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Immune and Inflammatory Role in Renal Disease

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Abstract

Chronic and acute renal diseases, irrespective of the initiating cause, have inflammation and immune system activation as a common underlying mechanism. The purpose of this review is to provide a broad overview of immune cells and inflammatory proteins that contribute to the pathogenesis of renal disease, and to discuss some of the physiological changes that occur in the kidney as a result of immune system activation. An overview of common forms of acute and chronic renal disease is provided, followed by a discussion of common therapies that have antiinflammatory or immunosuppressive effects in the treatment of renal disease.

Introduction

The kidneys have a pivotal role in a number of basic physiological functions including blood pressure control, salt and water homeostasis, blood cell production, acid-base balance, and calcium homeostasis. Therefore, it is not surprising that renal dysfunction can result from, or cause, a variety of pathologies. According to the National Center for Health Statistics, greater than 3.9 million adults (>18 years) have been diagnosed with kidney disease in the United States, a number that amounts to approximately 2% of adult population (214). Mortality resulting from renal disease in the form of nephritis, nephrotic, or nephrosis is the 8th leading cause of death and hypertensive renal disease is not far behind, ranking as the 13th most abundant cause of mortality (158). These data show that renal disease is a significant health problem and that understanding the mechanisms leading to renal disease is an important endeavor with a large potential health impact.

Kidney diseases are typically classified as either chronic or acute. Whereas acute kidney injury (AKI) is commonly associated with bacterial infection, sepsis or ischemia-reperfusion injury (I/R that can transition to chronic renal disease), chronic kidney disease (CKD) typically results from diabetic complications, hypertension, obesity, and autoimmunity. The initiating events that promote renal disease can be quite different; however, AKI can lead to CKD, and, if unchecked, both can lead to end-stage renal disease (ESRD). Importantly, inflammation and immune system activation represent a common underlying characteristic for both AKI and CKD (Fig. 1). The purpose of this review is to outline some of the evidence linking immune and inflammatory mechanisms to the progression of renal disease, discuss changes in renal function that occur as a result of immune system activation, and outline some of the common therapies used to target renal disease with an emphasis on their potential to suppress inflammation and immune system function.

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Contribution of Inflammation to Renal Disease

Inflammation and immune system activation are important causal factors in the development of both acute and chronic renal disease. The immune system is often discussed in the context of two main branches, adaptive and innate immunity. The innate immune response is nonspecific and is the first responder to potential invading pathogens. The adaptive immune response allows the body to efficiently recognize and respond to specific pathogens and has a memory in the event that a pathogen is encountered a second time. These responses have distinctive functions mediated by different protein cascades, immune cell subsets, and cytokines. Although, they are often discussed as separate systems, innate and adaptive immunity work in concert to regulate overall immune system function (Fig. 2).

Innate Immune Cells and Renal Disease

Several key components of innate immunity have been implicated in the progression of renal disease including the complement system, toll-like receptors (TLRs), dendritic cells, macrophages, natural killer (NK) cells, and inflammatory cytokines. Complement is a critical early component of the innate immune response. It consists of serum and cell surface proteins that work in a cascade culminating in the production of a cell membrane attack complex that destroys and removes pathogens. There are three major pathways for complement activation (classical, alternative, and lectin). Altered regulation of complement has been implicated in the development of chronic renal disease [reviewed in ref. (12)], although there are potential protective roles for complement as well. For example, lupus nephritis is associated with subendothelial immune complex deposition that promotes neutrophil infiltration leading to glomerular damage. Inhibiting complement proteins (C3, C5) reduces albuminuria and glomerular histological damage (proliferation and crescent formation) in experimental mouse models of lupus nephritis suggesting a pathogenic role for complement (5, 264). In contrast, early complement components are important for promoting the clearance of immune complexes and, therefore, can protect the kidneys from immune complex-mediated diseases. Indeed, humans with genetic deficiencies of either complement C1q or C4 have a greater risk of developing lupus nephritis (261). This protective role for complement is further supported by studies in mice showing that a genetic deletion of C4 or C1q promotes antibody production, immune complex-mediated renal injury, and mortality (19,51). This type of seemingly conflicting data underscores the complex role of the complement system in the pathogenesis of renal disease.

TLRs are a group of cell surface proteins that serve as pattern-recognition receptors that typically bind to microbial pathogens and initiate an inflammatory response. TLRs have been implicated in both AKI and CKD. For example, TLR4 knockout mice were protected against cisplatin-induced AKI, and nonspecific TLR inhibition with chloroquine protected against renal dysfunction in a mouse model of sepsis (278, 282). In addition to AKI, TLRs directly correlate with renal disease severity and inflammatory markers (116, 126) suggesting a pathogenic role for TLRs in CKD in humans.

Antigen presenting dendritic cells are critical for the activation of T cells and establishing T cell-mediated glomerular inflammation. Dendritic cells are hematopoietic in origin, are located in the kidney, and have cellular projections that contact and capture antigens. Upon antigen contact and activation the dendritic cells can signal T cell receptors resulting in activation. Renal dendritic cells and subsequent activation of T cells have been demonstrated in animal models of glomerulonephritis (6, 197).

Macrophages, phagocytic cells derived from monocytes, are located in peripheral tissues and act as important mediators of inflammation and immune modulation. They contribute both to normal physiological function and pathophysiology and are prevalent in the kidneys of

humans with chronic renal disease (61). Macrophages can be activated by immune complexes associated with complement or by cells of the adaptive immune system (T lymphocytes and their cytokines). In the setting of renal disease, macrophage activation often occurs secondarily to complement activation or effector T cells activated by antigens not specific to the kidney suggesting that macrophages may not be prominent initiators of renal disease (48). Nevertheless, both AKI and chronic renal diseases including autoimmune-mediated glomerulonephritis are associated with increased macrophage numbers in the kidney (219).

It is worth noting that there are a variety of different macrophage subpopulations. Although it is an oversimplification, they are most commonly classified as either M1 or M2. The subpopulation associated with renal disease is the classically activated proinflammatory M1 macrophages that are activated by inflammatory cytokines such as interferon gamma (IFN-γ) or tumor necrosis factor alpha (TNF-α) (156) and are derived from cells of the innate or adaptive immune systems. Classically activated macrophages release inflammatory cytokines, promote oxidative stress, and the development of renal fibrosis (195). The causal role for classically activated macrophages in nephritis is supported by studies showing that macrophage depletion (97) or inhibition of monocyte chemoattractant protein (MCP-1) (243) reduces renal macrophages and protects the kidney. While macrophages have an important role to scavenge cellular debris, increased renal infiltration of macrophages can tip the balance toward causing local injury and inflammation. The injury and inflammation are mediated by the release of macrophage-derived inflammatory cytokines like interleukin (IL)-1, IL-6, IL-23, and the generation of reactive oxygen/nitrogen species, each of which have been implicated in impaired renal function (73, 113).

NK cells can cause activation of macrophages through the release of IFN-γ and are, themselves, activated by cells that do not have major histocompatibility complex class 1 (MHC1) present on the cell surface (122). This nonspecific response to a foreign pathogen makes NK cells important mediators of innate immunity. In the kidney, NK cells are commonly associated with AKI. For example, NK cells that promote apoptosis in tubular epithelial cells, and NK cell depletion protects against ischemia-reperfusion injury (284). In chronic autoimmune renal diseases, the role for NK cells in renal injury remains unclear and is complex. Antigen presentation by dendritic cells, a key step in activation of adaptive immunity, can induce NK cell cytokine production (i.e., IFN-γ) and ultimately promote renal disease progression (62). On the other hand, NK cells can function to destroy autoreactive T cells that promote autoimmune disease (229). Therefore, by regulating adaptive immune system function, NK cells may actually provide protection against chronic renal disease. The ability for NK cells to respond to both nonspecific stimuli as well as recognizing autoreactive T cells suggests that they are at crossroads of the innate and adaptive immune response.

Adaptive Immune cells and renal disease

The function of the adaptive immune system is largely controlled by T lymphocytes (cell-mediated immunity) and B lymphocytes (humoral/antibody-mediated immunity). B Lymphocytes produce autoantibodies that contribute to renal diseases including systemic lupus erythematosus (SLE), Goodpasture's syndrome, and immunoglobulin A (IgA) nephropathy. Aberrantly glycosylated IgA1 molecules can deposit in the mesangium resulting in complement activation as well (74, 235). Two major T cell types comprise the cell-mediated arm of the adaptive immune system, CD8+ cytotoxic T cells and CD4+ T helper (Th) cells. CD8+ T cells are analogous to NK cells of the innate immune system in that their role is to destroy infected cells. However, cytotoxic T cells differ from NK cells in that they recognize specific antigens presented on an MHCI molecule (NK cells recognize cells that do not have MHC1). CD8+ T cells have a complex role, particularly in chronic

renal diseases like lupus nephritis. Cytotoxic T cells can be activated by specific renal autoantigens causing local damage and contributing to renal disease and inflammation. In this way, activated CD8+ T cells can release additional renal specific autoantigens that promote a vicious cycle leading to further activation of CD8+ cells and more renal damage (178). While CD8+ T cells are increased in kidneys from patients with SLE, there are also regulatory populations of CD8+ T cells that have the potential to protect against tissue injury, in part, by suppressing pathogenic CD4+ T cells (250).

CD4+ Th cells represent the other major players in cell-mediated immunity and are activated by inflammatory cytokines and antigen presenting cells. Th cells can be further classified into subsets based largely on the type of cytokine they produce or their primary function and include Th1 (154), Th2 (154), Th17 (87), and T regulatory cells (4). Th1 cells are characterized by the production of inflammatory cytokines including IFN-γ, IL-2, lymphotoxin-α, and TNF-α. The Th1 polarized subset of CD4+ cells promotes the activation of macrophages and CD8+ T cells that ultimately drive tissue injury (96). Th2-polarized cells primarily secrete cytokines (IL-4, IL-5, and IL-10) that are often referred to as “antiinflammatory” because they can downregulate Th1 cells and suppress macrophage activation (155). However, consistent with the complexity of many facets of immune system function, cytokines from Th2 polarized cells have multiple roles in immune regulation. Th2 cytokines promote B cell differentiation leading to the production of potentially pathogenic autoantibodies characteristic of autoimmune disorders (96). The differing functions of Th1 and Th2 cytokines ultimately led to a proposed model for describing renal diseases as either Th1 or Th2 dominated. For example, crescentic glomerulonephritis, a rapidly progressing acute form of nephritis that can quickly advance to end stage, is commonly considered to be a Th1-dominated disease (248). In contrast, membranous glomerulonephritis, a chronic form of nephritis caused by immune complexes formed in response to autoantigens from the glomerular basement membrane, is a Th2-dominated disease (94). Perhaps not surprisingly, there are renal diseases including lupus nephritis that are associated with both Th1 and Th2 cytokines.

While Th1 and Th2 cells represent the classical model for defining immune-based diseases, two other CD4+ T cells are now prominently recognized for their roles in inflammatory renal disease. Th17 cells are a relatively recently discovered T cell subset that are CD4+RORγ+ and produce IL-17, IL-21, and IL-22 cytokines (87, 104). Th17 cytokines can promote renal inflammation in part by increasing TNF-α expression and up-regulating chemokines that lead to the invasion of immune cells into the kidneys (252). Th17 cells are now recognized as important mediators of tissue injury and inflammation associated with autoimmune-mediated nephritis. An early study showed that inducing nephrotoxic nephritis by injecting sheep serum into mice caused renal injury associated with IL-17 producing T cells. When these studies were repeated in IL-17 knockout mice, the development of nephritis was blunted (181). In addition, infiltration of IL-17 producing cells is increased in the tubule interstitial space of the common MRL-Fas/lpr model of SLE (283). A similar relationship between IL-17 and autoimmune-associated renal disease was shown by knocking out both TNF-α receptor 1 (TNFR1) and TNFR2 in the New Zealand Mixed 2328 mouse model of SLE. Knocking out both TNFR1 and TNFR2 in this model accelerated renal injury in association with activation of a Th17 phenotype (105). Taken together, these studies demonstrate an important role for Th17 cells in the pathogenesis of chronic renal disease.

Finally, there is a regulatory T cell subset (Treg) that is CD4+CD25+FoxP3+. Tregs suppress adaptive immune system function and promote self-tolerance thereby protecting against autoimmune disease (205-207). The immunomodulatory actions of Tregs are proposed to occur by releasing cytokines like transforming growth factor beta (TGF-β) and

IL-10 that can inhibit the release of Th1 cytokines. Downregulation of Treg cells and/or dysfunction of Treg cells promote autoimmune disease and inflammation. The protective role for Tregs against renal injury is supported by evidence showing that expanding the Treg population can delay the onset of renal injury and inflammation associated with autoimmune-induced nephritis (251). The exact mechanisms by which this occurs, and the regulation of Tregs during the immune response, continue to be investigated.

Cytokines as mediators of renal disease

Regardless of whether innate or adaptive immunity is involved, or whether the renal disease is acute or chronic, it is clear that inflammatory cytokines have a central role as both mediators of immune function and initiators of renal injury. However, cytokines have immunomodulatory roles that can abrogate the development of renal disease as well. The Th1 cytokine IFN-γ, for example, has potential dual roles in the pathogenesis of renal disease, able to both promote and limit disease progression. Results show that direct transfer of IL-12 secreting cells under the renal capsule of the MRL-Fas(lpr) model of lupus nephritis, induces renal injury. However, when these studies were repeated in MRL-Fas(lpr) mice lacking the IFN-γ receptor, the kidneys were protected (218). On the other hand, the presence of IFN-γ receptors are required to blunt the progression of renal injury caused by macrophage-secreted growth factors in MRL-Fas(lpr) kidneys (217). Typically, when cytokines are involved in the pathogenesis of renal disease, they contribute by upregulating endothelial cell adhesion molecules and chemokines that further promote renal immune cell infiltration (8,25,190). In addition, signaling pathways activated by many cytokines increase Nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) activation, a transcription factor that further promotes a proinflammatory phenotype (210, 211). Indeed, NF-κB expression and/or activation are increased in the kidneys from patients with glomerulonephritis (208,285), diabetic nephropathy (151), and AKI (134). One of the consequences of this inflammatory cycle is to drive the development of local oxidative stress that enhances renal injury and impairs both renal tubular and renal hemodynamic function (discussed below). The renal hemodynamic changes resulting from common inflammatory cytokines that can ultimately promote renal injury are discussed in Section “Consequences of Renal Inflammation.”

Consequences of Renal Inflammation

Few studies have examined the chronic changes in renal hemodynamics and tubular transport that result from specific inflammatory mediators or cytokines. Renal inflammation occurs with the macrophage accumulation and infiltration of inflammatory cells. The contribution of inflammatory mediators to renal hemodynamic and tubular dysfunction depends on the pathological state, the inflammatory mediators, and the site of inflammation. This section will focus on renal inflammation and its impact on renal hemodynamic, glomerular, and renal tubular injury. The contribution of renal inflammatory mediators to fluid and electrolyte imbalances, diabetes, and blood pressure regulation and hypertension will also be briefly reviewed.

Renal hemodynamic changes

Inflammation results in changes in renal hemodynamics that can occur in minutes to hours or over the course of days to years. The majority of the experimental studies have determined the impact of inflammation and inflammatory mediators to renal hemodynamics in pathological states. In chronic autoimmune models, for example, renal hemodynamic function is impaired as evidenced by reduced renal blood flow and a hypertensive shift in the pressure natriuresis relationship (143, 256). While the mechanisms leading to renal hemodynamic changes are not clear, most studies have focused primarily on the association

with the infiltration of inflammatory cells, in particular activated T cells and monocytes, and the contribution of inflammation in general or specific cytokines. It is very difficult to determine the potential contribution of a single factor since the inflammatory state results in the generation of a multitude of cytokines. Experimental studies in genetically modified animals or selective pharmacological inhibitors have provided the most insight concerning the influence of a single chemokine or chemokine receptor. In general, renal inflammation results in decreases in renal blood flow and glomerular filtration rate (GFR) (88,168,185). Chronic inflammation leads to a progressive decline in GFR that ultimately results in ESRD (88,168). Thus, understanding the contribution of inflammatory mediators to renal hemodynamic function has the potential to lead to therapeutic approaches to preserve renal blood flow and GFR during pathological states.

The process of accumulation and activation of leukocytes, monocytes, and macrophages in the kidney can result in a progressive decline in renal blood flow and GFR (88, 168). Elevated plasma and kidney levels of MCP-1 and activation of the C-C chemokine receptor type 2 (CCR2) mediates macrophage accumulation and activation (50, 68). Improved renal hemodynamics has been demonstrated to correlate with decreased levels of MCP-1 and CCR2 inhibition (54). These studies have been primarily conducted in renal pathological states. Less is known about the influence of these cytokines and others on renal hemodynamics in nonpathological states.

Cytokines and inflammatory mediators such as TNF-α, TGF-β, and ILs can influence sodium excretion, renal blood flow, and GFR (88, 168). TNF-α administered acutely decreases renal blood flow and GFR and induces natriuresis in mice (220). This reduction in renal blood flow is consistent with an earlier study in rabbits (77). Increased renal generation of reactive oxygen species and thromboxane are potential mediators for TNF-α decreases in renal blood flow (77,220). These findings are also supported by data that increased levels of TNF-α correlate with decreased renal blood flow and GFR in patients with coronary artery disease (204). Another factor, TGF-β has been demonstrated to impair afferent arteriolar autoregulatory responses (224). This seemed to be specific to TGF-β since other growth factors had no effect on afferent arteriolar autoregulation (224). Interestingly, the effect of TGF-β is mediated by activation of TGF-β receptors on the afferent arteriolar and is dependent on generation of reactive oxygen species (224). TGF-β did not interfere with afferent arteriole vasoconstrictor responses to adenosine or angiotensin (224). Insulin-like growth factor-1 (IGF-1) is another factor that can influence afferent arteriolar autoregulatory responses (133). IGF-1 was demonstrated to restore afferent arteriolar autoregulation in experimental chronic renal failure (133). ILs have also been demonstrated to have renal vascular actions. IL-2 treatment to patients resulted in a decreased GFR when administered for four days (222). In contrast, IL-1 and IL-6 have been demonstrated to dilate skeletal muscle arterioles, basilar arteries, and coronary arteries (112,152,175). IL-1 has also been demonstrated to increase sodium excretion; however, this response is not associated with an increase in renal blood flow or GFR (11, 117). Thus, IL-1 dilates peripheral arteries but not renal arterioles and increases sodium excretion by directly acting on renal epithelial cells. These studies demonstrate that cytokines and inflammatory mediators can directly alter renal blood flow and GFR.

Although the experimental evidence for renal hemodynamic effects for cytokines and inflammatory mediators in nonpathological states is limited, there is a large body of evidence that cytokines and inflammatory mediators importantly contribute to renal hemodynamics and epithelial cell transport in pathological states. The following sections will review the contribution of cytokines and inflammatory mediators to renal hemodynamics and tubular function in pathological states.

Glomerular and tubulointerstitial pathology

The complex mechanism by which kidneys fail and progress to ESRD involves cytokine actions on renal hemodynamics, glomerular function, and tubular function. A progressive decline in GFR to ESRD is the final outcome of progressive renal disease. Glomerular and interstitial macrophage infiltration is a characteristic of acute and chronic renal diseases (88, 168). A number of studies have implicated angiotensin II as an essential contributor to progression of glomerular disease (168, 209). There is convincing evidence that, following an initial insult, glomerular hypertension results in increased angiotensin II and the start of the inflammatory response (168, 209). Angiotensin II can directly activate glomerular expression of cytokines, inflammatory, and fibrotic factors that can contribute to effects on renal hemodynamics (168, 209). These cytokines and chemokines include TGF-β, MCP-1, regulated on activation, normal T expressed and secreted (RANTES), and vascular endothelial growth factor (VEGF) (88,239). In addition to direct actions on renal glomerular and tubular cells, angiotensin II stimulates macrophage accumulation in the glomerulus and tubule cells (162,168). This influx of lymphocytes and macrophages further increases cytokine production of IL-1, TNF-α, and MCP-1 (98,271). Monocytes that express MCP-1 and CCR2 infiltrate damaged tissue (88, 98). The increase in cytokine production acts on glomerular cells and contributes to the development and progression of glomerular injury (88,98).

All types of glomerular cells contribute to the progression of glomerular injury; however, the podocytes that maintain the filtration barrier appear to be a primary target for VEGFinduced injury (88). VEGF plays a key role in the formation and maintenance of the filtration barrier and is expressed in podocytes and can act through receptors Flt-1 and Flk-1 on endothelial cells (88, 118). On the other hand, elevated VEGF levels have been associated with glomerular damage including hyperfiltration, hypertrophy, and proteinuria (57, 88). Experimental evidence for increased VEGF in podocytes contributing to glomerular sclerotic injury was demonstrated in transgenic mice (57).

Mesangial cells are another specialized glomerular cell type that cytokines act on to mediate glomerular injury (88, 168). During immune injury quiescent mesangial cells become activated to a fibroblast phenotype that releases cytokines and oxidants (168). Activated mesangial cells generate cytokines such as IL-1, RANTES, MCP-1, TGF-β, and heparin-binding epidermal growth factor (HB-EGF) (88, 239). Increased cytokine and growth factor levels result in mesangial cell proliferation (88, 168). The mesangial cell fibroblast phenotype then secretes extracellular matrix components and contributes to the development of glomerular sclerosis (63, 88, 109).

Glomerular endothelial cell generation of cytokines and growth factors can also contribute to progressive glomerular sclerosis (95, 124, 259). Endothelin, TGF-β, and platelet-derived growth factor (PDGF) increase in response to shear stress and glomerular injury (88,138). Activation of endothelial cells can also result in generation of IL-1, TNF-α, and MCP-1 that would ultimately result in attraction and proliferation of inflammatory cells (95, 124, 259). Endothelial expression of intracellular adhesion molecule 1 (ICAM-1) facilitates neutrophil adhesion and enables macrophage infiltration (88). Endothelial cell inflammation and injury could result in microthrombi, hyaline deposition, and destruction of the glomerular basement membrane (88,168).

Glomerular injury and the development of glomerular sclerosis are key features of progressive renal disease; however, it is now clear that tubulointerstitial damage correlates better with the long-term progression than glomerular damage (88,168). A key contributor to tublulointerstitial damage is the inflammation that occurs subsequent to the glomerular hypertension and hypertrophy (168, 209). Interstitial infiltration of inflammatory cells

occurs in the early phases of renal diseases irrespective of the initial renal insult. These are primarily macrophages and T and B lymphocytes and their migration to the interstitium is driven by increased tubular expression of chemokines and adhesion molecules (114,168,209).

Glomerular proteinuria resulting in downstream tubular cell injury is the generally accepted theory that links these two renal structures in regards to progressive kidney disease. Proteinuria may have a direct effect on tubular injury by damaging intracellular lysosomal pathways (24). Additionally, proteins such as albumin could increase the presentation of chemotactic and growth factors (88, 95). TGF-β and IGF-1 can be bound to proteins and could stimulate proximal tubule cells to release MCP-1 (88). Albumin can activate the expression of chemokines MCP-1 and RANTES by the proximal tubule (1,47,289). MCP-1 can induce tubulointerstitial fibrosis by recruiting and activating macrophages to release TGF-β (226). Osteopontin is another factor that can be increased by proteinuria and lead to macrophage recruitment (161). Generation of several inflammatory chemokines and extracellular matrix components by tubular cells results in further progression of tissue fibrosis and scarring (168, 209).

After the establishment of the inflammatory reaction, the repair process of fibrosis occurs; however, in progressive renal disease this repair response does not properly shut down. The process persists due to chronic inflammation that leads to progressive fibrosis and tissue scarring and severe renal damage. Tubular cells injured by lymphocytes and cytokines have a phenotypic conversion to fibroblasts (168,209). Fibroblasts synthesize extracellular matrix components leading to excessive collagen accumulation and fibrosis (168,202). A primary regulator of the generation of extracellular matrix proteins is TGF-β derived from macrophages and tubular cells (168). Extracellular matrix levels in the interstitium depend on the balance between production and degradation by proteases. TGF-β increases the synthesis of major matrix proteins such as fibronectin, proteoglycans, and collagens (88,168). Fibroblasts also release collagens in response to EGF and IL-2 (88). Matrix degradation is also decreased since TGF-β increases plasminogen activator inhibitors (PAI) and tissue inhibitors of metalloproteinases (TIMPs) (168). Then fibroblasts phenotypic transformation is regulated by fibrogenic cytokines IL-1, TNF-α, PDGF, TGF-β, and FGF (42,168). Fibroblasts eventually outlast their survival factors, they apoptose, and the renal scar becomes acellular (168).

In summary, progressive renal failure involves many different cellular processes with renal fibrosis as the pathology resulting in ESRD. Glomerular hemodynamics and proteinuria start the process leading to increased cytokine levels and chronic inflammation. The chronic inflammation is a key contributor to phenotypic conversion of epithelial cells to fibroblast and fibrosis. Once this process is triggered it becomes progressive leading to ESRD. Understanding the complexity of this process and the key inflammatory mediators will assist in defining targets for therapies.

Diabetes

Renal injury associated with diabetes is a leading cause of ESRD and is increasing in prevalence (196). Proteinuria and renal inflammation contribute to the tubulointerstitial injury and the progressive decline in GFR (196). The fact that activation of the immune system and chronic inflammation are intimately involved in diabetes has led to the concept that diabetes can be classified as an inflammatory disease (66,196). Renal inflammation and injury occur through many similar mechanisms in type 1 and type 2 diabetes; however, there are unique aspects to type 2 diabetes such as dyslipidemia, obesity, and atherosclerosis that result in a more complex pattern of nephropathy. This section will focus on the key inflammatory mediators contributing to renal inflammation and diabetic nephropathy.

Renal inflammation during diabetes can result in metabolic, hemodynamic, and tubular transport derangements. Inflammatory mediators such as IL-18 and TNF-α are increased in patients with diabetes and diabetic nephropathy (66, 196). IL-18 increases in diabetic patients and circulating levels correlate positively with changes in albuminuria (160). Another observational study has suggested that IL-18 levels may be a predictor of renal dysfunction in diabetes (3). TNF-α is another cytokine that has been demonstrated to increase in the kidney of several animal models of diabetes (66,196). Renal production of TNF-α appears to be related to hyperglycemia and advanced glycation end products (AGEs) (232). This cytokine may promote the development of inflammatory actions and progression of injury in the diabetic kidney. Sodium retention and renal hypertrophy are characteristics of early stage diabetic nephropathy and TNF-α appears to contribute significantly to these early stage characteristics (44). TNF-α also stimulates glomerular reactive oxygen species that impair barrier function resulting in increases in albumin permeability (147). Finally, TNF-α increases the expression and synthesis of chemoattractants and cell adhesion molecules like ICAM-1 (103,196).

Evidence from experimental animal models provides support to the notion that acute phase inflammation associated with increased renal ICAM-1 and MCP-1 levels has a causative role in diabetic nephropathy (247, 272). ICAM-1 likely interacts with T cells and stimulates migration into the diabetic kidney (196). In support of this notion, ICAM-1 deficient d*b*/d*b* obese diabetic mice have decreased homing of $CD4^+$ cells into the glomeruli (170, 247). A contribution for MCP-1 to diabetic nephropathy has been demonstrated by blocking the MCP-1/CCR2 pathway (66, 167). Glomerular sclerosis and progression of diabetic nephropathy are attenuated when the MCP-1/CCR2 pathway is blocked (111, 213). Other inflammatory mediators like IL-6 increase at a later time point (66, 196). Increased mesangial cell and podocyte IL-6 levels correlate with the severity of diabetic glomerulopathy (37). IL-1 levels are also increased in the diabetic kidney and are involved in proliferation of glomerular mesangial cells and matrix synthesis (163,196,200). Although these inflammatory mediators appear at similar time points in the development of nephropathy in type 1 and type 2 diabetes, the contribution of these inflammatory mediators to renal dysfunction differs between these diabetic types (66,196,247).

Type 1 diabetes results from autoimmune destruction of insulin-producing β cells of the pancreas leading to hyperglycemia. Hyperglycemia is known to increase NF-κB resulting in increased levels of CAMs (196,272). Other inflammatory mediators like TNF-α, MCP-1, IL-1, IL-6, and MCP-1 also increase under the transcriptional regulation of NF-κB. The profibrotic factor TGF-β increases in response to hyperglycemia (272,288). Plasma VEGF levels are also increased in type 1 diabetes (272). Other factors that stimulate renal inflammation in type 1 diabetes include reactive oxygen species and AGEs (272,277). Elevated profibrotic factors and inflammation would result in podocyte damage, proteinuria, extracellular matrix accumulation, renal scarring, and eventually ESRD.

The contribution of inflammation to the progression of nephropathy in type 2 diabetes has many similarities to that of type 1 diabetes. The primary difference is the contribution of adipocyte-derived cytokines, adipokines to type 2 diabetes. Because type 2 diabetes is associated with obesity adipocytes become inflammatory cells (196). The activation of TLR4 in adipocytes has been implicated in the onset of insulin resistance in obesity and type 2 diabetes (196). TLR4 activation triggers downstream signaling cascades to activate NF-κB and the release of inflammatory molecules (149). Interestingly, TLR2 and TLR4 can induce chemokine expression in renal tubular epithelial cells (196). TLR-mediated immune activation has been implicated in diverse renal disease models including diabetic nephropathy.

Type 2 diabetes and obesity are associated with changing levels of adipocyte-derived adipokines; adiponectin, leptin, and resistin. Adiponectin levels decrease in obesity and type 2 diabetes and are associated with abnormal leukocyteendothelium interactions (177,196). These decreased levels of adiponectin result in increased leukocyte rolling and adhesion to endothelial cells (177). Adhesion of leukocytes results in activation and release of inflammatory mediators that result in damage to the vascular endothelium. Adiponectin suppresses TNF-α actions and decreased adiponectin levels allow TNF-α induced inflammation of endothelial cells to go unchecked (176). On the other hand, accumulation of adiponectin in injured kidneys prevents glomerular and tubulointerstitial injury by decreasing inflammation and oxidative stress (169). A second adipokine, leptin exerts proinflammatory effects. Leptin increases matrix TIMP expression and stimulates TGF-p in mesangial cells (196). Elevated urinary leptin levels are associated with increased albuminuria and decreased GFR in Pima Indians that have a high incidence of type 2 diabetes (270). Lastly, resistin is a peptide hormone belonging to a class of cysteine-rich secreted proteins that contribute to dysglycemia and endothelial dysfunction in obesity. Resistin increases inflammation and results in increased levels of vascular adhesion molecule-1 (VCAM-1) and MCP-1 (43, 119). Elevated resistin levels that occur in type 2 diabetes also impair insulin signaling (187). Overall, obesity and type 2 diabetes result in a decrease in adiponectin levels and increases in leptin and resistin levels that contribute to inflammation and diabetic nephropathy.

It is now clear from experimental studies in animals and clinical studies in humans that renal inflammation is a key contributor to nephropathy in type 1 and type 2 diabetes (Fig. 3). The specific contributions for these inflammatory cytokines to renal glomerular and tubular dysfunction during the early and late stages of diabetic nephropathy require further investigation. This becomes even more important when considering the complexity that occurs in the clinical context where patients will also have infectious and cardiovascular diseases. If the specific contributions of inflammatory cytokines are determined then this will provide key targets to prevent diabetic nephropathy.

Hypertension

It is clear from animal and human studies that renal inflammation occurs during the development of hypertension and has been implicated in the genesis of hypertension. Human studies have demonstrated that hypertensive patients have increased levels of C-reactive protein, TNF-α, IL-6, MCP-1, PAI-1, and adhesion molecules (89, 153). Almost 50 years ago, immunosuppression was demonstrated to attenuate hypertension in rats (268). Interestingly, this group demonstrated that transfer of lymph node cells from rats with renal infarction hypertension caused hypertension when injected into a recipient rat (171). On the other hand, many early studies in the spontaneously hypertensive rat (SHR) found depressed T cell function (186, 242). These studies in SHR did not investigate 1the T cell subtypes involved and thus could have missed activation of specific T cell subtypes. In support of this notion, specific T cell subtypes could contribute to SHR hypertension is the fact that treatment with anithymocyte serum or the immunosuppressant cyclsophosphamide lowered blood pressure in SHR (49). Thymectomy also decreased blood pressure to normal in renal-mediated hypertension in rodents with thymic hypertrophy (238). Deoxycorticosterone acetate (DOCA) salt hypertension was not sustained in athymic immune-deficient mice (237). Additionally, transfer of splenocytes from DOCA salt hypertensive rats increased blood pressure in the recipient rat (173). These earlier studies demonstrated a potential role for inflammation in hypertension and with the development of technology have led to a more thorough evaluation of the contribution of renal inflammation to hypertension.

A number of studies in mice and rats have demonstrated that the adaptive immune response and renal inflammation contribute to hypertension and associated pathologies (89, 153). An

initial study using multiple pharmacological agents to cause immunosuppression demonstrated decreased renal damage in hypertension independent of lowering blood pressure (157). These studies demonstrated that the immunosuppressant, mycophenolate mofetil (MMF), the TNF-α receptor blocker etanercept, and dexamethasone prevented dendritic cell maturation and T-cell infiltration in hypertensive double transgenic rats harboring both human renin and angiotensinogen genes (157). Subsequent experimental studies in other rodent models of hypertension demonstrated that MMF and entanercept lowered blood pressure in addition to decreasing renal damage (51, 53, 138). A role for T and B cells in hypertension and renal damage has been further examined. Recombination activating gene-1 gene deficient mice resulting in a lack of T and B cells demonstrated an attenuated development of angiotensin II infusion hypertension (84). Angiotensin II hypertension was completely restored by adoptive transfer of T cells but not B cell transfer (84). Inhibiting T and B cell proliferation with MMF lowers blood pressure in Dahl salt sensitive hypertension (146). Renal injury associated with angiotensin II hypertension is also attenuated in mice lacking T and B cells and the major cell type responsible for the renal injury appears to be T cells (35). Additional studies have demonstrated a potential contribution of increased CCR5 positive cells and RANTES (89). Evidence for T cells and RANTES has also been determined in other animal models of hypertension (89).

The experimental studies demonstrating a contribution of T cells to hypertension have led to the concept that activated T cells in the kidney and release of cytokines increase blood pressure. The release of cytokines would act on adjacent renal vascular and tubular epithelial cells. There is a significant correlation between tissue and circulating levels of Th1 cytokines such as TNF-α and IL-6 and blood pressure (33,89,153). Interestingly, hypertensive patients appear to have an upregulation of the T cell renin angiotensin system (153). Angiotensin II hypertension is associated with increased TNF-α production by renal glomerular endothelial cells, and tubular epithelial cells (55). Angiotensin II can directly increase renal cytokine release, adhesion molecule expression, and the production of PAI-1, as well as, activate NF-κB and increase reactive oxygen species that would further increase renal cytokine levels (202). In support of this concept, a number of studies have demonstrated that the TNF-α antagonist etanercept decreases blood pressure in DOCA-salt, angiotensin II, and autoimmune-associated hypertension (53,55,255). TNF-α inhibition has been demonstrated in some studies to prevent renal injury without a significant lowering of blood pressure (55). IL-6 is another cytokine that has been implicated in renal inflammation and hypertension. Angiotensin II stimulates renal and vascular IL-6 production and the development of angiotensin II hypertension is attenuated in IL-6 gene deficient mice (22, 123). IL-6 appears to contribute to the hypertension by increasing angiotensin type 1 (AT1) receptor levels in the proximal tubules renal vasculature to enhance sodium absorption and cause vasoconstriction (129). Elevated levels of IL-6 appear to cause sodium retention through activation of JAK2/STAT3 signaling to increase epithelial sodium channel activity (22, 129). On the other hand, a recent study provides evidence that IL-6 does not contribute to decreased renal blood flow in angiotensin II hypertension (22). Further studies are required to determine the renal actions of IL-6 that contribute to hypertension. In any case, a number of studies have demonstrated that T cell infiltration into the kidney and subsequent generation of TNF-α and IL-6 are associated with the development of hypertension.

Other cytokines also appear to contribute to renal inflammation and hypertension. MCP-1 and activation of the CCR2 receptor contribute to renovascular hypertension and renal damage (54, 287). The MCP-1 inhibitor bindarit decreased tubulointerstitial inflammation and fibrosis, improved renal endothelial function but failed to lower blood pressure (287). Likewise, CCR2 inhibition decreases renal inflammation and delays the progression of angiotensin II salt hypertension (54). There also appears to be a contribution of the inflammatory cytokine IL-17 to hypertension. IL-17 is produced by Th17 cells, $CD8^+$ cells,

neutrophils, and T cells (89). Angiotensin II hypertension is decreased in IL-17$^{-/-}$ mice (137). Tregs are another cell type that could influence renal inflammation and hypertension. Tregs are protective in hypertension and reduce the number of activated T cells (9, 89). Reduced hypertension in a genetically modified Dahl salt-sensitive hypertension strain that harbor Brown-Norway chromosome 2 had increased Treg cells and increased generation of the protective cytokine IL-10 (258). Taken together these findings suggest that renal proinflammatory and hypertensive cytokines such as TNF-α and IL-6. MCP-1 and IL-17can be opposed by IL-10 and Tregs ability to limit T cell activation.

Obesity related renal inflammation is another factor that is contributing to hypertension and associated renal damage. There are a number of cardiovascular risk factors associated with obesity including hypertension, insulin resistance, and diabetes that together form the clinical pathology known as metabolic syndrome. Metabolic syndrome will increase renal inflammation in hypertension and hasten the progression of CKD (115). Interestingly, obese individuals demonstrate an increase in GFR and renal blood flow (29). There is renal hyperfiltration that is likely the consequence of afferent arteriolar dilation (90, 131, 159). Thus, renal functional changes in metabolic syndrome are due to macrophage infiltration and elevated levels of proinflammatory cytokines.

Cytokines such as IL-6, TNF-α, and MCP-1 are increased to a greater extent in obesity and hypertension than in hypertension in the absence of obesity (115). Adiposity and insulin resistance results in increased renal IL-6 levels (10). In the kidney, IL-6 enhances TNF-α and IL-1β that results in a positive feedback system in obesity and hypertension (180). On the other hand, IL-6 has catabolic action to reduce food intake and increasing physical activity that would have the beneficial actions in obesity (184). MCP-1 also increases in obesity and can contribute to renal cell proliferation and injury in obesity (115). Reduced MCP-1 activity prevents obesity-induced renal macrophage infiltration and supports the notion that that MCP-1 contributes to renal inflammation (265). These findings support the concept that obesity and metabolic syndrome are associated with a greater renal inflammation.

Changes in adipokines such as leptin, adiponectin, and resistin are more dramatic in obese patients with hypertension (115). Increased leptin levels in metabolic syndrome may contribute to the deterioration of renal function (231). Leptin stimulates the renal sympathetic nervous system that can lead to an increase in blood pressure and subsequent glomerular injury (244). Leptin can also increase glomerular endothelial cell proliferation and increase collagen production (127). Reactive oxygen species can be increased by leptin and cause renal endothelial dysfunction (20). In contrast to leptin, the cytokine adiponectin is anti-inflammatory and levels decrease in metabolic syndrome (52). This reduction in adiponectin in obesity could exacerbate the progression of renal injury in hypertension. The last adipokine to mention that is associated with metabolic syndrome is resistin. Resistin levels increase in diet-induced and genetic models of obesity (188). Macrophages produce resistin in obesity and resistin has proinflammatory actions (36, 140). The contribution of resistin to renal function and disease in metabolic syndrome remains unknown. On the whole, obesity-related changes in adipokine levels will further exacerbate renal inflammation and injury associated with hypertension.

Inflammation is a key contributor to impaired renal function and to the genesis and progression of hypertension. Animal studies in the 1960s provided evidence for a contribution of inflammation to the blood pressure elevation in hypertension (171, 268). Human studies have also provided ancillary evidence that anti-inflammatory treatments could lower blood pressure (89, 153). However, it was not until the last decade that the contribution of T cells, cytokines, and renal inflammation to hypertension was rigorously

studied (89,153). These studies have identified the inflammatory cells and cytokines that impact renal function and blood pressure control in metabolic syndrome and hypertension (Fig. 4). This novel insight and future studies will undoubtedly result in anti-inflammatory approaches to treat hypertension.

Immune-Mediated Renal Disease

Chronic immune-mediated renal diseases are commonly classified as nephrotic syndromes, nephritic syndromes, or a comination of both. Nephrotic syndromes are characterized as a nonspecific renal disease associated with high levels of urinary albumin, whereas nephritic syndromes are typically characterized by the presence of both albumin and blood cells in the urine. Immune system activation and inflammation are central to the development of both nephrotic and nephritic syndromes.

Nephrotic syndrome

Minimal change disease and focal segmental glomerulosclerosis are two of the most common nephrotic syndromes. While minimal change disease is prevalent in children, it is also among the most common forms of nephrotic syndrome in adults. It is named as such because there are no obvious glomerular changes detectable by light microscopy, or obvious signs of immune cell infiltration or immune complex deposition. Focal segmental glomerulosclerosis is the most common form of nephrotic syndrome in adults. It is a nonspecific glomerular disease characterized by the collapse of glomerular capillaries and sclerosis. The underlying mechanisms that promote nephrotic syndrome are still a subject of investigation. However, an immune component has long been speculated beginning with early work suggesting that a T cellderived “permeability” factor alters podocyte or glomerular capillary function (142, 150, 221). The T cell-derived factors were likely inflammatory cytokines consistent with work showing that mononuclear cells from patients with nephrotic syndromes produce elevated levels of IL-1, IL-2, and TNF (26,227,234). Overexpression of IL-13 in rats results in minimal change nephropathy that is characterized by increased proteinuria, hypercholesterolemia, and fusion of podocyte foot processes (121). The increased IL-13 can induce CD80 in tubular epithelial cells and CD80 is increased in patients suggesting a contribution in the pathogenesis of minimal change disease (70, 165). Functionally, the role for inflammatory cytokines in the pathogenesis of nephrotic syndrome is illustrated in experimental animal models of puromycin aminonucleoside nephrosis where combined anti-TNF-α and anti-IL-1β therapy significantly reduced proteinuria (227). The role for immune system involvement in nephrotic syndromes is further supported by evidence showing that immunosuppressive therapies, including corticosteroids, effectively treat the disorder (26).

Nephritic syndrome

Nephritis refers to a group of diseases that have inflammatory changes in glomerular capillaries and signs of an acute nephritic syndrome including hematuria, proteinuria, hypertension, and edema. Glomerulonephritis can occur as a primary renal disease or as a result of systemic disease such as vasculitis (34, 260). Worldwide, the prevalence of glomerulonephritis makes it a major cause for ESRD and accounts for 10% to 15% of the ESRD patients in the United States (260). This section will focus on glomerulonephritis as a primary renal disease and discuss IgA and rapidly progressive glomerulonephritis.

The most common form of glomerular disease in the world is IgA nephritis; however, the pathogenesis of primary IgA nephropathy remains unknown. IgA nephropathy is an immune-complex glomerulonephritis resulting from IgA deposits in the glomerulus (78). This deposition involves abnormally glycated IgA1 protein in the mesangial area (64, 78).

Damage in the glomerulus takes place in two phases, an acute phase with immune reactions in the glomerulus and a chronic progressive phase as a result of loss of filtering surface and increased glomerular pressures (64,78). The first phase involves complement components including C3, C5, and properdin that lead to leukocyte recruitment that leads to damage to glomerular cells (56,144). Coagulation factors lead to fibrin deposition and crescent formation (34,78). Local and systemic release of growth factors and cytokines also lead to activation and damage of glomerular cells (78, 260). Glomerular cells then have cell proliferation, generation of oxidants and proteases, and increased extracellular matrix leading to sclerosis and permanent renal damage (34,78). Subsequently, non-immune mechnisms develop in the chronic progressive phase. Decreased filtering and increase glomerular pressures lead to glomerular sclerosis and interstitial fibrosis (78). These are a consequence of ischemia, glomerular cytokine release, and adverse effects due to protein filtration on tubules (78). Although there is no one effective treatment for IgA nephropathy, therapies are being targeted to specific cytokines and other mediators of the renal injury.

The contribution of cytokines and growth factors to this progressive IgA nephropathy has been examined and IL-6, TNF-α, PDGF, and TGF-β1 are major players (78,260). IL-6 is one cytokine that is increased when mesangial cells are incubated with serum from IgA patients (132). IgA aggregates are catabolized by rat mesangial cells and induce IL-6 and TNF-α production resulting in mesangial cell proliferation (79). TNF-α and IL-6 levels increase in IgA nephropathy and are reduced by immunoglobulin therapy (78). The degree of renal damage in humans correlates with PDGF and IL-6 positive cells in the glomerulus (46, 245). Upregulation of PDGF gene expression in kidneys from IgA nephropathy patients corresponds to the degree of glomerular proliferation and extent of interstitial fibrotic lesions (166, 246). PDGF actions involve inositol triphosphate, diacylglycerol, protein kinase C, calcium release, and prenylation of G proteins to mediate its glomerular cell effects (65). TGF-β1 has been implanted in the fibrotic process and correlates with the severity of IgA-mediated tubulointerstitial damage (78). Intracellular mediators for TGF-β1 are Smad signaling proteins (78). TGF-β1 may also promote transcription of extracellular matrix glycoproteins and promote transdifferentiation of tubular epithelial cells to profibrotic myofibroblasts (78). Treatments for IgA nephropathy such as angiotensin-converting enzyme (ACE) inhibitors and corticosteroids have been demonstrated to decrease cytokines and growth factors that may be useful biomarkers for responsiveness to therapy (64, 78,260).

Rapidly progressive glomerulonephritis includes anti-glomerular basement membrane (anti-GBM) nephritis and renal vasculitis. This form of glomerulonephritis occurs rapidly with a loss of renal function within days to weeks. Anti-GBM nephritis can present with or without pulmonary hemorrhage (34). Glomerular deposits of IgG and high titers of anti-GBM antibody are diagnostic features for Goodpasture's syndrome (16). Renal injury is caused by interaction of antibody with GBM antigen resulting in complement activation, generation of chemotactic peptides, and neutrophils causing the release of oxidants and proteases (34). On the other hand, the most common type of rapidly progressive glomerulonephritis is renal vasculitis that occurs in the absence of immune deposits (59). Glomerular injury demonstrates focal or diffuse necrotizing glomerulonephritis with extensive glomerular crescents (34). The contribution of antibody to neutrophil cytoplasm (ANCA) to the pathogenesis has been controversial but could be responsible for neutrophil localization and activation (107). There is very good evidence that common forms of crescentic glomerulonephritis and necrotizing systemic vasculitis in adults are associated with ANCAs (59). Experimental studies in mice determined that ANCAs play a direct pathogenic role in human glomerulonephritis and vasculitis (275) A large body of evidence also suggests that renal vasculitis is mediated by cellular immune mechanisms with macrophages as the main effector cells (34, 193). Rapidly progressive glomerulonephritis requires urgent medical

attention and the success of treatment depends on how early in the disorder it is initiated (34).

Nephrotic and nephritic syndrome

There are renal diseases associated with inflammation that cannot be easily classified as nephrotic or nephritic because they exhibit characteristics of both. SLE is an example, with 90% of patients exhibiting signs of renal disease. Lupus nephritis is associated with high levels of urinary albumin consistent with nephrotic syndrome (>3 grams of urinary protein/day) while also presenting with hematuria (174). The mechanisms that drive the development of SLE continue to be investigated although it is clear that immune system activation and inflammation have a prominent role. A loss of immune tolerance ultimately drives the production of autoantibodies (commonly antinuclear) that promote immune complex formation and deposition in peripheral tissues including the glomeruli of the kidneys where they promote local injury and inflammation.

Anti-inflammatory and Immune Suppressive Therapies for Renal Disease

There are a number of standard treatment protocols for patients with kidney disease, the most common of which are related to the two most common causes of renal disease, hypertension and diabetes. Therefore, blood pressure control and glycemic control are important clinical targets for the treatment of CKD. General approaches to manage CKD also include dietary protein restriction, therapies to reduce uric acid, and plasma lipid control. The focus of this section will be to discuss he potential anti-inflammatory/immunomodulatory actions for a number of potential therapeutic approaches.

Renin-angiotensin-aldosterone system

Renin-angiotensin-aldosterone system (RAAS) inhibition is one of the most common and effective therapies for the treatment of hypertension, a leading risk factor for renal disease. ACE inhibitors and AT1 blockers (ARBs) are among the most widely used pharmacological tools and the RAAS has the potential to directly regulate immune system function. For example, angiotensin receptors are present on the surface of monocytes (225) and angiotensin II-mediated hypertension occurs, in part, through activation and recruitment of immune cells in the kidney and vasculature (84, 162) suggesting a direct interaction between RAAS and immune system activation. The connection between the RAAS and immune system activation is also supported by work showing that angiotensin II binds to splenocytes and increases their proliferation via an AT1 receptor (162). Whether targeting the RAAS protects against renal injury simply by reducing blood pressure or directly through anti-inflammatory mechanisms is always difficult to determine. However, some evidence in humans suggests that RAAS blockade provides renal protection beyond blood pressure lowering effects (82). This is largely based on evidence showing that RAAS blockade reduces urinary protein and overall renal risk to a greater degree than other blood pressure lowering therapies in diabetic and non-diabetic nephropathies (99,128,274). In addition, data shows that RAAS blockade reduces renal cell proliferation, circulating T cells, and cytokine production and overall renal inflammation (145,182,223). Taken together, these data suggest the possibility that RAAS blockade can provide renal protection above and beyond blood pressure effects, potentially through immune regulatory actions.

Recently, pharmacological tools have been developed to target novel components of the RAAS that may also have anti-inflammatory actions including the prorenin receptor. Inhibition of the prorenin receptor with aliskerin protects the kidneys in experimental models and humans with diabetic nephropathy, seemingly independent of hypertension (31,60). Although the protective effects of aliskerin can partially be attributed to

hemodynamic effects or to the downstream actions to reduce angiotensin II, evidence supports a direct anti-inflammatory component of prorenin receptor blockade. For example, aliskerin markedly reduced TGF-β, renal fibrosis, and albuminuria in a mouse model of progressive renal fibrosis ($COL4A3^{-/-}$) independently of change in blood pressure (83). The antifibrotic and inflammatory actions of prorenin receptor blockade continue to be elucidated.

Finally, it is worth briefly considering that renal protective effects of ARBs may result indirectly through an angiotensin receptor type 2 (AT2)-mediated mechanism. ARBs target the AT1 receptors leading to feedback induced increase in the production of angiotensin II. Because the AT1 receptors are blocked, angiotensin II preferentially binds to AT2 receptors that functionally oppose the actions of the AT1 receptor (236). However, whether targeting the AT2 receptor during CKD is beneficial remains unclear and controversial (267). AT2 activation by PD123319 appears to exacerbate renal injury in the renal wrap and renal ablation models (228, 254). In contrast, AT2 receptor activation reduces renal inflammatory cell infiltration in the unilateral ureteral obstruction model (58) and AT2 receptor knockout mice have enhanced mortality in response to renal ablation (28), suggesting a protective and anti-inflammatory role in the kidney. Therefore, additional work is required to fully understand the impact of AT2 on inflammatory and immune mediated pathways that can promote renal injury.

Glycemic control

Diabetes is a major risk factor for chronic renal disease making glycemic control of paramount importance for reducing renal risk. Therapies commonly used for the treatment of type II diabetes mellitus (the most common form of diabetes) are known to have potent anti-inflammatory effects. Metformin is among the most effective treatments for type II diabetes, promoting glycemic control by suppressing glucose production in the liver. Interestingly, there is evidence showing that metformin can suppress the proliferation of T cells suggesting that there may be a direct immunosuppressive role for this drug (216). However, metformin is not indicated for patients with existing renal disease, making it valuable mostly for the prevention of chronic renal disease in these patients.

Another class of drugs with anti-inflammatory effects, the insulin sensitizing thiazoladinediones (TZDs), has potential renal protective effects in both humans and experimental animal models (7,81,102,212,276,280). TZDs (pioglitazone and rosiglitzaone) are high-affinity pharmacological ligands for the orphan nuclear receptor, peroxisome proliferatoractivated receptor gamma (PPARγ). Activation of PPARγ causes the formation of a heterodimer with retinoid X receptor that recognizes a response element to regulate gene transcription. Although TZDs have pleiotropic actions, the anti-inflammatory properties of TZDs are thought to occur by a posttranslational modification (sumoylation) that stabilizes a protein complex and prevents the transcription of proinflammatory genes (179). TZDs, therefore, protect the kidneys by reducing profibrotic (TGF-β and PAI-1) and proinflammatory cytokines (TNF-α, IL-1, and IL-6) (2,15,108,281). The combination of metformin with TZDs in type II diabetic humans reduces the level of circulating markers of inflammation including C reactive protein and vonWillebrand factor (215). The anti-inflammatory and renal protective effect of glitazones is not limited to diabetic renal disease, but rather has been shown to protect the kidneys in a number of models including SLE (257).

More recently, AGEs and their receptors (RAGE) have garnered interest as potential therapeutic targets for diabetes. AGE formation is prominent in diabetics and promotes tissue damage and inflammation in part through activation of RAGE. RAGE is a transmembrane receptor that is a member of the immunoglobulin superfamily (164) and

leads to activation of proinflammatory pathways including activation of NF-κB (13), TGF-β, and oxidative stress (67,266). Therefore strategies to inhibit rage include antioxidants, and common treatments for type II diabetes (metformin and TZDs) have been shown to reduce AGE. In addition, compounds like aminoguanidine and other pharmacological tools are being designed to target AGE-RAGE and protect against diabetic complications including nephropathy (91).

Corticocsteroids

Corticosteroids are recognized for their general immune suppressive effects. The anti-inflammatory actions of corticosteroids to reduce cytokines and proinflammatory transcription factors like NF-κB have been reviewed (194) and cover obvious pathways by which they could provide protection against renal inflammation. Corticosteroid treatment can protect the kidney under conditions of acute injury. For example, inflammation associated with renal ischemia reperfusion injury is suppressed (tubular apoptosis, infiltrating neutrophils, and cell adhesion molecules) by treatment with dexamethasone (120,240), suggesting the possibility of a nongenomic mechanism. Despite their potential role in protecting against acute renal injury, the use of corticosteroids to treat renal disease is typically used in patients with chronic autoimmune diseases such as SLE. Corticosteroid treatment is included as part of the first line of therapy in patients with active lupus nephritis (86,120) and the renal protective effect of corticosteroids have been demonstrated in experimental animal models of lupus nephritis (proteinuria, glomerular injury, renal complement and IgG) (120, 135). Corticosteroid treatment, however, has significant potential side effects including increasing the risk of latent viral infections as well as promoting renal sodium and water retention, thus increasing the risk for hypertension. The standard for therapy in patients with lupus nephritis now includes a combination of corticosteroids with immunosuppressive drugs which can improve renal outcomes better than either alone (80, 100, 230, 279).

Immunosuppressive and cytotoxic drugs

Immunosuppressive and cytotoxic drugs commonly given in combination with corticosteroids include cyclophosphamide, azathioprine, or MMF. While cyclophosphamide and azathioprine are effective in the treatment of lupus nephritis, MMF is now the standard of treatment. MMF suppresses immune system function by inhibiting the *de novo* purine biosynthesis that is required for T and B cell growth and proliferation, and it has fewer side effects and reduced toxicity relative to other commonly used therapies (30, 76, 199, 286). In experimental mouse models of SLE, treatment with MMF delays the onset of albuminuria and preserves renal function in association with reduced autoantibody titers (148, 191, 253). Similarly, MMF treatment protects against lupus nephritis in humans further supporting an important role for the adaptive immune system in renal injury associated with autoimmune disease [reviewed in ref. (75)].

Interestingly, MMF has been reported to reduce blood pressure, a major risk factor for chronic renal disease, in experimental animal models of hypertension (14, 23, 41, 249). While MMF is not indicated for the treatment of uncomplicated essential hypertension, or in diabetic renal disease, evidence shows that essential hypertensive patients with either arthritisor psoriasis have lower blood pressure after a 3-month treatment (92). The MMF treatment and reduced blood pressure coincided with reduced levels of urinary markers of renal inflammation (TNF-α) (92). When MMF is administered to experimental animal models of hypertension or diabetes, renal inflammation, and injury are reduced. MMF treatment reduces blood pressure coincident with the number of renal T cells in a rat model with salt-sensitive hypertension (40). Similarly, in obese Zucker rats, treatment with MMF reduces renal injury, immune cell infiltration (ED1- and CD5-positive cells) and proteinuria

(198). Therefore, while MMF is not indicated for the treatment of hypertension or diabetes induced renal injury, these data further support a prominent role for the immune system in renal injury associated with these diseases.

Anticytokine therapy

Inflammatory cytokines play a critical role in regulating immune function. TNF-α and IL-6 are commonly implicated as contributing to renal inflammation and fibrosis making them a potentially useful clinical target. Both pharmacological and immune-based therapies are now available to target these cytokines. In the case of TNF-α, monoclonal antibodies (i.e., adalimumab and infliximab) and a soluble recombinant TNF-α receptor (etanercept) are currently in clinical use for patients with arthritis (27, 32, 71, 85, 269, 273). TNF-α inhibition also reduces renal injury and inflammation in models of hypertension and in models of autoimmune mediated renal disease. For example, in both angiotensin II and mineralocorticoid-induced hypertension, blockade of TNF-α significantly lowers blood pressure and protects the kidneys against injury while reducing renal inflammatory cells and markers of inflammation including MCP-1 (53). Similarly, although the role for TNF-α in SLE disease progression is controversial, evidence in a mouse model of SLE shows that TNF-α blockade reduces glomerulosclerosis, renal CD68+ cells and albuminuria (255). These studies suggest a causal role in for TNF-α in the development of renal disease.

Similar strategies are being used to target ILs in the treatment of renal inflammation and CkD. For example, toclizumab is a monocolonal antibody against the IL-6 receptor and is currently approved for use in patients with active rheumatoid arthritis (72, 172). However, some evidence suggests a potential therapeutic benefit for diseases like lupus nephritis where small trials have demonstrated that toclizumab reduces circulating neutrophils, B cells, and autoantibodies (101). In addition, treatment with toclizumab can cause remission in patients with crescentic glomerulonephritis (233) and has been used in phase 1 trials for patients with SLE (101). Taken together, these data support an important mechanistic role for IL-6 in the pathogenesis of renal disease.

Novel immune targets

Several novel immune system targets have become the topic of interest for therapeutic interventions that could impact renal inflammation. CD20 is a cell surface marker on antibody producing B cells. Rituximab is a monocolonal antibody against CD20 and has been used primarily for the treatment of B cell lymphomas (139, 192). However, evidence suggests that targeting CD20 during renal disease has beneficial effects (17). For example, rituximab treatment results in complete or partial remission of membranous nephropathy in humans, for which B cells play an important role in the progression (106, 201).

CD40 ligand (CD40L) is a cell surface molecule expressed on activated T cells that mediates their costimulation with antigen presenting cells (i.e., B cells, dendritic cells, and macrophage) (38). Immune complex glomerulonephritis is exaggerated in mice that over express CD40L on B cells (93) suggesting an important mechanistic role for this pathway. However the therapeutic benefit of anti-CD40L therapy requires further investigation. Some evidence suggests that anti-CD40L monoclonal antibody treatment of mice with SLE delays the onset of antibody production and renal disease (263) whereas others show that anti-CD40L alone does not alter the progression of SLE (262), or even advances renal disease in mice with SLE (proteinuria, glomerular inflammation, and glomerular cellularity) (203). In humans, the results of anti-CD40L therapy on indices of autoimmunemediated renal disease have been mixed. For example, one study showed that anti-CD40L therapy in patients with SLE was not more efficacious at improving SLE disease activity than placebo (110). However, in a different study, treatment with anti-CD40L reduced proteinuria in patients

with SLE (21). An alternative approach to targeting the adaptive immune system is to prevent antigen presentation to the T cell. Abatacept, binds to a cell surface protein on antigen presenting cells (B7) and prevents this activation. Anti-B7 therapy in a mouse model of crescentic glomerulonephritis has been shown to reduce injury (130).

An approach that has recently shown some promise is the use of a monoclonal antibody to C5 of the complement system. Eculizumab targets C5 to prevent the formation of the membrane attack complex and has been shown in small clinical studies to reduce markers of renal injury including serum creatinine and albuminuria (18). Eculizamab also exhibited promise in a patient with atypical hemolytic uremic syndrome. Treatment with eculizamab halted the hemolytic process during the course of the treatment suggesting that C5 may also be an important clinical target (136).

Other therapies with anti-inflammatory properties

Several other therapies have potential anti-inflammatory properties that could protect the kidney, but do not directly target specific immune system components. One example is bardoxolone methyl, a compound that induces the transcription factor (Nrf2) and suppresses inflammatory cytokines and oxidative stress. In humans with type 2 diabetes, treatment with bardoxolone methyl for 28 days improved renal function (GFR, blood urea nitrogen (BUN), and serum creatinine) in association with a reduction in vascular injury and markers of renal inflammation such as circulating endothelial cells (183). Another example with potential anti-inflammatory properties is relaxin, a protein hormone predominantly produced during pregnancy. Relaxin has promise for reducing renal inflammation in CkD through promoting nitric oxide release and reducing the expression of TGF-β in the kidneys (69,125,141). The antifibrotic effects of relaxin are a key mechanism by which relaxin can protect the kidney. Indeed, there are other antifibrotics currently being tested (pirfenidone) for their renal protective effects (189, 241). Finally, resveratrol has been tested for its beneficial effect to preserve renal hemodynamic function and reduce renal inflammation and oxidative stress that occur during acute renal failure (39, 45).

Conclusion

The contribution of the immune system and inflammation to renal function and disease is becoming more widely recognized and the immune pathways leading to ESRD are diverse (Fig. 5). Inflammatory mediators have actions to alter renal hemodynamics, salt and water homeostasis, and blood pressure control. Uncontrolled inflammation results in glomerular, tubular, and interstitial damage. These renal pathological actions can cause or significantly contribute to acute and CkDs. Inflammation associated with cardiovascular diseases and diabetes results in significant renal pathologies. Not surprisingly, novel therapeutic approaches for kidney disease are targeting the immune system and inflammation.

The advent of genetic manipulated mice, bone marrow-transplantation studies, and antibody-based therapeutic approaches has provided for great promise for defining the contribution of the immune system and inflammation to renal diseases. Even though there is significant knowledge on the key inflammatory mediators contributing to renal pathologies in hypertension, diabetes, and nephrotic and nephritic syndromes, there is still much to be learned. The specific contribution of cytokines, T cells, B cells, and surface molecules on inflammatory cells to renal function requires extensive investigations. How the immune system and inflammation alters renal hemodynamics and tubular transport function to impact electrolyte and water homeostasis remains largely unexplored. Exploration of these areas needs to be done in normal physiological conditions and more importantly pathological conditions. Further exploration of the cell signaling mechanisms and impact of

the immune system and inflammation to renal disease is bound to result in better targeting of therapeutics for renal diseases.

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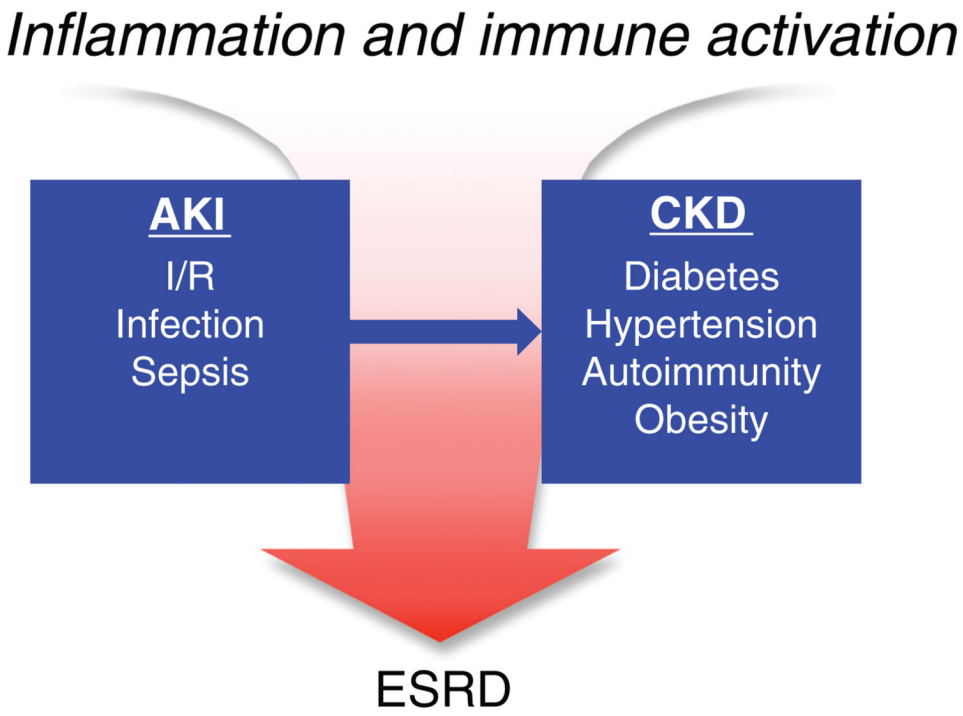

Figure 1.
Immune system activation and inflammation have a central role in the pathogenesis of acute kidney injury (AKI) and chronic kidney disease (CKD).

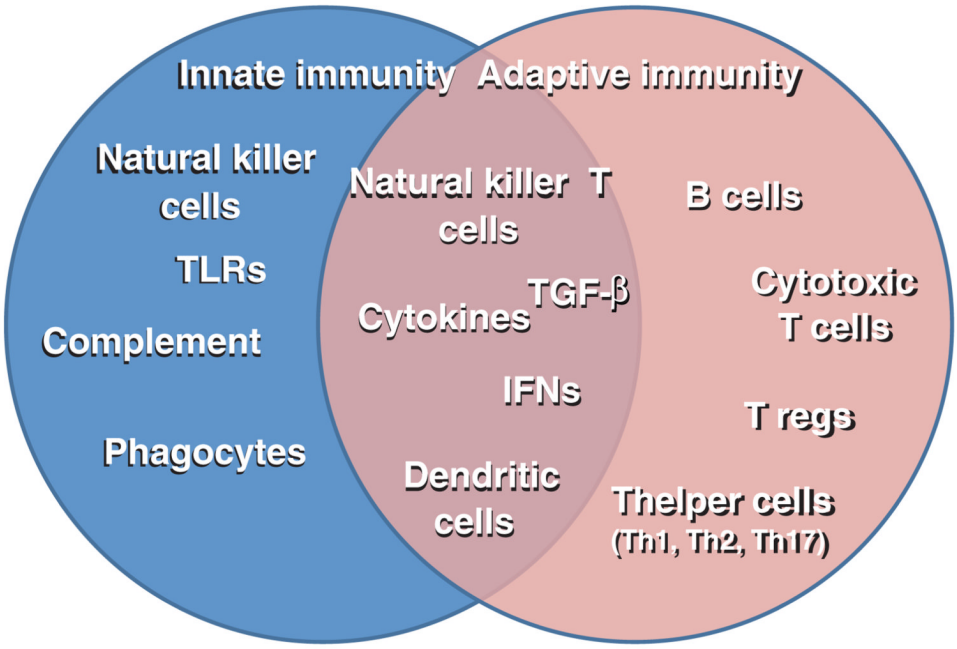

Figure 2.
Immune system components and proteins implicated in the pathogenesis of renal disease. The overlap represents components involved in cross-talk between innate and adaptive immunity.

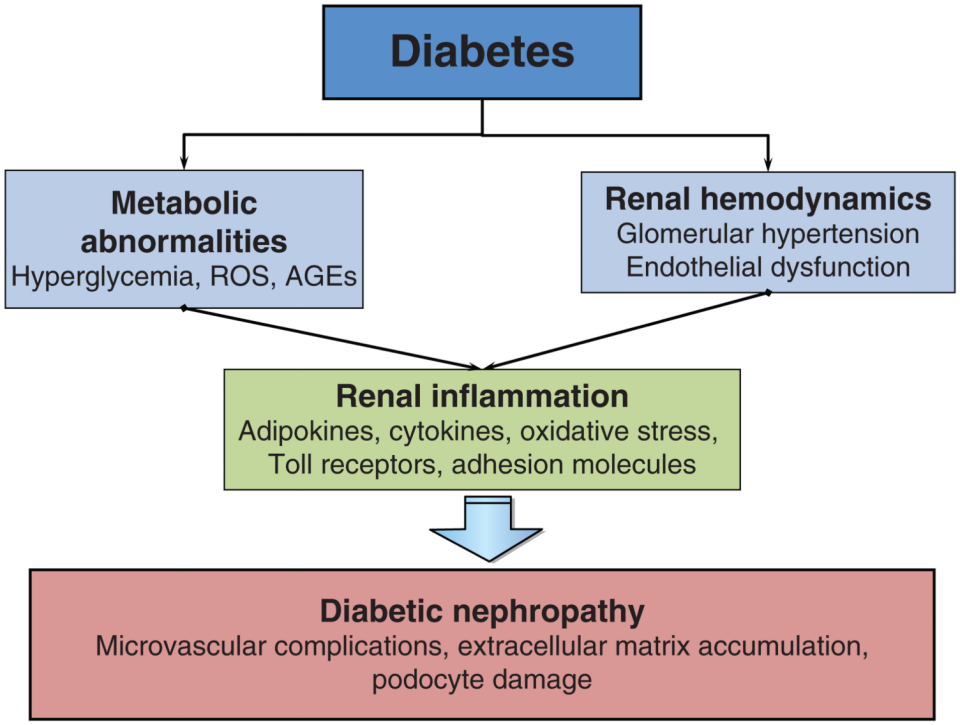

Figure 3.
Schematic of inflammatory events involved in the progression of diabetic nephropathy.

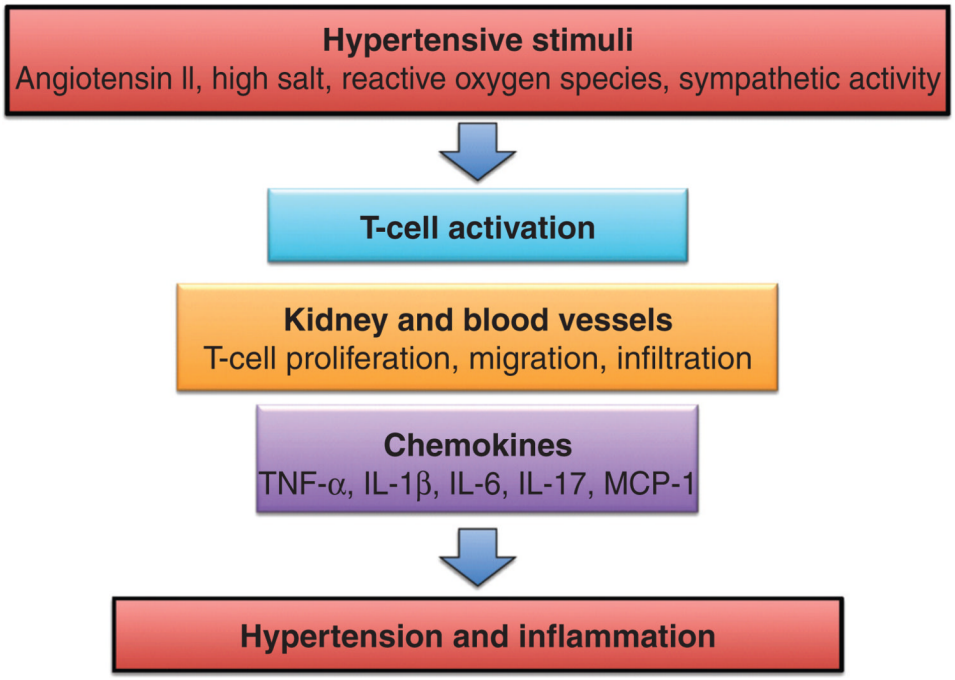

Figure 4.
Schematic of contribution of T cells and cytokines in hypertension.

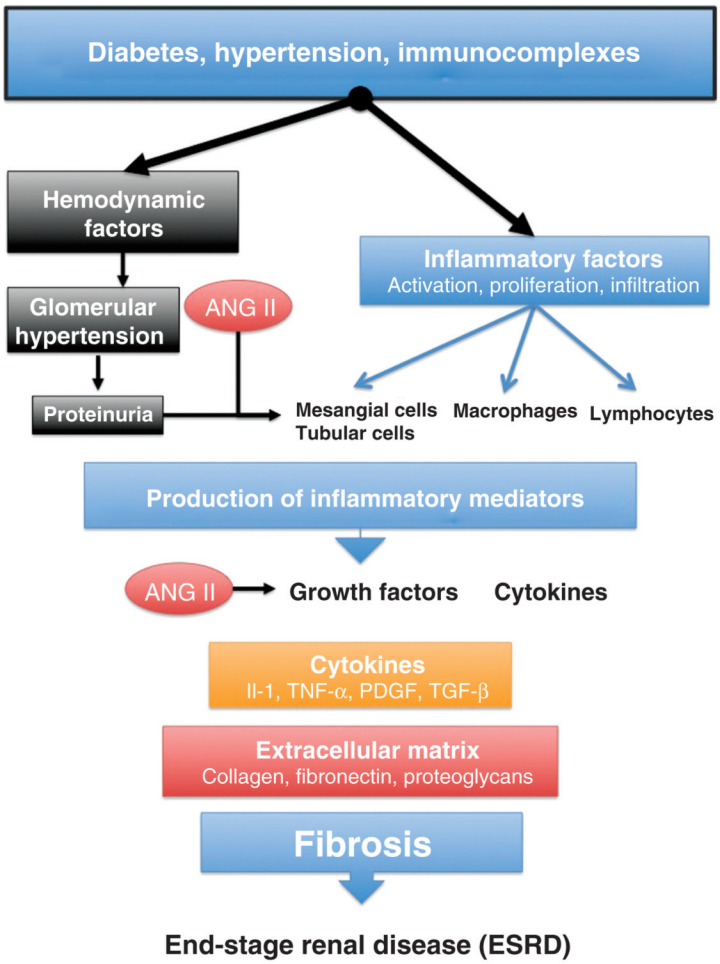

Figure 5.
Schematic of inflammatory events involved in the progression of renal disease.