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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,*]

[a] Department of Clinical Biochemistry, Faculty of Pharmacy, University of Mansoura, Mansoura 35516, Egypt
[b] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Tabuk, Tabuk 71491, Saudi Arabia

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ABSTRACT

Diabetic vascular complication is a leading cause of diabetic nephropathy, a progressive increase in urinary albumin excretion coupled with elevated blood pressure leading to declined glomerular filtration and eventually end stage renal failure. There is growing evidence that activated inflammation is contributing factor to the pathogenesis of diabetic nephropathy. Meanwhile, IL-18, a member of the IL-1 family of inflammatory cytokines, is involved in the development and progression of diabetic nephropathy. However, the benefits derived from the current therapeutics for diabetic nephropathy strategies still provide imperfect protection against renal progression. This imperfection points to the need for newer therapeutic agents that have potential to affect primary mechanisms contributing to the pathogenesis of diabetic nephropathy. Therefore, the recognition of IL-18 as significant pathogenic mediators in diabetic nephropathy leaves open the possibility of new potential therapeutic targets.

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1. Introduction

Considered as a leading reason for end-stage renal failure, diabetic vascular complications account for high mortality rates occurs in patients with diabetes [1]. Patients with diabetic kidney are at high risk of developing both renal disease and cardiovascular morbidity and mortality [2]. Chronic hyperglycemia induces abnormal pathology of various renal cells, which contributes to renal dysfunction in diabetes. High glucose plays detrimental role

Abbreviations: COX-2, cyclooxygenase-2; DN, diabetic nephropathy; ICAM-1, intracellular adhesion molecule-1; IL-18BP, IL-18 binding protein; IRAKs, IL-1R-associated kinases; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein-1; MyD99, myeloid differentiation 88; NFkB, nuclear factor kB; NIK, NFkB-inducing kinase; NK, natural killer; NO, nitric oxide; Th, T helper cells; TNF, tumor necrosis factor; TRAF-6, tumor necrosis factor receptor associated factor; TLR, Toll-like Receptor; UAE, urinary albumin excretion; VCAM-1, vascular cell adhesion molecule-1.

* Corresponding author at: Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Tabuk, Tabuk 71491, Saudi Arabia.
E-mail address: mhgayyar@yahoo.com (M.M.H. Al-Gayyar).

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Table 1
Causes of diabetic nephropathy.

Factors causing diabetic nephropathy		Reference
Metabolic factors	Advanced glycation end products	[10]
	Aldose reductase/polyol pathway	[11]
	Diacylglycerol (DAG)-protein kinase C (PKC) pathway	[12]
	Reactive oxygen species	[13]
Hemodynamic factors	Activation of rennin angiotensin system	[14]
	Endothelin	[15]
	Nitric oxide	[16]
Intracellular factors	Nuclear factor-kB (NF-KB)	[17]
Growth factors and cytokines	Transforming growth factor-β	[18]
	Growth hormone and insulin like growth factor	[19]
	Vascular endothelial growth factor	[20]
	Platelet derived growth factor	[21]

in development and progression of diabetic renal complications via various signaling pathways such as increased production of advanced glycation end products, expression of protein kinase C, activation of the polyol pathway and generation of reactive oxygen species [1,3–6].

2. Diabetic nephropathy

Diabetic nephropathy (DN) is a syndrome defined as a progressive increase in the excretion of urinary albumin (UAE), elevated blood pressure coupled with glomerular lesions leading ultimately to loss of glomerular filtration and eventually end stage renal failure [7]. DN remains the most prevalent chronic disease of the kidney. It is reported that about one third of patients with diabetes develops nephropathy. In addition, about 25–40% of type 1 diabetic patients develop DN within 20–25 year of diabetes [8]. Multiple mechanisms contribute to the development of DN. Sustained hyperglycemia and hypertension are the most important factors in the initiation and progression of nephropathy. Some of these mechanisms were summarized in Table 1. Regardless of multiple researches conducted on molecular and clinical basis, only partial protection is obtained by the available standard therapy that targets renin–angiotensin–aldosterone system by using angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers [9]. Therefore, new and effective therapeutic approaches are required especially with the alarming increase of diabetes globally.

2.1. Diabetic nephropathy and inflammation

There is growing proof that both activated innate immunity and inflammation engage to pathogenesis of diabetic nephropathy [22]. Therefore, multiple cells, including leukocytes, monocytes and macrophages as well as other molecules such as chemokines, adipokines, adhesion molecules, enzymes like cyclooxygenase-2 and nitric oxide synthase, receptors like toll-like receptors and nuclear receptors, growth factors and nuclear factors like nuclear factor κB (NFκB) are all implicated in processes related to diabetic nephropathy [23]. Inflammation plays vital role in the process of fibroblast activation and subsequent tissue fibrosis; the most fundamental and distinguished feature of DN. Therefore, inflammatory pathways that are activated by the different metabolic, hemodynamic and physiological factors appear to be critically involved in the development and progression of DN [24]. Further support for the contribution of inflammation to diabetic renal injury comes from studies where the use of immunosuppressive

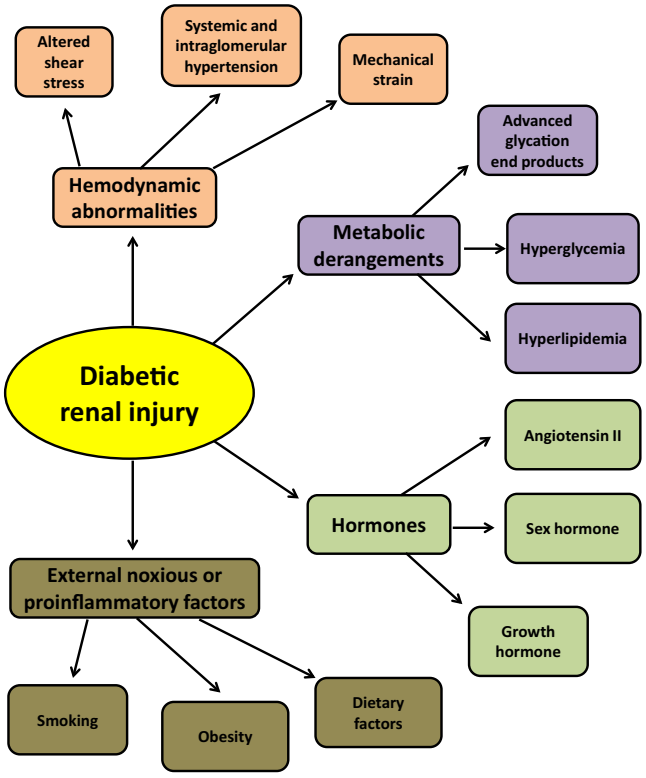

Fig. 1. Factors associated with diabetic renal injury that induced the activation of diverse signal transduction systems in kidney cells.

strategies declined the accumulation of renal macrophage leading to attenuation of the development of DN [25–27].

Hyperglycemia, advanced glycation products and other components of diabetic milieu induce activation of renal cells, which lead to expression of numerous compounds such as chemokines, adhesion molecules and proinflammatory cytokines. Collectively, these incidents contribute to renal cell injury and subsequent gross anatomical and functional alteration associated with DN including albuminuria, mesangial expansion, thickening of glomerular basement membrane, tubulointerstitial damage and fibrosis [28]. The factors associated with diabetic renal injury were summarized in Fig. 1.

It is now widely accepted that accumulation of inflammatory cell in the kidney is a key player in the induction of DN [29]. Indeed, blocking the recruitment of inflammatory cells to the kidney has been proved to protect against renal injury in animal models of DN [30]. Pro-inflammatory cytokines that are produced by inflammatory cells directly damage kidney architecture [31].

Cytokines are pleiotrophic low molecular weight polypeptides, which can produce autocrine, paracrine and juxtacrine effects. Cytokines play crucial role in regulating which inflammatory and immune responses. The role of Cytokines' inflammatory and immunologic pathways in the pathogenesis and progression of DN is well documented [32]. The major pro-inflammatory cytokines that have been reported to play a pivotal role in the pathogenesis of DN are interleukin (IL)-1, IL-6, IL-18 and tumor necrosis factor (TNF)-α. All these cytokines are increased in DN. Moreover, the elevated serum and urine levels of pro-inflammatory cytokines correlates with the progression of DN. Furthermore, gene polymorphism of both the pro-inflammatory cytokines and their receptors can be used as strong predictor of the susceptibility and progression of DN [33]. Indeed, targeting cytokines and/or their receptors ameliorated DN, implying significance of cytokines as key players involved in DN pathophysiology [34].