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Diabetic nephropathy and inflammation

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Abstract

Diabetic nephropathy (DN) is the leading cause of end-stage renal failure worldwide. Besides, diabetic nephropathy is associated with cardiovascular disease, and increases mortality of diabetic patients. Several factors are involved in the pathophysiology of DN, including metabolic and hemodynamic alterations, oxidative stress, and activation of the renin-angiotensin system. In recent years, new pathways involved in the development and progression of diabetic kidney disease have been elucidated; accumulated data have emphasized the critical role of inflammation in the pathogenesis of diabetic nephropathy. Expression of cell adhesion molecules, growth factors, chemokines and pro-inflammatory cytokines are increased in the renal tissues of diabetic patients, and serum and urinary levels of cytokines and cell adhesion molecules, correlated with albuminuria. In this paper we review the role of inflammation in the development of diabetic nephropathy, discussing some of the major inflammatory cytokines involved in the pathogenesis of diabetic nephropathy, including the role of adipokines, and take part in other mediators of inflammation, as adhesion molecules.

Key words: Diabetic Nephropathy; Inflammation; Albuminuria; Adhesion molecules; Cytokines

Core tip: In recent years, new pathways involved in the development and progression of diabetic kidney disease have been elucidated; accumulated data have emphasized the critical role of inflammation in its pathogenesis. Expression of cell adhesion molecules, growth factors, chemokines and pro-inflammatory cytokines increased in renal tissues of diabetic patients, and serum and urinary levels of cytokines and cell adhesion molecules, correlated with albuminuria. We review the role of inflammation in the development of diabetic nephropathy, discussing some of the major inflammatory cytokines involved in its pathogenesis, including the role of adipokines, and other mediators of inflammation, as adhesion molecules.

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INTRODUCTION

Diabetes mellitus (DM) is the leading cause of chronic renal failure in development countries and is increasing as a cause of morbility and mortality worldwide. Both type 1 and 2 diabetes, but principally the last one, plays an important role in this problem because of the impact of its complications[1-4].

Among all these complications, diabetic nephropathy (DN) has become the principal cause of end-stage renal failure and cardiovascular mortality, this condition appears after many years of diabetes beginning[3,5].

It is well understood that type-2 DM is not an immune disease but at this time we could consider that there is evidence that the combine of immunologic and inflammatory mechanisms play a pivotal role in its presentation, development and finally its progression.

The DN take place nearby one-third of patient with type 1 DM and 25% approximately of patients with type 2[4,6].

In México, it is described that the main cause of chronic renal failure is type 2 DM, nevertheless we know that not all diabetic patients develop DN, moreover glucose control is not a warranty of a life free of microangiopathic complications[7].

It has been found that despite all pharmacologic therapies available for DN treatment, some patients develop kidney damage, that is why the need of complete understanding of molecular, metabolic and environmental factors that lead to DN and their interaction between them.

Among diverse factors that could interact actively in pathogenesis and progression of DN have been studied the age, gender, smoking, hypertension and hyperuricemia, all of them with suggestive results of correlation with renal disease[2].

In this paper we review the inflammatory factors that lead to the development and progression of DN.

PHYSIOPATHOLOGY

DN is characterized by glomerular hypertrophy, thickness of basement, tubular and glomerular membranes and accumulation of extracellular matrix in these membranes that finally cause tubulointerstitial and glomerular fibrosis and sclerosis[2,6,8]. As we can see several kidney structures are susceptible to hyperglycemia, and this metabolic change cause organ damage due to several cellular *via* including genetic activation and expression, advanced glycation end products generation, polyol pathway activation, abnormal protein kinase activation (PKC), raise of oxidative stress and the molecules that act as growth factors, transcription factors and others[4,8].

There is a response for hyperglycemia from the system, the transcription factors regulate the gene encoding some cytokines like transforming growth factor β (TGF-β), chemokine C-C motif ligand 2, fibronectin, osteopontin, decorin, thrombospondin, aldose reductase and plasminogen activator inhibitor 1, all these molecules involved in inflammation, extracellular matrix synthesis and its degradation are increased in type-2 DM[4].

Some other factors in relation to DN, it is known that some metabolic *via* activated by hyperglycemia are not enough to cause the kidney complication. The family predisposition to disease, race and other environmental factors interact with hemodynamic changes producing, as a result, advanced glycation end products, glucose reduction and sorbitol accumulation into the cell, overproduction of reactive oxygen species and activation of signaling *via* as PKC and mitogen-activated protein kinase[2].

Diabetic patients then could have albuminuria since early phases or stages of organ damage, it is also considered as a very sensible marker of kidney disease progression. As a result there are many glomerular abnormalities including podocyte structure alteration, reduction of nephrin expression and increase of filtration rate, a hallmark of DN[9].

Many mechanisms were investigated in this process, for a better understanding these are divided in mechanisms of immune cell infiltration of kidney, molecules involved in progression and intracellular pathways activated in DN.

Role of inflammation

Now we know that activation of the immune system and chronic inflammation are both involved in pathogenesis of DM and as a result DN. Some studies have demonstrated that cytokines, chemokines, growth factors, adhesion molecules, nuclear factors as well as immune cells as monocytes, lymphocytes and macrophages are all involved in DM pathogenesis and of course play an important role in DM complications[1,5].

IMMUNE CELLS

Macrophages

Macrophages are recognized as the principal inflammatory cell involved in kidney damage, their accumulation relates with severity of DN in experimental models[3].

These cells are responsible of the calling "renal remodeling", so therapeutics proposed to inhibit their accumulation may help to stop progression.

Two subtypes are mainly involved in DN, M1 macrophages activated by Th1 cells, that are able to increase inflammatory response by cytokines expression [interleukins, tumor necrosis factor (TNF) and interferon γ]; and M2 macrophages activated by Th2 cells that promote tissue repairmen, remodeling and neovascularization by antiinflammatory cytokines expression[3]. Is in this way that investigations are working, it is known that the macrophage subtype levels related with recruitment of circulating monocytes from vascular space to glomerular tissue.

Meanwhile M1 macrophages enhance inflammatory response by upper production of reactive oxygen species (ROS), this point will be reviewed later.

As to activated M2 macrophages, they help in inflammation ending with the participation of interleukin 10 (IL-10), TGF-β1, both with anti-inflammatory functions. Besides they produce proinflammatory factors as chemokines, cytokines and superoxide anions[3].

Many investigations are directed to show that statins are capable to block M1 macrophage actions but at the same time improve M2 functions. It will be helpful as one of the strategies used in the treatment of DN directed to this point.

T lymphocytes

T lymphocytes play a determinant role in early kidney damage in DN, they have cytotoxic effects besides macrophages tissue activation[3].

The first contribution of the studies was about the increase in local accumulating T cells in diabetic experimental models. Xiao *et al*[10] and Moon *et al*[11] showed an increase in CD4 and CD8 lymphocytes in diabetic mouse, these changes were observed in glomeruli and interstice.

In type 1 DM there is an increase of T lymphocytes

in juxtaglomerular tissue that results in a disturbance in albumin glomerular excretion and a decrease of renal filtration. Many other studies have shown at this time that T lymphocytes systemic, specifically circulating CD8, correlated with albuminuria[6].

Lei *et al*[6] demonstrated with a multiple regression analysis a positive association between lymphocytes CD8 and albuminuria in type 2 DM patients and the cell activation could be a systemic response.

Several metabolic and genetic *via*, may activate systemic T lymphocytes. In type 2 DM those cells may be activated by hemodynamic, environmental and metabolic changes. The most important activation seen due to hyperglycemia, that activates nuclear factor κB and this results in an over stimulation of lymphocytes by specific cytokines as IL-12 produced by macrophages, and then, production of interferon further lymphocyte activation[6].

CHEMOKINES

These molecules are active components of inflammatory cells recruitment in kidney and are present in every phase of kidney damage[8].

Many chemokines are involved in the inflammatory response in DN, monocyte chemoattractant protein (MCP-1) was first described in its role in early phases of atherosclerosis[12].

MCP-1

MCP-1 can promote transformation of monocytes in macrophages, the last ones produce diverse cytokines as IL-6 and TNF-α, both induce atherosclerosis changes in vascular walls that results in illness progression. Because of its expression is as high in the atherosclerotic plaques than in impaired plaques, systemic MCP-1 was measured in many studies in order to show an association between this chemokine and DN markers. Takebayashi *et al*[12] found that patients with urinary albumin excretion presented higher circulating levels of MCP-1 than patients without this alteration.

All these findings could suggest that MCP-1 plays an important role in pathogenesis of DN as the protein produced not only in vascular wall, atherosclerotic plaques but also in tubular epithelial cells.

CYTOKINES

Cytokines are molecules with a wide spectrum of physiological actions, many of them due to their pleiotropic actions. They have capacity to combine actions in order to amplify their effects and then induce synthesis or expression of other cytokines if needed.

In 1991 it was suggested for the first time the participation of cytokines with inflammatory actions in the development of DN, by demonstration of high production of these molecules from macrophages in glomerular membranes from diabetic rats, but not from non-diabetic rats[5].

At this time we now that inflammatory cytokines play an important role in DN, but cytokines have been involved in the development of other microangiopathic complications of DM[1].

Interleukins

Interleukins are a group of cytokines produced by many cells in different tissues. According to their physiologic actions, they are classified as antiinflammatory and proinflammatory molecules[3].

IL-1

Many studies have shown that IL-1 promotes an increase of adhesion molecules in glomerular endothelium as well as expression of these molecules in other kidney structures[1].

Mesangial cells and renal tubular epithelium overexpress intercellular adhesion molecule-1 (ICAM-1) and E-selectin, additionally, IL-1 induces prostaglandin E2 synthesis in mesangial cells, this fact cause alterations in the glomerular hemodynamics[1].

Moreover, IL-1 stimulates hyaluronan synthesis, leading to cell proliferation in DM patients, this facts contributes to development of DN. It is known that this proinflammatory cytokin is increased in experimental models with albuminuria and at the same time with macrophages accumulation[1]. According to these pathological changes, IL-1 modifies vascular permeability and increase expression of chemokines that as a result leads proliferation and synthesis of extracellular matrix in mesangium[3].

IL-6

IL-6 is another molecule that has been studied in DN due to its pleiotropic effects. Many authors showed that IL-6 concentration is increased in DN. IL-6 has a direct effect in glomerular and infiltrating cells, this effect modified extracellular matrix dynamics affecting membrane thickening in renal glomeruli[1,3].

IL-6 is a cytokine that can enhance proliferation, overexpression of extracellular matrix and affect vascular permeability; these actions lead to DN progress[1].

It has been shown that serum IL-6 is increased in patients with type 2 DM with nephropathy[3].

IL-18

The principal actions of this inflammatory cytokine are; to enhance the production of other inflammatory cytokines by mesangial cells, and upregulation of ICAM-1. Its serum concentration is increased in DN as well as other interleukins and has a determinant role in endothelium apoptosis[1].

IL-18 has several sources in the diabetic kidney as infiltrating, T-lymphocytes, macrophages, monocytes as well as proximal tubule cells. There is a direct correlation between IL-18, albuminuria and albumin excretion rate, so it's relationship with nephropathy has been identified[13].

TNF-α

This is an inflammatory cytokine with many determinant

actions in inflammatory response by several tissues and pleiotropic effects. TNF-α is produced by infiltrating cells, as monocytes, macrophages and T lymphocytes, as well as kidney cells. Previous reports shown that TNF-α can be stored as a proactive form[1].

Its actions are widely known as systemic and in many cases direct cytotoxic effect in kidney cells principally. Nevertheless actions as activation of second messengers, transcription factors (TF), growth factors, cell adhesion molecules, express or synthesis of cytokines and others are recognized as variable biological effects of this molecule, of course all of them playing a determinant role in DN pathogenesis[1].

When TNF-α binds to the receptors, several signaling pathways are activated and a cascade of molecules begin their expression in renal cells, many of this actions results in apoptosis and necrosis[5].

The negative effects have been described in experimental models and in humans[1]. Those effects were manifested as DM nephropathy, hypertension, nephritis and glomerulonephritis, this fact could be demonstrated with the correlation found by Navarro-González *et al*[5]. in 2005 between renal TNF-α and albumin excretion in diabetic mice. This observation demonstrated that this inflammatory molecule is directly involved in pathogenesis of DN by leading cell and tissue damage; moreover albuminuria has been related to a enhanced stimuli for overexpression of TNF-α[3].

TNF-α alters glomerular hemodynamics and promotes increased vascular endothelium permeability. Infiltration by inflammatory cells, neo-formation of extracellular matrix, production of ROS and blood flow disturb are others recognized effects of TNF-α in renal structures[1].

TGF-β1

TGF-β1 is a cytokine member of TGF-β1 superfamily considered also as a transcription factor related to development of renal damage by promoting renal fibrosis. Its activity is recognized as inflammatory and fibrogenic, with two isoforms, TGF-β2 and TGF-β3, all produced by kidney cells, the union between this cytokine and its receptor phosphorylate the Smads. Smads are intracellular proteins that transduce extracellular signals from TGF-β ligands to the cellular nucleus and activate downstream gene transcription. This family is considered to be involved in development of inflammation and fibrosis in the kidney[4,8,13].

That is why TGF-β1 is recognized as one of the principal mediators of structural changes seen in DN, its concentration is higher in DM patients with urinary albumin excretion than in normal individuals[8].

The upregulation of TGF-β1 promotes extracellular matrix proliferation and at the same time inhibits the degradation, so that is why actually overexpression of this factor is directly associated with severe forms of glomeruloesclerosis and glomerulonephritis[8]. Some other changes are favored by TGF-β1, for example the induction of transforming epithelial cells of tubules into fibroblasts; this process is responsible of renal fibrosis, a result of persistent inflammation.

TGF-β1 is considered too as a cytokine which principal function in inflammation is to inhibit this process. Letterio *et al*[14] discovered that experimental models with impairment in *TGF-β1* gene are highly susceptible to several inflammation resulting in autoimmune diseases and even death[15,16].

El Mesallamy *et al*[8] correlated TGF-β1 concentrations with Connective tissue growth factor level; their findings showed that between these two molecules there is a closed interaction in DN. So as we can see, TGF-β1 is a molecule that can regulate not only its own release and its actions but also it has the ability to modulate other molecular releases and their interactions in signaling pathways.

It seems like TGF-β1 has a complex role in renal inflammation, we know that this protein is present as active and as a latent forms, the first one is related to mediator of renal fibrosis that can progress according to many other factors. The second form is a protective factor for the development of renal damage. Some mechanisms for these findings are not well understood yet[17].

TF

Proteins known as TF bind themselves to some gene specific regions to activate or inhibit nuclear transcription process[4].

TF were classified according to its main action, they can be constitutively active or regulatory factors and they can be activated by several metabolic and environmental stimuli in many cellular sites. Due to this last point we can subclassify TF in nuclear factors, cytoplasmic factors and steroid receptor superfamily[4].

Several TF are involved in DN development, here we have the most relevant.

Upstream stimulatory factors 1 (USF1) and USF2 are a part of Myc family and encoded by two different genes.

USF1 and USF2 are involved in some glucose genes responses in many types of cells including kidney cells. It has been shown that overexpression or increase in concentration of these TF are related with albuminuria development and even more the upregulation of many other molecules with proved actions in DN pathogenesis[4].

Smads

Smads conform a transcription factor family that regulates the expression of certain genes. Three classes are known: the receptor-regulated Smads (R-SMAD) which include SMAD1, SMAD2, SMAD3, SMAD5 and SMAD8/9; the common-mediator Smad (co-SMAD) which includes only SMAD4, which interacts with R-SMADs to take part in signaling and the antagonistic or inhibitory Smads which include SMAD6 and SMAD7, they block the activation of R-SMADs and co-SMADs[17].

As mentioned before this family is closely involved with TGF-β1, which phosphorylate Smad 2 and Smad 3 to form a complex with Smad 4, all this process leads to regulate gene in cell nuclei[17].

Smad 4 is the most related with inflammation, if there is an abnormality of this protein, the inflammatory response is more intense and leads a higher concentration of diverse cytokines and adhesion molecules.

There is another relationship that leads the process to be functional for kidney, this happens when TGF-β1 regulates Smad 7 transcription by Smad 3 and Smad 4 binding, so, when Smad 4 is impaired we can see and exaggerated inflammatory response for reduction of Smad 7 expression, activation of Nuclear Factor κB and fibrosis inhibition[17].

Smad 4 seems to be a key point in regulation of TGF-β1 and its different functions media the conjunction with Smad 7 and Smad 3 expression in kidney.

The case of Smad 7 is quiet interesting, it acts in an inhibitory way and regulates the active function of Smad 2 and Smad 3 but by a negative feedback.

The Smad 7 expression is enhanced by TGF-β1 that in normal condition has a negative feedback inhibit the action of Smad and at the same time degrade this transcription factors. When Smad 7 gets degraded then kidney fibrosis begins. If Smad 7 decline renal inflammation persists and as a result begins fibrosis *via* TGF-β and Smad 3.

In as much as the pivotal role of Smad 7 some investigators decided to study therapeutic effects of this factor in experimental models. When Smad 7 was transferred to kidney they found that if there is an overexpression of Smad 7, inflammation and fibrosis decrease.

Adhesion molecules

ICAM-1 and vascular adhesion molecule-1 (VCAM-1) are involved in the attachment of leukocytes to the vascular wall and penetration into the intima, once there, leukocytes can produce proteolytic enzymes that lead to tissue and organ damage, or differentiate into foam cells that lead to the atherosclerotic process[15].

Several animal models have shown that mice deficient in ICAM-1 are resistant to nephropathy in experimental models of diabetes, while treatment with anti-ICAM-1 monoclonal Ab prevents mononuclear cell infiltration into diabetic glomeruli[3].

Our group has shown that the levels of VCAM-1 correlate with the severity of albuminuria in diabetic hypertensive patients[15]. In addition, Seron *et al*[16] reported that VCAM-1 expression is increased in kidney biopsies from patients with DN, they also found a correlation between levels of VCAM-1 and numbers of infiltrating immune cells[18].

ADIPOKINES

Adiponectin and resistin were first described as adipocyte-secreted hormones (adipocytokines) that modulate insulin action. Both; hypoadiponectinemia and hyperresistinemia are associated with inflammation[19].

Hypoadiponectinemia has been reported as a risk factor for the development of albuminuria in mice[19], whereas in humans, resistin is mainly a monocyte-macrophage product. In humans hyperresistinemia promotes the expression of adhesion molecules[20], and is involved in the pathways that lead to albuminuria and renal damage[21].

WHICH INFLAMMATORY MOLECULE?

Certainly, inflammation is an important player in the pathogenesis of DN, However, because of multiple pathways that joint inflammation with diabetic complications, it looks unlikely that one single molecule be sufficient for the development of DN. It is also true that the blockade of the principal mediators could be useful in the prevention of this complication; several studies have been designed in order to indentify therapeutic targets.

The evidence suggest that TNF-α, MCP-1 and adhesion molecules have a prominent role in the development of DN, and all these mediators may be considered therapeutic targets for the prevention and treatment of DN, as we will discuss in the next section.

PERSPECTIVES

Microinflammation is the most important mechanism for development and progression of DN. Our knowledge related to signaling pathways involved in its pathogenesis has not been elucidated at all.

There are several pivotal mediators of inflammation, and their interactions are determinant in the process.

We have reviewed not only biological actions of these mediators, but also their possible therapeutic effects in experimental models.

The Smad family plays a very important role in inflammation and fibrosis in renal disease, its different actions among all molecular mediators leads to open several optional researches in DN.

A very interesting advanced is that if levels of Smad 7 could be restored in sick kidneys we could balance inflammatory responses in patients with renal diseases.

But not only Smad family could be a therapeutic option for DN patients, at this time it is very important take into a count that gene polymorphisms encoding several molecules in this patients have to be modified. Is in this way that investigations are aimed, looking to stop the progression of the disease, and not just for uncontrolled DM but also for other diseases involving the kidney.

Many options for interfering in transcription factors activation have been proposed, first blocking TF binding and second blocking TF pathways for activation. For these conditions there were used by both TF and experimental molecules.

Several studies are needed for interfering with signaling pathways not just for treatment of an abnormal condition as DN but also to prevent it.

Experimental studies have shown that inhibition of TNF-α (with the use of soluble TNF-α receptor fusion proteins, monoclonal antibodies or pentoxifylline) might be an efficacious treatment for renal disease secondary to diabetes mellitus, being pentoxifylline equivalent in efficacy and safety to captopril, and the addition of than drug to inhibitors of the renin-angiotensin system increases

their antiproteinuric effect[1,5].

Our group found that the reduction of urinary albumin excretion with the use of the fixed dose combination trandolapril-verapamil, depends not only from its antihypertensive effect, but also from its action on VCAM-1 adhesion molecules levels[22].

CONCLUSION

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.

Several components of the diabetic milieu, as hyperglycemia, renin-angiotensin system and oxidative stress can activate the inflammatory process in the kidneys, which results in the infiltration of the organ by monocytes and lymphocytes, which secrete injurious molecules, such as proinflammatory cytokines and reactive oxygen species.

This leukocyte activity amplifies the inflammatory response and promotes cell injury and the development of fibrosis. Better understanding of the inflammatory response in diabetic kidneys is expected to identify novel anti-inflammatory strategies for the potential treatment of human DN.

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