Current Research in Microbial Sciences 7 (2024) 100315

Contents lists available at ScienceDirect

Current Research in Microbial Sciences

journal homepage: www.sciencedirect.com/journal/current-research-in-microbial-sciences

Gut microbiota and bile acids: Metabolic interactions and impacts on diabetic kidney disease

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ARTICLE INFO

Keywords:
Bile acids
Intestinal flora
Diabetic nephropathy
Farnesoid receptor
G protein-coupled receptor

ABSTRACT

The intestinal microbiota comprises approximately 10^{13}–10^{14} species of bacteria and plays a crucial role in host metabolism by facilitating various chemical reactions. Secondary bile acids (BAs) are key metabolites produced by gut microbiota.Initially synthesized by the liver, BA undergoes structural modifications through the activity of various intestinal microbiota enzymes, including eukaryotic, bacterial, and archaeal enzymes. These modified BA then activate specific receptors that regulate multiple metabolic pathways in the host, such as lipid and glucose metabolism, energy balance, inflammatory response, and cell proliferation and death. Recent attention has been given to intestinal flora disorders in diabetic kidney disease (DKD), where activation of BA receptors has shown promise in alleviating diabetic kidney damage by modulating renal lipid metabolism and mitochondrial production. Imbalances in the intestinal flora can influence the progression of DKD through the regulation of bile acid and its receptor pathways. This review aims to propose a mechanism involving the gut-BA-diabetes and nephropathy axes with the goal of optimizing new strategies for treating DKD.

1. Introduction

The rise in global obesity rates has contributed to a surge in the prevalence of type 2 diabetes mellitus (T2DM), projected to increase by 54 % by 2030 (Verma et al., 2020). Approximately 30 % to 40 % of individuals with diabetes mellitus (DM) may develop diabetic kidney disease (DKD), posing a significant threat to their well-being. The pathogenesis of DKD is intricate and still not fully understood. Emerging research suggests that an imbalance in intestinal flora plays a role in the development of DKD (Zhang et al., 2022). The composition of the intestinal microbiota impacts various aspects such as the intestinal barrier, renal metabolism, inflammation, and immune system equilibrium (Lehto and Groop, 2018). Studies have shown an altered intestinal microbiota profile in fecal samples of DKD patients, characterized by reduced levels of beneficial probiotics like Bifidobacterium, Lactobacillus, and Prevotella, alongside an increase in pathogenic bacteria such as Faecalibacterium and Desulfovibrio (Li et al., 2020, Sheng et al., 2018).

Communication between humans and their microbiota primarily relies on the response of host receptors to microbial metabolites, with BA being the most significant type of metabolite in the intestinal microbiota. Various intestinal flora, including Bacteroidetes, Firmicutes, and Actinobacteria, can engage in the secondary metabolism of BA by hydrolyzing the amino acid moiety through bile salt hydrolase, thereby enhancing the diversity of the BA library (Foley et al., 2021). BAs are recognized as crucial endogenous steroid molecules that play a pivotal role in regulating and maintaining lipid, glucose, and energy metabolism, as well as in preventing liver, intestinal, and cardiac inflammation, diabetes, and obesity (Thibaut and Bindels, 2022). Reduced expression of FXR and TGR5 has been observed in human and rodent kidney disease models. Activation of FXR and TGR5 in animal models has shown nephroprotective effects by reducing renal inflammation, oxidative stress, and fibrosis (Wang et al., 2015, Wang et al., 2017, Gai et al., 2016). Therefore, activation of BA receptors may hold promise for the treatment of kidney disease. The microbiota in the distal small intestine and colon have the ability to modify BA structure, bioavailability, and bioactivity, which in turn can impact BA metabolism and its influence on host metabolic homeostasis (Collins et al., 2022).

This review explores the intricate relationship between gut microbiota and BA pools, detailing their various mechanisms that affect

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https://doi.org/10.1016/j.crmicr.2024.100315

Available online 17 November 2024

glucose and lipid metabolism. Additionally, it delves into the potential impact of microorganisms on BAs and their receptor signaling in relation to diabetic nephropathy. By understanding the complex interactions among gut microbiota, BAs, and DKD, there is potential for developing novel therapeutic approaches for managing DKD.

1.1. BA synthesis and regulation of BA homeostasis

The synthesis, breakdown, and reabsorption of cholic acid (BA) constitute a complex system involving nuclear receptors, enzymes, transporters, and the intestinal microbiota (Fig. 1). BAs are predominantly synthesized in the liver through two distinct pathways and regulated by precise feedback mechanisms to maintain equilibrium. The classical or neutral pathway, responsible for about 75 % of BA production, initiates with cholesterol 7α-hydroxylation by cholesterol 7α-hydroxylase (CYP7A1), followed by further modifications to the steroid core and cleavage of side chains with the involvement of sterol 12α-hydroxylase (CYP8B1). The acidic pathway, also known as the alternative pathway, commences with cholesterol hydroxylation catalyzed by CYP27A1, leading to subsequent hydroxylation by oxysterol 7α-hydroxylase (CYP7B1). BAs are released into the duodenum to facilitate the digestion and absorption of dietary lipids and fat-soluble nutrients (Chiang, 2013). Through enterohepatic circulation, over 95 % of BAs are reabsorbed via active transport in the ileum and passive transport in the gastrointestinal tract, returning to the liver (Dawson and Karpen, 2015). Unreabsorbed BAs are primarily eliminated through feces (approximately 0.2–0.6 g/day) and urine (approximately 0.5 mg/day). The excreted BAs are replenished through de novo synthesis from cholesterol in the liver (Chiang, 2013). The signaling activity of BAs primarily involves the activation of various nuclear receptors, including FXR, pregnane X receptor (PXR), vitamin D receptor (VDR), and G protein-coupled receptor (TGR5) (Chiang, 2013).

The loss of BA synthase disrupts BA homeostasis (Rizzolo et al., 2021). Bile acid receptors and downstream signaling pathways oxidize by regulating key enzymes such as CYP7A1 in the classical pathway and sterol 27 hydroxylase (CYP27A1) and CYP7B in the alternative pathway

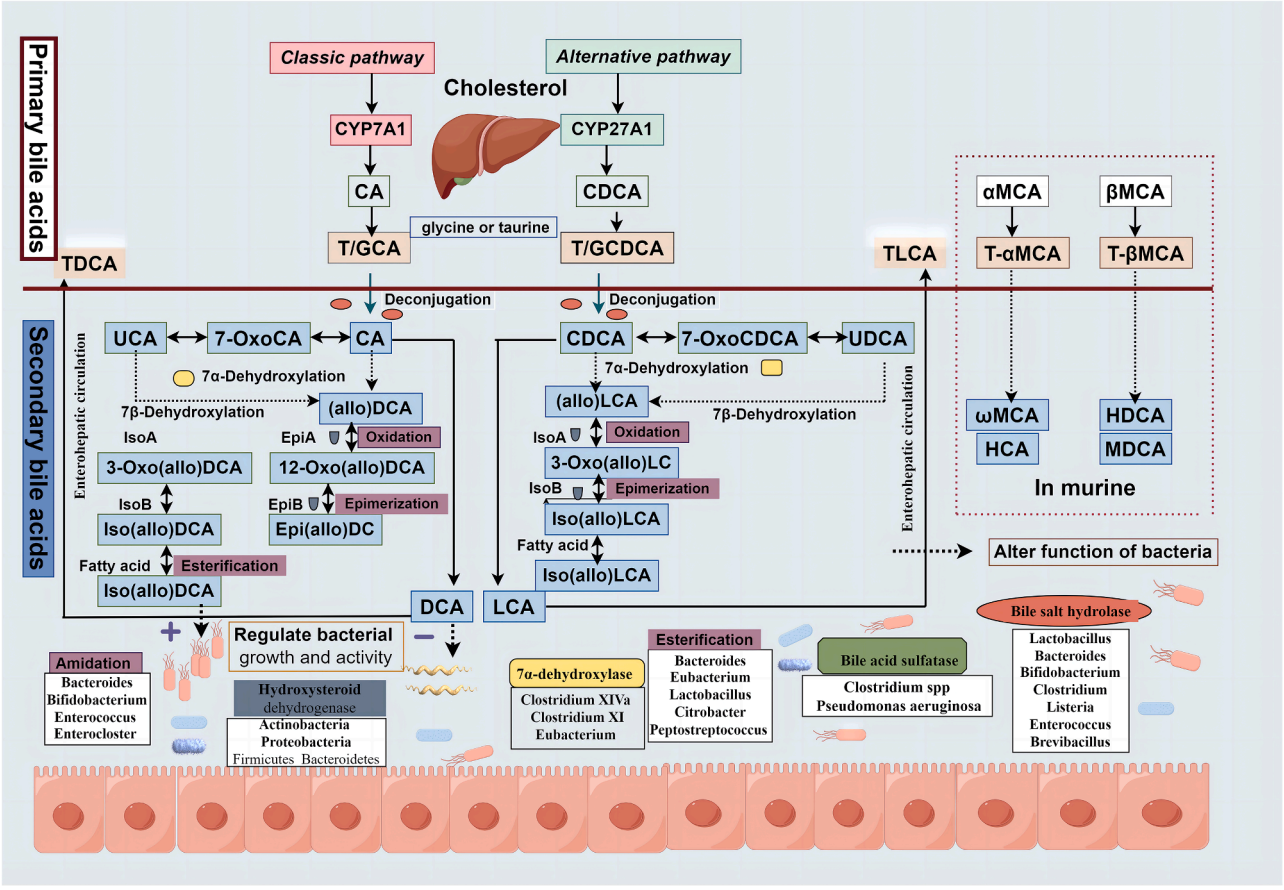

Fig. 1. Primary bile acid metabolism and secondary bile acid metabolism pathways with microbially encoded enzymes. The primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA), are synthesized from cholesterol in the liver through two metabolic pathways known as the classical pathway and the alternative pathway. In the intestine, bile acids are transformed by intestinal microorganisms into secondary bile acids, specifically DCA and LCA. The combined primary bile acids (taurocholic acid (TCA), glycocholic acid (GCA), taurochenodeoxycholate acid (TCDCA), and glycinchenodeoxycholic acid (GCDCA)) travel to the large intestine, where they are broken down by bile salt hydrolase (BSH) from various intestinal bacterial taxa. Additionally, they are further metabolized by different enzymes within intestinal cells, resulting in various iso- and oxygenated bile acids. In rodents, CDCA is converted into α-MCA and β-MCA. The primary bile acids cholic acid (CA) and chenodeoxycholic acid (CDCA) can undergo oxidation by 7α-hydroxysteroid dehydrogenase to form 7-oxoCA and 7-oxoCDCA, respectively. These can then be epimerized to urscholic acid (UCA) and ursodeoxycholic acid (UDCA) by 7β-hydroxysteroid dehydrogenase. Additionally, CA and CDCA can be converted to deoxycholic acid (DCA) and lithocholic acid (LCA) via the 7α-dehydroxylation pathway by intestinal bacteria. UCA and UDCA can undergo direct 7β-dehydroxylation or be epimerized back to CA and CDCA, followed by 7α-dehydroxylation to form DCA and LCA. These bile acids can also pass through epimers, known as 'ectopic' bile acids. The epimers of DCA and alloDCA are designated as (allo)DCA and (allo)LCA, along with their derivatives. (allo)DCA, which has two hydroxyl groups, can be oxidized to 3-oxoDCA by 3α-hydroxysteroid dehydrogenase (isoA) and/or to 12-oxoDCA by 12α-hydroxysteroid dehydrogenase (epiA). It can also be oxidized by 3β-hydroxysteroid dehydrogenase (isoB) or 12β-hydroxysteroid dehydrogenase (epiB) to form iso(allo)DCA and epi(allo)DCA, respectively. On the other hand, (allo)LCA is monohydroxylated at C3, leading to the production of only 3-oxo(allo)LCA and iso(allo)LCA. DCA and LCA reenter the liver through enterohepatic circulation, where they combine with glycine and taurine to form TDCA or TLCA.

to maintain BA balance (Monte et al., 2009). FXR, primarily found in the liver and distal ileum, tightly regulates BA synthesis through negative feedback inhibition. Activation of FXR by BA induces the upregulation of fibroblast growth factor 15 (FGF15) and its human counterpart FGF19 (also known as FGF15/19) in mice (Sayin et al., 2013). Once released into the enterohepatic circulation, FGF15/19 binds to the FGF receptor 4/β-klotho (FGFR4/KLB) complex in the liver, activating JNK/ERK signals and inhibiting hepatic CYP7A1 and CYP8B1 expression to modulate BA synthesis (Kim et al., 2007). In the liver, FGF15 suppresses CYP7A1 expression, thereby reducing BA production. Additionally, hepatic FXR influences CYP8B1 expression through transcriptional interaction with the small heterodimer chaperone (SHP) and, to a lesser extent, CYP7A1. FXR can enhance BA secretion by upregulating the bile salt export pump (BSEP) and related proteins. BAs are transported via various transporters, such as the apical sodium-dependent BA transporter (ASBT), organic solute transporters α and β (OSTa/b) in ileal enterocytes, sodium taurocholate co-transport polypeptide (NTCP), and organic anion transporting polypeptide (OATP) in hepatocytes facilitating reabsorption from the intestines back to the liver through the enterohepatic circulation (Makishima et al., 1999). FXR activation decreases BA reabsorption by reducing ASBT and NTCP levels. Notably, gut microbiota can influence BA composition, indirectly impacting the interactions of BA with FXR-FGF15 and CYP7A1 expression, underscoring the significance of gut microbes (Sayin et al., 2013).

2. Functions of BAs

2.1. BA regulates glucose and lipid metabolism

The metabolic regulatory effects of BAs on glucose metabolism and insulin sensitivity are dependent on its receptors FXR and TGR5 in various organs such as the liver, intestine, adipose tissue, and pancreas (Rajani and Wang, 2018). These effects are mediated through pathways including the BA-FXR-SHP pathway (Pathak et al., 2018), the BA-FXR FGFR15/19 pathway (Batterham and Cummings, 2016), the BA-TGR5-GLP-1 pathway (Guzior and Quinn, 2021), and the BA-TGR5-cAMP pathway (Lai et al., 2022) (Fig. 2). Ultimately, these pathways lead to improved insulin resistance, reduced hepatic gluconeogenesis, and enhanced insulin sensitivity in adipose tissue (Fig. 2). The downstream target FGF15/19 activated by BA-activated FXR plays a crucial role in maintaining glucose/insulin homeostasis. Additionally, FXR activation in a SHP-dependent manner can also increase the expression of gluconeogenic genes (Seok et al., 2020). Activation of intestinal FXR can stimulate TGR5/GLP-1 signaling, leading to the

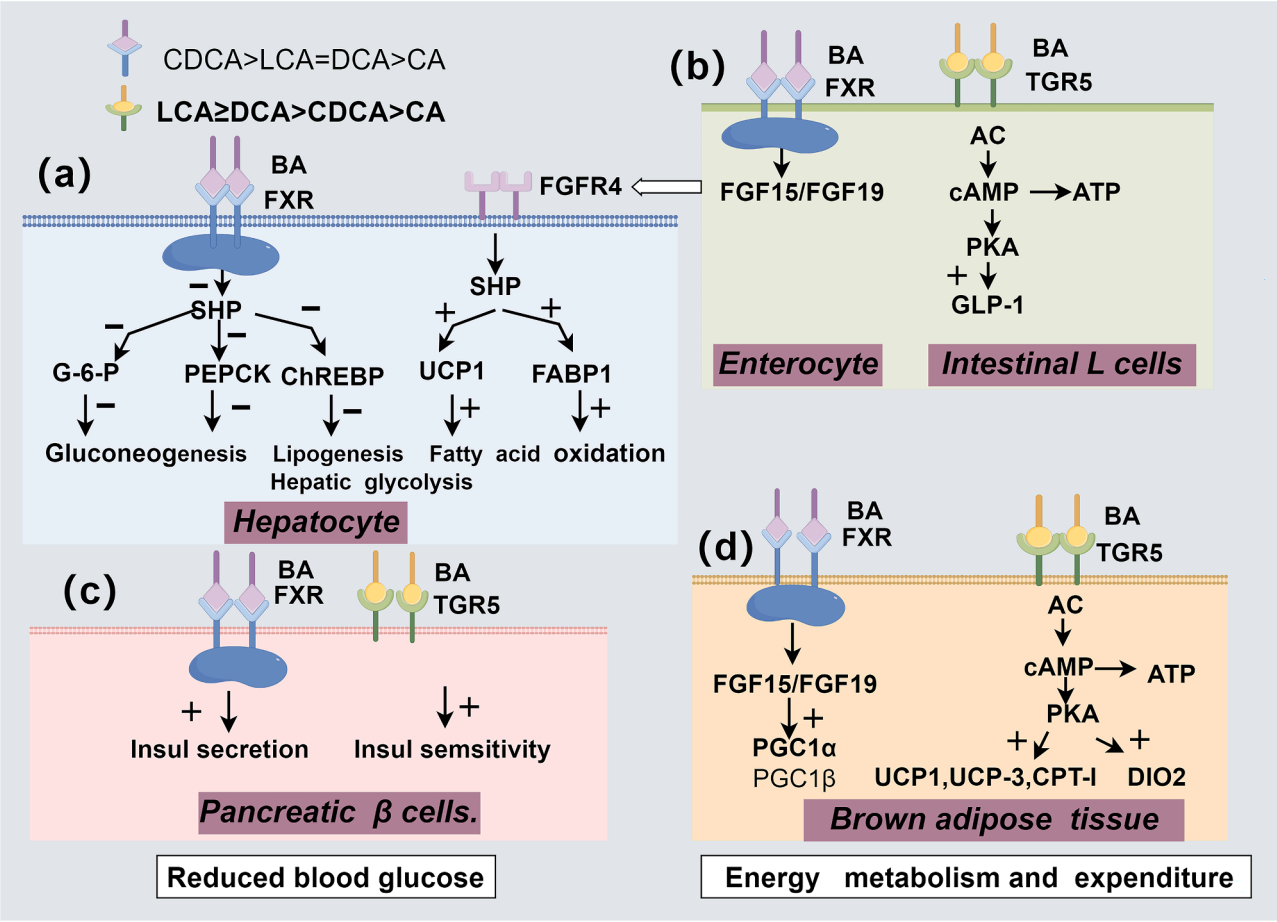

Fig. 2. BA regulates glucose homeostasis. (a) In hepatocytes, bile acids activate the farnesoid pathway, which in turn reduces the production of very low density lipoprotein (VLDL) and triglycerides (TG). The interaction between FGF15/19-FGFR4 enhances SHP expression, leading to increased fatty acid oxidation and maintenance of glucose homeostasis through upregulation of UCP1 and FEBP1. (b) In intestinal cells, activation of FXR by bile acids induces the production of fibroblast growth factor 19 (FGF19/15), which subsequently acts on hepatocytes through the FGFR4 complex to promote fatty acid oxidation. Furthermore, bile acid activation of TGR5 in intestinal L cells can elevate cAMP production, resulting in GLP-1 secretion and enhanced insulin sensitivity. (c) Activation of FXR and TGR5 in pancreatic β cells can also improve insulin secretion and sensitivity and reduce blood glucose levels. (d) Activation of TGR5 in adipose tissue stimulates cAMP production, leading to the synthesis of T3 by type 2 deiodinase (DIO2), which promotes energy metabolism and browning of adipose tissue. This activation also upregulates the expression of UCP-1 and CPT1, enhancing fatty acid oxidation. Additionally, FXR activation induces FGF19/15 to increase PGCα expression, thereby activating mitochondrial fatty acid oxidation and facilitating fat consumption for energy release in the form of heat.

secretion of GLP-1 from intestinal L cells. This, in turn, promotes insulin secretion from pancreatic islet β cells and reduces glucagon secretion from pancreatic islet α cells, thereby improving hepatic glucose and insulin sensitivity and promoting adipose tissue browning (Van Zutphen et al., 2019). BA can also repress the expression of gluconeogenic genes, including G6Pase and fructose 1,6-bisphosphatase (FBP1), through FXR, contributing to the maintenance of glucose homeostasis during the fasting-refeeding transition (Yamagata et al., 2004).

TGR5 activates the protein kinase A (PKA) signaling pathway by stimulating adenylyl cyclase, leading to a rapid increase in intracellular cyclic adenosine monophosphate (cAMP) production. Activation of the PKA pathway results in the phosphorylation of cAMP response element binding protein (CREB) and subsequent induction of target gene expression, ultimately enhancing hepatic lipid metabolism and fatty acid oxidation (Durán-Sandoval et al., 2005). Additionally, TGR5 activation stimulates type II iodothyronine deiodinase (DIO2) to activate thyroid hormone in brown adipose tissue and muscle cells, contributing to metabolic regulation (Anhê et al., 2017). In skeletal muscle, activated TGR5 promotes muscle hypertrophy and enhances glucose utilization through glycolytic flux, aiding in improving glucose metabolism dysfunction associated with diet-induced obesity and aging (Sasaki et al., 2021). Furthermore, bile acids (BA) activate TGR5 or FXR to impact glucose metabolism by stimulating insulin secretion in pancreatic β cells in a protein kinase A (PKA)-dependent manner.

BAs are a class of cholesterol metabolites that play a crucial role in regulating lipid homeostasis. Mechanistically, the farnesoid X receptor (FXR) is essential for cholesterol catabolism, transport, lipogenesis, and triglyceride (TG) metabolism. The FXR-SHP pathway regulates sterol regulatory element binding protein 1c expression, influencing lipogenesis and de novo cholesterol synthesis (Watanabe et al., 2006). FXR also modulates fatty acid (FA) oxidation through peroxisomes via proliferator-activated receptor α (PPARα) and its target genes (Pineda-Torra et al., 2003). Furthermore, FXR is involved in high-density lipoprotein (HDL) metabolism, including cholesterol transport and reverse cholesterol transport (RCT) (De Boer et al., 2017). Natural FXR agonists like CDCA or taurocholate can inhibit hepatic Apo CIII expression, counteract FA-induced TG accumulation, and prevent lipotoxicity [(Laskar et al., 2017) (Wu et al., 2020)]. FXR signaling in human ileal biopsies correlates positively with body mass index. High-affinity FXR antagonists have demonstrated potential in preventing or reversing genetic obesity, insulin resistance, and high-fat diet-induced hepatic steatosis in mice (Jiang et al., 2015). Besides FXR, TGR5 also plays a crucial role in lipid metabolism. TGR5 activation promotes mitochondrial fission in white adipose tissue, releasing free fatty acids via lipolysis, inducing beta-oxidation and thermogenic activity in adipocytes (Velázquez-Villegas et al., 2018). Rodent studies have shown that the TGR5-cAMP-2-type iodothyronine deiodinase (D2) signaling pathway in brown adipose tissue is activated by BAs, thus preventing obesity and insulin resistance (Sasaki et al., 2018).

2.2. BAs regulate immunity

BAs and innate immunity. Recent research indicates that bile acids (BAs) have a profound impact on both the innate and adaptive immune systems. BAs and their derivatives interact with various nuclear and cell surface receptors to regulate immune functions in both the intestines and throughout the body (Song et al., 2019). Specifically, BAs have been shown to have dual effects on macrophages (Macs) due to the expression of different receptors. While BAs and their metabolites can stimulate the production of immune-tolerant macrophages, they can also induce inflammatory macrophages, particularly conjugated bile acids (cBA). Activation of the TGR5 receptor can facilitate the transition of pro-inflammatory M1 macrophages to an immune-tolerant M2 phenotype, suppress the activation of the NLRP3 inflammasome, and reduce the release of pro-inflammatory cytokines (Shi et al., 2021). Additionally, studies have demonstrated that deoxycholic acid (DCA) or lithocholic acid (LCA) can act as endogenous inhibitors of NLRP3 inflammasome activation by activating TGR5 or FXR receptors. This inhibition mechanism may involve the suppression of TGR5-cAMP-PKA-dependent ubiquitination, leading to the inhibition of NLRP3 activation (Guo et al., 2016, Hao et al., 2017). Furthermore, TGR5 has been shown to downregulate the expression of NF-kB through the inhibition of TGR5-cAMP-PKA signaling (Hu et al., 2021). (Hu J. et al., 2021). DCA has been found to suppress the expression of pro-inflammatory cytokines such as IL-1, IL-6, and TNFα in dendritic cells in response to lipopolysaccharide (LPS) stimulation. Moreover, isoDCA can modulate FXR activity in dendritic cells, promoting an anti-inflammatory phenotype (Campbell et al., 2020).

BAs and adaptive immunity. The regulation of NKT and T cells by BA derivatives has been documented in various studies. Research has indicated a connection between bile acid metabolism, which is influenced by intestinal bacteria, and the surveillance of anti-tumor immunity in the liver. Intestinal microbial-mediated bile acid metabolism has the ability to modulate NKT cells in the liver, thereby impacting liver anti-tumor immunity (Ma et al., 2018). Recent findings suggest that bile acids may influence the homeostasis of intestinal retinoid-related orphan receptor (ROR) regulatory Treg cells through the BAeVDR axis (Gao et al., 2022). For instance, 3-oxoLCA has been shown to inhibit the differentiation of Th17 cells by directly interacting with the key transcription factor ROR-gt (RORgt), while isoalloLCA promotes the differentiation of Treg cells. Additionally, forkhead box protein 3 and mitoROS have been found to enhance Treg cell differentiation (Sasaki et al., 2018). Similarly, 3b-hydroxydeoxycholic acid (isoDCA) enhances the differentiation of peripheral Treg cells by acting on DCs to reduce their immunostimulatory properties, thereby increasing the induction of forkhead box protein 3 (Sasaki et al., 2021). Recent studies have highlighted changes in the size and/or composition of bile acid pools in individuals with type 2 diabetes, with evidence suggesting that bile acids and their derivatives can improve T2D by reducing inflammatory cytokine levels (Jackson et al., 2022). Furthermore, alterations in bile acid metabolism have been observed in patients with hepatic steatosis and abnormalities in glucose and lipid metabolism. Dysregulated bile acid metabolism is linked to steatosis, inflammation, and fibrosis in individuals with NAFLD (Jackson et al., 2022).

3. Interaction between gut microbiota and BA

3.1. Modification of bile acids by intestinal flora

BA bile salt hydrolase. Metabolism of primary BAs by intestinal bacteria enhances the diversity and overall hydrophobicity of the BA pool through various modifications. The initial step in secondary BA metabolism involves the hydrolysis of taurine and glycine conjugates by bile salt hydrolase (BSH), a key microbial enzyme widely distributed in the intestinal microbiome across different species and phyla. Gram-positive commensal bacteria like Lactobacillus, Bifidobacterium, and Enterococcus, as well as Gram-negative bacteria such as Bacillus and Listeria, exhibit BSH activity (Jones et al., 2008, Kawamoto et al., 1989, Dussurget et al., 2002, Chand et al., 2016). This deconjugation process enables the utilization of bile acids in microbial biotransformation pathways like 6-hydroxylation, exoisomerization, desulfurization, esterification, and unsaturation (Tanaka et al., 2000). The bacterial uncoupling of BAs not only provides energy from amino acids but also reduces host BA toxicity (Jones et al., 2014). BSH activity influences host gastrointestinal development, impacts hepatic and intestinal gene expression linked to circadian rhythms, hepatic glucose and lipid regulation, and immune function. Recent studies have revealed that the BSH enzyme can generate a specific form of bile acid called MCBA with distinct amino acid sequences and binding properties. MCBA, primarily synthesized in the small intestine with high BSH enzyme activity, can interact with PXR and FXR receptors, thereby influencing human metabolism (Rimal et al., 2024).

BA dehydroxylation. Decoupled primary BAs undergo a 7α-hydroxylation reaction catalyzed by bacterial 7α-dehydroxylases from the phylum Firmicutes and Eubacteria (Ridlon et al., 2006). The bile acid-inducible (bai) gene, present in Clostridium scientificum VPI 12708 and Clostridium hydroid, encodes an enzyme involved in the bile acid 7α-dehydroxylation pathway (Ridlon et al., 2010). Deconjugation and 7α-hydroxylation increase the hydrophobicity and pKa of BA, facilitating their passive absorption by the colonic epithelium and promoting BA recovery (Ridlon et al., 2006). Lithocholic acid (LCA) is produced by the microbial C7 dehydroxylation of chenodeoxycholic acid (CDCA) and ursodeoxycholic acid (UDCA). LCA, a significant bile acid in vertebrates, along with deoxycholic acid (DCA) found in human feces, is implicated in the pathogenesis of obesity, liver cancer, and colon cancer (Li et al., 2017, Ajouz et al., 2014, Yoshimoto et al., 2013), suggesting that 7α-dehydroxylation may play a crucial role in human intestinal physiology as a key bacterial BA biotransformation pathway.

Another significant microbial transformation occurs through bacterial hydroxysteroid dehydrogenase (HSDH), which catalyzes the reversible oxidation of the 3α-, 7α-, or 12α-hydroxyl groups of BA (Macdonald et al., 1983). This process leads to the formation of keto (oxy-)BAs, which can then be converted into β-hydroxy BAs or isoBAs through the stereospecific reduction of the oxygen group (Ridlon et al., 2006). The predominant bacterial phyla involved include Bacteroidetes (Bacteroidetes), Firmicutes (Clostridium, Eubacterium, Gastric Streptococcus, Ruminococcus), Actinobacteria (Bifidobacterium, Egg Fungus), and Proteobacteria (Enterobacter, Escherichia) (Ridlon et al., 2006, Macdonald et al., 1983, Doden et al., 2018). Exo-isomerization acts as a potential microbial adaptation strategy that generates more hydrophilic and less toxic isoBAs, thereby enhancing microbial resilience in a competitive and harsh intestinal environment (Ridlon et al., 2016). Recent research has highlighted the role of a steroid dehydrogenase called 5α-reductase (3-oxo-5α-steroid 4-dehydrogenase) present in various bacteria in the conversion of 5α bile acids (Ridlon et al., 2016, Wei et al., 2021).Once considered uncommon in human BAs (Satô et al., 2021), recent studies have emphasized the importance of permissive BAs in human health. In vitro studies have identified 11 bacterial genera from the Bacteroidetes phylum capable of converting the intermediate secondary BA metabolite 3-oxo-LCA into iso-alloo-LCA. Further investigations have shown that Odoribacter spp. and Allistipes spp. possess two gene clusters, 5α-reductase (5AR) and 3β-hydroxysteroid dehydrogenase (3β-HSDH), involved in BA generation from 3-oxolca (Lucas et al., 2021).

BA desulfurization, esterification, and unsaturation. Gastrointestinal bacteria have the ability to esterify BAs using alcohols, short-chain fatty acids, and long-chain fatty acids. Research has shown that processes of BA esterification linked to Lactobacillus, Eubacterium, and Bacteroidetes rely on the presence of ethanol. These bacteria can also generate BA fatty acid esters, where long-chain fatty acids (like C16 and C18) and short-chain fatty acids (such as acetate) are attached to the C3 position of isodeoxycholic acid and isolithocholic acid (Dawson and Karpen, 2015). Studies on human fecal isolates have demonstrated bacterial esterification activity, converting BAs into C24 ethyl esters. Comparing healthy human stool samples with or without strong alkaline hydrolysis revealed that 10 % to 30 % of total BAs (mainly isoDCA and isoLCA) were esterified (Takei et al., 2022). Early studies indicated that certain bacteria genera, such as Bacteroidetes, Eubacterium, Lactobacillus, Citrobacter, and Gastric Streptococcus, exhibit this activity (Edenharder et al., 1989). BA sulfatase activity has been observed in bacteria from genera like Clostridium, Pneumococcus, Fusobacterium, and Pseudomonas (Gérard, 2013). The conversion of BA sulfate into less polar and more easily absorbed desulfated BAs by bacteria with desulfatase activity suggests a potential role in regulating enterohepatic circulation and prolonging the half-life of BAs (Alnouti, 2009). Desulfated BAs, known to be more toxic and with a longer half-life compared to sulfated BAs, are potentially linked to hepatobiliary and intestinal toxicities such as cholestasis (reduced bile flow and BA excretion) and colon cancer (Alnouti, 2009).

Recoupling of BAs. Recent evidence indicates that bacteria have the ability to conjugate amino acids at the C24 carbonyl group instead of solely deconjugating them. When comparing gut metabolites from germ-free and conventional mice, it was discovered that microbiota-dependent cholic acid amides, such as phenylalanine, tyrosine, and leucine, interact with phenylalanine through the microbiome. Studies on acid, tyrosine, and leucine amide conjugation revealed the presence of 12 additional amino acid conjugated BA (AABA) in mouse feces, including conjugates of cholic acid, DCA, and CDCA (Quinn et al., 2020). Some AABAs may impact the host by modulating FXR or PXR activity (Quinn et al., 2020, Gentry et al., 2023). Phenylcholic acid and tyrosinocholic acid were identified as potent human FXR agonists. In vitro isolation experiments demonstrated that Clostridium strain WAL-14578 is capable of producing phenylcholic acid and tyrosinecholic acid. These findings were corroborated by another study showing that 27 out of 70 human intestinal species can conjugate CDCA, CA, and DCA with various amino acids, including phenylalanine and tyrosine (Lucas et al., 2021). Importantly, these conjugates have been detected in humans, particularly in patients with inflammatory bowel disease or cystic fibrosis. It was also noted that unconjugated BA is more harmful to bacteria than conjugated BA (Tian et al., 2020).

Oxidation and epimerization of BAs. Oxidation and epimerization of hydroxyl groups in BAs significantly increase the variety of BA metabolites. Early research has shown that certain species like E. lenta, Blautia producta, Clostridium absonum, Clostridium perfringens, Clostridium parasprucia, Escherichia coli, Bacteroides fragilis, and Ruminococcus are capable of oxidizing and reducing BAs (Liu et al., 2010)..It is crucial to identify and characterize the HSD genes that encode these enzymes. Oxygenated BAs and BA epimers play a significant role in physiological processes. For instance, 7-OxoCDCA can competitively inhibit hepatic 11β-HSD2 and impact glucocorticoid metabolism (Odermatt et al., 2011).

3.2. BA modulates the intestinal microbiota

BAs have the ability to regulate intestinal microbial communities and functions either directly or indirectly. They exhibit a bidirectional impact on the intestinal microbiota by stimulating the growth of bacteria dependent on BA metabolism while suppressing the growth of bile-sensitive bacteria. Numerous studies have indicated that individuals with cholestasis often exhibit reduced microbiota diversity (Van Best et al., 2020). In mouse models, bile duct ligation has been observed to decrease microbial beta diversity, a phenomenon that can be reversed by the administration of specific conjugated BAs (Lorenzo-Zúñiga et al., 2003). Particularly unconjugated BAs, such as DCA and CDCA, possess direct antibacterial properties and can disrupt bacterial cell membranes.

The bactericidal effect of BAs is likely due to their hydrophobic nature, which enhances their adherence to cell membrane phospholipids, ultimately causing cell damage (Watanabe et al., 2017). BAs induce DNA damage, protein misfolding, and oxidative stress, leading to reduced bacterial viability. For instance, tauroursodeoxycholic acid disrupts bacterial nucleotide and carbohydrate metabolism in mice (Tian et al., 2020). Moreover, BAs can impact the intestinal microbiota by activating FXR, which inhibits bacterial growth by inducing the expression of nitric oxide synthase and antibacterial agents like interleukin (IL)-18. Taurine-β-MCA and taurocholic acid (TCA) are pivotal in shaping the diverse microbiota (Van Best et al., 2020). Apart from changes in composition, BAs can also influence the function of the microbiota. Notably, isoBA has the potential to alter gut microbiota composition and host metabolism. For example, iso-DCA has been found to enhance the growth of Bacteroides, a significant genus linked with obesity and metabolic disorders (Devlin and Fischbach, 2015, Turnbaugh et al., 2006). HDCA significantly increases the abundance of probiotic species such as Parabacterium heterofidus, thereby promoting lipid catabolism and improving non-alcoholic fatty liver disease through the fatty

acid-hepatic peroxisome proliferator-activated receptor alpha (PPARa) signaling pathway (Kuang et al., 2023). Nevertheless, further research is required to fully comprehend the manipulation of the gut ecosystem.

Strong evidence suggests that BA metabolism plays a crucial role in resistance to Clostridium difficile colonization (Reed and Theriot, 2021). BA regulates fundamental aspects of the C. difficile pathogenic life cycle: TCA acts as a germinant for C. difficile spores, while CDCA can inhibit spore germination (Sorg and Sonenshein, 2008, Sorg and Sonenshein, 2008). Studies utilizing fecal microbiota transplantation in Clostridium difficile infections have demonstrated that its effects are linked to alterations in C. scinden, which occur due to antibiotic treatment, C. scindens encodes 7α-hydroxysteroid dehydrogenase genes essential for secondary bile acid biosynthesis, and further modifies endogenous bile salts to inhibit the growth of C. difficile (Buffie et al., 2014).Furthermore, antibiotic use results in BSH depletion, increased bound BA, and decreased secondary BA levels. (Theriot et al., 2014) The microbial conjugated bile acid (MCBA) pool can be modulated in vivo by enhancing BSH activity, and the sterol core of MCBA significantly influences C. difficile growth. These findings suggest that harnessing microbial bile acid metabolism to limit C. difficile colonization may offer a promising alternative strategy (Foley et al., 2023)

4. Gut microbiota and BA in diabetic nephropathy

4.1. The role of intestinal flora in diabetic nephropathy

In the context of diabetic nephropathy, there is growing evidence supporting bidirectional microbiota-kidney crosstalk. Gut microbiota richness is reduced, and beta diversity shows significant differences in DKD patients compared to healthy controls. Pathogenic bacteria like Klebsiella pneumoniae, Bacteroidetes immobilized, Enterobacteriaceae, and Legionella are found to proliferate abnormally in DKD (Kåhrström et al., 2016). The imbalance of intestinal flora in DKD rodent models is characterized by a decrease in probiotic bacteria such as Bifidobacterium, Lactobacillus, and Prevotella and an increase in pathogenic bacteria like Faecalibacterium and Desulfovibrio (Li et al., 2020, Sheng et al., 2018). Alterations in Escherichia coli, Citrobacter, Klebsiella, and Roseberia populations may have a significant impact on the abundance of their respective families and phyla, as well as on bacterial diversity and composition (Al-Obaide et al., 2017). Specifically, Citrobacter species were found to be increased in individuals with DKD compared to healthy controls, with no significant enrichment observed in those with T1D and T2D. Citrobacter infection can activate CD8+ T cells, leading to compromise of the intestinal barrier integrity and mucosal damage (Ma et al., 2006, Lee et al., 2009), allowing the entry of pathogens and toxins into the bloodstream. This process can result in chronic inflammation, thus promoting the onset and progression of DKD (Ramezani and Raj, 2014). Moreover, Escherichia may also play a crucial role in facilitating intestinal infiltration by breaching the intestinal epithelial barrier, enabling pathogenic and commensal bacteria to escape the intestinal lumen. This activation of the systemic immune system further contributes to the development of DKD (Shen et al., 2024). A Mendelian randomization study, which analyzed pooled data from 211 gut microbiota taxa in 18,340 participants, suggested that anomalies in Verrucomicrobiae were associated with a higher risk of DN, while native Eubacteria exhibited a protective effect against T1DN (Liu et al., 2024).

The fecal microbiota transplantation (FMT) trial showed that transferring microbiota from lean donors improved insulin sensitivity in patients with metabolic syndrome. This improvement was accompanied by changes in microbiota composition, indicating that the positive effects of FMT on glucose metabolism are associated with alterations in the gut microbiota (Kootte et al., 2017). Restoring intestinal structure can be achieved through the transplantation of F. prausnitzii, offering a potential treatment for inflammation and diabetes (Ganesan et al., 2018). Furthermore, a separate study demonstrated that FMT from healthy donors reduced foot cell and tubulointerstitial damage in diabetic rats by restoring cholesterol homeostasis. This highlights the therapeutic potential of FMT in diabetes and DKD (Hu et al., 2020, Lü et al., 2021).

4.2. Bile acid profile in diabetes and diabetic nephropathy

There are currently no reports of specific changes in bile acid profiles in patients with diabetic nephropathy. Xiao et al. reported the first cohort study linking bile acids to renal outcomes in patients with DKD, which examined histopathology and serum bile acid levels in 184 patients with biopsy-confirmed DKD. The study demonstrated that low levels of bile acids are an independent risk factor for adverse renal outcomes in this population. Specifically, serum bile acid levels below 2.8 mmol/L are independently associated with an increased risk of end-stage renal disease(ESRD). Moreover, higher bile acid levels may correlate with improved renal prognosis by enhancing glucose and lipid metabolism disorders in patients with DKD (Xiao et al., 2022). These findings suggest that bile acid analogs or agonists targeting their downstream signaling pathways could offer promising strategies for the treatment of DKD.Previous studies have not thoroughly investigated changes in BA profiles in diabetic nephropathy. However, research on circulating BA profiles in T2DM has demonstrated that, compared to healthy volunteers, fasting and postprandial plasma TBA levels are significantly elevated in T2DM patients. Specifically, unconjugated and glycine-conjugated secondary bile acids, such as DCA and UDCA, are found to be increased in the plasma of T2DM patients following a high-fat meal. Additionally, the concentration of fibroblast growth factor 19 (FGF-19) in T2DM patients is often lower than that observed in healthy volunteers (Sonne et al., 2016). These changes in bile acid profiles may result in alterations to the FXR/FGF-19 signaling pathway in the small intestine and liver, potentially exacerbating the deterioration of postprandial glucose homeostasis in T2DM.The levels of total TBA combined with BAs increased progressively from normoglycemic individuals to those with impaired glucose tolerance and T2DM. Moreover, levels of T-conjugated CDCA+DCA and T-conjugated CA were elevated in T2DM patients. Linear and multiple regression analyses indicated that T-bound total BA levels were positively associated with fasting plasma glucose, HbA1c, and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) (Wewalka et al., 2014). Another study reported that fasting plasma TBA levels were twice as high in T2DM subjects as controls, suggesting that circulating BA profiles could potentially serve as biomarkers for insulin resistance and T2DM. Additionally, BA analogs or agonists targeting their downstream signaling pathways could offer promising therapeutic approaches for DKD (Haeusler et al., 2013).

5. BA receptors in diabetic nephropathy

5.1. FXR and diabetic nephropathy

FXR (NR1H4) is a nuclear hormone receptor that is activated by both endogenous free and conjugated BAs (Fig. 3). Among these, CDCA is the most potent ligand for FXR, followed by LCA and DCA. Approximately 300 direct FXR target genes have been identified, including key transcription factors such as sterol regulatory element binding protein (SREBP), carbohydrate regulatory element binding protein (ChREBP), and peroxisome proliferator-activated receptor alpha (PPARa) (Ijssennagger et al., 2016). The impact of lipid metabolism on the development of diabetes-related kidney disease has been extensively studied. Excessive lipid accumulation can disrupt cellular homeostasis, leading to dysfunction (Yoon et al., 2021). Podocytes are particularly susceptible to lipid accumulation, which can impair their function, induce cytoskeleton rearrangement, provoke inflammatory responses, and ultimately affect renal function (Lee et al., 2021).

In streptozotocin-induced diabetic rat models and high-glucose-treated mouse cortical tubule cells, the expression levels of SREBP-1 and fatty acid synthase (FAS) were increased, leading to elevated

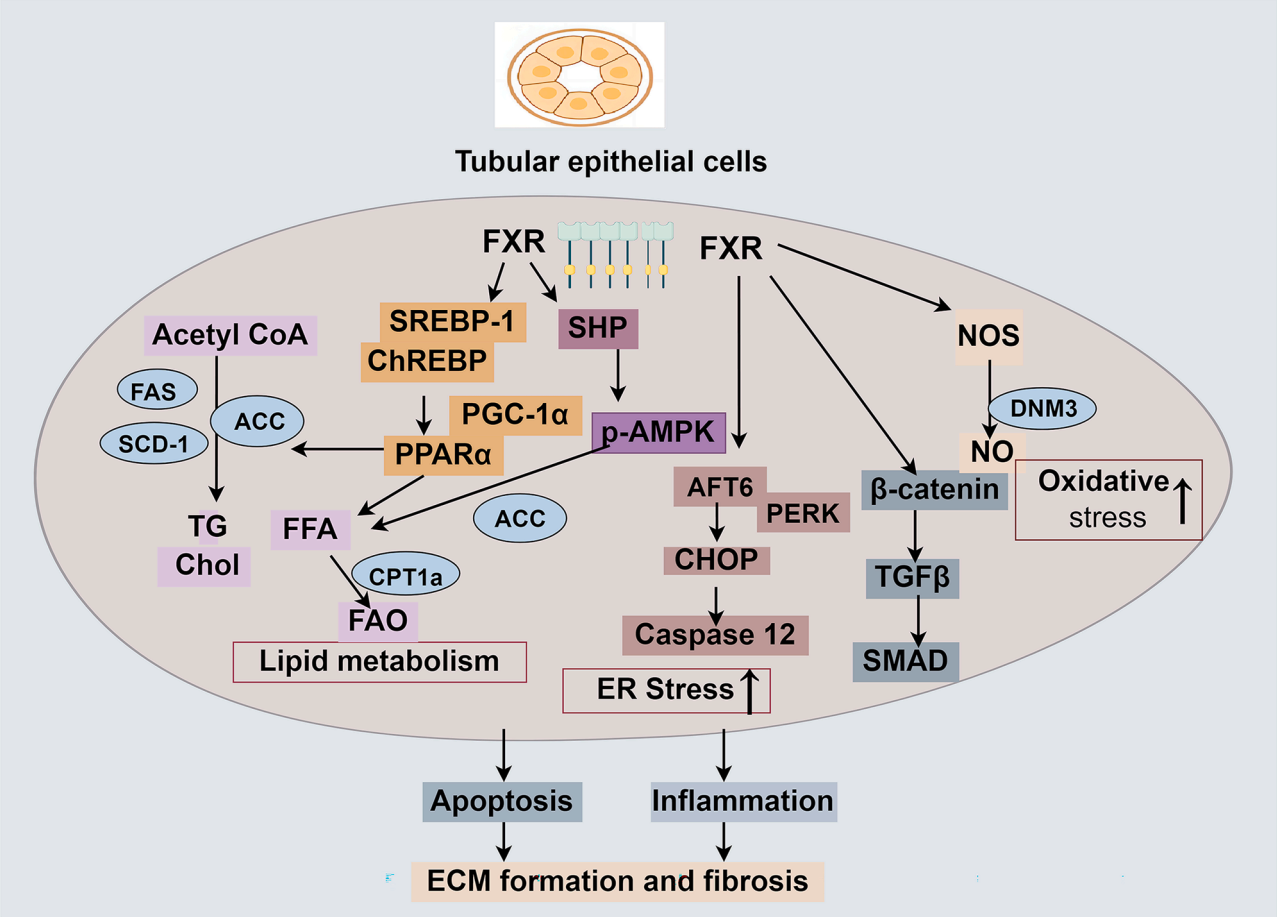

Fig. 3. FXR signaling in diabetic nephropathy. In the DKD mouse model and high-glucose-stimulated tubular epithelial cells, the expression of FXR and its target genes is decreased while the expression levels of SREBP-1 and fatty acid synthase (FAS) are elevated. This results in an increased accumulation of triglycerides, cholesterol, and fatty acids, along with reduced oxidation. Additionally, there is an increase in the expression of endoplasmic reticulum stress-related proteins, leading to the promotion of caspase-12 expression and exacerbating cell apoptosis and oxidative stress. Furthermore, this process activates the β-catenin/TGFβ/SMAD signaling pathway, intensifying the inflammatory response.

triglyceride and cholesterol accumulation (Sun et al., 2002). In type 1 diabetes genetic mouse models Akita and OVE26 mice, the expression levels of FXR, SHP, PPARα, and PPARδ in the kidney were reduced compared with WT. Conversely, the levels of triglycerides and cholesterol, as well as SREBP-1c and ChREBP, which increased fatty acid synthesis, were increased (Proctor et al., 2006). Renal FXR is highly expressed in renal tubular cells and glomerular cells in both human and animal models (Marquardt et al., 2017, Wang et al., 2010). Tubular expression exceeds glomerular expression, and FXR expression is downregulated in diabetic nephropathy. Studies using rodent models of type I diabetes, type 2 diabetes, and aging showed that FXR expression and its target genes were downregulated in the kidney, correlating with inflammation and fibrosis levels (Marquardt et al., 2017, Gao et al., 2017). In diabetic nephropathy models, FXR deficiency accelerates renal damage, while FXR agonist administration can reduce proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis, as well as regulate lipid metabolism by decreasing the expression of SREBPs to mitigate damage (Wang et al., 2010). TUDCA activates FXR, mediates the reduction of ATF6 and CHOP expression, and downregulates renal tubular ER stress in DKD mice (Marquardt et al., 2017).

5.2. TGR5 and diabetic kidney

TGR5, a member of the G protein-coupled receptor (GPCR) superfamily, serves as a membrane receptor for BAs. Its mRNA and protein are present in various tissues, including the liver, gallbladder, pancreas, intestine, fat, as well as the central and peripheral nervous systems, and the kidney (Wang et al., 2017, Yang et al., 2016). The interaction between TGR5 and the nuclear receptor FXR plays a crucial role in BA signaling. Unlike FXR, TGR5 influences mitochondrial genes like peroxisome proliferator-activated receptor gamma, NAD-dependent deacetylase Sirtuin-3 (SIRT3), and glucagon-like peptide-1 (GLP-1). (Fig. 4). TGR5 activation may benefit the kidney through mechanisms such as enhanced mitochondrial oxidative phosphorylation, fatty acid β-oxidation, superoxide dismutase activity, reduced ROS generation, and anti-inflammatory effects on renal receptors (Wang et al., 2017).

In the kidney, TGR5 is highly expressed in tubular cells as well as in glomerular cells, including podocytes and mesangial cells (Gao et al., 2017, Yang et al., 2016). TGR5 agonists have direct effects on regulating podocyte function. Kidney specimens from patients with obesity-related glomerulopathy or DKD show significantly lower levels of TGR5 mRNA and protein compared to normal kidney biopsy specimens, which are associated with disease progression. In human podocyte culture lines exposed to high glucose, the TGR5 agonist INT-777 induces mitochondrial biogenesis, reduces oxidative stress, and increases fatty acid beta-oxidation (Wang et al., 2017). Activation of TGR5 leads to a significant reduction in the expression of high glucose-induced intercellular adhesion molecule 1 (ICAM-1), transforming growth factor beta 1 (TGF-β1), and fibronectin (FN) in glomerular mesangial cells (GMC). Furthermore, TGR5 activation attenuates high glucose-induced S1P2 overexpression and weakens activating protein-1 (AP-1) activity, including c-Jun/c-Fos phosphorylation and AP-1 transcription activity

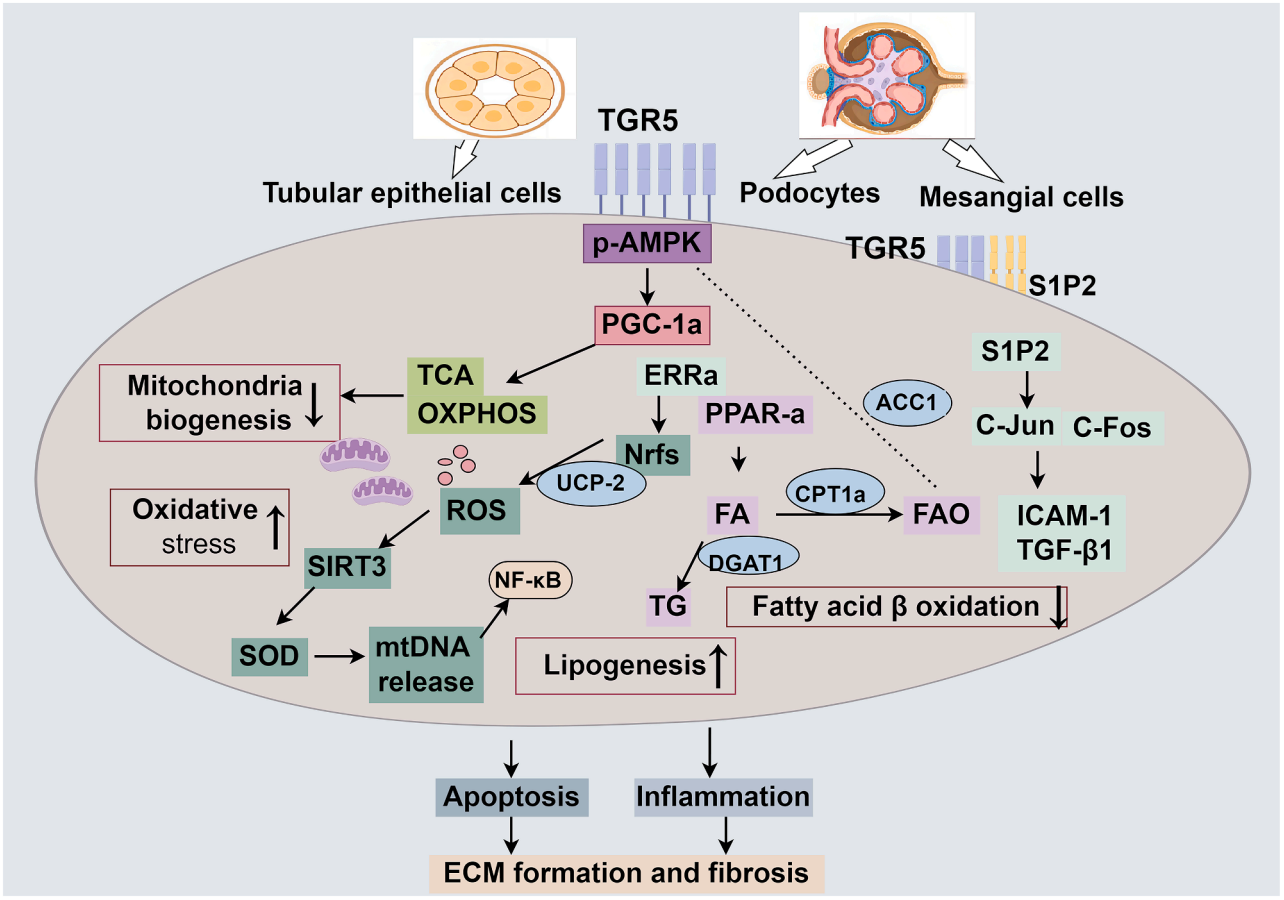

Fig. 4. TGR signaling in diabetic nephropathy. The potential mechanisms of decreased TGR5 expression and podocyte and renal tubular epithelial cell damage under DKD conditions include increased mitochondrial oxidative phosphorylation, mitochondrial fatty acid β-oxidation, and mitochondrial superoxide dismutase activity, inhibition of mitochondrial ROS production, and anti-inflammatory effects in the kidney. Decreased TGR5 promoted the expression of high glucose-induced intercellular adhesion molecule 1 (ICAM-1) and transforming growth factor beta 1 (TGF-beta1) as well as fibronectin (FN) in glomerular mesangial cells (GMC). S1P2 expression increased, and AP-1 activity, including c-Jun/c-Fos phosphorylation and AP-1 transcription activity was enhanced.

(Yang et al., 2016).

6. Interventions

6.1. Chinese medicine treatment

Oral administration of low-dose magnesium lithiolate (BMLB) has been shown to reduce kidney damage in rats with DKD by increasing total fecal BAs, particularly cholic acid (CA) and DCA, and inducing changes in the intestinal microbiome (Zhao et al., 2018). Notably, gentiopicroside (GPS) is identified as the primary active iridoid glycoside in Gentiana beichuanensis. Studies have demonstrated that GPS inhibits the reduction of IκBα by reversing the down-regulation of the BA receptor TGR5, consequently blocking NF-κB p65 nuclear translocation in the kidneys of diabetic mice to prevent renal inflammation and improve diabetic renal function (Xiao et al., 2020). Additionally, literature reports suggest that Qidi Tangshen Granules, a Chinese herbal medicine for diabetic nephropathy, can alter BA composition and intestinal microbiota, leading to reduced total BAs and specific BA profiles (e.g., β-murine cholic acid (β-MCA), taurocholic acid (TCA), tauroβ-muricholic acid (MCA), DCA, ultimately decreasing urinary albumin excretion and alleviating pathological kidney changes in db/db mice. However, it is important to note that Qidi Tang Shen Granules do not directly impact the expression of FXR (Wei et al., 2021).

6.2. BAs as interventions

Treatment options targeting BA metabolism have been studied in clinical research related to diabetes and non-alcoholic fatty liver disease (NALFD) (Pedrosa et al., 2020, Sun et al., 2019). Currently, research on DKD primarily involves animal experiments (Table 1). The use of the FXR agonist INT-747 has shown promising results in improving proteinuria, glomerulosclerosis, tubulointerstitial fibrosis, and modulating renal lipid metabolism, macrophage infiltration, SREBP, profibrotic growth factors, and oxidative stress expression, thereby reducing kidney damage (Wang et al., 2010, Jiang et al., 2007). Additionally, a different study explored the therapeutic potential of the chemical chaperone tauroursodeoxycholic acid (TUDCA) in diabetic nephropathy. The study revealed that TUDCA activated FXR and upregulated FXR-dependent genes such as suppressor of cytokine signaling 3 (SOCS3) and dimethylarginine dimethylaminohydrolase 1 (DDAH1), resulting in improvements in glomerular and tubulointerstitial damage in DKD mouse models. The impact of TUDCA on renal tubular injury in diabetic db/db mice involves inhibiting endoplasmic reticulum (ER) stress and reducing renal tubular epithelial cell apoptosis. This indicates the potential of TUDCA as a therapeutic target for preventing and treating DKD (Marquardt et al., 2017, Zhang et al., 2016). Furthermore, UDCA has been shown to improve glomerular lipid metabolism, decrease ER stress, oxidative stress, and other factors contributing to renal injury in diabetic mice (Marquardt et al., 2017, A et al., 2016). TGR5-specific agonists, similar to FXR agonists, can also alleviate lipotoxicity, oxidative stress, and ER stress, while enhancing mitochondrial biosynthesis and energy

Table 1
Summary of the role of FXR and TGR5 in the interventions for diabetic nephropathy.

Target	Treatment	Experimental model	Main mechanism	Biological effect	Reference
FXR	GW4064 CA	C57BLKS/J-db/db	Modulated renal lipid Metabolism; Attenuated inflammation; Attenuated fibrosis.	SREBP-1a,SCD-1,↑TG,CHOL ↓ TGF-β1,PAI-1, MCP-1 ↓ FSP-1,α-SMA ↓ Proteinuria ↓	Jiang,etal. (2007)
FXR	INT-747	STZ-DBA/2J	Attenuated profibrotic growth factor,macrophage and ECM accumulation; Reduce oxidative stress; Reduce lipid accumulation.	CD68,TGF-β1 ↓ α-SMA,FSP-1 ↓ NADPH oxidase Nox-2 ↓ SREBP-1c, SCD-1, ChREBP ↑ FAS,ACC ↑ TG,CHOL ↓	Wang,etal. (2010)
FXR	UDCA	C57BLKS/J-db/db	Attenuated ER Stress; Anti-oxidation; Regulate lipid metabolism.	ATF6,CHOP,PERK ↓ MDA,ROS,↓ SOD ↑ NEFA,LDL-C,↓ Oxidized,LDL-C↓	Cao,etal. (2016)
FXR	TUDCA	C57BLKS/J-db/db	Inhibit ER Stress–Associated Apoptosis Pathways	GRP78 and CHOP ↓ Cleaved caspase3,cleaved caspase12 ↓	Zhang,etal (2016)
FXR	TUDCA	C57BLKS/J-db/db eNOS KO - STZ	Attenuated glomerular and tubular injury Attenuated ER stress	UACR,KIM-1↓ ATF6, CHOP ↓	Marquardt,etal. (2017)
TGR5	Gentiopicroside	STZ-C57BL/6	Promoted TGR5-NF-κB signalling pathway; Enhanced the interaction between IκBα and β-arrestin2.	FN,TGF-β1 ↓ ICAM-1;VCAM-1 ↓ NF-κB ↓	Xiao,etal.(2019)
TGR5	INT-777	C57BLKS/J-db/db	Increases mitochondrial biogenesis, Decreases oxidative stress, Increases Fatty Acid β-Oxidation	p-AMPK,p-ACC, SIRT1,PGC-1a, ERRa, SIRT3,Nrf-1 ↑ ROS,SOD ↓ DGAT1,LCAD,CPT-1,UCP-2 ↑	Wang,etal. (2015)
FXR/ TGR5	OCA INT-777 INT-747 INT-767	STZ-DBA/2J C57BLKS/J-db/db	Enhanced mitochondrial biogenesis; Improved lipid metabolism; Inhibited ER stress; PreventsInflammation,oxidative Stress, profibrotic Signaling Pathways	Sirt1,Sirt3,PGC-1a,ERR-a,Nrf1 ↑ SREBP-1,SCD-1 ↑ CHOP,GRP78,XBP-1s Nox-2 ↓ HIF-1a and HIF-2a ↓NF-kB ↓ CTGF,TGF-b,FSP-1,a-SMA ↑	Wang,etal. (2018)

FXR,Farnesoid X receptor;TGR5,G-protein-coupled bile acid receptor 5;INT-777,selective TGR5 agonist;INT-767,dual FXR/TGR5 agonist;INT-747,FXR selective agonist;OCA, obeticholic acid;GW4064,FXR agonist;CA, cholic acid;UDCA Ursodeoxycholic acid;TUDCA,OCA;obeticholic acid;STZ streptozotocin;TCDCA, taurochenodeoxycholic acid ChREBP,carbohydrate responsive element binding protein;SREBP1c,sterol responsive element binding protein 1;ER,Endoplasmic reticulum; PGC1-α,Peroxisome proliferator-activated receptor-gamma coactivator 1-α;sirtuin 1,SIRT 1; ERR-a,estrogen-related receptor-a; a-SMA,a-smooth muscle actin;NADPH oxidase 2,Nox-2;CHOP,CCAAT-enhancer-binding homologous protein;ATF6,activating transcription factor 6;Nrf-1,nuclear respiratory factor 1;UCP2,uncoupling protein-2;SOD,superoxide dismutase;ECM,extracellular matrix;FN, fibronectin;LCAD,long-chain acylCoA dehydrogenase;FSP-1,fibroblast specific protein 1;SCD-1, Stearoyl-CoA desaturase1;TG,Triglyceride;CHOL,Cholesterol;TGF-β1,Transforming growth factor beta;PAI-1,plasminogen activator inhibitor-1;MCP-1,Monocyte Chemoattractant Protein-1;CD68,Cluster of Differentiation 68;FAS,Fatty Acid Synthase;ACC 1;acetyl coenzyme A carboxylase 1;PERK,Protein kinase R (PKR)-like endoplasmic reticulum kinase;MDA,Malondialdehyde;ROS,Reactive Oxygen Species; NEFA,LDL-C,Low Density Lipoprotein-Cholesterol; Oxidized,LDL-C↓UACR,Urinary Albumin to Creatinine Ratio; KIM-1, Kidney Injury Molecule 1;ICAM-1, Intercellular Cell Adhesion Molecule-1; VCAM-1; Vascular Cell Adhesion Molecule-1; DGAT1, Diacylglycerol Acyltransferase-1; CPT-1,Hypoxia-Inducible Factor, and HIF-2a; NF-kB,Nuclear Factor-B.

metabolism in renal podocytes and tubular epithelial cells. These agonists have been observed to reduce proteinuria, podocyte damage, mesangial expansion, fibrosis, and inflammation in db/db mice, ultimately helping to lessen diabetic kidney damage (Wang et al., 2015, Wang et al., 2017, Wang et al., 2017).

Research has explored the potential therapeutic implications of modulating BA metabolism and altering the intestinal microbiota for metabolic disorders. A recent study found that glycan ursodeoxycholic acid (GUDCA) can improve blood glucose levels in type 2 diabetic mice by modifying the gut microbiota through BA metabolism. Administration of GUDCA in mice led to increased levels of taurolithocholic acid (TLCA) and a higher abundance of Bacteroides vulgaris. These changes activated TGR5 and upregulated the expression of the coupling protein 1 (UCP-1), promoting thermogenesis in white adipose tissue (Chen et al., 2023). Administration of hydroxycitrate (HCA) significantly enhanced serum fasting GLP-1 secretion and improved glucose homeostasis to a greater degree than tauroursodeoxycholic acid in a diabetic mouse model. HCA boosts GLP-1 production and secretion in enteroendocrine cells by activating TGR5 and inhibiting FXR, a mechanism unique to HCA among BA species. These findings were validated in TGR5 knockout, intestinal FXR activation, and GLP-1 receptor inhibition mouse models. Additionally, a clinical cohort study confirmed that lower serum levels of HCA species are linked to diabetes and closely associated with blood glucose markers (Zheng et al., 2021).

These results suggest that alterations in BA metabolism may impact intestinal flora and cells, playing a crucial role in regulating glucose homeostasis. Further investigation is warranted to explore whether similar mechanisms are at play in diabetic nephropathy.

7. Conclusions and future perspectives

Recent advancements in the field of the 'gut-kidney axis' have shed light on the impact of changes in the intestinal microbiota and its metabolomics on chronic kidney disease (CKD) research. Studies have demonstrated the significant role of gut microbiota in the progression of DKD, with fecal microbiota transplantation from healthy donors showing promise in ameliorating this condition. As DKD is a metabolic disorder, recent findings emphasize the importance of mitochondrial dysfunction and renal lipid metabolism in podocyte injury. Activation of BA receptors has been found to promote mitochondrial biogenesis and lipid metabolism, leading to reduced damage to podocytes and renal tubular epithelial cells. Clinical evidence further supports the therapeutic potential of BA receptor activation in preventing diabetic complications, underscoring the intricate interplay between gut microbiota, diabetes, kidney disease, and BA signaling. Additionally, there exists a bidirectional relationship between intestinal flora and BA, where intestinal bacteria can metabolize BA and BA can influence the composition of intestinal flora. These findings hint at the possible involvement of BA metabolism in the pathogenesis of DKD.

The current study reveals novel and promising links between gut

microbiota, BA, and DKD. These findings provide exciting insights into this emerging field of research, and although the current study provides valuable clues into how the gut microbiome affects diabetic nephropathy, a causal link between gut microbiota dysbiosis and diabetic nephropathy in humans has not been confirmed yet. In vivo studies and human clinical trials on changes in BA profiles and the effects of specific BAs on diabetic nephropathy are limited, so further research is needed in this area. According to current evidence, intestinal microbiota may affect renal BA receptor levels by regulating the stimulation of BA metabolism, thereby affecting the interaction between microbiota, BA, and FXR signaling, providing a promising approach for the treatment of patients with diabetic nephropathy. We anticipate that this review will stimulate discussion and new research in this area.

CRediT authorship contribution statement

Ping Liu: Conceptualization, Methodology, Writing – original draft, Writing – original draft. **Meiping Jin:** Writing – original draft. **Ping Hu:** Visualization, Investigation. **Weiqian Sun:** Visualization, Investigation. **Yuyan Tang:** Visualization, Investigation. **Jiajun Wu:** Formal analysis, Resources. **Dongliang Zhang:** Formal analysis, Resources. **Licai Yang:** Formal analysis, Resources. **Haidong He:** Conceptualization, Supervision, Project administration. **Xudong Xu:** Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Reports a relationship with that includes:. Has patent pending to. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors acknowledge financial support from the National Natural Science Foundation of China (82304948); the school-level subject innovation project of Fudan University Minhang Hospital (2022MHCX01); the Shanghai Minhang District Medical Specialty Project (2020MWTZB07); the school-level discipline of Fudan University Minhang Hospital-Chronic Disease Group-Chronic Kidney Disease Project (YJXK-2021-13); and the Shanghai Minhang District Natural Science Research Project (2020MHZ065). The pictures in this article are drawn by Figdraw.

Data availability

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

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