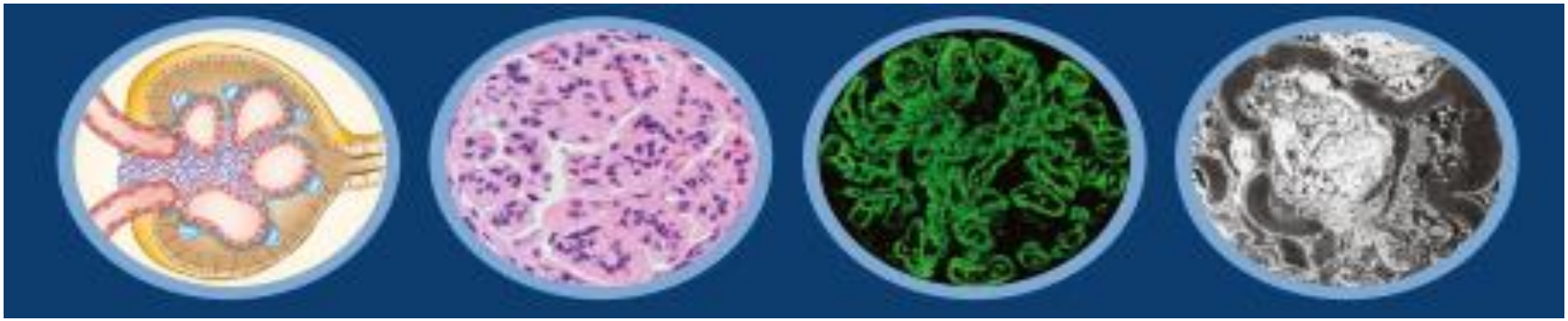
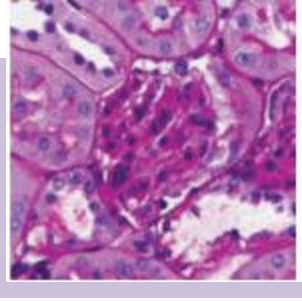


Renal inflammation , Its Pathogenic Role in Diabetic Kidney disease

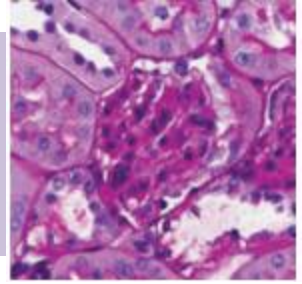
Dr. F. Ahmadi
Professor Of Nephrology
TUMS

Introduction



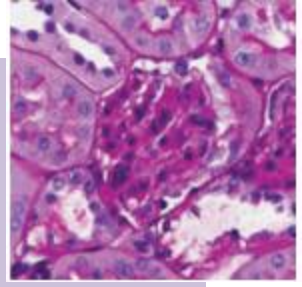
- Diabetic nephropathy, a major microvascular complication of both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), is an important cause of end-stage renal disease in Western nations
- Clear evidence indicates that the pathogenesis of diabetic nephropathy is multifactorial; both genetic and environmental factors are responsible for triggering a complex series of pathophysiological events

Introduction



- Inflammatory mechanisms are important in the pathophysiology of diabetic nephropathy and explain how metabolic and hemodynamic abnormalities in patients with diabetes mellitus translate to functional and structural kidney injury
- A wide range of proinflammatory molecules and pathways participate in the pathophysiological spectrum of diabetic nephropathy, including proinflammatory cytokines, chemokines and their receptors, adhesion molecules and transcription factors

Introduction



- Inflammatory cytokines involved in the pathogenesis of diabetes play a significant role in the development and progression of several renal disorders , including DN
- A potential participation of inflammatory cytokines in the pathogenesis of DN was suggested for the first time in 1991 by Hasegawa et al.

Inflammatory molecules and pathways in the pathogenesis of diabetic nephropathy

Juan F. Navarro-González, Carmen Mora-Fernández, Mercedes Muros de Fuentes and Javier García-Pérez

- Chemokines and their receptors(MCP-1, fractalkine, RANTES)
- Adhesion molecules(ICAM1,VCAM1, ESAM,E-selectin, α-Actinin4)
- Transcription factors(NF-kB)
- Inflammatory cytokines(IL-1, IL-6, IL-18), TNF-α

Nat. Rev. Nephrol. 7, 327–340 (2011)

TNF-α

- TNF-α is mainly produced by monocytes, macrophages, and T cells but also intrinsic kidney cells
- TNF-α may cause direct cytotoxicity to renal cells, inducing direct renal injury apoptosis, and necrotic cell death
- Changes in the permeability of endothelial cells
- TNF-α is able to directly induce the formation of ROS by renal cells
- Kidney hypertrophy and hyperfiltration are early and relevant findings of DN, and both are significantly related to TNF-α
- Activates the epithelial sodium channel resulting in an increased reabsorption of sodium
- Induce the expression of TFG-β, with the development of renal hypertrophy

Interleukin 18(IL-18)

- Tubular epithelial cells are the major source of IL-18 but recent studies have also demonstrated IL-18 production from infiltrating monocyte-macrophages and T cells
- Induces IFN-γ
- Production(IL-1 and TNF-α)
- Up regulation of ICAM-1
- Apoptosis of endothelial cells
- Serum and urinary IL-18 are increased in type 2 diabetes patients and correlate with urinary albumin excretion

Cytokine 81 (2016) 15–22

Contents lists available at ScienceDirect

Cytokine

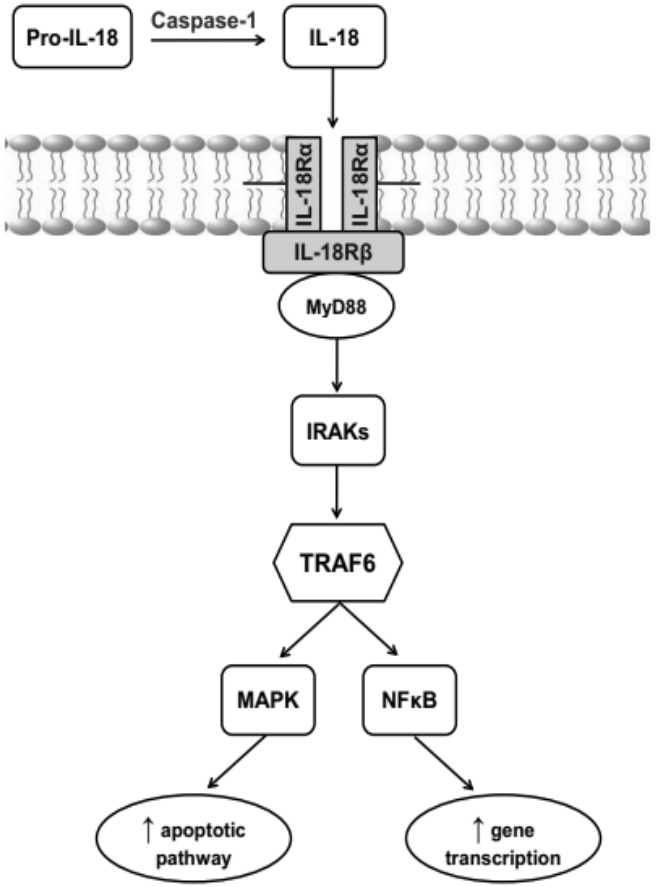
journal homepage: www.journals.elsevier.com/cytokine

Review article

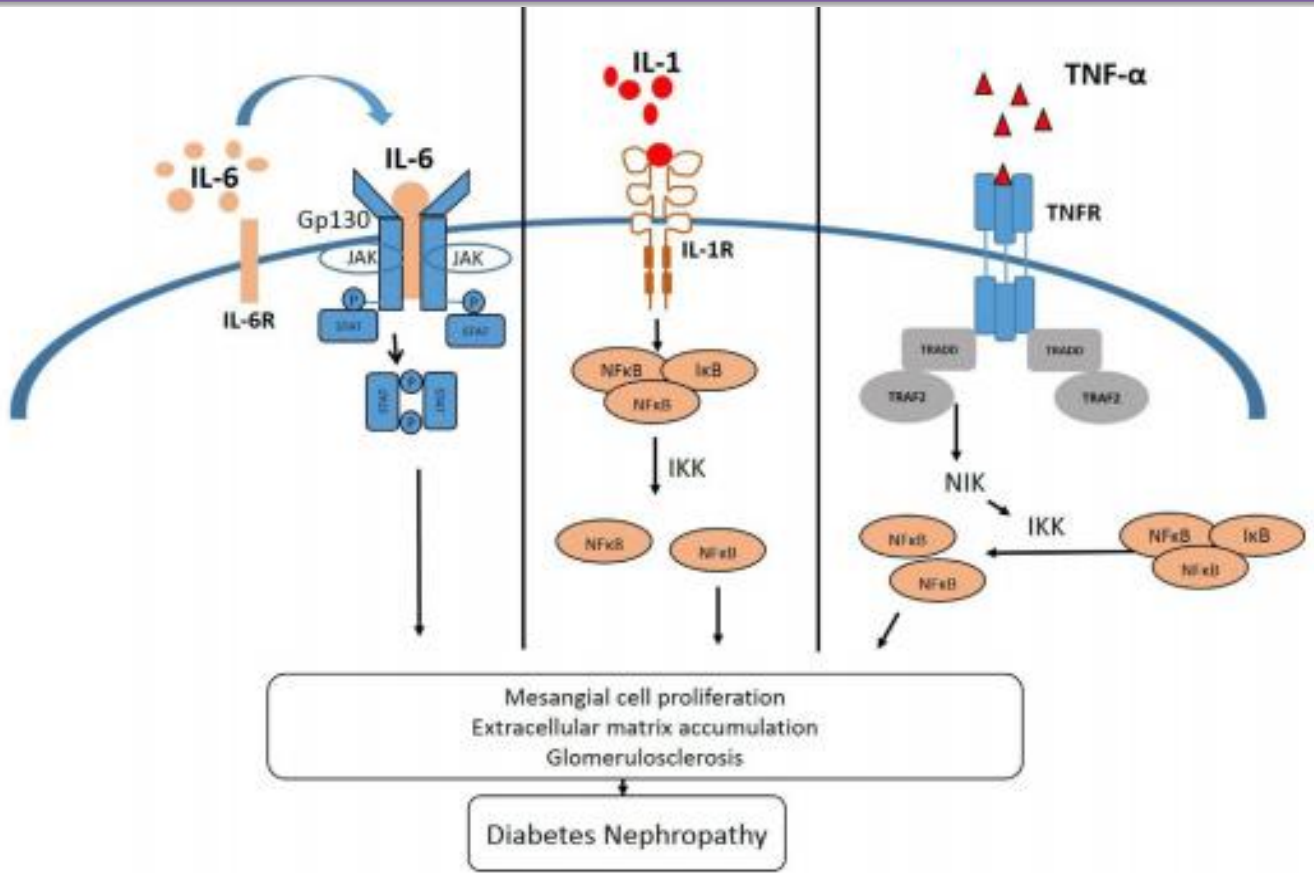
The role of IL-18 in type 1 diabetic nephropathy: The problem and future treatment

Nehal M. Elsherbiny [a], Mohammed M.H. Al-Gayyar [a,b,*]

- IL-18, a member of the IL-1 family of inflammatory cytokines, is involved in the development and progression of diabetic nephropathy.



Role of pro-inflammatory cytokines in DN

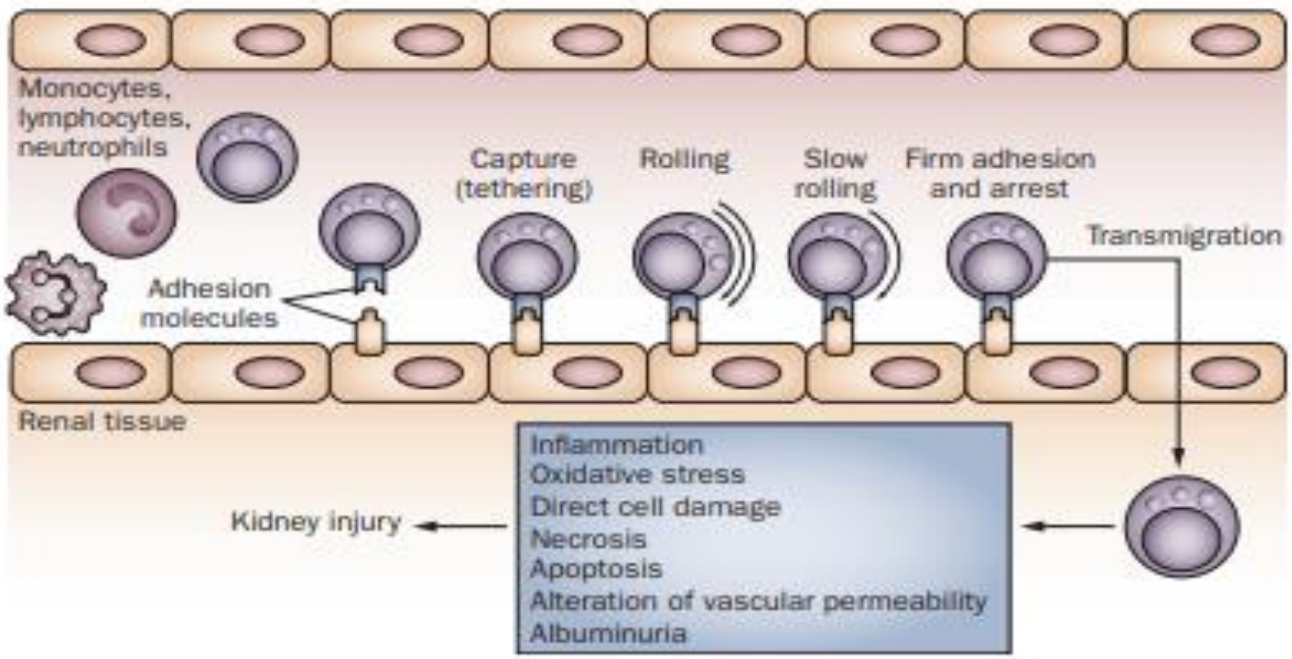


V.R. A/L B Vasanth Rao et al. / Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 754e762

Inflammatory Cells

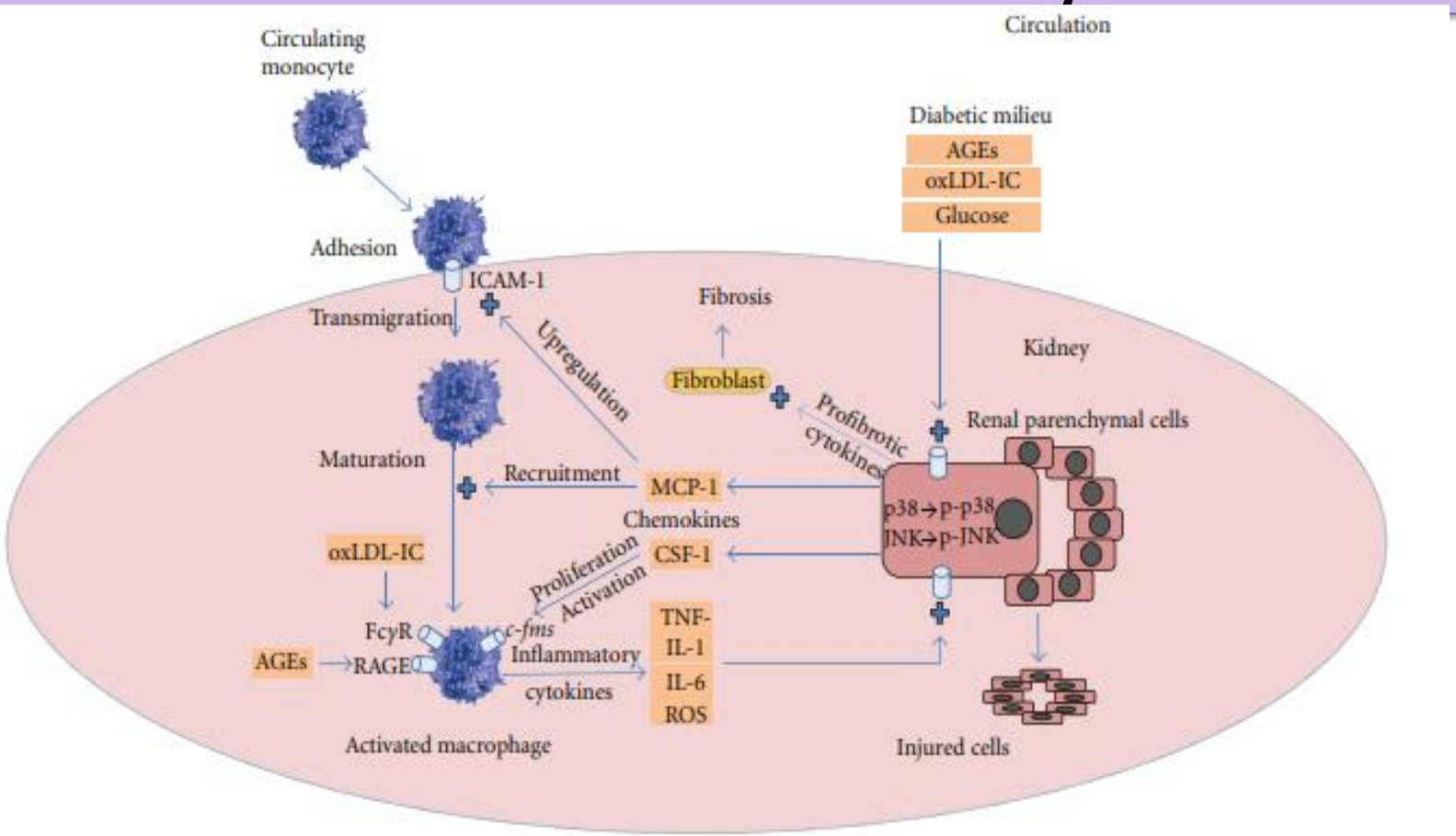
- Macrophages products TNF-α, IL-1, IL-6, reactive oxygen species (ROS), plasminogen activator inhibitor-1 (PAI-1), matrix metalloproteinases, transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), angiotensin II, and endothelin . In experimental diabetic mice, macrophage accumulation and activation are associated with prolonged hyperglycaemia, glomerular immune complex deposition, increased chemokine production, and progressive fibrosis
- Lymphocytes Activated T cells are thought to be part of an immunemediated process associated with the development of proteinuria in diabetic nephropathy.

Leukocyte infiltration into the diabetic kidney



Navarro-González, J. F. et al. Nat. Rev. Nephrol. 7, 327–340 (2011)

The inflammatory amplification loop in the diabetic kidney

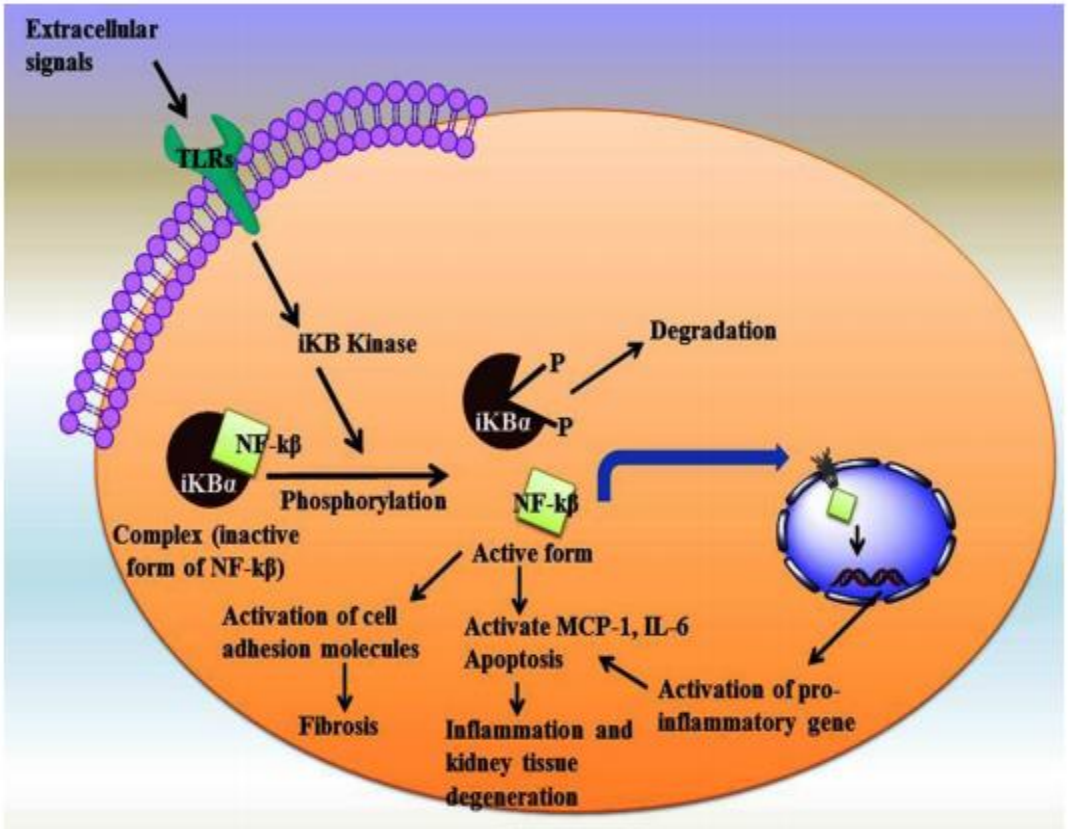


Mediators of Inflammation Volume 2012, Article ID 146154, 12 pages

NFκB

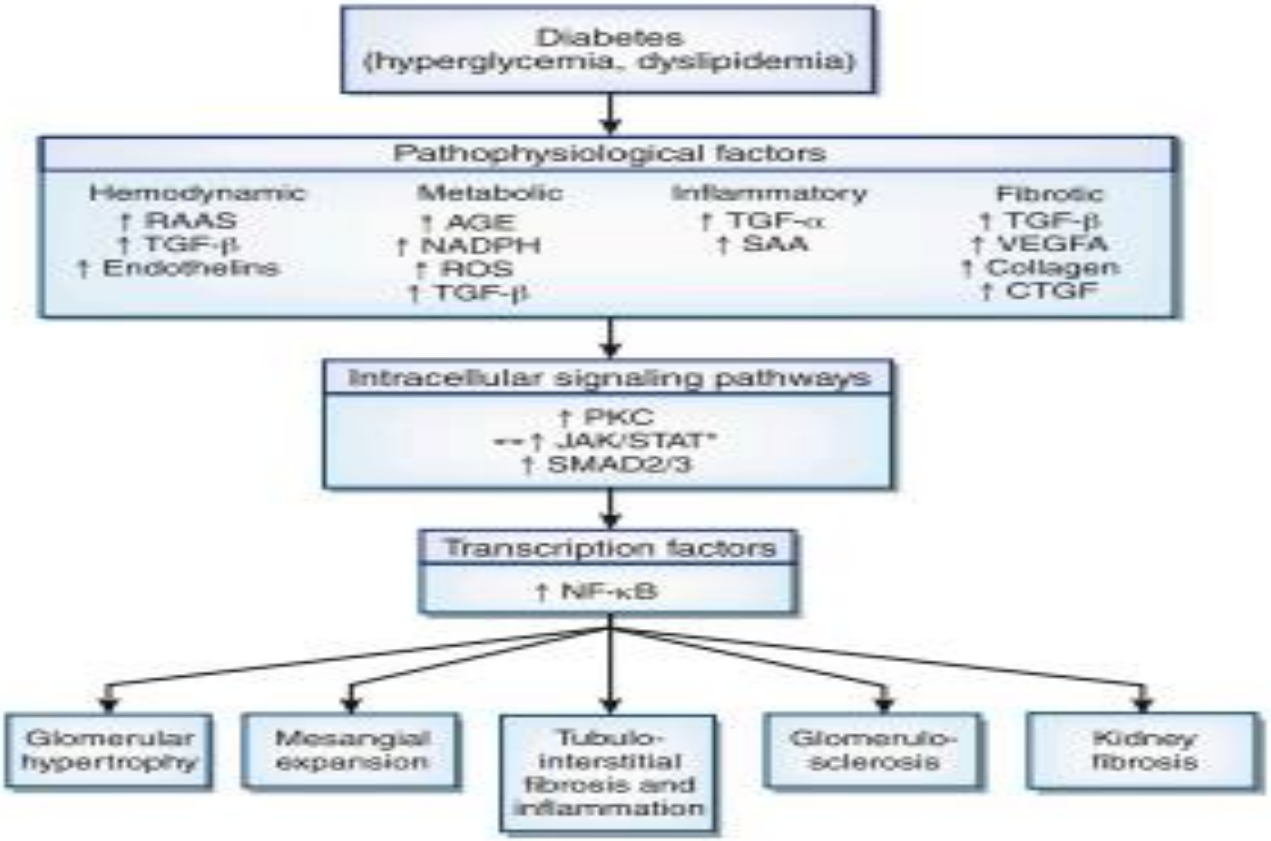
- NFκB is the most important transcription factor involved in the pathophysiology of diabetic nephropathy
- Hyperglycemia itself can activate NFκB in endothelial cells, vascular smooth muscle cells, and proximal tubule cells
- NFκB can be induced in a variety of cell types in response to many different stimuli, such as proinflammatory cytokines, oxidants, trafficking of proteins in renal tubular cells, and angiotensin II
- NFκB activity is mainly detected in cortical tubular epithelial cells and, to a lesser extent, in some glomerular cells (mainly podocytes), and correlates with the magnitude of proteinuria and the extent of interstitial cell infiltration

Hyperglycemia induced activation of NF-kb signaling



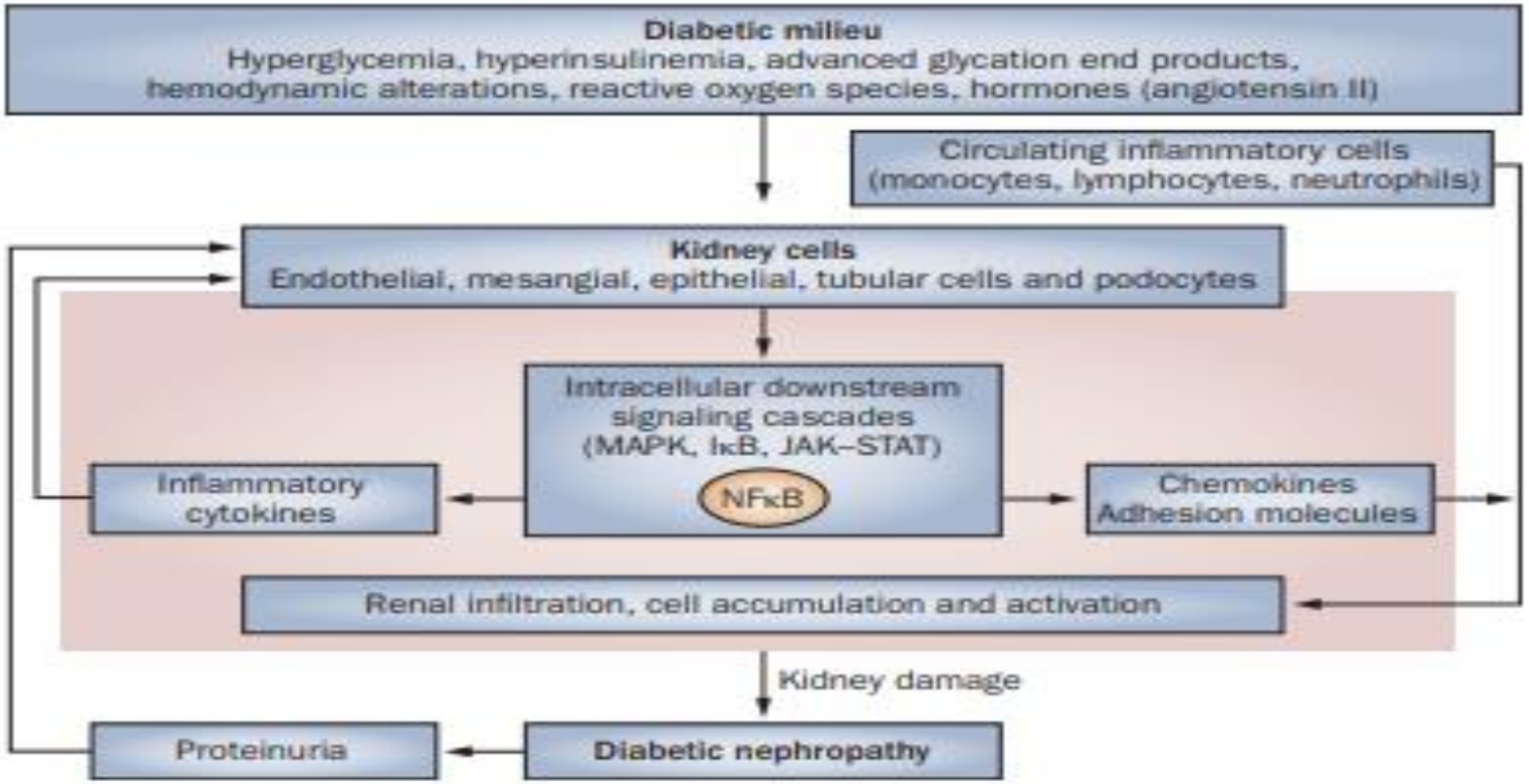
Diabetes research and clinical practice 128 (2017) 91 – 108

Different pathways and networks involved in the initiation and progression of diabetic kidney disease



Clin J Am Soc Nephrol 12: 2032–2045, 2017

Overview of inflammatory molecules and signaling pathways in diabetic nephropathy.



Navarro-González, J. F. et al. Nat. Rev. Nephrol. 7, 327–340 (2011)

International Journal of *Molecular Sciences*

MDPI

Review

Unraveling the Role of Inflammation in the Pathogenesis of Diabetic Kidney Disease

Keiichiro Matoba [1,*], Yusuke Takeda [1], Yosuke Nagai [1], Daiji Kawanami [2], Kazunori Utsunomiya [3] and Rimei Nishimura [1]

1 Division of Diabetes, Metabolism, and Endocrinology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo 105-8461, Japan
2 Department of Endocrinology and Diabetes Mellitus, Fukuoka University School of Medicine, Fukuoka 814-0180, Japan
3 Center for Preventive Medicine, The Jikei University School of Medicine, Tokyo 105-8461, Japan
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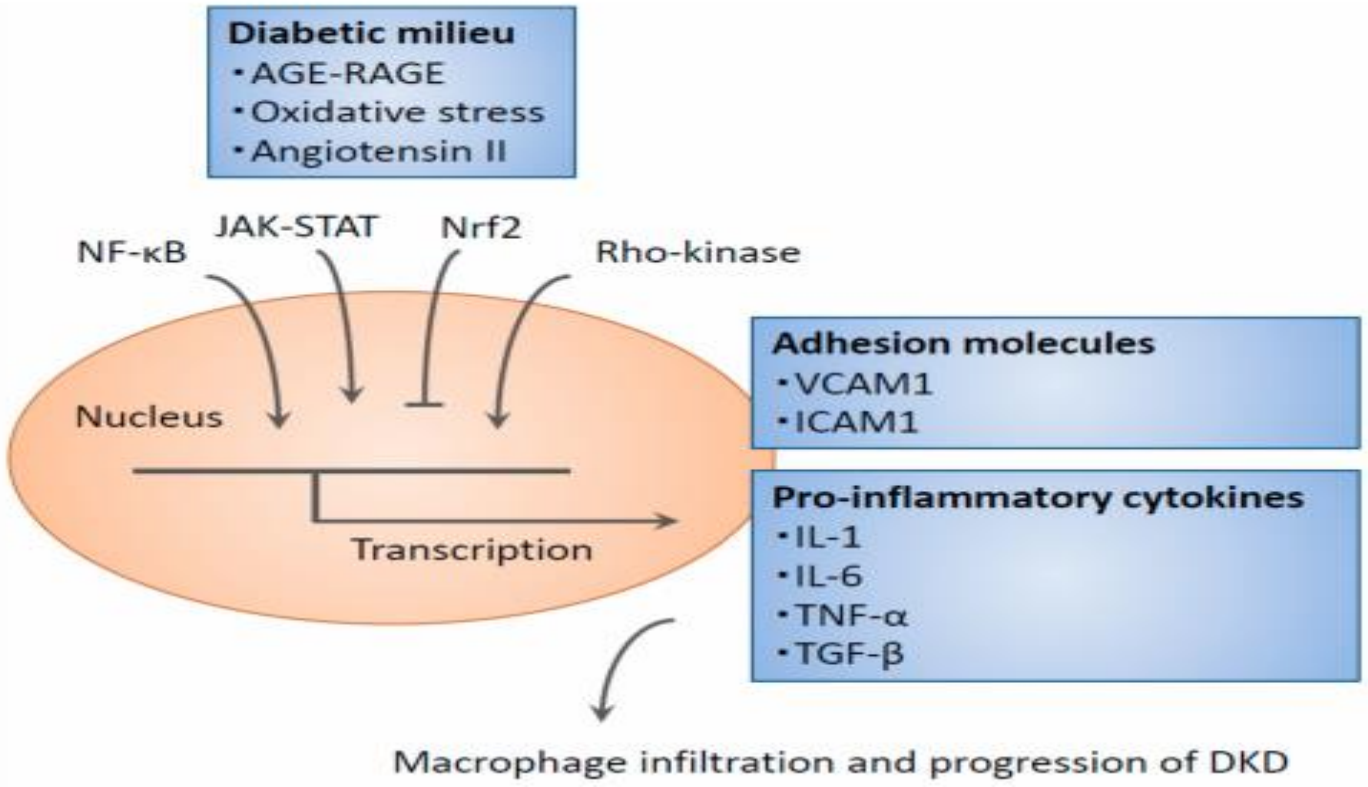


Potential implications of chemokines, adhesion molecules, pro-inflammatory cytokines and inflammatory markers in DN

Marker	Implication
MCP-1	Activation and recruitment of monocytes that promote macrophage accumulation and activation
Adhesion molecule	Attachment (sticking) of leucocytes, monocytes and macrophages to the endothelium and subsequent transendothelial transmigration
Pro-inflammatory cytokine	
IL-1	Increases vascular endothelial permeability and proliferation of mesangial cells and matrix synthesis; induces intraglomerular haemodynamic abnormalities related to prostaglandin synthesis by mesangial cells
IL-6	Stimulates mesangial cell proliferation, enhances fibronectin expression, affects extracellular matrix dynamics at both mesangial and podocyte levels, and increases endothelial permeability; increases the expression of adhesion molecules on endothelial and VSMCs; activates the local RAS, and enhances TGF-β signalling via modulation of TGF-β receptor trafficking
IL-18	Promotes development of a Th1 lymphocyte response by induction of IFN-γ production; modulates activity of NK cells, increases TNF-γ and IL-1 production by macrophages; up-regulates the expression of adhesion molecules, and induces NO production in the area of inflammation
TNF-α	Induces haemodynamic misbalance between vasodilator and vasoconstrictive mediators; promotes the local generation of ROS, with alteration of the barrier function of the glomerular capillary wall; significantly contributes to sodium retention and renal hypertrophy
Inflammatory marker	
CRP	Inflammatory and cardiovascular markers; immunoregulatory functions include enhancement of leucocyte reactivity, complement fixation, modulation of platelet activation and clearance of cellular debris from sites of active inflammation

Clinical Science (2009) 116, 479–492

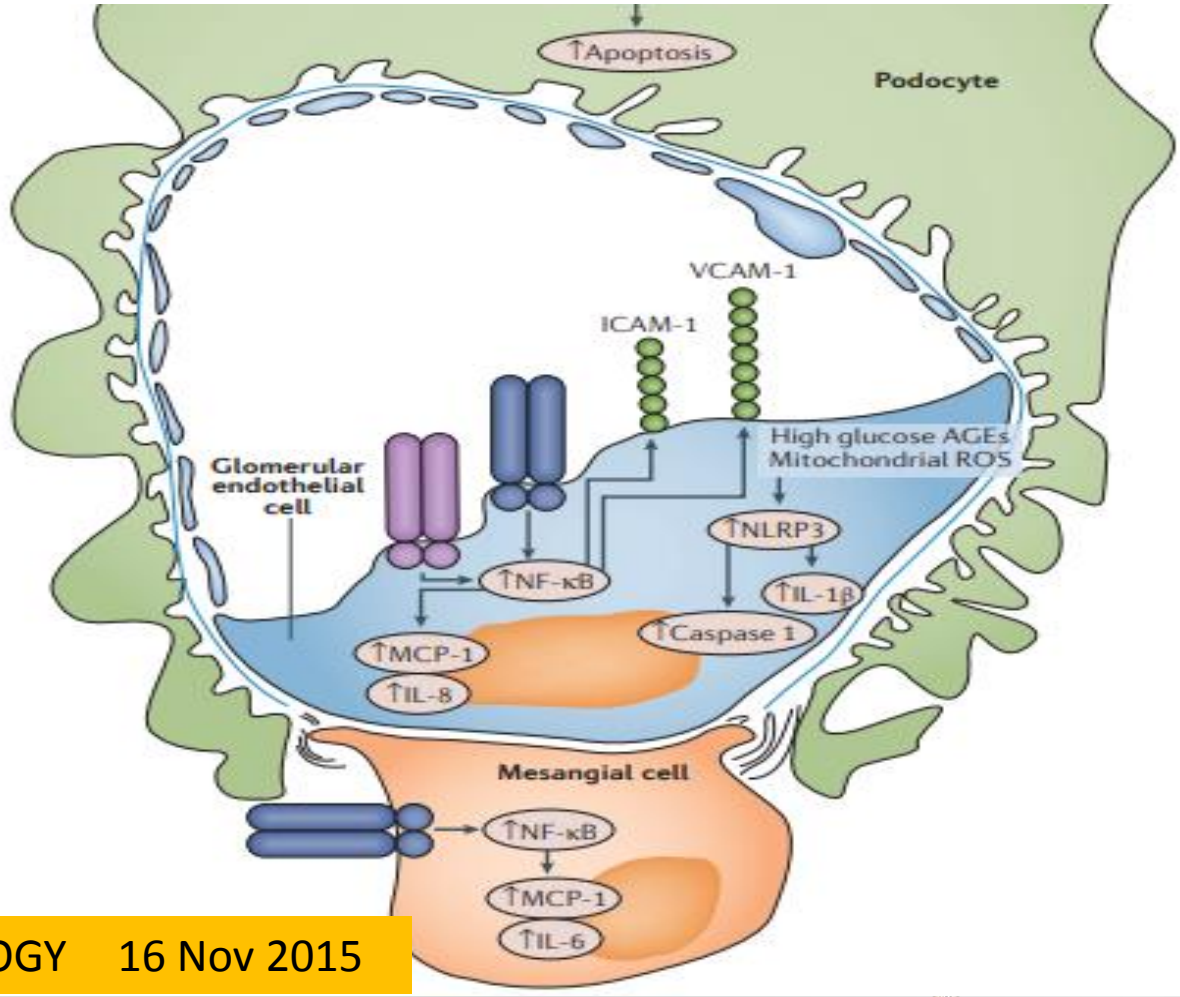
Cytokine actions in diabetic nephropathy

- Mediation of insulin resistance
- Increased expression and synthesis of cell adhesion molecules
- Induction of intraglomerular hemodynamic alterations (e.g. increased intraglomerular pressure)
- Increased vascular endothelial permeability

Cytokine actions in diabetic nephropathy

- Induction of mesangial cell proliferation
- Increased expression of fibronectin
- Induction of cellular apoptosis and necrosis
- Direct cytotoxicity to renal cells
- Increased tubular sodium reabsorption, urinary protein content and glomerular volume
- Increased synthesis and release of other inflammatory molecules (e.g. chemokines, cytokines and growth factors

Inflammatory pathways in diabetic nephropathy



NATURE REVIEWS | NEPHROLOGY 16 Nov 2015

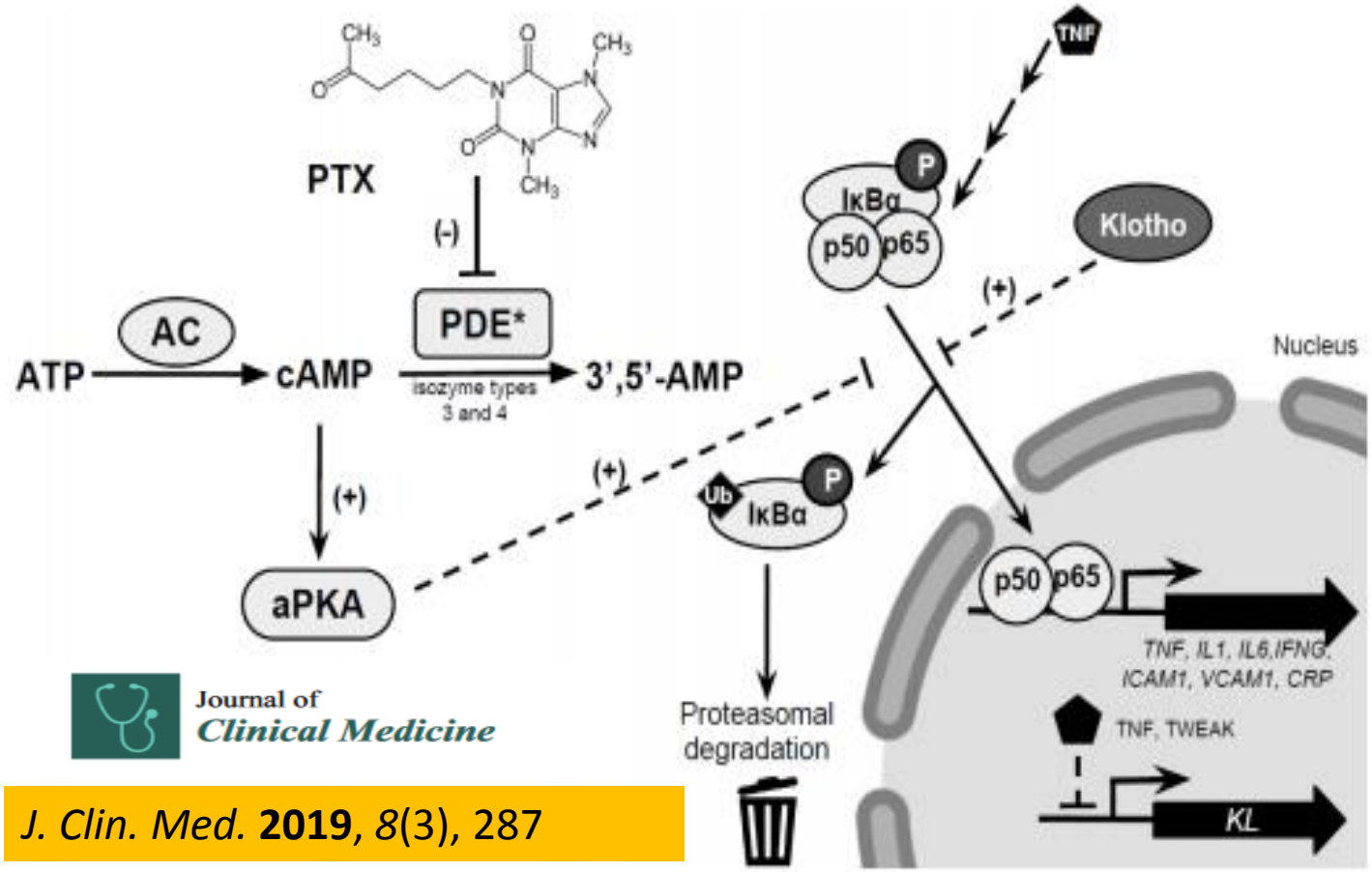
New Therapies Targeting Inflammation

- **RAAS bloker** : Both are effective strategies that reduce proteinuria and slow progression of diabetic and nondiabetic nephropathy by hemodynamic/antihypertensive and by antiinflammatory/antifibrotic actions
- The second action is mediated by the reduction in angiotensin II (AngII) levels, which activates nuclear factor (NF-κB) and interacts with transforming growth factor-β (TGF-β). The anti-inflammatory action occurs via inhibition of NF-κB-dependent pathways
- **Aldosterone receptor blockade** : in the kidneys of animals with experimental T2DM has a renoprotective effect associated with an anti-inflammatory mechanism related to inhibition of NFκB activation
- **Thiazolidinediones** : has renoprotective effects which are also related to inhibition of NFκB activation.

New Therapies Targeting Inflammation

- **Pentoxifylline (PTF)** :is a methylxanthine derivate and nonspecific phosphodiesterase inhibitor with anti-inflammatory, antiproliferative and antifibrotic actions in experimental studies
- This antiproteinuric effect has been related to a reduction in the concentrations of TNF-α,
- In addition, PTF has a considerable capacity to modulate other proinflammatory cytokines and molecules, including IFN-γ, IL-10, and IL-6
- One in vitro study has showed that PTF decreased cellular production of fibronectin and TGF-β

Suggested mechanisms of the anti-inflammatory effects of pentoxyfilline

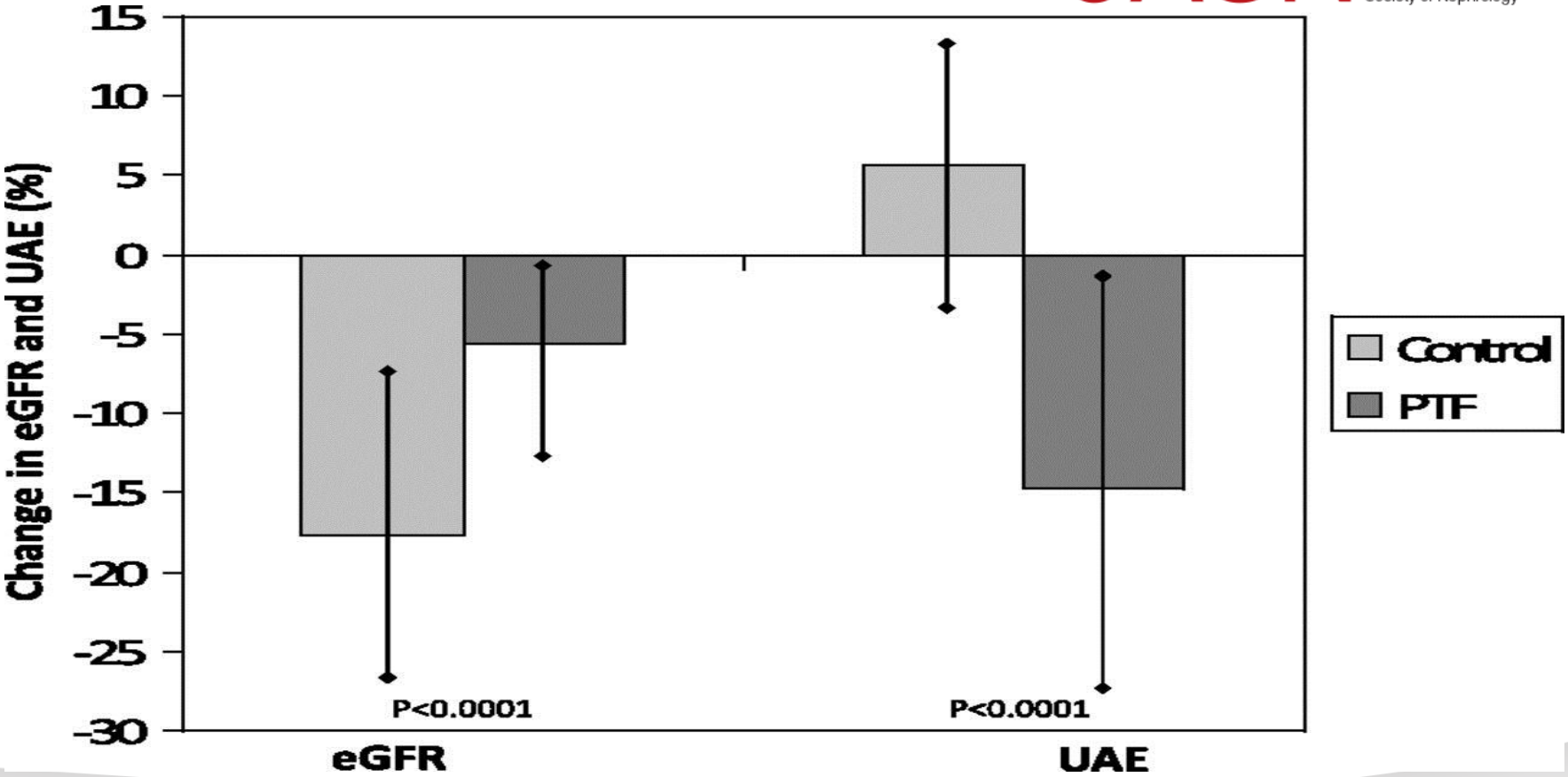


Journal of *Clinical Medicine*

J. Clin. Med. **2019**, *8*(3), 287

Effect of Pentoxifylline on Renal Function and Urinary Albumin Excretion in Patients with Diabetic Kidney Disease: The PREDIAN Trial

JASN Journal of the American Society of Nephrology



New Therapies Targeting Inflammation

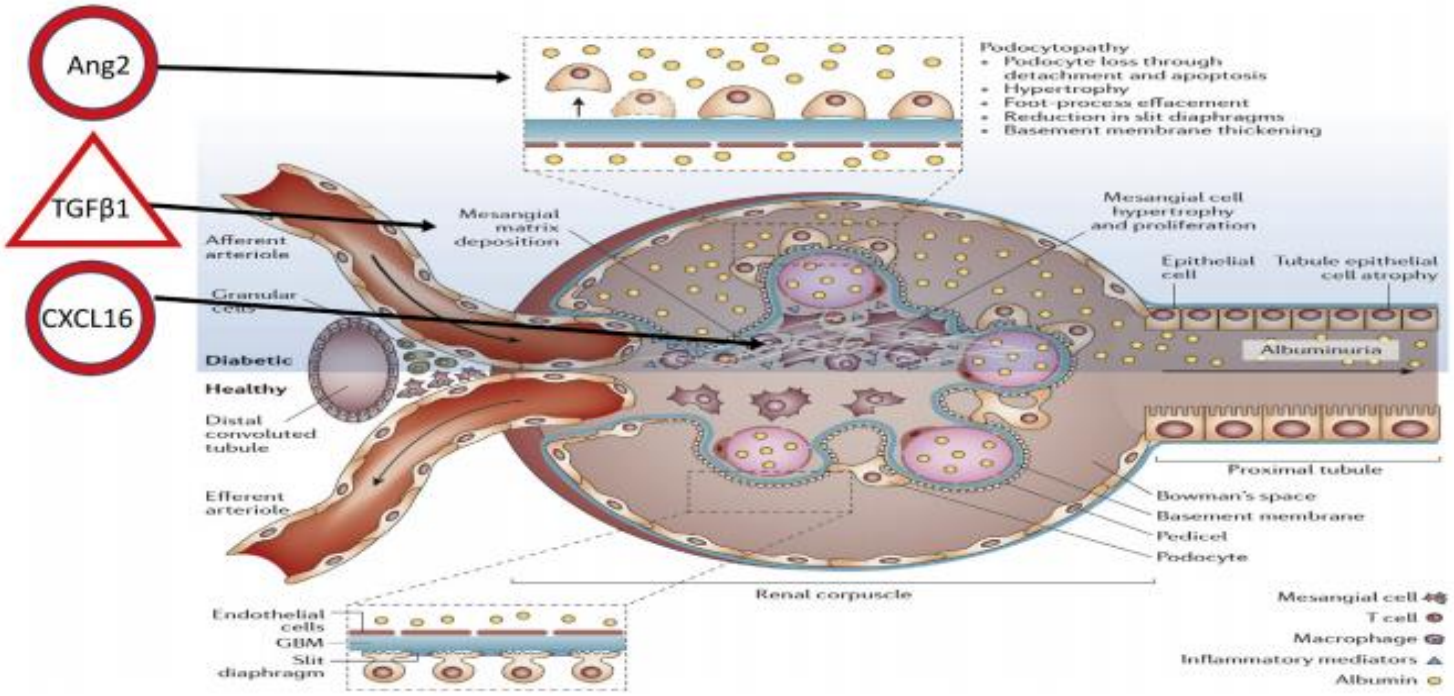
- **Mycophenolate mofetil :**, an immunosuppressive agent with anti-inflammatory properties which decreased proteinuria and improvements in glomerulosclerosis and interstitial fibrosis, as well as reduced inflammatory responses, as indicated by suppression of CCL2 synthesis, podocyte apoptosis and ROS production were attenuated in mycophenolate mofetil-treated diabetic mice
- **Infliximab :** a monoclonal antibody that targets TNF, resulted in a substantial decrease in both urinary TNF concentration and UAE.

New Therapies Targeting Inflammation

- SGLT2 inhibitors: Canagliflozin reduces the plasma levels of TNF-R1 and IL-6(CREDENCE) trial
- Empagliflozin: In diabetic Akita mice inhibited albuminuria via a reduction in the levels of inflammatory cytokines, including MCP1 and IL-6

Randomized Olmesartan And Diabetes MicroAlbuminuria Prevention (ROADMAP) biomarkers of microalbuminuria

Significant reduction in progression to microalbuminuria, which developed in 8.2% of the patients in the olmesartan group (178 of 2160 patients) and 9.8% in the placebo group (210 of 2139)



Kidney International Reports (2019) 4, 1362–1365

Potential therapies for diabetic kidney disease targeting inflammatory pathways

Drug	Target	Identifier	Study population	Outcomes
Pentoxifylline	Inflammatory Cytokines	EudraCT number 2007-005985-10	Type 2 diabetes eGFR 15–60 UAE >30 mg/24 h	Mean difference in UAE of 21% ($p < 0.001$) and eGFR decline 4.3 mL/min/1.73 m^2 lower than in the placebo group ($p < 0.001$)
Baricitinib	JAK1/JAK2	NCT01683409	Type 2 diabetes Macroalbuminuria eGFR 20–75 mL/min/1.73 m^2	Albuminuria reduction by 40% No effect on eGFR
Emanticap Pegol (NOX-E36)	CCL2	NCT01547897	Type 2 diabetes eGFR >25 mL/min/1.73 m^2 UACR >100 mg/g	Albuminuria reduction by 29% compared with baseline ($p < 0.05$), but no significant difference with placebo
CCX 140-B	CCR2	NCT01447147	Type 2 diabetes eGFR ≥25 mL/min/1.73 m^2 UACR 100–3,000 mg/g	18% reduction of albuminuria compared with placebo ($p < 0.0004$) in the 5 mg group. No reduction of albuminuria in the 10 mg group
CTP-499	PDE	NCT01487109	Type 2 diabetes eGFR no limit UACR 300–5,000 mg/g	16% UACR reduction
LY3016859	TGF-α/epiregulin	NCT01774981	eGFR <90 mL/min/1.73 m^2 UACR >400 mg/g	Study ongoing. No results available

eGFR, estimated glomerular filtration rate; TGF-α, transforming growth factor alpha; UACR, urinary albumin-to-creatinine ratio.

Nephron 2019;143:12–16

nephron

Take home massages

- Inflammation plays an essential role in the development of DN, this participation involves increased chemokine production, infiltration of inflammatory cells to the kidney, pro-inflammatory cytokine production and tissue damage.
- Better understanding of the inflammatory response in diabetic kidneys is expected to identify novel anti-inflammatory strategies for the potential treatment of human DN.

17th International Congress of Nephrology, Dialysis, and Transplantation

Tabriz , Iran 19-22 November 2019

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