapeutic strategy for DN, as the stromal interacting molecule-1-gated store-operated Ca(2+) entry pathway in mesangial cells was recently found to be antifibrotic.^{142–144}

HNF1 α is a homeodomain-containing transcription factor that plays an important role for modulating different metabolic functions in the liver, pancreatic islet, kidney, and intestine.¹⁴⁵ Maturity-onset diabetes of the young-3 result from rare mutations in *HNF1A*.^{146,147} Although genetic variants in HNF1 β are not a major cause of maturity-onset diabetes of the young or DN, they might lead to the manifestation of disease in Chinese.¹⁴⁸

Conclusion

The systematic and renal effects of nuclear hormone receptor activation in the context of diabetic nephropathy are shown in Table 1. Among the highlights, the fibrates class of PPAR α agonists have long been prescribed to reduce triglyceride (TG), increase high-density lipoprotein-C (HDL-C), and improve cardiovascular outcomes in diabetic patients,^{149,150} mainly by activating the expression of genes involved in lipid homeostasis.¹⁵¹ PPAR α agonists also have the ability to improve renal lesion in DN animal models; however, whether a similar efficacy is also observed in diabetic patients remains to be determined.¹⁵² The VDR agonist calcitriol might ameliorate albuminuria by reducing urinary angiotensinogen levels.⁸⁰ Furthermore, a combination treatment of mineralocorticoid receptor blockers with ACEI or ARB therapy has recently emerged, but the long-term efficacy and safety of such treatment has not been established.¹⁵³ Although only a few nuclear receptors were evaluated as potential targets for the treatment of DN, clinical trials and animal studies have put more focus into the function of nuclear hormone receptors for protection against kidney disease. Identifying the mechanism by which activation of nuclear hormone receptors

modulate kidney disease and determining their roles in the pathogenesis of DN, and the ultimate application of nuclear receptor targeting as a therapeutic strategy require considerably more experimentation.

DISCLOSURE

All the authors declared no competing interests.

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