GLUT1 Regulation of the Pro-Sclerotic Mediators of Diabetic Nephropathy

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Abstract

Diabetic glomerulosclerosis is characterized by accumulation of extracellular matrix proteins, mesangial expansion, and tubulointerstitial fibrosis. Hyperglycemia accelerates development of the disease, a direct result of increased intracellular glucose availability. The facilitative glucose transporter GLUT1 mediates mesangial cell glucose flux which leads to activation of signaling cascades favoring glomerulosclerosis, including pathways mediated by angiotensin II (Ang II), transforming growth factor β (TGF-β), connective tissue growth factor (CTGF), and vascular endothelial growth factor (VEGF). Ang II has both hemodynamic and metabolic effects directly inducing GLUT1 and/or matrix protein synthesis through diacyl glycerol (DAG) or protein kinase C (PKC) induction, mesangial cell stretch, and/or through transactivation of the epidermal growth factor receptor, the platelet-derived growth factor receptor, and the insulin-like growth factor-1 receptor, all of which may stimulate GLUT1 synthesis via an ERK-mediated pathway. Conversely, inhibition of Ang II effects suppresses GLUT1 and cellular glucose uptake. GLUT1-mediated glucose flux leads to metabolism of glucose via glycolysis, with induction of DAG, PKC, TGF-β_1, CTGF and VEGF. VEGF in turn triggers both GLUT1 and matrix synthesis. New roles for GLUT1-mTOR and GLUT1-mechano-growth factor interactions in diabetic glomerulosclerosis have also recently been suggested. Recent mouse models confirmed roles for GLUT1 in vivo in stimulating glomerular growth factor expression, growth factor receptors and development of glomerulosclerosis. GLUT1 may therefore act in concert with cytokines and growth factors to induce diabetic glomerulosclerosis. Further clarification of the pathways involved may prove useful for the therapy of diabetic nephropathy. New directions for investigation are discussed.

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Introduction

Diabetic nephropathy is the leading cause of end-stage kidney failure in the United States [1]. The disease is characterized by the accumulation of extracellular matrix protein in the mesangial space with mesangial expansion, thickening of the glomerular and tubular basement membranes, and tubulointerstitial fibrosis [2, 3].

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The exact pathogenesis of diabetic nephropathy is unknown; however, hyperglycemia has been shown to accelerate the development of clinical nephropathy in the Diabetes Control and Complications Trial (DCCT) [4, 5]. In this regard, the DCCT and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated a clear link between hyperglycemia and the development of microvascular complications [4, 5]. In addition, the treatment of diabetics with pancreatic transplantation and normalization of serum glucose levels has been associated with regression of diabetic glomerular disease [6].

Hyperglycemia has also been shown to drive the production or expression of many factors associated with the development of diabetic nephropathy, including angiotensin II (Ang II), transforming growth factor β (TGF-β), connective tissue growth factor (CTGF) and vascular endothelial growth factor (VEGF) [7]. This suggests that increased intracellular glucose availability may represent an important proximal stimulus in the development of fibrosis by activating these mediators.

At the cellular level, hyperglycemia generates incessant metabolic pressure for the activation of glucose-dependent biochemical and enzymatic pathways. In the kidney, the facilitative glucose transporter GLUT1 is a primary gatekeeper of this process by regulating glucose movement into the cell. Furthermore, in the glomerular mesangial cell the expression of GLUT1 is the rate-limiting step for glucose flux and utilization [8]. At the level of the organism, all of the above processes are highly integrated. To address these events in vivo, several novel transgenic mouse models have helped to advance our understanding of the role of GLUT1 in the development of glomerulosclerosis and nephropathy [9–11].

GLUT1-facilitated transport of glucose results in the activation of signaling cascades favoring glomerulosclerosis [8, 10–12]. Thus, GLUT1 activity may be a regulator of the development of fibrosis in this disease. In support of this contention, mesangial cells overexpressing GLUT1 and cultured in normal glucose exhibit a diabetic phenotype with an increase in matrix protein synthesis [8]. In addition, transgenic mice overexpressing GLUT1 develop diabetic glomerulosclerosis and nephropathy despite normoglycemia [10]. Conversely, overexpression of a GLUT1 antisense sequence prevented diabetic changes in mesangial cells cultured in high glucose [13], and in vivo, transgenic db mice expressing an antisense sequence to glomerular GLUT1 did not develop diabetic glomerulosclerosis despite hyperglycemia [14]. These data imply a regulatory role for GLUT1 in mediating the activation of pro-sclerotic events in diabetes, and suggest an additional active rather than a simple facilitative role of the transporter in this process.

The goal of this review is to assess the evidence supporting GLUT1 as a regulator of the cytokines and growth factors promoting diabetic glomerulosclerosis and nephropathy, and explore a new paradigm for GLUT1 in mediating the pathogenesis of this disease.

Facilitative Glucose Transport by GLUT1 and Diabetic Nephropathy

Enhanced cellular glucose uptake is mediated by the facilitative glucose transporter proteins (GLUT), part of a super family of SLC (solute carrier) genes [15]. At least 14 GLUT transporters have been identified and exhibit a broad distribution with tissue-specific regulation [15]. The GLUT proteins are hexose transporters with substrate specificity for glucose, fructose, and/or galactose [15]. Structurally, the GLUT proteins are thought to have 12 transmembrane domains, with an intracellular loop between domains 6 and 7, and, depending on the specific transporter, a long glycosylated extracellular loop between domains 1 and 2 or domains 9 and 10 [15]. The mechanisms by which the GLUT proteins transport their substrates are not fully defined, but it has been suggested that each transporter may have a form of selectivity filter at the entrance to the pore created by the protein [15].

In the glomerulus, GLUT1 and GLUT4 are the primary glucose transporters [16], with GLUT1 predominating in mesangial cells [17]. Under hyperglycemic conditions typical of the diabetic milieu, mesangial cell GLUT1 synthesis and expression is increased and is associated with enhanced glucose flux [18]. Similarly, overexpression of GLUT1 in mesangial cells cultured under normal glucose conditions mimics the diabetic state, and results in significant increases in both glucose uptake and utilization, as well as activation of matrix protein synthesis [8, 19]. These responses were prevented when an antisense sequence to GLUT1 was overexpressed in mesangial cells cultured in high glucose [13]. Thus, GLUT1 expression is the rate-limiting step for the movement of glucose into the cell, regardless of the extracellular glucose concentration.

Increased GLUT1 expression stimulates glucose flux and utilization, and thus triggers all downstream responses associated with increases in glucose availability. Factors known to stimulate the GLUT1 gene include glucose, serum, growth factors, hypoxia and hyperosmolarity [20–23]. The diverse number of activators of GLUT1 synthesis

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implies an important role for glucose flux and utilization from a variety of environmental stimuli, and suggests that GLUT1 may contribute to the regulation of glomerulosclerosis through these pro-sclerotic signaling pathways. Clinically, these events could have a direct effect on the pathogenesis of both diabetic and nondiabetic forms of glomerulosclerosis.

Recent developments highlighting a central role for GLUT1 in the development of mesangial matrix protein accumulation in glomerulosclerosis is further supported by three in vivo studies. First, overexpression of GLUT1 in nondiabetic C57BL6 mice resulted in the development of changes consistent with diabetic glomerulosclerosis [10], and suggests that an increase in GLUT1-mediated glucose flux is sufficient to drive pro-sclerotic pathways leading to diabetic glomerulosclerosis. Second, nondiabetic, nephron-deficient Fvb mice develop glomerulosclerosis in conjunction with increased GLUT1 synthesis and expression [10]. This work indicates that stimuli associated with reduced nephron mass, including glomerular hypertension with mesangial cell stretch, are sufficient to trigger increases in GLUT1 expression. Finally, it has been demonstrated in a preliminary report that mesangial mechano-growth factor (MGF), a splice variant of insulin-like growth factor-1 (IGF-1) involved in tissue repair and hypertrophy, is increased in glomeruli of diabetic mice and in nondiabetic GLUT1 – overexpressing transgenic mice [24], and is part of a GLUT1-MGF-positive feedback loop driving mesangial fibronectin synthesis [25]. In addition, recent data suggest a role for GLUT1-induced mTOR in mesangial dysfunction and glomerular disease in diabetes [26]. In experiments where GLUT1 was overexpressed in mesangial cells in the absence of high extracellular glucose, glucose flux and mTOR activity were increased. Increased mTOR activity also leads to increased GLUT1 and glucose flux [26]. These data together suggested a feed-forward mechanism resulting in persistently increased GLUT1 and mTOR activity in diabetic glomeruli [26].

Taken together, these data provide compelling evidence for a direct role of GLUT1 in facilitating the development of both diabetic and nondiabetic forms of glomerulosclerosis and would suggest that GLUT1 may be an important proximal regulator in the development of this disease. To address this question in the context of diabetic glomerulosclerosis, the following sections will examine the interactions between GLUT1 and the cytokines and growth factors mediating the development of the disease, and seek to define the role of GLUT1 as a potential gatekeeper of the these pathologic pathways.

Pro-Sclerotic Mediators of Diabetic Nephropathy and GLUT1

Angiotensin II (fig. 1a)

Ang II is a vasoactive cytokine mediating its major effects via the AT1 receptor [27]. In the kidney, Ang II has both hemodynamic and metabolic effects [28, 29]. In diabetes, increased glucose availability may increase Ang II levels by stimulating synthesis [30] or through vasoactive responses to a reduction in glomerular filtration surface area [31].

The AT1 receptor is a G-protein-linked receptor interacting with several intracellular signal conduction pathways. Through G proteins, the AT1 may trigger second messengers including diacyl glycerol (DAG) and reactive oxygen species [27]. DAG is also a product of glucose metabolism and is known to stimulate gene transcription via the protein kinase C (PKC) activation pathway [32].

Ang II signaling pathways interact with GLUT1 at several levels, providing potential opportunities for GLUT1 to amplify the pro-sclerotic effects of Ang II. In this regard, DAG production leads to an increase in GLUT1 gene expression via PKC [19, 21]. An increase in GLUT1 expression results in enhanced glucose flux and utilization, which triggers production of more DAG and additional PKC activation. The latter also includes stimulation of extracellular matrix protein synthesis and directly promotes the development of sclerosis [19, 33]. In this regard, mesangial cells overexpressing GLUT1 activate the PKCα and PKCβ1 isoforms with subsequent increases in the activating protein 1 (AP-1) transcription factor [34]. AP-1 binding to the fibronectin gene resulted in enhanced fibronectin synthesis [34].

Ang II has also been shown to trigger GLUT1 gene expression in association with epidermal growth factor receptor (EGFR) transactivation [35]. In this pathway, EGFR activation may lead to an induction of ERK [27], which has been shown to induce the GLUT1 gene and protein synthesis [36]. In mesangial cells, Ang II transactivation of platelet-derived growth factor receptor (PDGFR) and IGF-1 receptor (IGF-1R) may also represent additional stimuli to ERK activation [27].

The vasoactive effects of Ang II may stimulate GLUT1 synthesis [29]. In this regard, an increase in GLUT1 expression has been observed following mesangial cell stretch [11] and in conjunction with a nephron-deficient mouse model with glomerular hypertension and hyperperfusion [11, 37] and in Milan normotensive rats [38, 39], all of which would be an expected result of Ang II vasoactivity [40]. Furthermore, in 2010, Wang et al. [11]
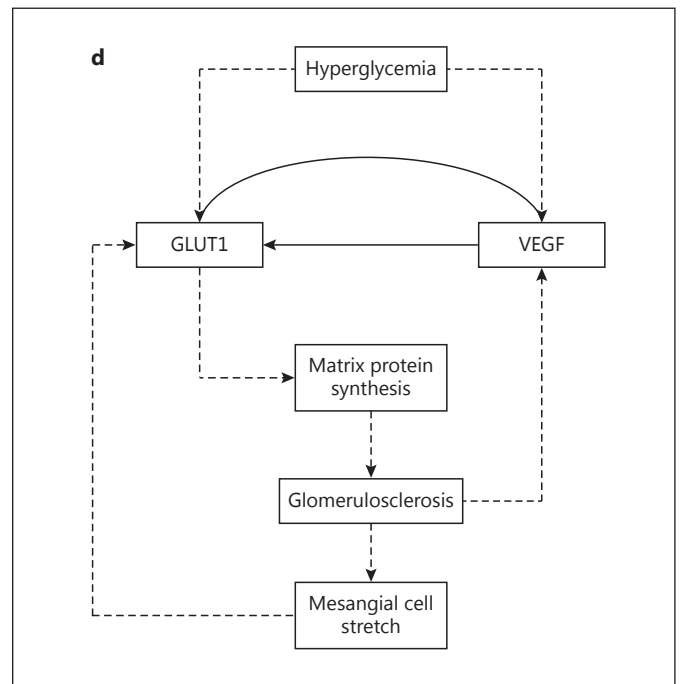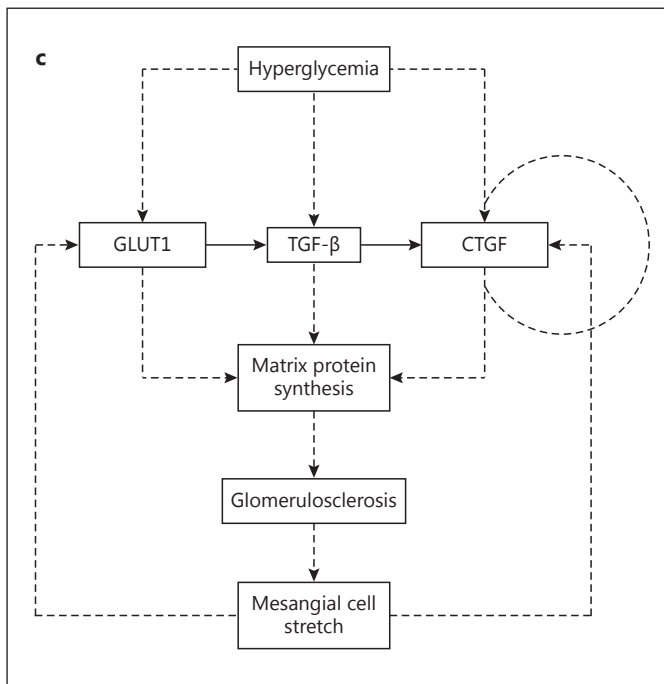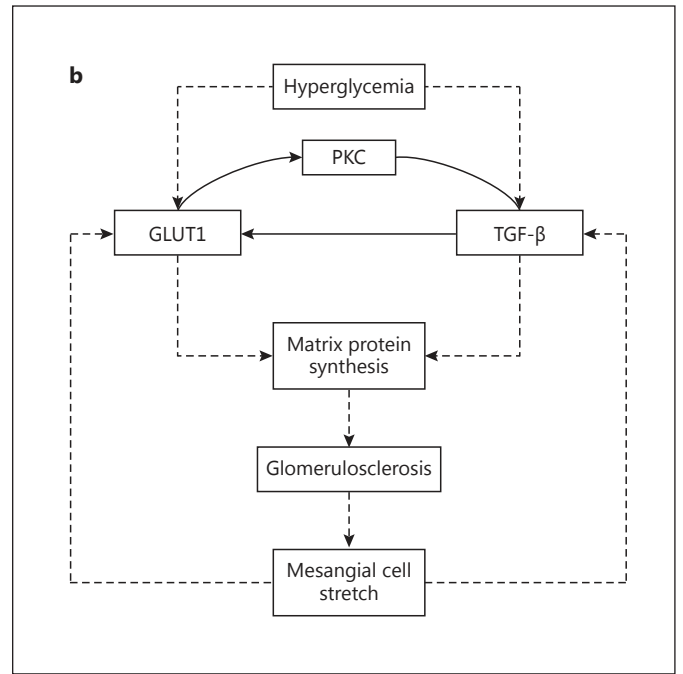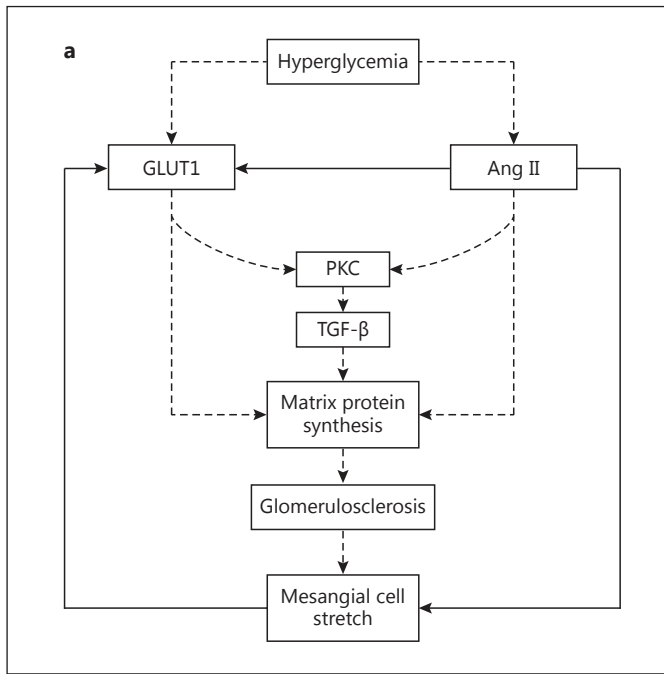
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linked GLUT1 expression and mesangial cell stretch to VEGF production and an associated increase in matrix protein synthesis, providing an additional conduit for Ang II induction of both GLUT1 and matrix protein synthesis. Finally, studies with ramipril in vivo and losartan in vitro have indicated that inhibition of angiotensin-converting enzyme or angiotensin receptor-1 can suppress renal cortical GLUT1 [41] and mesangial glucose uptake [42], respectively. Ramipril reduced renal cortical angiotensin-converting enzyme activity and GLUT1 expression in diabetic, hypertensive rats [41], while losartan blunted the effects of high glucose on mesangial cell
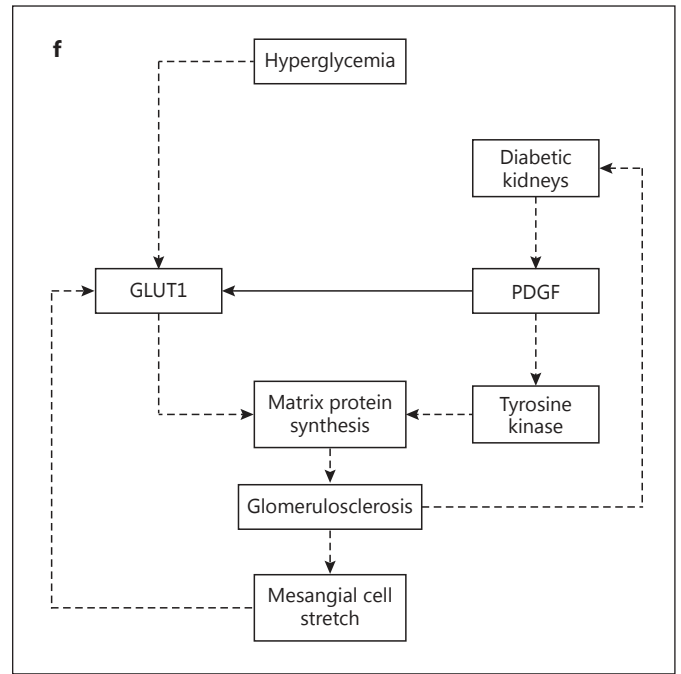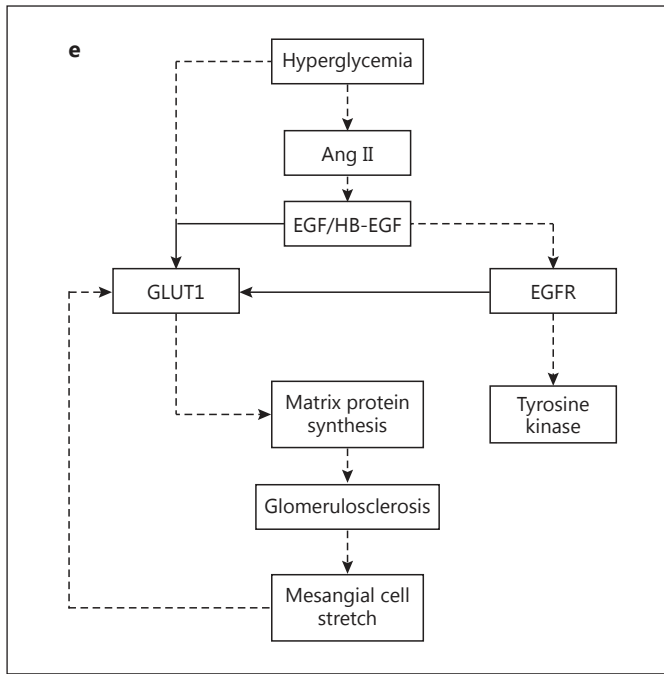
Fig. 1. Interactions of GLUT1 with six putative mediators of diabetic glomerulosclerosis. **a** Ang II. Hyperglycemia triggers Ang II production which induces GLUT1 expression and a GLUT1 amplification cascade. Progressive nephron loss from glomerulosclerosis also increases Ang II and GLUT1. Ang II and GLUT1 activation of PKC also promote glomerulosclerosis through TGF-β-dependent and -independent pathways. **b** TGF-β. A GLUT1 amplification loop is augmented by TGF-β production which is in turn driven by hyperglycemia and GLUT1 activation of PKC. As glomerulosclerosis progresses, mesangial cell stretch also induces TGF-β production. The increase in TGF-β stimulates additional GLUT1 expression, invoking a GLUT1 amplification cascade. **c** CTGF. CTGF is activated by hyperglycemia, TGF-β and an autoinduction cascade. In the presence of elevated glucose levels and mesangial cell stretch, GLUT1 is activated and increases CTGF expression through TGF-β. **d** VEGF. Hyperglycemia and GLUT1 induce VEGF synthesis, which in turn activates a GLUT1 amplification loop. VEGF expression is also increased in glomerulosclerotic kidneys. **e** EGFR. Elevated glucose levels induce Ang II which, through G-protein-linked PKC activation, releases membrane-bound EGF and HB-EGF. These ligands bind the EGFR which activates tyrosine kinase and, along with free EGF and HB-EGF, triggers GLUT1 synthesis and the GLUT1 cascade. **f** PDGF. PDGF expression is increased in diabetic glomerulosclerosis and triggers matrix protein synthesis through a tyrosine kinase-mediated pathway. PDGF also invokes a GLUT1 amplification loop by stimulating GLUT1 synthesis. Solid lines depict effects directly related to GLUT1 and a given mediator.

GLUT1, GLUT4, glucose uptake and fibronectin expression [42]. These data suggested potential protective effects of the drugs via these mechanisms against progression of diabetic nephropathy.

Taken together, the above studies demonstrate interactions between Ang II and GLUT1 through both metabolic and mechanical pathways. These events offer several examples of Ang II-driven processes that also stimulate GLUT1 synthesis, and thus trigger pro-sclerotic pathways resulting from increased glucose flux. In this model, GLUT1 may act to amplify the pro-fibrotic effects of Ang II, and thus serve as a potential regulator of the process.

Transforming Growth Factor β (fig. 1b)

TGF-β is a pro-sclerotic cytokine directly involved in the pathogenesis of diabetic glomerulosclerosis and interstitial fibrosis [43]. TGF-β activity is increased by a variety of stimuli [43], including hyperglycemia [44], DAG [32], Ang II [45], and cyclic mesangial cell stretch [46]. TGF-β promotes glomerulosclerosis and interstitial fibrosis by stimulating matrix protein synthesis [44, 47] and inhibiting degradation [48].

TGF-β signaling is mediated through a receptor complex that activates the Smad protein system [49]. Smad activation results in the assembly of a DNA-binding protein that can activate matrix protein synthesis, angiogenesis, and apoptosis [50]. TGF-β may also signal through

Smad-independent pathways and activate mitogen-activated protein kinase (MAPK) which can regulate cell proliferation [51].

TGF-β activation of MAPK may trigger GLUT1 synthesis [52, 53]. In this regard, adipocytes mutated to constitutively express MAPK were shown to increase GLUT1 but not GLUT4 expression [53]. Transcriptional activator protein-1 may be a target of the MAPK system, and associate with the four, 12-*O*-tetradecanoylphorbol-13-acetate-response elements present in the GLUT1 gene, and thus trigger GLUT1 synthesis [52].

MAPK induction of GLUT1 and the associated increase in glucose transport would be expected to increase DAG levels. In mesangial cells, TGF-β activation of GLUT1 results in an increase in glucose flux [54] with induction of the DAG-PKC pathway [8]. The increase in PKC leads to further stimulation of TGF-β synthesis [32] and may effectively define a DAG-mediated amplification loop between GLUT1 and TGF-β. In this regard, GLUT1 induction of TGF-β was observed in whole glomeruli from transgenic mice overexpressing-GLUT1, but it remains unknown which cells in the glomerulus are responsible for this effect [10].

The development of glomerulosclerosis results in loss of filtration surface area, glomerular hypertension and mesangial cell stretch. Mesangial cell stretch activates both GLUT1 and TGF-β [11, 46] and may reactivate or bolster the above amplification cycle. Taken together, TGF-β may trigger GLUT1 through MAPK and/or mesangial cell stretch. GLUT1 activation, through increased glucose flux in turn drives additional TGF-β synthesis via DAG and PKC. The pro-sclerotic effects of TGF-β and their subsequent amplification by GLUT1-mediated pathways may thus contribute to the development and progression of glomerulosclerosis.

Connective Tissue Growth Factor (fig. 1c)
CTGF is a pro-sclerotic cytokine and a member of the CCN gene family [55]. CTGF is induced by TGF-β and promotes matrix protein synthesis [56, 57]. In this regard, it is an important mediator of matrix accumulation in glomerulosclerosis [58]. Gene and protein expression of CTGF are increased in fibrotic tissues [55] and glomerular CTGF gene expression has been shown to be increased in diabetic rats [58]. Mediators of CTGF gene or protein expression include TGF-β [57], elevated glucose [58, 59], mechanical strain [58] and an autoinduction pathway [58].

Increased glucose availability increases mesangial cell CTGF via a TGF-β-dependent pathway [60]. This implies that upregulation of GLUT1, through an increase in glucose flux, may result in an increase in CTGF by stimulating TGF-β, suggesting a potential role for GLUT1 in this activation loop. The mechanism by which mechanical strain may stimulate CTGF is unclear; however, GLUT1 induction and/or increases in TGF-β may underlie the process [11, 46]. These data suggest a potential amplification loop between GLUT1 and CTGF via TGF-β-dependent pathways, but the relationship remains to be defined.

Vascular Endothelial Growth Factor (fig. 1d)
VEGF (same as VEGF-A) is part of a family of VEGF proteins which includes VEGF-A, -B, -C, -D and placental-derived growth factor [61]. VEGF promotes angiogenesis, is highly expressed by podocytes, and is important in glomerular development [61–63]. VEGF is expressed in the adult kidney and has a paracrine role in glomerular endothelial cell signaling and fenestration formation [61, 64]. VEGF signaling in diabetic nephropathy appears via the VEGF receptor type 2 [61, 65–67].

VEGF may contribute to the pathogenesis of diabetic nephropathy [68–73]. In experimental diabetes, VEGF expression is increased in some studies [68], while in some others it is not [74, 75], or demonstrated a protective effect by deletion of VEGF-A from podocytes [76]. Treatment with antibody to VEGF prevented diabetes-induced increases in glomerular volume and albuminuria [69]. Using a nitric oxide (NO) knockout mouse, Nakagawa [70] induced diabetes and showed the development of diabetic glomerulosclerosis with elevated VEGF expression. In these studies, it was proposed that VEGF may promote the development of diabetic nephropathy through an 'uncoupling' with NO [70]. In this model, VEGF triggers NO release, and acts with NO as a trophic factor for the endothelium [70]. NO derived from endothelial cells prevents endothelial cell and smooth muscle proliferation, and macrophage infiltration [70]. In the knockout mice, unmitigated VEGF was associated with the development of glomerulopathy consistent with diabetic glomerulosclerosis [70, 77]. Taken together, these data suggest a role for VEGF in promoting the development of diabetic nephropathy, and imply a link with endothelial NO production [70, 71].

GLUT1 overexpression in transduced mesangial cells has been associated with increased VEGF gene expression [78]. More recently in nephron-deficient transgenic Fvb mice with glomerulosclerosis, mesangial cell and glomerular VEGF expression was increased [11]. Furthermore, in cultured mesangial cells cyclic stretch induced an in-

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crease in GLUT1 expression which preceded an elevation in VEGF [11]. When these cells were treated with VEGF, an increase in both GLUT1 and glucose uptake was demonstrated, indicating that VEGF is a potent stimulus to GLUT1 synthesis. VEGF also triggered matrix protein synthesis in mesangial cells, which was suppressed by an antisense sequence to GLUT1 [11]. Data in podocytes are consistent with the finding of VEGF-induced matrix expression [79, 80]. These data provide compelling evidence for bidirectional stimulation between GLUT1 and VEGF, with VEGF induction of matrix protein synthesis dependent, at least in part on GLUT1 expression. Taken together, these studies, and the work of others, suggest a pro-sclerotic role for VEGF in diabetic nephropathy, and indicate that GLUT1 may regulate and/or augment some facets of VEGF-induced matrix protein synthesis in this disease.

Epidermal Growth Factor and the EGFR (fig. 1e)

The EGFR is a tyrosine kinase-linked transmembrane glycoprotein influencing proliferation, differentiation and tumorigenesis [81]. In addition, the EGFR has been shown to regulate cardiac hypertrophy and vascular smooth muscle tone [82, 83]. In diabetes, EGFR signaling may modulate vascular wall thickening and the microvascular complications of the disease [82]. In this regard, vascular wall remodeling in diabetic mice was improved with tyrosine kinase inhibition [82].

The EGFR may be activated by several ligands, including epidermal growth factor (EGF) and heparin-bound EGF (HB-EGF) [81]. HB-EGF is released from the cell surface by enzymatic cleavage [81]. Ligand binding to G-protein-linked receptors can also result in EGFR-mediated responses by triggering the cleavage of surface-bound EGFR ligands like HB-EGF [81] In this regard, Ang II engagement of the AT1 receptor has been shown to induce EGFR responses via this mechanism (see Angiotensin II, above) [83].

Using cultured mesangial cells, Nose et al. [35] demonstrated Ang II induction of GLUT1. The process was partially attenuated by an EGFR inhibitor, indicating that Ang II activation of GLUT1 expression was in part mediated via the EGFR [35]. This observation is consistent with transactivation of the EGFR by Ang II with downstream induction of tyrosine kinase-mediated pathways [83]. The authors also showed that EGF and HB-EGF triggered GLUT1 synthesis [35]. Taken together, these studies indicate a role for the EGFR in mediating Ang II induction of GLUT1, and demonstrate that activation of the EGFR with EGF and HB-EGF may activate GLUT1

synthesis independent of Ang II. These observations suggest that mediators acting via the EGFR may induce GLUT1 synthesis and provide additional pathways for GLUT1 induction of pro-sclerotic events in diabetic nephropathy.

Platelet-Derived Growth Factor (fig. 1f)

Platelet-derived growth factor (PDGF) is a glycoprotein dimer mediating its effect via two related tyrosine kinase PDGFR [7, 84]. PDGF is expressed in mesangial cells and mediates cellular proliferation and matrix protein deposition [84]. PDGF and PDGFR expression were increased in experimental diabetic nephropathy [85] and Langham et al. [85] demonstrated increased PDGF expression in renal biopsies from diabetic patients. Finally, Lassila et al. [86], using an animal model of accelerated diabetic nephropathy, showed increased renal PDGF expression, and increased glomerular and tubulointerstitial matrix protein accumulation in diabetic animals. These changes were attenuated in diabetic mice treated with a tyrosine kinase inhibitor [86]. These studies support a role for PDGF in the pathogenesis of diabetic glomerulosclerosis, and suggest the effects of the growth factor may be inhibited by tyrosine kinase blockade.

GLUT1 may potentiate the effect of PDGF on the kidney in diabetes. In this regard, the GLUT1 promoter region has specific PDGF response elements [21], and under the influence of PDGF, GLUT1 has been shown to translocate to the cell membrane of adipocytes, where it increased glucose uptake [87]. Finally, PDGF has been shown to stimulate GLUT1 synthesis and glucose transport in skeletal muscle from transgenic mice overexpressing the PDGFR [88]. These data suggest a model whereby PDGF may stimulate GLUT1 expression and glucose utilization, triggering GLUT1-mediated pro-sclerotic cascades associated with the development of diabetic glomerulosclerosis.

GLUT1 as a Facilitator of the Pro-Sclerotic Mediators of Diabetic Glomerulosclerosis

GLUT1 promotes the development of glomerular disease resembling diabetic glomerulosclerosis via the cellular uptake and utilization of glucose [10]. In diabetes, GLUT1-mediated utilization of glucose activates at least 4 pro-sclerotic pathways, all of which may facilitate the development of glomerulosclerosis. The loss of filtration surface area from glomerulosclerosis leads to glomerular hypertension and mesangial cell stretch. Mesangial
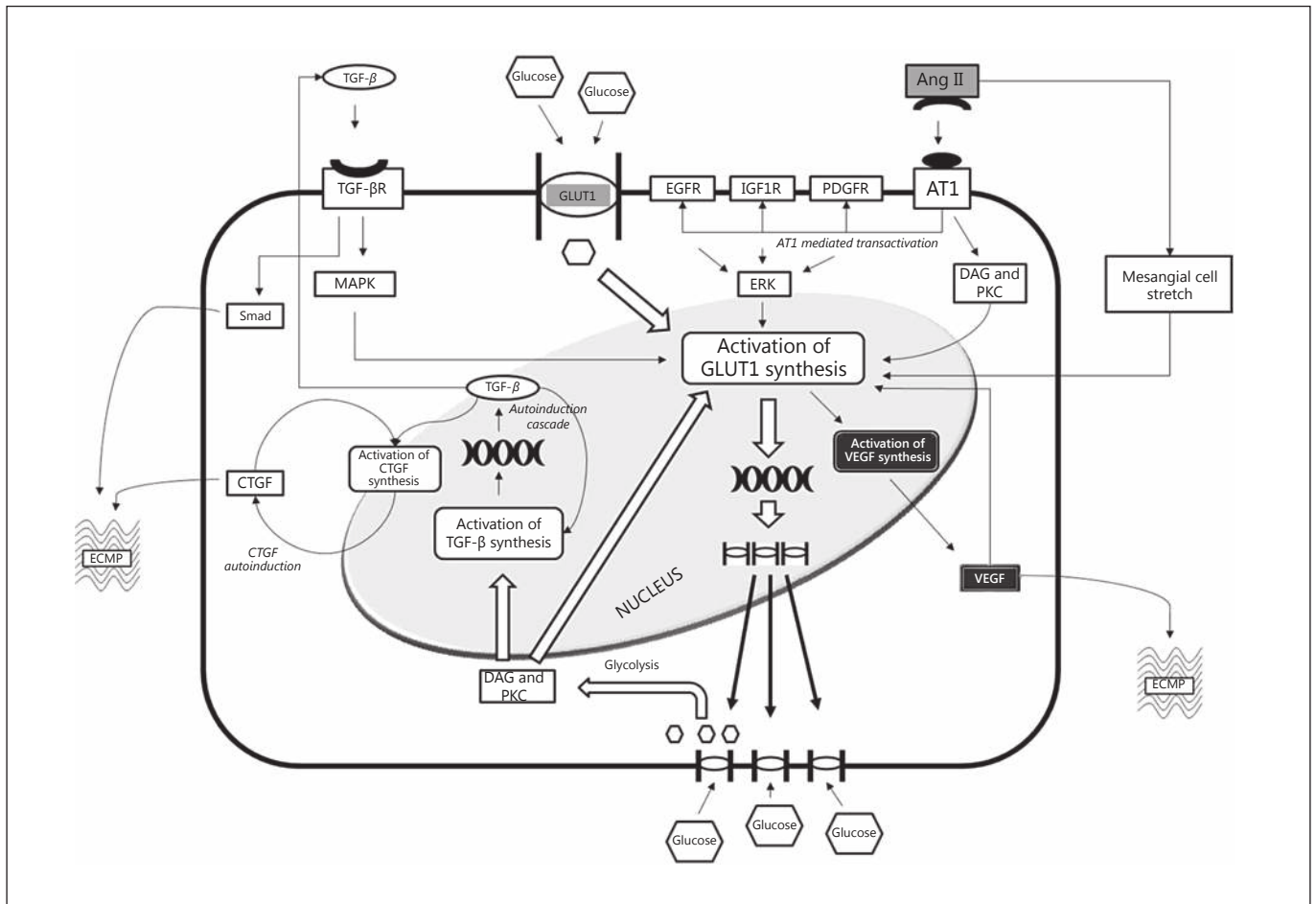
Fig. 2. Summary of pathways interacting with GLUT1. GLUT1 facilitates the movement of glucose into the cell (top and bottom) and triggers GLUT1 synthesis (top). Activation of GLUT1 synthesis is also associated with an increase in VEGF and extracellular matrix protein (ECMP) synthesis (lower right). GLUT1-mediated intracellular transport of glucose increases intracellular glucose availability leading to glucose metabolism via glycolysis, with generation of DAG and activation of PKC, which stimulates TGF-β, as well as more GLUT1 (bottom left). TGF-β-mediated events include an autoinduction cascade, activation of the highly pro-fibrotic cytokine CTGF, and engagement of the TGF-β receptor, triggering more GLUT1 synthesis through MAPK, as well as ECMP synthesis via Smads. Ang II (top right) induces mesangial cell strain and GLUT1 synthesis. In addition, Ang II engagement of the AT1 receptor triggers DAG/PKC, and additional GLUT1 synthesis. AT1 binding also is associated with transactivation of the EGFR, IGF-1R and PDGFR, all of which may trigger ERK and more GLUT1 synthesis.

stretch triggers GLUT1 synthesis and expression, effectively defining a GLUT1 self-expression loop that promotes glomerulosclerosis. Hyperglycemia also upregulates GLUT1 expression, initiating and constantly stimulating this amplification cascade.

Cytokines and growth factors promoting the development of glomerulosclerosis may activate the GLUT1 amplification cascade at numerous levels, thus invoking this parallel pro-sclerotic pathway. In many cases, the recruitment of GLUT1-mediated pathways may intensify or augment fibrotic events directly stimulated by a given cytokine or growth factor, making GLUT1 a strong co-mediator of diabetic glomerulosclerosis in this setting. This stance is supported in recently developed transgenic mouse models in which diabetic glomerulosclerosis was the pathologic result in nondiabetic mice overexpressing GLUT1, and raises interesting questions about a more global role for GLUT1 in the pathogenesis of glomerulosclerosis (summarized in fig. 2).

Finally, the role of GLUT1 as a mediator of glomerulosclerosis, and as a potential therapeutic target, will be further elucidated as pharmacologic inhibitors of GLUT1

are developed. In this regard, naturally occurring flavones as well as synthetic tyrphostins have been recently shown to inhibit GLUT1 through distinct mechanisms [89]. Continued work in this area will likely generate compounds of therapeutic potential in the treatment of GLUT1-driven glomerulosclerosis.

In summary, GLUT1 may act in concert with cytokines and growth factors, in some cases in positive feedback fashion, to mediate development of diabetic glomerulosclerosis. Defining the role of GLUT1 in facilitating these pro-sclerotic events may give new insights for the therapy and management of diabetic glomerulosclerosis, and provide strategies for slowing the development and progression of this disease. Recent findings of potential roles for MGF and mTOR in GLUT1-mediated extracellular matrix production provide important avenues for future investigation in this field, as do the findings of potentially important therapeutic roles for angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in suppression of diabetes-induced GLUT1 and glucose uptake in the kidney.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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