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Podocytes, Signaling Pathways, and Vascular Factors in Diabetic Kidney Disease

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Abstract

Alterations and injury to glomerular podocytes play a key role in the initiation and early progression of diabetic kidney disease. Multiple factors in the diabetic milieu cause abnormalities in podocyte signaling that lead to podocyte foot process effacement, hypertrophy, detachment, loss and death. Alterations in insulin action and mTOR activation have been well documented to lead to pathology. For example, reduced insulin action directly leads to albuminuria, increased glomerular matrix accumulation, thickening of the glomerular basement membrane, podocyte apoptosis and glomerulosclerosis. In addition, the podocyte generates factors that alter signaling in other glomerular cells. Prominent among these is VEGF-A which plays a complex role in maintaining glomerular endothelium viability but causes endothelial cell pathology when generated at too high a level. Finally, circulating vascular factors, such as activated protein C have a profound effect on podocyte stability and survival. This cytoprotective factor is critical for podocyte health and its deficiency promotes podocyte injury and apoptosis. Thus, the podocyte sits in the center of a network of paracrine and hormonal signaling systems that in health keep the podocyte adaptable and viable, but in diabetes can lead to pathologic changes, detachment and death. This podocyte injury is a critical determinant of the progression of diabetic kidney disease.

Keywords

insulin; glucose; diabetes; glomerulus; mammalian target of rapamycin

Alterations and injury to glomerular podocytes play a key role in the initiation and early progression of diabetic kidney disease. While the development and progression of diabetic changes in the renal glomerulus clearly involve all resident cells as well as several passers-by such as macrophages, podocyte abnormalities are among the first manifestations to be detected morphologically in humans and animal models with diabetic kidney disease

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(DKD)[1-3]. In humans, reduction in podocyte number predicts future progression of nephropathy[1,4] and in animal models podocyte loss can directly lead to glomerulosclerosis[5], one of the hallmarks of DKD. In addition, the damaged podocyte may contribute to nephropathy via alterations in its expression of paracrine factors that impact other glomerular cells. Therefore, it is imperative to understand the metabolic and vascular factors, as well as, the signaling abnormalities that lead to podocyte dysfunction, damage and loss in early DKD in order to be able to develop effective treatments or preventive strategies that could forestall this process and thereby prevent progression of nephropathy.

Podocyte injury in diabetes is manifested morphologically by foot process effacement, hypertrophy, detachment, loss and death (not necessarily in that order)[1,3,6,7]. Studies suggest that diabetic podocytes become less stably anchored to the underlying glomerular capillary basement membrane and therefore can be more easily dislodged into the urinary space, in part due to reduction in alpha3beta1 integrin expression resulting from hemodynamic-induced stretch and TGF-β signaling[8]. In addition, podocyte loss may occur via apoptotic cell death as has also been demonstrated in several animal models of diabetes[9,10].

The podocyte acts as a signaling pericyte[11] to the glomerular endothelium and elsewhere in the glomerulus. Pericytes are contractile cells that support and wrap themselves around capillaries; they are widely distributed throughout the body and have different actions depending on their location. The podocyte receives signals from the endothelium and from circulating vascular factors[12]. It is now clear that there are a number of signaling pathways, some of which are interrelated in the podocyte that may be important and relevant in DKD. Potential molecular causes of the various alterations that lead to podocyte loss will be examined in the remainder of this review.

Podocyte Signaling Pathways in DKD

Insulin signaling in the podocyte

Insulin is a small 6 KD molecule that is freely accessible to the podocyte when released into the circulation from the pancreas. Insulin can rapidly signal to the podocyte[13] after a meal to trigger a number of potentially beneficial homeostatic responses. These include the rapid absorption of glucose through translocation of glucose transporters to the plasma membrane of the cell, remodelling of its actin cytoskeleton[13], and incorporation of potassium[14] and calcium channels[15] into the plasma membrane. Together these responses allow the cell a readily accessible energy source (glucose) and the ability to contract and remodel the cytoskeleton. These varied responses may allow podocytes to physiologically respond to the increased glomerular pressure and filtration that occurs after a meal.

There is accumulating evidence that glomerular and renal function is impaired when the podocyte is rendered insulin resistant. Specific deletion of the insulin receptor (IR) from the podocyte transgenically causes a number of features of DKD including albuminuria, increased glomerular matrix accumulation, thickening of the glomerular basement membrane, podocyte apoptosis and glomerulosclerosis, all occurring in a completely normoglycemic environment[16]. This suggests that a loss of podocyte insulin sensitivity could have an important effect on the development of DKD. Data from diabetic rodents

support a loss of podocyte and glomerular insulin signaling in the early stages of DKD[17]. Indeed Mima, et al.[18] have shown in models of both type 1 and type 2 diabetes that glomerular insulin signaling is lost early in disease progression. Conversely, insulin signaling in the tubular compartment, which controls ion reabsorption from the filtrate, as well as blood pressure and systemic glucose control[19] are not affected. Compelling evidence from human studies shows that systemic insulin resistance is associated with proteinuric kidney disease in non-diabetic patients[20] and that, in the setting of diabetes, insulin resistance predicts those patients who will develop nephropathy in both type 1[21-23] and type 2 diabetes[24].

A number of other systemic changes that occur in early type 1 and type 2 diabetes can directly inhibit insulin signaling in the podocyte. These include exposure of podocytes to high glucose, which directly abrogates insulin signaling by increasing the molecule Src homology-2 domain-containing phosphatase-1 (SHP-1) which binds to the IR and prevents downstream signaling[25]. There is also evidence that insulin receptor substrate I (IRS-I) protein is ubiquinated more rapidly in the presence of high glucose in the glomerulus which leads to increased proteosomal degradation of this important downstream signaling molecule and therefore insulin resistance[18]. Activated innate immune responses and inflammation also may disrupt podocyte signaling in early DKD[26]. It has recently been shown that early glomerular inflammation, activation of the innate immune system and podocyte insulin resistance in diabetes are linked. The innate immune system is controlled by pattern recognition receptors which bind pathogen-associated molecules. Nucleotide-binding oligomerization domain containing 2 (NOD2) is an intracellular pattern recognition receptor that is responsible for immune activation following recognition of the bacterial cell wall component muramyl dipeptide (MDP). In a set of elegant experiments Du, et al.[27] have shown that NOD2 is increased in animal models and in humans with DKD. Their studies have further shown that the MDP-NOD2 complex within podocytes abrogates insulin signaling. Moreover, mice with deletion of NOD2 are protected from DKD[27]. Finally, free fatty acids such as palmitate that are elevated in early diabetes and the metabolic syndrome also can directly impair podocyte insulin responsiveness[28]. In summary there is accumulating evidence that a number of systemic changes which occur early in diabetes can impair podocyte insulin sensitivity and signaling which in turn contributes to the development of DKD (Fig 1).

Insulin like growth factors (IGFs) in the podocyte

IGFs are structurally related to insulin and can signal through the same family of receptors as insulin via the IR, the IGF-I receptor (IGF-IR), and hybrid IR/IGF-IR receptors. IGFs have an increased affinity for the IGF-IR, whereas insulin has an increased affinity for the IR. Podocytes are the only glomerular cells that clearly produce IGF-I and IGF-II and both of these podocyte hormones signal in an autocrine manner. IGF stimulation of the podocyte causes different biological effects when compared to those resulting from insulin action even though they stimulate the same signaling pathways[29]. The IGF system appears to be more important for cell survival, whereas insulin stimulates glucose uptake and rapid actin remodeling.[16,29] In contrast to insulin that is released into the circulation and rapidly and directly binds with its receptors, the IGFs are regulated in a much more complicated manner.

These hormones are produced by the liver and also other tissues in the body and bind to a network of regulating proteins including the insulin like growth factor binding proteins (IGFBP), which control their delivery to the surrounding cell types[29]. In the setting of diabetes there is evidence that systemic IGF production decreases[30,31] but that renal production may increase[32]. There are also a variety of alterations in the renal IGFBP system in diabetes[33]. It is therefore unclear how local delivery of biologically active IGF to the podocyte changes in diabetes[34] and if this is important in modulating disease progression. However, the survival properties of these hormones on the podocyte would intuitively seem to be beneficial in this setting.

Adipokine signaling may modulate insulin action in the podocyte

Reduction in the adipokines and adiponectin, has also been shown to inhibit insulin signaling and podocyte function in DKD. Levels of adiponectin are decreased in obesity and linked to cellular insulin resistance[35] and albuminuria[36]. The adiponectin knockout mouse model develops albuminuria with pathologic changes that are focused in the podocyte[37]. Specifically, these mice develop increased albuminuria and fusion of podocyte foot processes. When treated with adiponectin, the mice show reduced albuminuria, diminished podocyte foot process effacement, enhanced glomerular AMP kinase activation, and reduced urinary and glomerular markers of oxidant stress suggesting that maintenance of normal levels of adiponectin in obesity and diabetes could in turn help maintain normal signaling and normal podocyte function. However, it is unclear which, if any, of these adiponectin effects are due to maintenance of normal insulin signaling.

Mammalian target of rapamycin (mTOR) signaling and the podocyte

The mTOR pathway is important for cellular sensing of nutrient and growth factor levels, as well as cellular stress. In response to these inputs, mTOR signaling coordinates an array of cellular responses including increased protein synthesis, removal of intracellular organelle debris (autophagy), growth and survival. mTOR participates in two distinct complexes, mTORC1 and mTORC2. mTORC1 has several downstream effects but its primary role is to enhance protein synthesis via phosphorylation of two important downstream regulators, S6 kinase and 4-Elongation Factor Binding Protein-1. mTORC2 on the other hand, primarily enhances Akt activity by phosphorylating serine 473[38]. The importance of the mTOR pathway in the podocyte has been clearly demonstrated through the development of a number of sophisticated transgenic mouse models that have examined different aspects of this pathway[39-41]. Activation of mTORC1 specifically in podocytes by genetic deletion of an upstream negative regulator leads to many changes of DKD including albuminuria, glomerular basement membrane widening, podocyte loss, mesangial expansion and glomerular mesangial accumulation of fibronectin and collagen IV. All of these alterations can be at least partly prevented by treatment with the mTORC1 inhibitor, rapamycin, as well as by a podocyte-specific reduction in mTORC1 expression via heterozygous deletion of raptor, a specific component of mTORC1. Rapamycin treatment also reduces glomerular disease in the type 2 diabetic *db/db* model of DKD[39]. Although these studies indicate that targeting mTORC1 for therapy of DKD is attractive, the necessity of maintaining mTOR activity at a normal level was underlined by the finding that elimination of raptor expression in podocytes resulted in significant proteinuria[41]. These studies have clearly shown that

modulation of mTOR activity in the podocyte in either direction can result in pathogenic changes.

The insulin/IGF and mTOR pathways are closely associated. Insulin/IGF activates mTORC1 through AKT signaling and conversely mTORC2 inhibits insulin signaling. The close relationship of these pathways may explain why overexpressing or depleting specific insulin regulatable glucose transporters in the podocyte[42,43] do not result in glucose toxicity or glucose debt effects in the podocyte as they seem to in other glomerular cells such as the mesangial cell[44]. Indeed, podocyte-specific overexpression of the glucose transporter, GLUT1, in podocytes leads to reduced nephropathy in animal models of diabetes[42] while conversely deletion of GLUT4 from podocytes also reduces nephropathy even though it stimulates podocyte hypertrophy via an mTOR-independent mechanism[43]. While the complexities of the interactions between insulin signaling, mTOR activation and glucose uptake and glucose transporter expression remain to be elucidated, it seems likely that a balance of nutrient and growth factor stimulation of this cell is critical for its function. This is perhaps not surprising as the podocyte needs biological strategies to survive for a prolonged time *in vivo* as a terminally differentiated cell.

A recent study found that Akt2 which functions in the PI3K signaling pathway is critically important for podocyte, glomerular and renal survival in a number of rodent and human models of chronic kidney disease (CKD)[45]. This molecule is activated by both insulin and also the mTOR2 complex[45]. In low GFR glomerular stress situations it is up-regulated in the podocyte and when mTOR is inhibited genetically or pharmacologically with rapamycin it accelerates kidney damage. Assessing Akt2 in the setting of DKD will be critical especially in light of the evidence that mTOR in the podocyte is activated in a detrimental way in diabetes and that treatment with an mTOR inhibitor may be beneficial[39]. These recent findings indicate that such treatment could also be detrimental since mTORC2, as well as mTORC1, can be inhibited by long-term rapamycin treatment and the kidney protective effect of Akt2 could be eliminated.

Vitamin D signaling in the podocyte

There is strong evidence that the vitamin D receptor is highly expressed in podocytes in culture and in vivo[46]. It also appears that vitamin D treatment protects podocytes from injury in non-diabetic[47] and diabetic animal models[46,48,49] and may work synergistically with renin-angiotensin-aldosterone system (RAAS) blockade to further reduce injury in diabetes. The VITAL study, a randomized controlled clinical trial, showed that vitamin D therapy modestly reduced proteinuria in type 2 diabetic patients on RAAS blockade with progressive nephropathy[50]. A more recent mouse study found that podocyte-specific expression of a human vitamin D receptor reduced albuminuria, podocyte loss and other signs of nephropathy in streptozotocin diabetes and, importantly, rescued the nephropathic phenotype found in vitamin D receptor knockout mice[51]. Although the signaling mechanisms responsible for the podocyte protective effects are not completely clear there is evidence that vitamin D treatment may prevent podocyte apoptosis by inhibition of p38 MAP kinsase signaling, PI3 kinase, Akt[51], as well as, RAAS signaling[52].

Estrogen mediated signaling and the diabetic podocyte

There is relatively convincing evidence that female gender, at least in premenopausal women, protects against progression of non-diabetic glomerular diseases[53]. However, there is less evidence that female gender is protective in DKD[54]. Nonetheless, a number of reports suggest that podocyte estrogen receptor signaling may be protective in DKD. Estrogen effects are mediated by two distinct estrogen receptor subtypes, ERá and ERâ and both receptors are present in podocytes[54]. Estradiol has been shown to stimulate ERá protein expression as well as to reduce podocyte apopotosis after puromycin aminonucleoside exposure[55]. There is less compelling evidence that ER signaling is protective in diabetic models or humans. However it has recently been reported that a genetic variant found in the FinnDiane cohort is associated with ESRD in type 1 diabetic females[56]. This is located on 2q31.1 and is potentially a variant in SP3 which is a transcription factor that interacts with the estogen receptor alpha. Furthermore a recent rodent study suggests that estradiol administration prevents podocyte apoptosis in a diabetic mouse model[57] possibly by Rac1-mediated stabilization of F-actin[58]. However, because the studies were performed in an inadequate model of diabetic nephropathy, the C57BL/6 db/db mouse, these results will need to be verified in other more robust models and in humans with DKD.

Vascular factors, the podocyte and DKD

Vascular endothelial growth factor-A (VEGF-A)

The podocyte both generates and responds to a number of angiogenic growth factors. The best known is vascular endothelial growth factor A (VEGF-A). This molecule is produced in great quantities by the podocyte in the glomerulus. It does not cause neovascularization as it does in the eye[59] or in neoplastic tissue[60] but is important for maintaining the integrity of the glomerular filtration barrier as well as a survival factor for the podocyte[61]. It does this by signaling through the VEGF-Receptor-2 (VEGFR2) which is most abundantly expressed in the glomerular endothelium. Podocyte specific VEGF-A excess or deficiency in development[62] or maturity[63] causes glomerular damage. Too much VEGF-A induces endothelial growth and swelling, a condition known as endotheliosis, whereas inadequate VEGF-A release results in endothelial damage and apoptosis leading to glomerulosclerosis[64]. As is the case for mTOR, VEGF-A levels and signaling need to be regulated closely to maintain healthy glomerular structure and function. In diabetes there is evidence that glomerular VEGF-A levels can be both elevated[65,66] or reduced[67] and this may be related to the duration of the disease. The human data suggest that VEGF-A expression may be elevated early in DKD and then probably goes down below normal levels as the disease progresses. Therapeutic strategies to elevate[68] and suppress local VEGF-A expression[69] have both been shown to be beneficial depending on experimental conditions. Going forward it will be interesting if we can delineate how to regulate this signaling pathway in a beneficial manner in DKD. Recently there has also been a link made between the production of VEGF-A and the insulin signaling pathway in the podocyte[70]. Similar to retinal pigment epithelial cells in the eye, insulin is able to control the release of VEGF-A. It is possible that VEGF-A production may be at least partially governed by insulin sensitivity of the podocyte.

An interesting development in this field is the proposition that as well as pro-angiogenic VEGF isoforms there are complementary antagonistic anti-angiogenic forms that have been generated through splicing variants of the VEGF mRNA causing the final 6 amino acids of the molecule to be altered. These are called VEGFxxb isoforms[71]. This is currently a controversial field and it is unclear if these forms exist in all species[72,73]. However, if these isoforms are present they could represent another method of manipulating this system in the setting of diabetes.

Angiopoietins and the podocyte

Another class of angiogenic growth factors in the glomerulus are the angiopoietins, Ang-1 and Ang-2. Manipulating these molecules has shown some therapeutic promise in DKD. Ang-1 is produced by the podocyte and signals through the Tie-2 receptor which is found on the glomerular endothelium. Ang-2 is released from endothelial cells and acts as an autocrine competitive inhibitor of Tie-2[74]. Encouragingly, there are several reports that demonstrate that Ang-1 production either by podocytes[74,75] or mesangial cells[74], or via exogenous administration[76] can slow DKD in rodent models. Moreover, altering the Ang-1/Ang-2 ratio in favor of Ang-2 has been shown to be detrimental in DKD[77] suggesting this pathway is important.

Activated protein C

In addition to producing angiogenic factors the podocyte is responsive to circulating factors that are altered by endothelial dysfunction in diabetes. The vascular factor that most clearly affects podocyte behaviour in diabetes is the anti-thrombotic agent, activated protein C (APC). The circulating zymogen, protein C, binds endothelial thrombomodulin and is activated by thrombin to APC. APC is a serine protease that proteolytically inactivates coagulation Factors V and VIII; however, it has several effects independent of its coagulation regulatory role. It has been shown to be cytoprotective, anti-apoptotic and have anti-inflammatory effects[78,79]. Glomerular APC formation, which is regulated by endothelial thrombomodulin, is reduced in diabetic mice and APC deficiency promotes podocyte injury and apoptosis at least in part via reduced activation of its receptors, PAR1 and 3[78], and downstream signaling via the pro-oxidant factor, p66^{Shc80}_ENREF_79. Restoration of APC levels in diabetic mice reverses enhanced oxidative stress as well as podocyte loss, both hallmarks of early DKD.

In summary, the podocyte is an important source of a number of angiogenic growth factors that signal to the glomerular endothelium. These factors change in diabetes and may be able to be therapeutically modifiable (Fig 2). The podocyte also responds to circulating factors, such as APC, insulin and adipokines and very likely to yet unknown factors from the endothelium. All of these factors may impact podocyte signaling and how podocytes respond to metabolic stress thus heightening podocyte susceptibility to injury.

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Clinical Summary

- Podocyte pathology is central to the progression of diabetic kidney disease.
- Signaling abnormalities within the podocyte (e.g., changes insulin action and mTOR signaling) are central to the development of podocyte pathology.
- The podocyte secretes paracrine factors, such as VEGF-A, that alter endothelial cell function and morphology in diabetes.
- Cytoprotective vascular factors such as activated protein C are reduced in diabetes which promote podocyte injury and death.

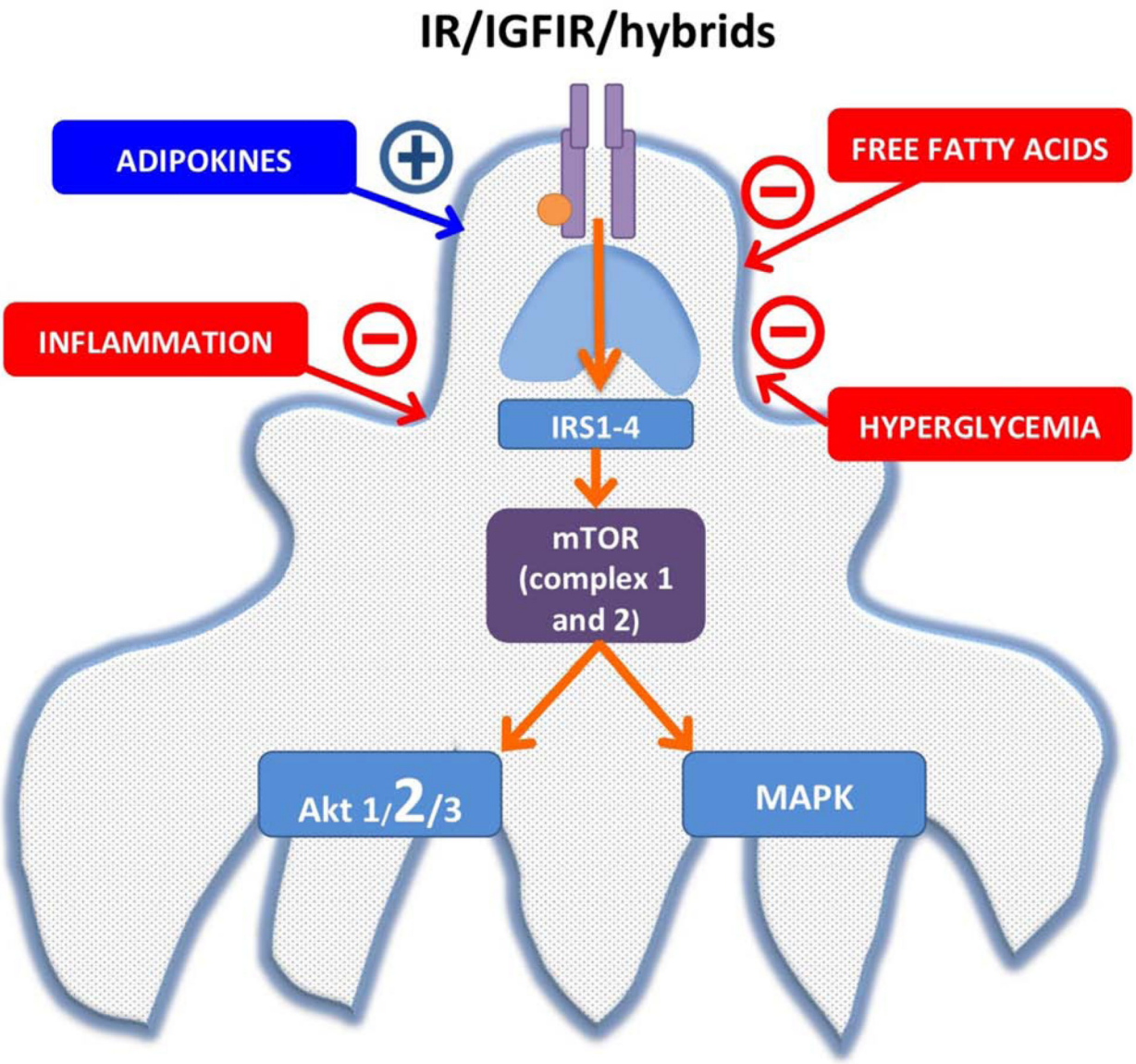

Figure 1.
Insulin/mTOR signaling pathway and also the extrinsic modifiers that are present in diabetes.

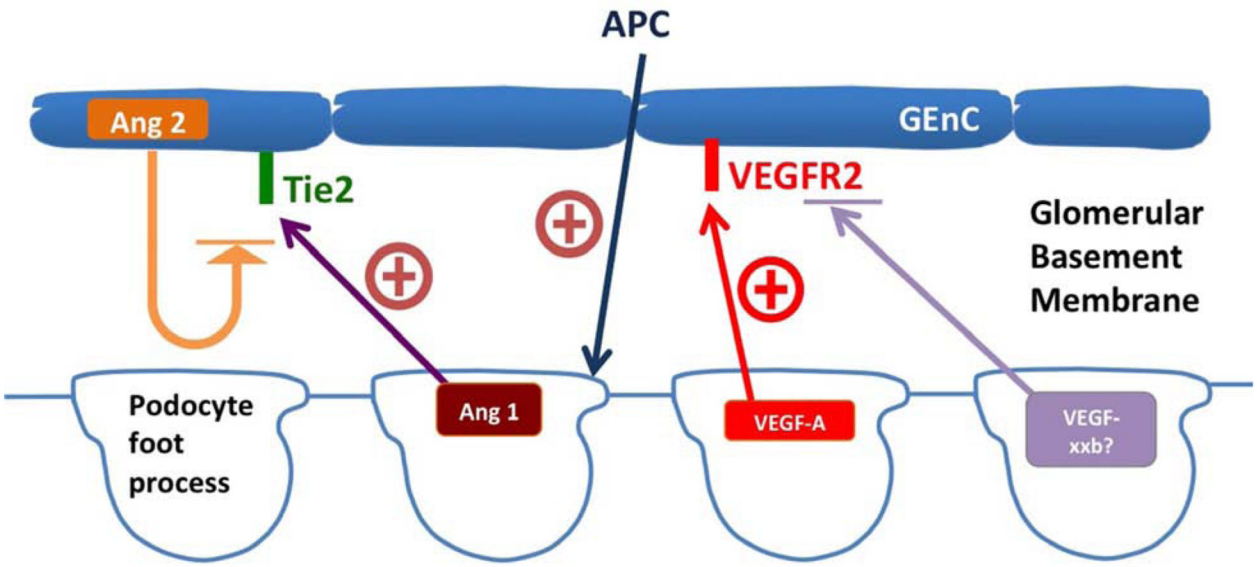

Figure 2.
Podocyte and VEGF/angiopoietins and regulation in diabetes