Cytokines and T Helper Cells in Diabetic Nephropathy Pathogenesis

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Abstract

Diabetic Nephropathy (DN) is considered the main cause of end stage kidney disease around the world. However, its pathogenesis is not completely established. More than just a direct consequence of chronic glycemic changes, recent studies had suggested Diabetic Nephropathy could be considered an inflammatory disease. It has been shown that concentrations of pro-inflammatory cytokines, as IL-1, IL-6, IL-18, IL-33, IFN-γ and TNF-α actively participate in development and progression of DN, and thus, are involved in pathogenesis. Besides, changes in acquired immune response, especially the presence of cellular immune response profiles of pro-inflammatory and effector nature, mainly Th1 and Th17, as the imbalance between interaction of cytokines and T regulatory cells, foment the onset and progression of DN. Here we summarize the main evidences that support the critical role of the immune system in this condition. These new conceptual advances in DN understanding are essential for development of new therapeutical strategies and prognostic factors, which could be protagonists or adjuvants to the current ones, leading ultimately to a better clinical management of DN patients.

Keywords

Diabetic Nephropathy, Cytokines, Cellular Immunity

1. Introduction

Diabetic Nephropathy (DN) is the main cause of end stage renal disease (ESRD) in the world and reaches around 30% of diabetic patients. Besides, it contributes to the risk of developing cardiovascular diseases which progressively increase as DN evolves, and most of these patients die due to these events [1]. DN affects around 35% of people with Diabetes Mellitus type 1 (DM1) and 10% to 40% of those with Diabetes Mellitus type 2 (DM2) [2]. In Brazilians with DM2, the cumulative incidence in 10 years was 31% [3], similarly to 34% in Finnish [4], 35% in Israeli [5] and 31% in UKPDS-*United Kingdom Prospective Diabetes Study* [6].

Morphological changes in DN are similar in patients with DM1 and with DM2 [7]. Functional changes occur in nephrons, especially in glomeruli, including hyperfiltration and hyperperfusion [8]. All cellular elements of the kidney as glomerular endothelium, mesangial cell, podocytes and tubular epithelium are potential targets for hyperglycemic injury [9]. Among the main morphological changes, there are diffuse and nodular glomerulosclerosis, glomerular basement membrane thickening, glomerular hypertrophy, mesangial cells expansion, foot process effacement and tubular interstitial fibrosis, resulting in progressive albuminuria, reduction of glomerular filtration rate and blood pressure elevation [10]-[13].

DN is characterized by extracellular matrix (ECM) excessive accumulation, especially collagen and fibronectin, thickening of all basement membranes, including the glomerular (GBM) and tubular (TBM) ones and mesangial matrix increase, which leads to diffuse and nodular glomerulosclerosis—"Kimmelstiel and Wilson nodules", interstitial fibrosis and foot process effacement [14] [15]. Therefore, fibrosis is the essential and most important characteristic in DN and inflammation seems to be the central trigger in the onset and progression of renal fibrosis [16].

While it was thought the main causes of injury in DN were related to metabolic and hemodynamic factors, in the last years, studies have emphasized increasing evidences on the critical role of inflammation and immunomodulation, both in pathogenesis and progression of DN. Therefore, nowadays it is considered an inflammatory disease [17]-[20]. As an example, plasma concentration of some inflammatory cytokines is increased in diabetic patients, being strong predictors of development of diabetic secondary changes, particularly DN [21]-[23]. DM2 by itself is associated with inflammation, but inflammation also contributes significantly to the development of DN [24]. Here we summarize recent advances in DN understanding demonstrating immune system protagonism and the balance between regulation and inflammation in the establishment and progression of this disease.

2. Proinflammatory Cytokines and DN

The role of inflammatory cytokines in DN pathogenesis was suggested for the first time in 1991 by Hasegawa and collaborators [25]. In that paper, authors demonstrated that peritoneal macrophages cultured with glomerular basement membrane of diabetic animals produced significantly higher quantities of inflammatory cytokines, as tumor ne-

crosis factor-alpha (TNF-α) and interleukin (IL) 1, compared with those cultured with glomerular basement membrane of normal animals.

In clinical studies, increased serum concentration of inflammatory markers has been found in DM1 and DM2 patients, which seems to predict the onset and progression of diabetic complications [26] [27]. It was demonstrated proinflammatory cytokines concentrations increase with DN progression [28] [29] and are independent related with albumin urinary excretion showing a direct association with clinical markers of glomerular and tubular-interstitial lesions [30]. Experimental studies with diabetic models demonstrated inhibiting the recruitment of inflammatory cells to the kidney is a protective factor in DN [31] [32].

All renal cells (endothelial, epithelial, mesangial and tubular) are also able to synthesize proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1) and IL-6, and therefore these cytokines, acting in a paracrine or autocrine manner can induce a variety of effects in different renal structures with an important role in development and progression of many renal diseases including DN [33] [34]. It is now known that among the inflammatory cytokines, IL-1, IL-6, IL-18 and TNF-α are relevant for DN development, performing many actions potentially involved in the development of its complications [35].

In DN experimental models, were observed an increase in IL-1 renal expression, related to chemotactic factors and adhesion molecules expression [36] [37]. IL-l improves the synthesis of intercellular adhesion molecule 1 (ICAM-1) and vascular cellular adhesion molecule-1 (VCAM-1) by glomerular endothelial cells and induces *de novo* synthesis and expression of ICAM-1 by glomerular mesangial cells and renal tubular epithelium. Besides, this cytokine induces transient expression of E-selectin by endothelial cells [38] [39] as is also involved in development of intraglomerular changes related to prostaglandins synthesis by mesangial cells [40] and is directly related to increase in vascular endothelial cells permeability [41].

Currently, IL-33 other interleukin belonging to IL1 family, has been studied. Initially defined as a proinflammatory cytokine, some studies suggest that it can be associated with immune responses involving T cells and B regulators, indicating that IL-33 has a complex feature [42] [43]. IL-33 role in DN is not well defined [44]. A study that evaluated serum levels of Th1 and Th2 cytokines in diabetic patients with and without DN observed that patients with no DN showed an increase in IFN-γ, IL-12, IL-4 and IL-13 and a reduction of IL-33, with the involvement of both Th1 and Th2 response. In contrast, patients with DN had a more evident Th1 profile characterized by increased IFN-γ, IL-2 and IL-12 and decreased Th2 cytokines IL-33 and IL-13, indicating that DN can be characterized by an increase in Th1 associated with suppression of Th2 response. Furthermore, the higher were microalbuminuria levels and more severe insulin resistance, the lower were IL-33 levels, which can indicate a protective effect of IL-33 during the progression of DN [45].

Furthermore, in experimental studies in which diabetes was induced in rats by means of intraperitoneal injection of Streptozotocin, an increase of IL-33 was demonstrated in

serum and/or in renal parenchyma of diabetic rats, and this increase was even more evident in diabetic rats with contrast-induced nephropathy. These studies suggest that IL-33 may be associated with the onset and progression of ND [46] [47]. In a clinical study in which serum levels of IL-33 were compared between healthy patients, diabetic patients without nephropathy and patients with DM associated with microalbuminuria, which indicates nephropathy, an increase in IL-33 was observed in diabetic patients with or without nephropathy when compared to healthy patients. However, there was no difference when diabetic patients with or without nephropathy were compared. The results of this study suggest that IL-33 cannot be used as a marker of renal injury [48]. These controversial data in the literature show that the exact role of IL-33 in DN remains unknown and therefore more clinical and experimental studies are needed.

Others studies have reported an increase in plasmatic and urinary IL-18 levels in DN patients comparing with control group and also presented a significantly positive correlation with albumin urinary excretion rate in patients with DN [49] [50]. IL-18 is a potent cytokine implicated in various actions, including release of interferon-γ (IFN-γ) which stimulates expression of chemokines receptors in human mesangial cells [51], synthesis of others inflammatory molecules as IL-1 and TNF-α, increase of ICAM-1 and apoptotic process in endothelial cells [52]-[54].

IL-6 is a proinflammatory cytokine and an important mediator of cell proliferation, endothelial cell permeability and increase in matrix production [55]. IL-6 plasma levels are increased in DN patients comparing with diabetic patients without nephropathy [56]. Besides, immunohistochemistry by hybridization in human renal biopsies showed an increased expression of RNAm which codifies IL-6 in infiltrating cells in mesangium, interstitium and tubules which also show a positive relationship with the severity of mesangial expansion [57]. IL-6 has been also related with increased expression of fibronectin [58] and increase in GBM thickness [24]. DM2 patients had an increase in IL-6 production associated not only with DN, but also with GBM thickness, crucial and earlier injury of DN, being considered a strong marker of declining renal function [24].

TNF-α is produced primarily by monocytes, macrophages and T cells, but also intrinsically by kidney cells [59]. Many studies with DN patients have found high plasmatic and urinary TNF-α levels comparing with non-diabetic patients and these concentrations increased with DN progression. These findings show there is a strong relation between increased levels of this inflammatory cytokine and development and progression of renal lesion in DM [30] [60]. Results of a recent Brazilian study showed that patients with DM1 macroalbuminuria had urinary levels of TNF-α and IL-10 significantly higher compared to normoalbuminuric, microalbuminuric and healthy groups. Besides, it was shown that only urinary TNF-α was correlated with the presence and severity of macroalbuminuria, been suggested by researchers as a useful marker in assessing progression of nephropathy in DM1 patients [61].

3. Cellular Immune Response and DN

Among the cells involved in inflammatory process, it is believed that T cells play a key

role in DN early renal damage, especially by presenting cytotoxic effects, and activating tissue macrophages [62]. The first contribution in this regard was pointed to be the increased accumulation of local T cells in diabetic experimental models, being observed an increase in CD4+ and CD8+ T lymphocytes in the interstitium and glomeruli of diabetic rats [63] [64]. One study with diabetic models induced by Streptozotocin (STZ) demonstrated that in a gap of one month, CD4+ were the predominant cells in diabetic kidney, however, in a total period of eight months, the number of CD8+ cells became significant. These data suggests the kidney damage process is initiated by Th profile cells but cytotoxic T cells also play a role in later stages of disease [65].

In general, both activation of immune response mediated by T cells and humoral response mediated by B cells, can participate in type 1 DM pathogenesis [66] [67]. In a study with non-obese diabetic rats for evaluating cellular and humoral immune response in DN early phase, was observed that both T cells and B cells infiltrate glomeruli in this phase [63]. On the other hand, in DM2, considered a non-autoimmune disease, characterized by insulin resistance and/or relative insulin deficiency, not much is known about T cells role in its pathogenesis [68].

InDM1, an increase in T cells was shown in juxtaglomerular region leading to disorder in glomerular albumin excretion and decreased renal filtration. It was also demonstrated that systemic T lymphocytes, especially CD8+ T cells in circulation, are correlated with albuminuria [69]. A multiple regression analyzes showed a positive association between T CD8+ lymphocytes and albumin in patients with DM2 and that activation of these cells could be a systemic response. T cells can be activated by many metabolic and genetic pathways, and in DM2 can be activated by hemodynamic, environmental and metabolic changes [69].

Mensah-Brown *et al.*, showed a T cell increase in glomeruli and interstitium of diabetic mice compared with nondiabetic ones [70]. Studies have demonstrated that DM1 patients presenting proteinuria have increased circulating T cells levels when comparing with non-proteinuric patients, and this accumulation is correlated with albumin urinary excretion rate [71] [72]. Similarly, a more recent study showed the amount of CD4 + T cells in interstitium of DM2 patients correlates with proteinuria level in these patients [64].

Based on cytokines profile and effector function, CD4 + T helper cells can be divided into subfamilies such as Th1, Th2, Th17, regulatory T (Treg) CD4+ CD25+ cells [73] [74]. Th1 cells mainly produce gamma interferon (IFN-γ) and TNF-α and express transcription factor T-box expressed in T cells (T-bet), induce delayed hypersensitivity reactions, activate macrophages and promote cell-mediated immune response [75]. In contrast, Th2 profile is characterized by production of IL-4, IL-5 and IL-13. IL-4 is the cytokine responsible for activating IL-5 and IL-13 expression, as well as transcription factor Gata-binding protein-3 (GATA-3) which regulates these cytokines expression. Furthermore, Th2 cells suppress the differentiation of cells with Th1 profile responses, induce immunoglobulin E (IgE) production and, consequently, contribute for humoral immunity [76] [77].

T cells differentiation for Th17 profile is given by TNF-β and IL-6 in these cells activation. These cytokines activate STAT-3, which increases expression of transcription factor receptor-related orphan receptor γ-t (RORγt) and these factors increase the production of IL-17, a proinflammatory cytokine [78]. T-regulatory cells are characterized by the presence of transcription factor forkhead box protein 3 (Foxp3) and act regulating proinflammatory immune response, being able to suppress effector activity of various T helper cells subtypes in order to avoid damage to host due to excessive inflammatory response [79] [80].

Recent studies indicate that not only the cell imbalance between Th1/Th2 but also between Th17/Tregcontribute to pathogenesis of some inflammatory/autoimmune diseases, as rheumatoid arthritis [81], acute coronary syndrome [82], and diabetes type 1 and 2 [83] [84].

Studies indicate that increased levels of ICAM-1 and P-selectin in diabetic kidney combined with increase in IFN-γ and migration inhibitory factor (MIF) levels, are associated with action of Th1 cells in glomeruli [85]. Little is known about mechanisms of action of Th1 cells in DM2 models for the development and progression of kidney disease. However, increased plasma levels of IFN-γ and positive correlations between plasmatic IFN-γ, proteinuria and glomerular filtration rate were found in type 2 diabetic patients with declared nephropathy [86]. These results indicate that Th1 response together with proinflammatory cytokines could mediate tissue damage in patients with DN [86].

One study comparing patients with type 2 DN and patients without nephropathy revealed no significant change in IL-4 plasma level [86]. Th17 cells produce IL-17A, IL-17F, TNF-$\alpha$and IL-6, and induce inflammation in auto-immune diseases pathogenesis [77]. Studies have related the presence of Th17 cells in murine and human model of DM1 demonstrating their association in pathogenesis of type 1 diabetes [87]-[89]. It was showed that T cells from patients with DM2 have been diverted to exert a proinflammatory phenotype, thus requiring monocytes for maintenance and consequently promoting chronic inflammation by increasing IFN-γ and IL-17 [90].

Recently, the role of IL-17 isoforms in DN has been investigated [91]. A study that evaluated the role of isoform IL-17A in DN observed that diabetic patients with advanced DN showed decreased serum and urinary levels of IL-17A and that DM1 animals with genetic deficiency of IL-17A developed more severe nephropathy. In DM1 and DM2 animals receiving low dose of IL-17A, DN onset was prevented, as well as an attenuation of established DN in those animals with genetically diabetes. These results suggest beneficial effects of IL-17A low doses administration in DN treatment [92]. However, IL-17A cannot be definitely associated with DM2 nephrotic complications, as increased plasmatic levels of IL-17A have been found in patients without nephropathy [93].

Treg cells (imunorregulators) exert important effects on immune homeostasis maintenance and immune tolerance by producing anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β) [94]. Recently, was reported that im-

balance of Th17/Th1/Tregs can contribute to development of type 2 diabetes and its complications [83]. Another previous study demonstrated Treg (CD4+ CD25+FoxP3+) cells could contribute for development and progression of DN in patients with DM2 [95]. Recently, was observed that Treg (CD4+FoxP3+) transfer in animal model resulted in decreased glomerular diameter and albuminuria. On the other hand, Treg cells depletion using monoclonal antibody anti-CD25 resulted in accelerating of DN symptoms progression with increased glomerular hyperfiltration and presence of albuminuria [96]. It has been demonstrated that in DM2 patients, the presence of Treg cells (CD4+ CD25+FoxP3+) is significantly reduced in patients with microalbuminuria comparing with control group, and the number of these cells in the kidney has an inverse correlation with albumin urinary excretion rate, thus suggesting that manipulation of the number or the function of Treg cells may be a strategy in order to reduce inflammation in DN [97]. However, the relation between Tregcells (CD4+ CD25+ FoxP3+) nd DN pathogenesis still requires further investigation [95].

Another anti-inflammatory cytokine produced by Treg cells is IL-35. Its role in type 1 diabetes is not well elucidated; however, a recent study reported an increase of Treg cells in DM1 mice (induced by multiple low doses of Streptozotocin). However, there was a decrease in production of anti-inflammatory cytokines (IL-10, IL-35, TGF-β) and an increase of proinflammatory cytokines (IFN-y, IL-2, IL-17) by these cells, indicating a phenotypic change of Treg cells in DM1 conditions. Furthermore, a reduction in serum levels of IL-35 in DM1 patients was observed compared with healthy control group. These results suggest that IL-35 decrease could be related to development of DM1 [98].

Regarding IL-10, initially described as an important cytokine of Th2 profile, with predominantly anti-inflammatory and immunosuppressive effects [99], it has been reported that the low capacity of production of this interleukin is associated with metabolic syndrome and DM2 [100]. In addition, other studies have shown elevated levels of IL-10 in the serum of patients with diabetic nephropathy, but also a positive correlation between IL-10 and albuminuria levels, thus suggesting a possible involvement of IL-10 in DN pathogenesis [101]-[103].

Recently, two new subfamilies of T effector cells, Th9 and Th22, have been identified [104]. The Th9 cells are characterized by production of IL-9 and IL-10 and are developed from naive CD4 + T precursor cells in response to TGF-β and IL-4 [87] [105] [106]. It was also shown that IL-9 secretion by murine Th2 cells was strongly dependent on TGF-β and TGF-β can redirect Th2 cells to a Th9 phenotype [105]. Besides, TGF-β not only induces differentiation in anti-inflammatory Treg cells, but also in proinflammatory Th9, Th17 cells and inhibits Th22 differentiation [107]. A study with diabetic patients to determine whether the co-production of IL-9/IL-17 by CD4 cells is altered under inflammatory conditions, has shown that these subjects had more frequently memory CD4 cells with transitional capacity to produce IL-9 and IL-17. These data demonstrate the presence of IL-9+IL-17+ cells can play a role in autoimmune human diseases [108].

Another study evaluated serum levels of IL-9 and IL-17 in patients with diabetic kidney disease (DKD). It was suggested that there is a linear negative association between serum levels of IL-17 and DKD, whereas serum IL-9 levels were significantly reduced in diabetic group compared to the group DKD. IL-9 also showed a positive correlation with urea and microalbuminuria. These results suggest the involvement of these cytokines in the DKD, but more studies are needed to further elucidate their role [109].

Regarding Th22 cells, they produce IL-22 and differ from Th17 and Th1 cells due to their differentiation and function. They may be involved in pathology of inflammation, tumors and autoimmune diseases. However, until a few years ago, there were no data on Th22 cells in patients with DM1 [110] [111]. But recently, Xu and contributors conducted a study to identify and quantify different Th cells profiles by flow cytometry in DM1 patients in different phases. The study demonstrated changes in the amount of circulating Th1, Th17 and Th22 cells and data demonstrated that the increase of Th22 cells correlated with Th17 cells in patients with DM1, suggesting that Th22 cells may contribute to its pathogenesis [104]. In another study, it was also observed a link between Th22 and Th9 cells in DM1 patients. These patients showed an increase in Th9 and Th22 cells, as well as increased serum levels of IL-9 and IL-22 compared with healthy individuals [112].

4. Conclusion

Currently, DN has been considered an inflammatory disease with participation of both immune responses, innate and adaptive (humoral and cellular). Cells of immune system and various cytokines play important roles in complex pathogenesis of DN development and progression. These new conceptual advances in DN understanding can be crucial for the development of new therapeutic strategies and to determine prognostic, either protagonists or adjuvants to current ones, leading ultimately to a better clinical management of DN patients.

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Conflict of Interests

The authors declare no conflict of interests.

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