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REVIEW

Cellular crosstalk of glomerular endothelial cells and podocytes in diabetic kidney disease

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Abstract

Diabetic kidney disease (DKD) is a serious microvascular complication of diabetes and is the leading cause of end-stage renal disease (ESRD). Persistent proteinuria is an important feature of DKD, which is caused by the destruction of the glomerular filtration barrier (GFB). Glomerular endothelial cells (GECs) and podocytes are important components of the GFB, and their damage can be observed in the early stages of DKD. Recently, studies have found that crosstalk between cells directly affects DKD progression, which has prospective research significance. However, the pathways involved are complex and largely unexplored. Here, we review the literature on cellular crosstalk of GECs and podocytes in the context of DKD, and highlight specific gaps in the field to propose future research directions. Elucidating the intricates of such complex processes will help to further understand the pathogenesis of DKD and develop better prevention and treatment options.

Keywords Diabetic kidney disease · Glomerular endothelial cell · Podocyte · Cellular crosstalk · High glucose

Introduction

Diabetic kidney disease (DKD) is a serious microvascular complication of diabetes and the main cause of end-stage renal disease (ESRD) (Shaw et al. 2010). Therapies for early stage DKD are limited. Traditional methods include strict control of blood glucose and use of renin–angiotensin system (RAS) antagonists, which can reduce proteinuria to a certain extent. Some emerging therapies are increasingly being applied in clinical setting, including sodium-glucose cotransporter 2 (SGLT2) inhibitors (Hanai and Babazono 2020), dipeptidyl peptidase-4 (DPP-4) inhibitor (Guo et al. 2016), and glucagon-like protein 1 receptor (GLP-1R) agonists (Greco et al. 2019). However, they can only delay the progression of DKD and cannot prevent the progression to ESRD. Potential therapeutic targets and current clinical trial results are shown in Table 1. The metabolism in patients with DKD is highly disordered, which complicates the treatment of ESRD. Therefore, DKD is considered a major health and financial burden (Wada and Makino 2012).

Owing to the destruction of the glomerular filtration barrier (GFB), persistent proteinuria is an important feature of DKD (Phillips and Steadman 2002). The GFB includes fenestrated endothelium and its associated glycocalyx, glomerular basement membrane (GBM), and podocyte foot processes with slit diaphragms (SDs). Damage to any part of the GFB can lead to persistent proteinuria. Glycosaminoglycans, proteoglycans, and adsorbed plasma components form a surface-bound ('endothelial glycocalyx') and loosely adherent matrix that covers the luminal surface of glomerular endothelial cells (GECs), which is called the endothelial surface layer (ESL) (Salmon et al. 2012). GECs are covered with glycocalyx to form an osmotic barrier that prevents the development of proteinuria under healthy conditions (Satchell and Braet 2009). GECs serve as the primary barrier against exposure to hyperglycaemia, to which they are particularly vulnerable (Lassén and Daehn 2020). Podocytes are highly specialised pericytes that surround glomerular capillaries, and their dysfunction is critical to the pathophysiology of DKD (Torban et al. 2019). Nephrin, a podocyte protein, is essential for the structural integrity of the SD between podocytes. Podocin, another SD protein, is encoded by *NPSH2* in podocytes. The lack of expression of nephrin and podocin has negative effects on the phenotype

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Table 1 Potential therapeutic targets of DKD

Target	Medication	Current clinical trial result	Reference
Mineralocorticoid receptor	Finerenone	Effective	Bakris et al. (2019)
SGLT2	Dapagliflozin	Effective	Mosenzon et al. (2019)
GLP-1	Liraglutide	Effective	Thornton et al. (2017)
DPP-4	Linagliptin	Effective	Perkovic et al. (2020)
AGEs	Pyridorin	Ineffective	Lewis et al. (2012)
Vascular adhesion protein-1	ASP8232	Effective	Dick de Zeeuw et al. 2018)
Nuclear 1 factor (erythroid-derived 2)–related factor 2	Bardoxolone methyl	Ineffective	de Zeeuw et al. (2013)
Janus kinase	Baricitinib	Effective	Tuttle et al. (2018)
Vitamin D receptor	Paricalcitol	Effective	Dick de Zeeuw et al. (2010)
Methylxanthine phosphodiesterase	Pentoxifylline	Effective	Shan et al. (2012)
Endothelin receptor	Atrasentan	Effective	Heerspink et al. (2019)
Apoptosis signal-regulating kinase 1	Selonsertib	Effective	Chertow et al. (2019)
C–C chemokine receptor type 2	CCX140-B	Effective	Dick de Zeeuw et al. (2015)
TGF-β1, TNF-α, NF-κB	Tocotrienol-rich vitamin E	Effective	Koay et al. (2021)
miRNA		Unproved	Jiang et al. (2020) Cheng et al. (2020) Kölling et al. (2017)
Endoplasmic reticulum (ER) stress		Unproved	Xiong et al. (2020)
Caveolin-1		Unproved	Van Krieken and Krepinsky (2017)
Complement		Unproved	Tang et al. (2020a) Ling Li et al. (2015) Li et al. (2014)

and function of podocytes (Saleem et al. 2002). The role of GECs and podocytes in the pathophysiology of DKD has been reported (Sol et al. 2020; Zhang et al. 2020b).

The mechanism of kidney cell damage caused by diabetes is highly complex, and it mainly includes hemodynamic factors and metabolic abnormalities (Arora and Singh 2013). Hemodynamic pathways include the renin–angiotensin–aldosterone system (RAAS), urotensin systems, and endothelin (ET). Metabolic factors are associated with advanced glycation end-products (AGEs), reactive oxygen species (ROS), and nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), etc. (Volpe et al. 2018). Hemodynamic and metabolic factors activate various pathways, including the mitogen-activated protein kinase (MAPK), Notch, NF-κB, Wnt, protein kinase C (PKC), and various cytokine signalling pathways (Tesch 2017; Zeng et al. 2019). A meta-analysis of genetic association studies of diabetic nephropathy (DN) further revealed six signalling pathways, namely, the RAAS, pyruvate metabolism, adipocytokine signalling pathway, cytokine–cytokine receptor interaction, and renal cell carcinoma- and type II diabetes mellitus (T2DM)-related pathways (Tziastoudi et al. 2020). These mechanisms lead to the characteristic pathological changes, including thickening of GBM, accumulation of extracellular matrix (ECM), and diffuse or nodular mesangial expansion. Kimmelstiel–Wilson lesions are characteristic pathological changes and are associated with a poor prognosis (Hong et al. 2007).

In recent years, studies have found that cellular crosstalk directly affects the progression of DKD, and it has prospective research significance (Chen et al. 2020; Gil et al. 2020; Mahtal etal. 2021). Thus, research on crosstalk of GECs and podocytes may further reveal the mechanism of DKD and guide its treatment. Here, we review available literature on the crosstalk of GECs and podocytes, and highlight the aspects of the field that require further investigation. Herein, we first deal with the crosstalk of GECs, describing the different molecules and signalling pathways involved. Similarly, we describe the crosstalk of podocytes. This review may help guide future research on elucidating the complex pathogenesis of DKD.

Cellular crosstalk of GECs.

Transforming growth factor-β (TGF-β)

TGF-β is an important growth factor with a variety of regulatory effects. TGF-β1 is the most abundantly expressed isoform and is associated with susceptibility to various

diseases (Martelossi Cebinelli et al. 2016). Monica et al. reported that TGF-β1 plays a leading role in fibrosis and immunity (Lodyga and Hinz 2020). Wu et al. treated GECs with high glucose (HG) and used their supernatant to culture podocytes. In the cultured podocytes, the expression of epithelial markers nephrin, zonula occludens-1 (ZO-1), and Wilms' tumour 1 (WT-1) decreased, and the expression of mesenchymal markers including α-smooth muscle actin (α-SMA), desmin, and fibroblast-specific protein-1 (FSP-1) increased compared with those in podocytes co-cultured with exosomes from normal glucose (NG)-treated GECs. They demonstrated that HG-treated GECs can secrete exosomes in a paracrine manner, mediating podocyte epithelial–mesenchymal transition (EMT). The increased levels of TGF-β1, Wnt1, β-catenin, and Snail demonstrated the activation of the Wnt/β-catenin signalling pathway (which can lead to EMT) in exosome-treated podocytes. On this basis, further experiments proved that exosomes secreted by HG-treated GECs are rich in *TGF-β1* mRNA. In an HG environment, GECs cause podocyte dysfunction through increases in TGF-β1 expression and activation of Wnt/β-catenin signalling (Wu et al. 2017).

Han et al. showed that the genetic deletion of bone morphogenetic protein and activin membrane-bound inhibitor (BAMBI), a negative regulator of TGF-β signal transduction, in diabetic mice can accelerate DKD progression (Lai et al. 2020). They observed that BAMBI is expressed in podocytes and GECs, and TGF-β1 is expressed in GECs by single-cell RNA-Seq. By specifically knocking out *BAMBI* in GECs (*EC-Bambi-/-*) and in podocytes (*Pod-Bambi-/-*), they found that activin receptor-like kinase 1 (ALK1)-Smad1/5 is activated in *EC-Bambi-/-* diabetic mice, resulting in GEC proliferation, whereas ALK5-Smad3 is activated in *Pod-Bambi-/-* diabetic mice, resulting in podocyte damage. Interestingly, the damage and loss of podocytes marked by WT-1 in *EC-Bambi-/-* diabetic mice were comparable with those in *Pod-Bambi-/-* diabetic mice, whereas GEC proliferation was only observed in *EC-Bambi-/-* diabetic mice, demonstrating that GEC-to-podocyte crosstalk is complex and occurs via the TGF-β/Smad1/5 signalling pathway. Furthermore, by measuring 8-oxo-2'-deoxyguanosine, they demonstrated that the oxidative stress in *EC-Bambi-/-* diabetic mice and *Pod-Bambi-/-* diabetic mice is aggravated, leading to the disappearance of podocyte foot processes, loss of podocytes and proliferation of GECs.

Jin et al. demonstrated that HG activates TGF-β-dependent Smad signalling, which promotes the synthesis of collagen and results in ECM production (Li et al. 2003), which is related to Kimmelstiel–Wilson lesions (Glick et al. 1992). Wu et al. showed that exosomes released by HG-treated GECs can promote the expression and proliferation of α-SMA, type IV collagen, and fibronectin in mesangial cells (MCs). Furthermore, they found that exosomes released by HG-treated GECs were rich in *TGF-β1* mRNA. Finally, they used *TGF-β1* small interfering RNA to decrease TGF-β1 expression in GEC-derived exosomes and found that MCs were not activated. Overall, TGF-β1 from HG-treated GECs was demonstrated to mediate MC activation and ECM protein overproduction through the TGF-β1/Smads signalling pathway (Wu et al. 2016). Crosstalk of GECs with podocytes and MCs through TGF-β is one of the reasons that TGF-β is considered a key cytokine in the development of glomerular fibrosis in patients with DKD. Urine TGF-β and serum TGF-β1 can predict renal function in DN (Shaker and Sadik, 2013; Verhave et al. 2013). In conclusion, the role of TGF-β in DKD is important and complex, and requires further exploration.

Leucine-rich α-2-glycoprotein 1 (LRG-1)

LRG-1 is a secreted glycoprotein that mediates protein interaction and is widely involved in signal transduction (Zhang et al. 2020a). Plasma LRG-1 is considered a marker of DKD progression (Liu et al. 2017). Fu et al. conducted a transcriptome analysis of GECs from diabetic mice and nondiabetic controls and found that the expression of genes related to angiogenesis and endothelial proliferation pathways were up-regulated in diabetic mice, including *LRG-1* (Fu et al. 2018). LRG-1, which is mainly expressed in GECs, with no obvious expression in podocytes, promotes the progression of DKD by enhancing angiogenesis through TGF-β/ALK1 (Hong et al. 2019). *LRG-1* ablation in DKD not only reduces glomerular angiogenesis but also attenuates foot process disappearance, podocyte loss, and mesangial expansion. Thus, LRG1 seems to participate in the crosstalk between GECs and podocytes; however, the specific mechanism remains unclear.

Hepatocyte growth factor (HGF)

HGF was originally discovered as a mitogen in adult rat liver cells. c-mesenchymal-epithelial transition factor (c-Met) is an HGF receptor, and HGF/c-Met plays a role in promoting liver repair (Nakamura 1994). In the kidney, HGF/c-Met has also been shown to induce kidney regeneration and repair (Igawa et al. 1993). Through transcriptome analysis, Tang et al. found that *HGF* is one of the differentially expressed genes (DEGs) in the glomeruli and tubules of patients with DKD and healthy controls, and its expression in patients with DKD is down-regulated compared with that in the healthy controls (Tang et al. 2020b). Moreover, correlation analysis revealed that HGF may serve as a biomarker for diagnosing DKD. In normal glomeruli, GECs express HGF, and MCs hardly express c-Met. In DKD, HGF increases briefly and then drops below the basic level (Mizuno and Nakamura 2004). This may be due to the damage to

GECs caused by HG. In contrast, the expression of c-Met increases significantly in HG-treated MCs. HGF exerts a paracrine effect, and the combination of HGF and c-Met can protect MCs from HG-mediated oxidative stress. The levels and activities of malondialdehyde, glutathione, antioxidant enzymes, and glucose-6-phosphate dehydrogenase revealed that HGF/c-Met inhibits the production of ROS and increases their clearance (Li et al. 2006). This anti-oxidative stress effect is achieved by inhibiting PKA and activating PKG (Hui et al. 2010). HGF can also inhibit the production of TGF-β1, thus playing a protective role (Mizuno and Nakamura 2004). Furthermore, Li et al. added exogenous HGF to HG-treated tubular epithelial cells (TECs) and found that c-Met is also up-regulated in TECs, playing a role in alleviating DKD (Xing and Muxun, 2007). However, Lucia et al. considered that c-Met activation in TECs is independent of HGF (Mesarosova et al. 2017). Thus, the role of HGF/c-Met requires further exploration.

Endothelial nitric oxide synthase (eNOS)

eNOS-derived nitric oxide (NO) can relax blood vessels (Sol et al. 2020) and block the activation of cytokines such as tumour necrosis factor to protect GECs (Takahiko Nakagawa et al. 2011). Fu et al. conducted a transcriptome analysis on GECs from streptozotocin (STZ)-induced diabetic wildtype and diabetic eNOS-null mice and compared DEGs (Fu et al. 2018). Pathway analysis has shown that eNOS deficiency is related to abnormal angiogenesis, cytoskeletal organization, and epigenetic regulation. eNOS is expressed in GECs but not in podocytes. Darren et al. demonstrated that the lack of eNOS in diabetic mice can cause podocyte damage including the disappearance of foot processes and the accumulation of vacuoles, pseudocysts, and electron-dense droplets in the cytoplasm (Yuen et al. 2012). eNOS deficiency has been shown to play a role in DN via the activation of RAAS or increased RAAS sensitivity (Takahashi and Harris, 2014). Takahiko et al. found that eNOS knockout in diabetic mice results in an increased expression of vascular endothelial growth factor (VEGF) in podocytes (T. Nakagawa 2008). Diabetic eNOS-knockout mice have abnormal angiogenesis, GBM thickening, mesangial expansion, macrophage infiltration, and Kimmelstiel–Wilson-like lesions in the kidney. These findings indicate that the absence of eNOs may be related to Kimmelstiel–Wilson lesions.

Kruppel-like factors (KLFs)

KLFs are involved in a wide range of cellular processes, such as cell differentiation, angiogenesis, erythropoiesis, and immunomodulation (Bai et al. 2007; Pearson et al. 2008). Moreover, their deficiency leads to serious damage of the cardiovascular system (Chiplunkar et al. 2013; Lee et al. 2006). In DKD, KLFs are regarded as protective factors (Zhong et al. 2018), although the specific mechanism of KLFs in DKD is still unclear. KLF2 is expressed in GECs but not in podocytes (Mallipattu et al. 2017). A previous study showed that KLF2 expression is inhibited in HG-treated GECs (Lee et al. 2012). Zhong et al. performed microarray gene expression analysis on the glomeruli of diabetic rats and found that many DEGs are GEC-specific genes, *KLF2* being one of them. Furthermore, they induced diabetes by STZ in GEC-specific KLF2 knockout mice (KO-STZ) and found that the expression of podocyte-specific genes encoding nephrin, podocin, and synaptopodin in the kidney decreased compared with that in wild-type diabetic mice. Moreover, podocyte foot processes and the number of podocytes (marked by WT-1) decreased in KO-STZ mice (Zhong et al. 2015). This indicates that KLF2 is involved in the interactions between GECs and podocytes. The specific mechanism remains unclear, and may be related to key molecules such as eNOS, thrombomodulin, endothelin-1(Slater et al. 2012).

Platelet-derived growth factor B (PDGFB)/ platelet-derived growth factor receptor β

The PDGFB/PDGFRβ axis plays an angiogenic role in kidney tumours, causing tumour endothelial cell proliferation and migration (Cumpănas et al. 2016). Changes in the expression of PDGFB and/or its receptors are associated with many kidney diseases. The expression of PDGFB/PDGFRβ is significantly increased in DN (Langham et al. 2003) and mesangial proliferative glomerulonephritis (Matsuda et al. 1997). The over-expression of PDGFB is one of the reasons for ECM protein production (Floege et al. 1993). By inactivating *PDGFB/PDGFRβ* in developing mice, Betsholtz et al. demonstrated that *PDGFB/PDGFRβ* can promote the survival and recruitment of MCs and the production of mesangial matrix (Betsholtz, 1995). PDGFB can stimulate the rapid mobilisation of intracellular calcium, increase cyclin A and cyclin dependent kinase 2, and reduce p27, leading to considerable cell proliferation (Shankland et al. 1997; Wallmon et al. 1993). In addition, through synergy with TGF, it promotes the synthesis of mesangial matrix (Throckmorton et al. 1995). Lindahl et al. found that PDGFB is mainly expressed in GECs, whereas PDGFRβ is mainly expressed in MCs (Lindahl et al. 1998). Defective MC ingrowth and, consequently, failure of capillary loop development have been found in PDGFB mutant mice with inhibited PDGFB expression in GECs (Leveén et al. 1994). Overall, the findings suggest that the paracrine function of PDGFB controls the development of MCs. Moreover, by measuring α-SMA and proliferating cell nuclear antigen, Eunjin et al. demonstrated that

inhibition of PDGFB and its receptors can inhibit mesangial proliferation in diabetic rats (Sohn et al. 2014). Further evidence indicating that the PDGFB/PDGFRβ axis is the main mediator of GEC-to-MC crosstalk in DKD was provided by Jia et al. (Fu et al. 2015).

Lipids and fatty acid translocase (FAT/CD36)

In DKD, lipid deposits in the glomeruli and renal tubules can be observed, and abnormal lipid metabolism is nephrotoxic (Thongnak et al. 2020). The deposition of lipids in the kidney is related to glomerular hypertrophy and interstitial fibrosis, causing various types of cell damage (Jiang et al. 2005). Lipid deposition is part of the original description of Kimmelstiel-Wilson lesions (Gröne, 1999). Although GECs are not prone to lipid accumulation, they play an important role in the transport of lipids to other tissues in the kidney. GECs are the main source of lipid supply to glomerular cells (Hagberg et al. 2010). Importantly, lipid delivery between cells may amplify the pathogenic effect. To our knowledge, the mechanism behind cellular crosstalk through lipids remains unreported. However, we speculate that FAT/CD36 may be involved.

FAT/CD36 is a cell-surface protein and a member of the class B scavenger receptor family. It can bind to oxidised low-density lipoproteins, long-chain fatty acids, phospholipids, and collagen (Bonen et al. 2004; Martin et al. 2011), and directly promote the transport of fatty acids across the plasma membrane (Schneider et al. 2014). Furthermore, its overexpression in muscle and liver cells can cause muscle and liver steatosis (Bechmann et al. 2010; Ibrahimi et al. 1999). The increase in FAT/CD36 permanently fixed on the cell membrane is considered the main factor leading to the early onset of T2DM (Steinbusch et al. 2011). Aiko et al. have shown that in the state of hyperglycaemia, the endothelial cell glycocalyx is damaged, causing MCs to express LDL and FAT/CD36 receptors (de Vries et al. 2014). Down-regulating the expression of CD36 can reduce the deposition of free fatty acids in MCs, and reduce oxidative stress and fibrosis (Y. Su et al. 2019). Moreover, Lei et al. measured the levels of CD36 and peroxisome proliferator-activated receptor γ (PPARγ) separately in TECs cultured in HG and an AKT pathway inhibitor and evaluated the lipid content in TECs by Oil Red O staining. They demonstrated that HG can promote FAT/CD36 expression in TEC by upregulating the levels of PPARγ (Feng et al. 2017). Increased expression of FAT/CD36 leads to lipid deposition in kidney cells and exerts lipotoxicity through the Wnt/β-catenin pathway in DKD (X. Li et al. 2019). Nevertheless, the mechanism of GEC crosstalk with other cells through lipids needs to be further clarified.

Activated protein C (APC)

APC is an effector enzyme involved in the protein C pathway. It not only acts as an inhibitor of the coagulation system but also as a regulator of inflammation, tissue remodelling, and apoptosis (Suzuki et al. 2004). Berend et al. reported that the levels of pro-apoptotic proteins p53 and Bax substantially increased in diabetic wild-type mouse glomeruli, whereas the levels in diabetic APC-high mice were normal, indicating that APC regulates the mitochondrial apoptosis pathway in DKD (Isermann et al. 2007). The protective effects of APC on GEC are mainly mediated through endothelial protein C receptor (EPCR) and protease activated receptor-1 (PAR-1). The protective effect of APC on podocytes in DKD is through PAR-3 by inhibiting the RhoA signalling pathway and requires the participation of integrin β3 (Madhusudhan et al. 2020, 2012). However, in patients with diabetes, the level of APC, regulated by endothelial thrombomodulin, is decreased compared with physiologic conditions (Tan et al. 2016), leading to activation of the mitochondrial apoptotic pathway in podocytes (Isermann et al. 2007). Maestroni et al. also indicated that APC is involved in the crosstalk between GECs and podocytes in DKD (Maestroni and Zerbini 2018). Meanwhile, Berend et al. revealed that APC can also play a protective role in DKD by regulating caspase activation and nitrosative stress.

A summary of the cellular crosstalk of GECs is shown in Fig. 1.

Cellular crosstalk of podocytes

VEGF

Podocyte damage is considered the main feature of DKD and includes podocyte hypertrophy, foot process shedding, and podocyte apoptosis (Bose et al. 2017; Su et al. 2010). In the glomerulus, podocytes produce large amounts of VEGF. Podocyte-produced VEGF regulates the structure and function of adjacent GECs by binding to VEGF receptors 1 and 2 (VEGFR1 and VEGFR2) and neuropilin-1/2 (NP1/NP2) (Melincovici et al. 2018). VEGF, which has both autocrine and paracrine effects (Stieger et al. 2011), is considered an important factor in diabetes and its complications. Plasma VEGF can be used as a marker of DKD progression(Aly et al. 2019). The VEGF family consists of several members. Among them, VEGF-A plays a major role in vasculogenesis (Tufro and Veron, 2012), and VEGF-B is related to the promotion of lipid accumulation and lipotoxicity (Karpanen et al. 2008). Early studies have shown that VEGF has a complicated pathogenic mechanism in DKD. In the early stage, human kidney biopsies show high VEGF expression. In

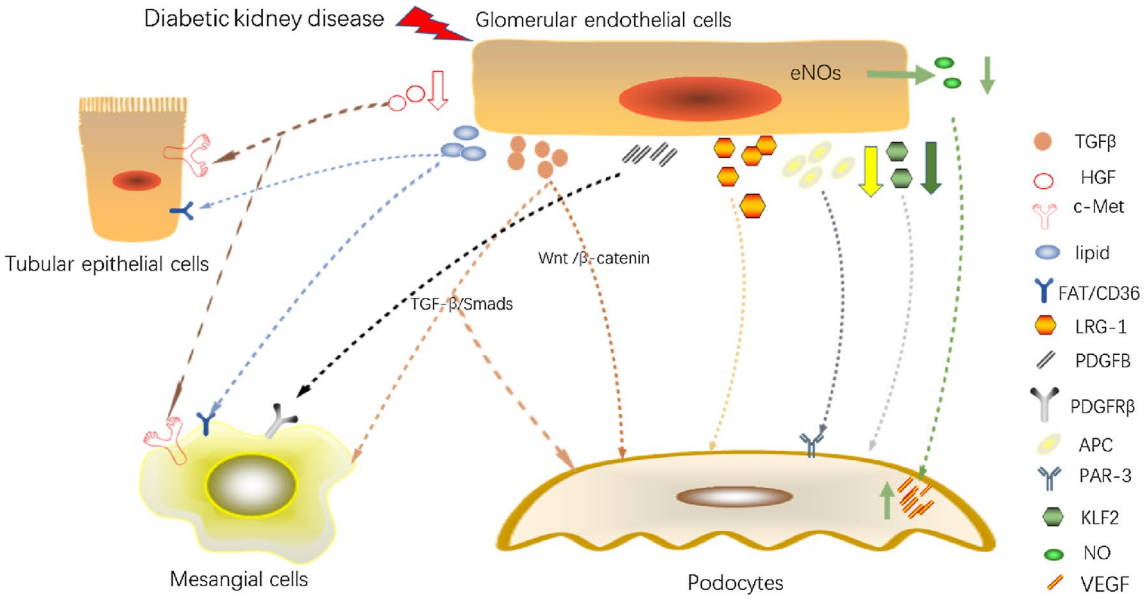

Fig. 1 Cellular crosstalk of glomerular endothelial cells. (TGF-β, transforming growth factor-β; HGF, hepatocyte growth factor; c-Met, c-mesenchymal-epithelial transition factor; FAT, fatty acid translocase; LRG-1, leucine-rich α-2-glycoprotein 1; PDGFB, platelet-derived growth factor B; PDGFRβ, platelet-derived growth factor receptor β; APC, activated protein C; PAR-3, protease activated receptor-3; KLF2, Kruppel -like factor 2; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; VEGF, vascular endothelial growth factor; Smad, small mother against decapentaplegic; Wnt, Wingless and Int-1;)

contrast, the loss of podocytes in the late stage leads to low VEGF expression (Shulman et al. 1996).

Although the highest expression of the VEGF-A receptor VEGFR-2 is found in GECs, it is also expressed in podocytes (Villegas et al. 2005). Systemic loss of VEGFR-2 leads to abnormal GECs. Karen et al. inhibited VEGFR-2 expression in podocytes and found that autocrine signal transduction of podocytes through VEGFR-2 had no major effect on glomerular function (Sison et al. 2010). This showed that the paracrine function of VEGF-A plays a major role in regulating glomerular function. Du et al. identified 142 DEGs between DN and normal glomeruli through the GSE30122 and GSE1009 databases, including *VEGF-A* (Du et al. 2021a). Meanwhile, Masahiro et al. observed that fenestrations of GECs were reduced, the subendothelial space was enlarged, and staining of plasmalemmal vesicle-associated protein-1 was generally positive in VEGF-A-overexpressing podocytes, indicating the overexpression of VEGF-A in podocytes can weaken the differentiation of GECs (Suyama et al. 2018). In addition, the lack of VEGF-A in diabetic mouse podocytes can cause GEC damage, including shedding of GECs and loss of capillary loops (Sivaskandarajah et al. 2012). The combination of VEGF-A expression in podocytes and VEGFR-2 expression in GECs plays a role in the cellular crosstalk of DKD.

In recent years, the inhibition of VEGF-B signalling has been suggested as a promising option for the treatment of T2DM and its complications (Hagberg et al. 2012). Woroniecka et al. conducted analysis using Affymetrix expression arrays on micro-dissected glomeruli and tubules from healthy subjects and patients with DKD, and found that *VEGF-B* was up-regulated in the glomeruli of patients with DKD (Woroniecka et al. 2011). Inhibition of VEGF-B signalling in DKD mouse models has been found to prevent pathological lipid deposition; improve podocyte abundance; and reduce mesangial expansion, hyaline arteriole degeneration, and glomerular sclerosis (GS). Furthermore, VEGFR1 and NP-1 (receptors of VEGF-B) expressed on GECs (Falkevall et al. 2017). The expression analysis of whole kidney lysate showed that with the progression of DKD, the transcription level of fatty acid transport protein 4 (Fatp4) increases in the glomeruli. VEGF-B may play a pathogenic role through Fatp4. Thus, the crosstalk between podocytes and GECs through VEGF-B is one of the mechanisms of lipotoxicity in DKD.

Moreover, macrophage infiltration in DKD is partially due to the increased expression of VEGF in podocytes. Waichi et al. demonstrated that VEGF produced by podocytes in diabetic eNOS-deficient mice regulates actin recombination and mediates macrophage migration through VEGFR1. Furthermore, they found that the p38 MAPK-specific blocker 31,169 can supress the migration of macrophages caused by VEGF, indicating that this process is dependent on p38 MAPK (Sato et al. 2008). Meanwhile, other studies have suggested that VEGF can inhibit pericyte function and vascular maturation by inducing the VEGF-R2/PDGF-Rβ

complex (Greenberg et al. 2008). Similarly, the expression of VEGFR2 has been detected in MCs. Masahiro et al. found upregulation of VEGF in podocytes leading to significant down-regulation of MC markers, α-SMA, desmin, and PDGFRβ, indicating that MCs are reduced (Suyama et al. 2018). A decrease of MCs leads to GBM damage, aneurysm and cluster collapse. Although the levels of PDGFB did not change substantially, the immunoreactivity of phosphorylated PDGFRβ is substantially reduced. These results indicate that PDGFRβ may be involved in the crosstalk of podocytes with MCs through VEGF.

The role of VEGF in cellular crosstalk is illustrated in Fig. 2.

Angiopoietin (Ang)/Tyrosine kinase receptor-2 (Tie-2)

In DKD, Ang-1 can prevent damage to the capillary wall from hyperglycaemia, and Ang-2 expression is directly proportional to the degree of endothelial damage. Ang-1 is mainly expressed by podocytes, while Ang2 is mainly produced by GECs and antagonises Ang1 through competitive inhibition of Tie-2 receptors (Satchell et al. 2002). However, Tie-2 is localised on GECs (Yuan et al. 2000). Ang-2 is an antagonistic ligand for Tie-2 on GECs, inhibiting the binding of Ang-1 to Tie-2 in an autocrine fashion (Maisonpierre et al. 1997). Belinda et al. emphasised the role of Ang2 in glomerular damage and aggravation of proteinuria (Davis et al. 2007). Cecile et al. reported that a reduced level of Ang1 in diabetic mice leads to vascular instability, albuminuria, and GEC proliferation. Moreover, supplementation of Ang1 did not reverse the down-regulation of nephrin in DKD, but increased Tie-2 phosphorylation and significantly reduced albuminuria, VEGFR2 phosphorylation, and nephrin phosphorylation. No significant difference in the Ang2 level was observed between non-diabetic and diabetic mice (Dessapt-Baradez et al. 2014). Yoshihiko et al. found that Ang2 was significantly increased in diabetic mice kidney. Tumstatin peptide can improve glomerular hypertrophy, glomerular matrix expansion, and monocyte accumulation in diabetic mice. In diabetic mice treated with tumstatin, Ang2 expression was substantially reduced and nephrin level was restored. However, the Ang1 level did not change substantially in the kidneys of diabetic mice in response to tumstatin (Yamamoto et al. 2004). Importantly, the difference in the expression levels of Ang2 and Ang1 plays a role in the pathogenesis of DKD (Gnudi 2016). Serum Ang2 is an effective predictor of DKD(Sokolovska et al. 2020).

The role of Ang in cellular crosstalk is shown in Fig. 3.

Endothelin (ET)

ET has a significant regulatory effect on the kidneys under physiological and pathological conditions. The main

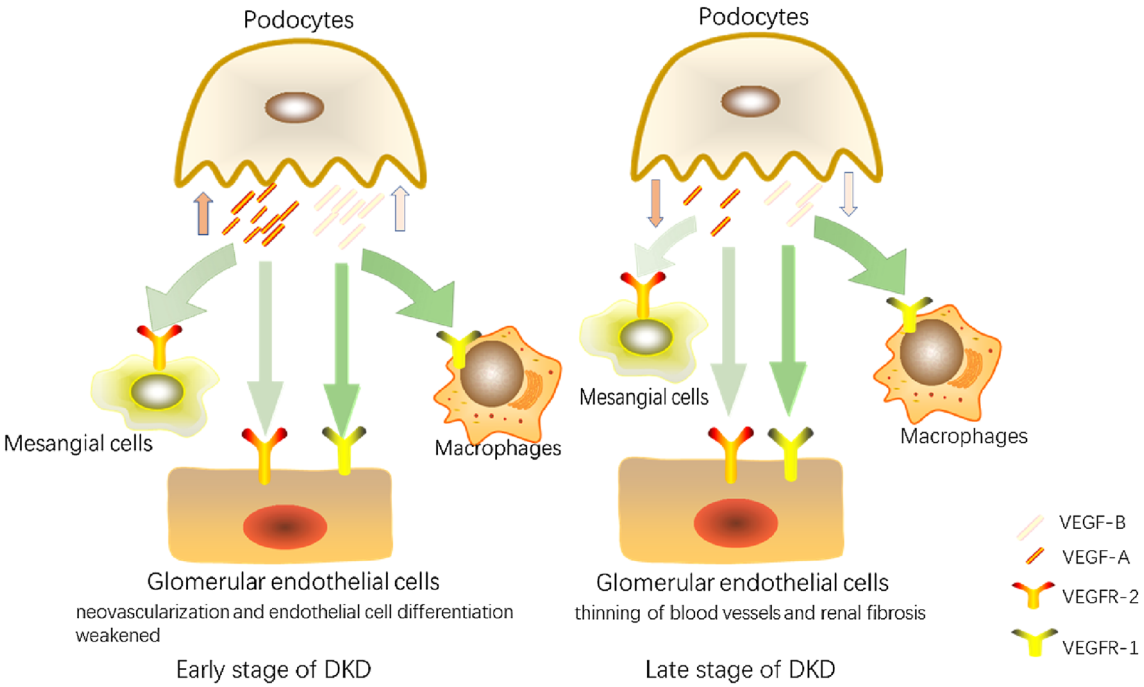

Fig. 2 Cellular crosstalk of VEGF produced by podocyte in DKD. (DKD, diabetic kidney disease; VEGF-A, vascular endothelial growth factor A; VEGF-B, vascular endothelial growth factor B; VEGFR-1, vascular endothelial growth factor receptor 1; VEGFR-2, vascular endothelial growth factor receptor 2;)

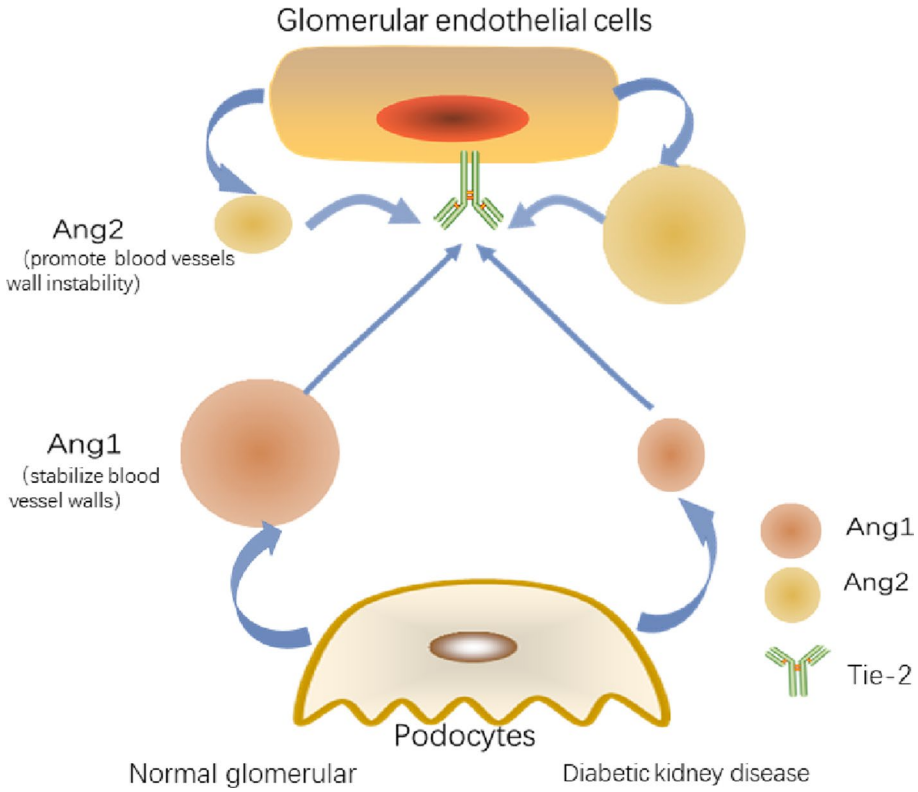

Fig. 3 Ang-1 and Ang-2 in DKD. (Ang1, angiopoietin 1; Ang2, angiopoietin 2; Tie-2, tyrosine kinase receptor-2;)

members of the ET family include ET-1–3. Among them, ET-1 is involved in kidney disease (DKD (Zeravica et al. 2016), focal segmental glomerulosclerosis (Daehn et al. 2014), etc.). It has two receptor (ETR) subtypes, endothelin receptor-A (ET-A) and endothelin receptor-B (ET-B). Margien et al. found that ET-A antagonists can improve GECs mitochondrial oxidative damage, proteinuria, and podocyte damage in DN (Boels et al. 2016). Several studies have reported various mechanisms of ET-1 in cellular crosstalk. Qi et al. demonstrated that ET-1/ET-A in GECs promotes the progression of DKD by mediating mitochondrial dysfunction(Qi et al. 2017). Marjolein et al. showed that glomerulosclerosis and podocyte loss are attenuated in podocyte-specific ETR-deficient (Pod-ETRKO) diabetic mice. They treated podocytes and GECs with ET-1 and found that heparanase expression increased in podocytes, whereas that in GECs was not affected. This is due to the difference in ETR distribution in podocytes and GECs. Podocytes express both ET-A and ET-B, whereas GECs only express ET-B. ET-1 plays an autocrine role by binding to ET-A to mediate the increased expression of heparanase in podocytes. Heparanase acts on the ESL of GECs to reduce its hardness and induce proteinuria (Garsen et al. 2016). Olivia et al. found the same phenomenon in Pod-ETRKO diabetic mice. ET-1 binds to its receptor and mediates rapid calcium transients. Thrombin or ET-1 was used to stimulate podocytes and variations in Ca^{2+} were measured. Calcium transients decreased with the addition of ET-B and ET-A selective inhibitors separately, illustrating that ET-A and ET-B play the same role, and that their downstream pathways involve NF-κB and β-catenin (Lenoir et al. 2014). Despite possible differences in the mechanisms, the observations confirm the crosstalk between podocytes and GECs through ET.

Stromal cell-derived factor-1 (SDF-1)/ CXC chemokine receptor 4(CXCR4)

Chemokines are 8–12 kDa peptides that play roles in cell activation, differentiation, and transportation. SDF-1, also known as C-X-C motif chemokine ligand 12 (CXCL12), plays roles in osteoarthritis (Wang et al. 2017), and chronic skin inflammation (Zgraggen et al. 2014) through its interactions with CXC chemokine receptors 4 (CXCR4) and 7 (CXCR7) (Hunger et al. 2012; Puchert and Engele, 2014). The SDF-1/CXCR4 axis has a crosstalk effect between the subchondral bone and articular cartilage in osteoarthritis (Qin et al. 2019). It is related to cancer metastasis (Gelmini et al. 2008) such as breast cancer (Duan et al. 2020), non-small cell lung cancer (Otsuka and Bebb 2008), and gastric cancer (Zhao et al. 2011), and promotes the development of glomerular blood vessels (Floege et al. 2009). SDF-1α is an isoform of SDF-1 (Gahan et al. 2012). The SDF-1α/CXCR4 pathway has been considered a protective mediator in cell and tissue repair in DKD. SDF-1α expression is

considerably reduced in DKD compared with that in normal condition (Chang et al. 2017; Lovshin et al. 2017). Some researchers speculate that SDF-1/CXCR4 may be involved in the cellular crosstalk of DKD. Yoshitsugu et al. observed developing kidney and CXCR4-knockout mice by immunohistochemistry (IHC) and demonstrated the important role of SDF-1/CXCR4 in the development of renal blood vessels. Podocytes were found to express CXCL12 and GECs expressed CXCR4 in mature glomeruli (Takabatake et al. 2009). CXCL12- null and CXCR4-null kidneys showed a similar pathology, including glomerular capillary malformations, abnormal angiogenesis, and decreased MC number. Moreover, linagliptin improved the renal outcome of diabetic mice by increasing the expression of SDF-1, and this protective effect could be eliminated by CXCR4 blockers (Takashima et al. 2016). These results suggest that the SDF-1/CXCR4 axis plays a protective crosstalk role between podocytes and GECs in DKD.

Secondary lymphoid tissue chemokine (SLC)/C–C chemokine receptor type 7 (CCR7)

SLC, also called C–C chemokine ligand 21 (CCL21), can promote healing in vitro injury models. Banas et al. clarified the localisation of SLC and CCR7 by IHC staining. They revealed that podocytes specifically express SLC, whereas its receptor, CCR7, is located on MCs (Banas et al. 2002). Migration assays confirmed that SLC/CCR7 mediates the directional migration of MCs to podocytes. Culturing MCs at different SLC concentrations confirmed that SLC/CCR7 mediates the proliferation of MCs. Analysis using a Fas/CD95-mediated cell death test showed that SLC/CCR7 can promote the survival of MCs. Furthermore, Banas et al. confirmed that SLC/CCR7 enhances cell adhesion and firmness (Bernhard Banas et al. 2004). SLC/CCR7 increased the phosphorylation of glycogen synthase kinase-3 and PKB. This shows that the downstream pathway of SLC/CCR7 involves the activation of integrin-linked kinase. In a previous study, CCL21 was found to be up-regulated in podocytes that were damaged as a result of systemic polyomavirus administration. HG also increased *CCL21* mRNA level in podocytes (Valiño-Rivas et al. 2016). In addition, SLC/CCR7 can recruit macrophages. Blocking SLC/CCR7 can reduce macrophage aggregation and renal fibrosis (T. Wada et al. 2007). It was observed that CCR7 was also present in M1 macrophages. Torres et al. found that A_{2B} adenosine receptor ($A_{2B}AR$) antagonist can reduce the characteristic symptoms of GS, macrophage infiltration, and mesangial expansion in diabetic rats. Moreover, transcriptome analysis of chemokines and other related genes in DN rats treated with $A_{2B}AR$ antagonist showed considerable decrease in *CCL21* compared with that in the control group (Torres et al. 2020).

Monocyte chemotactic protein 1 (MCP-1)/ C–C chemokine receptor type 2 (CCR2)

The presence of MCP-1 (also known as C–C chemokine ligand 2 [CCL2]) in urine is considered a potential marker of DN (Siddiqui et al. 2020; Titan et al. 2012). CCR2, MCP-1 receptor, is mainly expressed in monocytes (Awad et al. 2011). The pathogenic role of MCP-1/CCR2 in DKD is widely recognised. Tarabra et al. demonstrated that MCP-1 not only recruits monocytes, but also reduces the expression of nephrin and synaptopodin, causing podocyte damage in DKD (Tarabra et al. 2009). Lack of MCP-1 in mice (F. Y. Chow et al. 2006) and the use of CCR2 antagonists(Sullivan et al. 2013) can reduce macrophage aggregation in the kidney and proteinuria. Priscila et al. showed that renal tubular reabsorption proteins, AGEs, angiotensin II, and pro-inflammatory cytokines induce podocytes to produce MCP-1 (Calle and Hotter, 2020). Fiona et al. showed that MCP-1 is mainly expressed in podocytes in DKD (F. Chow et al. 2004). Gu et al. incubated podocytes with AGE, and measured dichlorofluorescein-sensitive intracellular ROS production by confocal microscopy, and proved that AGE stimulates podocytes to express MCP-1 through the ROS signalling pathway. MCP-1 expressed by podocytes promotes DN progression by recruiting macrophages (Gu et al. 2006). This may be related to MAPK phosphatase 1 (Kim et al. 2012), NADPH oxidase 4(Ullevig et al. 2012), and RAS (Kato et al. 1999). Infiltration of inflammatory cells (such as monocytes and macrophages) are signs of DKD progression (Furuta et al. 1993). Blocking MCP-1/CCR2 can reduce infiltration of macrophages and mesangial matrix expansion of DKD (Du et al. 2021b). Through prospective follow-up in 83 patients with DN and analysis of relevant urine biomarkers, Verhave et al. reported that urine MCP-1 could independently predict the progression of renal function (Verhave et al. 2013).

Cellular communication network factor 2 (CCN2)

CCN2, also known as connective tissue growth factor (CTGF), is a cytokine that plays an important role in chronic renal fibrosis, promoting EMT and inhibiting matrix degradation (Grotendorst et al. 2004; Yang et al. 2004). Nguyen et al. conducted a prospective study and found that plasma CCN2 has a significant effect on the poor prognosis of patients with T1DM nephropathy (McLennan et al. 2013). In DKD, the expression of CCN2 in podocytes and MCs is significantly up-regulated compared with that in physiological condition. Yokoi et al. established podocyte-specific CCN2 transgenic diabetic mice and found more severe podocyte damage, mesangial expansion, and lower podocin expression than those in diabetic wild-type mice (Yokoi et al. 2008). Moreover, CCN2 in the mesangial region also increased

significantly in transgenic mice compared with that in wild-type diabetic mice. These findings showed that podocytes affect MCs through CCN2, leading to the accumulation of glomerular mesangial matrix and progressive glomerulosclerosis in diabetic mice. Furthermore, they found that fibronectin and collagen did not increase significantly in transgenic mice, whereas the expression and activity of matrix metalloproteinase-2 (an ECM-degrading enzyme) decreased. Therefore, CCN2 produced by podocytes does not directly increase the production of ECM, but inhibits the degradation of ECM.

Heparin-binding epidermal growth factor-like growth factor (HB-EGF)

HB-EGF is a ligand of the epidermal growth factor receptor (EGFR), and it is increased in the kidney of diabetic rats, which can be counteracted by strict control of blood glucose (Lee et al. 1995). Uttarwar et al. showed that HB-EGF mediated glucose-induced EGFR activation in MCs (Uttarwar et al. 2011). In a study that used a three-dimensional (3D) multiscale model to simulate the glomerular microenvironment, HB-EGF, ET-1, and TGF-β were found to be accumulated under diabetic conditions (HG), whereas VEGF-A and APC expression was attenuated. Moreover, in diabetic conditions, damaged podocytes secreted HB-EGF, which stimulated the activation and proliferation of parietal epithelial cells (PECs) and interfered with their compensatory differentiation into podocytes (Tan et al. 2016). This may be related to EGFR transactivation. Under physiological conditions, PECs can differentiate to supplement the loss of podocytes (Poulsom and Little, 2009). Under DKD conditions, this supplementary repair effect is impaired by the crosstalk between podocytes and PECs through HB-EGF.

miR-221

miRNAs are small endogenous RNAs of approximately 21 nucleotides that are involved in protein–protein and protein–RNA interactions (Krol et al. 2010), and participate in important biological processes such as cell growth, tissue differentiation, cell proliferation, and apoptosis (Sayed and Abdellatif, 2011). miRNAs can regulate the expression of target genes after transcription (Gommans and Berezikov, 2012), and one single miRNA can simultaneously target multiple genes within the same cell signalling pathway (Correia de Sousa et al. 2019). Anthony et al. and Christian et al. have emphasised the paracrine role of miRNAs (Bär et al. 2019; Leung, 2015). miRNAs are emerging biomarkers of DKD, potentially important regulatory factors, and feasible targets for clinical diagnosis and therapeutic interventions (Alvarez and Distefano 2013). For example, urinary miR-3137 and miR-4270 have been described as potential biomarkers for DKD (Li et al. 2020). In addition, urinary miR-196a level is associated with the progression of kidney damage in patients with DN (An et al. 2020). In T2DM, the level of miR-152-3p is significantly correlated with indicators of the severity of kidney disease (Nasser et al. 2020). Urine miR-27b-3p and miR-1228-3p are associated with the progression of renal fibrosis in DN (Conserva et al. 2019). Cui et al. reported that miR-17-5p, miR-20a and miR-106a can be used as biomarkers for DKD (Cui et al. 2018).

Su et al. co-cultured labelled podocytes by PKH26, a fluorescent dye, with HG-treated proximal TECs (PTECs) and red fluorescence was observed in the PTECs, indicating crosstalk between them. This crosstalk can be inhibited in co-culture with podocytes supplemented with GW4869 (a EV secretion inhibitor). In PTECs treated with extracellular vesicles (EVs) produced by HG-induced podocytes, the expression of epithelial markers, E-cadherin and ZO-1 was absent, whereas the expression of mesenchymal markers such as vimentin and α-SMA was up-regulated. At the same time, PTECs are morphologically manifested by a decrease in the number of microvilli and mitochondria and an increase in the volume density of the rough ER. Furthermore, they transfect the labelled miR-221 mimics into the podocytes, co-cultured with PTECs under HG conditions, and found the presence of the labelled miR-221 mimics in PTECs. These results support the hypothesis that miR-221 plays a role in crosstalk in DKD. Moreover, podocyte miR-221 directly targets Dickkopf-2, an inhibitor of Wnt signalling, in the PTECs, resulting in the damage of these cells (Su et al. 2020).

Cellular crosstalk of podocytes is summarised in Fig. 4.

Conclusions

Many studies have reported the characteristics and important pathogenic effects of GEC and podocyte damage in DKD. Here, we have reviewed the studies demonstrating that cellular crosstalk from these cell types exacerbates damage and promotes DKD progression (Table 2 and Fig. 5). MCs and TECs also play a cellular crosstalk role in DKD and promote DKD progression. We summarised the factors involved in the cellular crosstalk of these two types of cells in Table 3. The main conclusions are:

1. Under HG conditions, GEC-to-podocyte crosstalk causes podocyte dysfunction through a variety of disturbed signalling pathways, leading to DKD development. These include, TGF-β1/Wnt/β-catenin and TGF-β/Smad signalling, and LRG-1, KLF, eNOS, and APC signalling.
2. Podocyte-to-GEC crosstalk results in lipotoxicity and alterations in the structure and function of GECs. This

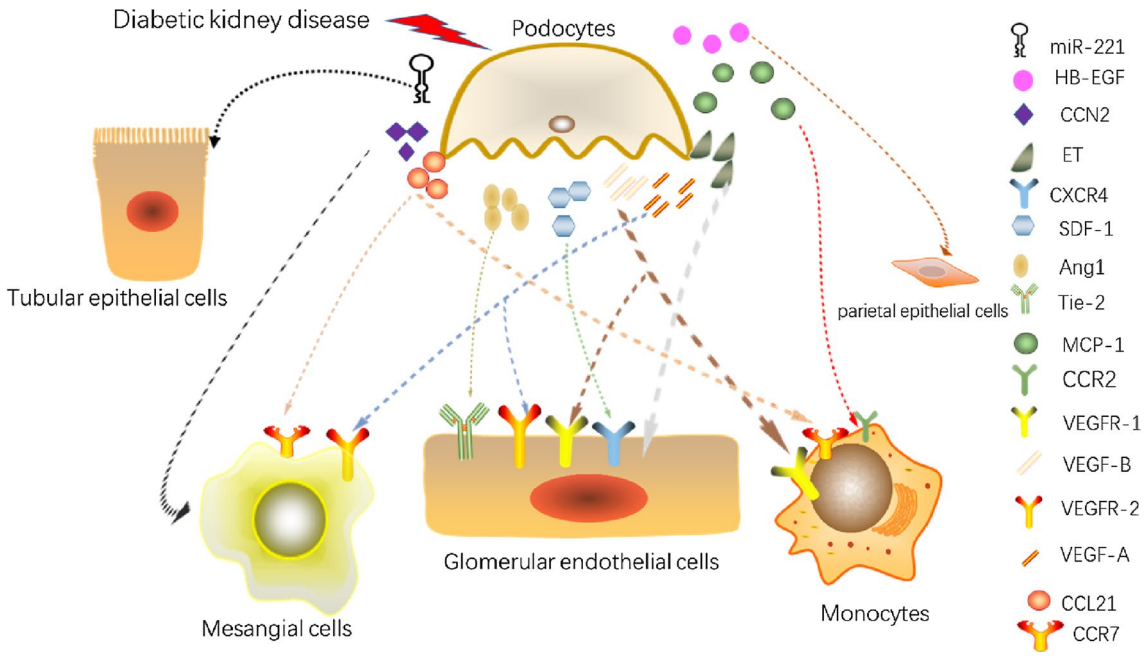

Fig. 4 Cellular crosstalk of podocytes. (HB-EGF, heparin-binding epidermal growth factor-like growth factor; CCN2, cellular communication network factor 2; ET, endothelin; CXCR4, CXC chemokine receptor 4; SDF-1, stromal cell-derived factor-1; Ang1, angiopoietin 1; Tie-2, angiopoietin receptor-2; MCP-1, monocyte chemotactic protein 1; CCR2, C–C chemokine receptor type 2; VEGFR-1, vascular endothelial growth factor receptor 1; VEGF-B, vascular endothelial growth factor B; VEGFR-2, vascular endothelial growth factor receptor 2; VEGF-A, vascular endothelial growth factor A; CCL21, C–C chemokine ligand 21; CCR7, C–C chemokine receptor type 7;)

crosstalk involves diverse molecules, including VEGF, Ang/Tie-2, ET, and SDF-1/CXCR4.

3. Abnormal GEC and podocyte signalling affects other cells, such as MCs, proximal tubular epithelial cells, and macrophages, promoting DKD progression.

Furthermore, we identified the following unclear/unexplored aspects in the field:

1. TGF-β and VEGF are key cytokines in the process of DKD. However, their role is complex and requires further investigation.
2. Lipotoxicity is considered to promote DKD progression. GECs are considered to be a source of lipid deposits in other cells. We speculate that FAT/CD36 is involved in lipid transport in kidney cells. However, the specific mechanism is currently unknown and needs to be explored, as this will help to further guide the prevention and treatment of DKD.
3. The pathogenic crosstalk factors of DKD include TGF-β, LRG-1, FAT/CD36, PDGFB, VEGF-B, ET-1, SLC, MCP-1, CCN2, miR-221, and HB-EGF. The protective factors include eNOS, KLF2, APC, HGF, Ang1, VEGF-A, and SDF-1. Decreased expression of protective factors and upregulation of pathogenic factors lead to DKD progression. Although these factors have been shown to be involved in the cellular crosstalk of DKD, their specific mechanisms need to be further elucidated.
4. The role of miRNAs in DKD has been described. While the expression of some miRNAs is upregulated in DKD, the expression of others is downregulated. As emerging biomarkers of DKD, miRNAs have research significance in the cellular crosstalk of DKD. However, the role of miRNAs in cellular crosstalk needs to be further elucidated.

In conclusion, a better understanding of the cellular crosstalk of GECs and podocytes will help to further reveal the pathogenesis of DKD and develop better prevention and treatment options. Cellular crosstalk in DKD is highly complex and remains largely unknown. Efforts should be made toward elucidating the intricates of such complex processes.

Table 2 Crosstalk of endothelial cells and podocytes to other cells

	Factor	Crosstalk cell	Reference
Glomerular endothelial cells	TGF-β	Podocytes	Wu et al. (2017) Lai et al. (2020)
	eNOS		Yuen et al. (2012) Takahashi and Harris (2014) Nakagawa, 2008)
	LRG1		Hong et al. (2019)
	KLF2		Zhong et al. (2015)
	APC		Isermann et al. (2007) Madhusudhan et al. (2012)
	TGF-β	Mesangial cells	Wu et al. (2016)
	PDGFB		Levéen et al. (1994) Sohn et al. (2014) Fu et al. (2015)
	HGF		Mizuno and Nakamura, 2004) Li et al. (2006)
	FAT/CD36		Hagberg et al. (2010) de Vries et al. (2014)
	HGF	Tubular epithelial cells	Xing and Muxun, 2007)
	FAT/CD36		Hagberg et al. (2010) Feng et al. (2017)
Podocytes	VEGF-A	Endothelial cells	Sivaskandarajah et al. (2012)
	Ang		Satchell et al. (2002) Yuan et al. (2000) Dessapt-Baradez et al. (2014) Yamamoto et al. (2004)
	VEGF-B		Falkevall et al. (2017)
	ET-1		Garsen et al. (2016) Lenoir et al. (2014)
	SDF-1		Takabatake et al. (2009) Takashima et al. (2016)
	VEGF-A	Mesangial cells	Shulman et al. (1996) Suyama et al. (2018)
	CCL21		Banas et al. (2002; Bernhard Banas et al. (2004; Valiño-Rivas et al. (2016)
	CCN2		Yokoi et al. (2008)
	VEGF-B	Monocytes	Sato et al. (2008)
	CCL21		Torres et al. (2020)
	MCP-1		Calle and Hotter, 2020) Gu et al. (2006)
	miR-221	Proximal tubular epithelial cells	Su et al. (2020)
	HB-EGF	Parietal epithelial cells	Tan et al. (2016)

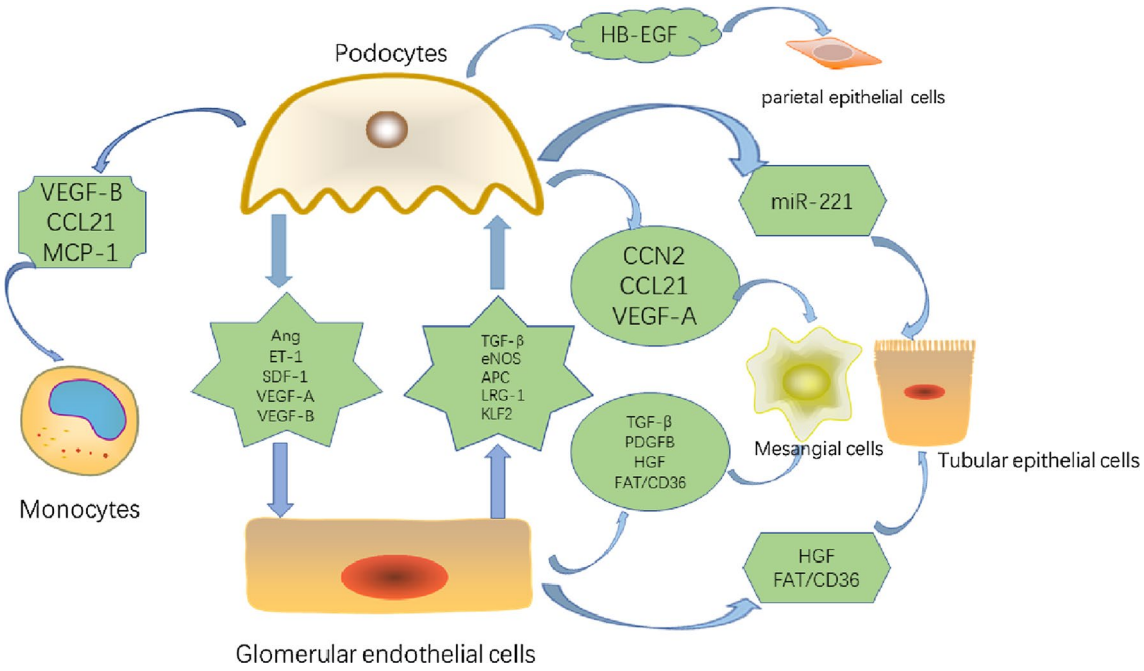

Fig. 5 Cellular crosstalk of endothelial cells and podocytes in diabetic kidney disease. (HB-EGF, heparin-binding epidermal growth factor-like growth factor; TGF-β, transforming growth factor-β; HGF, hepatocyte growth factor; FAT, fatty acid translocase; LRG-1, leucine-rich α-2-glycoprotein 1; PDGFB, platelet-derived growth factor B; APC, activated protein C; KLF2, Kruppel -like factor 2; eNOS, endothelial nitric oxide synthase; VEGF-A, vascular endothelial growth factor A; VEGF-B, vascular endothelial growth factor B; MCP-1, monocyte chemotactic protein 1; ET-1, endothelin-1; SDF-1, stromal cell-derived factor-1; Ang, angiopoietin; CCL21, C–C chemokine ligand 21; CCN2, cellular communication network factor 2;)

Table 3 Crosstalk of mesangial cells and tubular epithelial cells

	Factor/ Signal pathway	Crosstalk cell	Reference
Mesangial cells	α8-integrin	Podocytes	Hartner et al. (2010)
	ER-associated degradation		Fujimoto et al. (2020)
	TGF-β		Wang et al. (2018)
Tubular epithelial cells	B cell lymphoma 2-interacting mediator (Bim)	Podocytes	Xu et al. (2020)
	Sirt1		Hasegawa et al. (2013)
	Gremlin		Marchant et al. (2015)
	Ang	Endothelial cells	Rizkalla et al. 2005)
	miR-196b-5p	Fibroblast	Hu et al. (2020)
	MCP-1	Monocytes	Chow et al. (2006)

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Code availability Not applicable.

Declarations

Conflicts of interest The authors declare that they have no conflicts of interest.

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