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CHARACTERISTICS AND CAUSES OF IMMUNE DYSFUNCTION RELATED TO UREMIA AND DIALYSIS

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From the immunologic viewpoint, chronic kidney disease (CKD) is characterized by disorders of both the innate and adaptive systems, generating a complex and still not fully understood immune dysfunction. Markers of a chronically activated immune system are closely linked to several complications of CKD and represent powerful predictors for mortality in the CKD population. On the other hand, CKD patients respond poorly to vaccination and to challenges such as bacterial infection. Interestingly, the main causes of death in patients with CKD are cardiovascular and infectious diseases, both being pathologic processes closely linked to immune function. Therefore, accelerated tissue degeneration (as a consequence of chronic inflammation) and increased rate of sepsis (because of a poorly orchestrated immune response) represent the most important targets for interventions aiming to reduce mortality in CKD patients. Understanding the mechanisms behind the immune dysfunction that is peculiar to CKD generates a perspective to improve outcomes in this group of patients.

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KEY WORDS: Immune dysfunction; uremic toxicity; chronic kidney disease; inflammation.

Chronic kidney disease (CKD) patients present a chronically activated immune system, which is associated with vascular calcification, accelerated atherosclerosis, loss of appetite, insulin resistance, increased muscle catabolism, bone remodeling, and increased peritoneal membrane permeability. On the other hand, CKD patients respond poorly to vaccination and to challenges such as bacterial infection. Interestingly, the main causes of death in patients with CKD are related to cardiovascular and infectious diseases, both being pathologic processes closely linked to immune function. Therefore, accelerated tissue degeneration (as a consequence of chronic inflammation) and increased rate of sepsis (because of a poorly orchestrated immune response) represent the most important targets for interventions aiming to reduce mortality in CKD patients. Understanding the mechanisms behind the immune dysfunction that is peculiar to CKD generates a perspective for improving outcome in this group of patients. The aim of the present article is to review the characteristics and causes of the immune dysfunction related to uremia and dialysis.

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CHARACTERISTICS OF IMMUNE DYSFUNCTION IN CKD

Uremia-related immune dysfunction is a complex interaction between the innate and adaptive systems, in which immune activation (hypercytokinemia and acute-phase response) and immune suppression (impairment of response to infections and poor development of adaptive immunity) coexist. On the one hand, as a consequence of tissue damage, the innate immune system is triggered, and although inflammation in principle is an essential response to eliminate aggressors, it can be considered a double-edged sword when the initial reaction is not limited. During inflammation, vasodilatation, vascular permeability, movement of inflammatory cells, and activation of cells of the immune system are increased. In addition, acute-phase reactants can be produced, as can complement components, fever, and activation of systemic immunity. Therefore, to avoid tissue damage, inflammatory responses must be well organized and controlled by inflammatory mediators as cytokines, proteases, prostaglandins, leukotrienes, and vasoactive molecules.

Cytokines act by binding to specific membrane receptors, which signalize secondary messengers to

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alter their behavior. Cytokine responses include increasing or decreasing expression of membrane proteins (cytokine receptors), proliferation, and secretion of effector molecules, leading to a chronic inflammatory state, as consequence of an immune response to chronic stimulus. Since the end of the 1990s, it has been repeatedly demonstrated that various inflammation biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), fibrinogen, and leukocyte count are linked to complications of CKD and, most importantly, are strong and independent predictors of mortality in this group of patients (1–5).

In the process of the chronic response to stimuli in CKD, generating chronic inflammation, toll-like receptors (TLRs) appear to be of critical importance (Figure 1), TLR4 being one of the key receptors involved in innate immunity and the recognition of lipopolysaccharides [LPSs (a component of endotoxin-originated gram-negative bacteria)]. Tumor necrosis factor α (TNFα) and IL-1 are the major cytokines produced by the activation of the TLR signaling pathway. Moreover, TLR4 has been reported to recognize dietary saturated fatty acids (6) and endogenous ligands of ischemic origin (7). Potentially, several uremic toxins could also serve as ligands in the activation of TLRs. It has been confirmed that TLR4 has been widely expressed not only in macrophages, but in many other organs, including kidney, heart, vessels, and adipose tissues. It is considered to be involved in chemokine production and apoptosis, sensing stimulation with endogenous and food-derived ligands, uremic toxins, and infections.

Concerning the molecular mechanisms of TLR4 in cytokine production, TLR4 is known to be expressed

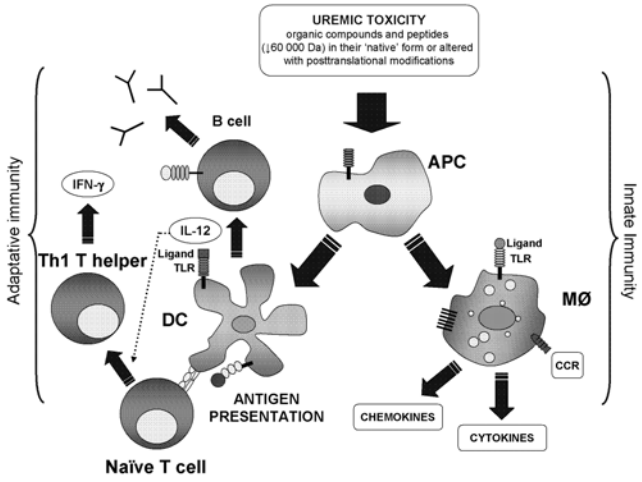

Figure 1 — Effect of uremic toxicity in adaptive and innate immune response.

by many cell lines in different organs. In the kidney, monocyte chemoattractant protein 1 (MCP-1) and RANTES are produced after LPS stimulation in a TLR4-dependent manner (8). Production of these chemokines passes peculiar signaling pathways, because both JNK and p38 contribute to RANTES expression, MAPK is not involved in MCP-1 expression, and nuclear factor κB (NF-κB) activation is essential to both (8).

Recently, it was shown that ischemic injuries directly activate TLR4 and MyD88, and participate in renal injury through apoptosis and the production of several cytokines in a model of ischemic renal reperfusion injury (9). In the clinical setting, genetic background related to TLR pathways appears to be associated with affect on patient outcome. First, inflamed patients with the LPS-hyporesponsive TLR4 allele presented an increased risk of death (10). Moreover, patients with TNFα(a cytokine involved in TLR4 signaling) genetic polymorphism, presented higher mortality from cardiovascular disease than did their counterparts with other genetic backgrounds (11).

On the other hand, regarding poor response to infectious challenges, recent data have proposed that innate immunity, particularly related to neutrophils, plays an important role. Firstly, the main cause of infections in CKD is bacteria (12). Reduced killing capabilities (13), modulated spontaneous apoptosis of neutrophils (14), and inhibited NO synthesis by macrophages (15) have been described in the presence of uremia. In addition, the harmful influence of adaptive immunity dysfunction could lead to a worse response to viral and mycobacterial infections and to vaccinations (16). Vaccines based on polysaccharide antigens generally result in particularly efficient responses, suggesting that the T-helper cells are particularly affected during renal failure (17).

From a cellular viewpoint, monocytes and monocyte-derived dendritic cells of CKD patients impaired endocytosis and maturation *in vitro,* but the impairment of IL-12 production and allogeneic T cell proliferation was reversed when cells were cultured in sera from healthy donors (18). This alteration of the immune system may be the missing link between innate and adaptive immune dysfunction in uremia, justifying both the activation of cellular reaction and immune incompetence.

CAUSES OF IMMUNE DYSFUNCTION IN CKD

The causes for the immune reaction that characterizes immune dysfunction related to uremia and dialysis are multiple. Accumulation of uremic toxins, strongly present in CKD and only partially corrected by

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dialysis, plus dialysis-related factors such as interactions between blood and dialyzer, endotoxin presence in water, access-related infections, and peritoneal dialysis solutions with high glucose concentration, low pH, and the presence of glucose degradation products represent an interesting model of chronic stimuli to the inflammatory response.

The proinflammatory and pro-oxidant effects of dialysis therapies have been widely discussed, and it is now well-established that those effects are particularly pronounced in extracorporeal treatments, with the main underlying events being material bioincompatibility and contamination of the dialysis fluid by bacterial wall components (19). Also, in peritoneal dialysis, high glucose concentration, bioincompatible profile of the dialysis solution, fluid overload, and access-related infections are potential triggers of a chronic immune response.

An issue that has emerged in recent years is related to uremic toxicity (independent of dialysis) as a trigger of immune response in CKD. Reduction of renal function *per se,* and consequently uremic toxicity, can be responsible for increased plasma concentrations of systemic and vascular inflammatory biomarkers, derivate from increased proinflammatory cytokines (20–22), and despite the progression of new technologies of renal replacement therapy, it is almost impossible to completely remove the uremic toxins retained by impaired renal function (23). The uremic toxins consist of heterogeneous substances, including organic compounds and peptides, with proinflammatory effects (22). Urea is quantitatively the most important solute excreted by the kidney and was the first organic solute detected in the blood of patients with kidney failure. Hemodialysis and peritoneal dialysis are both currently prescribed so as to achieve target values for urea clearance, although urea itself causes only a minor part of uremic illness (23).

Another important group of compounds is the advanced glycation end products (AGEs). When aldehyde or ketone groups of carbohydrates react with amino acids, various AGEs are formed. In CKD patients, it is possible that an accumulation of AGEs caused by decreased renal clearance might also promote inflammation (24). More efficient removal of uremic toxins by dialysis therapy could improve immune function in CKD patients.

Other causes of elevated systemic inflammation in CKD patients might include fluid overload related to chronic heart failure (25). Fluid overload is a common complication in advanced CKD patients (26) and may be associated with immune activation (25). This activation could be explained by bacterial or endotoxin translocation in patients with severe gut edema as a result of extreme volume overload (27), which in turn may lead to increased production of proinflammatory cytokines (28).

IMMUNE DYSFUNCTION IN UREMIA: THE ROLE OF VITAMIN D DEFICIENCY

Vitamin D deficiency is a very common finding in CKD stages 3 – 5 and may be related to reduced survival in the dialysis population, based on information from retrospective and epidemiologic studies (29,30). Recently, because of the extensive list of cells expressing vitamin D receptors, pleiotropic functions have emerged, including the role of this vitamin as a potent immunomodulator. Animal models have suggested that vitamin D could play an important role in controlling immune effector responses subsequent to either infection or vaccination (31). In CKD patients, treatment with calcitriol may increase response to influenza vaccination (32). Monocytes and macrophages exposed to a bacterial LPS upregulate the vitamin D receptor gene, resulting in the synthesis of cathelicidin, a peptide capable of destroying bacterial agents (33).

From the atherosclerotic point of view, vitamin deficiency may also play an important role through its involvement in the immune response. Current models of atherosclerosis include an intriguing interrelated function of T lymphocytes and macrophages as initial stimulators of intimal thickening and plaque formation. Interestingly, all of these processes can be inhibited by vitamin D and stimulated by high parathyroid hormone and phosphate (34). Other potential ameliorative effects of vitamin D on the pathogenesis of atherosclerosis may occur by enriching the Th-2 cell population of lymphocytes, which are responsible for production of IL-10, exhibiting a marked anti-atherogenic function.

CONCLUSIONS

In summary, CKD is characterized by disorders in both the innate and the adaptive systems, generating a complex and still not fully understood immune dysfunction. The immune dysfunction observed in dialysis and uremia is a combination of chronic inflammation and poor response to vaccination and to challenges such as bacterial infection. Interestingly, the main causes of death in patients with chronic kidney disease (CKD) are cardiovascular and infectious diseases, both being pathologic processes closely linked to immune function. Therefore, accelerated tissue degeneration (as a

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consequence of chronic inflammation) and increased rate of sepsis (because of a poorly orchestrated immune response) represent the most important targets for future interventions aiming to reduce mortality in CKD patients.

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