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The involvement of proinflammatory cytokines in diabetic nephropathy: Focus on interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF-A) signaling mechanism



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ABSTRACT

About 20-40% of type 2 diabetic patients may develop diabetic nephropathy (DN) as its complication. The pathogenesis of DN is complex. Classically, metabolic and hemodynamic impairment are considered as its pathogenesis. However, large number of evidences point that inflammation is a key event in the development and progression of DN. Among several inflammatory molecules, pro-inflammatory cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF- α) are known to be involved. Chronic condition of hyperglycemia responsible for the formation of pro-inflammatory

cytokines via advanced glycation end products (AGE) pathway and protein kinase C (PKC) pathway. These pro-inflammatory cytokines exert signaling pathway that lead to extracellular matrix (ECM) accumulation, glomerular basement membrant (GBM) thickening, and glomerulosclerosis, ultimately lead to development and progression of diabetic nephropathy. Understanding the detail of this mechanism will be beneficial for future research or treatment development of DN. Intervention in these signaling pathways may lead to development of novel therapeutic approach.

Keywords: Diabetic nephropathy, Proinflammatory cytokines, IL-1, IL-6, TNF- α

Cite This Article: Sindhughosa, D., Pranamartha, A. 2017. The involvement of proinflammatory cytokines in diabetic nephropathy: Focus on interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF- α) signaling mechanism. *Bali Medical Journal* 6(1): 44-51. DOI:10.15562/bmj.v6i1.299

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INTRODUCTION

Diabetic nephropathy is a metabolic disorder with high morbidity and mortality. Global pattern of diabetic nephropathy incidence is not entirely explored, but its incidence has already occurred widely and is estimated to be increased in prevalence.¹ It occur in 20-40% of people with type 2 DM and the most frequent cause of end stage renal disease (ESRD).^{2,3,4}

Fundamental concepts and pathophysiological mechanism of DN have growing rapidly. Traditionally DN is considered as non-immune disease. Classic view of pathomechanism of DN is hyperglycemic condition, which lead to molecular modifications. It also resulted in metabolic and hemodynamic impairment. Those views have been evolving recently and become more complex. Pathogenesis of DN includes multifactorial element, involving genetic and environmental factors, that trigger more complex pathological events.^{5,6}

Intensive research on cellular and molecular levels in recent years found that immunological and inflammatory factors play important roles in DN and its progression.^{7,8} Involvement of various cells including macrophages, leucocytes, and monocytes,^{9,10} and also other molecules like chemokines, adhesion molecules, growth factors, enzyme, and nuclear factor

(NF- κ B) implicated in development and progression of DN. Adhesion molecule which involved in DN is intracellular adhesion molecule-1 (ICAM-1),¹¹ while growth factors which associated with DN are vascular endothelial growth factors (VEGF), growth hormone (GH), and insulin-like growth factor (IGF).¹² However, the role of inflammatory cytokines in development and progression of DN is still lacking. Extending the knowledge regarding the role of inflammation in the development and progression of DN is useful to find novel therapeutic strategies.

The aim of this review is to further describe the role of inflammation, especially inflammatory cytokines, on the development and progression of DN. This review focused on recent information concerning inflammatory cytokines pathway and its relation with DN, since information regarding the involvement of inflammatory cytokines with DN is still less known.

Early kidney changes in diabetic nephropathy and inflammation.

Significant changes in DN are renal hypertrophy and hyperfiltration. Those two changes are associated with inflammation processes, particularly proinflammatory cytokine TNF- α .^{13,14} TNF- α intensify the reabsorption of sodium via epithelial sodium channel activation in renal distal tubule.

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It subsequently trigger TGF- β release, along with development of renal hypertrophy.¹⁵ The occurrence of renal hypertrophy in diabetic condition also proven through research in animal model with diabetes, in which the wet kidney weight was increased. Wet kidney weight is a marker of renal hypertrophy and an early phenomenon of renal involvement in diabetic patients. The increase in wet kidney weight associated with gene expression levels and urine concentration of proinflammatory cytokines IL-6.¹⁶ Those structural changes responsible to alteration in renal function that is albumin leakage.¹⁷ Furthermore, the earliest changes in kidney of diabetic patients is not alteration of serum creatinine, but proteinuria in termed of albuminuria, caused by hemodynamic changes of glomerular hypoperfusion with elevated GFR, also known as hyperfiltration, that lead to albumin leakage from glomerular capillaries and resulting in proteinuria.¹⁸

Identifying and monitoring DN commonly involve two diagnostic modalities, assessment of kidney function in the form of estimated glomerular filtration rate (eGFR) and kidney impairment in the form of albuminuria. Albuminuria is a sensitive marker of chronic kidney disease (CKD) and VCD risk factors.² Normal kidney function seen from GFR of ≥ 90 mL/min/1.73 m² without albuminuria. Equation from Modification on Diet in Renal Disease (MDRD) study and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) may be used to calculating GFR.^{19,20}

Chronic kidney disease defined as abnormality of kidney structure of function for > 3 months accompanied with structural damage that proved histologically.²⁰ There are 5 categories of GFR function

(Table 1), while albuminuria classified into 3 categories (Table 2).²¹ Albuminuria of > 300 mg/day in diabetic patients and decrease in GFR are considered significant to indicate the presence or development of DN.²²

To date several studies reported that inflammatory elements involved in diabetes and it estimated involved in complications of diabetes. Plasma concentration of several proinflammatory molecules, including proinflammatory cytokines, increase in diabetic patients.^{23,24} Study showed that enhancement of these molecules occurred with progressivity of nephropathy.²⁵ It also independently associated with urinary albumin excretion.²⁶ Accumulation of inflammatory cells in kidney also related with DN, it also has been proved that inhibition toward recruitment of inflammatory cells to kidney has protective effect.^{11,27}

Inflammatory Cytokines in Diabetic nephropathy

Hasegawa et al²⁸ in 1991 demonstrated for the first time the involvement of inflammatory response in pathogenesis of DN. The study showed that production of TNF- α and IL-1 by peritoneal macrophage cultured with glomerular basement membrane from diabetic rats were significantly higher compared to peritoneal macrophage cultured with glomerular basement membrane from normal rats.

Numerous researchers found that interleukin-18 (IL-18) levels in DN patients higher than control. IL-18 levels also positively correlated with UAE rate in DN patients.^{29,30,31} Other study also showed that in patients with DN, IL-18 levels increased in tubular renal cells.³² In its process, IL-18 induces the release of interferon- γ (IFN- γ). Interleukin-1 and TNF- α are proinflammatory cytokines in which its formation influenced by the release of IFN- γ .³³

Other than IL-18, TNF- α also involve in the occurrence of nephropathy. A number of researches showed the increase of serum and urinary TNF- α levels in patients with DN compared with non-diabetic patients and diabetic patients. TNF- α levels also increased along with progressivity of DN. It indicates that there is an association between the increase of TNF- α proinflammatory cytokine levels with development and progression of renal injury in diabetic patients.^{29,34,35}

Others pro-inflammatory cytokines such as IL-1 and IL-6 also play important role in pathogenesis of DN. In several studies with model of DN, expression of IL-1 was known to be increased.^{16,36} IL-1 is known to be involved in the impairment of interglomerular hemodynamic. It related with synthesis of prostaglandin by mesangial cells. Pfeilschifter et al³⁷ administered recombinant human IL-1 to

Table 1 Classification of glomerular filtration rate (GFR) in CKD

Category	Glomerular filtration rate (GFR)	
	(mL/min/1.73m ²)	
G1 (normal or high)	≥ 90	
G2 (slightly decreased)	60-89	
G3a (slight or moderately decreased)	45-59	
G3b (moderately-to-severely decreased)	30-44	
G4 (severely decreased)	15-29	
G5 (renal insufficiency)	<15	

Table 2 Classification of albuminuria in CKD

Category	AER		
	(mg/24h)	(mg/ mmol)	(mg/g)
A1 (normal to slightly elevated)	<30	<3	<30
A2 (moderately elevated)	30-300	3-30	30-300
A3 (severely elevated)	>300	>30	>300

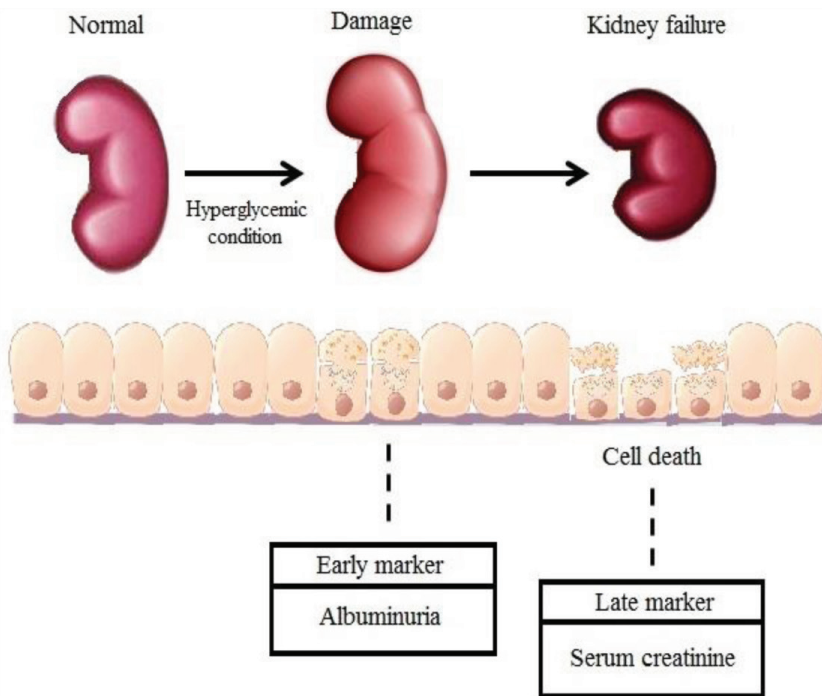


Figure 1 Early kidney changes and its biomarker

glomerular mesangial cells. The administration of recombinant human IL-1 induced the synthesis of prostaglandin E2 and release of phospholipase A2.³⁷ Others studies also found significant relation between IL-6 and glomerular basement membrane thickening. This change in renal structure is a crucial event in the development of DN and a predictor to renal injury.^{38,39} The formation of these proinflammatory cytokines, which triggered by hyperglycemic condition that occurs in diabetic patients, resulted in renal damage, either glomerulus or other structures.

Hyperglycemic conditions which occur in patients with DM lead to activation of numerous pathways (Figure 2). Protein kinase c (PKC) and advanced glycation end products (AGE) pathways are metabolic pathways that activated by hyperglycemic conditions. Activation of AGE pathway resulted in production of various AGE products, act on its receptors i.e. receptor for advance glycation end products (RAGE). RAGE found in monocytes and endothelial cells, and its activation increases the production of cytokines via complex signaling pathways. In AGE pathway, reactive oxygen species (ROS) production initiated and amplified in chronic hyperglycemic condition. It may result in depletion of antioxidants, which causing oxidative stress, tissue injury, activation of nuclear factor (erythroid-1) related factor (Nrf2), and activation of inhibitory kappa B kinase (IKK). Activation of Nrf2 occur via direct oxidation of thiol residues on kelch-like ECF associated protein (Keap-1). It migrates into nucleus to activate antioxidant

response element (ARE) of genome, producing several antioxidants and cyto protective enzymes (SOD, GSH, HO-1, and glutathione s-transferase).⁴⁰ Activation of Nrf2 is a cellular mechanism to maintain homeostatic and protect cell from elevation of oxidative stress, thus preventing inflammation. However, its activation inhibited by activation of extracellular related kinase (ERK) caused by hyperglycemic conditions, which occur in diabetic patients, resulted in impairment of cellular homeostasis function and inflammation.⁴¹ Hyperglycemic condition also resulted in activation of PKC pathway. Activation of PKC leads to upregulation of MAPK signaling pathway. Activation of IKK by ROS induces phosphorylation of inhibitory kappa B protein (I κ B). Phosphorylation of I κ B labels it for ubiquitination and proteosomal degradation,⁴² hence releases free NF- κ B heterodimer from I κ B, allows it to enter into nucleus and bind with kappa region of genome increasing production of cytokines.⁴³

INTERLEUKIN 1 (IL-1)

Interleukin 1 is one of proinflammatory cytokines which predicted to be involved in inflammation-based disease e.g. sepsis, autoimmune disease, including DN. The two main ligands are IL-1 α and IL-1 β . It produced primarily by macrophage, but lymphoid, epidermal, vascular, and epithelial tissues also synthesize IL-1.⁴⁴ Furthermore, renal cells, i.e. tubular, endothelial, mesangial, and epithelial cells, capable of producing cytokines including IL-1, which interact with other cytokines and acting in some manners (autocrine or paracrine) to inflict renal damage; hence involved in several renal diseases, including DN.⁴⁵ Research by Sassy-Pigent et al dan Navaro et al found that expression of IL-1 also increase in kidney of experimental models with diabetic nephropathy.^{36,16} Furthermore, research conducted by Hasegawa et al found that IL-1 production increase when peritoneal macrophages cultured with glomerular basement membranes from diabetic rats.²⁸ Interleukin 1 induce the production and expression of ICAM-1 by glomerular mesangial cells and tubular epithelia.⁴⁶

As response to various stimuli, transcription of the gene encoding IL-1 β is initiated. The precursor of IL-1 β is pro-IL-1 β and caspase-1 cleaves this protein to make active form of IL-1 β . Release of IL-1 comes through cell lysis, secretory lysosomes, and micro vesicle shedding, then binds to IL-1RI, as its receptor, alongside IL-1 receptor accessory protein (IL-1RAcP). The binding of ligand and its receptor initiates signaling transduction, which includes myeloid differentiation primary response protein 88 (MyD88), IL-1 receptor associated kinase (IRAK-1) and IRAK-2, recruitment of

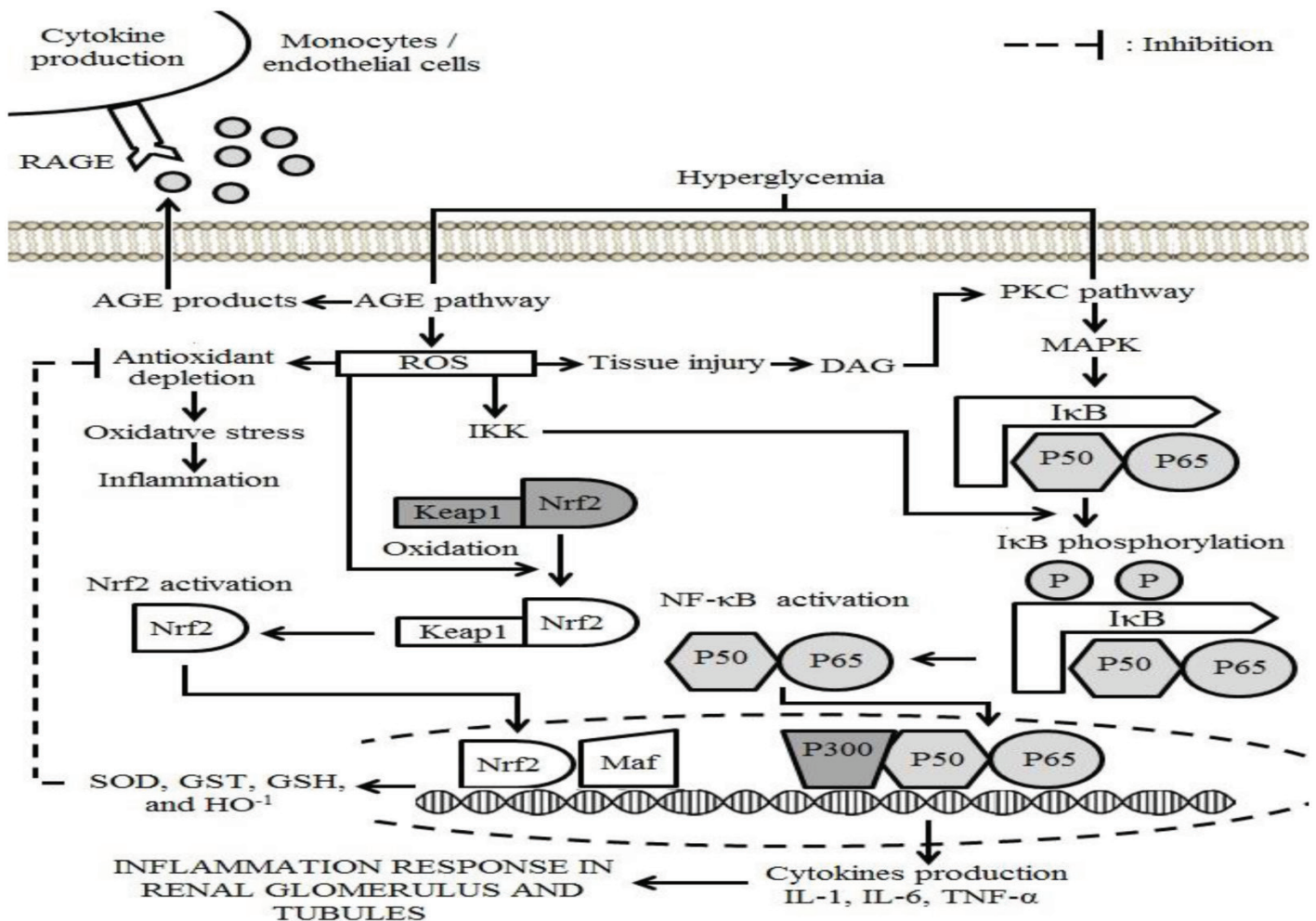


Figure 2 Hyperglycemia-induced production of proinflammatory cytokines

TNF receptor associated factor 6 (TRAF-6) and activation of nuclear factor kappa B (NFκB) from complex with IκB.⁴⁷ NFκB subsequently migrate into nucleus and bind with genome, ultimately lead to various events, that is accumulation of extracellular matrix and glomerulosclerosis (Figure 3).⁴⁸

ICAM-1 is an adhesion molecule which facilitates leukocyte-endothelial adhesion and infiltration into diabetic kidneys. Augment expression of ICAM-1 occur in models of type 1 and 2 of diabetes.⁴⁹ Furthermore, mice models of type 1 and 2 diabetes which deficient in ICAM-1 are shown to be protected towards macrophage accumulation and nephropathy.⁵⁰

INTERLEUKIN 6 (IL-6)

Research conducted by Sekizuka et al⁵¹ showed that serum IL-6 levels increased in type 2 diabetic nephropathy patients compared with diabetic patients without nephropathy. It suggests that proinflammatory cytokines are involved in path-mechanism of DN. Suzuki et al⁵² also found that the cells which infiltrated mesangium, interstitium,

and tubules were positive for mRNA that encoding IL-6, by analyzed kidney biopsies in diabetic nephropathy patients. To date plasma IL-6 levels known to be increased in diabetic patients. Research by Choudhary et al⁵³ involved 60 patients with diabetes showed that serum IL-6 in diabetic patients was higher than control group. Serum IL-6 also positively correlated with UAE and high sensitivity C-reactive protein (HS-CRP). Similar result also found by Shelbaya et al⁵⁴ involved 50 subjects, consisted of 40 patients with type I diabetes and 10 normal subjects. The research found that serum IL-6 levels was significantly higher in diabetes type I and positively correlated with UAE.

The signaling mechanism of IL-6 mediated by unique receptor system (Figure 3). It consists of two functional membrane proteins, i.e. an 80 kDa ligand-binding IL-6R and 130 kDa signal-transducing chain gp130. The activation of these receptors system by IL-6 ligand results in transphosphorylation and activation of JAKs. The gp130 tails phosphorylated and STAT3 proteins are recruited. Phosphorylated STAT3 is followed by nuclear

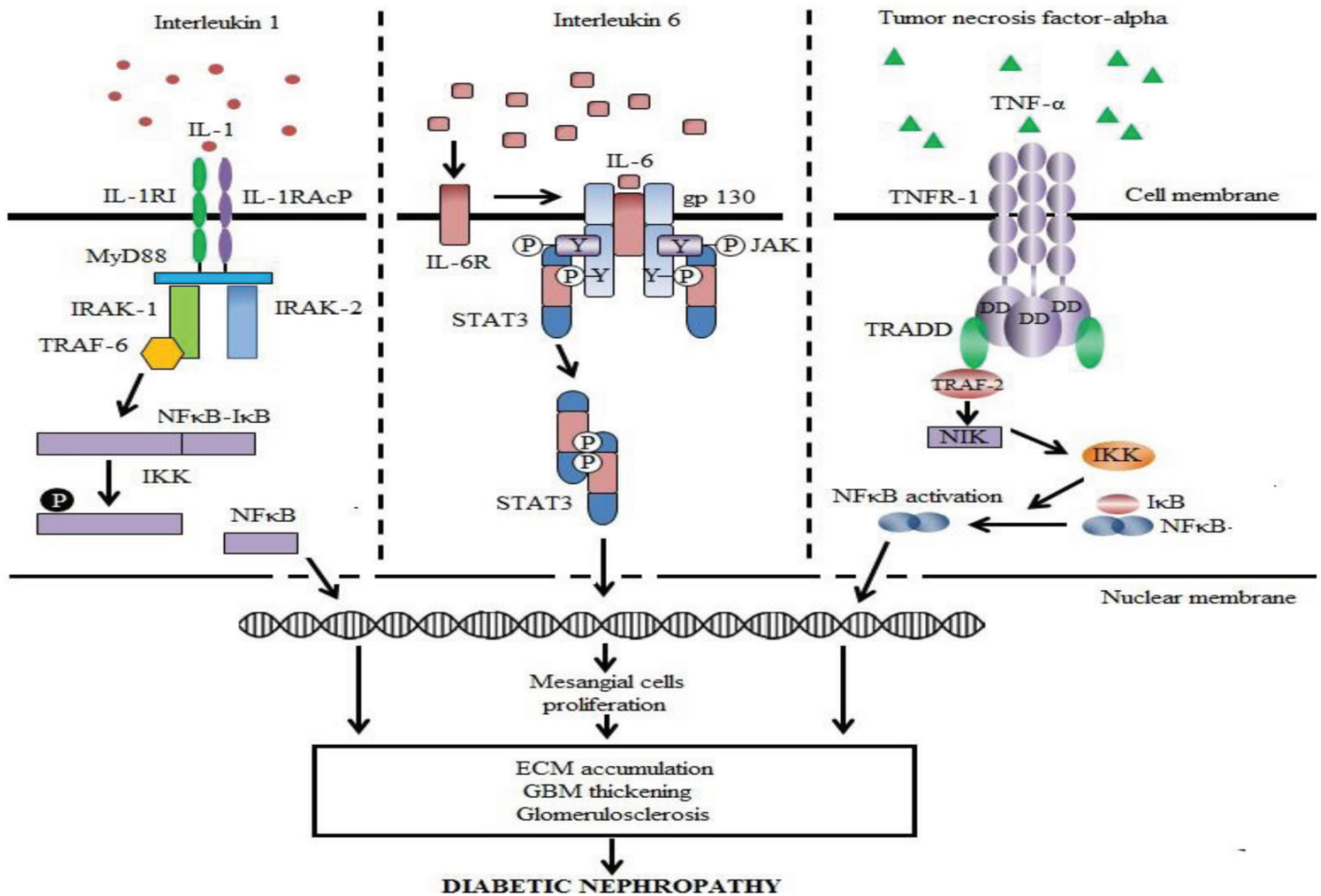


Figure 3 IL-1, IL-6, and TNF- α signaling mechanism in relation to diabetic nephropathy

entry, subsequently enhance transcription of many genes.⁵⁵ IL-6 also promotes growth and proliferation of mesangial cells.⁵⁶ It has been known that increase proliferation and activity of mesangial cells resulting in extracellular matrix (ECM) accumulation, glomerular basement membrane (GBM) thickening, and glomerulosclerosis,⁵⁷ ultimately lead to diabetic kidney disease.⁴⁸

TUMOR NECROSIS FACTOR-A (TNF-A)

(TNF- α) is a pleiotropic inflammatory cytokine, not only synthesized by hematopoietic cells, e.g. monocytes, macrophage, and T cells, but also produced by intrinsic renal cells, e.g. mesangial, endothelial, dendritic, and renal tubular cells.^{58,59,60} TNF- α exert various effects to cells including apoptotic and necrotic cell death by direct and autocrine mechanism, also alterations of endothelial permeability.⁶¹ TNF- α also related with ROS in variety of cells including mesangial cells,⁶² lead to impairment of glomerular capillary wall barrier function, hence increasing albumin permeability.⁶³

TNF- α acts on its receptors, which is TNF receptor 1 and 2 (TNFR-1 and TNFR-2). Affinity of TNFR-2 is five times TNFR-1, but TNFR-1 exerts

many biological activities. TNFR-1 also expressed in all cell types, while TNFR-2 expressed limited to immune cells. Binding of TNF- α to TNFR-1 resulting in TNFR-associated death domain (TRADD) binds to the DD of TNFR-1 and recruits TNFR-associated factor 2 (TRAF-2). This adaptor protein recruit NF- κ B-inducing kinase (NIK) and IKK complex, which activates NF- κ B. Subsequently, NF- κ B enter to nucleus, to bind to its genome lead to detrimental effect (Figure 3).⁶⁴

Future Strategies Targeting Inflammation

To date there is still no treatment to prevent the development and progression of DN. Tight control of glucose levels and blood pressure, blockade of renin-angiotensin system, and regulation of lipid levels (dyslipidemia) still become main strategies in the prevention of DN development.⁶⁵ Unfortunately, these approaches still not completely protect the kidney from injury. Therefore, novel therapeutic agents that intervene with major path mechanism of DN are still needed.

Regulation of TNF- α may reduce progressivity of renal damage in diabetic conditions. Moriawaki et al⁶⁶ reported the effect of infliximab

to diabetic nephropathy. Infliximab is a chimeric anti-TNF- α antibody. In the study, the levels of albuminuria and TNF- α urinary excretion in diabetic rats treated with infliximab were found to be decreased.

Other study with pentoxifylline (PTF) also showed that inhibition in TNF- α may be used as therapeutic approach of DN.^{67,68} PTF is a methylxanthine-derived phosphodiesterase inhibitor which have the capability as anti-inflammation. Beside its effect to TNF- α , PTF also involved in modulation of IL-1 β and IL-6.⁶⁹

Studies found that PTF able to reduce urinary protein excretion in patients with diabetes, both in normal renal function or insufficiency.^{70,71,72} Antiproteinuric effect of PTF is associated with reduction in TNF- α concentration. PTF inhibits TNF- α genes transcription and blocks TNF- α mRNA accumulation resulted in significant decrease of TNF- α levels and urinary protein expression without neither metabolic nor hemodynamic changes.^{67,70}

CONCLUSION

Diabetic nephropathy remains a major challenge in the field of medicine. Huge number of evidence now exist to prove that several proinflammatory cytokines are known to be involved in its mechanism, including IL-1, IL-6, and TNF- α . These cytokines exert important events in development and progression of DN. Knowing this pathway in detail has the benefits for the development of novel therapeutic approach. Intervention in inflammatory pathway may able to interrupt progression and development of DN.

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