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Review

Hippo/YAP signaling pathway: a new therapeutic target for diabetes mellitus and vascular complications

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***Abstract*:** Diabetic angiopathy, which includes diabetic kidney disease (DKD), cardio-cerebrovascular disease, and diabetic retinopathy (DR) among other diseases, is one of the most common complications affecting diabetic patients. Among these, DKD, which is a major cause of morbidity and mortality, affects about 40% of diabetic patients. Similarly, DR involves retinal neovascularization and neurodegeneration as a result of chronic hyperglycemia and is the main cause of visual impairment and blindness. In addition, inflammation also promotes atherosclerosis and diabetes, with atherosclerosis-related cardiovascular diseases being often a main cause of disability or death in diabetic patients. Given that vascular diseases caused by diabetes negatively impact human health, it is therefore important to identify appropriate treatments. In this context, some studies have found that the Hippo/Yes-associated protein (YAP) pathway is a highly evolutionarily conserved protein kinase signal pathway that regulates organ growth and size through its effector signaling pathway Transcriptional co-Activator with PDZ-binding motif (TAZ) and its YAP. YAP is a key factor in the Hippo pathway. The activation of YAP regulates gluconeogenesis, thereby regulating glucose tolerance levels; silencing the YAP gene thereby prevents the formation of glomerular fibrosis. YAP can combine with TEA domain family members to regulate the proliferation and migration of retinal vascular endothelial cells (ECs), so YAP plays a prominent role in the formation and pathology of retinal vessels. In addition, YAP/TAZ activation and translocation to the nucleus promote endothelial inflammation and monocyte-EC attachment, which can increase diabetes-induced cardiovascular atherosclerosis. Hippo/YAP signaling pathway provides a potential therapeutic target for diabetic angiopathy, which can prevent the progression of diabetes to DR and improve renal fibrosis and cardio-vascular atherosclerosis.

Keywords: atherosclerosis, diabetic kidney disease, diabetic retinopathy, Hippo/YAP pathway

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Introduction

Diabetes mellitus is often the cause of diabetic kidney disease (DKD), diabetic retinopathy (DR), or a number of other vascular lesions, such as cardiac and cerebral atherosclerosis, which may seriously endanger patients' lives while affecting their health and quality of life. A reduced rate of glomerular filtration, as well as increased excretion of urinary albumin, are the main clinical manifestations of DKD, with the latter also commonly responsible for chronic renal failure.[1] Similarly, DR, which involves retinal neovascularization and neurodegeneration as a result of chronic hyperglycemia, is a major cause of visual impairment and blindness, thereby affecting the quality of life of patients. In addition, high blood glucose levels can easily promote endothelial inflammation and monocyte adhesion to endothelial cells (ECs), thus increasing the likelihood of atherosclerosis, which is further accelerated by diabetes.[2,3] The Hippo pathway, which is important for cell proliferation, regulates organ size and

growth through its effector signaling pathway Transcriptional co-Activator with PDZ-binding motif (TAZ) as well as its Yes-associated protein (YAP).[4] In the 'active' state, this pathway involves the phosphorylation of YAP/TAZ and its subsequent inactivation in the cytoplasm. On the other hand, the dephosphorylation of YAP/TAZ, leading to its expression within the nucleus, is referred to as the 'inactive' Hippo pathway. YAP, a key factor of the Hippo pathway that mediates epithelial–mesenchymal transformation and regulates cell contact inhibition, apoptosis, as well as cell differentiation and proliferation, is a transcriptional coactivator with only one transcriptional activation domain.[5,6] Over the years, it has attracted interest in the field of vascular diseases such as DKD and DR. In addition, Hippo pathway is a key regulator of liver size, regeneration, development, metabolism, and dynamic balance. Because the liver can maintain the blood glucose level, Hippo pathway also plays an important role in non-alcoholic fatty liver disease (NAFLD)/metabolism-related fatty liver disease (MAFLD), which is closely related to diabetes. In short, targeting the YAP pathway could provide a novel and more effective approach to the treatment of diabetes and angiopathy.

Introduction to the Hippo/YAP pathway

The constituent modules of the Hippo/YAP pathway

The Hippo pathway is a highly evolutionarily conserved protein kinase signaling pathway that is made up of three interconnected modules, namely an upstream regulatory module, a downstream transcription module, and a core protein kinase module.[7] In particular, this pathway includes a transcriptional coactivator with PDZ binding motif, YAP, large tumor suppressor kinases 1 and 2 (LATS1/2), and mammalian sterile 20-like protein kinases 1/2 (MST1/2),[8,9] while in terms of its signaling functions, it involves the activation of the large tumor suppressor kinases LATS1/2 and MST1/2 as well as the phosphorylation of YAP, thereby leading to the latter's inactivation through lysosome/proteasome-mediated degradation or cytoplasmic isolation. On the other hand, the inactivation of the Hippo pathway inhibits LATS kinases and leads to YAP's translocation to the nucleus, where it interacts with transcription factors to induce the expression of downstream target genes.[10]

Functions of the different components of the Hippo/YAP pathway

MST1, a key mediator of fibrosis, participates in the differentiation and proliferation of cells, and as such, it is a major factor involved in DKD's pathogenesis.[11] In the Hippo pathway, LATS1 and MST1 are protein kinases which, on activation, stimulate LATS1 phosphorylation of important downstream effectors such as TAZ and YAP.[12] In particular, as a key factor in the pathway, YAP controls the size of organs by mediating epithelial–mesenchymal transformation and regulating cell contact inhibition as well as cell apoptosis, differentiation, and proliferation. It has been previously shown that targeting the activation of YAP in human cancer was of interest for the development of chemotherapeutic drugs.[13] YAP is a core feature of the Hippo pathway, and it undertakes its functions by shuttling between the cytoplasm and the nucleus. Indeed, YAP can be phosphorylated by LATS1 at the S127 site, leading to its cytoplasmic isolation and the subsequent inhibition of its activity.[14] In contrast, the dephosphorylation of YAP leads to its translocation to the nucleus, where it causes target genes such as cyclinD1, MMP9, and MMP2 to be transcribed while promoting the proliferation and migration of vascular smooth muscle cells (VSMCs).[15] In renal tubular cells, the inactivation of MST1, the reduced phosphorylation of LATS1 and MST1, the activation of YAP, and translocation to the nucleus result in increased nuclear expression of YAP/TAZ as well as a subsequent increase in the binding of YAP/TAZ and TEA domain (TEAD). Such interactions between YAP/TAZ and TEAD are enhanced to activate TEAD, resulting in epithelial–interstitial transformation of renal tubular epithelial cells.[16] These transformed cells can, in turn, overproduce and secrete large amounts of extracellular matrix (ECM), including laminin and type IV collagen, that can lead to renal fibrosis and, eventually, chronic renal failure.[17]

YAP is the key factor of the Hippo pathway

The Hippo pathway, which is important for cell proliferation, regulates organ growth and size through its effectors TAZ and YAP, with the latter being a key factor of the pathway. An 'active' Hippo pathway refers to the inactivity of YAP/TAZ as a result of phosphorylation in the cytoplasm, while in an 'inactive' state, the pathway involves the dephosphorylation of YAP/TAZ and

its subsequent expression in the nucleus.[18,19] YAP, a transcriptional coactivator with only one transcriptional activation domain, can mediate epithelial–mesenchymal transformation in addition to the regulation of cell contact inhibition, apoptosis, differentiation, and cell proliferation. On the other hand, TEAD refers to one type of factor bearing a deoxyribonucleic acid (DNA) binding domain that can bind to activated YAP for controlling the expression of connective tissue growth factor (CTGF), with the latter being a major target that regulates genes that induce proliferation and inhibit apoptosis. When the Hippo signal pathway is inhibited, it promotes the relocalization of YAP into the nucleus, where it can bind to the transcription factor TEAD to induce its expression.[20,21] Over the past few years, this pathway has gradually attracted interest in the field of diabetes and angiopathy, especially due to its involvement in cell apoptosis, proliferation, and growth through the regulation of downstream genes as well as metabolic homeostasis.[8,10] Inhibiting the Hippo pathway causes the dephosphorylation of YAP and its subsequent migration from the cytoplasm to the nucleus where it binds to TEAD, a transcription factor bearing a DNA binding domain. The binding of YAP to TEAD then induces the expression of cyclin E as well as other target genes that regulate cell cycle and DNA synthesis. Furthermore, it also enhances the expression of the CTGF and other profibrotic factors, which subsequently results in cell proliferation and synthesis of the ECM. Activating the Hippo pathway of DKD can, therefore effectively inhibit gene activation, mediated by tissue growth factor beta-1 (TGF-β1) in renal fibroblasts, by silencing the YAP gene, thus preventing glomerular fibrosis (Figure 1).[22,23] In fact, a recent study showed that high glucose could activate and increase the expression of YAP in kidneys, leading to renal injury.[24] In addition, the binding of YAP to TEAD can regulate the ability of retinal vascular ECs to proliferate and migrate, thus highlighting YAP's importance in the formation and pathology of retinal vessels.[25]

Role of the Hippo/YAP pathway in diabetes mellitus

Type 1 and type 2 diabetes are usually characterized by the loss or dysfunction of functional pancreatic β-cells, and hence, identifying means of promoting β-cell proliferation could be a potential strategy for the treatment of diabetes. In this context, YAP, an oncogene that inhibits apoptosis while promoting cells' proliferation and malignant transformation, is a major effector downstream of the Hippo pathway.[26] Indeed, its activation or overexpression not only increases the expression of tumor markers but also cancer incidence. In contrast, knockout or inactivation of the YAP gene was shown to inhibit cell migration and tumor growth *in vitro* and *in vivo*, respectively. Moreover, YAP's functions in diabetic vascular ECs were also explored, with results showing that inhibiting YAP decreased tube formation, cell proliferation, and cell migration under hypoxic conditions.[12,17] Therefore, YAP is a key regulator of tumor growth and invasion while being an important link in glucose metabolism as its activation regulates gluconeogenesis and hence glucose tolerance levels.[27] The localization of YAP, which is the nuclear sensor of the Hippo pathway, is indicative of the activation state of the Takeda G-coupled receptor 5 (TGR5), and as such, YAP is important to determine the intestinal structure as well as the fate of different cells, particularly during epithelial regeneration.[28] For instance, TGR5 is expressed throughout the whole intestinal epithelium. In this case, YAP participates in the activation of TGR5 and triggers Glucagon-Like Peptide-1 (GLP-1) secretion, which then promotes the recovery of intestinal insulin and regulates inflammation as well as glucose and lipid metabolism.[29] YAP is associated with a number of physiological processes, such as the regulation of cell cycle and proliferation, with its overexpression enhancing the proliferation of human β cells. Therefore, the re-expression of YAP in β cells can significantly inhibit apoptosis and promote proliferation.[30] For example, activating the EGFR–phosphatidylinositol 3-kinase (PI3K)–Akt–CREB pathway induces the expression of YAP, with the latter's subsequent translocation to the nucleus and interactions with the TEAD transcription factor complex eventually upregulating two TEAD-dependent genes, namely CTGF and dual regulatory protein genes. The Hippo signaling pathway, mediated through the G protein-coupled receptor pathway, is also important for regulating the peripheral insulin pathway. Glucagon or epinephrine may stimulate Gs-coupled receptors for maintaining homeostasis of blood glucose through the regulation of YAP, LATS1, or MST1 expression.[31] At the same time, overexpression of the active form of YAP components can result in oxidative stress,

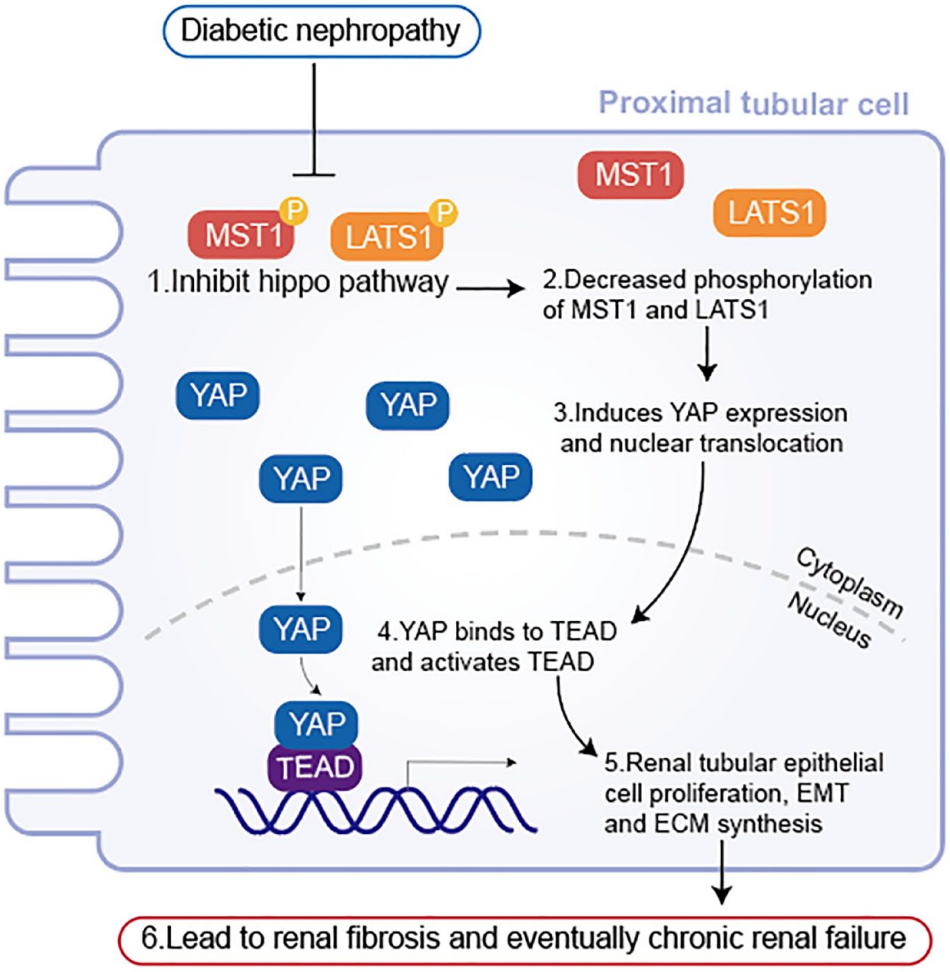

Figure 1. The Hippo/YAP pathway plays a key role in the formation of glomerular fibrosis. When Hippo signaling is inhibited, dephosphorylated YAP migrates from the cytoplasm to the nucleus, where binding to TEAD, a transcription factor, occurs. TEAD includes a DNA-binding domain, and binding of YAP and TEAD promotes the expression of Cyclin E as well as other target genes, leading to increased expression of pro-fibrosis factors and CTGF, thus inducing cell proliferation and extracellular matrix synthesis. Hippo pathway activation of DKD silencing YAP gene effectively inhibits TGF-β1-mediated gene activation in renal fibroblasts, hence preventing the formation of glomerular fibrosis.
CTGF, connective tissue growth factor; DKD, diabetic kidney disease; TEAD, TEA domain; TGF-β1, tissue growth factor beta-1; YAP, Yes-associated protein.

glycolipid toxicity, and the release of pro-inflammatory cytokines. However, in other cases, YAP can be important to regulate podocyte apoptosis, with reduced YAP expression leading to increased apoptosis.[32] Therefore, targeting YAP could be a therapeutic tool to restore β-cell functions in diabetes. Since the ECM is significantly involved in maintaining the normal function of islets, YAP can sense both the stiffness of the matrix and mechanical changes induced by the cytoskeleton to generate a biological response. In particular, the activation of YAP transcription factors can upregulate the expression of several cytoskeleton regulatory factors, activate the Wnt signaling pathway as well as promote the nuclear translocation of β-catenin, thus participating in cell proliferation.[33] For instance, Rosado-Olivieri *et al.*[34] have shown that the down-regulation of nuclear YAP promotes the differentiation of endocrine progenitor cells and the production of β cells, thus improving insulin secretion. Similarly, Tian *et al.*[35] indicated that the Hippo-Yap/TGR5 signaling pathway is largely involved in diabetes and vascular diseases by regulating the abundance of

intestinal endocrine L cells, cell proliferation, and migration, inflammatory response, as well as glucose and lipid metabolism. Furthermore, in diabetic mice, extracellular vesicles derived from plasma ECs also prevent senescence of fibroblasts and stimulate healing of skin wounds by inducing the translocation of YAP to the nucleus, reducing its phosphorylation and eventually activating the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway.[36] In another study, Jere *et al.*[37] found that the up-regulation of YAP was linked to cell proliferation and could promote aging, especially since YAP played a role in skin repair, angiogenesis, and re-epithelialization in diabetic patients. Finally, Cui *et al.*[38,39] studied how GPR87 regulated the activity of YAP/TAZ before inducing the expression of hexokinase-2 (HK-2) in renal tubular epithelial cells. This process, in turn, accelerates glycolysis and mitochondrial damage. Thus, the Hippo/YAP pathway is a major factor in diabetes. Hippo pathway is also a key regulator of liver size, regeneration, development, metabolism, and dynamic balance. Hippo pathway and its effector protein YAP/TAZ also play an active role in hepatocyte proliferation and resistance to hepatocyte apoptosis. In the absence of its downstream effectors YAP and TAZ, liver regeneration is seriously impaired, and the proliferation and expansion of hepatocytes are blocked. Disruption of Hippo pathway or abnormal activation of YAP and TAZ can lead to liver inflammation, fibrosis, and cancer. Driskill and other scholars have shown that YAP/TAZ is thought to regulate liver fibrosis through stellate cells, and the pharmacological targeting of Hippo pathway may be used to promote regeneration and prevent the development and progression of NAFLD. Nguyen-Lefebvre *et al.* have found that Hippo pathway regulates the dynamic cell fate in the liver. The activation of YAP/TAZ promotes liver fibrosis by activating hepatic stellate cells and differentiating into myofibroblasts to deal with chronic liver injury. Hippo pathway plays an important role in NAFLD/MAFLD, which is closely related to diabetes and can be used as a therapeutic target for NAFLD/MAFLD.

Renal damage caused by activated YAP in DKD

DKD is a common complication of diabetes that is often clinically manifested in terms of reduced rates of glomerular filtration and increased excretion of urinary albumin. It is also commonly responsible for chronic renal failure. The pathological features of DKD include renal hypertrophy, tubular atrophy, nodular and diffuse glomerulosclerosis, tubulointerstitial fibrosis, and increased glomerular basement membrane thickness.[1,40] Three layers are present in the glomerular filtration membrane, namely the podocytes, the glomerular basement membrane, and the glomerular ECs. When abnormal, these renal structures lead to a number of important functional changes, including decreased glomerular filtration rate (GFR), production of albuminuria, intraglomerular hypertension, systemic hypertension, and decreased renal functions. In addition, once the structural damage of the kidney occurs, it is difficult to reverse.[41] The early stages of DKD are mostly characterized by glomerular hypertrophy, especially mesangial hypertrophy, with the latter subsequently leading to mesangial matrix increase, ECM synthesis and deposition, mesangial cell (MCs) proliferation, mesangial matrix expansion, basement membrane thickening, and ECM protein production, resulting in glomerulosclerosis. In addition, the death of renal tubular epithelial cells, increased secretion of fibrogenic factors, inflammatory reactions, thickening of the basement membrane, and tubulointerstitial fibrosis can also lead to end-stage renal failure, which eventually results in DKD.[42] Podocytes are terminally differentiated cells of the renal filtration barrier with a complex actin cytoskeleton structure and they are important as they help to maintain the integrity of the glomerular filtration barrier.[43] During a kidney injury, the glomerular cytoskeleton and morphology change, and the filtration barrier may be damaged, causing proteinuria, where proteins leak into the urine. Therefore, glomerular diseases are usually caused by the loss of podocytes, with increasing evidence showing that injury to podocytes is among the main contributing factors to proteinuria.[44] Avoiding the apoptosis of podocytes can hence be of therapeutic value for DKD. Therefore, new mechanisms to prevent glomerular sclerosis, renal tubule atrophy, renal tubule interstitial fibrosis, and podocyte apoptosis could be of potential for future therapies, especially since at present, there is no specific treatment for DKD.

YAP is an important transcriptional factor regulated by the Hippo pathway, and in the case of podocytes, it acts as an antiapoptotic protein. Being a transcriptional coactivator, dephosphorylated

YAP, located in the nucleus, interacts with transcription factors from members of the TEAD family to induce target gene expression for cell survival and proliferation. On the other hand, phosphorylated YAP is isolated in the cytoplasm and remains inactive.[5] Activated Hippo signals maintain cell functions by inhibiting the nuclear interactions of transcriptional coactivators with TAZ and their homologous YAP-related proteins. In fact, with TAZ and YAP being the final effectors of the pathway, they have become the key factors of DKD. Indeed, their expression is highly increased in the MC of patients with DKD and diabetes. For instance, Choi *et al.*[4] showed that high glucose levels directly induced cultured MC to activate YAP/TAZ through the typical Hippo pathway, with the activated YAP/TAZ binding and stabilizing N-Myc proteins in the oncogene Myc family. Such stability of N-Myc further leads to abnormal enhancement of its transcriptional activity, which eventually results in MC damage and the pathogenesis of DKD. In addition, it was found that overactivation of YAP/TAZ could lead to excessive deposition of the ECM, injury of ECs, glomerulosclerosis, proteinuria, proliferation of MCs, and decreased GFRs.[5,18]

YAP has been attracting increasing interest from scholars, with some studies reporting that, in diabetic mice, the renal cortex displayed increased phosphorylation and expression of the YAP protein. Similarly, various works have shown the importance of YAP in the survival of glomerular podocytes and maintenance of the cytoskeleton's integrity. YAP can also lead to a significant decrease in the quality and quantity of podocytes, resulting in increased proteinuria in patients with diabetes and DKD. Therefore, knocking down the YAP gene in podocytes could have a protective effect on renal functions.[45] In this context, Huang *et al.*[46] reported that a deficiency of A (RhoA), a member of the Ras homologous gene family, induced apoptosis in A549 and HepG2 cells by inhibiting YAP, thereby reducing the formation of stress fibers and inducing podocyte apoptosis. It is speculated that RhoA may regulate the expression of YAP to inhibit its expression of YAP and increase podocyte apoptosis. Overexpression of YAP also leads to podocyte injury, basement membrane thickening, and subsequent sclerosis. Therefore, YAP can be used as a potential therapeutic target for podocyte apoptosis and proteinuria in diabetes and DKD (Figure 2). This shows that there is a strong correlation between YAP and DKD. For instance, Zeng *et al.*[47] found that the level of YAP was related to the glomerular filtration rate, pathological classification, serum albumin, blood urea nitrogen, creatinine, and DKD stage for DKD. The level of YAP expression generally increases with the progression of DKD. In addition, high expression of CTGF, TEAD, and YAP was observed in the nuclei of glomerular podocytes, alongside continuous activation of cell proliferation and repair in the injured kidney. It is therefore speculated that YAP is a major contributor to the occurrence and development of renal fibrosis in diabetic nephropathy while being closely associated with the severity of renal insufficiency. Hence, inhibiting YAP's activity could help to delay the progress of DKD. Since the prevention of tubulointerstitial fibrosis is an effective measure to prevent the progression of DKD, targeted treatment of YAP could be a novel and feasible strategy to this end (Figure 2).

Liu *et al.*[48] found that the YAP–TEAD–CTGF pathway could be involved in the renal damage of DKD. In this case, interactions between YAP and TEAD result in the overexpression of the target gene CTGF in the kidney, thus promoting the formation of renal fibrosis. As DKD occurs and develops, it can reduce YAP levels by preventing the binding between YAP and TEAD, thereby reducing albuminuria, inflammation, fibrosis, and glomerular injury. Del *et al.*[15,49,50] further found that the TEAD/YAP–TAZ axis was upregulated under hyperglycemic conditions, hence suggesting that the YAP signaling pathway could be a major mechanism that leads to the occurrence and development of DKD. When effective drug intervention is carried out on Hippo pathway, they may slow down the progress of DKD. Lei *et al.*[51] reported the up-regulation of YAP in diabetes and DKD environments, with this change promoting the expression and nuclear localization of YAP, increased binding with TEAD, and eventually increased expression of fibrogenic factor CTGFs that regulate of cell proliferation. Ma *et al.*[52] also found that YAP was a physiological antagonist of podocyte apoptosis. When it is activated, it translocates to the nucleus where, after binding to TEAD, it regulates a number of transcription factors to cause fibrosis of CTGF and other factors. This fibrogenic response eventually leads to the thickening and stiffness of the renal basement membrane and further enhances the activity of YAP, thus

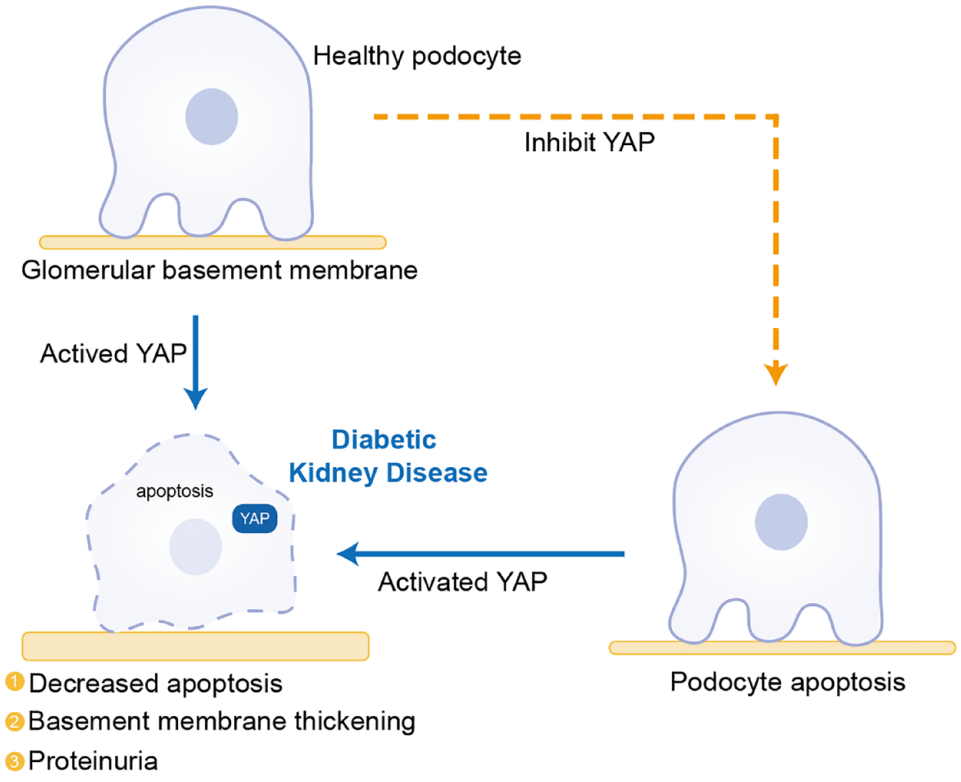

Figure 2. YAP involved in podocyte injury in DKD. Inhibition of YAP can induce podocyte apoptosis, inhibit inflammatory response, and protect podocytes. Activation of YAP reduces podocyte apoptosis, and its overexpression leads to podocyte damage, basement membrane thickening, and subsequent hardening, resulting in increased albuminuria.
DKD, diabetic kidney disease; TEAD, TEA domain; TGF-β1, tissue growth factor beta-1; YAP, Yes-associated protein.

aggravating the progression of renal disease by destroying the glomerular filtration barrier and increasing the production of urinary protein. Szeto *et al.*[53] recently reported that activated YAP could trigger inflammation and fibrogenic activity in kidney diseases. Therefore, high levels of YAP may exacerbate inflammation or kidney damage caused by diabetes. Similarly, Anorga S *et al.*[39] reported YAP as the downstream target of epidermal growth factor receptor in DKD and that its pharmacological inhibition could inhibit fibrosis progression. Both findings highlight the role of YAP in the occurrence/development of DKD. Qi *et al.*[54] showed that verteporfin could inhibit YAP nuclear translocation in renal tubular epithelial cells of DKD rats and inhibit transforming growth factor-β 1/Smad pathway in renal tubular epithelial cells, thus reducing renal fibrosis. Luo *et al.*[55] indicated that activation of YAP, which promotes proliferation and migration of VSMCs *via* the Nrp2/PlexinA1 receptor. Therefore, inhibition of YAP can prevent intimal hyperplasia after vascular injury and prevent vascular restenosis, thus reducing diabetes and angiopathy. Cui *et al.*[38] studied the regulation of YAP/TAZ activity by GPR87 and induced the expression of HK-2 in renal tubular epithelial cells, which accelerated glycolysis, mitochondrial damage, and tubulointerstitial fibrosis. These findings reveal the key functions of inhibiting YAP in affecting glomerular function and preventing proteinuria and suggest that YAP plays a key role in the occurrence and development of DKD. YAP may be a new therapeutic target for diabetes and DKD and is considered to be a therapeutic target for reversing this chronic diabetes-related disease.

DR and YAP

DR is the formation of retinal neovascularization and neurodegeneration caused by chronic hyperglycemia. Being a highly common complication of diabetes, it is mainly responsible for visual

impairment and blindness, thereby affecting the quality of life of patients. The pathological process of DR includes retinal vascular occlusion, losing the integrity of the blood–retinal barrier, and the migration and proliferation of vascular ECs.[56] Improving current understanding of the pathogenesis associated with DR is important in order to identify new therapeutic targets. Retinal Müller cells (RMCs) are the main neuroprotective macroglial cells in the retina. The dysfunction of neurons and glial cells in the retina promotes the progress of DR.[57] YAP induces endothelial cells migration and tube formation through vascular endothelial growth factor-mediated process, inhibits YAP to block Müller cell fibrosis activity, and reduces cell proliferation, migration, and vascular endothelial growth factor expression. In addition, the activation of YAP and its subsequent transfer to the nucleus, where binding to the TEAD transcription factor complex occurs, stimulate the expression of target genes, such as CTGF and AREG, which trigger cell proliferation, migration, and differentiation.[58] Since CTGF is closely linked to DR's occurrence and development, upregulating YAP represents the decisive factor for increasing the expression of CTGF and ECM protein fibronectin and promote its fibrosis activity. Xing *et al.*[59] showed that targeting YAP inhibits cell migration and tubular formation, while its silencing prevents the formation of HG-induced tubules and higher levels of vascular endothelial growth factor. Therefore, YAP could be a novel target of drug therapy in the case of DR.

Under the condition of high glucose, protein phosphatase 1 catalytic subunit α (PPP1CA) is an important regulator of Hippo pathway, which promotes dephosphorylation and nuclear translocation of YAP. Then, it promotes the transcription of glutamine synthetase (GS). GS catalyzes the conversion of neurotoxic glutamate (Glu) to non-toxic glutamine (Gln) and activates mammalian target of rapamycin complex 1 (mTORC1), thus promoting the activation of RMCs. YAP can directly enhance the expression and activity of GS, thus increasing the level of glutamine in steady state. Increasing evidence shows that YAP plays a prominent role in the formation and pathology of retinal blood vessels. Blocking PPP1CA/YAP/GS/Gln/mTORC1 can inhibit the proliferation and activation of RMC during DR, thus protecting RMCs and alleviating the development of DR.[60] Guo *et al.*[61] also reported that YAP/TAZ gene knockout attenuates the effects of ECM on intracellular Gln, Glu, and aspartic acid. In addition, YAP gene knockout reduces the production of lactic acid in ECs and reduces the ratio of extracellular lactic acid to pyruvate.

YAP, one of the signal cascades of the Hippo pathway, has various transcription targets in the process of angiogenesis, and it is regulated by the PI3K/Akt signal cascade. The latter is involved in retinal angiogenesis, characterized by the proliferation and migration of ECs.[62] YAP is phosphorylated by LATS1/2, while PI3K induces its translocation to the nucleus by inhibiting LATS activity. AkT also regulates the expression of angiotensin-converting enzyme 2 by regulating the expression of YAP in VSMCs, thus promoting vascular maturation. YAP is activated through the PI3K/Akt pathway, and it promotes the proliferation and fibrosis of Müller cells. YAP was also shown to upregulate vascular endothelial growth factor A (VEGFA) by inducing Hypoxia-Inducing Factor-1α. VEGFA binds to vascular endothelial growth factor receptors expressed on vascular ECs, with this being a key process responsible for regulating vascular permeability, migration, and proliferation of ECs.[63,64] Hamon *et al.*[65] identified the key role of YAP in regulating the proliferative response of Müller cells to injury. The activation of YAP and the increased expression of CTGF and fibronectin promote the proliferation and migration of Müller cells and rapid fibrosis through the YAP–CTGF axis. Pan *et al.*[66] showed that YAP promotes HIF-1a function by enhancing its stability, thereby further triggering cell proliferation. The upregulation of Sirtuin1 prevents both angiogenesis and proliferation of retinal microvascular ECs by down-regulating YAP/HIF-1a/VEGFA induced by miR-20a, thereby preventing the development of DR. YAP is also a transcription factor involved in the regulation of ECs and was shown to play a key part in DR retinal angiogenesis. YAP is therefore expected to be a major factor that influences the function of DR vascular ECs.

The Hippo-YAP/TAZ signaling pathway is involved in many metabolic processes, such as glycolysis, gluconeogenesis, fatty acid accumulation, and amino acid metabolism, just to name a few. For instance, Han *et al.*[67] reported a high

expression of YAP in the retina of DR mice and promoted the cellular process of RMECs by upregulating the expression of metastasis-associated lung adenocarcinoma transcript-1 (MALAT1). MALAT1 can be combined with miR-200b-3p that can directly target VEGFA. When YAP was silenced, there was a decrease in the angiogenesis, migration, and proliferation of RMECs in the retina of DR mice. A previous study showed that YAP up-regulation accelerated choroidal neovascularization by promoting EC proliferation.[1,68] Therefore, the current authors believe that YAP may promote the development of DR retinal angiogenesis by regulating the MALAT1/miR-200b-3p/VEGFA axis, hence suggesting that the silencing of YAP could contribute to the targeted therapy of DR. Therefore, the use of YAP inhibitors could repair retinal fibrosis in the future. The development of effective anti-YAP drugs, especially in combination with the regulation of Hippo pathway, could represent a new way to prevent retinal fibrosis and other fibrosis-related eye diseases.

Accelerated atherosclerosis and YAP in diabetes mellitus

Inflammation promotes atherosclerosis and diabetes, with atherosclerosis-related cardiovascular diseases being largely responsible for the death and disability of diabetic patients.[69] In the accelerated atherosclerotic process of diabetes, high glucose, and oxidized low-density lipoprotein increased the *S*-nitrosation of guanine nucleotide-binding protein G (I) subunit alpha-2 (SNO-GNAI2) in ECs, and this decreases cyclic adenosine monophosphate (cAMP) levels while enhancing coupling to chemokine receptor type 5 (CXCR5). The decrease in cAMP leads to the dephosphorylation of YAP and LATS1, as well as YAP's translocation to the nucleus, before eventually inducing the transcription of chemokines and other adhesion molecules to enhance the inflammation of ECs. Therefore, inhibition of the SNO-GNAI2–YAP pathway is an effective strategy to alleviate atherosclerosis accelerated by diabetes. In addition, Chao *et al.*[70] also found that coupling CXCR5 with SNO-GNAI2 and inactivated LATS1/2 kinase caused YAP to be dephosphorylated and translocated before triggering an inflammatory expression. Indeed, YAP/TAZ is activated and translocated to the nucleus under the action of SNO-GNAI2, with the process promoting endothelial inflammation, adhesion of monocytes to ECs, and increased atherosclerosis accelerated by diabetes. Li *et al.*[71] further found that YAP's activation could induce the formation of macrophage inflammatory bodies and increase the level of inducible Nitric Oxide Synthase (iNOS) Hippo-YAP pathway plays an important role in inflammatory response, maintenance of vascular homeostasis, and atherosclerosis. Therefore, SNO-GNAI2–YAP pathway may be a potential target for the treatment of accelerated atherosclerosis in diabetes. Diabetic cardiomyopathy is also a major vascular disease associated with diabetes. Liu *et al.*[72] found that diabetic cardiac fibroblasts can be regulated through Hippo/YAP signaling pathway. This shows that YAP is connected to diabetes mellitus-related accelerated atherosclerosis and that YAP might be a novel therapeutic target for this condition.

Conclusion

Diabetic angiopathy is one of the most common complications affecting diabetic patients, and it includes DR, DKD, atherosclerosis, and other vascular diseases. The Hippo pathway, involved in cell apoptosis, differentiation, and proliferation as well as in the regulation of inflammatory response, glucose, and lipid metabolism, is a highly evolutionarily conserved protein kinase signaling pathway that regulates organ growth and size through its effectors TAZ and its YAP. The latter, a key factor of the Hippo pathway, could play a more basic and powerful role in regulating the progression of diabetes and angiopathy. Inhibition of YAP functions through various direct/indirect activators has achieved promising results in the treatment and control of diabetic angiopathy such as DKD and DR. These inhibitors may become new therapies for diabetic angiopathy. In short, targeting the Hippo/YAP pathway therapy could be an effective way to prevent DKD, diabetic angiopathy, and atherosclerosis.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Lan Wei: Writing – original draft.

Jingjing Gao: Software; Visualization.

Liangzhi Wang: Writing – original draft.

Qianru Tao: Supervision; Writing – review & editing.

Chao Tu: Conceptualization; Supervision; Writing – original draft; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

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