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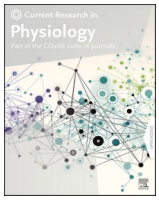

How PPAR-alpha mediated inflammation may affect the pathophysiology of chronic kidney disease

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ABSTRACT

Chronic kidney disease (CKD) is a major risk factor for death in adults. Inflammation plays a role in the pathogenesis of CKD, but the mechanisms are poorly understood. Peroxisome proliferator-activated receptor alpha (PPAR-α) is a nuclear receptor and one of the three members (PPARα, PPARβ/δ, and PPARγ) of the PPARs that plays an important role in ameliorating pathological processes that accelerate acute and chronic kidney disease. Although other PPARs members are well studied, the role of PPAR-α is not well described and its role in inflammation-mediated chronic disease is not clear. Herein, we review the role of PPAR-α in chronic kidney disease with implications for the immune system.

1. Introduction

Chronic kidney disease (CKD) affects more than 37 million adults in the United States and carried an estimated financial burden of $87.2 billion USD in 2019. As the internationally 16th leading cause of mortality, CKD poses a great risk to global public health despite being underrecognized by many clinicians and patients (Chen et al., 2019). CKD, characterized by prolonged damage to kidney structure and function, can promote a plethora of other deleterious conditions including cardiovascular disease, end-stage kidney disease, and even death (Chen et al., 2019; Nephrology, 2011; Ertuglu et al., 2022a). Common risk factors associated with CKD development include chronic inflammation, diabetes, hypertension, and obesity (Akchurin et al., 2015). Importantly, recent studies have affirmed that high sodium (HS) diet can also increase the risk for kidney disease (Malta et al., 2018).

From a public health standpoint, these findings are highly consequential as Americans on average consume more than 3400 mg of sodium per day despite the recommended daily consumption being less than 2300 mg (Sodium Intake and Health, 2023). Excessive sodium consumption leads to several detrimental effects including hypertension (Grillo et al., 2019), fluid retention (Chrysohoou et al., 2022), glomerular hyperfiltration (Barnett et al., 2022; Rossitto et al., 2020; Mallamaci et al., 1996), progression of existing kidney disease (Ohta et al., 2013), inflammation (Afsar et al., 2018), and CKD (Borrelli et al., 2020). Salt sensitivity of blood pressure (SSBP), a concept where blood pressure mirrors sodium intake, is a major contributor to the development of CKD (Borrelli et al., 2020). Increased production of inflammation associated with salt-sensitive hypertension has been implicated in driving and contributing to the pathogenesis of CKD (Maaliki et al., 2022). Nevertheless, the molecular mechanism behind this process remains unclear.

Peroxisome proliferator-activated receptors (PPARs), a group of nuclear hormone receptors, have been implicated in CKD pathogenesis. PPARs belong to a superfamily of ligand-activated transcription factors that consist of three subtypes (PPAR-α, PPAR-β/δ, and PPAR-γ) (Xi et al., 2020). PPARs regulate gene transcription through ligand-dependent or -independent mechanisms. PPAR-α, the first member of the PPAR subfamily identified, is expressed ubiquitously; however, it is most highly expressed in tissues that exhibit high levels of mitochondrial and fatty acid oxidation (FAO) activity, including those of the liver, kidney, intestinal mucosa, and heart (Dixon et al., 2021; Rakhshandehroo et al., 2010). Recently, PPAR-α has also been identified in immune cells and has been increasingly recognized for its influence on the innate and adaptive immune systems that may contribute to exacerbated inflammation (Christofides et al., 2021). Further, PPAR-α also plays a critical

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role as a primary sensor and regulator of lipid metabolism, and this emerging vital role can be important when investigating inflammation-derived disorders including hypertension, metabolic disorders, cardiovascular disease, atherosclerosis, and inflammation-induced acute renal failure (Robinson et al., 2009). With the growing mounting evidence that connects immune-regulated inflammation to disorders such as hypertension and CKD, expansion on PPAR-α investigations is imperative and may uncover a novel therapeutic target that ameliorates cardiovascular and renal pathophysiology. Herein, we review the function and activity of PPAR-α to further deepen our current-state of understanding on the underlying connections between CKD, inflammation, and hypertension.

2. Distribution, structure, and physiological function of peroxisome proliferator-activated receptors

Peroxisome proliferator-activated receptors (PPARs) are expressed across an array of tissues including hepatocytes, adipocytes, muscles, and endothelial cells (Grygiel-Gó and rniak, 2014a), Table 1. The family of PPARs are comprised of three isoforms (PPAR-α, PPAR-β/δ, and PPAR-γ) that are differentially expressed based on their respective physiological roles, tissue distributions, and ligand specificities (Grygiel-Gó and rniak, 2014a), (**Fig. 1**). Previous studies, employing experimental and clinical models, have shown that PPARs play important roles in lipid metabolism and energy homeostasis in the kidney (Tovar-Palacio et al., 2012a; Corrales et al., 2018; Gao et al., 2022). Further, despite all PPAR isotypes being implicated in glucose and lipid mechanistic pathways, PPAR-α has been most extensively examined in fatty acid metabolism as its activation decreases lipid levels. Specifically, PPAR-α is highly expressed in metabolically active tissues, such as liver, heart, skeletal muscle, intestinal mucosa, and brown adipose tissue (Grygiel-Gó and rniak, 2014a). In the kidney, PPAR-α is abundant in the proximal tubules and medullary thick ascending limbs, with much lower levels in glomerular mesangial cells (Guan et al., 1997; Kamijo et al., 2002a). Given the increased expression of PPAR-α in the proximal tubules and medullary thick ascending limbs, PPAR-α has been implicated in the regulation of inflammatory responses in the kidney (Di Paola et al., 2007). PPAR-α knockout mice have been shown to have reduced kidney function during sepsis-induced acute kidney injury (AKI), which is also related to reduced FAO and increased inflammation (Iwaki et al., 2019). PPAR-α exhibits a protective role against sepsis-associated AKI by improving reduced FAO and increased inflammation (Iwaki et al., 2019). PPAR-α ligands attenuate cisplatin-induced AKI by preventing the inhibition of FAO, reducing apoptosis and necrosis in the proximal tubule cells, and limiting inflammatory processes by blocking NF-κB (Li et al., 2004a, 2005; Baud et al., 2007). PPAR-α also plays an important role in glomerulonephritis.

The Human PPAR-α gene encoding a protein of 468 amino acids is located on chromosome 22q12-q13.1 (Desvergne et al., 1999; Pyper et al., 2010). The mechanisms that mediate the transactivation or transrepression of PPARs are well coordinated. PPARs have four main functional domains, the N-terminal contains the ligand-independent transactivation domain AF1 (A/B), DNA-binding domain (C), co-factor docking domain (D) and the ligand-binding domain with ligand-dependent transactivation domain AF2 (E/F) where ligands bind and interact with PPARs (Miyachi, 2021). The E/F is on the C-terminal (**Fig. 2**). Once the ligand has bound to the E/F domain, the PPARs translocate to the nucleus where the C terminal binds to the retinoid X receptor (RXR) forming a dimer which then binds to peroxisome proliferator response elements on the DNA to activate transcription and coordinate normal physiology and pathological process (Berger et al., 2002; Grygiel-Gó and rniak, 2014b). The C domain with its conserved finger motifs binds to the peroxisome proliferator response element while the D Domain is the docking site for coactivator bindings sites (Usuda et al., 2014; Guo et al., 2006). The E/F site is where ligands bind to activate PPARs through trans-AF-2 (Usuda et al., 2014; Guo et al., 2006). Disruptions in PPARs signaling creates a fertile environment for disease progression.

Table 1
PPAR expression sites and their physiological functions.

Organ/ System	Site of Expression	Function and Implications
Kidney	Proximal tubules	Regulate metabolism in the kidney and increase FAO (Chambers et al., 2020)
	Medullary thick ascending limbs Glomerular mesangial cells and podocytes (Kamijo et al., 2002b; Berger et al., 2002)	Reduce inflammation, glomerular and tubulointerstitial fibrosis, inhibit apoptosis and necrosis and improve insulin resistance (Gao et al., 2022; Derosa et al., 2018; Tovar-Palacio et al., 2012b)
Liver	Hepatocytes	Regulates whole-body fatty acid homeostasis and protective against non-fatty liver disease (Montagner et al., 2016). Impairment of PPAR-α is associated with hepatic steatosis, liver inflammation and fibrosis and liver cancer (Wang et al., 2020).
Intestinal Mucosa	Epithelial cells Villi of enterocytes Paneth cells of intestinal crypts Immune cells like lamina propria macrophages & dendritic cells	Regulate microbiota homeostasis, contributes to immunological tolerance and gut permeability (Grabacka et al., 2022)
Heart and Vasculature	Endothelial cells and myocytes	Preserves myocardial energy and improves cardiac function in various heart pathologies including heart failure and cardiac hypertrophy (Kaimoto et al., 2017; Warren et al., 2017). In vascular endothelial cells, PPAR-α contributes to delayed atherosclerotic plaque formation and improves endothelial function by increasing Nitric Oxide Synthase Expression in Vascular Endothelial Cells (Dou et al., 2021; Reiterer et al., 2004; Goya et al., 2004)
Immune System	$CD45^{+}$ leukocytes (Kaipainen et al., 2007), monocytes and macrophages (Chinetti et al., 2003), basophils (Fujimura et al., 2002), eosinophils (Woerly et al., 2003), Langerhans cells (Dubrac et al., 2007), Kupffer cells (Brocker et al., 2017), microglia (Warden et al., 2016) and osteoclasts (Poulsen et al., 2007).	Reduce inflammation and coagulable states (Grabacka et al., 2021a)

Endogenous PPAR-α agonists are mostly fatty acids and their derivatives such as oleylethanolamide, palmitoylethanolamide, 5-(S)-hydroxyeicosatetraenoic acids (HETE) and 8-(S)-HETE, stearic and palmitic acids and leukotriene B4 (LTB4) (Kamata et al., 2020). PPAR-α activation via its ligands has a variety of function in pathology such as reducing fibrinogen (Kockx et al., 1999), increase high density cholesterol (HDL-c) (Staels et al., 1998), reduce atherosclerosis, oxidative stress, endothelial dysfunction and inflammation among others (Zandbergen et al., 2007; Zheng et al., 2024; Luan et al., 2023).

3. Inflammation, hypertension, and sodium contribute to chronic kidney disease

Studies in the last decade have highlighted the strong relationship

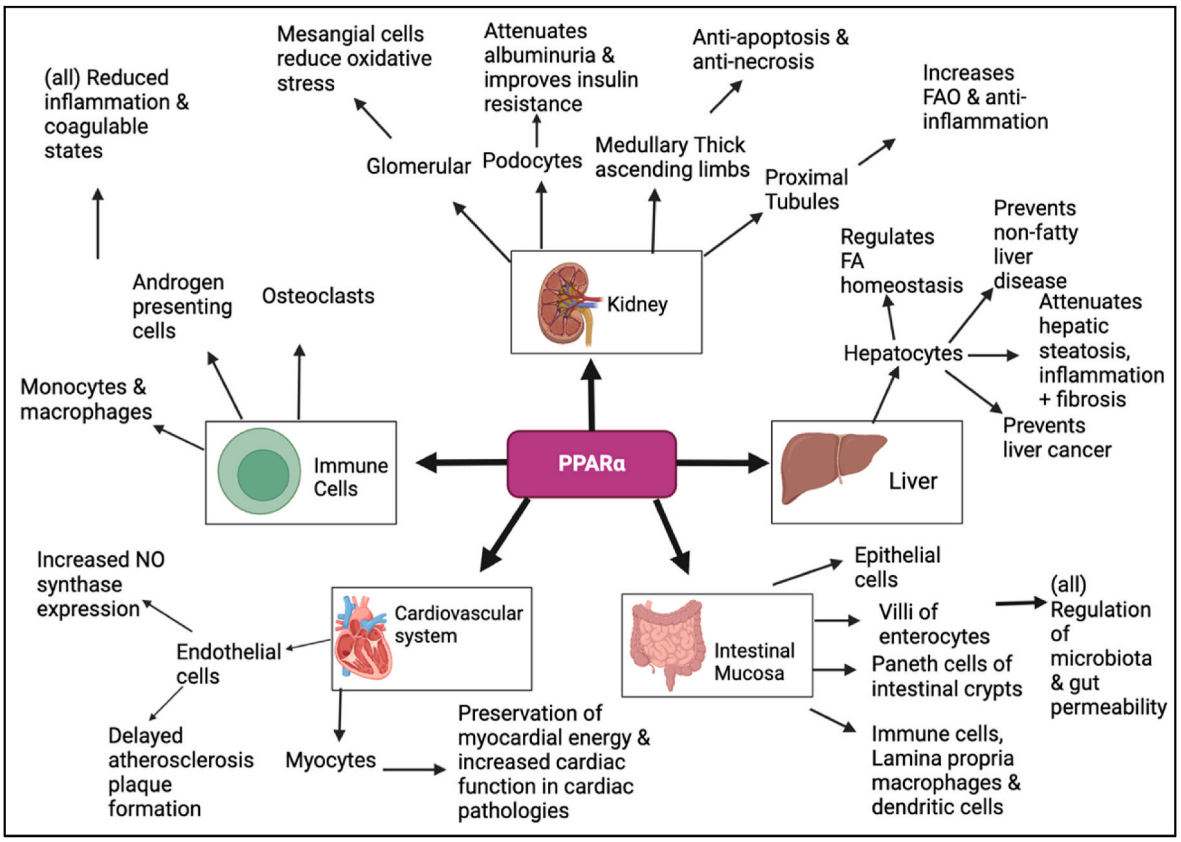

Fig. 1. Map of PPAR expression sites and their physiological functions. The family of PPARs are comprised of three isoforms (PPAR-α, PPAR-β/δ, and PPAR-γ) that are differentially expressed based on their respective physiological roles, tissue distributions, and ligand specificities. PPAR-α is highly expressed across an array of metabolically active tissues, such as liver, heart, skeletal muscle, and intestinal mucosa (Grygiel-Gó and rniak, 2014a).

between high salt (HS) diet, inflammation, hypertension, and CKD (Ertuglu et al., 2022a; Chaudhari et al., 2022). The progression of CKD is closely associated with hypertension, systemic inflammation, and oxidative stress (Rapa et al., 2019). Hypertension, a condition developed largely through prolonged inflammation, has been well-established as an influential remediable risk factor for developing CKD (Lee et al., 2022; Pugh et al., 2019; Burnier et al., 2023). Prior data from a 2010 national survey in the United States revealed that hypertension is observed in 35.8% of stage 1 CKD patients, 48.1% of stage 2, 59.9% of stage 3, and 84.1% of stage 4–5 (Tedla et al., 2011). Further, a cohort study involving 7343 individuals led by Lee et al. uncovered that high blood pressure, defined by SBP ≥130 mmHg and DBP ≥90 mmHg, was associated with elevated hazard for CKD development (Lee et al., 2022). Additionally, prior work by Kovesdy et al. reported that systolic BP > 170 mmHg was related to a significantly increased risk for end-stage renal disease (ESRD) after analyzing a cohort of 5161 ESRD patients (Kovesdy et al., 2016).

Excessive sodium consumption is a well-known risk factor for developing hypertension (Grillo et al., 2019; Ma et al., 2015; Denton et al., 1995; Mutchler et al., 2021). Raised interstitial sodium levels have the ability to act as a hypertensive and inflammatory stimuli, even in normotensive individuals. Inflammation has been recognized as a vital and potent contributor to CKD pathology (Qian, 2017). Moreover, elevated sodium intake has been acknowledged to promote, not only hypertension, but also CKD, tissue inflammation, and autoimmune disease in mice (Nephrology, 2011; Burnier et al., 2023; Tedla et al., 2011; Kovesdy et al., 2016; Ma et al., 2015; Denton et al., 1995; Mutchler et al., 2021; Qian, 2017). A study conducted by Yoon et al. found that excessive sodium intake led to heightened risk for CKD development in 3106 hypertensive patients while this relationship was not observed in the 4781 normotensive patients. From their work, Yoon et al. concluded that dietary sodium consumption influences renal function in a BP-dependent manner further highlighting the significance of the relationship between sodium, BP, and CKD (Yoon et al., 2018). In addition, previous work unveiled that short-term consumption of a HS diet (2–4 weeks) caused increased infiltrates and that Angiotensin II together with HS (4%) caused elevated albumin excretion, an index of kidney injury (Lee et al., 2006).

Salt sensitivity of blood pressure (SSBP), characterized by blood pressure fluctuations that mirror dietary sodium (Na^+) intake, is a known risk factor for CKD (Pitzer et al., 2022). The pathological mechanisms behind SSBP development remain controversial. The traditional hypothesis proposed by Guyton et al. implicated dysfunctional renal Na^+ handling as a primary cause for salt-sensitivity. Per this notion, until isosmotic homeostasis is met, salt-loading would increase plasma volume and thusly lead to pressure natriuresis and renal sodium excretion in order to restore BP to the baseline level (Grillo et al., 2019; El-Sayed et al., 1996; Guyton, 1991). Accordingly, sodium-induced hypertension has previously been associated with an impaired renal natriuretic system. Extensive investigation has revealed variations in renal Na^+ channels, the renin-angiotensin system, and the sympathetic system in SSBP (Ertuglu et al., 2022a). Interestingly, hemodynamic studies following salt loading and depletion unveiled no variations between salt-sensitive and salt-resistant individuals in Na^+ balance and plasma volume. Rather, it was shown that salt-sensitive patients are deprived of the vasodilator response exhibited in salt-resistant patients essentially implying that SSBP development may be related to other pathophysiologic mechanisms, namely inflammation (Laffer et al., 2016).

Studies in the last decade have illustrated a strong connection between inflammation and SSBP. Peripheral blood antigen-presenting cells (APCs), including monocytes, macrophages, and dendritic cells, are

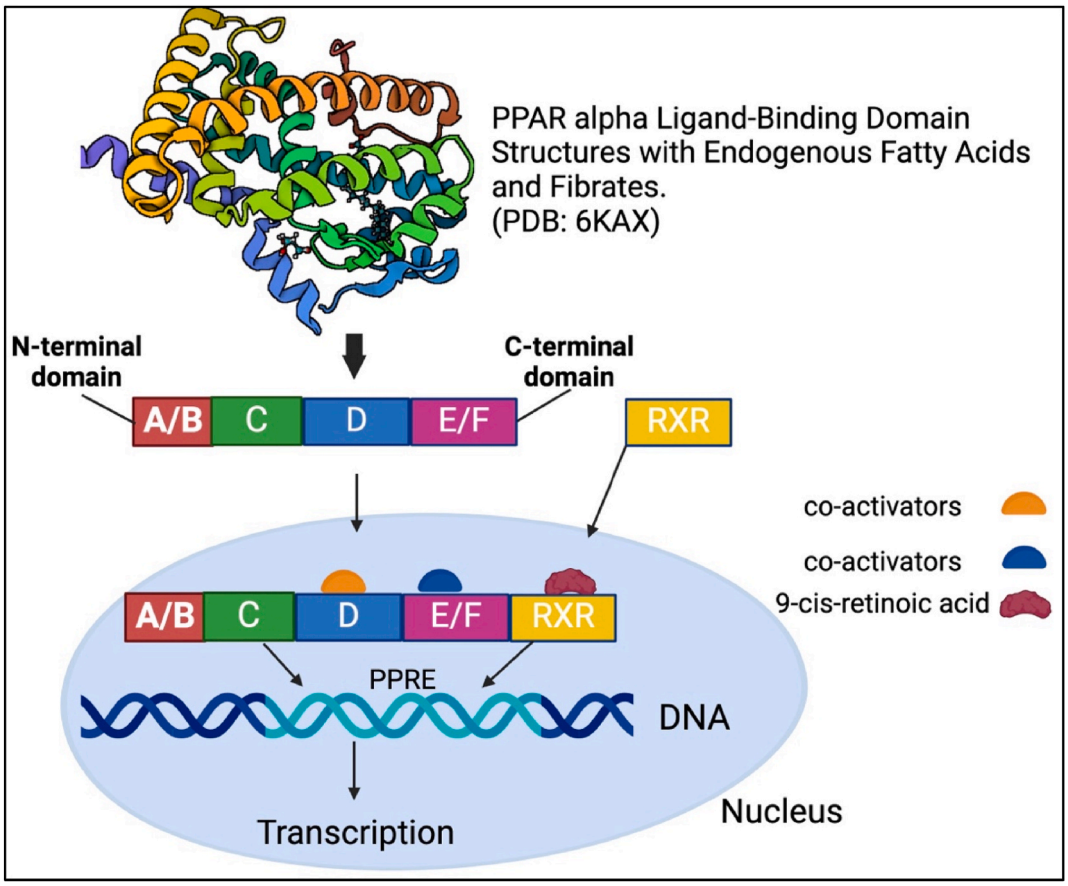

Fig. 2. Structure and transactivation of PPARs. A/B, Ligand-independent transactivation domain (AF1), DNA-binding domain (C), co-factor docking domain (D) and the ligand-binding domain with ligand-dependent transactivation domain AF2 (E/F).

immune cells that are essential for initiating innate and adaptive immune responses that contribute to inflammatory conditions (Demirci et al., 2024). Dendritic cells (DCs), a type of immune cell designated as professional APCs, are chief inducers of adaptive immunity and regulate local inflammatory responses across the body (Schmidt et al., 2012). Together, with macrophages, DCs constitute the most abundant component of the intrarenal immune system (Kurts et al., 2020). The pro-inflammatory actions of DCs can contribute to tissue damage in various types of acute kidney injury and chronic glomerulonephritis, as DCs recruit and activate effector T cells that release toxic mediators and maintain tubulointerstitial immune infiltrates (Ahadzadeh et al., 2018). DCs orchestrate the inflammatory response via its ability to concurrently stimulate T cells through the antigen-MHC receptor complex and express proinflammatory stimulators (Ertuglu et al., 2022a). Notably, hypertensive stimuli have been shown to incite the infiltration of APCs and T cells in the kidneys and vasculature which could ultimately be promotive of the renal injury and endothelial damage observed in CKD (Ertuglu et al., 2022a; Baaten et al., 2023).Our lab has previously established that hyperosmolar Na^+ enters APCs through the amiloride-sensitive epithelial sodium channel (ENaC) to induce oxidative stress and increase isolevuglandin production to stimulate T-cell activation and cytokine release **(Fig. 3)** (Laffer et al., 2016; Barbaro et al., 2017). The precise molecular mechanism by which this process unfolds has yet to be fully elucidated (Rapa et al., 2019).

Nevertheless, ongoing investigation on SSBP pathogenesis persists. Recent animal and human studies indicate that proinflammatory cytokines such as IL-1β mediate renal, endothelial, and immune responses which in turn influences blood pressure elevation. Investigation of IL-1β levels following IL-1β pharmacological inhibition, targeted antibody treatment, and genetic deletion all indicate that targeting of IL-1β decreases blood pressure. Moreover, prior work has demonstrated that high sodium environments increased IL-1β production in DCs to modulate SSBP by enticing T cells to produce interleukin 17-A (IL-17A) **(Fig. 3)** (Barbaro et al., 2017; Shapiro et al., 1997). Intriguingly, recent work suggests that inflammasome activation serves as a regulator of both IL-1β levels and SSBP progression. As aforementioned, hypertensive stimuli, including sodium, induces oxidative stress in APCs through reactive oxygen species (ROS) generation and recent findings suggest that ROS activates NLRP3 inflammasome (Pitzer et al., 2020). NLRP3 stimulation leads to caspase-1 cleavage and subsequent release of IL-1β and IL-18, all of which are observed at high levels in the plasma of hypertensive individuals (Ertuglu et al., 2022b). Elevated levels of these cytokines are also related to renal and vascular dysfunction within this population (De Miguel et al., 2021).

Additionally, transforming growth factor β1 (TGFβ1) is another proinflammatory cytokine implicated in the development of chronic kidney disease, hypertension, diabetes mellitus, and end organ damage (e.g. cardiac dysfunction, arteriosclerosis, and chronic renal failure) (Matsuki et al., 2014; Chen et al., 2018). Prior work by Ying and Sanders revealed that prehypertensive Dahl/Rapp salt-sensitive rats exhibited heightened TGFβ1 expression which was further exacerbated by HS diet. These findings suggest that augmented vascular and glomerular TGFβ1 production may contribute to hypertensive nephrosclerosis in Dahl rats (Ying et al., 2003). Activation of the TGFβ1 pathway leads to signal propagation by at least two routes: the suppressor of mothers against decapentaplegic (SMAD)-dependent canonical pathway and SMAD-independent non-canonical pathways. During the SMAD-dependent canonical pathway, TGFβ1 triggers phosphorylation of receptor regulated SMAD2 and SMAD3. Upon TGFβ1 activation, SMAD complexes with co-SMAD (e.g. SMAD4) and translocate to the

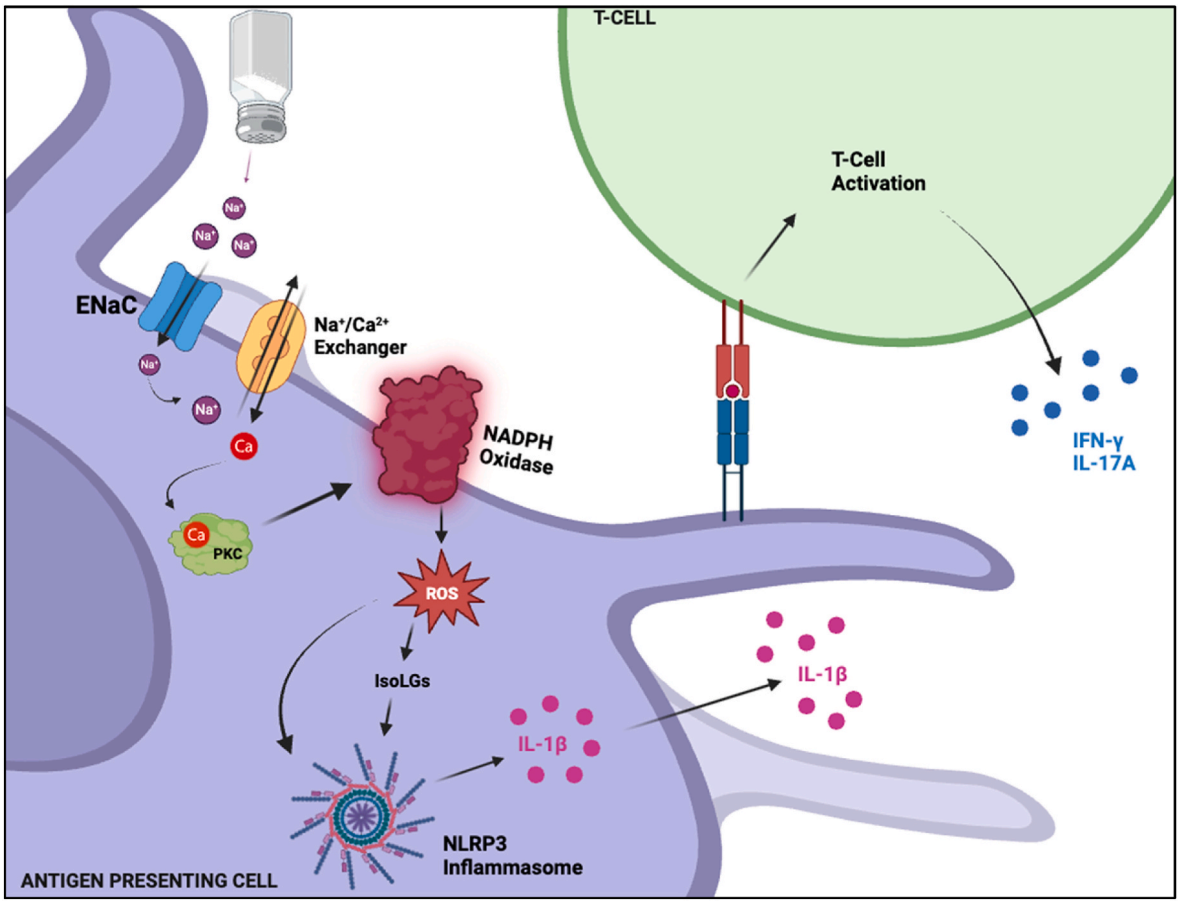

Fig. 3. Sodium triggers an inflammatory response in antigen-presenting cells. Hyperosmolar Na^+ enters APCs through the ENaC to induce oxidative stress and increase isolevuglandin (IsoLG) production which stimulates T-cell proliferation and proinflammatory cytokine release. High sodium environments have also been shown to increase IL-1β production in DCs to modulate SSBP by enticing T cells to produce IL-17A.

nucleus where it associates with other transcription factors and regulates transcriptional responses (Matsuki et al., 2014). Under pathological conditions, there is observed SMAD2 and SMAD3 upregulation, hence, the TGFβ/SMAD pathway serves a crucial role in progressive renal injury and inflammation. Novel findings by Meng et al. indicated that SMAD3-deficient mice are protected against myocardial and renal fibrosis following Ang II treatment (Meng et al., 2020). Moreover, novel findings suggest that DC-specific SMAD3 mediates IsoLG-protein adducts formation, T cell activation, and inflammation which is promotive of SSBP development (Saleem et al., 2023, 2024). SMADs have also been shown to interact with other regulators of renal and hepatic inflammation and fibrosis such as Janus kinase 2 (JAK2) and nuclear factor kappa B (NF-κB) (Chen et al., 2018; Saleem et al., 2024; Xu et al., 2020; Dai et al., 2021). In the SMAD-independent non-canonical pathways, TGFβ1 signaling triggers the activation of other proinflammatory modulators implicated in SSBP and CKD progression, including p38 mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), or c-jun N-terminal kinase (JNK) (Matsuki et al., 2014).

Beyond its ability to initiate differing inflammatory signaling pathways, sodium also has profound effects on immune cell phenotypes. Previous conducted studies have established that macrophages no longer polarize in the presence of high sodium concentrations, which is linked with proinflammatory (M1) macrophage preponderance (Schatz et al., 2017; Binger et al., 2015). Novel experiments have also shown that increased sodium concentration significantly boosted T-cell differentiation, stimulated tumor necrosis factor – alpha (TNF-α) expression and led to cell death (Binger et al., 2015; Lang et al., 2002; Junger et al., 1994). In C57BL6J/N genetic background, with no episodes of arterial hypertension detected by intermittent tail cuff measurements, prominent phenotypic changes of proximal and distal tubular cell phenotypes and tubularization of glomerular structures, pronounced immune cell infiltration, especially of macrophages and T cells were observed (Bernhardt et al., 2021). It is also well known that interleukin-6 (IL-6), a pro-inflammatory cytokine, modulates monocytes differentiation between macrophages and DCs (Su et al., 2017). IL-6 also switches the differentiation of monocytes from DCs to macrophages (Barbaro et al., 2017; Griendling et al., 2000).

Taken altogether, there is a clear relationship between excessive dietary sodium intake, hypertension, inflammation, and CKD. The highlighted findings discussed in this section provide insight on the underlying interrelationship between the mechanistic pathways that contribute to these pathological conditions. These reports illustrate how consequential the regulation of sodium consumption is on renal and cardiovascular pathogenesis. Managed sodium intake may help to alleviate these pathogenic conditions in order to attenuate the hazard for CKD development and progression, particularly in hypertensive patients.

4. The role of PPAR-alpha in chronic kidney disease

PPAR-α is a nuclear receptor and transcription factor whose main role is to regulate lipid metabolism in the liver as well as promote gluconeogenesis and the synthesis of glycogen (Peeters et al., 2010). PPAR-α also reduces atherosclerosis and inflammation by inhibiting macrophage uptake of glycated low-density lipoprotein (Rigamonti et al., 2008).

PPAR-α plays a key role in kidney health. PPAR-α regulates lipid metabolism and energy homeostasis in the kidney (Tovar-Palacio et al.,

2012a). Evidence from animal models has shown that PPARs including PPAR-α and its ligands reduce and protect the kidneys from injury and dysfunction (Letavernier et al., 2005; CHUNG et al., 2005; Cuzzocrea, 2004; Portilla et al., 2000; Li et al., 2004b). In the kidney, PPAR-α is thought to regulate kidney metabolism and mediate adaptive response to dietary fatty acids (Tovar-Palacio et al., 2012a). Hence, loss of PPAR-α may result in abnormal metabolism that may accelerate injury during starvation (Sugden et al., 2001). A recent experimental study by Comella et al. has shown evidence of the mechanistic role that PPAR-α plays in protecting kidneys of mice from fatty acid induced injury mediated by oleylethanolamide, an endogenous PPAR-α agonist (Comella et al., 2024). When PPAR-α was activated by oleylethanolamide, this activation protected the kidneys of mice from lipotoxicity, inflammation and fibrosis by promoting anti-inflammatory effects and regulating inflammatory genes while PPAR-α-deficient mice had worsening of tubular epithelial injury and renal damage (Grabacka et al., 2021a; Comella et al., 2024; Bougarne et al., 2018). Previous work by Park et al. also unveiled that the PPAR-α agonist, fenofibrate, decreases excretion of albumin and improve glomerular function in mice with diabetic nephropathy (Park et al., 2006a, 2006b). In addition, PPAR-α expression in mesangial kidneys cells inhibit the TGF-β signaling pathway reducing fibrotic changes and glomerular matric proliferation (Li et al., 2010). PPAR-α activation was associated with reduced levels of TGF-β1, fibronectin, collagen IV, reduced expression of neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 and ultimately improved kidney function (Comella et al., 2024).

Further, as previously mentioned, DCs constitute the most abundant component of the intrarenal immune system. DCs exhibit PPAR-α expression and they may help in the regulation of inflammatory responses to protect against renal inflammation and injury (Grabacka et al., 2021b; Yin et al., 2020; Cheng et al., 2010a). Previous results demonstrate that PPAR-α exerts anti-inflammatory effects in a chronic model of Angiotensin II (Ang II) (400 ng/kg/min) treatment and fenofibrate lowers plasma interleukin-6 (IL-6), renal monocyte chemoattractant protein-1 (MCP-1), and mean arterial pressure (MAP) in wild-type (WT) mice (Wilson et al., 2012). Preliminary results also demonstrate that the baseline glomerular filtration rate (GFR) is lower in PPAR-α knockout (KO) mice and during Ang II treatment, when compared to WT controls.

The proximal tubule epithelial cells (PTECs) are the most abundant cells in the kidney that play key and diverse regulatory and endocrine roles (Nakhoul et al., 2011). PTECs express several key transporters to facilitate transport of metabolic compounds, waste products and water across the nephron (Nakhoul et al., 2011; Brown et al., 2008). PTECs are also a primary target of injury and progression of CKD (Jang et al., 2021; Chevalier, 2016; Peng et al., 2023). In acute kidney injury, transgenic expression of proximal tubule PPAR-α in mice serves a protective role (Li et al., 2009). PTECs have the highest expression of PPAR-α than any other segment along the nephron and the presence of PPAR-α reduces tubulointerstitial fibrosis and inflammation associated with obstructive uropathy (Cheng et al., 2010a; Li et al., 2013). Additionally, the abundance of PPAR-α in the kidney has also been shown to be associated with reduced tissue renin-angiotensin system (RAS) activity (Shin et al., 2009).

PPAR-α also plays a role in modulating blood pressure to ameliorate CKD. Angiotensin-induced hypertension in rats was blunted and reduced by PPAR-α agonists via improvement of endothelial function (Diep et al., 2002). PPAR-α activation by various agonists has also been shown to reduce blood pressure in DOCA-salt-induced hypertensive mouse by reducing sodium retention via increase of renal 20-hydroxyeicosatetraenoic acid production (Duan et al., 2009). Further investigation utilizing mouse models of salt-sensitive hypertension can help to determine how PPAR-α expression in DCs and PTECs influence the interactions between those two cell types and modulate inflammatory mechanisms that initiate SSBP and CKD. Nevertheless, the causative role of DC PPAR-α salt-sensitive hypertension is not known.

Taken together, PPAR-α is a potential target for therapeutic interventional studies that aim to reduce and prevent kidney injury and disease. Because of its major role in regulating lipid metabolism and maintaining kidney energy homeostasis, emerging evidence now shows that PPAR-α agonists can be used to treat diabetic nephropathy and reduce oxidative stress in glomerular mesangial cells (Cheng et al., 2010b; Wilmer et al., 2002). Overall, targeting PPAR-α has beneficial effects that go beyond the kidney to reduce local and systemic inflammation as well as improve lipid metabolism (Cheng et al., 2010b). Future research could focus on the role of PPAR-α in HIV-associated kidney disease and metabolic disease especially affecting the liver. In persons with HIV, kidney disease is more prevalent due to HIV viral protein- and antiretroviral therapy-induced kidney injury and toxicity, respectively (Wyatt, 2017; Bertoldi et al., 2017).

5. PPAR-alpha interacts with key immunoregulators to reduce inflammation

PPAR-α activation has the ability to exert protective effects that ameliorates kidney disease. The immune regulatory effects of PPAR-α responsible for reducing inflammation stems from its interactions with intracellular signaling proteins systems (Delerive et al., 1999a). As of yet, mechanistically, there is no consensus model that describes how the anti-inflammatory activity of PPAR-α directly alleviates chronic kidney disease. Hence, we discuss the signaling systems involving PPAR-α that have been mooted to have a role in preventing inflammation to disincentivize CKD progression.

5.1. PPAR-alpha and NLRP3

The NLR family pyrin domain containing 3 (NLRP3) inflammasome is an intracellular protein complex that regulates innate immune responses by promoting secretion of inflammatory cytokines (Chen et al., 2023). The NLRP3 inflammasome is a complex of 3 proteins, NLRP3 which functions as the sensor protein, the adaptor protein called adaptor molecule apoptosis-associated speck-like protein containing a CARD (ASC) and the enzyme procaspase-1 (Yang et al., 2019; Masenga et al., 2024). NLRP3 inflammasome stimulation is a central mechanism in renal pathophysiology (Huang et al., 2023). It has been implicated in promoting renal inflammation and fibrosis to contribute to CKD (Vilaysane et al., 2010).

Activation of NLRP3 leads to the cleavage of caspase-1 and subsequent release of IL-1β and IL-18, all of which are conducive to CKD development (Ertuglu et al., 2022b). Recent studies indicate that toll-like receptor 4 (TLR4) and PPAR-α knockout (KO) mice demonstrate a significant increase in NLRP3, ASC-1, and Caspase-1 expression when compared to wild-type (WT) mice (Gugliandolo et al., 2019). Further, prior work by Brocker et al. indicates that PPAR-α activation leads to the upregulation of the long non-coding RNA gene Gm15441 which subsequently suppresses its antisense transcript, encoding thioredoxin interacting protein (TXNIP). This, in turn, leads to decreased NLRP3 stimulation, caspase-1 cleavage, and IL-1β maturation. This study additionally revealed that Gm15441-deficient mice were more susceptible to caspase-1 and NLRP3 activation and exhibited higher levels of IL-1β in response to PPAR-α agonism **(Fig. 4)** (Brocker et al., 2020) (see Fig. 5).

Recent investigations have also implicated oleoylethanolamide, an endogenous bioactive lipid and a natural ligand of PPAR-α, to play a role in hepatocyte protein levels of IL-1β and NLRP3 components. Oleoylethanolamide administration was shown to augment PPAR-α expression which alleviated inflammation by downregulating NLRP3 and IL-1β (Grabacka et al., 2021b). In monocytes, PPAR-α activation blocks the secretion of tissue factor to inhibit coagulable states by blocking lipopolysaccharide or IL-1β induction (Marx et al., 2001). Further, Gu et al. unveiled in a recent experiment that chronic exposure to a low-dose lipopolysaccharide environment leads to heightened levels of PPAR-α

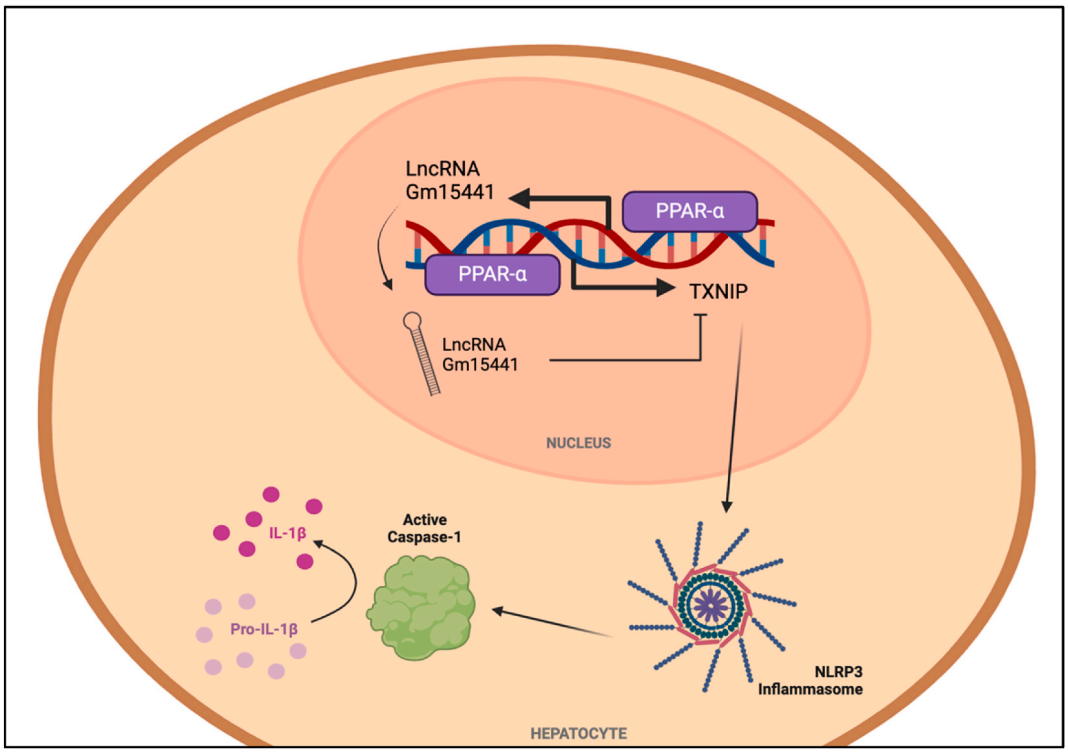

Fig. 4. PPAR-α activation upregulates LncRNA Gm15441. PPAR-α activation leads to the upregulation of the long non-coding RNA gene Gm15441 which subsequently suppresses its antisense transcript, encoding thioredoxin interacting protein (TXNIP). This, in turn, leads to decreased NLRP3 stimulation, caspase-1 cleavage, and IL-1β maturation (Brocker et al., 2020).

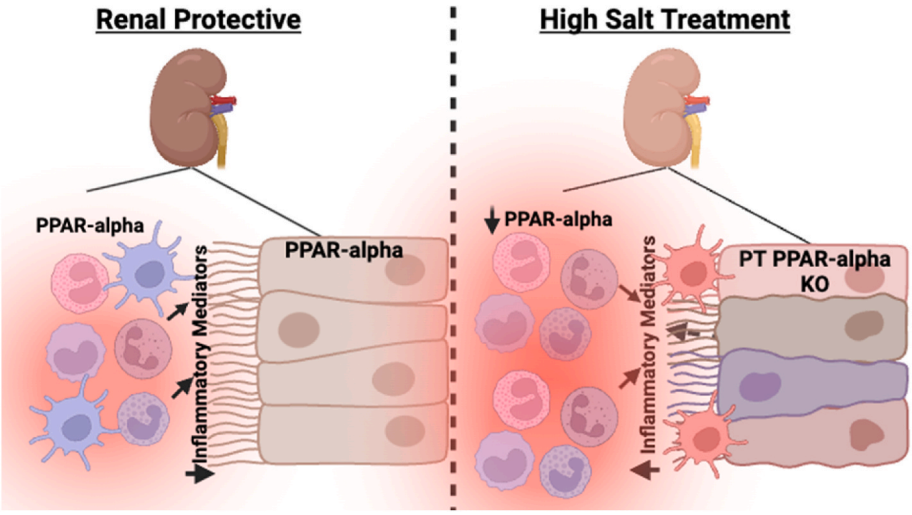

Fig. 5. Hypothesized role of Inflammation and Immune Cell Activation in Chronic Kidney Disease.

thus dampening NLRP3 inflammasome activation and the NF-κB signaling pathway (Gu et al., 2023).

Taken together, these findings indicate that PPAR-α may modulate the activity of NLRP3 inflammasome to attenuate inflammation. However, the underlying mechanisms relating PPAR-α and NLRP3 in CKD require further investigations. Future studies centered around on stimulating PPAR-α to reduce renal inflammation and injury via attenuated NLRP3 activity may provide a clearer role of how PPAR-α influences NLRP3 action. Since the NLRP3 inflammasome promotes inflammation and is an underlying contributor to many metabolic and cardiorenal diseases, we have postulated that PPAR-α agonists could potentially influence and regulate overall inflammatory responses that use the NLRP3 inflammasome as an underlying driver of renal pathogenesis.

5.2. *PPAR-alpha and NF-κB*

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a multiprotein complex family of inducible transcription factors that play regulatory roles during immune responses and inflammation (Liu et al., 2017a). The NF-κB family is comprised of five different members: p50 (also named NF-κB1), p52 (also named NF-κB2), p65 (also named RelA), RelB, and c-Rel. NF-κB components can form homo- or hetero-dimers to modulate transcription by binding to specific DNA sites (Liu et al., 2017b). Under typical conditions, NF-κB members

directly interact with the inhibitory IκB family and are sequestered from the nucleus in order to obstruct transcriptional activity (Liu et al., 2017b). NF-κB signaling activation manifests through either the canonical or noncanonical pathway to modulate inflammatory stimulation. IκBα is the most extensively studied component of the IκB family and has an established role in the NF-κB canonical signaling pathway (Liu et al., 2017b; Lawrence, 2009). In fact, canonical signaling is distinguished by IκB kinase (IKK) complex phosphorylation of IκBα which induces IκBα degradation and rapidly permits NF-κB components to enter the nucleus (Liu et al., 2017b). Canonical activation is triggered by a pleothra of different stimuli such as pattern-recognition receptors (PRRs), T-cell receptors (TCR), B-cell receptors (BCR), TNF receptors (TNFR), and other ligands of differing cytokine receptors (Liu et al., 2017b; Zhang et al., 2015a). Contrastingly, NF-κB noncanonical activation is dependent on exposure to specific stimuli such as ligands of a subgroup of TNFR members including RANK, CD40, BAFFR, and LTβR (Liu et al., 2017b; Sun, 2012). Further, IκBα degradation is not observed in noncanonical NF-κB stimulation; rather, it involves NF-κB-inducing kinase (NIK) which functions as a vital component in triggering activation (Liu et al., 2017b; Sun, 2012). NF-κB family members are ubiquitously expressed in virtually all cell types and tissues, and have been implicated in a wide range of disorders (Oeckinghaus et al., 2009).

Increased NF-κB activity has been associated with triggering proinflammatory cytoke production which is a hallmark contributor to most diseases (Barnabei et al., 2021; Zhang et al., 2015b; Tak et al., 2001). Further, accumulated evidence demonstrates that NF-κB maintains a crucial role in a wide array of inflammation-mediated renal pathological conditions (Liu et al., 2017b; Lawrence, 2009; Zhang et al., 2024; White et al., 2020).

Past experimental models of renal disease have demonstrated increased NF-κB activation during proteinuria and glomerular injury in podocytes, mesangial, and tubular cells (Poveda et al., 2017). Previous work by Loverre et al. unveiled elevated NIK phosphorylation during ischemia reperfusion injury in podocytes and tubular cells (Loverre et al., 2004). Another study by Chade et al. sought to obstruct NF-κB proinflammatory transcriptional actions in renal cells and reported that this treatment was effective in ameliorating renal inflammation and injury to improve kidney function (Chade et al., 2020). Further, a study performed by Starkey et al. uncovered heightened tubular NIK and RelB DNA interactions which indicated prolonged NF-κB activation in the renal cortex of diabetic nephropathy experimental models (Starkey et al., 2006). Intriguingly, novel findings by Zhang et al. have revealed that there is an optimal range of NF-κB activity that is quintessential in maintaining healthy kidney morphology and function as both activation and partial inactivation of the NF-κB pathway contributes to both hypertension and CKD (Zhang et al., 2024). With the findings presented in these investigations, targeting NF-κB to exert anti-inflammatory effects could be a therapeutic strategy in CKD treatment.

Notably, it has been reported that PPAR-α interacts with the NF-κB signaling pathway to reduce inflammation (Decara et al., 2020). Recent work using Western blot analysis by Gugliandolo et al. illustrated that TLR4 and PPAR-α deficiency in mice led to a significant increase in IκB degradation and NF-κB expression compared with WT mice following pulmonary infection (Tergaonkar et al., 2003; Guijarro et al., 2001). A recent study regarding hepatocarcinogenesis also found that PPAR-α−null mice exhibited downregulation of IκB when compared to WT mice (Zhang et al., 2014). Additionally, during IL-1β-induced IL-6 production, the NF-κB p65 subunit and c-Jun N-terminal kinases (JNK) can bind to the IL-6 promoter region to upregulate IL-6 and accelerate CKD progression through increased endothelial injury and athersclerosis (Delerive et al., 1999a; Pecoits-Filho et al., 2003; Huber et al., 1999). Interestingly, in PPAR-α deficient mice, augmented expression of active forms of NF-κB was also revealed alongside IL-6 upregulation (Zhang et al., 2014). PPAR-α is also known to physically interact and complex with sirtuin 1 (Sirt1) and p65 which has been shown to attenuate expression of proinflammatory genes including monocyte chemoattractant protein 1 (MCP1) (Planavila et al., 2011).

It is also noteworthy to discuss the growing evidence that suggests NF-κB operates downstream of TGFβ/SMAD signaling pathways which promotes an inflammatory response (Saleem et al., 2023). Mechanistically, the molecular systems for TGFβ-stimulated NF-κB-dependent inflammatory responses have been yet to be fully elucidated (Ishinaga et al., 2007). SMAD signaling is discussed in more detail in the next section; however, recent findings suggest that the TGFβ pathway may interact with PPAR-α, which could inadvertently suggest that NF-κB transcriptional activity is regulated by PPAR-α in a TGFβ-dependent manner. Nevertheless, much more extensive analysis is required to elucidate any mechanistic model that postulates PPAR-α modulation of TGFβ-dependent NF-κB transcriptional activity.

5.3. PPAR-alpha and TGFβ/SMAD signaling

Transforming growth factor-β (TGFβ) represents a family of polypeptide factors that are involved in adult tissue homeostasis and pathogenic mechanisms that underlie many diseases (Tzavlaki et al., 2020).

Hence, NF-κB stimulation is not the only way TGFβ/SMAD signaling has been shown to contribute to inflammatory-related disorders. As aforementioned, TGFβ1 pathway activation leads to signal propagation by at least two routes: the SMAD-dependent canonical pathway and the SMAD-independent non-canonical pathways. During the SMAD-dependent canonical pathway, TGFβ1 triggers SMAD2 and SMAD3 phosphorylation which allows them to complex with co-SMAD (e.g. SMAD4) in order translocate to the nucleus and regulates transcriptional responses (Matsuki et al., 2014). Under pathological conditions, there is observed SMAD2 and SMAD3 upregulation, hence, the TGFβ/SMAD pathway serves a crucial role in progressive renal injury and inflammation. New insights brought forth by Oruqaj et al. demonstrated that treating idiopathic pulmonary fibrosis (IPF) human fibroblasts with ciprofibrate, a PPAR-α agonist, resulted in reduced levels of TGFβ-stimulated Smad-binding element (SBE) promoter activity in a dose-dependent manner (Oruqaj et al., 2023). This study also found that PPAR-α blockade significantly increased SBE promoter activity in both control and IPF fibroblasts. Accordingly, PPAR-α modulation of inflammatory responses via TGFβ pathway activity has potential to serve as a therapeutic mechanism in CKD treatment in a NF-κB-independent manner.

SMAD3 is a critical regulator of TGFβ signaling and possesses a pathophysiological function in both renal inflammation and fibrosis. Recent studies indicate that SMAD3 deletion was shown to suppress renal fibrosis in varied rodent models, such as diabetic nephropathy, obstructive kidney diseases, hypertensive nephropathy, and drug-associated nephropathy (Wu et al., 2022). Intriguingly, PPAR-α has been shown to influence SMAD2/3 activity. An investigation conducted by Chen et al., unveiled that treatment with OEA, the PPAR-α agonist, inhibited TGFβ-activation of hepatic stellate cells through suppression of SMAD2/3 phosphorylation and α-SMA expression (Chen et al., 2015). Another study revealed that Wy14643 and clofibrate, PPAR-α agonists, significantly decreased SMAD2 and SMAD3 phosphorylation in 10T1/2 cells (Lien et al., 2013).

SMAD3 has been demonstrated to operate upstream of various immunoregulators to contribute to renal fibrosis (Lai et al., 2022). SMAD7, an inhibitory Smad, is transcriptionally induced by SMAD3 to maintain TGFβ/SMAD3 signaling homeostasis. Under pathological conditions, SMAD3 is overexpressed and has the ability to trigger activation of Smurf1, Smurf2, and arkardia which, in turn, causes proteasomal degradation of SMAD7 to enhance renal fibrosis. Further, SMAD3 activation is a prerequisite for the efficient transition of recruited macrophages to become collagen I-producing α-SMA myofibroblasts during renal injury (Wu et al., 2022). Altogether, the ability of PPAR-α to attenuate SMAD3 phosphorylation suggests that it potentially plays a critical role in TGFβ/SMAD pathway activity in kidney disease.

5.4. PPAR-alpha and AP-1

Activator protein-1 (AP-1) is an inducible transcription factor complex composed of 26 monomers that, depending on amino acid sequencing similarities, are categorized into five different families: JUN family (c-Jun, JunB, and JunD), FOS family (c-Fos, FosB, Fra-1, and Fra-2), MAF family (c-Maf, MafA, MafB, MafF, MafG, MafK, and Nrl), ATF family (Atf, Atf2, Atf3, Atf4, Atf5, Atf6B, Atf7, BATF, BATF2, and BATF3), and JUN-dimerizing partners (JDP1 and JDP2) (Li et al., 2024). Based on the presence of the basal-leucine zipper (bZIP) domain, AP-1 family members can either homodimerize or heterodimerize to modulate transcriptional activity (Li et al., 2024). Accordingly, the bZIP-containing JUN family can both homodimerize or heterodimerize to form Jun–Jun, Jun-Fos, or Jun-ATF dimers; however, the bZIP-deficient FOS family strictly form heterodimers such as Jun-Fos to regulate transcription (Li et al., 2024; Kyriakis, 1999). Several signaling pathways can stimulate AP-1 activation via either direct phosphorylation/dephosphorylation or increased expression of AP-1 components like c-Jun or c-Fos (Kyriakis, 1999). AP-1 expression is observed in most cell types and heightened expression is typically exhibited following extracellular signaling (Vierbuchen et al., 2017). AP-1 complex overactivity has been related to the progression of several diseases, including inflammatory-related disorders, cancer, asthma, rheumatoid arthritis, and psoriasis (Kyriakis, 1999; Bejjani et al., 2019; Barnes et al., 1998; Hannemann et al., 2017; Novoszel et al., 2021). Most notably, AP-1 activation has been shown to enhance tubular atrophy and tubulointerstitial fibrosis, a hallmark of CKD development (Liu et al., 2023; Wernig et al., 2017; Sun et al., 2018). Liu et al. reported elevated expression of AP-1 members in unilateral ureteric obstruction (UUO) kidney models and MST1/2-deficient kidneys, both of which are conditions conducive to CKD pathology (Liu et al., 2023). Moreover, a recent study by Yu et al. uncovered that, in murine kidneys and livers, AP-1 regulates inflammaging, a condition distinguished by prolonged mild inflammation in various tissues due to aging, further implicating AP-1 complex in CKD (Yu et al., 2023).

Prior investigations have demonstrated that PPAR-α negatively influences AP-1 activity. PPAR-α has the ability to operate in complex signaling pathways to mediate cross-talk in inflammatory mechanisms. A study by Gervois et al. uncovered that hepatocyte treatment of PPAR-α agonist fenofibrate resulted in attenuated IL-6 receptor components gp80 and gp130 which was conducive to decreased c-Jun and STAT3 activation (Gervois et al., 2004). Another investigation by Grau et al. reported that, in human colorectal carcinoma cell lines, PPAR-α activation by LY-171883 and WY-14643 suppressed AP-1 transcriptional activity and disrupted COX2 and VEGF actuation by blocking c-Jun transactivating ability and prohibiting AP-1 binding to a consensus DNA sequence (Grau et al., 2006). Further, Delerive et al. reported that PPAR-α directly complexes with p65 and c-Jun to sequester them from the nucleus and inhibit IL-6 production during the vascular inflammatory response (Delerive et al., 1999b). Interestingly, a recent study led by Goujon et al. found that AP-1 and NF-κB maintain transcriptional control over miR-21, which is an oncogenic miRNA that has been shown to suppress PPAR-α expression in clear cell renal cell carcinoma models. Goujon et al. concluded from their findings that a negative regulatory feedback loop exists between miR-21, PPAR-α, AP-1 and NF-κB that was promotive of renal cancer (Goujon et al., 2022). Altogether, these findings insinuate that the complex relationship between PPAR-α and AP-1 could be contributing to renal inflammation observed in CKD patients; however, PPAR-α−mediated AP-1 activity has yet to be extensively studied in CKD models.

6. Implications for therapy

Since PPAR-α acts as a ligand-activated transcription factor, the effects of its activity can be invoked in the presence of natural and synthetic ligands (Grygiel-Gó and rniak, 2014a).

PPAR-α ligands have been used in clinical settings for several decades now. PPARα stimulation has been shown to improve endothelial and kidney function while reducing inflammation ultimately making it a good candidate for a therapeutic target in CKD treatment (Cheng et al., 2010a). Fibric acid derivatives (fibrates), which are synthetic PPARα ligands, have long been used to modulate dyslipidemia, exert anti-inflammatory effects, improve atheroschlerotic conditions, and ameliorate vascular function (Staels et al., 2005; Israelian-Konaraki et al., 2004). Accordingly, fibrates (e.g. bezafibrate, fenofibrate, and clofibrate) have the potential to play a protective role in CKD progression. Fenofibrate has been shown to increase PPAR-α expression to blunt renal lipotoxicity, albuminuria, glomerular fibrosis, and oxidative stress and lipid accumulation in the glomeruli (Tanaka et al., 2011; Chung et al., 2012). Long-term treatment with fenofibrate also reduced total cardiovascular events and preserved renal function without adverse effect in type 2 diabetic patients, aged 50–75 years old (Ting et al., 2012). In addition, fenofibrate facilitates albumin reabsorption in the nephron and downregulates TGF-β signaling to decrease glomeruli injury and deposition of collagen IV in diabetic rats (Li et al., 2010; Chen et al., 2009; Liao et al., 2009). Moreover, previous studies indicate that fenofibrate ameliorates glomerular injury, inflammation, and renal fibrosis in a high fat diet animal model (Tanaka et al., 2011; Kang et al., 2015; Yuan et al., 2022). It has also been reported that bezafibrate decreased $CD8^{+}$ infiltrates in the glomeruli to reduce the severity and extent of glomeruli injury (Saga et al., 2005). Generally, fibrates are known to attenuate proinflammatory compounds such as TNF-α, IL-6, IL-2, IFN-γ, CRP and the endothelial adhesion marker VCAM-1 (Gilde et al., 2003; Zambon et al., 2006). Interestingly, in the vascular endothelium, fibrates also contribute to increased NO production via increased expression of endothelial nitric oxide synthase (eNOS) (Cheng et al., 2010).

Statins have also been shown to exert beneficial effects for CKD patients with a higher cardiovascular risk. Simvastatin, a type of statin, has been associated with a decreased proteinuria which is observed at high rates in CKD patient populations. Further, simvastatin treatment has been linked to significantly greater decreases in total cholesterol and LDL-cholesterol when compared to untreated groups (Satirapoj et al., 2015). Previous investigations have uncovered that, during simvastatin treatment, PPAR-α KO mice exhibit a reduced anti-inflammatory response when compared to WT mice which indicates that PPAR-α may contribute to simvastatin-induced anti-inflammatory actions (Esposito et al., 2012).

Furthermore, AVE8134, a PPAR-a agonist, has been shown to possess beneficial effects on hypertensive organs to prevent myocardial hypertrophy and dysfunction resulting in reduced mortality. AVE8134 treatment led to decreases in plasma ProBNP and L-arginine as well as increased nitric oxide/creatinine ratio at a low dose. Nitric oxide/creatinine accounts for variations in urine concentration, providing a more accurate assessment. Changes in the NO/creatinine ratio may help in monitoring the progression of CKD and the effectiveness of therapeutic interventions. The compound exerts its protective properties by a direct effect on cardiomyocyte dysfunction, but also indirectly via monocyte signaling and increased endothelial NO production (Linz et al., 2009). Previous studies found that pretreatment with nitric oxide or L-arginine can be preventive of ischemic acute renal injury suggesting that AVE8134 has therapeutic effects (Linz et al., 2009; Lee, 2008). These findings suggest that AVE8134 could potentially also ameliorate CKD progression, however, further testing is needed.

Studies have also reported that irbesartan (Irbe), an angiotensin II receptor blocker (ARB) widely prescribed for CKD, activates hepatic PPAR-α. However, Irbe's renal PPARα-activating effects and the role of PPARα signaling in the renoprotective effects of Irbe are unknown. PPAR-α and its target gene expression were significantly increased only in the kidneys of Irbe-treated WT mice and not in KO or Losartan, an ARB, treated mice, suggesting that the renal PPARα-activating effect was Irbe-specific. Irbe-treated mice exhibited decreased urine protein excretion, tubular injury, oxidative stress (OS), and pro-inflammatory

and apoptosis-stimulating responses, and they exhibited maintenance of fatty acid metabolism. These renoprotective effects of Irbe were reversed by the PPAR-α antagonist MK886. These results suggest that Irbe activates renal PPAR-α and that the resultant increased PPARα signaling mediates its renoprotective effects (Harada et al., 2016).

Gastrin has also been shown to be protective against hypertensive nephropathy (HN) by normalizing blood pressure, decreasing renal tubule cell apoptosis, and increasing macrophage efferocytosis. Gastrin-mediated renal cholecystokinin receptor B (CCKBR) nuclear translocation may serve as a transcription factor of PPAR-α, which is a novel signaling pathway (Gu et al., 2021). In a mouse model, anti−microRNA-21 (miR-21) oligonucleotides increased PPAR-α transcriptional activity and reversed kidney disease (Gomez et al., 2015). Further studies are needed to elucidate specific mechanisms linking PPAR-α to immune-mediated hypertensive disease including salt sensitivity of blood pressure.

Credit author statement

SKM wrote the draft manuscript. SD made extensive revisions to the draft. MH revised the final draft. All authors approved the final version of this manuscript. AK revised the final draft. All authors approved the final version of this manuscript. DLL revised the final draft, All authors approved the final version of this manuscript

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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