Genes Nutr (2012) 7:483–498
DOI 10.1007/s12263-012-0295-5

REVIEW

The role of nuclear receptors in the kidney in obesity and metabolic syndrome

Claudia Tovar-Palacio · Nimbe Torres · Andrea Diaz-Villaseñor · Armando R. Tovar

Received: 13 February 2012 / Accepted: 2 April 2012 / Published online: 25 April 2012

Abstract Nuclear receptors are ligand-activated transcriptional regulators of several key aspects of renal physiology and pathophysiology. As such, nuclear receptors control a large variety of metabolic processes, including kidney lipid metabolism, drug clearance, inflammation, fibrosis, cell differentiation, and oxidative stress. Derangement of nuclear receptor regulation, that is, mainly due to obesity may induce metabolic syndrome, may contribute to the pathogenesis and progression of chronic renal disease and may result in end-stage renal disease. This places nuclear receptors at the forefront of novel therapeutic approaches for a broad range of kidney disorders and diseases, including glomerulosclerosis, tubulointerstitial disease, renal lipotoxicity, kidney fibrosis, and hypertension. This review focuses on the importance of the transcription factors peroxisome proliferator-activated receptor alpha, peroxisome proliferator-activated receptor beta, peroxisome proliferator-activated receptor gamma, liver X receptors, farnesoid X receptor, and the pregnane X receptor/steroid and xenobiotic receptor (PXR) on the physiology and pathophysiology of renal diseases associated with obesity and metabolic syndrome.

C. Tovar-Palacio (✉)
Department of Nephrology and Mineral Metabolism, National Medical Science and Nutrition Institute, Salvador Zubirán, Vasco de Quiroga No. 15, Tlalpan, 14000 Mexico, D.F., Mexico
e-mail: tovarpal@gmail.com

N. Torres · A. Diaz-Villaseñor · A. R. Tovar
Department of Nutrition Physiology, National Medical Science and Nutrition Institute, Salvador Zubirán, Vasco de Quiroga No. 15, Tlalpan, 14000 Mexico, D.F., Mexico

Keywords Kidney · Nuclear receptors · Obesity · Metabolic syndrome

The role of nuclear receptors in kidney disease

Due to the consumption of a Western-style diet and a sedentary lifestyle, obesity is rapidly becoming the most important health problem challenging developed and non-developed countries. Although obesity is often associated with diabetes and hypertension, which are the two most common risk factors for the development of end-stage renal disease, obesity has been suggested as an independent risk factor for the development of chronic kidney disease (Praga and Morales 2006; Rutkowski et al. 2006; Wahba and Mak 2007; Wang et al. 2008). Early in the course of obesity, structural and functional changes similar to diabetic kidney disease occur (Henegar et al. 2001). These changes, considered to be precursors to more severe renal injury, include glomerular hyperfiltration, glomerular basement membrane thickening, mesangial cell proliferation, mesangial matrix thickening, and expansion of the Bowman's capsule. Morbid obesity has been associated with the eventual development of focal and segmental glomerulosclerosis even in the absence of diabetes (Kambham et al. 2001; Praga 2002). Studies in humans and in animal models have reported that accumulation of lipids in the kidney has been shown to promote renal disease (Kimmelstiel and Wilson 1936; Wilens and Elster 1950; Proctor et al. 2006; Jiang et al. 2005; Tovar-Palacio et al. 2011). Heavy glomerular proteinuria (nephritic syndrome) is associated with hyperlipidemia, lipiduria, and progressive kidney disease. Glomerular and tubular epithelial cells in the nephritic kidney are exposed to large quantities of lipids bound to filtered proteins, the uptake of which raises cellular lipids.

Cellular lipid homeostasis is regulated by the influx, synthesis, and efflux of lipids (Kim et al. 2009). The accumulation of triglycerides and cholesterol in the kidney is mediated by increased expression and activity of the transcriptional factors sterol regulatory element–binding proteins 1 and 2 (SREBP-1 and SREBP-2), which are regulators of fatty acid and cholesterol synthesis. Additionally, these alterations are accompanied by renal mesangial expansion, accumulation of extracellular matrix proteins, and activation of oxidative stress, pro-inflammatory cytokines, and profibrotic growth factors that mediate increases in fatty acid and cholesterol synthesis (Jiang et al. 2005).

Although they are poorly understood in the setting of altered metabolic conditions in obesity, several hormonal and metabolic factors have been shown to contribute to the pathogenesis of obesity-related renal disease, including oxidative stress, angiotensin II, inflammatory cytokines, and hyperinsulinemia/insulin resistance. In addition, it has also been proposed that nuclear receptors, which are master regulators of lipid and carbohydrate metabolism, play an important pathogenic role as regulators of renal lipid accumulation. Nuclear receptors and their target genes and coregulators have been shown to play a crucial role in the development of alterations in normal kidney physiology (Levi et al. 2011). Nuclear receptors are transcription factors that play an important role in regulating gene expression (Francis et al. 2003) and are members of a large superfamily of evolutionarily related DNA-binding transcription factors that control programs involved in a broad spectrum of physiological phenomena (Germain et al. 2006). From the phylogeny study of nuclear receptors, it has been established that they emerged in the earliest of metazoan evolution, long before the divergence of vertebrates and invertebrates (Escriva et al. 1997; Owen and Zelent 2000) (Table 1).

Historically, the most studied nuclear receptors have been those for steroid hormones, particularly for estrogens, androgens, progesterone, glucocorticoids, and mineralocorticoids. These receptors, typically bind with high affinity (Kd in the nanomolar range) and high specificity to their specific ligands and form homodimers that interact with the DNA to activate the expression of specific genes (Chawla et al. 2001; Francis et al. 2003). However, attention has turned to several nuclear receptors whose endogenous ligands, target genes, and physiological functions are not known. Hence, traditionally, they are known as "orphan receptors" (Chawla et al. 2001). In contrast with the classic steroid receptors, the orphan receptors bind their ligands with a lower affinity (Kd in the micromolar range) and have a broader repertoire of ligands. However, once a natural ligand has been discovered for an orphan nuclear receptor, the receptor is no longer considered to be an orphan. During the last years, endogenous ligands for several of the orphan receptors have been discovered, and they are classified as adopted orphan nuclear receptors (Table 1). However, there are some orphan nuclear receptors whose ligands are still unknown. Thus, several of the adopted orphan nuclear receptors are considered as natural sensors, since they are capable to bind a large diversity of ligands, most of them are essential biomolecules. Changes in the concentration of these metabolites are signals to promote metabolic changes that are sensed by the nuclear receptors to trigger modifications in the rate of transcription of specific genes with the final goal to maintain homeostasis.

At present, 48 genes in humans (Benoit et al. 2006) are known to belong to the family of nuclear receptors, and there is a notable structural similarity among them (Fig. 1) (Germain et al. 2006; Ruan et al. 2005). Nuclear receptors have a common structure consisting of the following domains: (1) an NH_2-terminal ligand-independent activation domain, called AF-1, for interaction with cofactors (A/B domain); (2) a central DNA-binding domain, which consists of two zinc finger motifs and allows binding to distinct recognition sites of the DNA known as hormone response elements (DBD or C domain); (3) a hinge region (D domain); and (4) a C-terminal ligand-binding domain (LBD), which is unique to each nuclear receptor and allows for distinct binding, receptor dimerization, and coregulator interactions (E/F domain) (Wagner et al. 2011; Sonoda et al. 2008).

After the nuclear receptors bind with their specific ligands, they bind to certain regions of the genome that are known as DNA-response elements that regulate the rate of transcription of many genes (Table 2) (Rosenfeld and Glass 2001; Cortes et al. 2005). Nuclear receptors interact with the corresponding response elements to form homodimers or heterodimers. They use several partners, but mainly use the 9-cis-retinoic acid receptor (RXR). Binding of dimerized nuclear receptors to specific response elements can promote and/or enhance transcription (Germain et al. 2006). Because of the essential roles nuclear receptors play in virtually all aspects of mammalian development, metabolism, and physiology, a dysfunction of signaling controlled by these receptors is associated with reproductive, proliferative, and metabolic diseases (Table 1) (Germain et al. 2006). Additionally, nuclear receptors can recruit several proteins known as coregulators, which determine the function of a specific nuclear receptor (Table 2) (Ruan et al. 2005; Francis et al. 2003). The protein level of the coregulator is crucial for driving transcription that is mediated by nuclear receptors. Several coregulators are activated or repressed by various intracellular signaling pathways and posttranslational modifications (Ruan et al. 2005). Because coregulator levels in cells are normally tightly regulated, a small change in their

Table 1 Metabolic nuclear receptors in the kidney: natural and synthetic ligands, and main functions

Name	Abbreviation	Nuclear receptor nomenclature	Natural ligand	Synthetic ligands	Function	References
Peroxisome proliferators activated receptor α	PPARα	NR1C1	Fatty acids, leukotrienes B4	Pterostilbene, MK-0767, GW2331, GW7647, GW9578, imiglitazar, NS-220, farglitazar, reglitazar, DRF 2519, bezafibrate, GW409544, LY-518674, TZD18, LY-510929, LY-465608, pirinixic acid, regaglitazar, AD-5061, fenofibric acid, clofibrate	PPARα is a global regulator of fatty acid catabolism. PPARα target genes function together to coordinate the complex metabolic changes necessary to conserve energy during fasting and feeding	Michalik et al. (2006), Chawla et al. (2001), Ruan et al. (2005), Moore et al. (2006)
Peroxisome proliferators activated receptor δ	PPARδ	NR1C2	Fatty acids	L-783483, GW-501516; L-796449, L-165461, L-165041, GW2433, GW9578, GW0742X	PPARδ ligands suggest a role in lipid metabolism	Michalik et al. (2006), Chawla et al. (2001), Ruan et al. (2005), Moore et al. (2006)
Peroxisome proliferators activated receptor γ	PPARγ	NR1C3	15-deoxy-Δ-prostaglandin J2 and a variety of long-chain fatty acids and oxidized metabolites of fatty acids and phospholipids	LS-191838, diclofenac, DRF 2519, ibuprofen, LG100754, farglitazar, indomethacin, rosiglitazone, GW2331, MK-0767, PAT5A, netoglitazone, BADGE, GW1929, L796449, GW7845, CDDO, L-783483, L-165461, AD5075, FMOC-L-Leucine, troglitazone, GW409544, reglitazar, MK0767, GW9578, ciglitazone, SB-219994, LY510929, AD-5061, TZD18, L-764406, ragaglitazar, thiazolidinone, troglitazone, LY-465608, pioglitazone, SB-219993, 5-ASA	PPARγ is a key regulator of adipogenesis, but it also plays an important role in cellular differentiation, insulin sensitization, atherosclerosis, and cancer	Michalik et al. (2006), Chawla, et al. (2001), Rosen and Spiegelman (2001)
Liver X receptor	LXRα	NR1H3	Oxysterols	L-783483, acetyl-podocarpic dimmer, T0901317, GW3965, paxilline	LXRs act as cholesterol sensors that respond to elevated sterol concentrations, and transactivate a cadre of genes that govern transport, catabolism, and elimination of cholesterol. LXRs also regulate a number of genes involved in fatty acid metabolism	Benoit et al. (2006), Moore et al. (2006)
	LXRβ	NR1H2	A series of oxysterols	L-783483, acetyl-podocarpic dimmer, GW3965, T0901317		
Farnesoid X receptor	FXRα	NR1H4	A series of bile acids	GW4064, fexaramine	FXR is a bile acid sensor	Benoit et al. (2006), Moore et al. (2006)
	FXRβ	NR1H5	A series of oxysterols	–		
Pregnane X receptor	PXR	NR1I2	Xenobiotics	Clotrimazole, mifepristone, nifedipine, phenobarbital, vitamin K2, hyperforin, SR12813, pregnenolone-16α-carbonitrile, dexamethasone, schisandrin A, rifampinin, taxol	PXR has as role as xenobiotic sensors	Benoit et al. (2006), Moore et al. (2006)

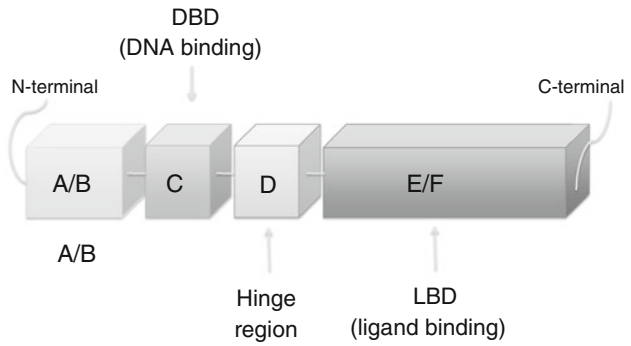

Fig. 1 Nuclear receptors share common structure function domains. A typical nuclear receptor contains a variable N-terminal region (*A/B*), a conserved DBD (*C*), a variable hinge region (*D*), a conserved LBD (*E*), and a variable C-terminal región

concentration can greatly influence the function of a nuclear receptor, and it is believed that over- or underexpression of coregulators can contribute to the development of certain pathologies (Lonard et al. 2007).

Some nuclear receptors are considered to be *metabolic nuclear receptors* as defined by Francis et al. because they are activated by nutrients, diet metabolites, or drugs and act as metabolic and toxicological sensors. These nuclear receptors allow the body to adapt to environmental changes by inducing the appropriate metabolic genes and pathways (Francis et al. 2003). The metabolic nuclear receptors are master regulators integrating the homeostatic control of (a) energy and glucose metabolism through peroxisome proliferator-activated receptor gamma (PPAR γ); (b) fatty acid, triglyceride, and lipoprotein metabolism via PPAR α, δ, and γ; (c) reverse cholesterol transport and cholesterol absorption through the liver X receptors (LXRs); (d) bile acid metabolism through the farnesoid X receptor (FXR) and LXRs; and (e) the defense against xeno and endobiotics by the pregnane X receptor/steroid and xenobiotic receptor (PXR) (Table 1).

Because the binding of small, lipophilic ligands that include hormones and metabolites such as fatty acids, bile acids, oxysterols, and xeno and endobiotics controls the activity of these nuclear receptors, when the concentrations of these metabolites are modified, alterations in the homeostasis of the signaling pathways may trigger various diseases (Ruan et al. 2005), several of which are associated with the development of degenerative chronic diseases, including hypercholesterolemia, insulin resistance, and obesity.

Recently, obesity has increased dramatically worldwide, and it has been associated with a high incidence of metabolic syndrome (Ruan and Guan 2009). This syndrome is defined as a constellation of physiological changes including hypertriglyceridemia, hyperglycemia, and hypo alpha-lipoproteinemia, which are mainly caused by excess calorie intake that results in excess body fat. Metabolic syndrome has been strongly associated as a risk factor for the development of chronic kidney disease and end-stage renal disease (Hsu et al. 2006; Iseki et al. 2004).

The progression of renal diseases is accompanied by inflammation, metabolic disorders of the glucose and lipid metabolism, hypertrophy and apoptosis, matrix expansion and oxidative stress. Thus, the aim of the present review is to summarize the current knowledge and the potential role of nuclear receptors as metabolic regulators involved in some of the abnormalities associated with the development of renal diseases in the setting of obesity and metabolic syndrome.

The role of PPARs in metabolic renal dysfunction

PPARs are nuclear hormone receptors that stimulate transcription of specific genes by binding to specific DNA sequences. The three PPAR subtypes are products of the distinct genes commonly designated as PPARα, PPARγ, and PPAR β/δ, or merely δ (Berger et al. 2005). These lipid sensors are "master" transcriptional regulators of nutrient metabolism and energy homeostasis that modulate the expression of unique groups of genes. The PPARs usually heterodimerize with another nuclear receptor, the RXR, to form a complex that interacts with specific DNA-response elements within the promoter region of the target genes. Ligand binding can activate this heterodimer complex, which recruits transcription coactivators and regulates the transcription of genes involved in the regulation of lipid and carbohydrate metabolism (Michalik et al. 2006; Moore et al. 2006; Rosen and Spiegelman 2001). PPARα, PPARγ, and PPAR δ are differentially expressed in various tissues (Robinson and Grieve 2009). In general, PPARα is highly expressed in tissues that possess high mitochondrial and β-oxidation activity, including the renal cortex. PPARγ is highly enriched in adipose tissue, while lower expression levels are reported in the urinary bladder and kidney. Unlike PPARα and PPARγ, low-level expression of PPARδ is found ubiquitously in almost every tissue examined. In the kidney, PPARα is abundantly expressed in the proximal tubules and the medullary thick ascending limb, with much lower expression in the glomerular mesangial cells (Ruan et al. 2003; Guan et al. 1997). PPARγ is primarily expressed in the distal medullary collecting ducts, with lower expression in the glomeruli and renal microvasculature (Guan et al. 2001). In the kidney, PPARδ is diffusely expressed in the renal cortex and medulla, including medullary interstitial and stromal cells (Guan et al. 1997). This differential distribution of the three PPAR isoforms within different tissues may be related to their distinct roles in the kidney. Because the target genes of PPARα, δ, and γ in many tissues are mainly involved in

Table 2 Metabolic nuclear receptors in kidney: DNA-binding sites, main coregulators and target genes

Name	Structure	DNA-binding	Response element	Coregulators		Main target genes
Abbreviation		HRE core sequence		Coactivators	Corepressors	
PPARα	Heterodimer, RXR partner	5′-AACTAGGNCA A AGGTCA-3′	DR1, DR2	MED1, NCOA1, NCOA6, HADHA, SMARCA2, CREBBP, CITED2, NCOA3, PPARGC1A, PPARGC1B	NCOR1, NRIP1	CPTI, MCAD, Acyl-CoA oxidase, G0/G1 switch gene 2, Fiat, Bifunctional enzyme, SIc27a1, Apolipoprotein A-II, Liver fatty acid binding protein
PPARδ	Heterodimer, RXR partner	AACTAGGNCA A AGGTCA	DR1	NCOA1, NCOA3, NCOA6, PPARGC1A	NCOR2, NCOR1,	ANGPTL4, Pdpk1, Ilk, Pink1, Dffa
PPARγ	Heterodimer, RXR partner	5′-AACTAGGNCA A AGGTCA-3′	DR1	SCAND1, NCOA4, PPARGC1A, PPARGC1B, CREBBP, EP300, CITED2, NCOA7, MED1, NCOA6, PRMT2, TGS1, NCOA1, NCOA2, NCOA3, SMARCA1	NCOR2, NRIP1, SAFB, TAZ, NCOR1	Fabp4, Apoa2, Pck1, Ucp1, Acsf2, Lpl, Slc27a
LXRα	RXR partner	AGGTCANNNNAGGTCA	DR4, RXR binds the 5′ half-site while LXR binds the 3′ half-site of DR4 HREs	EP300, NCOA1, TRRAP, NCOA2, PPARGC1B	NCOR1, NCOR2	CETP, ABCA1, ABCG1, SREBF1, APOE, APOD, LPL, PLTP, NR1H3, FAS, SLC2A4, ApoCI/IV/II, Cyp7a1, Vegfa
LXRβ	RXR partner	AGGTCANNNNAGGTCA	DR1	NCOA1, EP300, NCOR1	NCOR2 (NONE)	ABCA1, SREBF1, ABCG1, CPOC1, APOC2, APOC4, APOE, CETP, NR1H3, FAS, SLC2A4, VEGF
FXRα	RXR partner	AGTTCAnTGAACT	FXR binds IR1	PPARGC1A, NCOA1, MED1, CARM1, PRMT1, TRRAP		KNG1, NROB2, ABCB11, FABP6, ABCB4, FGF19, ABCC2, SLCO1B3, SLC27A5, SLC3A1, APOAI, APOC2, APOE, C3, PDK4, PLTP, PPARA, VLDLR, Fibrinogen, SDC1, VIPR1, Alpha-crystallin, Organic solute transporter α-β, Abcb4, Apoc3
FXRβ	Heterodimer	AGTTCA N TGAACT	Also binds as RXR heterodimer to an everted repeat with a spacer of 2 (ER2)	NCOA1		
PXR	Heterodimer, RXR partner	AGGTCA	DR3, IR6, DR4, ER8, IR0, PBRE	NCOA1, NRIP1, PPARGC1A, FOXO1, GRIP1	NR0B2, NCOR2	Cytochrome P450, Slco1a4, Abcc2, Ugt1a1, Sult2a1, Abcb1b, Alas1

adipogenesis, lipid metabolism, insulin sensitivity, glucose homeostasis, and cell growth and differentiation, PPARs could be target candidates for the modulation of body metabolism.

PPARα

PPARα is highly expressed in the proximal tubules and plays an important role in the metabolic control of renal energy homeostasis (Portilla 2003). Fatty acids constitute a major source of metabolic fuel for energy production in the kidney. PPARα controls a set of genes essential for fatty acid β-oxidation in the renal cortex and contributes to an appropriate adaptive response to dietary lipids by the kidney. Specifically, PPARα plays a critical role in the regulation of fatty acid transport protein (FATP), which facilitates the uptake of long-chain fatty acids across the plasma membrane and several key enzymes involved in their subsequent catabolism within the cell (Fig. 2). PPARα has been shown to induce activation of acyl-CoA oxidase (ACO), thiolase, acyl-CoA dehydrogenase, and cytochrome P-450 ω-hydroxylase, which are all essential to the β-oxidation of fatty acids within peroxisomes, mitochondria, and microsomes (Fig. 2) (Schoonjans et al. 1996). PPARα expression has also been found to be significantly increased in situations of metabolic stress, such as fasting or severe cold, when increased energy production requires the release of fatty acids from adipose tissue (Lemberger et al. 1996). The kidney response to starvation in PPARα-null mice has been shown to be blunted, supporting this finding (Sugden et al. 2001). These observations collectively suggest that PPARα may participate in certain renal pathophysiological settings associated with deregulation of energy homeostasis such as diabetic nephropathy and kidney lipotoxicity (Ruan et al. 2008). Additionally, PPARα stimulates the expression

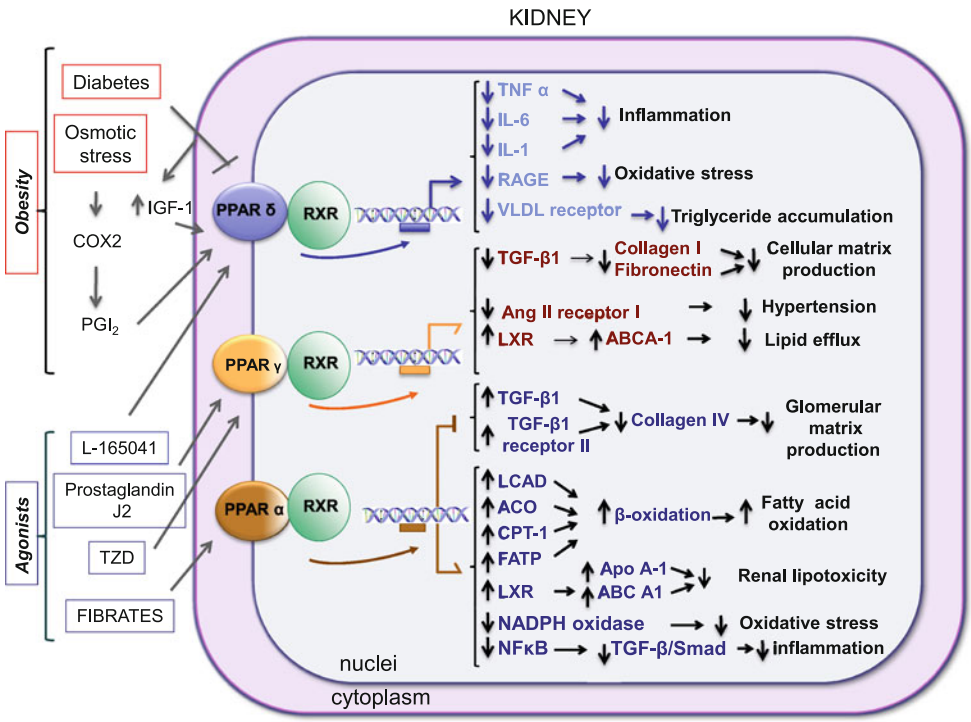

Fig. 2 Nuclear receptors PPARα, PPARβ and PPARγ as central regulators of renal lipid, inflammation, and oxidative stress. PPARα agonists confer a renoprotective effect by increased gene expression of enzymes involved in β-oxidation (LCAD, MCAD, ACO, CPT-1, FATP), additionally, attenuated renal lipotoxicity is increased by an augmented gene expression of LXRα, ABCA1. Finally, PPARα agonist decreased renal expression of anti-inflammatory factors such as NFκB and TGF-β/Smad. In an animal model of type I diabetes, the renal expression of PPARδ is greatly suppressed, which may contribute to renal lipotoxicity due to reduced fatty acid oxidation. Treatment of mesangial cells with insulin-like growth factor-1 (IGF-1), a cytokine up-regulated in the diabetic kidney, enhanced triglyceride accumulation, possibly by increasing very low-density lipoprotein receptor (VLDLr) expression resulting from PPARδ suppression. In addition, PPARδ down-regulates the expression of the receptor for advanced glycation end products (RAGE) and pro-inflammatory cytokines (TNF-α, IL-1 and IL-6) in the kidney of diabetic mice. These finding suggest that the reduction in renal PPARδ expression possibly represents an underlying mechanism involved in diabetic kidney injury. Activation of PPARγ by prostaglandin J2 or TZD increased LXRα and ABCA1 gene expression in mesangial cells. Interestingly, PPARγ is a negative modulator for transcription of both angiotensin II receptor type 1 (AT1 receptor) and leptin genes. Additionally, PPARγ agonists can suppress TGFβ-induced collagen I and fibronectin production in mesangial cells. In the case of renal disease, the use of PPARγ agonists has positive effects on renal hemodynamics and renal injury

of lipoprotein lipase (Fig. 2) that it is known to promote the release of fatty acids from lipoprotein particles, as well as their subsequent uptake (Schoonjans et al. 1996). Several recent clinical studies provide clear evidence that the fibrate class of PPARα agonists confer a renoprotective effect in patients with type 2 diabetes. The renal protective effect of PPARα agonists is apparently multifactorial. In addition to systemically attenuating insulin resistance and dyslipidemia, the agonists may have a direct beneficial action on the kidney. Indeed, PPARα agonists are widely used in the treatment of disorders characterized by elevated levels of plasma lipids. Fibrates exert their positive effect on lipid handling by inducing hepatic uptake and β-oxidation of fatty acids and increasing lipoprotein disassembly, while also conferring beneficial effects on the high-density lipoprotein (HDL) to low-density lipoprotein (LDL) ratio. PPARα activation has also been shown to have anti-inflammatory effects. The control of inflammatory pathways by PPARα occurs mainly via repression of target genes caused by negative interference in a DNA-binding-independent manner (trans-repression) (Zambon et al. 2006). Although inflammatory processes are important for the initiation of the defense mechanism (Streetz et al. 2001), they can become deleterious in situations of chronic activation. Fibrates can exert anti-inflammatory effects in patients with atherosclerosis by decreasing plasma levels of cytokines, interleukin 6 (IL-6), tumor necrosis factor α (TNFα), and interferon-gamma (INFγ), while decreasing levels of C-reactive protein (CRP) in patients with cardiovascular disease will also result in anti-inflammatory effects (Zambon et al. 2006). In a study conducted by Li and coworkers, the investigators demonstrated that fenofibrate decreased renal expression of pro-inflammatory factors, tubulointerstitial fibrosis, and interstitial macrophage infiltration in Zucker diabetic rats (Li et al. 2010). Moreover, the anti-inflammatory and anti-fibrotic effect of the PPARα activator was accompanied by a suppression of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and transforming growth factor β1 (TGF-β1), mothers against decapentaplegic homolog 3 (Smad3) in the diabetic kidney (Fig. 2). Additionally, in a study conducted by Lin et al., PPARα overexpression also inhibited the induction of the activity of NFκB, which was associated with an interaction between PPARα and the NFκB p65 subunit as revealed in immunoprecipitation assays (Lin et al. 2007). PPARα agonists (fenofibric acid and eicosapentanoic acid) enhance endothelial nitric oxide synthase (eNOS) expression and nitric oxide (NO) release, which suggests a vasoprotective effect. In other studies, synthetic PPARα activators (fenofibric acid and WY14643) were shown to diminish thrombin-induced and oxidized LDL (ox-LDL)-induced expression of endothelin-1 (Gilde et al. 2003). PPARα activators can also modify the activation of inflammatory vascular smooth muscle cells (VSMCs) by inhibiting interleukin-1 (IL-1)-induced production of IL-6 and prostaglandins and by reducing the expression of cyclooxygenase-2 (COX-2). Moreover, PPARα activation, in the presence of TNFα and INFγ, may promote macrophage apoptosis (Cheng et al. 2010).

Regulation of PPARα unmasks an interaction area for coactivators such as cAMP response element binding protein (CREB)-binding protein (CBP) and p300. The latter possesses histone acetyl transferase (HAT) activity that results in chromatin decondensation and PPARα heterodimerization with RXR. The binding of this heterodimer to PPRE on PPARα-containing promoters results in the regulation of expression of the target genes. In addition, PPARα is a substrate for several kinases that are activated by a variety of endogenous or exogenous signals. These kinases include the following: extracellular receptor kinase-mitogen-activated protein kinase (ERK-MAPK), c-Jun N-terminal kinase (JNK) and p38 MAPK, Protein kinase A (PKA), Protein kinase C (PKC), 5′-AMP-activated protein kinase (AMPK), and glycogen synthase kinase 3 (GSK3). Recent studies of the SUMOylation of PPARα have reported that SUMOylated hPPARα on lysine 185 results in down-regulation of this transcriptional activity by promoting its interaction with the corepressor NCoR (Pourcet et al. 2010). Therefore, it is interesting to investigate whether PPARα modifications, including phosphorylation, SUMOylation, and ubiquitination, are involved in inflammation-induced renal failure. Recently, it was demonstrated that adiponectin exerts a protective effect against renal ischemic-reperfusion injury via the prostacyclin-PPARα-heme oxygenase-1 signaling pathway. Despite much information on the role of PPARα on renal tissue, little is known about its behavior in the kidney during the development of obesity that may result in up- or down-regulation of the expression of its target genes that can increase susceptibility to kidney disease.

In addition, PPARα exerts antioxidant effects (Kono et al. 2009; Girnun et al. 2002; Diep et al. 2002; Devchand et al. 1996). Activation of PPARα inhibits angiotensin II-induced activation of nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase) and suppressed reactive oxygen species (ROS) production in the vascular wall (Fig. 2) (Diep et al. 2002). Furthermore, a PPRE has been identified in the promoter regions of catalase and Cu/Zn superoxide dismutase (Cu/Zn SOD) genes that are key enzymes that reduce ROS production (Girnun et al. 2002). Hou and collaborators showed that the PPARα agonist fenofibrate exerts a renoprotective effect against hypertensive renal injury in an animal model of spontaneous hypertension by inhibiting cell recruitment and TGF-β1

expression through suppression of NADPH oxidase activity and up-regulation of Cu/Zn SOD activity, thus inhibiting phosphorylation of p38MAPK and JNK (Hou et al. 2010). Finally, PPARα agonists increase both LXR and ABC1 gene expression and enhanced apo A1-mediated cholesterol efflux from lipid-loaded mesangial cells, thereby attenuating renal lipotoxicity (Fig. 2) (Ruan et al. 2003, 2008).

PPARδ

Although PPARδ seems to be abundant in the kidney and ubiquitously expressed along the nephron, the role of this PPAR isoform in the kidney remains poorly understood (Guan et al. 1997; Hao et al. 2002). PPARδ may play an important role in the renal metabolic adaptation to fasting and refeeding (Escher et al. 2001). A dramatic decrease in renal PPARδ mRNA expression was observed during fasting, which was rapidly restored to control levels by refeeding. The regulation of PPARδ expression may be related to metabolic fates, for example, gluconeogenesis and lipogenesis. As gluconeogenesis is increased during fasting, PPARδ would be a negative regulator of this pathway. These findings suggest its involvement in metabolic kidney diseases such as diabetic nephropathy. In fact, in Akita and OVE26 mice with type I diabetes, the renal expression of PPARδ is greatly suppressed, which may contribute to renal lipotoxicity due to reduced fatty acid oxidation (Fig. 2) (Proctor et al. 2006). Consistent with this hypothesis, treatment of mesangial cells with insulin-like growth factor-1 (IGF-1), a cytokine up-regulated in the diabetic kidney (Chan et al. 2001), enhanced triglyceride accumulation, possibly by increasing very low-density lipoprotein receptor (VLDLr) expression resulting from PPARδ suppression (Berfield et al. 2006). These finding suggest that the reduction in renal PPARδ expression possibly represents an underlying mechanism involved in diabetic kidney injury. Abundant and active PPARδ is present in cultured renal medullary interstitial cells. In addition, overexpression of PPARδ provides protection against hypertonicity-induced cell death in cultured medullary interstitial cells, which suggests that PPARδ is an important survival factor in the kidney (Hao et al. 2002). Letavernier et al. demonstrated that PPARδ can provide strong protection against ischemia-induced renal injury as a result of its combined action on cell survival and cytoskeletal reorganization (Letavernier et al. 2005). In addition, PPARδ down-regulates the expression of the receptor for advanced glycation end products (RAGE) and pro-inflammatory cytokines (TNF-α, IL-1 and IL-6) in the kidney of streptozotocin-induced diabetic mice (Fig. 2) (Liang et al. 2011). Collectively, PPARδ agonists may be considered a novel means of conferring renal protection in diabetic nephropathy and other diseases.

PPARγ

PPARγ is expressed predominantly in adipose tissue, where it is a key regulator of adiposity differentiation, triglyceride storage, and energy homeostasis (Lehrke and Lazar 2005; Balakumar et al. 2007) In the kidney, PPARγ is expressed in different cells, including the inner medullary collecting ducts, proximal tubules, thick ascending limb of Henle's loop (THAL), glomeruli and renal microvascular endothelial cells in rats (Yang et al. 1999; Satoh et al. 2004; Nicholas et al. 2001), rabbits, and humans (Guan et al. 1997, 2001) Because multiple renal cell types have endogenous PPARγ expression and activity, the kidney has been suggested as a direct target of PPARγ agonists, and PPARγ activation in the kidney may be critical for maintaining normal renal function. Since the introduction of thiazolidinediones (TZDs), insulin sensitizers in diabetic clinical treatment, the role of PPARγ in the kidney and the potential for PPARγ agonists as therapy for diabetic nephropathy have been extensively investigated. Some animal studies have suggested a protective effect of TZD in both diabetic and non-diabetic models of renal disease (Ma et al. 2001; McCarthy et al. 2000). Most currently available studies demonstrate a renoprotective effect of PPARγ agonists in patients with type 2 diabetes with or without hypertension, as indicated by reduced albuminuria (Yano et al. 2007; Sarafidis and Bakris 2006; Iglesias and Diez 2006). Activation of PPARγ prostaglandin J2 increased LXRα and ABCA1 gene expression and enhanced apo A1-mediated cholesterol efflux from human mesangial cells (HMC), even in the presence of IL-1β. This was supported by the observation that overexpression of PPARγ by transfection enhanced LXRα and ABCA1 gene induction in HMC (Fig. 2) (Ruan et al. 2003) Obesity is frequently accompanied by renal dysfunction reflected in hypertension and renal injury. Interestingly, PPARγ is a negative modulator for transcription of both angiotensin II receptor type 1 (AT1 receptor) and leptin genes, suggesting that activation of PPARγ in obesity may be beneficial for blood pressure reduction associated with the down-regulation of the latter genes (Fig. 2) (Dobrian 2006). Additionally, PPARγ is an important regulator of lipid homeostasis. PPARγ controls the expression of an array of genes involved in lipogenesis and triglyceride storage. Also, TZD can suppress TGFβ-induced collagen I and fibronectin production in mesangial cells (Guo et al. 2004; Zheng et al. 2002). In contrast, stimulation of PPARγ by fatty acids presented to proximal tubular cells bound to albumin results in profound apoptosis (Arici et al. 2003). In addition, an increasing number of

studies suggest that TZDs possess anti-inflammatory properties independent of their insulin-sensitizing action and protect renal function in various models of acute and chronic renal injury (Jiang et al. 1998; Ma et al. 2001; Matsuyama et al. 2005; Yang et al. 2006). Furthermore, TZDs have been shown to reduce proteinuria and delay the progression of diabetic nephropathy independent of glycemic control (Miyazaki-Anzai et al. 2010; Okada et al. 2006). Although PPARγ is generally accepted as a renoprotective factor in type 2 diabetes mellitus, the mechanism by which it exerts these favorable effects remains unclear. Moreover, little is known about the renal expression of PPARγ in chronic kidney disease. In addition, human data on PPARγ expression are very scarce. An important issue to be addressed is the fact that TZD treatment frequently results in sodium and water retention, possibly by activating PPARγ in the renal microvasculature smooth muscle and collecting duct. The long-term consequences of TZD-associated fluid retention on blood pressure remain to be determined.

The Liver X receptors (LXRs)

Liver X receptors (LXRs) are nuclear hormone receptors that act as transcription factors. As such, LXRs regulate the expression of genes involved in cholesterol and fatty acid metabolism (Kuipers et al. 2010; Tontonoz and Mangelsdorf 2003). In the liver, LXRs regulate the expression of genes involved in bile acid and cholesterol metabolism, as well as the SREBP-1c, which stimulates lipogenesis via its target genes (Peet et al. 1998). In the macrophage, gut and other cell types and tissues, LXRs play a crucial role in reverse cholesterol transport, thereby stimulating the efflux of cholesterol from the peripheral tissue to the liver. Two different, yet highly homologous, isoforms of LXR have been described, LRX-α and LXR-β. Both LXRs heterodimerize with RXR bind to the DR-4 response element with the sequence 5′-GGTTTAAATAAGTTCA-3′ in the promoter of target genes (Kuipers et al. 2010; Willy et al. 1995). These targets include ATP-binding cassette transporters A1, G5, and G8 (ABCA1, ABCG5, ABCG8), apolipoprotein E (Apo E), cholesterol ester transport protein (CETP), lipoprotein lipase (LPL), fatty acid synthase (FAS), and SREBP-1c, suggesting that LXRs are key players in lipid and cholesterol metabolism (Steffensen and Gustafsson 2004; Ulven et al. 2005). Natural ligands for LXRs are oxysterols, but strong synthetic agonists such as T0901317 (T09) and GW3965 have been developed. Although LXR-β is ubiquitously expressed, LXR-α is expressed mainly in the liver, adipose tissue, macrophages, intestine, spleen, kidney, and heart. A PPAR response element has been identified in the LXR gene promoter; it therefore seems likely that PPAR regulates ABCA1 gene expression through the LXR pathway (Ruan et al. 2003).

In the kidney, LXRs are specially expressed in renin-producing juxtaglomerular (JG) cells (Morello et al. 2005). In JG cells, renin transcriptional and translational control is meticulously regulated at multiple levels. The hormone renin is the rate-limiting step in the renin–angiotensin–aldosterone system (RAAS), which is a critical regulator of blood pressure and salt-volume homeostasis in physiological and pathological conditions. LXRs have been shown to regulate renin expression in vivo, suggesting crosstalk between the RAAS and lipid metabolism (Fig. 3). Oxidized cholesterol derivatives (oxysterols) are endogenous ligands for LXR (Janowski et al. 1996). Thus, elevated cellular cholesterol levels lead to accumulation of these cholesterol metabolic byproducts and activation of the LXR target genes (Fig. 3). Activation of the genes of reverse cholesterol transport by LXR increases the transport of cholesterol from peripheral tissues, including the macrophages, to the liver for catabolism and excretion (Laffitte et al. 2001; Luo and Tall 2000; Venkateswaran et al. 2000) (Fig. 3). In addition to these processes that maintain cholesterol homeostasis, LXR-mediated gene regulation in the intestine decreases dietary cholesterol absorption (Tontonoz and Mangelsdorf 2003). SREBP-1 up-regulation by LXR causes an increase in lipogenesis, leading to elevation of serum free fatty acids (Peet et al. 1998; Schults et al. 2000). LXR agonists also increase murine renin gene expression in vivo, suggesting a link between cholesterol and lipid metabolism, the renin–angiotensin–aldosterone system and blood pressure regulation (Morello et al. 2005) (Fig. 3).

It has been reported that LXRs regulate renin gene expression in a ligand-independent manner by interacting with a specific responsive element in the renin promoter known as the cAMP-negative response element (CNRE) (Morello et al. 2005). However, it has also been shown that treatment of rats with the synthetic LXR agonist GW3965 interferes with angiotensin II-mediated pressor responses (Leik et al. 2007), suggesting that the LXR agonist may affect vascular reactivity. These observations indicate that there is crosstalk between LXR activation and RAAS activation, but it remains unknown whether long-term LXR stimulation modulates RAAS activity and, if so, which enzymes or peptides of RAAS are affected by LXR stimulation. Additionally, a study conducted by Wu et al. demonstrated that glomerular LXR α expression was markedly induced by TZD. A similar effect was observed with the use of LXR α agonist T-0901317, which markedly increased the apolipoprotein AI (Apo AI)-mediated cholesterol efflux in cultured mesangial cells, suggesting that LXR α may participate, at least in part, in cholesterol transport in renal mesangial cells (Wu et al. 2004) (Fig. 3).

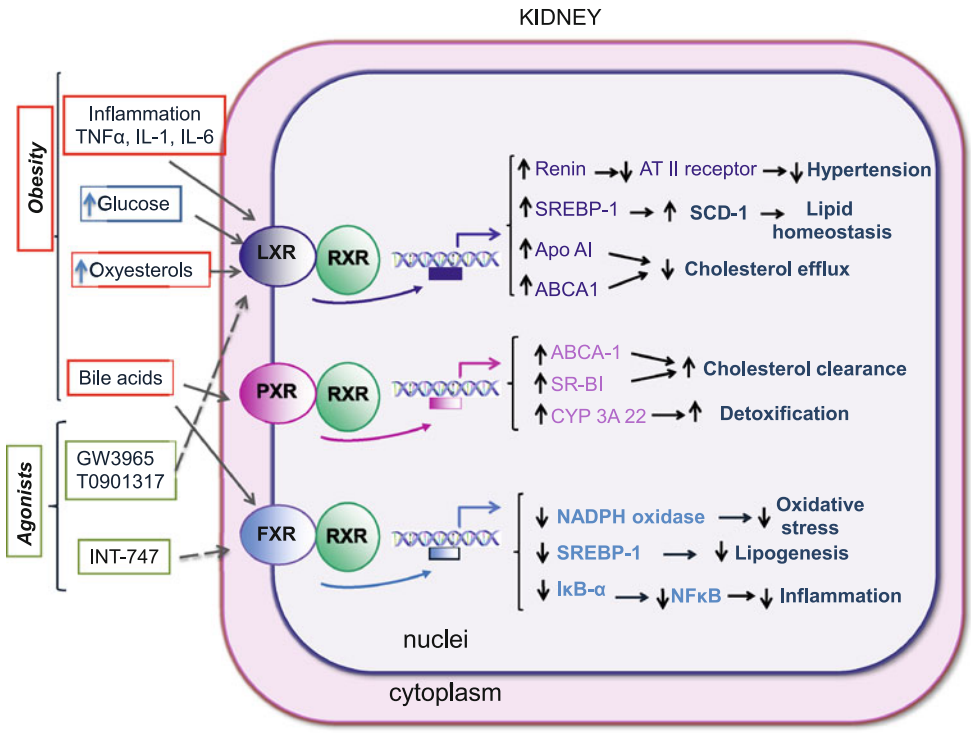

Fig. 3 Nuclear receptors LXRs, FXR, and PXR as central regulators of renal lipid, inflammation and oxidative stress. Increase in inflammatory response, glucose concentration, and oxysterols or LXR agonist stimulate LXR and increases renin gene expression in vivo, suggesting a link between cholesterol and lipid metabolism, the renin–angiotensin–aldosterone system and blood pressure regulation. Bile acids or FXR agonist reduces the renal expression of SREBP-1, prevents the progression of proteinuria and glomerulosclerosis, the renal accumulation of triglycerides, and the increased expression of profibrotic growth factors, NADPH oxidase. In addition, FXR agonist negatively interferes with the inflammatory response by antagonizing the NFκB signaling pathway, to support its role as a modulator of inflammation. Activation of PXR in the kidney stimulates the expression of ABCA1, as well as the scavenger receptor class B type I (SR-BI), which are both involved in the exchange of cholesterol between HDL lipoproteins and cells, increasing the renal cholesterol clearance. This is important since lipid abnormalities in ESRD are characterized by reduced serum apo A-1 and HDL concentration, this in turn promotes an influx of ox-LDL in macrophages and resident cells in the artery wall and facilitates foam cell formation and atherosclerosis

The Farnesoid X receptor (FXR)

The farnesoid X receptor (FXR) is a bile acid-activated nuclear receptor that plays an important role in regulating bile acid metabolism (Goodwin and Kliewer 2002). FXR is a bile acid sensor and is activated by binding to endogenous bile acids (Makishima et al. 1999; Parks et al. 1999; Wang et al. 1999). High levels of FXR have been described not only in the liver and intestine but also in the kidney and adrenals (Forman et al. 1995; Lu et al. 2001). However, the physiological function of FXR in these tissues, which are not normally exposed to bile acid circulation, remains controversial. In the mouse kidney, FXR has been detected in both isolated glomeruli and proximal tubules. The expression level in proximal tubule cells is much higher than in glomeruli (Jiang et al. 2007). In addition, FXR is expressed in both cultured mouse mesangial cells and podocytes (Jiang et al. 2007).

FXR has been shown to control lipid metabolism through a mechanism that involves repression of hepatic SREBP-1c expression (Watanabe et al. 2004; Zhang et al. 2004) (Fig. 3). Moreover, FXR activation prevents liver fibrosis (Fiorucci et al. 2004) and atherosclerotic lesions (Hartman et al. 2009; Li et al. 2007).

Jiang et al. demonstrated that C57BL76J mice treated with FXR agonist did not experience a high fat-induced increase in the renal expression of SREBP-1 (Jiang et al. 2007) (Fig. 3). In addition, treatment of db/db mice with FXR agonists prevents the progression of proteinuria and glomerulosclerosis, the renal accumulation of triglycerides, and the increased expression of profibrotic growth factors, pro-inflammatory cytokines, and NADPH oxidase (Fig. 3). Furthermore, cell culture studies indicate that in a high-glucose milieu, FXR plays a direct role in inhibiting SREBP-1-mediated fatty acid synthesis and expression of profibrotic growth factors and pro-inflammatory cytokines.

In a study conducted by Wang et al., the investigators demonstrated the key role of FXR in modulating SREBP-1 activity, glomerular lesions, and proteinuria. They found that feeding a Western-style diet to DBA/2J mice resulted in proteinuria, product loss, mesangial expansion, renal lipid accumulation, increased expression of pro-inflammatory factors, oxidative stress, and profibrotic growth factors (Fig. 3). Treatment of these mice with the highly selective and potent FXR-activating ligand 6-α-ethyl-chenodeoxycholic acid (INT-747) ameliorates triglyceride accumulation by modulating fatty acid synthesis and oxidation, improves proteinuria, prevents podocyte loss, mesangial expansion, accumulation of extracellular matrix proteins, and increased expression of profibrotic growth factors and fibrosis markers, and modulates inflammation and oxidative stress in the kidney (Wang et al. 2009) (Fig. 3). Additionally, FXR has been shown to negatively interfere with the inflammatory response by antagonizing the NFκB signaling pathway (Li et al. 2007) to support its role as a modulator of inflammation (Fig. 3).

Pregnane X receptor (PXR)

The xenobiotic nuclear receptor PXR functions as an endobiotic and xenobiotic sensor that coordinately regulates drug and endogenous metabolites clearance via induction of genes coding for oxidation and conjugation enzymes (phase I and II, respectively), as well as for transporters (Francis et al. 2003). Furthermore, transcriptional activity of this nuclear receptor is regulated by signaling pathways associated with NFκB and JNK, which are known to be induced in obesity (Cai et al. 2005; Hirosumi et al. 2002). PXR is predominantly expressed in the liver and intestine, both of which are sites of elevated steroid xenobiotic metabolism. Nevertheless, it is also expressed to a lesser extent in the kidney and other tissues such as the stomach and lung (Kliewer et al. 1998; Miki et al. 2005; Zhang et al. 1999), although its role in these tissues is not so well defined. Numerous structurally unrelated drugs and environmental contaminants can bind and activate PXR, including the antibiotic rifampicin and endobiotics such as precursor, intermediate and secondary bile acid metabolites. The canonical function of the PXR is therefore to sense elevations in xenobiotics and endobiotics and to orchestrate a response that promotes xenobiotic/endobiotic metabolism and excretion (Kliewer 2003). Among the consequences of obesity are changes in the pharmacokinetics and pharmacodynamics of many therapeutic drugs, although the mechanism of obesity-mediated alterations of drug metabolism in unknown (Blouin et al. 1999; Cheymol 2000) in settings where the kidney plays a major function as the natural filter of the blood and the remover of wastes. For instance, the metabolism of acetaminophen and verapamil is altered in the kidney of obese rats (Chen et al. 2008; Osabe et al. 2008). Recent studies indicate that PXR can be activated by endogenous cholesterol metabolites, implicating its involvement in the clearance of potentially toxic intermediates. Cholic acid is a cholesterol metabolite and a signaling molecule known to block cholesterol catabolism. In a study conducted by Sonoda et al. in mice lacking PXR that were challenged with a diet supplemented with cholic acid, addition of cholesterol to their diet resulted in acute lethality associated with signs of hepatorenal failure (Sonoda et al. 2005). It was speculated that the renal failure might be the direct cause of death. These results reveal an essential and unique role of PXR in the protection from cholesterol and its metabolites. Other targets of PXR include the ABCA1, as well as the scavenger receptor class B type I (SR-BI), which are both involved in the exchange of cholesterol between HDL lipoproteins and cells (Fig. 3). Because lipid abnormalities in ESRD are characterized by reduced serum apo A-1 and HDL concentration, this in turn promotes an influx of ox-LDL in macrophages and resident cells in the artery wall and facilitates foam cell formation and atherosclerosis (Fig. 3). For this reason, it is necessary to investigate its relationship in the kidney. In addition to playing important roles in cholesterol detoxification, PXR can also modulate SREBP-dependent and SREBP-independent lipogenic pathways in vitro and in vivo. PXR can mediate a SREBP-independent lipogenic pathway by activating the free fatty acid (FFA) uptake transporter CD36, PPARγ, and several accessory lipogenic enzymes, such as stearoyl CoA desturase-1 (SCD-1) and long-chain free fatty acid elongase (FAE) (Zhou et al. 2006). PXR activation is also associated with induction of Insig-1, a protein with anti-lipogenic properties and with reduced protein levels of the active form of SREBP-1 (Roth et al. 2008). A functional PXR binding site was found in the Insig-1 promoter, and it was suggested that Insig-1 expression stimulated by PXR could lead to decreased levels of active SREBP-1 and reduced triglyceride synthesis (Fig. 3). Taken together, these studies suggest that PXR plays important roles in cholesterol metabolism and lipid homeostasis. However, the precise mechanisms by which PXR modulates lipid metabolism and cholesterol levels in vivo remains unclear, and the effects of this nuclear receptor in the kidney on lipid metabolism and its possible association with renal abnormalities are poorly defined.

Although several cholesterol metabolites, such as bile acids, bile alcohol, and epoxycholesterols, have been shown to activate PXR, there has been little evidence for the physiological or pathological importance of PXR function in their detoxification (Ambroziak et al. 2010; Cheng and Klaassen 2006; Nannelli et al. 2008; Zhang et al. 1999). Not much is known in regard to PXR functions and its target

genes in the kidney. Because lipid metabolism deregulation in the kidney has been identified as a major factor in the development of chronic kidney disease and because PXR seems to be highly implicated in the regulation of lipid metabolism, further studies are required to assess the potential role of PXR activation in the kidney for the development of chronic kidney disease.

Concluding remarks

The prevalence of obesity has risen dramatically in developing and developed countries. This phenomenon has led to an increase in the so called metabolic syndrome. The relationship between metabolic syndrome and chronic kidney disease has recently been examined (Nitta 2010; Takahashi et al. 2006). Several nuclear receptors can mediate some of the abnormalities that occur in the kidney during the development of metabolic syndrome. These nuclear receptors can activate genes in the kidney or in other organs that can contribute directly or indirectly to the pathophysiology of metabolic alterations present in chronic kidney diseases. For instance, the dyslipidemia associated with the progression of chronic renal failure (Fried et al. 2001), inflammation, lipid accumulation, and foam cell formation that are features of glomerular and tubulointerstitial injury, as well as renal injury and atherosclerosis, share common pathophysiological mechanisms that involve several nuclear receptors (Moorhead et al. 1982). Thus, the global obesity problem presents urgent demands for improved means of disease prevention through the introduction of new drugs, the improvement of diet recommendations and increased patient compliance (Seedorf and Aberle 2007). Ligands of some of the nuclear receptors can be used as therapeutic agents to ameliorate the renal abnormalities that are frequently found in obese subjects who develop type 2 diabetes. Thus, metabolic nuclear receptors and their coregulators may be useful targets for medications. Several abnormalities in the kidney diseases that appear as a consequence of the development of metabolic syndrome are in part associated with alterations in the renal lipid metabolism. The control of renal lipid levels in situ with the use of specific ligands with a large spectrum of full, partial, or inverse agonist or antagonist activity as well as compounds called selective nuclear receptor modulators in the kidney that activate only a subset of the function induced by cognate ligand or that act in specific cell-types in the kidney can prevent or revert the rates of lipogenesis and fatty acid oxidation, resulting in an improvement of renal lipid concentrations, which has been recently considered extremely important factor to improve renal function.

References

Ambroziak K, Kuteykin-Teplyakov K, Luna-Tortos C, Al-Falah M, Fedrowitz M, Loscher W (2010) Exposure to antiepileptic drugs does not alter the functionality of P-glycoprotein in brain capillary endothelial and kidney cell lines. Eur J Pharmacol 628(1–3):57–66. doi:10.1016/j.ejphar.2009.11.051

Arici M, Chana R, Lewington A, Brown J, Brunskill NJ (2003) Stimulation of proximal tubular cell apoptosis by albumin-bound fatty acids mediated by peroxisome proliferator activated receptor-gamma. J Am Soc Nephrol 14(1):17–27

Balakumar P, Rose M, Ganti SS, Krishan P, Singh M (2007) PPAR dual agonists: are they opening Pandora's Box? Pharmacol Res 56(2):91–98. doi:10.1016/j.phrs.2007.03.002

Benoit G, Cooney A, Giguere V, Ingraham H, Lazar M, Muscat G, Perlmann T, Renaud JP, Schwabe J, Sladek F, Tsai MJ, Laudet V (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. Pharmacol Rev 58(4):798–836. doi:10.1124/pr.58.4.10

Berfield AK, Chait A, Oram JF, Zager RA, Johnson AC, Abrass CK (2006) IGF-1 induces rat glomerular mesangial cells to accumulate triglyceride. Am J Physiol Renal Physiol 290(1):F138–F147. doi:10.1152/ajprenal.00054.2005

Berger JP, Akiyama TE, Meinke PT (2005) PPARs: therapeutic targets for metabolic disease. Trends Pharmacol Sci 26(5):244–251. doi:10.1016/j.tips.2005.03.003

Blouin RA, Farrell GC, Ioannides C, Renton K, Watlington CO (1999) Impact of diseases on detoxication. J Biochem Mol Toxicol 13(3–4):215–218

Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, Shoelson SE (2005) Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. Nat Med 11(2):183–190. doi:10.1038/nm1166

Chan W, Wang M, Martin RJ, Trachtman H, Hisano S, Chan JC (2001) mRNA expression for insulin-like growth factor 1, receptors of growth hormone and IGF-1 and transforming growth factor-beta in the kidney and liver of Zucker rats. Nutr Res 21(7):1015–1023

Chawla A, Repa JJ, Evans RM, Mangelsdorf DJ (2001) Nuclear receptors and lipid physiology: opening the X-files. Science 294(5548):1866–1870. doi:10.1126/science.294.5548.1866

Chen M, Xu D, Hu XL, Wang H (2008) Effects of liver fibrosis on verapamil pharmacokinetics in rats. Clin Exp Pharmacol Physiol 35(3):287–294. doi:10.1111/j.1440-1681.2007.04826.x

Cheng X, Klaassen CD (2006) Regulation of mRNA expression of xenobiotic transporters by the pregnane x receptor in mouse liver, kidney, and intestine. Drug Metab Dispos 34(11):1863–1867. doi:10.1124/dmd.106.010520

Cheng CF, Chen HH, Lin H (2010) Role of PPAR alpha and its agonist in renal diseases. PPAR research 2010:345098. doi:10.1155/2010/345098

Cheymol G (2000) Effects of obesity on pharmacokinetics implications for drug therapy. Clin Pharmacokinet 39(3):215–231

Cortes V, Quezada N, Rigotti A, Maiz A (2005) New heterodimeric nuclear receptors: key metabolic regulators with relevance in the pathophysiology and therapy of dyslipidemias and diabetes mellitus. Rev Med Chil 133(12):1483–1492

Devchand PR, Keller H, Peters JM, Vazquez M, Gonzalez FJ, Wahli W (1996) The PPARalpha-leukotriene B4 pathway to inflammation control. Nature 384(6604):39–43. doi:10.1038/384039a0

Diep QN, Amiri F, Touyz RM, Cohn JS, Endemann D, Neves MF, Schiffrin EL (2002) PPARalpha activator effects on Ang II-induced vascular oxidative stress and inflammation. Hypertension 40(6):866–871

Dobrian AD (2006) The complex role of PPARgamma in renal dysfunction in obesity: managing a Janus-faced receptor. Vascul Pharmacol 45(1):36–45. doi:10.1016/j.vph.2006.01.017

Escher P, Braissant O, Basu-Modak S, Michalik L, Wahli W, Desvergne B (2001) Rat PPARs: quantitative analysis in adult rat tissues and regulation in fasting and refeeding. Endocrinology 142(10):4195–4202

Escriva H, Safi R, Hanni C, Langlois MC, Saumitou-Laprade P, Stehelin D, Capron A, Pierce R, Laudet V (1997) Ligand binding was acquired during evolution of nuclear receptors. Proc Natl Acad Sci USA 94(13):6803–6808

Fiorucci S, Antonelli E, Rizzo G, Renga B, Mencarelli A, Riccardi L, Orlandi S, Pellicciari R, Morelli A (2004) The nuclear receptor SHP mediates inhibition of hepatic stellate cells by FXR and protects against liver fibrosis. Gastroenterology 127(5):1497–1512

Forman BM, Goode E, Chen J, Oro AE, Bradley DJ, Perlmann T, Noonan DJ, Burka LT, McMorris T, Lamph WW, Evans RM, Weinberger C (1995) Identification of a nuclear receptor that is activated by farnesol metabolites. Cell 81(5):687–693

Francis GA, Fayard E, Picard F, Auwerx J (2003) Nuclear receptors and the control of metabolism. Annu Rev Physiol 65:261–311. doi:10.1146/annurev.physiol.65.092101.142528092101.142528

Fried L, Bernardini J, Piraino B (2001) Charlson comorbidity index as a predictor of outcomes in incident peritoneal dialysis patients. Am J Kidney Dis 37(2):337–342. doi:10.1053/ajkd.2001.21300

Germain P, Staels B, Dacquet C, Spedding M, Laudet V (2006) Overview of nomenclature of nuclear receptors. Pharmacol Rev 58(4):685–704. doi:10.1124/pr.58.4.2

Gilde AJ, van der Lee KA, Willemsen PH, Chinetti G, van der Leij FR, van der Vusse GJ, Staels B, van Bilsen M (2003) Peroxisome proliferator-activated receptor (PPAR) alpha and PPARbeta/delta, but not PPARgamma, modulate the expression of genes involved in cardiac lipid metabolism. Circ Res 92(5):518–524. doi:10.1161/01.RES.0000060700.55247.7C

Girnun GD, Domann FE, Moore SA, Robbins ME (2002) Identification of a functional peroxisome proliferator-activated receptor response element in the rat catalase promoter. Mol Endocrinol 16(12):2793–2801

Goodwin B, Kliewer SA (2002) Nuclear receptors. I. Nuclear receptors and bile acid homeostasis. Am J Physiol Gastrointest Liver Physiol 282(6):G926–931. doi:10.1152/ajpgi.00044.2002

Guan Y, Zhang Y, Davis L, Breyer MD (1997) Expression of peroxisome proliferator-activated receptors in urinary tract of rabbits and humans. Am J Physiol 273(6 Pt 2):F1013–F1022

Guan Y, Zhang Y, Schneider A, Davis L, Breyer RM, Breyer MD (2001) Peroxisome proliferator-activated receptor-gamma activity is associated with renal microvasculature. Am J Physiol Renal Physiol 281(6):F1036–F1046

Guo B, Koya D, Isono M, Sugimoto T, Kashiwagi A, Haneda M (2004) Peroxisome proliferator-activated receptor-gamma ligands inhibit TGF-beta 1-induced fibronectin expression in glomerular mesangial cells. Diabetes 53(1):200–208

Hao CM, Redha R, Morrow J, Breyer MD (2002) Peroxisome proliferator-activated receptor delta activation promotes cell survival following hypertonic stress. J Biol Chem 277(24):21341–21345. doi:10.1074/jbc.M200695200M200695200

Hartman HB, Gardell SJ, Petucci CJ, Wang S, Krueger JA, Evans MJ (2009) Activation of farnesoid X receptor prevents atherosclerotic lesion formation in LDLR−/− and apoE−/− mice. J Lipid Res 50(6):1090–1100. doi:10.1194/jlr.M800619-JLR200

Henegar JR, Bigler SA, Henegar LK, Tyagi SC, Hall JE (2001) Functional and structural changes in the kidney in the early stages of obesity. J Am Soc Nephrol 12(6):1211–1217

Hirosumi J, Tuncman G, Chang L, Gorgun CZ, Uysal KT, Maeda K, Karin M, Hotamisligil GS (2002) A central role for JNK in obesity and insulin resistance. Nature 420(6913):333–336. doi:10.1038/nature01137

Hou X, Shen YH, Li C, Wang F, Zhang C, Bu P, Zhang Y (2010) PPARalpha agonist fenofibrate protects the kidney from hypertensive injury in spontaneously hypertensive rats via inhibition of oxidative stress and MAPK activity. Biochem Biophys Res Commun 394(3):653–659. doi:10.1016/j.bbrc.2010.03.043

Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS (2006) Body mass index and risk for end-stage renal disease. Ann Intern Med 144(1):21–28

Iglesias P, Diez JJ (2006) Peroxisome proliferator-activated receptor gamma agonists in renal disease. Eur J Endocrinol 154(5):613–621. doi:10.1530/eje.1.02134

Iseki K, Ikemiya Y, Kinjo K, Inoue T, Iseki C, Takishita S (2004) Body mass index and the risk of development of end-stage renal disease in a screened cohort. Kidney Int 65(5):1870–1876. doi:10.1111/j.1523-1755.2004.00582.xKID582

Janowski BA, Willy PJ, Devi TR, Falck JR, Mangelsdorf DJ (1996) An oxysterol signalling pathway mediated by the nuclear receptor LXR alpha. Nature 383(6602):728–731. doi:10.1038/383728a0

Jiang C, Ting AT, Seed B (1998) PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. Nature 391(6662):82–86. doi:10.1038/34184

Jiang T, Wang Z, Proctor G, Moskowitz S, Liebman SE, Rogers T, Lucia MS, Li J, Levi M (2005) Diet-induced obesity in C57BL/6J mice causes increased renal lipid accumulation and glomerulosclerosis via a sterol regulatory element-binding protein-1c-dependent pathway. J Biol Chem 280(37):32317–32325. doi:10.1074/jbc.M500801200

Jiang T, Wang XX, Scherzer P, Wilson P, Tallman J, Takahashi H, Li J, Iwahashi M, Sutherland E, Arend L, Levi M (2007) Farnesoid X receptor modulates renal lipid metabolism, fibrosis, and diabetic nephropathy. Diabetes 56(10):2485–2493. doi:10.2337/db06-1642

Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD (2001) Obesity-related glomerulopathy: an emerging epidemic. Kidney Int 59(4):1498–1509. doi:10.1046/j.1523-1755.2001.0590041498.x

Kim MK, Ko SH, Baek KH, Ahn YB, Yoon KH, Kang MI, Lee KW, Song KH (2009) Long-term effects of rosiglitazone on the progressive decline in renal function in patients with type 2 diabetes. Korean J Intern Med 24(3):227–232. doi:10.3904/kjim.2009.24.3.227

Kimmelstiel P, Wilson C (1936) Inflammatory lesions in the glomeruli in pyelonephritis in relation to hypertension and renal insufficiency. Am J Pathol 12(1):483–495

Kliewer SA (2003) The nuclear pregnane X receptor regulates xenobiotic detoxification. J Nutr 133(7 Suppl):2444S–2447S

Kliewer SA, Moore JT, Wade L, Staudinger JL, Watson MA, Jones SA, McKee DD, Oliver BB, Willson TM, Zetterstrom RH, Perlmann T, Lehmann JM (1998) An orphan nuclear receptor activated by pregnanes defines a novel steroid signaling pathway. Cell 92(1):73–82

Kono K, Kamijo Y, Hora K, Takahashi K, Higuchi M, Kiyosawa K, Shigematsu H, Gonzalez FJ, Aoyama T (2009) PPAR{alpha} attenuates the proinflammatory response in activated mesangial cells. Am J Physiol Renal Physiol 296(2):F328–F336. doi:10.1152/ajprenal.00484.2007

Kuipers I, van der Harst P, Kuipers F, van Genne L, Goris M, Lehtonen JY, van Veldhuisen DJ, van Gilst WH, de Boer RA (2010) Activation of liver X receptor-alpha reduces activation of the renal and cardiac renin-angiotensin-aldosterone system. Lab Invest 90(4):630–636. doi:10.1038/labinvest.2010.7

Laffitte BA, Joseph SB, Walczak R, Pei L, Wilpitz DC, Collins JL, Tontonoz P (2001) Autoregulation of the human liver X receptor

alpha promoter. Mol Cell Biol 21(22):7558–7568. doi:10.1128/MCB.21.22.7558-7568.2001

Lehrke M, Lazar MA (2005) The many faces of PPARgamma. Cell 123(6):993–999. doi:10.1016/j.cell.2005.11.026

Leik CE, Carson NL, Hennan JK, Basso MD, Liu QY, Crandall DL, Nambi P (2007) GW3965, a synthetic liver X receptor (LXR) agonist, reduces angiotensin II-mediated pressor responses in Sprague-Dawley rats. Br J Pharmacol 151(4):450–456. doi:10.1038/sj.bjp.0707241

Lemberger T, Saladin R, Vazquez M, Assimacopoulos F, Staels B, Desvergne B, Wahli W, Auwerx J (1996) Expression of the peroxisome proliferator-activated receptor alpha gene is stimulated by stress and follows a diurnal rhythm. J Biol Chem 271(3):1764–1769

Letavernier E, Perez J, Joye E, Bellocq A, Fouqueray B, Haymann JP, Heudes D, Wahli W, Desvergne B, Baud L (2005) Peroxisome proliferator-activated receptor beta/delta exerts a strong protection from ischemic acute renal failure. J Am Soc Nephrol 16(8):2395–2402. doi:10.1681/ASN.2004090802

Levi M, Wang X, Choudhury D (2011) Nuclear hormone receptors as therapeutic targets. Contrib Nephrol 170:209–216. doi:10.1159/000325668

Li YT, Swales KE, Thomas GJ, Warner TD, Bishop-Bailey D (2007) Farnesoid × receptor ligands inhibit vascular smooth muscle cell inflammation and migration. Arterioscler Thromb Vasc Biol 27(12):2606–2611. doi:10.1161/ATVBAHA.107.152694

Li L, Emmett N, Mann D, Zhao X (2010) Fenofibrate attenuates tubulointerstitial fibrosis and inflammation through suppression of nuclear factor-kappaB and transforming growth factor-beta1/Smad3 in diabetic nephropathy. Exp Biol Med (Maywood) 235(3):383–391. doi:10.1258/ebm.2009.009218

Liang YJ, Chen SA, Jian JH (2011) Peroxisome proliferator-activated receptor delta downregulates the expression of the receptor for advanced glycation end products and pro-inflammatory cytokines in the kidney of streptozotocin-induced diabetic mice. Eur J Pharm Sci 43(1–2):65–70. doi:10.1016/j.ejps.2011.03.011

Lin H, Hou CC, Cheng CF, Chiu TH, Hsu YH, Sue YM, Chen TH, Hou HH, Chao YC, Cheng TH, Chen CH (2007) Peroxisomal proliferator-activated receptor-alpha protects renal tubular cells from doxorubicin-induced apoptosis. Mol Pharmacol 72(5):1238–1245. doi:10.1124/mol.107.037523

Lonard DM, Lanz RB, O'Malley BW (2007) Nuclear receptor coregulators and human disease. Endocr Rev 28(5):575–587. doi:10.1210/er.2007-0012

Lu TT, Repa JJ, Mangelsdorf DJ (2001) Orphan nuclear receptors as eLiXiRs and FiXeRs of sterol metabolism. J Biol Chem 276(41):37735–37738. doi:10.1074/jbc.R100035200

Luo Y, Tall AR (2000) Sterol upregulation of human CETP expression in vitro and in transgenic mice by an LXR element. J Clin Invest 105(4):513–520. doi:10.1172/JCI8573

Ma LJ, Marcantoni C, Linton MF, Fazio S, Fogo AB (2001) Peroxisome proliferator-activated receptor-gamma agonist troglitazone protects against nondiabetic glomerulosclerosis in rats. Kidney Int 59(5):1899–1910. doi:10.1046/j.1523-1755.2001.0590051899.x

Makishima M, Okamoto AY, Repa JJ, Tu H, Learned RM, Luk A, Hull MV, Lustig KD, Mangelsdorf DJ, Shan B (1999) Identification of a nuclear receptor for bile acids. Science 284(5418):1362–1365

Matsuyama M, Yoshimura R, Hase T, Uchida J, Tsuchida K, Takemoto Y, Kawahito Y, Sano H, Nakatani T (2005) Expression of peroxisome proliferator-activated receptor-gamma in renal ischemia-reperfusion injury. Transplant Proc 37(4):1684–1685. doi:10.1016/j.transproceed.2005.02.068

McCarthy KJ, Routh RE, Shaw W, Walsh K, Welbourne TC, Johnson JH (2000) Troglitazone halts diabetic glomerulosclerosis by blockade of mesangial expansion. Kidney Int 58(6):2341–2350. doi:10.1046/j.1523-1755.2000.00418.x

Michalik L, Auwerx J, Berger JP, Chatterjee VK, Glass CK, Gonzalez FJ, Grimaldi PA, Kadowaki T, Lazar MA, O'Rahilly S, Palmer CN, Plutzky J, Reddy JK, Spiegelman BM, Staels B, Wahli W (2006) International Union of Pharmacology. LXI. Peroxisome proliferator-activated receptors. Pharmacol Rev 58(4):726–741. doi:10.1124/pr.58.4.5

Miki Y, Suzuki T, Tazawa C, Blumberg B, Sasano H (2005) Steroid and xenobiotic receptor (SXR), cytochrome P450 3A4 and multidrug resistance gene 1 in human adult and fetal tissues. Mol Cell Endocrinol 231(1–2):75–85. doi:10.1016/j.mce.2004.12.005

Miyazaki-Anzai S, Levi M, Kratzer A, Ting TC, Lewis LB, Miyazaki M (2010) Farnesoid X receptor activation prevents the development of vascular calcification in ApoE−/− mice with chronic kidney disease. Circ Res 106(12):1807–1817. doi:10.1161/CIRCRESAHA.109.212969

Moore DD, Kato S, Xie W, Mangelsdorf DJ, Schmidt DR, Xiao R, Kliewer SA (2006) International Union of Pharmacology. LXII. The NR1H and NR1I receptors: constitutive androstane receptor, pregnene X receptor, farnesoid X receptor alpha, farnesoid X receptor beta, liver X receptor alpha, liver X receptor beta, and vitamin D receptor. Pharmacol Rev 58(4):742–759. doi:10.1124/pr.58.4.6

Moorhead JF, Chan MK, El-Nahas M, Varghese Z (1982) Lipid nephrotoxicity in chronic progressive glomerular and tubulo-interstitial disease. Lancet 2(8311):1309–1311

Morello F, de Boer RA, Steffensen KR, Gnecchi M, Chisholm JW, Boomsma F, Anderson LM, Lawn RM, Gustafsson JA, Lopez-Ilasaca M, Pratt RE, Dzau VJ (2005) Liver X receptors alpha and beta regulate renin expression in vivo. J Clin Invest 115(7):1913–1922. doi:10.1172/JCI24594

Nannelli A, Chirulli V, Longo V, Gervasi PG (2008) Expression and induction by rifampicin of CAR- and PXR-regulated CYP2B and CYP3A in liver, kidney and airways of pig. Toxicology 252(1–3):105–112. doi:10.1016/j.tox.2008.08.004

Nicholas SB, Kawano Y, Wakino S, Collins AR, Hsueh WA (2001) Expression and function of peroxisome proliferator-activated receptor-gamma in mesangial cells. Hypertension 37(2 Part 2):722–727

Nitta K (2010) Possible link between metabolic syndrome and chronic kidney disease in the development of cardiovascular disease. Cardiol Res Pract 2011. doi:10.4061/2011/963517

Okada T, Wada J, Hida K, Eguchi J, Hashimoto I, Baba M, Yasuhara A, Shikata K, Makino H (2006) Thiazolidinediones ameliorate diabetic nephropathy via cell cycle-dependent mechanisms. Diabetes 55(6):1666–1677. doi:10.2337/db05-1285

Osabe M, Sugatani J, Fukuyama T, Ikushiro S, Ikari A, Miwa M (2008) Expression of hepatic UDP-glucuronosyltransferase 1A1 and 1A6 correlated with increased expression of the nuclear constitutive androstane receptor and peroxisome proliferator-activated receptor alpha in male rats fed a high-fat and high-sucrose diet. Drug Metab Dispos 36(2):294–302. doi:10.1124/dmd.107.017731

Owen GI, Zelent A (2000) Origins and evolutionary diversification of the nuclear receptor superfamily. Cell Mol Life Sci 57(5):809–827

Parks DJ, Blanchard SG, Bledsoe RK, Chandra G, Consler TG, Kliewer SA, Stimmel JB, Willson TM, Zavacki AM, Moore DD, Lehmann JM (1999) Bile acids: natural ligands for an orphan nuclear receptor. Science 284(5418):1365–1368

Peet DJ, Turley SD, Ma W, Janowski BA, Lobaccaro JM, Hammer RE, Mangelsdorf DJ (1998) Cholesterol and bile acid metabolism are impaired in mice lacking the nuclear oxysterol receptor LXR alpha. Cell 93(5):693–704

Portilla D (2003) Energy metabolism and cytotoxicity. Semin Nephrol 23(5):432–438

Pourcet B, Pineda-Torra I, Derudas B, Staels B, Glineur C (2010) SUMOylation of human peroxisome proliferator-activated receptor alpha inhibits its trans-activity through the recruitment of the nuclear corepressor NCoR. J Biol Chem 285(9):5983–5992. doi:10.1074/jbc.M109.078311

Praga M (2002) Obesity—a neglected culprit in renal disease. Nephrol Dial Transplant 17(7):1157–1159

Praga M, Morales E (2006) Obesity, proteinuria and progression of renal failure. Curr Opin Nephrol Hypertens 15(5):481–486. doi:10.1097/01.mnh.0000242172.06459.7c00041552-200609000-00003

Proctor G, Jiang T, Iwahashi M, Wang Z, Li J, Levi M (2006) Regulation of renal fatty acid and cholesterol metabolism, inflammation, and fibrosis in Akita and OVE26 mice with type 1 diabetes. Diabetes 55(9):2502–2509. doi:10.2337/db05-0603

Robinson E, Grieve DJ (2009) Significance of peroxisome proliferator-activated receptors in the cardiovascular system in health and disease. Pharmacol Ther 122(3):246–263. doi:10.1016/j.pharmthera.2009.03.003

Rosen ED, Spiegelman BM (2001) PPARgamma: a nuclear regulator of metabolism, differentiation, and cell growth. J Biol Chem 276(41):37731–37734. doi:10.1074/jbc.R100034200

Rosenfeld MG, Glass CK (2001) Coregulator codes of transcriptional regulation by nuclear receptors. J Biol Chem 276(40):36865–36868. doi:10.1074/jbc.R100041200R100041200

Roth A, Looser R, Kaufmann M, Meyer UA (2008) Sterol regulatory element binding protein 1 interacts with pregnane X receptor and constitutive androstane receptor and represses their target genes. Pharmacogenet Genomics 18(4):325–337. doi:10.1097/FPC.0b013e3282f706e0

Ruan X, Guan Y (2009) Metabolic syndrome and chronic kidney disease. J Diabetes 1(4):236–245. doi:10.1111/j.1753-0407.2009.00042.x

Ruan XZ, Moorhead JF, Fernando R, Wheeler DC, Powis SH, Varghese Z (2003) PPAR agonists protect mesangial cells from interleukin 1beta-induced intracellular lipid accumulation by activating the ABCA1 cholesterol efflux pathway. J Am Soc Nephrol 14(3):593–600

Ruan XZ, Varghese Z, Powis SH, Moorhead JF (2005) Nuclear receptors and their coregulators in kidney. Kidney Int 68(6):2444–2461. doi:10.1111/j.1523-1755.2005.00721.x

Ruan X, Zheng F, Guan Y (2008) PPARs and the kidney in metabolic syndrome. Am J Physiol Renal Physiol 294(5):F1032–F1047. doi:10.1152/ajprenal.00152.2007

Rutkowski P, Klassen A, Sebekova K, Bahner U, Heidland A (2006) Renal disease in obesity: the need for greater attention. J Ren Nutr 16(3):216–223. doi:10.1053/j.jrn.2006.04.017

Sarafidis PA, Bakris GL (2006) Protection of the kidney by thiazolidinediones: an assessment from bench to bedside. Kidney Int 70(7):1223–1233. doi:10.1038/sj.ki.5001620

Satoh N, Naruse M, Usui T, Tagami T, Suganami T, Yamada K, Kuzuya H, Shimatsu A, Ogawa Y (2004) Leptin-to-adiponectin ratio as a potential atherogenic index in obese type 2 diabetic patients. Diabetes Care 27(10):2488–2490

Schoonjans K, Staels B, Auwerx J (1996) Role of the peroxisome proliferator-activated receptor (PPAR) in mediating the effects of fibrates and fatty acids on gene expression. J Lipid Res 37(5):907–925

Schultz JR, Tu H, Luk A, Repa JJ, Medina JC, Li L, Schwendner S, Wang S, Thoolen M, Mangelsdorf DJ, Lustig KD, Shan B (2000) Role of LXRs in control of lipogenesis. Genes Dev 14(22):2831–2838

Seedorf U, Aberle J (2007) Emerging roles of PPARdelta in metabolism. Biochim Biophys Acta 1771(9):1125–1131. doi:10.1016/j.bbalip.2007.04.017

Sonoda J, Chong LW, Downes M, Barish GD, Coulter S, Liddle C, Lee CH, Evans RM (2005) Pregnane X receptor prevents hepatorenal toxicity from cholesterol metabolites. Proc Natl Acad Sci USA 102(6):2198–2203. doi:10.1073/pnas.0409481102

Sonoda J, Pei L, Evans RM (2008) Nuclear receptors: decoding metabolic disease. FEBS Lett 582(1):2–9. doi:10.1016/j.febslet.2007.11.016

Steffensen KR, Gustafsson JA (2004) Putative metabolic effects of the liver X receptor (LXR). Diabetes 53(Suppl 1):S36–S42

Streetz KL, Wustefeld T, Klein C, Manns MP, Trautwein C (2001) Mediators of inflammation and acute phase response in the liver. Cell Mol Biol (Noisy-le-grand) 47(4):661–673

Sugden MC, Bulmer K, Gibbons GF, Holness MJ (2001) Role of peroxisome proliferator-activated receptor-alpha in the mechanism underlying changes in renal pyruvate dehydrogenase kinase isoform 4 protein expression in starvation and after refeeding. Arch Biochem Biophys 395(2):246–252. doi:10.1006/abbi.2001.2586S0003-9861(01)92586-X

Takahashi S, Tanaka T, Kodama T, Sakai J (2006) Peroxisome proliferator-activated receptor delta (PPARdelta), a novel target site for drug discovery in metabolic syndrome. Pharmacol Res 53(6):501–507. doi:10.1016/j.phrs.2006.03.019

Tontonoz P, Mangelsdorf DJ (2003) Liver X receptor signaling pathways in cardiovascular disease. Mol Endocrinol 17(6):985–993. doi:10.1210/me.2003-0061me.2003-0061

Tovar-Palacio C, Tovar AR, Torres N, Cruz C, Hernandez-Pando R, Salas-Garrido G, Pedraza-Chaverri J, Correa-Rotter R (2011) Proinflammatory gene expression and renal lipogenesis are modulated by dietary protein content in obese Zucker fa/fa rats. Am J Physiol Renal Physiol 300(1):F263–F271. doi:10.1152/ajprenal.00171.2010

Ulven SM, Dalen KT, Gustafsson JA, Nebb HI (2005) LXR is crucial in lipid metabolism. Prostaglandins Leukot Essent Fatty Acids 73(1):59–63. doi:10.1016/j.plefa.2005.04.009

Venkateswaran A, Laffitte BA, Joseph SB, Mak PA, Wilpitz DC, Edwards PA, Tontonoz P (2000) Control of cellular cholesterol efflux by the nuclear oxysterol receptor LXR alpha. Proc Natl Acad Sci USA 97(22):12097–12102. doi:10.1073/pnas.200367697200367697

Wagner M, Zollner G, Trauner M (2011) Nuclear receptors in liver disease. Hepatology 53(3):1023–1034. doi:10.1002/hep.24148

Wahba IM, Mak RH (2007) Obesity and obesity-initiated metabolic syndrome: mechanistic links to chronic kidney disease. Clin J Am Soc Nephrol 2(3):550–562. doi:10.2215/CJN.04071206

Wang H, Chen J, Hollister K, Sowers LC, Forman BM (1999) Endogenous bile acids are ligands for the nuclear receptor FXR/BAR. Mol Cell 3(5):543–553

Wang YD, Chen WD, Moore DD, Huang W (2008) FXR: a metabolic regulator and cell protector. Cell Res 18(11):1087–1095. doi:10.1038/cr.2008.289

Wang XX, Jiang T, Shen Y, Adorini L, Pruzanski M, Gonzalez FJ, Scherzer P, Lewis L, Miyazaki-Anzai S, Levi M (2009) The farnesoid X receptor modulates renal lipid metabolism and diet-induced renal inflammation, fibrosis, and proteinuria. Am J Physiol Renal Physiol 297(6):F1587–F1596. doi:10.1152/ajprenal.00404.2009

Watanabe M, Houten SM, Wang L, Moschetta A, Mangelsdorf DJ, Heyman RA, Moore DD, Auwerx J (2004) Bile acids lower triglyceride levels via a pathway involving FXR, SHP, and SREBP-1c. J Clin Invest 113(10):1408–1418. doi:10.1172/JCI21025

Wilens SL, Elster SK (1950) The role of lipid deposition in renal arteriolar sclerosis. Am J Med Sci 219(2):183–196 (illust)

Willy PJ, Umesono K, Ong ES, Evans RM, Heyman RA, Mangelsdorf DJ (1995) LXR, a nuclear receptor that defines a distinct retinoid response pathway. Genes Dev 9(9):1033–1045

Wu J, Zhang Y, Wang N, Davis L, Yang G, Wang X, Zhu Y, Breyer MD, Guan Y (2004) Liver X receptor-alpha mediates cholesterol

efflux in glomerular mesangial cells. Am J Physiol Renal Physiol 287(5):F886–F895. doi:10.1152/ajprenal.00123.2004

Yang T, Michele DE, Park J, Smart AM, Lin Z, Brosius FC 3rd, Schnermann JB, Briggs JP (1999) Expression of peroxisomal proliferator-activated receptors and retinoid X receptors in the kidney. Am J Physiol 277(6 Pt 2):F966–F973

Yang HC, Ma LJ, Ma J, Fogo AB (2006) Peroxisome proliferator-activated receptor-gamma agonist is protective in podocyte injury-associated sclerosis. Kidney Int 69(10):1756–1764. doi:10.1038/sj.ki.5000336

Yano M, Matsumura T, Senokuchi T, Ishii N, Murata Y, Taketa K, Motoshima H, Taguchi T, Sonoda K, Kukidome D, Takuwa Y, Kawada T, Brownlee M, Nishikawa T, Araki E (2007) Statins activate peroxisome proliferator-activated receptor gamma through extracellular signal-regulated kinase 1/2 and p38 mitogen-activated protein kinase-dependent cyclooxygenase-2 expression in macrophages. Circ Res 100(10):1442–1451. doi:10.1161/01.RES.0000268411.49545.9c

Zambon A, Gervois P, Pauletto P, Fruchart JC, Staels B (2006) Modulation of hepatic inflammatory risk markers of cardiovascular diseases by PPAR-alpha activators: clinical and experimental evidence. Arteriosc Thromb Vasc Biol 26(5):977–986. doi:10.1161/01.ATV.0000204327.96431.9a

Zhang H, LeCulyse E, Liu L, Hu M, Matoney L, Zhu W, Yan B (1999) Rat pregnane X receptor: molecular cloning, tissue distribution, and xenobiotic regulation. Arch Biochem Biophys 368(1):14–22. doi:10.1006/abbi.1999.1307

Zhang Y, Castellani LW, Sinal CJ, Gonzalez FJ, Edwards PA (2004) Peroxisome proliferator-activated receptor-gamma coactivator 1alpha (PGC-1alpha) regulates triglyceride metabolism by activation of the nuclear receptor FXR. Genes Dev 18(2):157–169. doi:10.1101/gad.1138104

Zheng F, Fornoni A, Elliot SJ, Guan Y, Breyer MD, Striker LJ, Striker GE (2002) Upregulation of type I collagen by TGF-beta in mesangial cells is blocked by PPARgamma activation. Am J Physiol Renal Physiol 282(4):F639–F648. doi:10.1152/ajprenal.00189.2001

Zhou C, Tabb MM, Nelson EL, Grun F, Verma S, Sadatrafiei A, Lin M, Mallick S, Forman BM, Thummel KE, Blumberg B (2006) Mutual repression between steroid and xenobiotic receptor and NF-kappaB signaling pathways links xenobiotic metabolism and inflammation. J Clin Invest 116(8):2280–2289. doi:10.1172/JCI26283