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Chapter 7

Inflammation in Nonimmune-Mediated Chronic Kidney Disease

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Abstract

Regardless of its etiology, chronic kidney disease (CKD) is characterized by proteinuria, serum creatinine retention, glomerulosclerosis (GS), and tubulointerstitial damage. Notably, the last one has been correlated more closely with the evolution to kidney failure than the extent of glomerular injury. Tubulointerstitial inflammation comprises the activation of tubular epithelial cells, which release inflammatory mediators and chemokines promoting the influx of leukocytes in the renal parenchyma and the activation/proliferation of resident fibroblasts, leading to excessive production of extracellular matrix (EM), fibrosis, and renal function loss. Therefore, inflammation exerts a key role in the pathogenesis of CKD, although the mechanisms by which this process is activated and perpetuated, even when the initial insult is not immune-mediated, such as in the hypertensive nephrosclerosis, in the diabetic nephropathy, and in the crystal-induced renal disease, remain unclear. This chapter provides an overview on inflammation and CKD development not related to autoimmunity or caused by presence of foreign antigens. Cellular and molecular mechanisms involved in different pathways and its potential therapeutic targets to detain the progression of inflammation and fibrosis in CKD are also presented ahead as a contribution in this book.

Keywords: chronic kidney disease, inflammation, immune system, innate immunity, adaptive immunity

1. Introduction

Chronic kidney disease (CKD) is considered a global health problem that motivates life science researchers and physicians to investigate the mechanisms beyond its development, and to seek for new therapeutic strategies to detain the evolution of renal function loss [1].

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Progressive CKD may be initiated by several conditions of different etiological basis; however, in almost all cases, renal disease progresses with the development of a chronic and self-sustained inflammatory reaction, which involves both innate and adaptive arms of immune response and leads to kidney fibrosis. Reasons why inflammation parallels CKD progression even when the initial renal injury does not involve autoimmune disorders or infection episodes remain unclear [2]. In the following sections, we are going to discuss some epidemiological data on CKD in the United States (US) and in the World, as well as briefly review the pathophysiological mechanisms involved in CKD development and progression, with special attention to the participation of inflammatory components in this process.

2. Chronic kidney disease and inflammation: definition and numbers

CKD is a general term used to define a group of heterogeneous disorders that structurally compromise the kidneys, resulting in reduction or insufficiency of renal function. CKD is one of the major degenerative conditions that lead to progressive disability, and is the ninth cause of death in the US [3]. Every year, kidney disease kills more people than breast or prostate cancer. According to the National Kidney Foundation, CKD assumed epidemic proportions in the last decades and meets all the required criteria to be considered as a major public health concern [3–8]. The 2016 Annual Data Report of the US Renal Data System (USRDS) showed that around 26 millions of American adults have some degree of kidney disease, of which, more than 661,000 have end-stage renal disease (ESRD), defined by the requirement of renal replacement therapy (RRT) for life-saving [4, 5]. Accordingly, there were 468,000 Americans on dialysis and approximately 193,000 individuals living with a transplanted kidney, in the last year [5].

This reality is also true for the other countries around the world. The Bulletin of the World Health Organization estimated the global number of patients receiving RRT to be higher than 1.4 million, with incidence of growing by around 8% annually [6]. This high prevalence and mortality, allied to the elevated costs of treating this growing epidemic represents a big burden on healthcare systems worldwide, especially in low and middle income countries, where long term dialysis is financially unaffordable [7–9]. This dramatic scenario motivates the medical community to intensify the efforts in preventing kidney injury and to improve the early detection of this condition. Moreover, scientific investigation to elucidate the pathophysiological mechanisms involved in the evolution of chronic nephropathies is of paramount importance to the development of more effective therapeutic strategies to slow or even stop the progression of CKD.

Gradual renal function deterioration is generally caused by an initial kidney injury, which acutely or chronically affects both the glomerular filtration rate (GFR) and/or the tubular reabsorption/excretion [2, 10]. The decrease of renal blood flow and the blockage of the urinary tract are the main causes of acute kidney injury (AKI). Kidneys' hypoperfusion can be caused by hypovolemia, septic shock, bleeding, hypotension, or due to renal ischemia, caused by abnormal vasoconstriction, or by the presence of blood clots, arteriosclerosis or other renal

blood flow blocking agents. Bladder and/or ureteral obstruction, in turn, can occur due to anatomic alterations, prostate hypertrophy, and cancer, or by the presence of kidney/ureteral stones. AKI can be additionally caused by some specific health conditions such as the multiple myeloma or the tubular necrosis, which can result from the administration of nephrotoxic drugs and compounds. In general, these conditions reduce the GFR, promoting a sharp decrease of renal function, that can be transitory; if the renal blood hypoperfusion or the obstruction of the urinary tract is rapidly corrected, or permanent, if the regular renal blood flow and the urinary output are not restored. There are actually growing evidence that, even when an AKI episode is properly solved, and there is a complete reestablishment of renal function, the patients should be closely followed for a long period, since this population is more prone to manifest CKD in the future [10, 11].

Although acute renal lesions may lead to the development of progressive kidney insufficiency, the two main causes of CKD are still diabetes and hypertension [3–6]. Such insidious diseases are, together, responsible for up to two-thirds of the cases of CKD in the American population [3–5]. If poorly or inefficiently controlled, both diabetes and hypertension may cause significant damage to human body, especially when it is exposed to these conditions for a long period. Many organs and systems can be affected, such as the blood vessels, the central nervous system (CNS), the eyes and, finally, the kidneys [2, 10]. The exact pathophysiological mechanisms through which sustained high serum glucose concentration and blood pressure lead to renal injury have not yet been fully elucidated. Proposed theories and mechanisms based on experimental studies, clinical trials, and medical observation will be discussed further on.

The third more common cause of CKD in the US is a group of autoimmune disorders, generally designated by Glomerulonephritis (GN) [3–5]. There are a number of different kinds of GN, which differ one from the other by the type of local renal infiltrating cells, by the presence and subtyping of autoantibodies, by the accumulation of complement system components, by the specific antigens that starts the renal local immune response, and also by some differential clinical and laboratorial features, including proteinuria, hematuria, and edema [12]. Although GN is an important cause of CKD, the molecular and cellular mechanisms involved in their onset and progression are beyond the scope of this revision, since GN is considered an immune-mediated kidney condition.

In a less extent, inherited diseases like different forms of polycystic kidney disease (PKD) and genetic syndromes, such as Von Hippel-Lindau, Alport's, and Bartter's can also lead to CKD, as well as congenital malformations of the urinary system and repeated urinary tract infections (UTI) [3–6, 13].

3. Overview of CKD pathophysiology

Regardless of the nature of the initial renal insult, CKD is characterized by proteinuria, serum urea and creatinine retention, blood pressure rising, and imbalance in renal perfusion, which lead to the development of glomerular hypertension and hypertrophy,

mesangial cells proliferation, and extracellular matrix (EM) overproduction, culminating in irreversible changes in glomerular and tubular architecture that impairs the function of the nephron [2, 9]. Notably, the involvement of the tubulointerstitial compartment has been correlated more closely with the evolution to kidney failure than the extent of glomerular injury per se [2, 9, 14]. The more filtering units are injured, the more overburdened the remaining nephrons become, which in turn end up succumbing due to overload in a vicious cycle of positive feedback. This process leads to global glomerulosclerosis (GS), tubular atrophy (TA), interstitial fibrosis, peritubular capillary rarefaction, and progressive renal function loss [2, 9, 14, 15], as illustrated in **Figure 1**.

The inordinate activation of the renin-angiotensin-aldosterone system (RAAS) is one of the major factors that can stimulate CKD progression [9]. Traditionally, RAAS used to be considered only as an endocrine system, whose major function was to maintain the blood pressure, even in situations of hypovolemia [16]. In the traditional description of RAAS, Renin, a hormone synthesized by the renal juxtaglomerular cells, promotes the conversion of angiotensinogen, produced in the liver, into angiotensin I (Ang I). This peptide is further cleaved by angiotensin-converting enzyme (ACE) into its active form, the Angiotensin II (Ang II), which, in turn, binds to its specific receptors (AT1) in the adrenal cortex, resulting in the release of aldosterone. Once released in the blood stream this

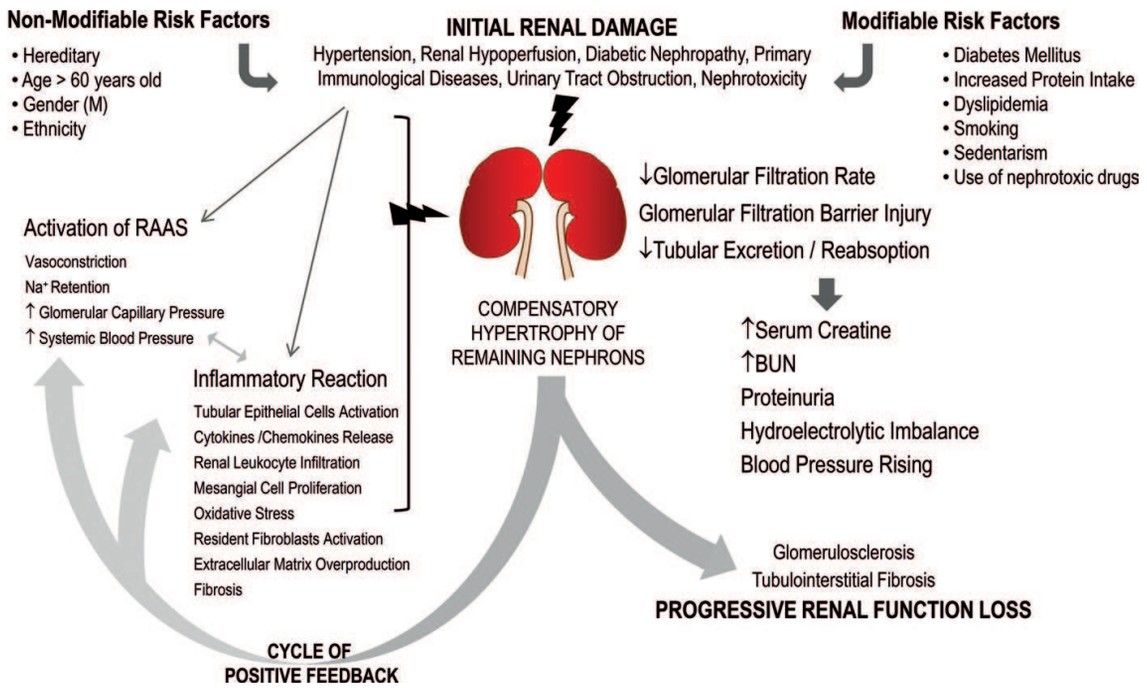

Figure 1. CKD pathophysiology. Different immune and nonimmune conditions may cause the initial renal insult that is been influenced by both modifiable and non-modifiable risk factors. This original damage causes several changes on renal function reducing the glomerular filtration rate, impairing the renal tubular hydroelectrolytic balance and damaging the glomerular filtration barrier. In a forward positive feedback, these events are able to lead to glomerulosclerosis, renal fibrosis and progressive loss of function.

mineralocorticoid steroid promotes renal and systemic vasoconstriction and tubular sodium conservation, leading to the elevation of blood pressure [9, 16]. In spite of its first description, RAAS became much more complex in the recent years, after the identification of many novel components, such as the enzyme chymase, which exerts the same function of ACE, the biologically active peptides angiotensin III, IV, 1–9 and 1–7, and a number of different Ang II receptors (AT2, AT4, among others) [16]. Moreover, depending on which intracellular downstream system is activated by Ang II, different physiological responses can be triggered [16, 17].

Ang II has been related to inflammation followed to chronic nephropathy developed by the enhancing of the immune response and favoring renal infiltration by leukocyte [18, 19]. Additionally, there are growing *in vitro* and *in vivo* evidence that Ang II promotes cell proliferation and fibroblast activation, worsening the accumulation of EM and contributing to the development of renal fibrosis [18, 20, 21]. Furthermore, a variety of studies showed the presence of both Ang II and the receptor AT1 in the renal parenchyma of animals submitted to experimental models of CKD, leading to the discovery of a complex intrarenal pro-inflammatory RAAS that seems to become overactivated under kidney injury [18–22]. Accordingly, suppression of RAAS with both ACE inhibitors (ACEi) and/or AT1 receptor blockers (ARB) become a mainstay of treatment of progressive nephropathies and, although several innovative therapeutic measures have been recently proposed for the treatment of CKD, RAAS blockage, associated to diuretics or not, remains the best available resource in this regard [9, 16, 23, 24].

In 1984, Schwartz and collaborators demonstrated for the first time an increase in fibroblast and the appearance of macrophages and lymphocytes in the renal parenchyma of rabbits submitted to a sterile model of renal ischemia/reperfusion [25]. This was one of the first studies suggesting that the inflammatory process, including mononuclear cell infiltration and fibroblast proliferation was a final pathway common to different forms of renal injury, independent of its etiology. We currently know that inflammation exerts a key role in the pathogenesis of CKD, although the mechanisms by which this process is activated and perpetuated, even when the initial insult is not immune-mediated, remain unclear.

There is growing evidence that the activation of both cellular and humoral immunity is related to the progression of renal insufficiency and a worse prognosis in nonimmune-mediated CKD. Renal infiltration by macrophages has been demonstrated in a variety of human nonimmune-mediated renal diseases, such as diabetic nephropathy (DN) [26] and hypertensive nephrosclerosis (HN) [27]. Moreover, this phenomenon was also observed in different experimental models of CKD over the last years. Accordingly, the number of inflammatory cells in the renal *interstitium* closely correlates with the severity of nephropathy and with glomerular and tubulointerstitial lesions in these experimental models [28–30]. The increase of dendritic cells (DCs) in the renal parenchyma, in turns, is believed to indicate the spreading of inflammation from glomerular to the tubulointerstitial compartment, playing a pivotal role in the progression of both AKI and CKD [31, 32]. Finally, cortical

T-lymphocyte infiltration is a common finding in both genetic [33] and pharmacologically induced [34] DN in rodents. Moreover, it has also been described in the 5/6 renal ablation model (NX) [35] and in the chronic inhibition of nitric oxide synthase model (L-NAME) [29], among others [19]. In most of these studies, the amount of T-cells in the renal *interstitium* correlates positively with the progression of albuminuria, creatinine retention, and renal structural damage, as shown in **Table 1** [36–43]. Corroborating these findings, a number of experimental studies showing significant evidence that anti-inflammatory treatment, as well as the knockout (KO) of specific pro-inflammatory genes can be effective to detain the evolution of nephropathy in different animal models of CKD, have been recently published, as shown in **Table 2** [44–52].

Although the exact sequence of the inflammatory events in progressive CKD has not been completely elucidated yet, we are currently aware that, the activation of tubular epithelial cells, inordinate production of cytokines, activation of resident phagocytes and fibroblasts, as well as the transdifferentiation of these last into pro-fibrotic myofibroblasts, parallels renal leukocyte infiltration, from the early beginning of renal disease. Furthermore, these processes follow the evolution of CKD, becoming autonomic and leading to excessive production of EM and fibrosis [9, 14, 32, 53].

Authors (first, last) and year	Ref.	Species	CKD studied	Molecules/cells studied
Gong W, Zhang A. 2016	[36]	Mouse	5/6 nephrectomy (NX)	NLRP3
Souza AC, Star RA. 2015	[37]	Mouse	5/6 nephrectomy (NX)	TLR4
D'Apolito M, Giardino I. 2015	[38]	Mouse	5/6 nephrectomy (NX)	Urea as a DAMP
Lehners A, Wenzel UO. 2014	[39]	Mouse	5/6 nephrectomy (NX)	Myeloperoxidase (MPO)
Correa-Costa, Camara NOS. 2011	[40]	Mouse	Adenine-induced tubule interstitial nephritis	TLR2, TLR4, MYD88, ASC, CASP1
Fanelli C, Zatz R. 2011	[19]	Rat	CKD caused by AT1 blockade during nephrogenesis	T-lymphocytes
Vilaysane A, Muruve DA. 2010	[41]	Mouse	Unilateral ureteral obstruction (UUO)	NLRP3
Rodriguez-Iturbe, Vaziri ND. 2004	[42]	Rat	Spontaneously hypertensive rats (SHR)	NFKB system, T-cells
Utimura R, Zatz R. 2003	[28]	Rat	ST-induced DN	T-lymphocytes
Fujihara CK, Zatz R. 2001	[29]	Rat	L-NAME-induced nitric oxide synthase inhibition	T-lymphocytes
Donadelli R, Zoja C. 2000	[43]	Rat	5/6 nephrectomy (NX)	NFKB system
Fujihara CK, Noronha IL. 1998	[35]	Rat	5/6 nephrectomy (NX)	T-lymphocytes

Table 1. Evidences of innate and adaptive immunity activation in nonimmune-mediated CKD.

Authors (first, last) and year	Ref.	Species	CKD studied	Target cell/molecule	Drug/compound	Related improvements
Ludwig-Portugall I, Kurts C. 2016	[44]	Mouse	Adenine/oxalate-induced nephritis	NLRP3	CP-456,773	CP-456,773 prevented kidney fibrosis in a murine model of crystal nephropathy induced by diets rich in oxalate or adenine.
Okabe C, Fujihara CK. 2013	[45]	Rat	Adenine-induced nephritis	NFKB system	PDTC	PDTC prevented p65 nuclear translocation, limited formation of renal interstitial foreign body granulomas, reduced the expression of Ifng, Il6, Fsp1, Mcp1 genes, and strongly attenuated interstitial fibrosis/inflammation
Kim JE, Cha DR. 2013	[46]	Mouse	db/db genetically-induced DN	NFKB system	Celastrol	Celastrol not only improved insulin resistance, glycemic, control, and oxidative stress, but also improved renal functional and structural changes through both metabolic and anti-inflammatory effects in the kidney
Gilbert RE, Kelly DJ. 2012	[47]	Rat	5/6 nephrectomy (NX) and ST-induced DN	TGFβ	FT011	FT011 attenuated hypertension, GS, and renal macrophage infiltration in Nx, as well as reduced albuminuria, GS, renal interstitial fibrosis, and inflammation in ST-DN
Ding W, Gu Y. 2012	[48]	Rat	Aldosterone/salt-induced renal injury	NFKB system	PDTC	PDTC significantly decreased the percentage of $CTGF^+$ cells, the mRNA for TGF-β, CTGF, TGF-β, ICAM-1 and collagen IV, and protein levels of CTGF and ICAM-1
Kaneyama T, Ehara T. 2010	[49]	Rat	Unilateral ureteral obstruction (UUO)	TGFβ	Tranilast	Fibrosis and tubular injuries were attenuated in UUO rats treated with tranilast compared with untreated UUO animals
Fujihara CK, Zatz R. 2007	[50]	Rat	5/6 nephrectomy (NX)	NFKB system	PDTC	PDTC attenuated renal injury and inflammation, as well as the density of cells staining positively for the phospho p65 subunit

Authors (first, last) and year	Ref.	Species	CKD studied	Target cell/molecule	Drug/compound	Related improvements
Utimura R, Zatz R. 2003	[28]	Rat	ST-induced DN	T-lymphocytes	MMF	MMF prevented albuminuria, GS, and renal cortical macrophage infiltration in DN
Shihab FS, Andoh Tf. 2002	[51]	Human	Human DN	TGFβ, TNFa	Pirfenidone	Treatment with pirfenidone, which has been shown to inhibit renal fibrosis in experimental models, prolonged the period of conservative treatment of CKD in patients with ND, delaying the need for dialysis
Fujihara CK, Zatz R. 2001	[29]	Rat	L-NAME-induced NO inhibition	T-lymphocytes	MMF	MMF significantly reduced glomerulosclerosis, renal interstitial expansion, macrophage and lymphocyte infiltration
Romero F, Tapia E. 1999	[52]	Rat	5/6 nephrectomy (NX)	T-lymphocytes	MMF	Segmental sclerosis, interstitial fibrosis, and renal infiltration by $CD43^+$ and $ED1^+$ cells were significantly reduced with MMF
Fujihara CK, Noronha IL. 1998	[35]	Rat	5/6 nephrectomy (NX)	T-lymphocytes	MMF	MMF significantly prevented GS and interstitial expansion in NX rats

Table 2. Studies using experimental CKD development and its renoprotective effects.

4. The immune system and kidney disease

The immune system (IS) is composed by a set of structures, cells, and processes that together enable an organism to recognize their self-elements from the foreign and potentially pathogenic ones, producing then, a physiological response consistent with the nature of the recognized element, which can be either a self-harmless protein or a dangerous bacterium [54]. As part of these systems, there are the so-called nonimmunological physical, chemical, and biological barriers and the immunological components itself, represented by innate and adaptive mechanisms of cellular and humoral immune response [54, 55].

In a simplistic way, the IS is responsible for four different body functions. The first one is the immune tolerance, the property that allows the body to recognize self-cells, proteins, and

other constitutive elements, producing a response of tolerance and preventing autoimmune reactions. This particular state of IS unresponsiveness is also essential to ensure the regular fetal development during pregnancy and to allow the colonization of human skin, digestive tract, and vagina by beneficial microorganisms referred as microbiota [56, 57].

The second and most well-known function of IS is the immunity itself. It is the ability to recognize foreign proteins and molecules, which may indicate the presence of invading microorganisms, such as bacteria or other parasites, and respond to these foreign elements with both cellular and humoral defenses, protecting the organism against infection [54]. Additionally, through its third property, immune surveillance, the IS patrols the body to recognize and destroy self-cells infected by virus or even constitutive cells that become cancerous or suffer phenotype alterations due to genetic mutations [54, 55]. For immune surveillance to work, cancer and/or mutated cells must express specific antigens that are not frequently found on normal cells, otherwise the IS would recognize them as "self" and be tolerant of them [58, 59].

Finally, the last property of IS is the ability of self-controlling the immune response. Through a complex mechanism of feedback and cell-to-cell communication, involving a number of cytokines and cell-cytokine receptors, IS modulates its response, which can be either tolerance or immunity, according to the specific stimulus to which the organism is subjected to [54]. This property is known as immunoregulation and is of paramount importance, not only for the kidneys but also for the whole organism. Failures on the immunoregulation may lead either to the development of autoimmune diseases that can impair renal function, such as systemic lupus erythematosus (SLE), whose renal involvement is a severe type of GN called lupus nephritis or to the vulnerability to opportunistic infections, leading to repeated episodes of pyelonephritis and/or immune-mediated GN due to the accumulation of antigen-antibody complexes in the glomerular filtration barrier (GFB) [12].

The integrity of the epithelial tissue can be listed as one of the most important nonimmunological physical barriers against infection. The skin represents the largest organ of the human body and its main function is to delimit the organism, separating it and protecting it from the environment that surrounds it. Of course, it is not an insurmountable insulation, since this would be incompatible with the maintenance of life: water, atmospheric gases, and ions are able to cross the epithelial barrier simply due to passive processes such as osmosis and diffusion or through active transmembrane transport.

However, macromolecules, such as high-weight proteins or even whole cells are not able to transpose the barrier formed by epithelial tissue in a normal physiological situation, making the area covered by the intact epithelium protected from invasive pathogens. Accordingly, epithelial injury and/or scarification provide the invasive parasites a chance to enter into their future host [54, 55]. Some virulent microorganisms can produce elements capable of puncturing or injuring the epithelial tissue, opening a gateway to the host organism. Certain strains of uropathogenic *Escherichia coli* (UPEC), for instance, produce proteolytic enzymes, cytotoxic necrotizing factors, and numerous adhesive molecules (adhesins) as part of their invasion arsenal [60].

UTI is a worldwide health problem that affects over 13 million of people each year in the US. It is currently the most common infection in adult females and, in nearly all cases, it is caused by a few strains of UPEC. Although the symptoms of an uncomplicated UTI can be relatively mild, it can progress to pyelonephritis, leading to fever, nausea, vomiting, and, in about 30% of cases, bacteremia and risk of sepsis. Moreover, recurrent UTI may contribute to additional problems, including renal scarring, CKD, and an increased risk for developing bladder cancer [60]. Besides the presence of UPEC and the toxins produced by them in the urinary tract, there are evidence that proteinuria can itself cause injury to the renal and urinary epithelium. Since proteins are expected to be retained in the GFB, increased protein concentration in the urinary fluid is considered an irritating and pro-inflammatory factor for the tubular, ureteral, and bladder epithelium, leading to enhanced protein reabsorption by the tubular epithelial cells, overload of their catabolic capacity, leukocytes infiltration, and corruption of the integrity of the urinary epithelial barrier [54].

The intestinal and ureteral peristaltic movement and the flow of fluids like vomiting, diarrheal, or the urinary stream itself are also important physical barriers against infection, preventing the onset and permanence of microorganisms in the digestive system and in the lower urinary tract. In addition to these physical barriers, the maintenance of low pH in some body fluids is one of the chemical physiological strategies of greater prominence to avoid infections. Accordingly, low stomach and urinary pH can destroy most of the parasitic organisms which, by chance, succeed in penetrating these systems [55]. The last, but not least, of the "nonimmunological" barriers that protect our body from infection is the biological barrier, represented by the normal microbiota, a complete ecosystem composed by harmless microorganisms that live in balance with our body. The benefits of having the intestines, skin, and vagina occupied by specific strains of innocuous bacteria were once thought to be limited to the reduction of pathological colonization, due to the competition among the invaders and the resident flora. Nowadays, we know that the microbiota lives in fact in a mutualistic symbiosis with our body, benefiting themselves and the host [54, 55, 61].

The integrity of our intestinal microbiota, for instance, is essential to the digestion of a number of food components, making the absorption of important nutrients easier. Moreover, the anaerobic bacilli that inhabit the vaginal cavity are responsible for the maintenance of acid pH in that region, since they produce lactic acid as an anaerobic respiration metabolite, keeping the vagina free of fungal colonization. It is of note that the resident microbiota lives in a delicate balance with our IS. Its growth is controlled and limited by phagocytic cells and other elements of the IS, and the occurrence of imbalances in the property of immunoregulation, such as immunity reduction due to illness, immunosuppression, stress, or malnutrition, may lead to an exacerbated growth of microbiota population, which is potentially harmful for the human organism and should be controlled [54, 61].

5. Inflammation and innate immune response

When the above mentioned nonimmunological natural barriers are overcome by pathogens or other irritative elements, the immune response is initiated through the inflammatory reaction,

as an attempt to restore tissue integrity. In case of infection, for instance, the elimination of invading microorganisms becomes a necessary condition for tissue repair. Inflammatory reaction depends on the action of specific blood cells called leucocytes. Under normal physiological conditions, there are around 5000 and 10,000 leukocytes per blood microliter, but these numbers significantly rise in the presence of an infection. Mature leukocytes can be classified both according to their original lineage (myeloid or lymphoid cells) and/or to the number of cellular nuclei they appear to have under light microscopy (mononuclear or polymorphonuclear cells), as illustrated in **Figure 2** [32, 54].

Mononuclear cells represent 35% of the total peripheral blood leukocytes. This broadest category is composed by monocytes: phagocytic cells that give rise to both macrophages and dendritic cells; mast cells, which are mainly responsible for vasodilation on inflammatory processes; lymphocytes, the effectors of our specific immune response, and finally, the natural killer cells (NK). The remaining 65% of blood leukocytes are represented by the polymorphonuclear cells, which are didactically subdivided into three different groups, according to their affinity with acid (eosinophils), alkaline (basophils) or both (neutrophils) histological dyes; these last being the first cell type to reach an injured area of the organism and initiating the inflammatory response. Leukocytes whose cytoplasm is rich in granules of enzymes and cytotoxic substances, such as reactive oxygen species, are generally called granulocytes. Basophils, eosinophils, and neutrophils can be called granulocytes. Macrophages and dendritic cells also have a considerable amount of granules in their cytoplasm; however, they are described as phagocytes, due to their ability to phagocyte invading microorganisms. All leukocytes are capable of producing a broad range of chemical mediators involved in the immune response (generally called cytokines) in response to lesions or to the presence of microorganisms. In addition to being responsible for the synthesis of these cytokines, leukocytes are also responsive to the action of these mediators, which promote, among other biological effects, leukocyte chemotaxis toward the inflammatory focus as well as its activation [32, 54, 55]. Cytokines are soluble glycoproteins, which may have autocrine, paracrine, or endocrine action. A fraction of these mediators have been at least partially described, however, there is still an almost infinite range of little known pro-inflammatory cellular signaling molecules, whose activity has not yet been fully established.

As far as we currently know, once the nonimmune body barriers are overcome by a pathogen or a dangerous substance, a microscopic battle begins in the injured tissue. The first line of defense of our immune system is the innate immunity, which comprises a group of cells, intracellular mechanisms, and chemical mediators, extremely conserved evolutionarily. Long before vertebrates first appeared on Earth, their primitive ancestors already had effective systems of immune cells recruitment, production of cytokines, activation of the complement cascade, identification of foreign elements through transmembrane and intracellular molecular pattern recognition receptors (MPRR), inactivation of pathogens through the production of reactive oxygen species (ROS), antimicrobial peptides and lytic enzymes, and, finally, removal of invader microorganisms through phagocytosis. Although innate immune system is a nonspecific evolutionarily older defense strategy, it is a fast mechanism that comes into play immediately or within hours of the appearance of a foreign element in the body, initiating the inflammatory process [32, 37–42, 54].

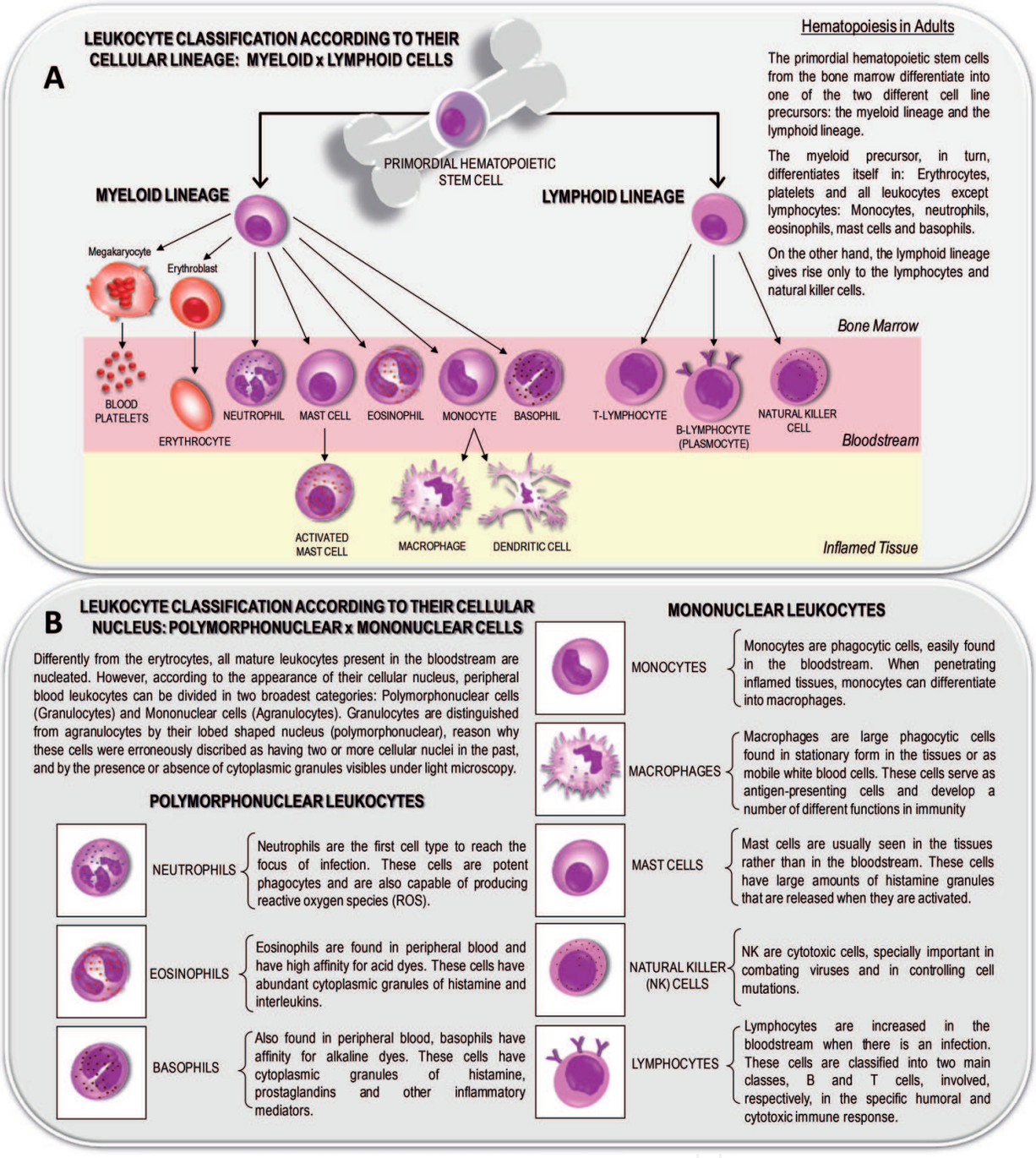

Figure 2. Leukocyte classification. Leukocytes can be classified as myeloid or lymphoid cells, according to their hematopoietic origin, or as mononuclear or polymorphonuclear cells, according to the number of cellular nuclei and cytoplasmic granules they appear to have, in their mature circulating form, under light microscopy.

Right after tissue aggression, the MPRRs of injured cells, which may be epithelial, endothelial, or mesangial cells, as well as resident phagocytes and fibroblasts, recognize pathogen-associated molecular patterns (PAMPs) that may indicate the presence of invading microorganisms and damage-associated molecular patterns (DAMPs), released by self-cells under cellular

suffering. Bacterial lipopolysaccharide (LPS), flagellin, peptidoglycans, glycolipids, zymosan, and profilin, as well as single-stranded DNA (ssDNA) and double-stranded RNA are examples of PAMPs. In turn, Interleukines IL-1β and IL-18, extracellular HMGB1, ATP, and DNA, as well as uric acid crystals can be considered DAMPs [37–42].

After this first identification, local cells synthesize and release vasoactive mediators that promote vasodilatation and increase the local blood supply, causing heat and flushing; common features of inflammation. The concomitant activation of resident innate immune cells also takes part in the process. Under physiological conditions, the most common kidney resident immune cells are tissue macrophages and dendritic cells. It is of note that these last acts as sentinels in homeostasis, local injury, and infection, rapidly producing neutrophil-recruiting chemokines. In a less extent, mast cells are also seen in renal tissue and have been pointed out as local renal producers of RAAS components [14, 18]. Once activated, in addition to increasing the renal production of Ang II, mast cells release the content of their cytoplasmic granules of histamine; a biogenic amine that promotes increased vascular permeability by distancing endothelial cells (enlargement of endothelial fenestrae) near the injured region. As a result, there is a blood plasma extravasation from local blood vessels to the injured region, diluting eventual toxins produced by invading microorganisms, and bringing the proteins of complement system to the inflammation site [54, 55]. This interstitial accumulation of plasma promotes both edema and local pain, due to the compression of nerve endings. The next step is the diapedesis, or transendothelial migration, which is the leukocyte outflow from the bloodstream toward the focus of inflammation. This process is only possible due to a complex chemical communication system between the injured local tissue, the endothelial cells and the leukocytes itself, as illustrated in **Figure 3**.

The first cell types to reach the inflammatory focus are neutrophils, followed by circulating monocytes, which upon reaching the tissues become macrophages. Phagocytes also are able to reach the inflammatory spot and recognize PAMPs and DAMPs through two potential strategies: (1) phagocytosis followed by digestion of the microorganism and (2) production and excretion of anti-microbial compounds, as nitric oxide (NO), and ROS such as superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2). The acute phase of inflammation can promote systemic effects. Activated macrophages, for example, release IL-1β and tumor necrosis factor (TNFα), cytokines that bind to our thermoregulatory receptors causing body temperature rising (fever), and stimulate the hypothalamic-pituitary-adrenal axis, leading to increased production of corticoid hormones, including renin, by the adrenal gland [54, 55]. Moreover, TNFα acts on the bone marrow, accelerating leukocyte proliferation. At this initial nonspecific phase of inflammatory response, the phagocytic capacity of neutrophils, monocytes, and macrophages does not depend on specific antigenic recognition, on neither the immune memory nor the presence of antibodies. Resistant microorganisms, as well as remaining phagocytes, are then drained through the lymphatic vessels to the nearest lymph node, where the antigens will be presented to the lymphocytes, initiating a more complex and long-lasting reaction, the adaptive immune response [32, 54, 55].

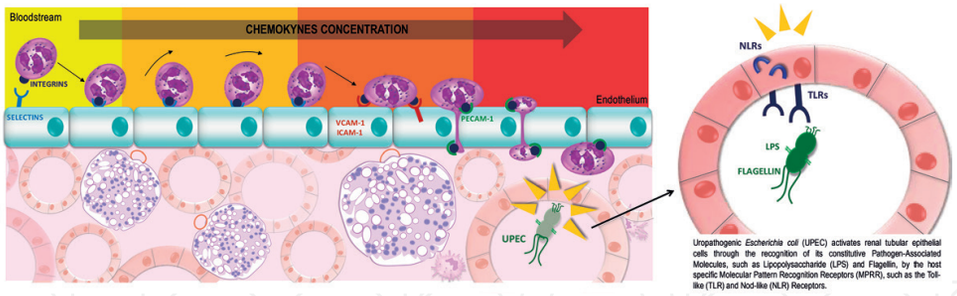

Figure 3. Diapedesis. Inflammatory response initiates right after the recognition of a foreign element by the MPRRs of host cells, particularly the toll-like (TLRs) and NOD-like receptors (NLRs). Damaged cells release specific chemokines (CCL-2, -3, -4, -5, -11, -20 and CXCL10), which attract the circulating leukocytes, guiding their migration through a gradient of concentration in the bloodstream toward the inflamed area. When these cells reach the blood vessels with the highest concentration of chemokines, they firmly adhere to the endothelium and initiate a rolling process, getting closer to the inflamed region. Once near from the inflammation site, leukocytes stop rolling, change their shape by spreading on the endothelium, and finally pass through the enlarged endothelial fenestrae, reaching the potentially infected tissue. This process is called diapedesis and it is only possible due to the chemical affinity between the constitutive integrins, present on the surface of leukocyte cellular membrane, and some specific endothelial adhesion molecules, such as selectins E and P, which stimulate leukocyte rolling, vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ECAM-1) and platelet and endothelial cell adhesion molecule 1 (PECAM-1), which contribute to the attachment of leukocytes to the endothelial membrane and to their transmigration through the endothelial barrier.

6. Innate immune response and nonimmune-mediated CKD

In the past years, renal activation of innate immune mechanisms by sterile elements has been demonstrated in nonimmune-mediated human nephropathies. Moreover, such activation of innate immunity seems to be positively correlated with the progression of renal injury in a variety of experimental models of CKD (**Table 1**). Our understanding of the mechanisms underlying the triggering of sterile inflammation was largely enhanced after the discovery of specific MPRRs: the toll-like receptors' (TLRs) and the NOD-like receptors' (NLRs) families; primarily found in leukocytes, but also present in epithelial and endothelial cells. Once activated, transmembrane and cytoplasmic TLRs trigger multiple intracellular events, involving adaptor proteins, such as MyD88, Mal/TIRAP, and TRAM, leading to nuclear translocation of transcription factors such as IRF3, IRF7, and NFKB, known to induce a variety of pro-inflammatory genes [32, 40]. On the other hand, NLRs are another class of intracellular MPRRs, very responsive to the presence of DAMPs. Their activation promotes the assembly of molecular complexes known as inflammasomes, such as the NOD2, NLRP1, NLRP3, NLRC4, etc. Inflammasomes assembly also promotes NFKB and MAPK activation, as well as the conversion of the inactive Pro-caspase 1 into the pro-inflammatory enzyme Caspase 1 (CASP1), which in turn, promotes the maturation of interleukins IL1β and IL18, thus amplifying the inflammatory response [36–41]. As mentioned above, the activation of these two main families of MPRRs, as well as, the components related to their intracellular signaling pathway were already described to be present in both human and experimental CKD. A proposed mechanism for sterile activation of immune response in nonimmune-mediated CKD is illustrated in **Figure 4**.

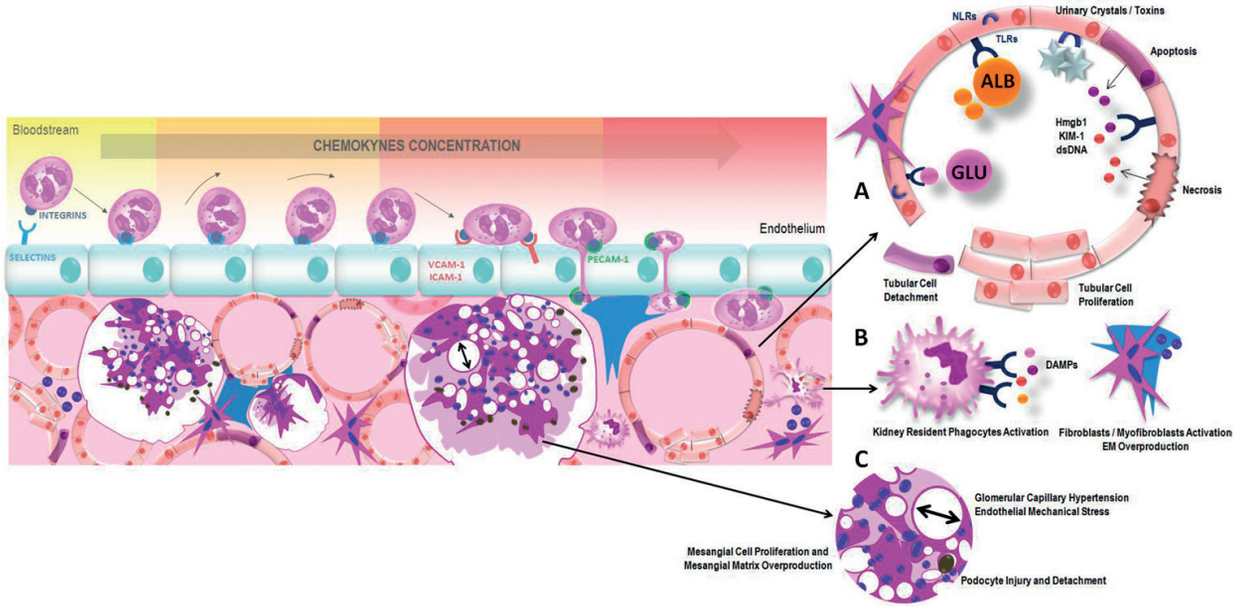

Figure 4. Renal sterile inflammation. Beyond to be activated by pathogens, MPRRs are also sensible to molecules currently related to cell damage (DAMPs). These sterile stimuli may represent the link between the initial features of nonimmune renal aggression and the establishment of chronic kidney inflammation. It is currently known that different renal cells present the intracellular machinery necessary to activate innate immune response, from endothelial to resident dendritic cells. TLRs and NLRs are stimulated in tubular epithelial cell exposed to DAMPs starting an intracellular intricate response that leads to the release of pro-inflammatory interleukins and chemokines (A). These intercellular signaling compounds are capable of recruiting circulating leukocytes to the renal parenchyma, as well as to activate resident interstitial macrophages, dendritic and mast cells, similarly to what occurs in an infection episode (B). Moreover pro-inflammatory interleukins released by both epithelial cells and renal immune sentinels can activate resident fibroblasts leading to their transdifferentiation into profibrotic myofibroblasts; cells specialized in producing large amounts of EM proteins and further pro-inflammatory signaling molecules. Additionally, glomerular sterile damage can also trigger leukocyte recruitment through the activation of innate immunity pathways. Endothelial cells of glomerular capillaries potentially react to mechanical stress caused by tissue stretching due to glomerular hypertension and hypertrophy by releasing DAMPs. This possible event promotes mesangial cells proliferation and EM overproduction, which may lead to glomerulosclerosis and the activation of further pro-inflammatory mechanisms (C).

Accordingly, experimental studies have been shown that chemical blockage of inflammasome NLRP3, NFKB system, and IL1β, limits blood pressure rising, albuminuria, creatinine retention, and renal histological alterations in different murine CKD models. Moreover, *Tlr2*, *Tlr4*, and *Nod2* knockout (KO) mice develop less tubulointerstitial nephritis and renal fibrosis when submitted to kidney injury [40]. The activation of innate immunity pathways in nonimmune-mediated CKD may represent an important link between nonspecific insults; such as glomerular wall stretching, due to glomerular hypertension and hypertrophy, tubular exposure to high protein, glucose or uremic toxins concentration, tissue damage by the presence of crystals; and late events, such as GS and interstitial fibrosis. Innate immune intracellular mechanisms are represented in detail in **Figure 5** [2, 18, 21, 54]. Since cell damage may further stimulate innate immunity, a positive feedback may establish, leading to the engagement of adaptive immunity, perpetuating inflammation, and culminating in the establishment of end-stage renal disease (ESRD).

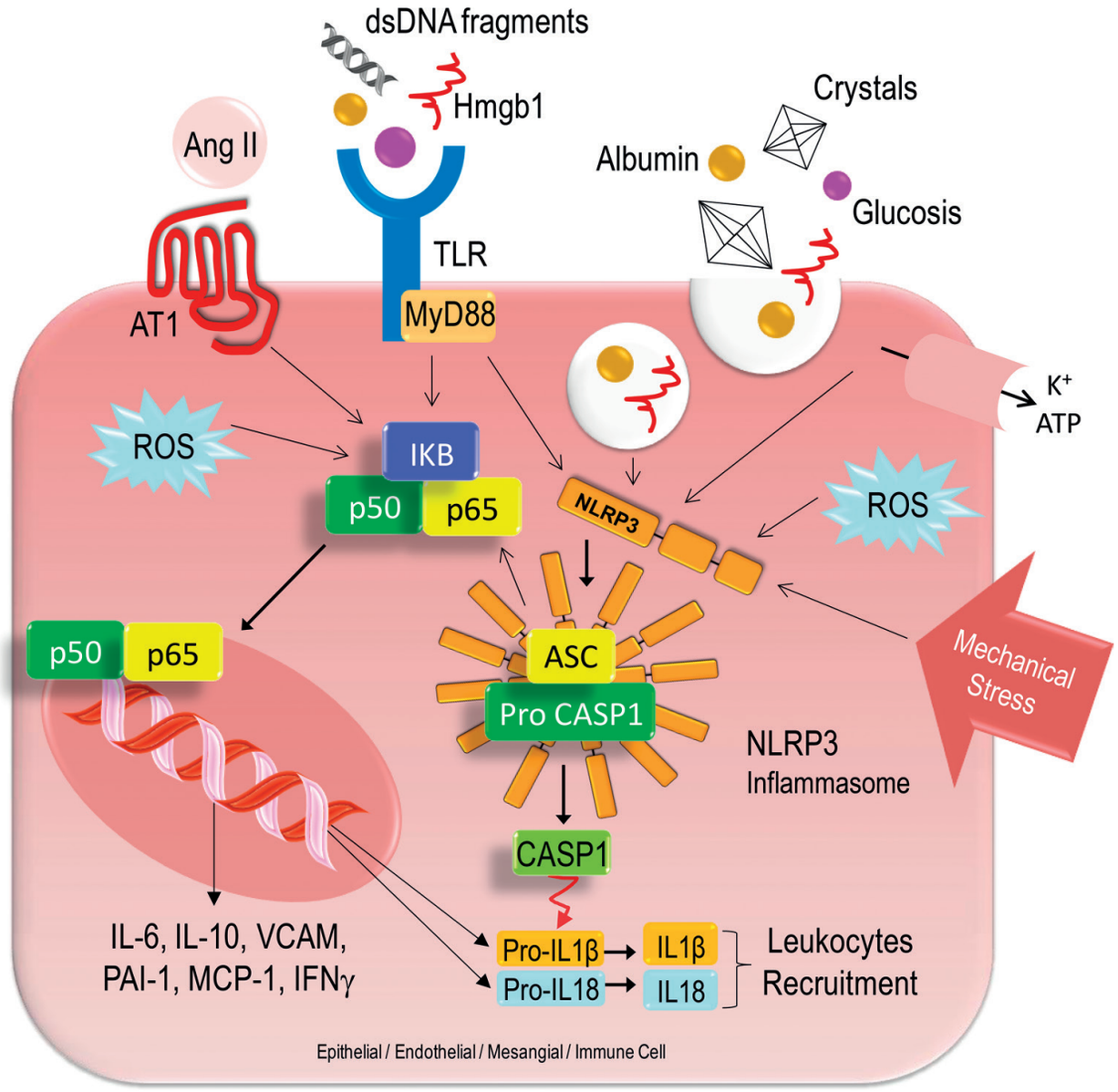

Figure 5. Some intracellular mechanisms of sterile innate immune reaction. Many different sterile stimuli can be identified as DAMPs by epithelial, endothelial, mesangial cells and also by renal resident leukocytes. Once a DAMP is recognized by a TLR, for instance, it leads to the activation of NFKB system, one of the most important intracellular pro-inflammatory pathways. The NFKB system is composed by the subunits p50 and p65, which in physiological conditions are maintained in their inactive form in the cytoplasm due to binding to the inhibitory protein IKB. Under stimulation, IKB is degraded, releasing the p50/p65 heterodimer, which penetrates into the cell nucleus to bind to DNA and act as a transcription factor, promoting the synthesis of a bunch of pro-inflammatory proteins, including the immature interleukins pro-IL1β and pro-IL18 and the active IL-6, VCAM, PAI-1, MCP-1 and IFNγ. It is of note that the NFKB system is not exclusively activated by TLRs signaling, but also by oxidative stress, Ang II and other pro-inflammatory mediators. On the other hand, the identification of intracellular DAMPs by a NLR, such as the NLRP3 for instance, promote the assembly of a molecular complex known as NLRP3 inflammasome, that also promotes NFKB system activation, as well as the conversion of the inactive pro-caspase 1 into the pro-inflammatory Caspase 1 (CASP1), promoting IL1β and IL18 maturation, thus amplifying the inflammatory response.

7. Adaptive immune response

As previously mentioned, in the presence of an infection the microorganisms, which were not eliminated by the innate immune response, are drained together with remaining phagocytes

through the lymphatic vessels to the nearest lymph node, where a most specific and long lasting reaction begins: the adaptive immune response. It is important to emphasize that macrophages, dendritic cells, and other innate phagocytes represent the link between the nonspecific and the specific immune response. These leukocytes are designated as antigen presenting cells (APCs), since they have the ability of presenting foreign molecules to the lymphocytes in the lymph nodes, thereby activating and stimulating these specific cells. Lymphocytes are mononuclear leukocytes involved with the specific immune response. They originate from a lymphoid progenitor cell in the bone marrow, and may undergo differentiation in the bone marrow itself, been called B-lymphocytes or simply B-cells, or in the thymus, called T-lymphocytes or T-cells [54, 55]. Once the APCs phagocyte an invading microorganisms, they digest their proteins (antigen processing) and migrate to the lymph nodes, where they expose small peptide portions of the invader in the surface of their cellular membrane, associated with their molecules of the major histocompatibility complex of class II (MHC II). Both types of lymphocytes are able to recognize processed antigens associated with molecules of the MHC II of APCs through their membrane receptors (TCR of T-lymphocytes or BCR of B-lymphocytes). Unstimulated B or T lymphocytes, also called "naive" cells are generally small and present scarce cytoplasm. However, once stimulated, they became "effector lymphocytes," increase in size, have the cytoplasm hypertrophied and suffer mitosis, promoting clonal amplification, thus increasing the number of cells that would be sensitive to that specific activating antigen [32, 54].

In an extremely simplified view, when an antigen is recognized by the TCR of a naive T-cell, this leukocyte is activated, initiating the cellular adaptive response. First of all, the effector t-cell give rise to two different cell types through cell division: the T-Helper lymphocyte, that have the CD4 glycoprotein on the surface of their cell membrane ($CD4^+$ T-cell), and the Cytotoxic T lymphocyte, characterized by the presence of CD8 in its membrane ($CD8^+$ T-cell). Both $CD4^+$ and $CD8^+$ T-cell will be sensitive to the same antigen that promoted the activation of the T-Helper cells migrate to the inflamed area and, according to the type of stimulus they receive, these cells differentiate into one of the five known phenotypes: Th1, Th2, Th17, Tfh, and Treg [55]. Most of these subtypes of T-cells produce pro-inflammatory cytokines that acts especially upon macrophages, attracting them close to the target antigen, giving them increased membrane mobility and increasing their phagocytic and microbicidal potential. Only the Treg phenotype is described to release anti-inflammatory mediators, thus contributing to immunotolerance.

Cytotoxic T lymphocytes, in turn, can directly lysate bacteria, virus-infected cells, as well as self-cells that have suffered genetic mutation. Once the cytotoxic T-lymphocyte gets in touch with the target microorganism or antigen, a series of granzymes, perforins, and other cytotoxic molecules are released from within their cytoplasmic granules directly into the extracellular medium. Perforins are molecules that promote the formation of pores in the plasma membrane of target cells, causing abrupt entry of liquid, due to osmotic pressure, into the cytoplasm of these cells, leading to its apoptosis. Furthermore, both T-Helper and Cytotoxic lymphocytes give rise to memory $CD4^+$ and $CD8^+$ cells, respectively. This process is illustrated in **Figure 6**. Unlike the other populations of T-lymphocytes, memory T-cells may be inactive for years in the bloodstream, generating copies of themselves; thus, maintaining the memory of the recognition of the antigen that caused the activation of its precursor. Such cells are readily activated in the presence of a reinfection, being extremely important to defend our body from recurrent infections.

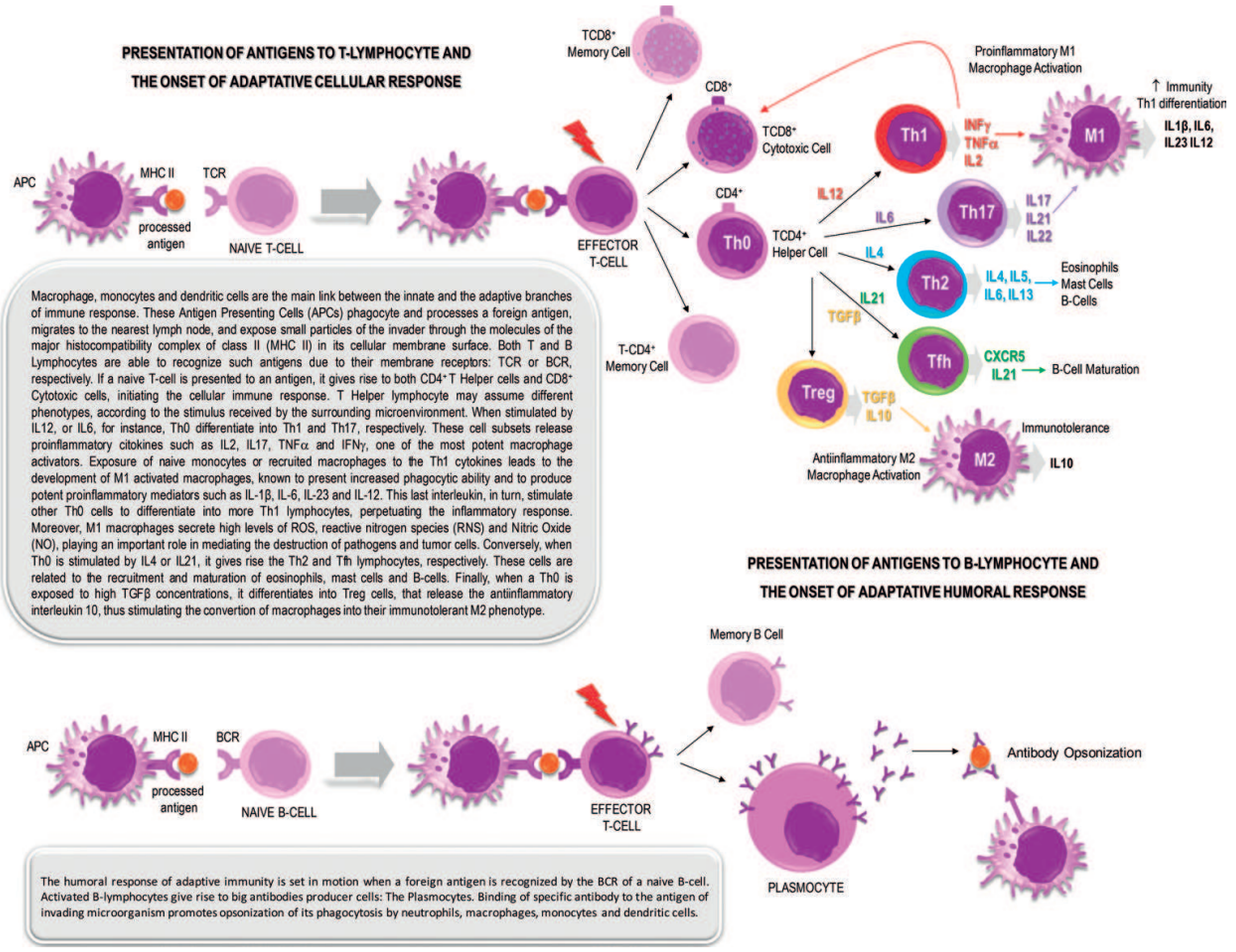

Figure 6. Presentation of antigens to lymphocytes and the onset of adaptive immune response. Mechanisms that link innate and adaptive immunity and the onset of the activation of lymphocytes.

On the other hand, when a foreign antigen is recognized by the BCR of a naive B cell, the humoral branch of adaptive immune response sets in motion. Activated B lymphocytes, or plasmocytes, synthesize specific antibodies against the invading microorganism. The antibodies produced by plasma cells may remain adhered to the cellular membrane of B-cells, promoting the binding of the cell as a whole to the parasite antigen, or be released to the bloodstream. In both cases, binding of the specific antibody to the antigen of invading microorganism promotes opsonization of its phagocytosis by neutrophils, macrophages, monocytes, and dendritic cells, besides promoting the neutralization of microbial toxins. Activated B-cells also produce memory B-cells, important to generate an accelerated and more robust antibody-mediated immune response in the case of re-infection by the same antigen [54].

8. Adaptive immune response in nonimmune-mediated CKD

Similar to the innate arm of immune response, adaptive immunity seems to be activated in both human and experimental CKD, even when the initial renal injury is not caused by infection or by any autoimmune condition. Moreover, the recruitment of lymphocytes to the renal parenchyma

often correlates positively with worsening of renal function loss. T-lymphocytes are commonly seen in the kidneys of rats submitted to NX, streptozotocin-induced (ST) DN, chronic nitric oxide inhibition, among others. Accordingly, the treatment of these animals with mycophenolate mofetil (MMF), a lymphocytic inhibitor, was shown to reduce albuminuria, hypertension, glomerular, and interstitial damage. Although the exact mechanisms by which adaptive response is triggered in such "sterile" conditions are presently unclear, some hypotheses have gained strength with the development of experimental studies over the last decades [28, 29, 35, 52].

One of these hypotheses points to Ang II as a pivotal element to stimulate the activation of specific cellular immunity in nonimmune-mediated nephropathies. The role of Ang II in the activation of adaptive immunocompetent cells *in vivo* is increasingly recognized by the beneficial effects of ARBs and ACE is in several models of immune-mediated diseases and even as an adjuvant in avoiding allograft rejection after kidney transplantation. It was widely demonstrated that experimental venal infusion of Ang II in rodents induces T lymphocyte migration to specific target organs, such as the kidneys and the spleen. Moreover, these infiltrating lymphocytes assume mainly Th1 and Th17 pro-inflammatory phenotypes, increasing the release of IFN-γ and decreasing IL4 concentration in these organs, thus participating in the mechanism that drives to inflammation and hypertension. Accordingly, *in vitro* studies showed Ang II to act as an "antigen" upon cultured mouse spleen lymphocytes, promoting their activation and further clonal proliferation. T-cells have been shown to be also activated in the murine model of DOCA-salt hypertension, supposedly a nonimmune-mediated condition, in which Ang II plays an important role. In this model, pharmacological inhibition of the T-lymphocyte CD28 receptor and of its co-stimulatory protein CD80 prevented the development of hypertension and consequent renal injury. Corroborating these findings, further studies showed that *Cd80* KO mice are renoprotected when submitted to the Ang II-induced hypertension model [35, 52].

Curiously, Ang II was shown to be released by activated T cells during the blood-stage of plasmodium infection in an experimental model of malaria. Once T-cells are described to have the complete intracellular machinery to synthesize all RAAS components, including transmembrane AT1 receptors, Ang II produced by the infected cells may promote the recruitment and activation of further naive lymphocytes. According to this study, Ang II binding to the AT1 receptors of cultured T-cells leads to: upregulation of CD69 and CD25, increased cellular adhesion, and migration due to overexpression of CCR2 and CCR5 chemokine receptors and LFA-1 adhesion molecule, as well as T-cell differentiation, observed by the increased production of IL17 and IFN-γ and by the presence of cell perforins. However, the reasons why intracellular RAAS seems to be overactivated in T-cells exposed to inflammation, remains unknown.

Besides Ang II, advanced glycation end products (AGEs), represent another possible sterile "antigen" which may activate adaptive immunity in nonimmune-mediated CKD. AGEs are proteins or lipids that become glycated as a result of exposure to high glucose levels. Under some pathologic conditions, such as DM, sustained hyperglycemia and ROS production lead to increased AGE formation. Excessive AGE production is involved with the development and worsening of many degenerative diseases; including DN. Human AGE receptor (RAGE) is a multiligand cell surface MPRR that also binds Hmgb1, S100, and other DAMPs. Highly expressed in macrophages, T-, and B lymphocytes, RAGE contributes to inflammatory mechanisms, including the differentiation of Th0 in Th1 cells. RAGE-mediated leukocyte

recruitment is particularly important in conditions associated with higher RAGE expression, such as DM. In these cases, when overexpressed in the surface of endothelial cells, RAGE directly mediate leukocyte recruitment, acting as a cell adhesive receptor. Moreover, AGE binding to RAGE result in overexpression of cytokines and pro-inflammatory molecules.

As illustrated in **Figure 7**, it is finally possible that the sterile DAMPs, which were, recognized by the innate MPRR of APCs, processed as antigens and presented to naive t-cells

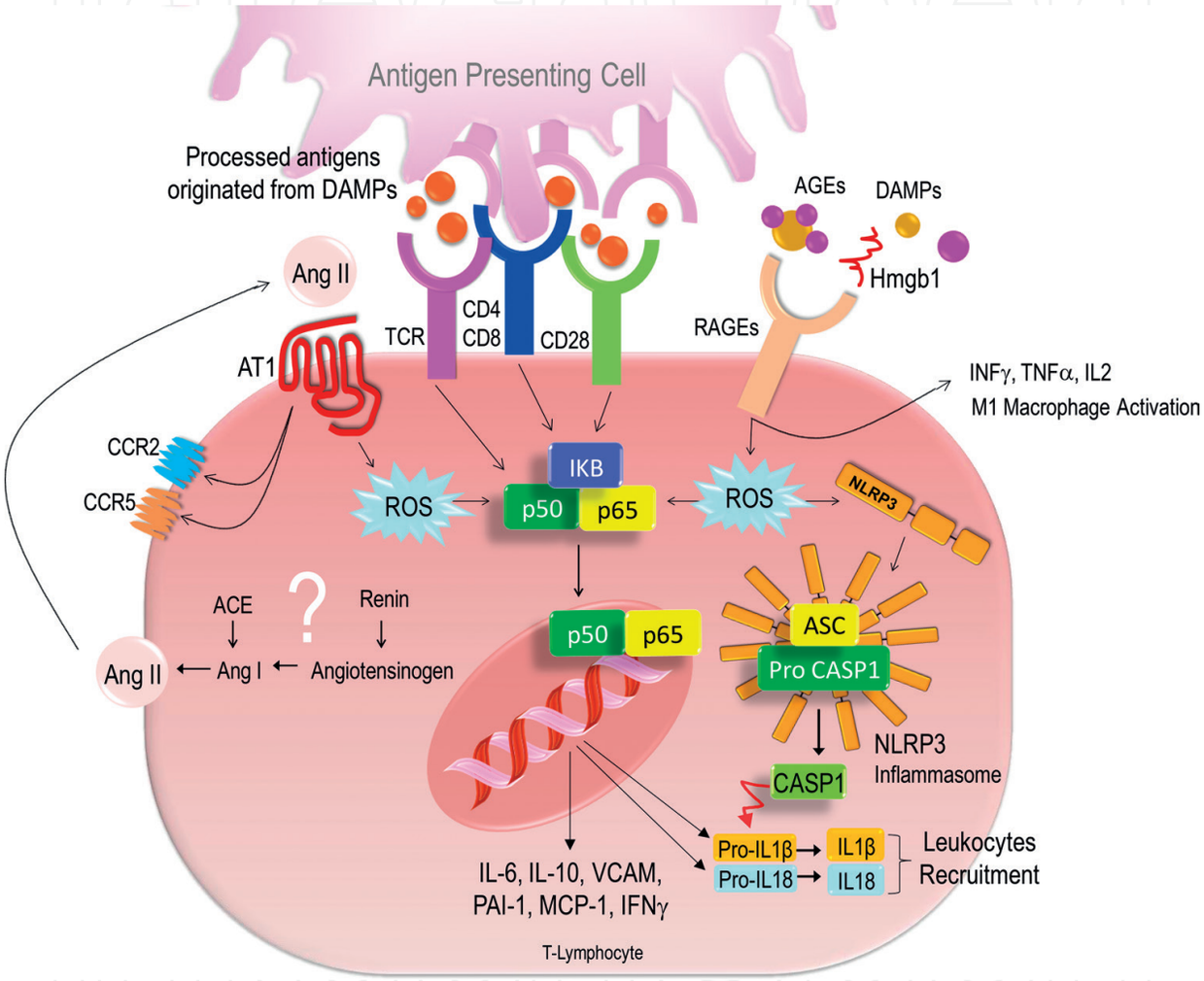

Figure 7. Some mechanisms of adaptive T-cell sterile activation. Through the binding of processed antigens to the T-lymphocyte receptors TCR, CD4, CD8 and CD28, an intracellular mechanism is set in motion, leading to the activation of NFKB system, with further production of immature interleukins pro-IL1β and pro-IL18 among other mediators. Such sterile antigens particles are believed to be originated from phagocyted DAMPs, recognized by the innate immune APCs, as previously described. Ang II also exerts a pivotal role in the activation of T cells. Although the mechanism that leads activated T cells to overproduce intracellular RAAS components remains unclear, it is well known that, in addition to enhance Ang II production, when subjected to inflammatory stimuli, T cells also expose more AT1 receptors, making themselves more responsive to Ang II produced by other leukocytes or by the cells of injured tissue. Through the binding of Ang II to its AT1 receptor, T-cells become more active, thus expressing a greater number of CCR2 and CCR5 chemokine receptors. Finally, T-lymphocytes have constitutively high expression of the advanced glycation end products receptor (RAGE). Once it binds to its specific ligand (AGE), or to other DAMPs, such as Hmgb1 or S100 proteins, it starts the conversion of Th0 lymphocyte toward the pro-inflammatory Th1 phenotype, which in turn, produces some of the most potent pro-inflammatory mediators that will further increase M1 macrophage population.

are able to trigger adaptive immune response in the same way PAMPs would be. However, further studies are required for the complete elucidation of the mechanisms involved in this process.

9. Conclusion

Sterile inflammation exerts a key pathogenic role to the development and evolution of CKD. Although all the mechanisms involved in the activation of immune response in nonimmune-mediated kidney conditions are not yet fully elucidated, some of the main assumptions for this phenomenon were discussed here. Based on our review of the literature and on the proposed integrative schemes, we can conclude that both innate and adaptive arms of immunity can be activated in CKD, with no pathological stimulus needed. Moreover, chronic inflammation contributes to CKD worsening and progression, leading to GS and renal fibrosis. The use of anti-inflammatory drugs, chemical blockers of innate immunity and anti-lymphocyte drugs have been shown to be partially effective to decelerate the chronic inflammatory process that accompanies nephropathy in experimental models of CKD (**Table 2**). However, to date, blockade of systemic and intrarenal RAAS by ACEis and/or ARBs remains the most effective treatment for delaying renal function loss.

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