Pathogenesis of diabetic nephropathy

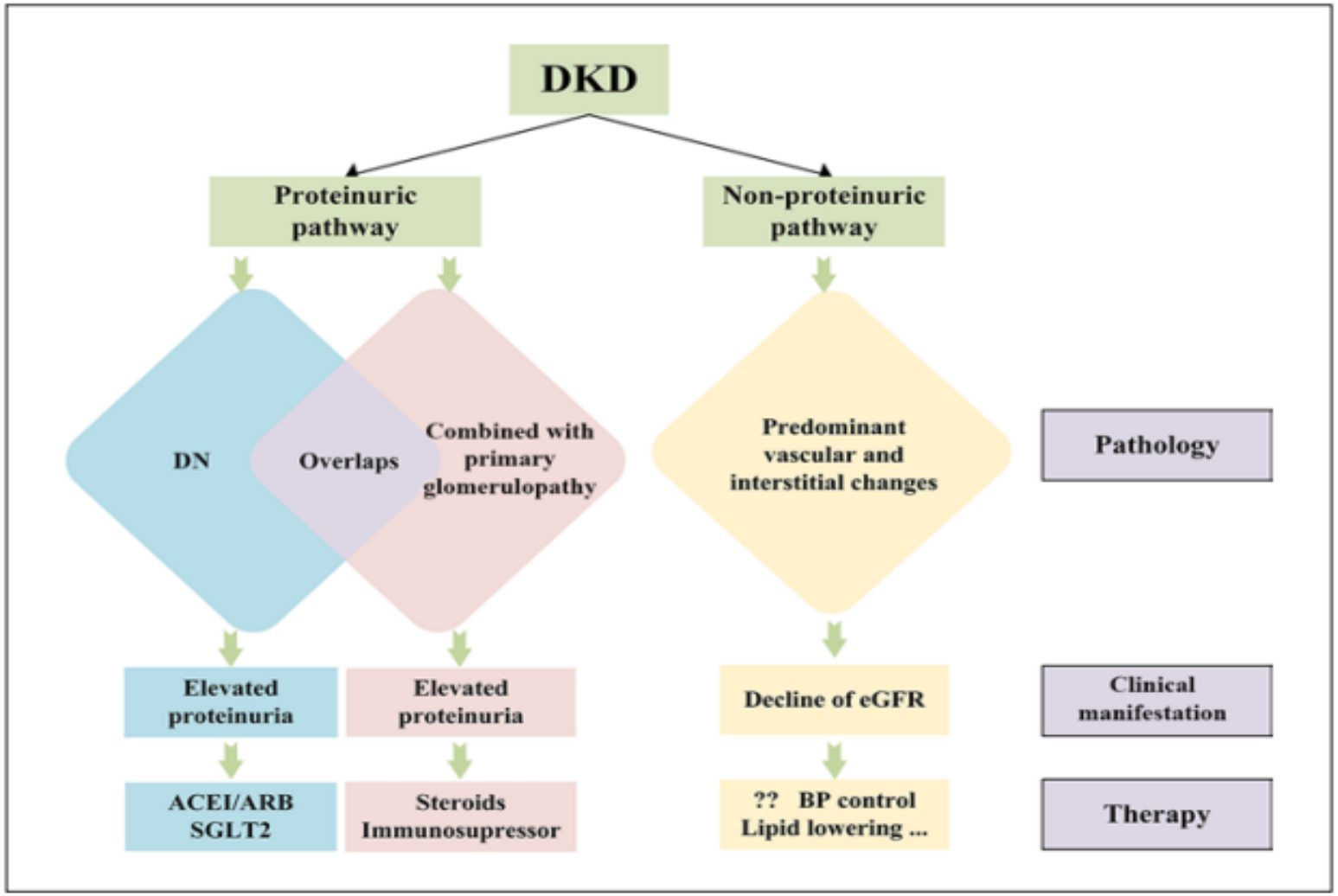
Farzaneh Najafi ,MD

Nephrologist

Associate Professor Of Shahid Sadoughi University Of Medical Sciences-Yazd

Introduction

- DM currently affects more than 463 million people worldwide(9.3%of adults aged 20-79 years),and the number of patients with this is estimated to rise up to 578 million by 2030 and700 million by2045. The number of people with DKD is expected to increase in parallel with the rise in global diabetes prevalence.
- DKD is leading cause of CKD, and additionally is closely associated with heightened cardiovascular risks, including coronary artery disease, heart failure, sudden cardiac death, and increased morbidity and mortality.
- WHO projects that diabetes with be the 7^{th} leading cause of death by 2030.
- Intensively controlling hyperglycemia only modestly reduces the risk of DKD onset or progression in people with long-term diabetes
- Despite treatment, there is substantial residual risk of disease progression with existing therapies. Therefore, there is an urgent need to better understand the molecular mechanisms driving diabetic kidney disease to help identify new therapies that slow progression and reduce associated risks.



Kidney Dis 2020;6:215–225

Pathogenesis

- **The pathogenesis of DKD is intricate**, originating with hyperglycemia, which triggers various mechanisms and pathways: metabolic, hemodynamic, inflammatory, and fibrotic which ultimately lead to renal damage. **Within each pathway, several mediators contribute to the development of renal structural and functional changes. Some of these mediators, such as inflammatory cytokines, reactive oxygen species, and transforming growth factorβ are shared among the different pathways, leading to significant overlap and interaction between them.**

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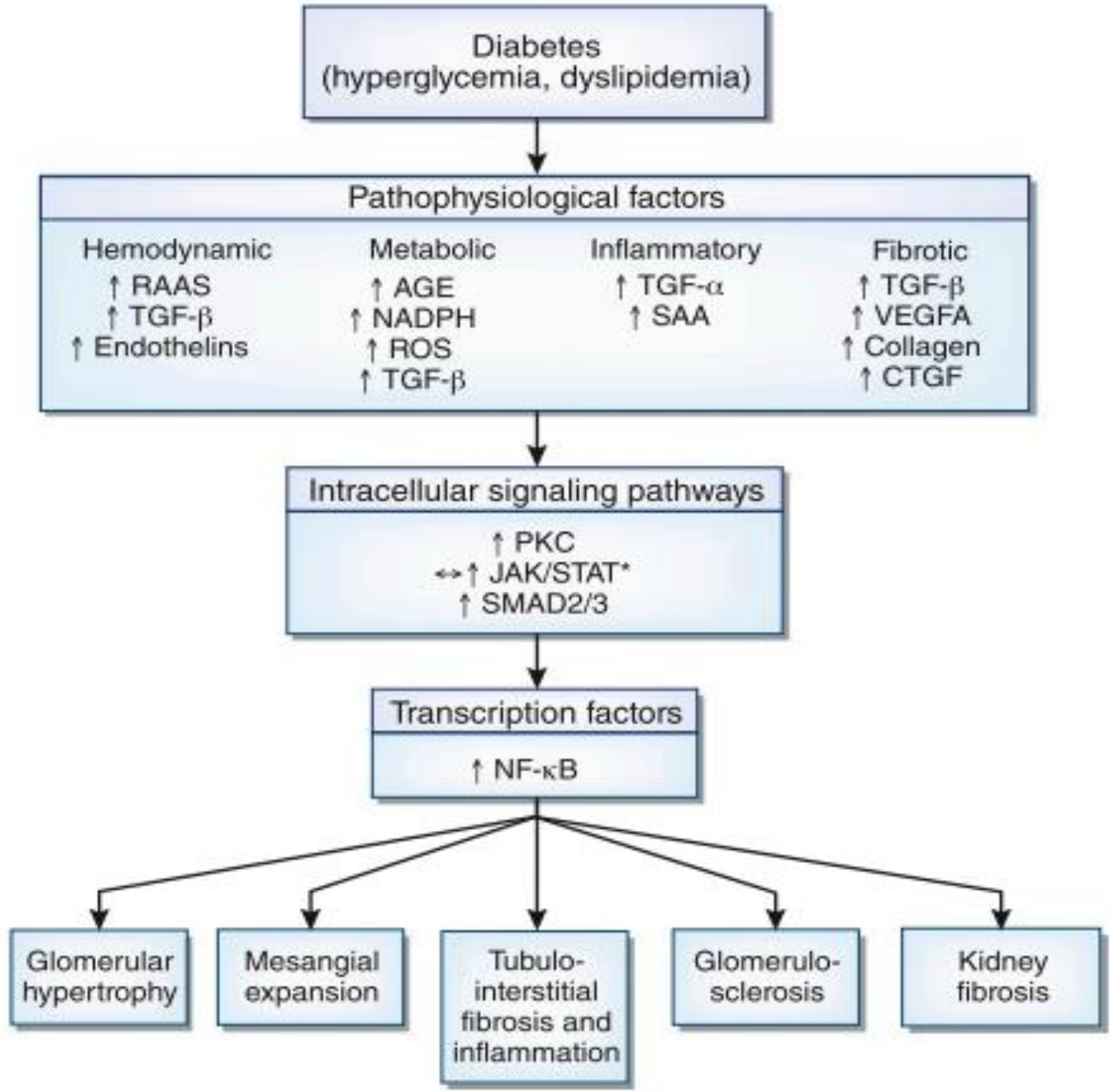
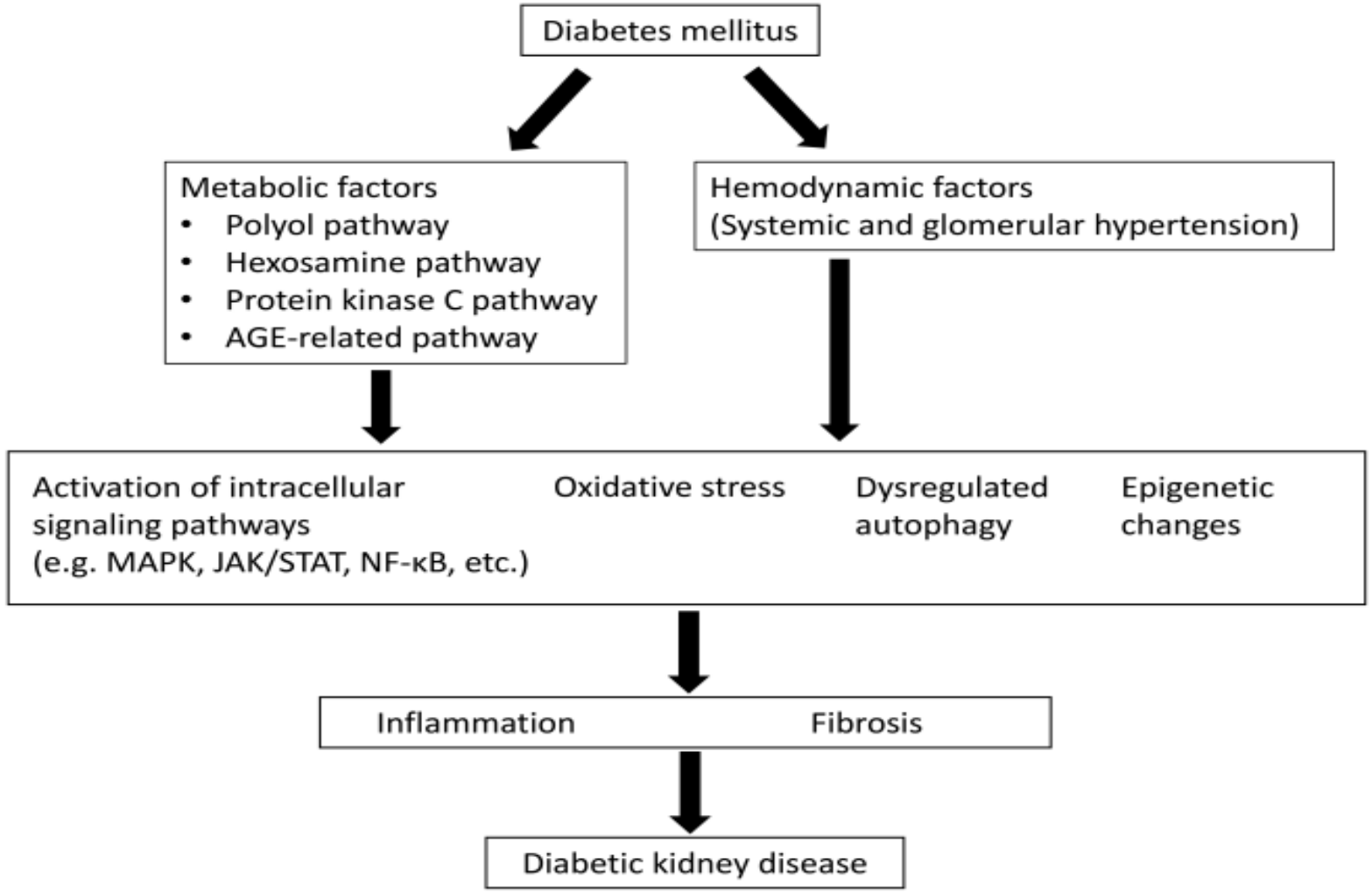


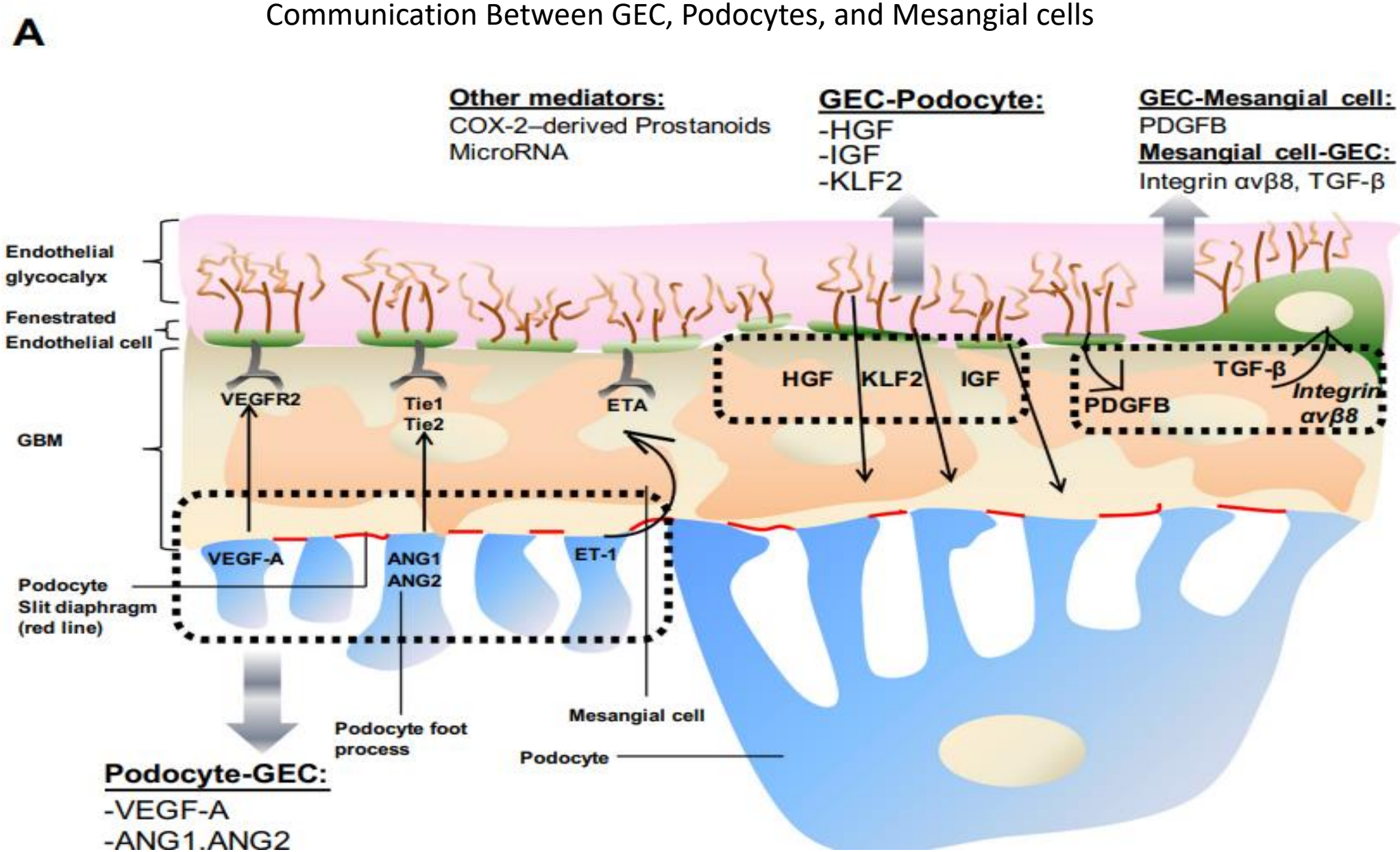
FIGURE 1 The pathogenesis of DKD. Diabetic milieu induces metabolic and haemodynamic abnormalities that trigger a complex network of pathological events. AGE, advanced glycation end-product; DKD, diabetic kidney disease; JAK/STAT, Janus kinase-signal transducers and activators of transcription; MAPK, mitogen-activated kinase; NF-κB, nuclear factor kappa-B



Nephrology. 2021;26:491–500.

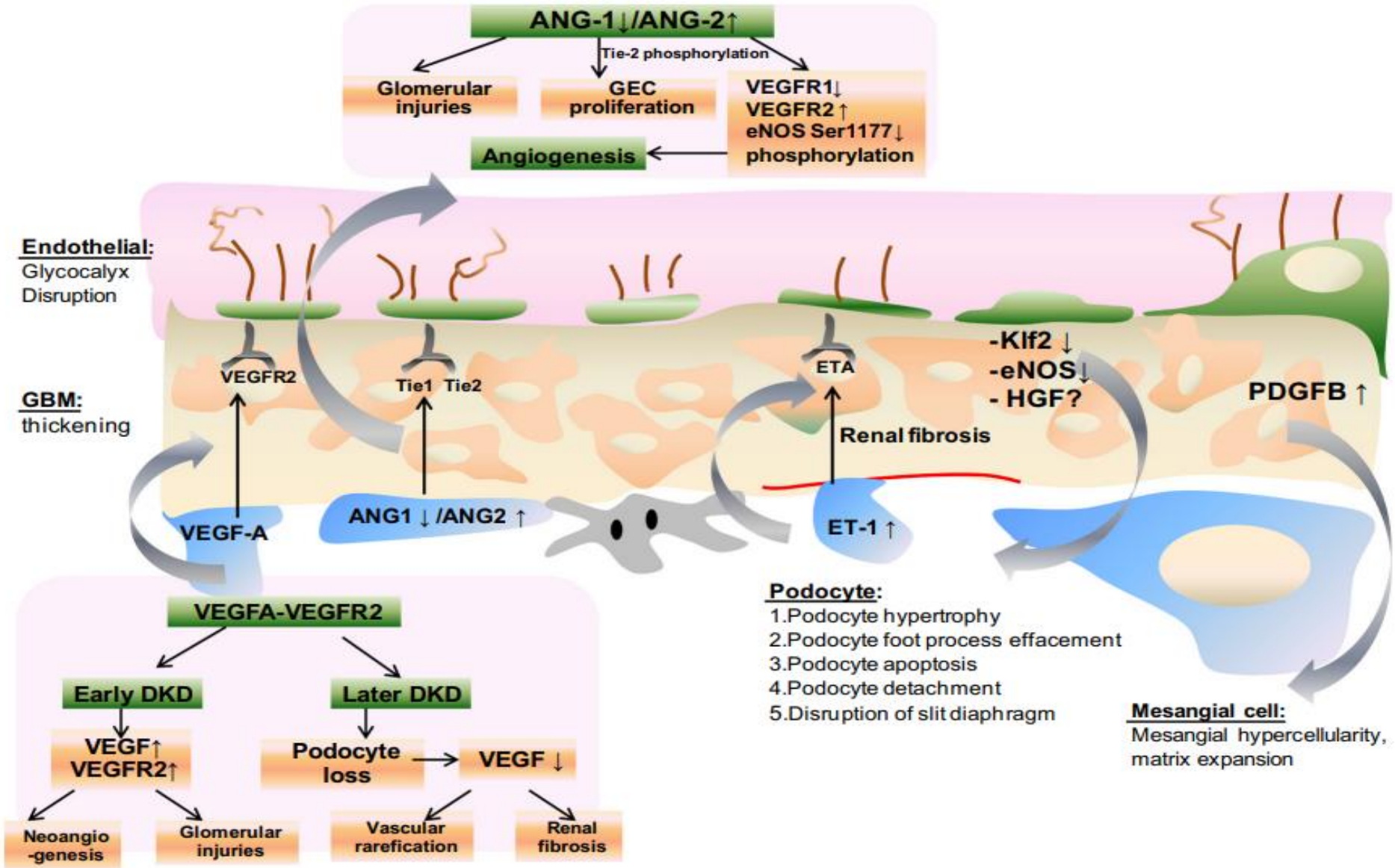
GLOMERULAR ENDOTHELIAL CELL CROSS TALK

Communication Between GEC, Podocytes, and Mesangial cells



The pathological crosstalk among podocytes, GECs, and MCs in DKD

B



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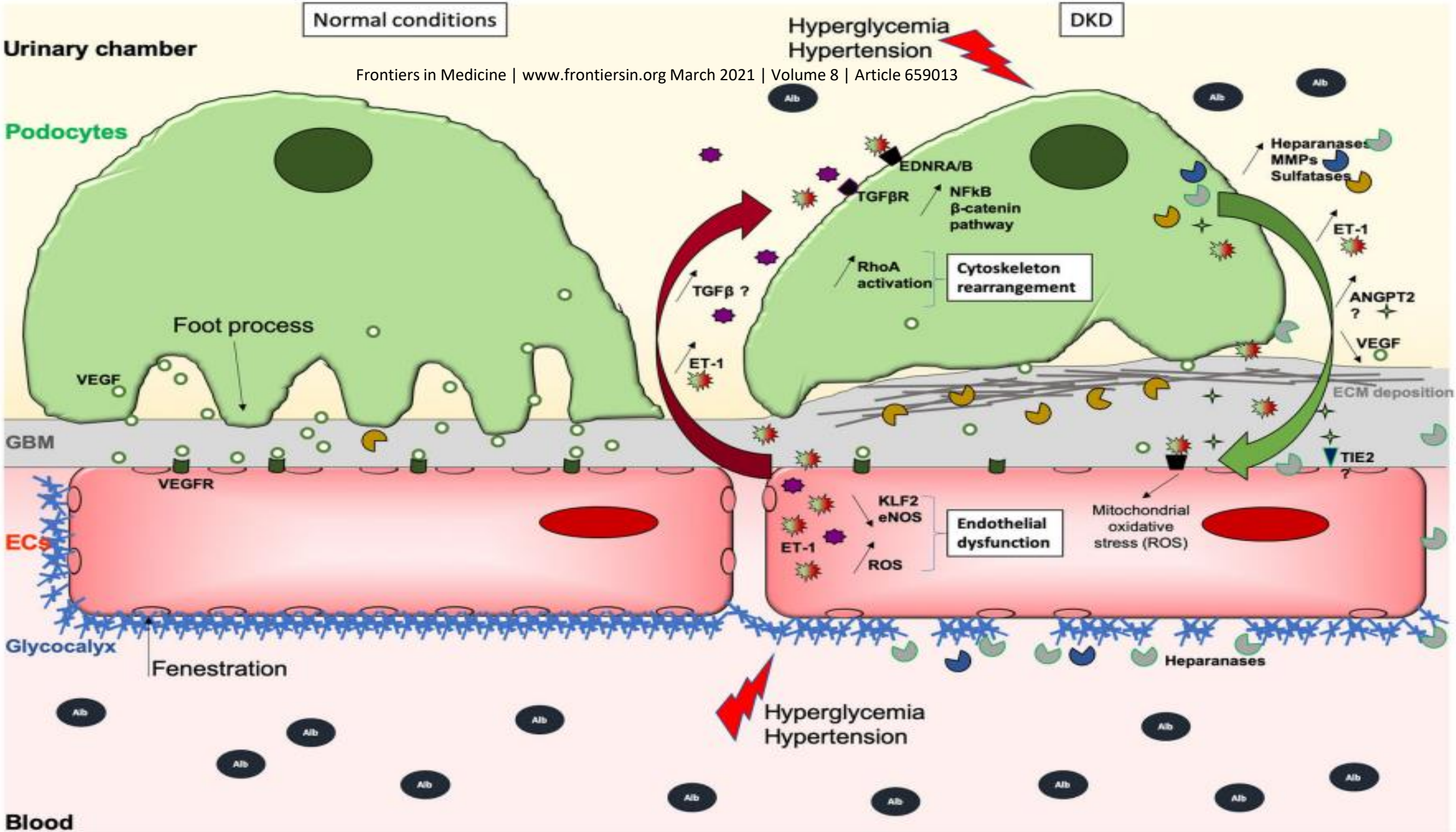
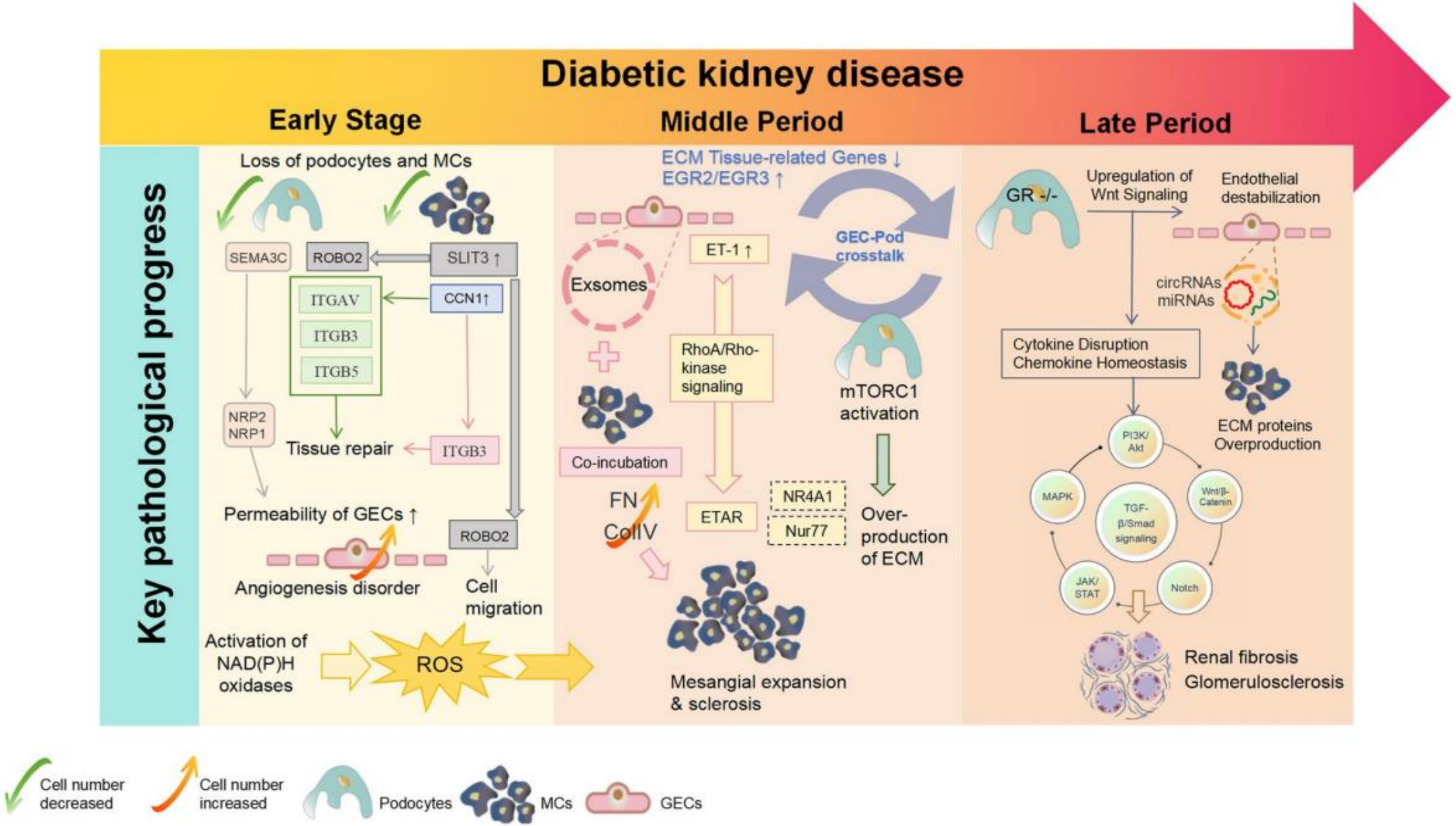



Diabetic kidney disease
Early Stage
Middle Period
Late Period
Key pathological progress
Loss of podocytes and MCs
SEMA3C
ROBO2
SLIT3 ↑
ITGAV
ITGB3
ITGB5
CCN1↑
NRP2
NRP1
Tissue repair
ITGB3
Permeability of GECs ↑
ROBO2
Angiogenesis disorder
Cell migration
Activation of NAD(P)H oxidases
ROS
ECM Tissue-related Genes ↓
EGR2/EGR3 ↑
Exsomes
ET-1 ↑
GEC-Pod crosstalk
RhoA/Rho-kinase signaling
mTORC1 activation
Co-incubation
FN
ColIV
ETAR
NR4A1
Nur77
Over-production of ECM
Mesangial expansion & sclerosis
GR -/-
Upregulation of Wnt Signaling
Endothelial destabilization
circRNAs
miRNAs
Cytokine Disruption
Chemokine Homeostasis
ECM proteins Overproduction
PI3K/ Akt
MAPK
Wnt/β-Catenin
TGF-β/Smad signaling
JAK/ STAT
Notch
Renal fibrosis
Glomerulosclerosis
Cell number decreased
Cell number increased
Podocytes
MCs
GECs

GECs injury in DKD

- Blood glucose levels, Increased oxidative stress, pro-inflammatory activation contribute to the progression of endothelial dysfunction observed in DKD .
- Within the milieu of DKD, signaling pathways governing endothelial nitric oxide synthase (eNOS) activation in GECs undergo alterations, leading to diminished nitric oxide (NO) production and subsequent GEC injury .
- The localized accumulation of excess reactive oxygen species (ROS) within glomerular compartments contributes to glomerular damage, encompassing GEC apoptosis and the attenuation of glomerular glycocalyx expression ,ultimately culminating in albuminuria.
- Under the influence of HG conditions, the process of endothelial-mesenchymal transition (EndMT) in GECs predominantly involves responses mediated by transforming growth factor-beta (TGF-β) signaling pathways The consequence of EndMT in GECs includes the development of albuminuria and fibrosis within the glomeruli, resulting in the disruption of the normal structural and functional integrity of the kidney, ultimately leading to ESRD .

- **In summary, the multifaceted injury observed in GECs in DKD is brought about through various mechanisms, with apoptosis being a predominant factor. Recognizing the signifcance of protecting GECs is crucial for retarding the progression of DKD.**

MCs injury in DKD

- Under various pathological conditions, including high glucose (HG) levels, hyperfiltration, elevated intraglomerular pressure, and advanced glycation end products, MCs transdifferentiate, characterized by the expression of actin and α-smooth muscle actin. . Activation of MCs is closely linked to mesangial expansion and the eventual development of glomerulosclerosis. As mesangium expands, it comes into contact with the inner most regions of the thickened GBM, leading to the detachment of capillaries from the GBM and initiating their collapse.
- Ang II has been implicated in promoting glomerular mesangial expansion. Moreover, Ang II contracts MCs by activating the angiotensin II type 1 receptor (AT1 receptor),and representing a crucial factor in glomerulosclerosis.
- Aldosterone upregulates plasminogen activator inhibitor 1, promotes macrophage infiltration, and mediates the proliferation of MCs and ECM, and contributes to renal fibrosis .
- Tumor necrosis factor-α (TNF-α) and connective tissue growth factor (CTGF) have been implicated in contribute to the progression of mesangial expansion and DKD.
- Recent studies have also shed light on the role of RNA within MCs, with evidence suggesting that miR-422a and miR-15b-5p in DKD not only drive increased matrix production by MCs but also lead to MC apoptosis.
- MCs, along with their associated matrix, constitute the central stalk of the glomerulus, functioning as a part of an integrated unit in close communication with endothelial cells and podocytes .

Podocytes injury in DKD

- In HG conditions, the podocyte's morphological changes will occur, which means the injury of the podocytes. The main morphological and functional changes of podocytes in DKD involve hypertrophy, foot process effacement, epithelial-mesenchymal transdifferentiation (EMT), apoptosis and autophagy.
- Oxidative stress has been established as the underlying cause of podocyte hypertrophy in DKD. Furthermore, increased expressions of factors such as TGF-β1, Angiotensin II (AngII), and mammalian target of rapamycin complex 1 (mTORC1) have been implicated in promoting podocyte hypertrophy in response to HG .
- Podocyte EMT as a potential pathway leading to proteinuria ,with pathways like the Wnt/β-catenin signaling pathway, SDF-1α, and PI3K/AKT signaling pathway being confirmed as promoters of podocyte EMT .
- Podocyte apoptosis can lead to proteinuria and glomerulosclerosis in DKD ,with two pathways, namely, the extrinsic pathway (centered on extracellular ligands such as tumor necrosis factor - TNF) and the intrinsic pathway (centered on mitochondria-mediated mechanisms) identified as contributors to podocyte apoptosis
- Podocyte autophagy, a type II programmed cell death, plays a critical role in the pathogenesis of podocyte loss, leading to extensive proteinuria in DKD .Notably, while podocyte autophagy serves a renoprotective role in early-stage DKD, dysregulation of autophagy occurs in advanced stages, contributing to podocyte injury.

TEC INJURY AND DKD

Compared with GEC lesions, TECs are more closely related to the deterioration of renal function. The manifestations are thickening of the renal tubular basement membrane, tubular inflammatory lesions, renal tubular atrophy, increased apoptosis, interstitial fibrosis and thinning of peritubular capillaries.

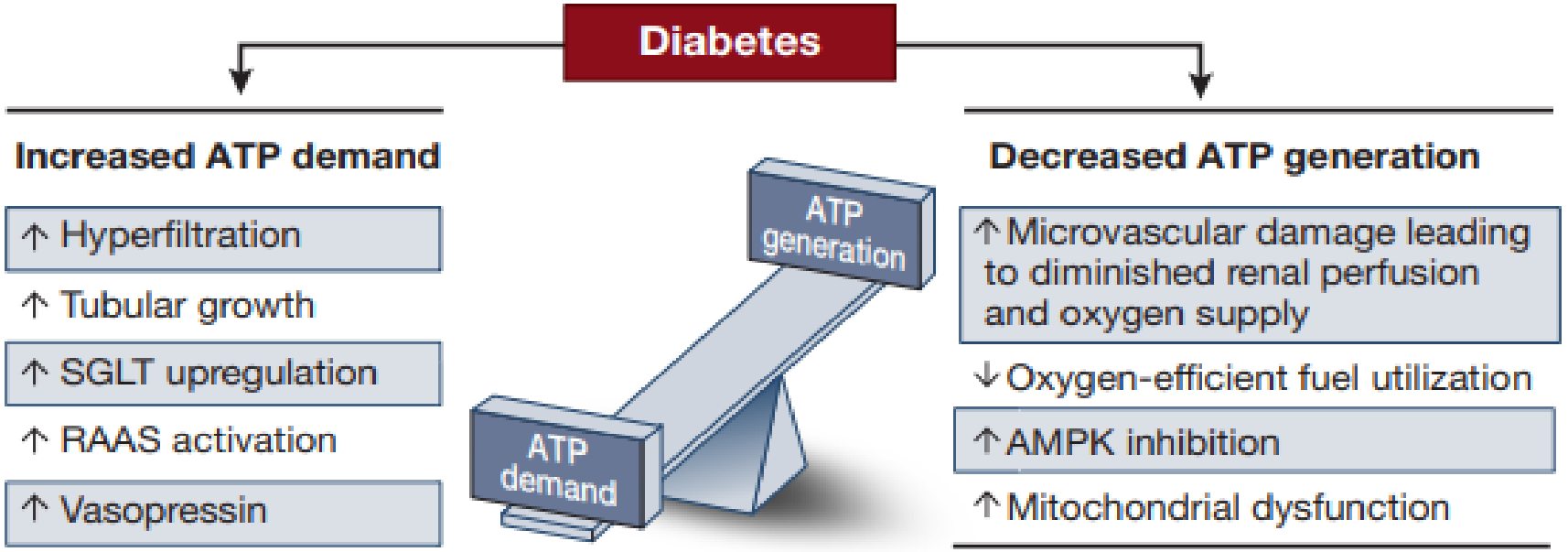
- Various factors, including hyperglycemia, lipid accumulation, oxidative stress, hypoxia, RAAS, ER stress, inflammation, EMT and programmed cell death, have been shown to induce renal tubular injury and contribute to the progression of DKD.

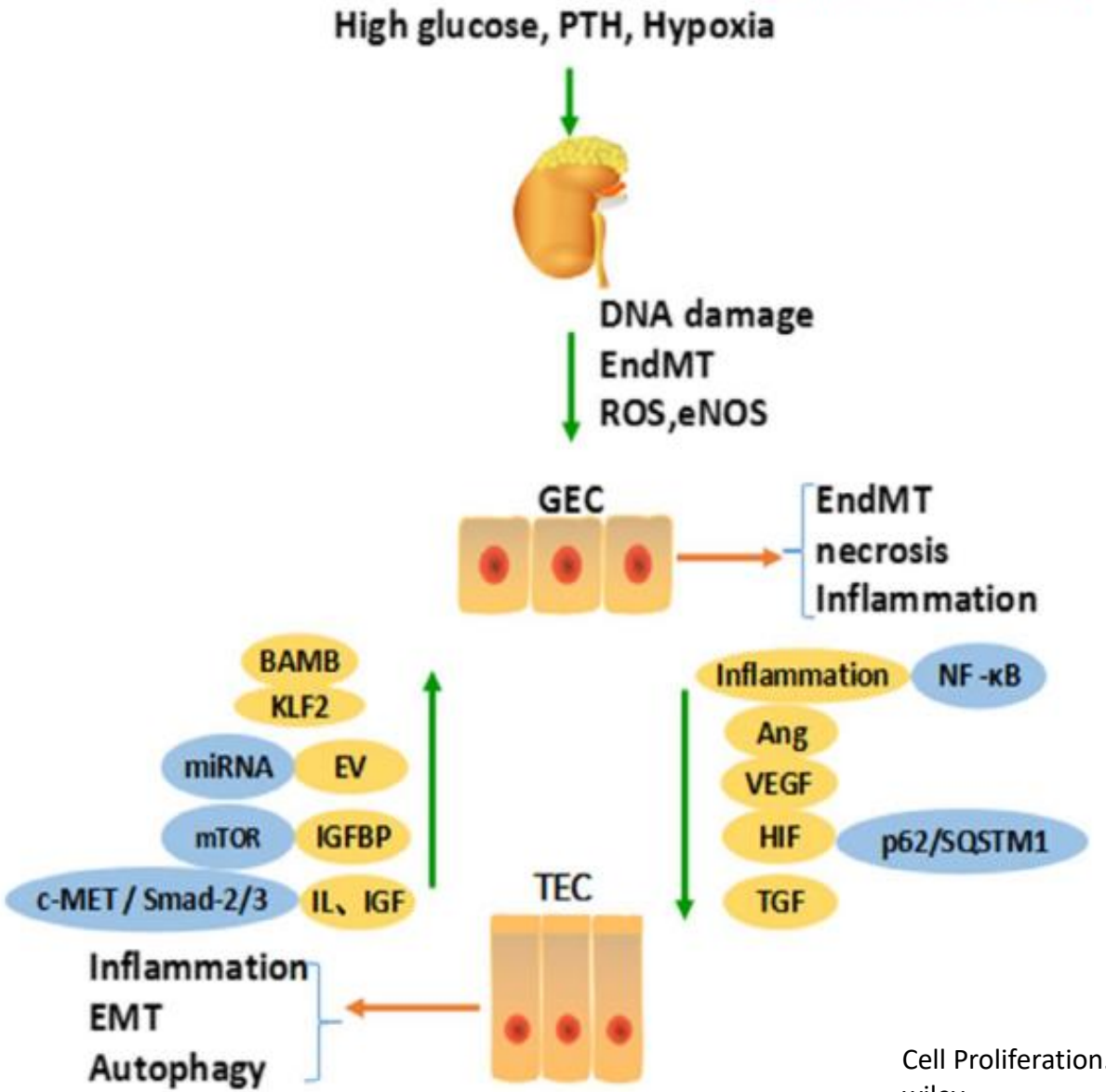
- **Massive proteinuria** in DKD patients causes inflammatory responses, oxidative stress, activation of transforming growth factor-β (TGF-β) and the renin-angiotensin system (RAS) and accumulation of advanced glycation end products (AGEs), resulting in changes in TEC function and morphology, epithelial cell hypertrophy, epithelial-mesenchymal transition (EMT), epithelial cell detachment and apoptosis. Exfoliation and apoptosis of TECs eventually lead to renal fibrosis and promote the progression of DKD to ESRD.
- **mTOR activation** was induced by hyperglycemia was closely associated with proliferation and apoptosis of tubular cells in diabetic nephropathy, while tubular injury was ameliorated after knocking down the mTOR gene in proximal tubular cells.
  (mTOR belongs to the PI3K-related protein kinase family and is a serine/threonine protein kinase.) Medicine (2023) 102:30

The role of renal hypoxia in the pathogenesis of diabetic kidney disease: a promising target for newer renoprotective agents including SGLT2 inhibitors?

Anne C. Hesp[1], Jennifer A. Schaub[2], Pottumarthi V. Prasad[3,4], Volker Vallon[5], Gozewijn D. Laverman[6], Petter Bjornstad[7,8] and Daniël H. van Raalte[1,8]

Kidney International (2020) 98, 579–589





During the occurrence of DKD, abnormal secretion of vascular endothelial growth factor (VEGF),angiopoietin-1 (Ang-1) and inflammatory factors and hypoxia promotes injury to GECs. Moreover, injured GECs secrete hepatocyte growth factor (HGF), insulin-like growth factor binding proteins (IGFBPs), extracellular vesicles (EVs) and Kruppel-like factor (KLF), and autophagy can also act on TECs, causing changes in the structure and function of TECs to different degrees.

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EDITED BY
Zongli Diao,
Capital Medical University, China

REVIEWED BY
Xuefei Tian,
Yale University, United States
Mary L Taub,
University at Buffalo, United States

*CORRESPONDENCE

Tubular injury in diabetic kidney disease: molecular mechanisms and potential therapeutic perspectives

Yu Wang[1,2†], Mingyue Jin[1†], Chak Kwong Cheng[3*] and Qiang Li[1*]

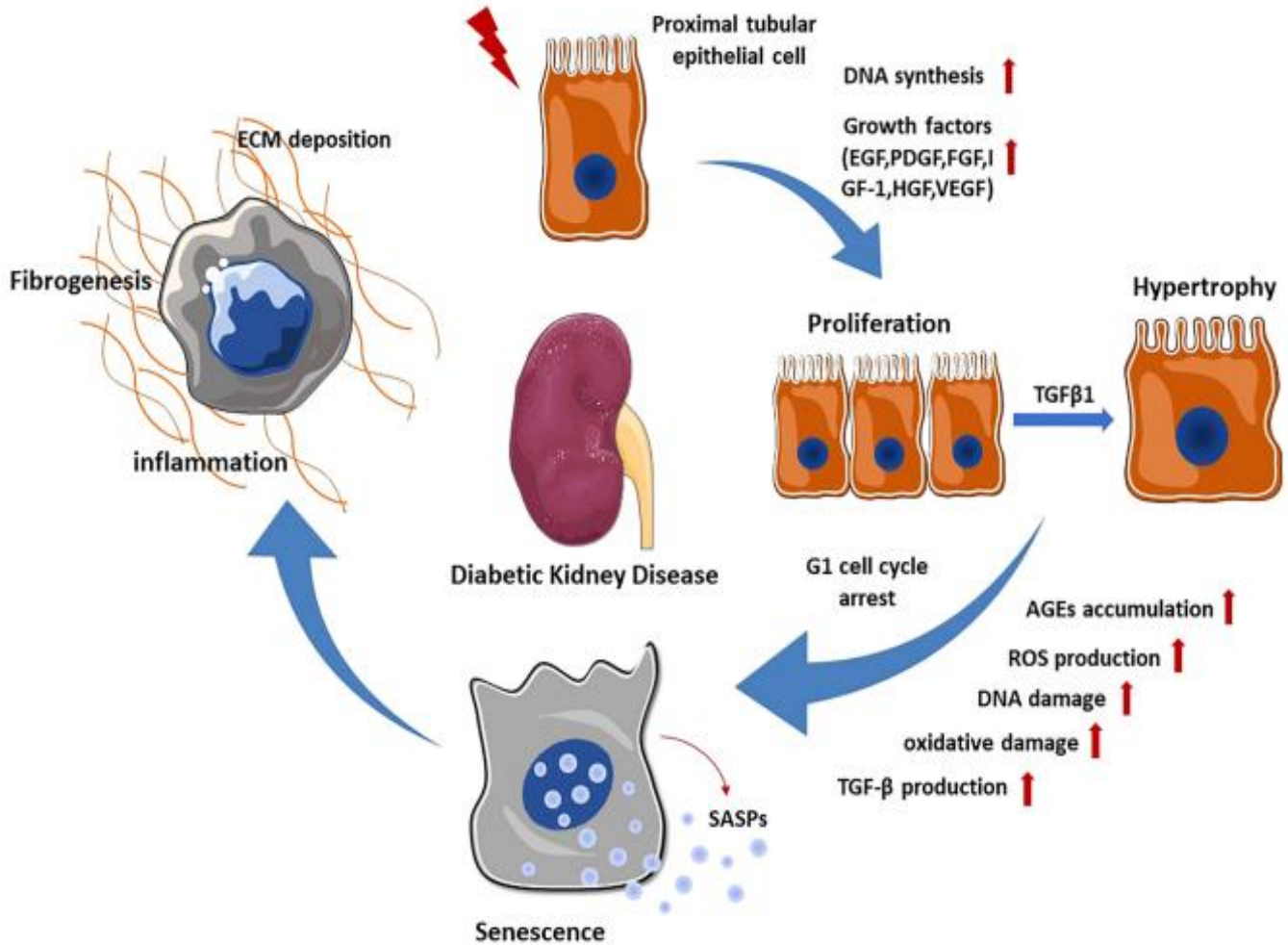
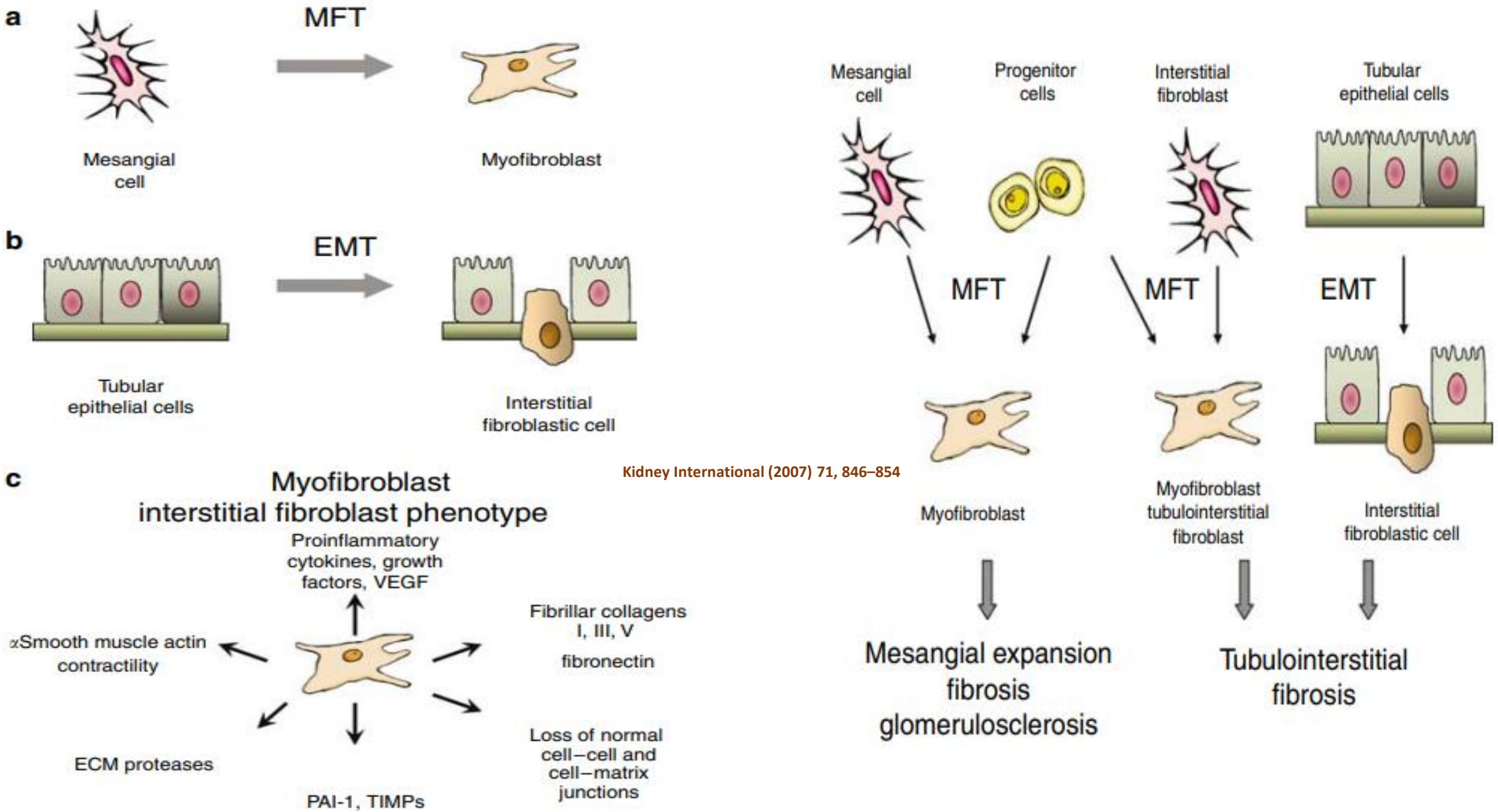
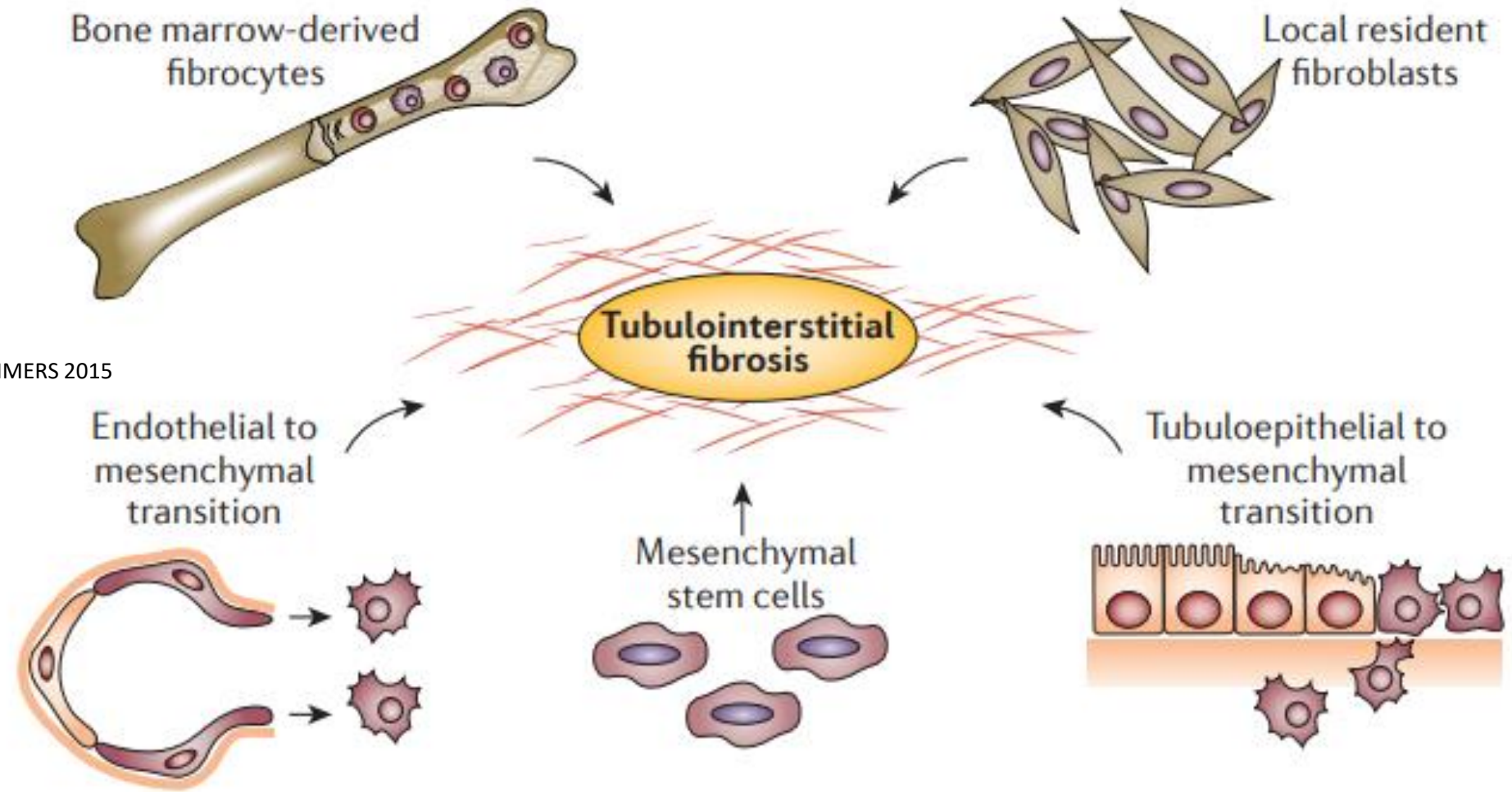


FIGURE 1
Renal tubular epithelial cell changes in DKD. When exposed to various stimuli, PTECs express and secrete multiple growth factors, which promote the proliferation of PTECs. Subsequently, TGF-β1 stimulates the transformation of PTECs from proliferation to hypertrophy through ERK and P38 pathway. In order to prevent excessive proliferation, PTECs undergo G1 cell cycle arrest and transition to senescence. Senescent PTECs can secrete SASPs, promoting renal inflammation and fibrosis.



Kidney International (2007) 71, 846–854

Cellular contributors to myofibroblast recruitment and subsequent tubulointerstitial fibrosis in DKD



NATURE REVIEWS | DISEASE PRIMERS 2015

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Inflammatory Cytokines in Diabetic Kidney Disease: Pathophysiologic and Therapeutic Implications

Javier Donate-Correa[1,2†], Carla M. Ferri[1,3†], Fátima Sánchez-Quintana[1,3], Atteneri Pérez-Castro[1], Ainhoa González-Luis[1], Ernesto Martín-Núñez[1,2,3], Carmen Mora-Fernández[1] and Juan F. Navarro-González[1,2,4,5]*

[1] Unidad de Investigación, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain, [2] GEENDIAB (Grupo Español para el Estudio de la Nefropatía Diabética), Sociedad Española de Nefrología, Santander, Spain, [3] Doctoral and Graduate School, University of La Laguna, San Cristóbal de La Laguna, Spain, [4] REDINREN (Red de Investigación Renal-RD16/0009/0022), Instituto de Salud Carlos III, Madrid, Spain, [5] Instituto de Tecnologías Biomédicas, Universidad de La Laguna, Santa Cruz de Tenerife, Spain

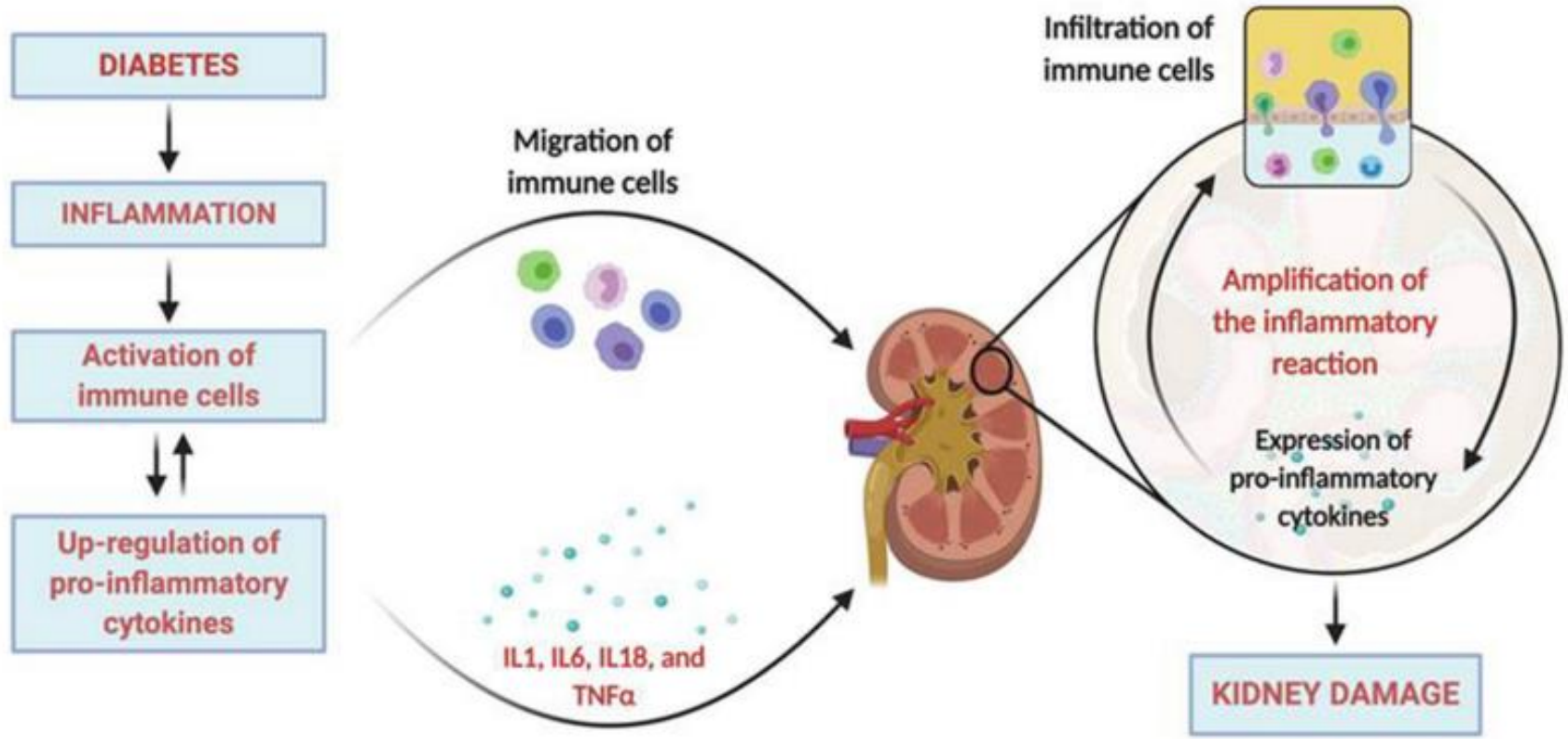

FIGURE 1 | Inflammatory pathophysiology in diabetic kidney disease. The diabetic milieu drives to the development of inflammation that includes the activation of immune cells and the upregulation of pro-inflammatory cytokines. Activated immune cells migrates and infiltrates the renal tissue locally producing more inflammatory mediators and chemokines that recruit more immune cells into the kidney. Moreover, activated resident renal cells can also produce additional proinflammatory mediators, contributing to sustained inflammation, and the induction of kidney damage. Created with BioRender.com.

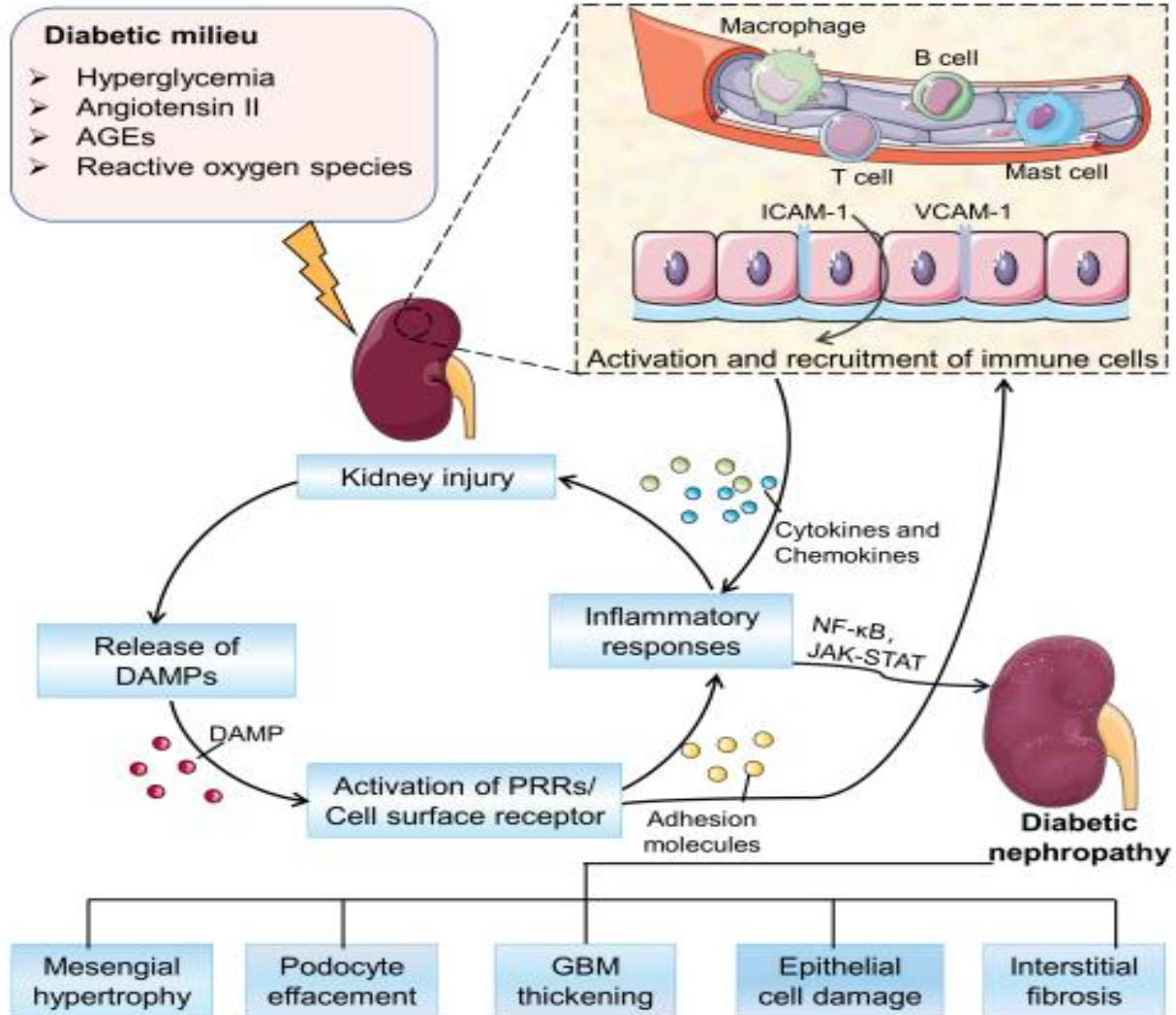

FIGURE 1
Overview of the pathogenesis of DN. In the diabetic milieu, hyperglycemia, advanced glycation end-products (AGEs), angiotensin II, and oxidative stress activate a variety of signaling cascades driving the recruitment and activation of immune cells to promote the development of inflammation and ultimately leading to a series of pathological changes in DN. AGEs, advanced glycation end products; DAMPs, damage associated molecular patterns; PRRs, pattern recognition receptors; GBM, glomerular basement membrane.

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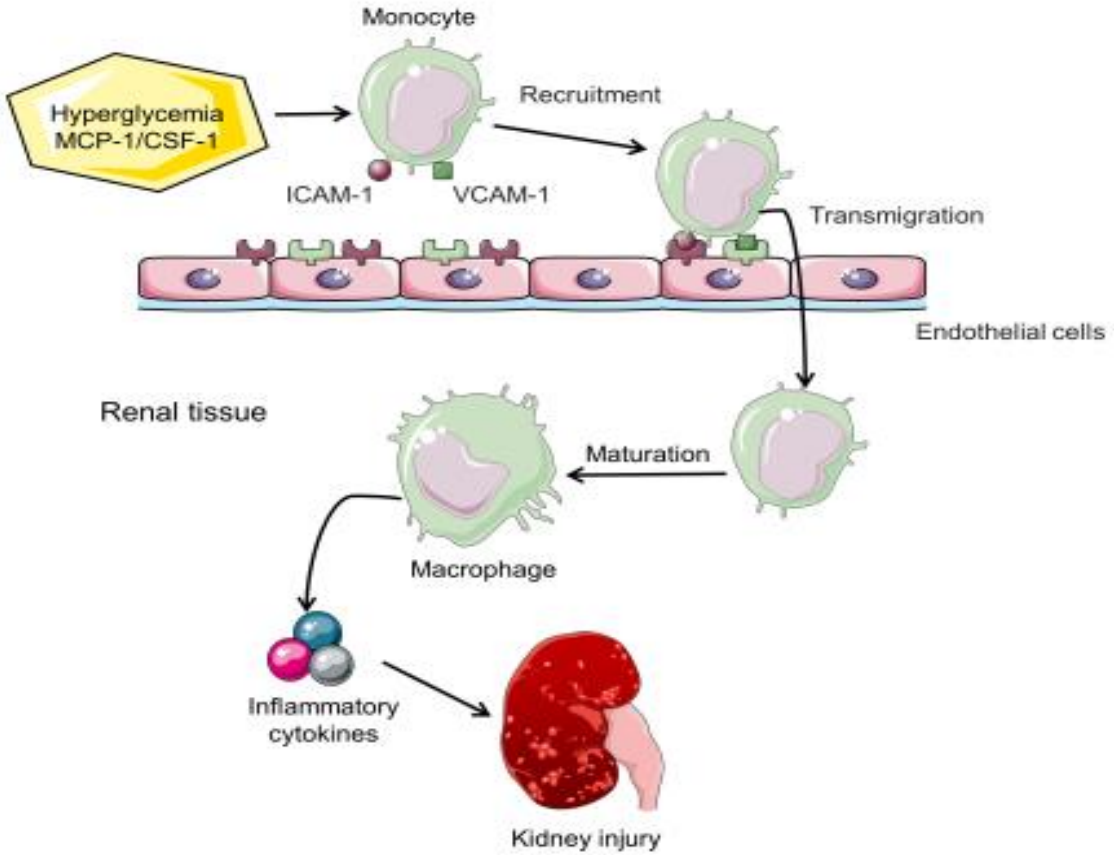

FIGURE 2
Macrophage recruitment and activation in DN. Hyperglycemia induces increased expression of cell adhesion molecules (ICAM-1/VCAM-1) and chemokines (MCP-1/CSF-1), thereby enhancing the recruitment of monocytes to the kidney. Chemokines also promote transendothelial migration. Monocytes mature into macrophages and subsequently release inflammatory cytokines, leading to the progression of DN.

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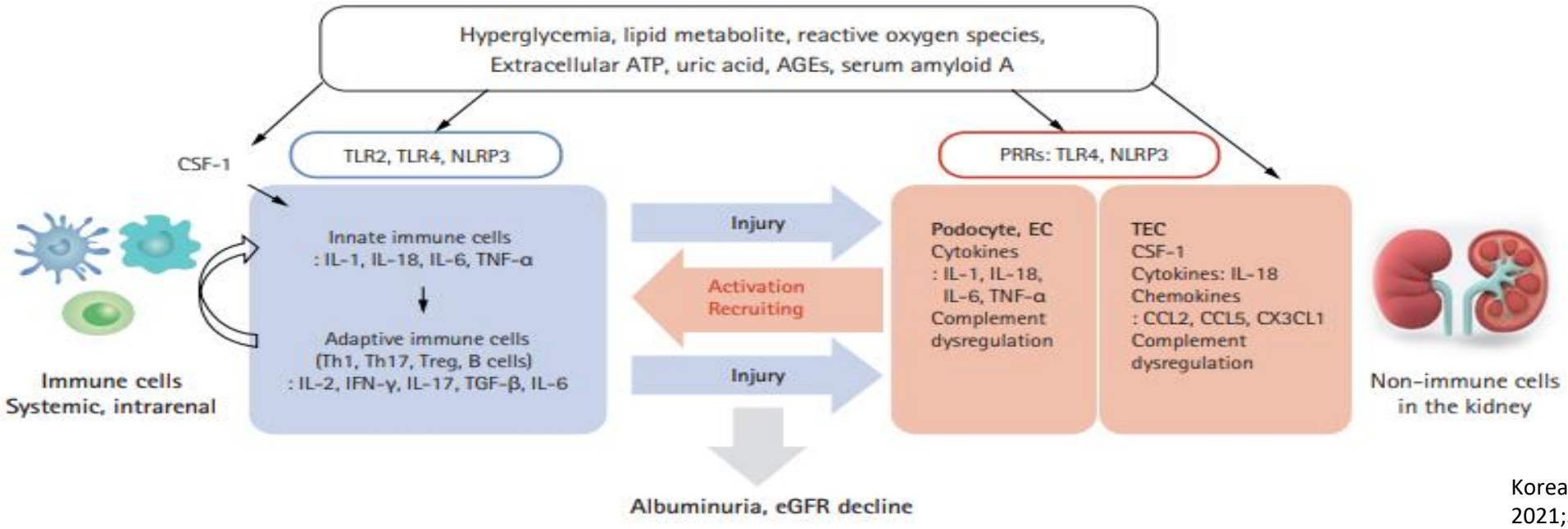
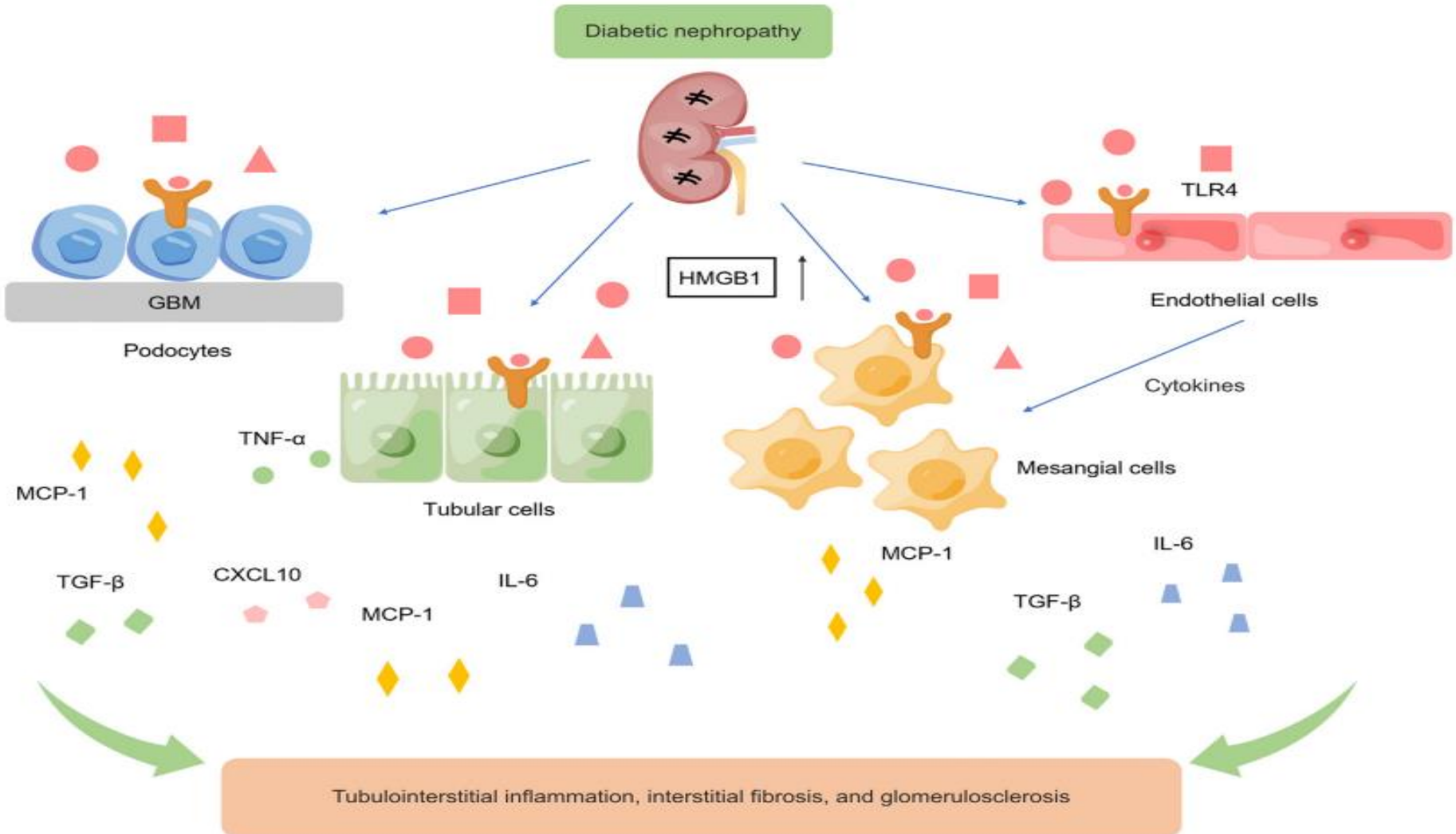
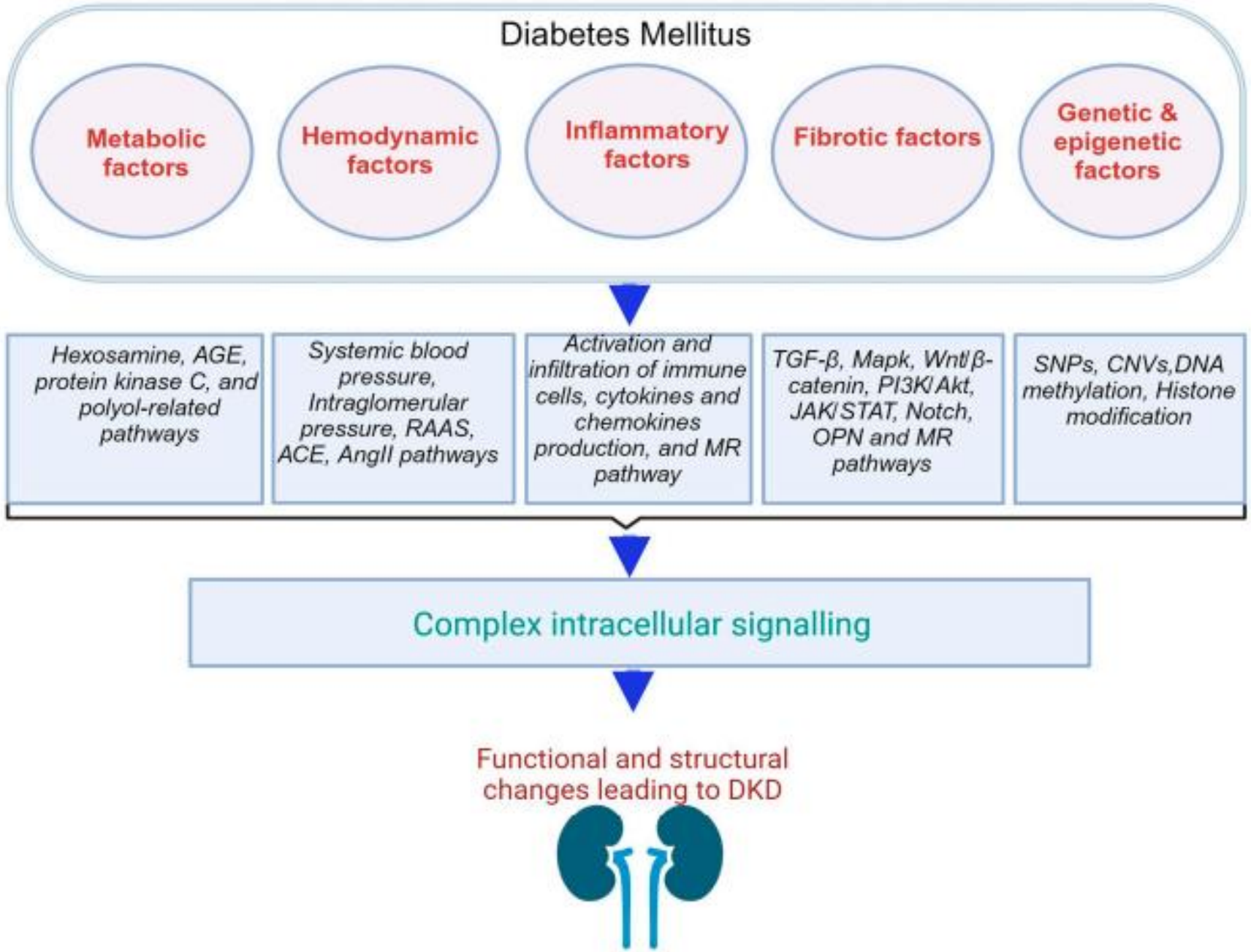


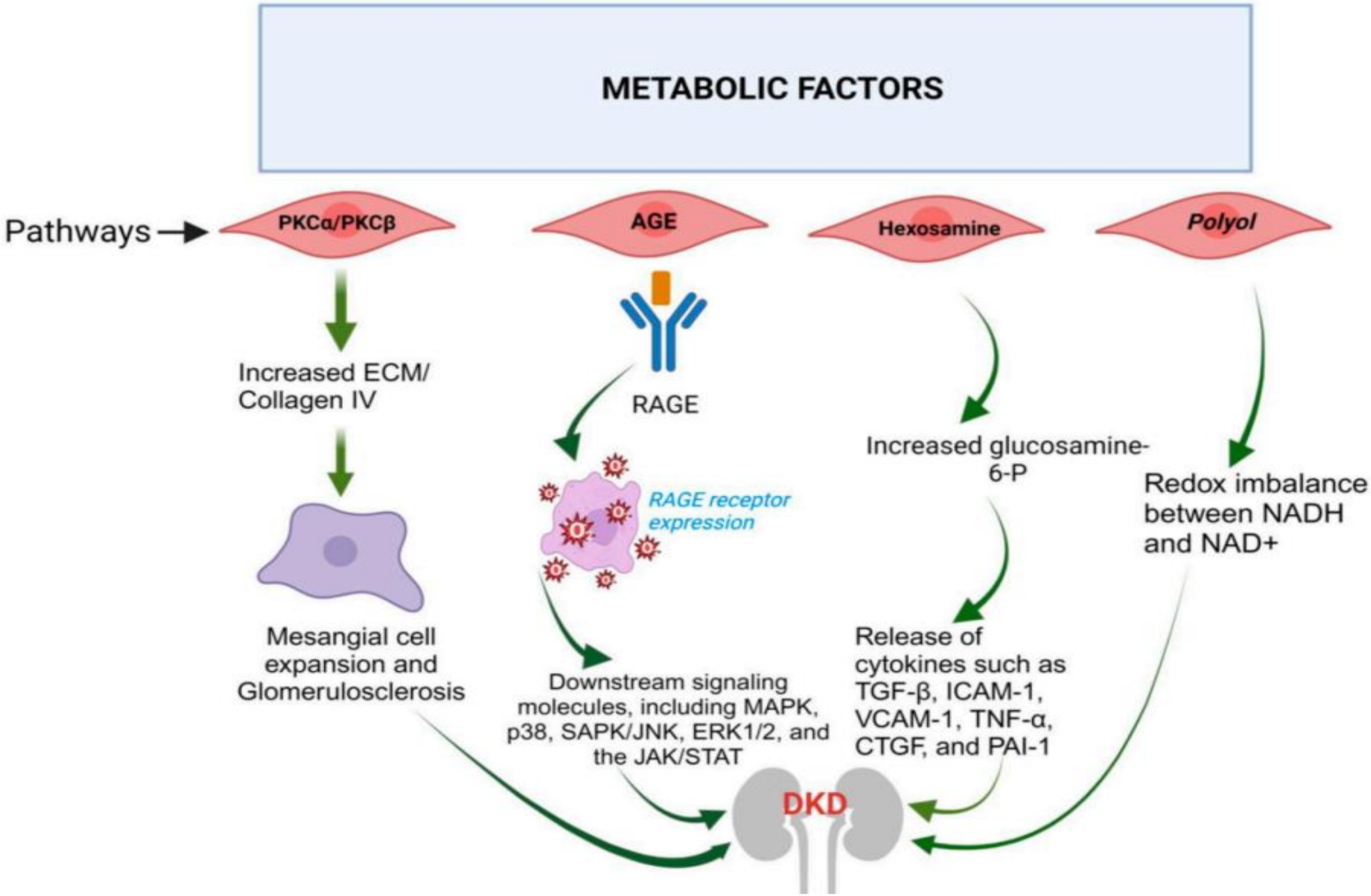
Korean J Intern Med
2021;36:753-766

Figure 1. Activation of Inflammation in diabetic kidney disease. Activation of Inflammation in diabetic kidney disease. Various inflammatory factors such as pattern recognition receptor (PRR), inflammatory cytokines, chemokines, innate immune cells, complement pathways, and adaptive immune cells are linked to activate the immune and inflammatory responses in diabetic kidney disease. ATP, adenosine triphosphate; AGE, advanced glycation end product; CSF-1, colony-stimulating factor-1; TLR, Toll-like receptor; NLRP, nucleotide-binding oligomerization domain-, leucine rich repeat-, and pyrin domain-containing; IL, interleukin; TNF-α, tumor necrosis factor α; IFN-γ, interferon-γ; TGF-β, transforming growth factor-β; EC, endothelial cell; TEC, tubular epithelial cell; CCL, C-C motif chemokine ligand; CX3CL1, C-X3-C motif chemokine 1; eGFR, estimated glomerular filtration rate.

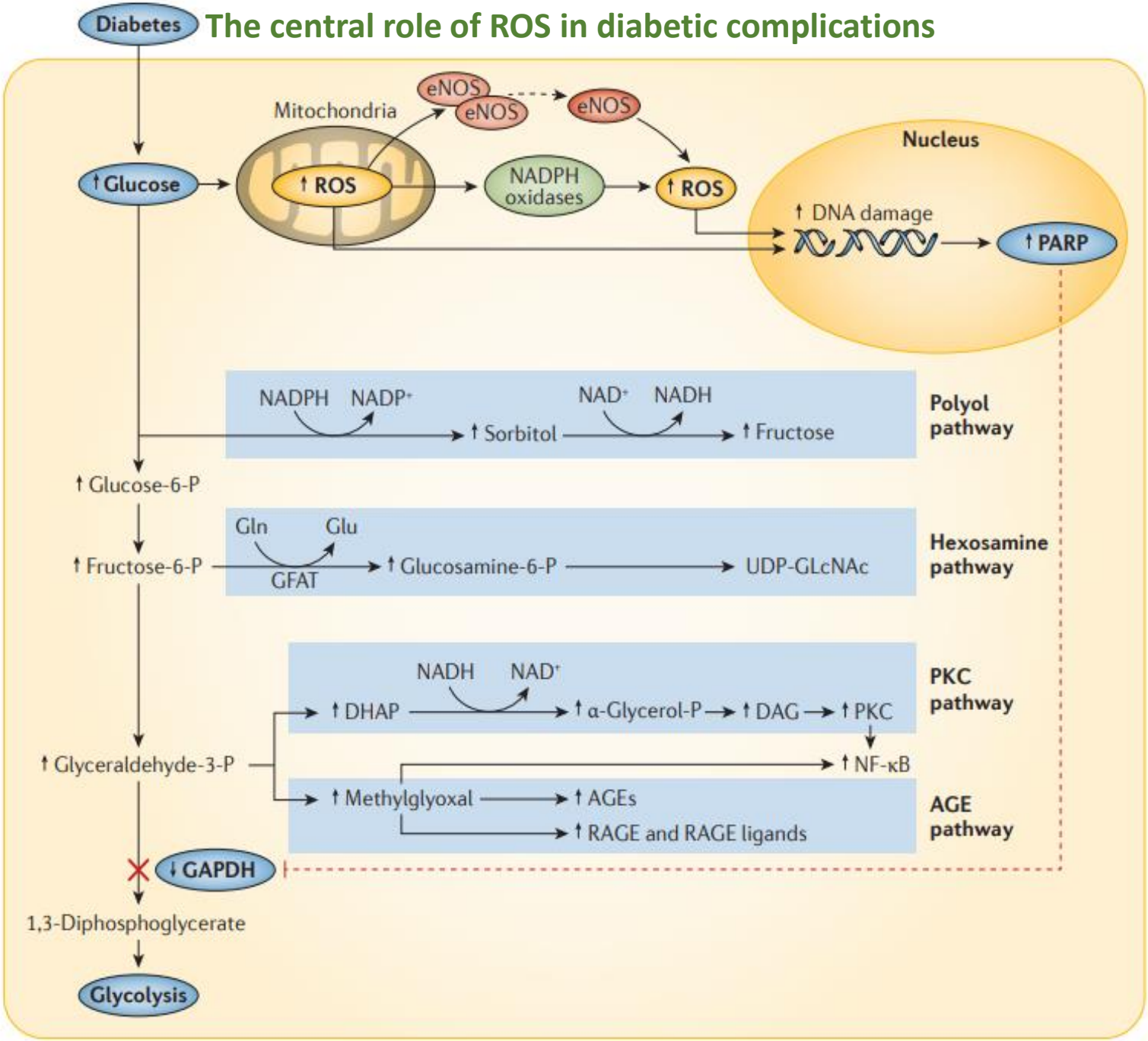

Diabetic nephropathy
TLR4
HMGB1
GBM
Podocytes
Endothelial cells
Cytokines
TNF-α
MCP-1
Tubular cells
Mesangial cells
MCP-1
IL-6
TGF-β
CXCL10
IL-6
MCP-1
TGF-β
Tubulointerstitial inflammation, interstitial fibrosis, and glomerulosclerosis



J. Clin. Med. 2023, 12, 7349


METABOLIC FACTORS
Pathways
PKCα/PKCβ
AGE
Hexosamine
Polyol
Increased ECM/
Collagen IV
RAGE
Increased glucosamine-
6-P
Redox imbalance
between NADH
and NAD+
RAGE receptor
expression
Mesangial cell
expansion and
Glomerulosclerosis
Downstream signaling
molecules, including MAPK,
p38, SAPK/JNK, ERK1/2, and
the JAK/STAT
Release of
cytokines such as
TGF-β, ICAM-1,
VCAM-1, TNF-α,
CTGF, and PAI-1
DKD

The central role of ROS in diabetic complications



Mitochondrial production of reactive oxygen species (ROS) accelerates in response to an increase in intracellular glucose. In addition, pathogenetic ROS are also generated through the ROS-induced uncoupling of nitric oxide synthase (eNOS) and inactivation of NADPH oxidases. ROS can mediate DNA damage, which in turn activates poly(ADP ribose) polymerase (PARP). PolyADP-ribosylation of glyceraldehyde-3-dehydrogenase (GAPDH) by PARP leads to the inhibition of this key glycolytic enzyme and a subsequent bottleneck in glycolysis. As a result, early glycolytic intermediates accumulate and are then diverted into pathogenetic signalling pathways.

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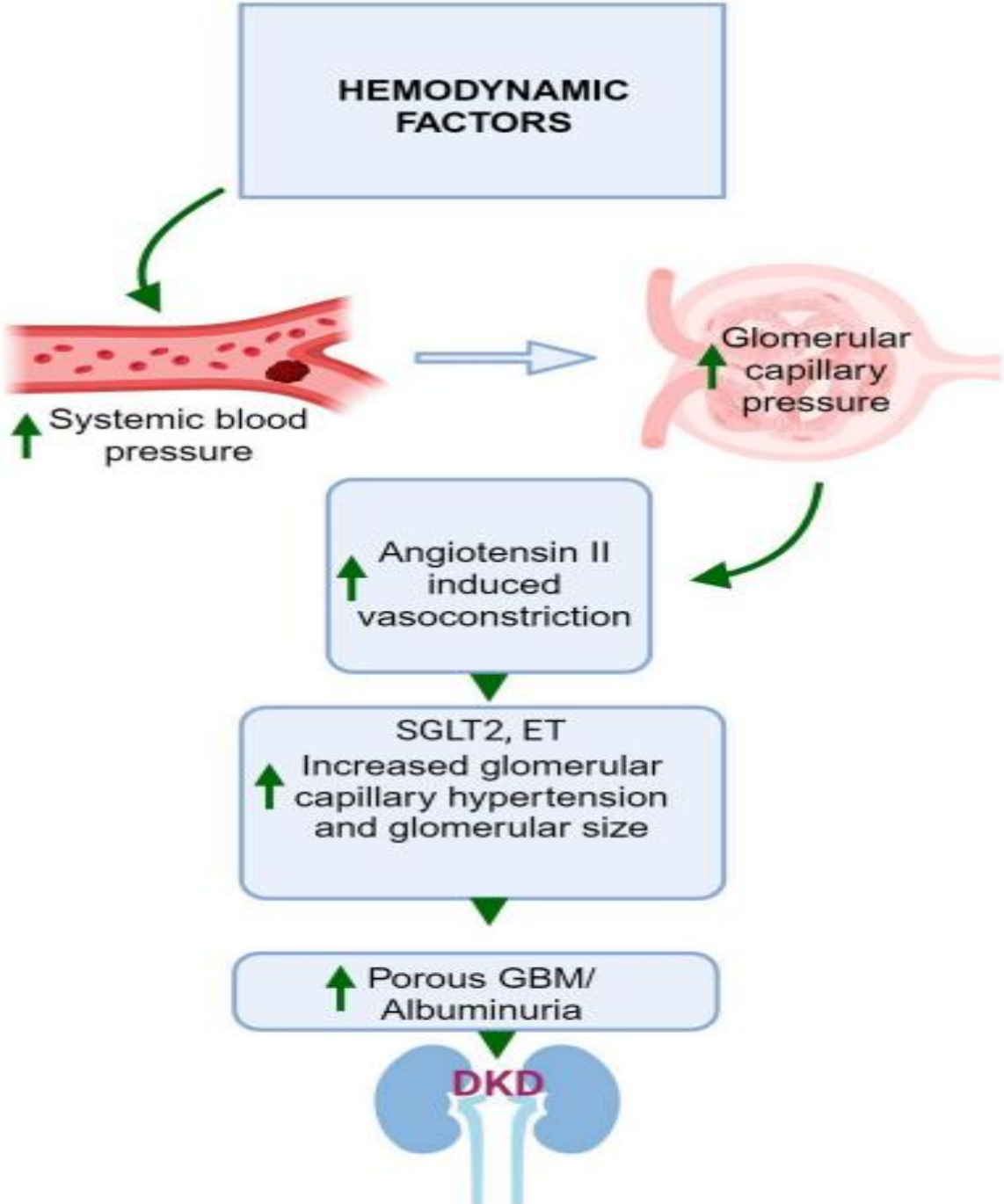
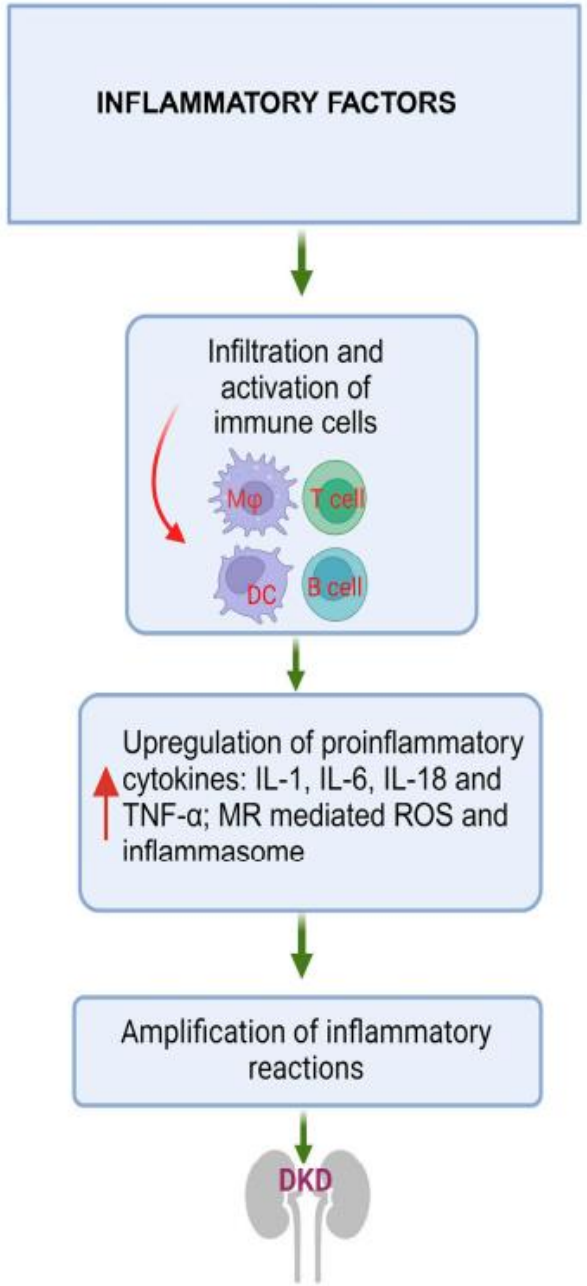


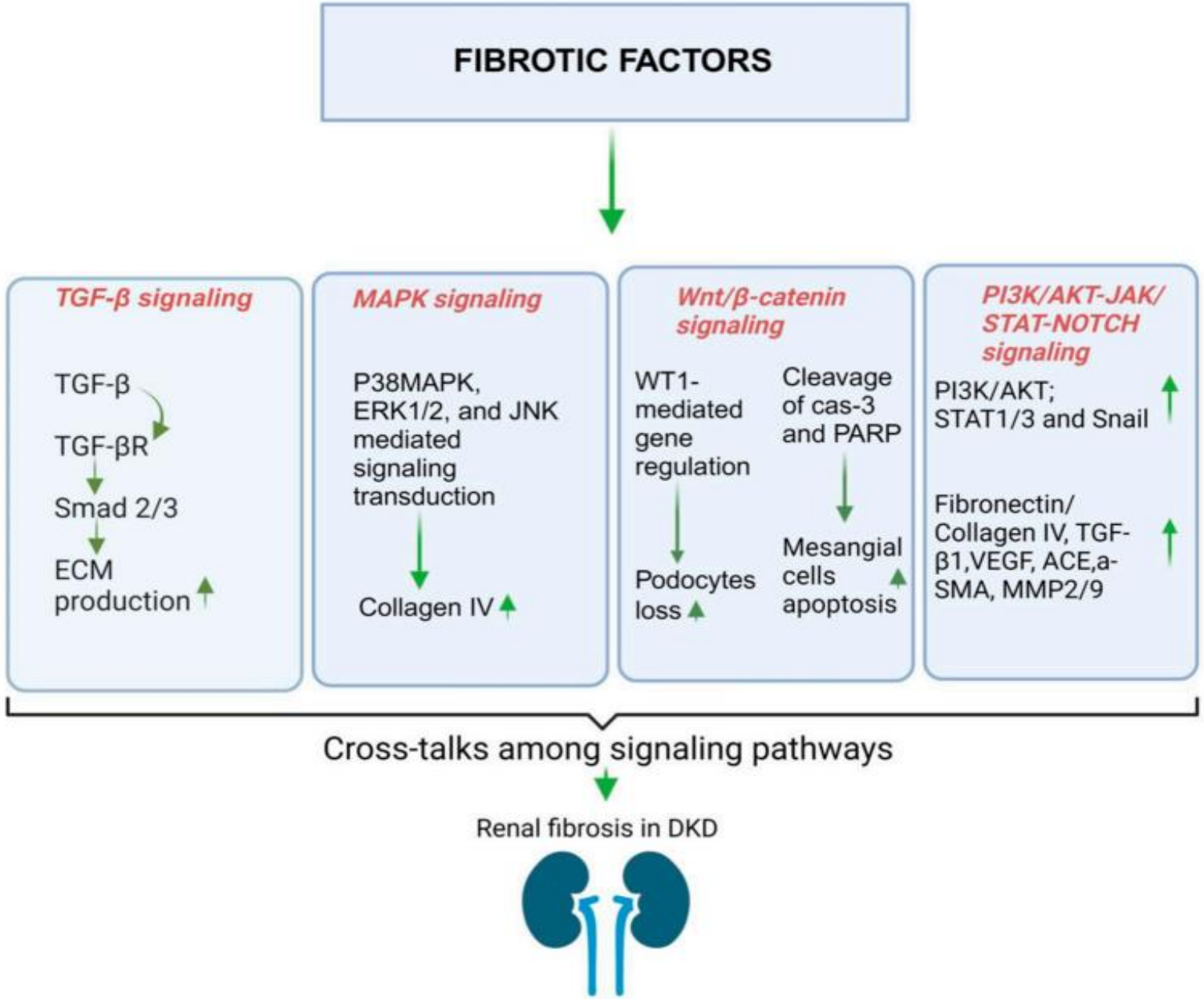
J. Clin. Med. 2023, 12, 7349

Inflammation serves as a cross road in its pathogenesis. DM initiates inflammatory processes mediated by several factors like oxidative stress, AGEs, obesity, ischemia, and cellular damage..

Moreover, the activation of the complement system significantly influences the progression of DKD. The activation of the complement system in DKD has been linked to mannose-binding lectins and the ficolin-associated activation of the lectin pathway within the complement cascade. Hyperglycemia results in higher levels of glycan and galactosamine-bound substances that are recognized by these receptors, leading to complement activation.

Ongoing research may yield new complement inhibitors that offer benefits to DKD patients; however, careful monitoring is crucial to evaluate any impact on susceptibility to infections or immune complex diseases.

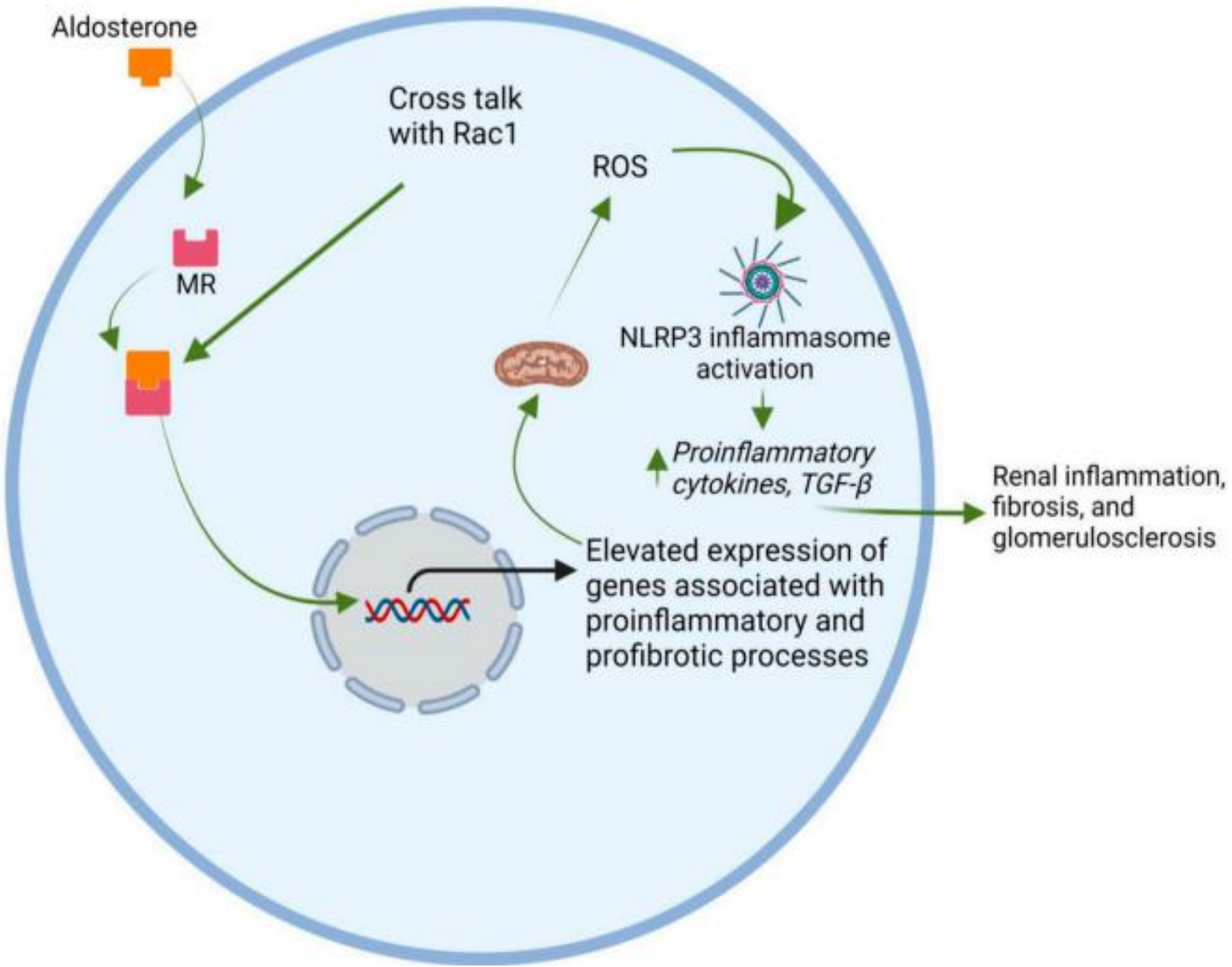




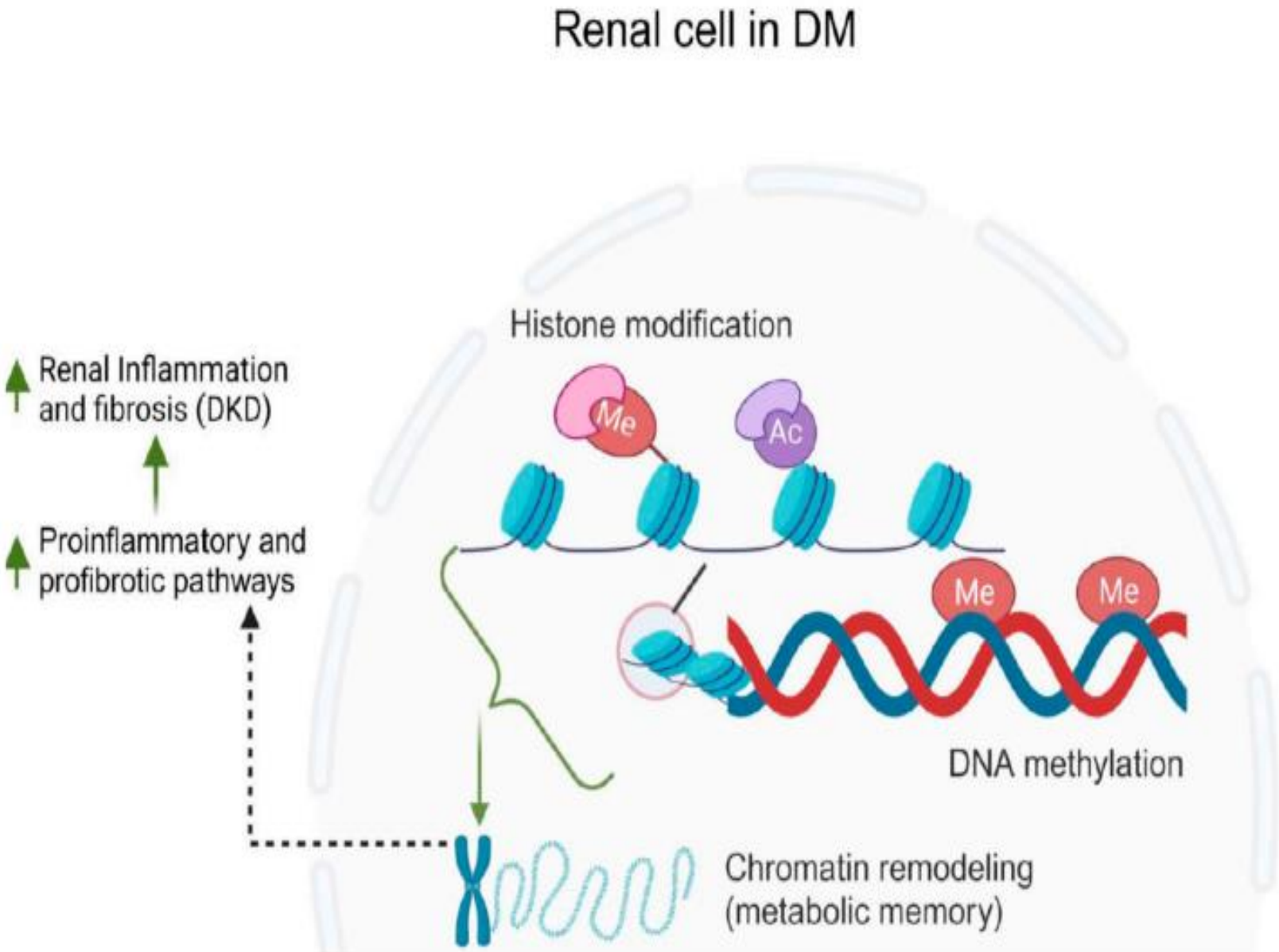
Renal fibrosis refers to an excessive buildup of ECM in the kidney, which can manifest as either glomerulosclerosis or tubulointerstitial fibrosis .The main components of this fibrotic ECM consist of collagens I and III, known as fibrillar collagens, fibronectin along with glycoproteins and proteoglycans .The extent of fibrosis is closely linked to the decline in renal function and the progression towards ESRD.

Myofibroblasts play a pivotal role in facilitating ECM deposition due to their robust capacity to produce ECMs like collagens, thus contributing to the advancement of renal fibrosis .In individuals with DM, there is a notable infiltration of activated myofibroblasts, a phenomenon generally not observed in a healthy physiological states.

Mineralocorticoid Receptor (MR) and Aldosterone



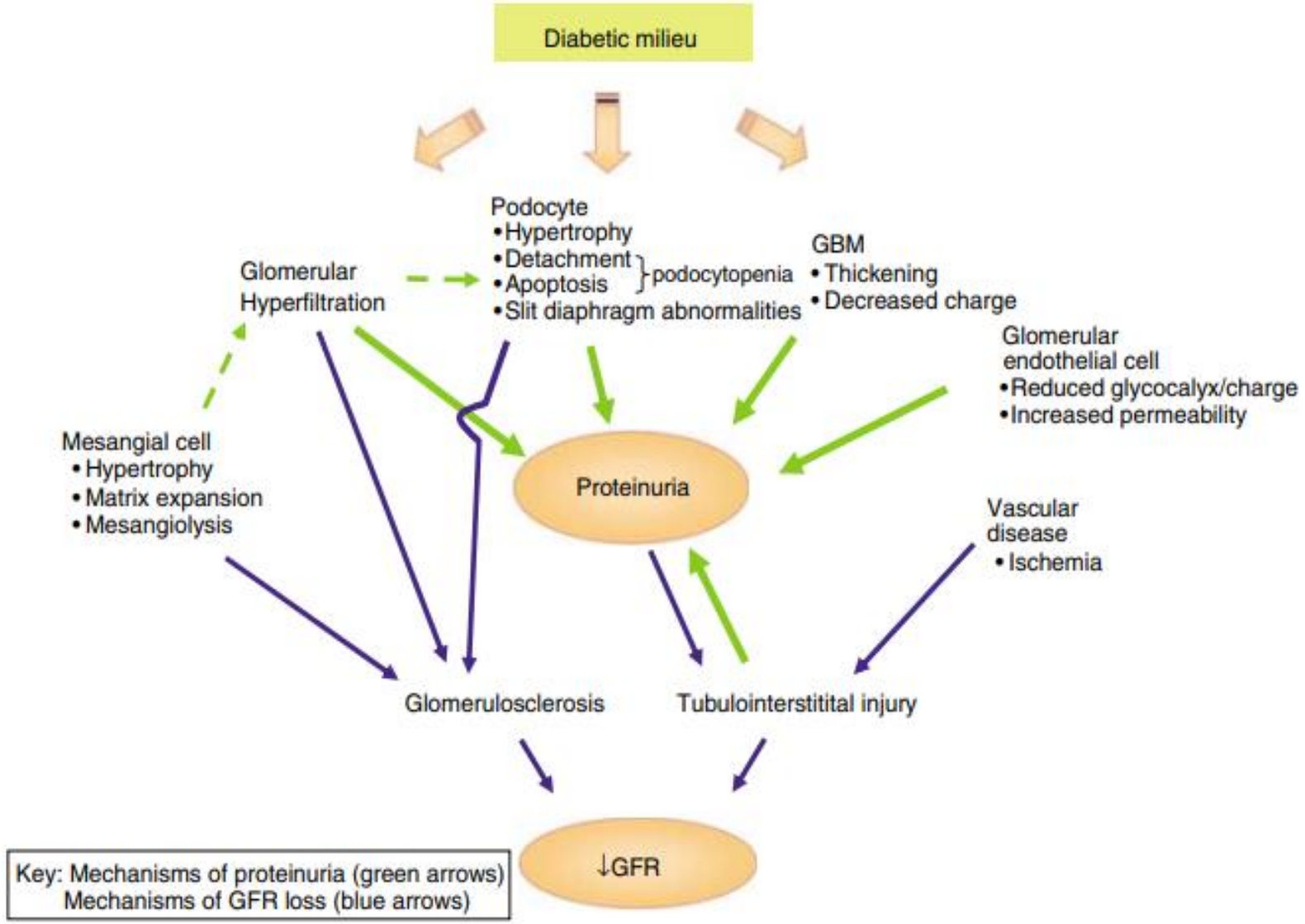
There is growing evidence indicating the existence of an intricate network involving aldosterone, the MR, and Ras-related C3 botulinum toxin substrate 1 (Rac1) as crucial
elements in the generation of ROS and subsequent damage caused by oxidative stress. This dynamic interaction plays a significant role in initiating interstitial nephritis, ultimately
culminating in fibrosis in cases of DKD.
Aldosterone triggers the activation of inflammasomes in macrophages, provoking an inflammatory tubulointerstitial region. Additionally, macrophages play a crucial
role in generating renal TGF-β, a key factor in renal fibrosis .The pathway leading to TGF-β-driven renal fibrosis seems to be facilitated by Rac1, which acts as a substantial redox-dependent non-SMAD (noncanonical) regulatory factor .
Clinical evidence supports the efficacy of the novel non-steroidal MR antagonist (nsMRA), finerenone, in slowing the progression of DKD.



Epigenetics in DKD

Histone modifications, specifically acetylation and methylation, along with DNA methylation, are linked to the aberrant regulation of genes associated with inflammation and fibrosis in DKD.

Past hyperglycemia leads to long-lasting epigenetic modifications, for example, histone methylation or acetylation, and subsequent upregulation of proinflammatory and profibrotic genes. Consequently, pathways initially activated by metabolic disturbances may become self perpetuating



Kidney International (2008) 74, 22–36

conclusion

- Improved methods to identify signaling pathways and regulators have greatly improved our understanding of glomerular cross-communication in vivo and should lead to the identification of new targets for the prevention and treatment of glomerular diseases to help reduce the growing number of patients with diabetes who may require dialysis.
- paying attention to the protection of GECs in early DKD is of great significance in delaying the progression of DKD and improving the prognosis of DKD.
- There are many common signalling pathways between TECs and GECs, and the crosstalk between them plays an important role in the occurrence and development of DKD. Improving the injury to TECs and GECs and maintaining normal crosstalk between them may become a new strategy for the prevention and treatment of DKD in the future.
- Already under investigation are therapies focusing on the regulation of inflammatory pathways and, involving targets such as immune cells, pro-inflammatory cytokines, adhesion molecules, chemokines, JAK-STAT signaling, or NF-kB signaling. Additional promising targets may be the complement system, microRNAs and downstream targets of specific inflammatory signaling pathways.(can be troubled by off-target effects)
- Linking genetic attributes to DKD is a key piece of the puzzle that will be central to further unraveling disease susceptibility and potential therapeutic targets.

Table 1 | Targeted interventions for inflammation and fibrosis to treat diabetic kidney disease

Intervention	Diabetic populations	Therapeutic targets	Proposed mechanisms	Clinical outcomes
Therapies with regulatory approval				
SGLT2 inhibition[11-13,15-17,30,31,81-84] *Canagliflozin* *Dapagliflozin* *Empagliflozin*	DKD or CVD	• Block reabsorption of glucose in the proximal tubule	• Restore tubuloglomerular feedback and reduce glomerular hyperfiltration • Decrease oxidative stress and AGE formation in proximal tubular cells • Natriuresis • Decrease blood levels of IL-6, CRP, TNFR1, MMP7, and fibronectin-1	• Reduce risks of substantial eGFR decline, kidney failure, heart failure as well as death from kidney and CV causes • Glycemic efficacy lost at low eGFR
Nonsteroidal mineralocorticoid receptor antagonists[85,86,97] *Finerenone*	DKD	• Downregulate proinflammatory and profibrotic pathways in non-epithelial cells • Downregulate ion channels for sodium and potassium in kidney tubular epithelial cells	• Decrease kidney inflammation and fibrosis • Decrease in the number of macrophages with proinflammatory phenotype in the kidney	• Reduce risks of substantial eGFR decline, kidney failure, heart failure, atherosclerotic CV events as well as death from kidney and CV causes
GLP-1R agonists[32,87-89] *Liraglutide* *Semaglutide* *Dulaglutide* *Efpeglenatide*	DKD or high CV risk	• Downregulate proinflammatory pathways	• Decrease kidney expression of TGF-β1, ICAM-1, TNF-α, and IL-1β • Decrease macrophage infiltration of the kidney • Increase cellular cAMP and inhibit NADPH oxidase	• Reduce risks of atherosclerotic CV events and deaths, albuminuria, rate of eGFR decline • Glycemic efficacy preserved at low eGFR • Weight loss

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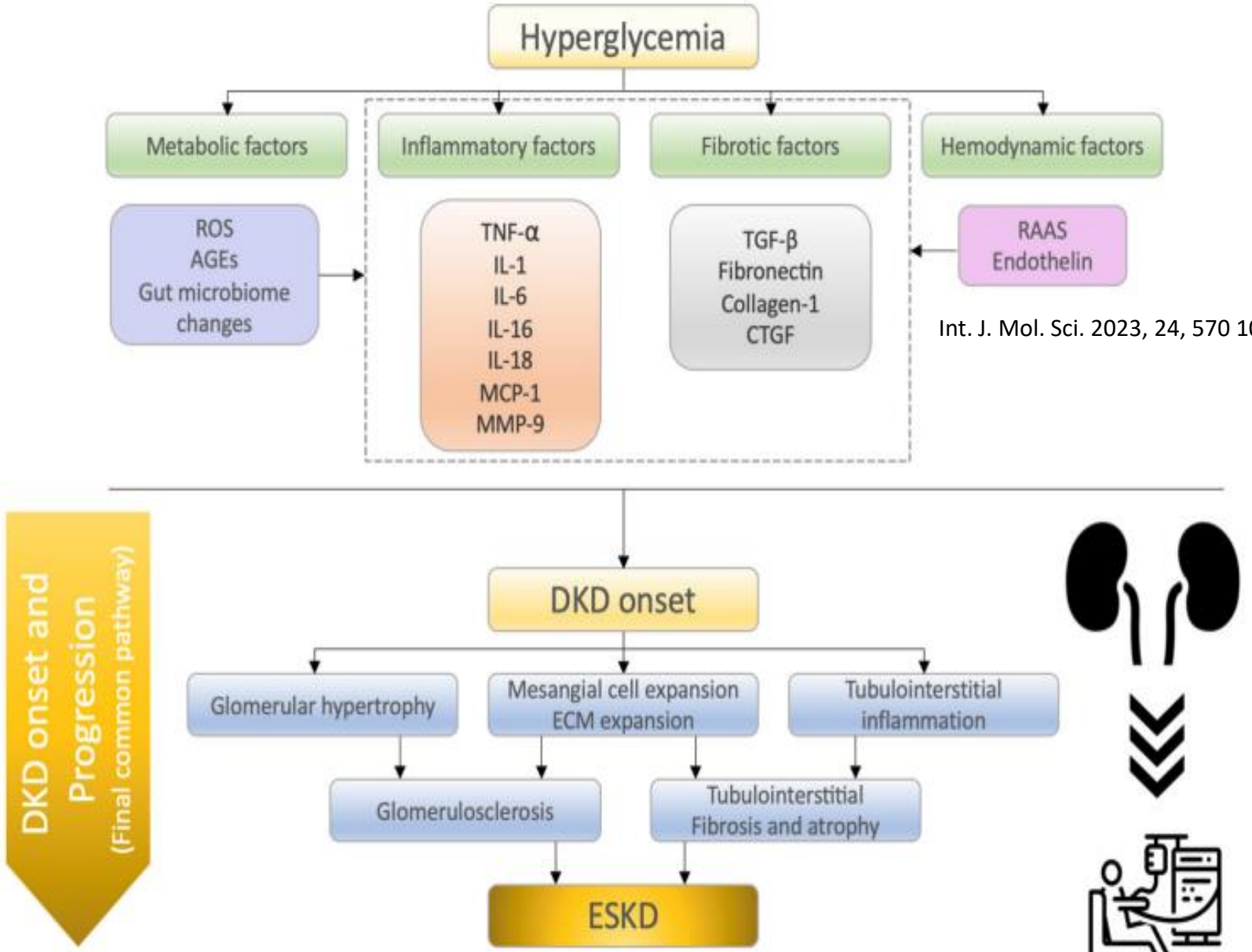
Investigational agents				
Endothelin receptor antagonists[90-92] *Atrasentan*	DKD	• Downregulate proinflammatory and profibrotic pathways • Efferent artery vasodilation	• Preservation of endothelial and podocyte integrity • Reduce glomerular hypertension • Decrease kidney inflammation and fibrosis	• Reduces albuminuria, substantial eGFR decline, kidney failure, death due to kidney disease
Inhibition of apoptosis signal-regulating kinase 1 activation[93] *Selonsertib*	DKD	• Inhibit signal transduction for proinflammatory and profibrotic pathways	• Decrease kidney inflammation and fibrosis	• Slow rate of eGFR decline
JAK-STAT inhibition[94] *Baricitinib*	DKD	• Inhibit signal transduction for proinflammatory and profibrotic pathways	• Decrease kidney inflammation and fibrosis • Decrease urine levels of CXCL10 and CCL-2 • Decrease blood levels of soluble TNF receptors-1 and 2, SAA, and ICAM-1	• Reduce albuminuria
Reduced dietary AGEs[95,96]	DKD	• Less inflammatory responses in gut and systemically	• Decrease blood levels of insulin, TNF-α, and VCAM-1 • Increase blood levels of adiponectin	• Preserve eGFR



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Thank you

for your attention