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Mini-Review

Changes in innate immunity in patients with chronic kidney disease

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ABSTRACT

Chronic kidney disease (CKD) is a common disease in the 21st century. Infections and their complications are the second cause for morbidity and mortality in patients with CKD, undergoing hemodialysis. Recent data show that immune dysfunction is probably responsible for the high frequency of infections in those patients. The aim of this review is to present current concepts for the abnormalities in the innate immunity in patients with CKD, which are clinically relevant in nephrologists' practice and can be basis for further research.

KEYWORDS: Chronic kidney disease, innate immunity, dialysis treatment.

1. Introduction

Chronic kidney disease (CKD) is becoming more common globally. Most published work is based on one timepoint to define elevated albumin: creatinine ratio (ACR) or decreased estimated glomerular filtration rate (eGFR), which includes persistence for at least 3 months. The CKD prevalence has been evaluated to about at 9.1% (8.5% to 9.8%) of the world's population and the absolute number of patients with this condition was around seven hundred million in 2017 [1]. According to data from European Renal Association–European Dialysis and Transplant Association (ERA-EDTA). Registry form 2016, the relative number of new patients, starting dialysis treatment in Europe, ranges between 29 per million (of population) in Ukraine to 251 per million in Greece [2]. Despite significant technical improvements in dialysis treatment, mortality in those patients remains high, and the main reasons are cardiovascular diseases and infections [3-5]. The immune system is a complex system, which protects the body and is subdivided into two main categories: Innate (non-specific) immunity – activation of innate mechanisms such as natural barriers (skin and mucous membranes) and secretions; Acquired (adaptive) or specific immunity, which is aimed directed against a specific microorganism or an antigen, already recognized.

Innate immunity is the first line of defense that responds almost instantly - in minutes or hours, while the specific response takes longer (days to weeks) [6].

2. Innate immunity – general information

Innate immunity developed earlier in human evolution than the adaptive one. It evolved in order to protect the organism from the surrounding environment, filled with various toxins and infectious agents, including bacteria, fungi, viruses and parasites [7].

It includes physical and anatomical barriers, effector cells, antimicrobial peptides, soluble mediators and cell receptors (Table 1).

The response of the innate immune system to pathogens is rapid and is characterized by specific pathogen-related molecular patterns (PAMPs) that do not require the genetic readjustments characteristic of adaptive immunity. Innate immune system

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Table 1. Components of the innate immune system and mechanisms of action [8] (Anaya, J. M., Shoenfeld, Y., Rojas-Villarraga, A., Levy, R. A. and Cervera, R. 2013, Autoimmunity From Bench to Bedside. Bogota (Colombia). El Rosario University Press. ISBN: 978-958-738-376-8, Table 1, p. 32).

Component	**Function**
Barriers	
Skin	Prevents microorganism entry
Mucosa	Prevents the entry of microbes, secretes proteins and enzymes, absorbs metabolic substrates
Effector cells	
Granulocytes	Phagocytosis, cytokine production, secretion of proteins and enzymes, destruction of pathogens
Monocytes/macrophages	Phagocytosis, cytokine production, secretion of proteins and enzymes, destruction of pathogens
Dendritic cells	Phagocytosis, cytokine production, secretion of proteins and enzymes, destruction of pathogens
Natural killer cells (NK)	Lysis of infected and tumor cells, activation of macrophages by cytokine production
Congenital lymphoid cells	Mediate the immune response and regulate tissue homeostasis and inflammation
Endothelial/epithelial cells	Microbial recognition, cytokine production
Antimicrobial peptides	
	Destruction of invading pathogens
Soluble mediators	
Cytokines	
TNF-α, IL-1, chemokines	Mediate the immune response and inflammation
IFN-α	Participates in resistance to viral infections
IFN-γ	Participates in resistance to intracellular pathogenic infection and activation of macrophages
IL-12	Stimulates the production of IFN-γ by NK cells and T-lymphocytes
IL-15	Stimulates NK cell proliferation
IL-10	Regulates and controls the inflammatory process
TGF-β	Regulates and controls the inflammatory process
Serine proteases	
Complement system	Opsonization, destruction of pathogens and activation of T-lymphocytes
Collectins	Opsonization of pathogens and complement activation
C-reactive protein	Opsonization of pathogens and complement activation
coagulation system	Localization of damaged or infected tissue
Cellular receptors	
TLRs	Recognizes various microbial components
NLRs	Sensitive to bacterial components, present in the cytoplasm
CLRs	Recognize carbohydrate sites from bacteria and fungi
RLRs	Sensitive to viral RNA

(TNF: tumor necrosis factor; IFN: interferon; IL: interleukin; TGF: transforming growth factor; TLR: Toll-like receptor; NLR: nod-like receptor; CLR: C-type lectin receptor; RLR: RIG-I-like receptor.)

receptors are encoded in the germ line and are expressed in many effector cells, including macrophages and dendritic, antigen-presenting cells (APCs). Once pattern recognition receptors identify PAMPs, effector cells are activated to perform their functions [9].

3. Elements of innate immunity and their changes in patients with CKD

3.1. Effector cells

3.1.1. Polymorphonuclear leukocytes (PMNs)

Polymorphonuclear leukocytes (PMNs) have a short life (up to 5 days); they are occupational (and present) phagocytes that absorb antibody- and/or complement-coated microbes, damaged cells, and cell debris. They have many intracellular granules containing bactericidal proteins, such as cationic proteins and defensins, proteolytic enzymes, cathepsin G (for the breakdown of bacterial proteins), lysozyme (for lysis of bacterial cell walls), nicotinamide-dinucleotide NAD(P)H-oxidase-II (for the production of reactive oxygen species - ROS), myeloperoxidase (for the production of HOCl) and lactoferrin (for the inhibition of bacterial replication by iron deprivation). PMNs are the first line of defense against invading microbes. They are an important player in inflammation. Patients with CKD are characterized by basic regulation of toll-like receptors (TLR-4, TLR-2) and expression of integrins, increased production of oxygen radicals and pronounced degranulation of PMNs, which reflect their spontaneous activation [10]. These abnormalities contribute to the maintenance of inflammation, oxidative stress and the tissue damage in these patients. This is often combined by increased apoptosis and reduced phagocytic activity of PMN [11]. These processes are intensified especially during the hemodialysis sessions, which is presumedly related to the contact of the blood with dialysis membrane, the influx of impurities from the dialysis stream and the trauma of the cells from the roller pump of dialysis machine [10].

3.1.2. Monocytes/macrophages

Monocytes are produced in the bone marrow, then stored in the spleen and distributed to body tissues as macrophages. They absorb microbes, damaged cells and tissue debris - directly or with the help of proteins such as antibodies or complement ingredients. This process is essential for the Body's defense against microbial infections and for the healing of damaged tissues. Monocytes are classified based on the expression of CD14 (pattern recognition receptor) and CD16 (Fc gamma III receptor) into 4 main subgroups: CD14++ / CD16−; CD14++ / CD16+; CD14+ / CD16− and CD14+ / CD16+. CD14+ / CD16+ monocytes have a large capacity to produce inflammatory cytokines (TNF-alpha, IL-6 and IFN-α) and to stimulate inflammation [12]. Patients with CKD show a general expansion of circulating monocytes - especially those of the subgroup CD14+ / CD16+. This is associated with increased basal expression of Toll-like receptors - TLR-2 and TLR-4, increased regulation of cellular surface expression of integrins and increased basal production of cytokines and ROS [10]. These changes indicate that spontaneous activation of monocytes is observed and reflect their influence on the predominant oxidative stress and systemic inflammation in the end-stage renal disease (ESRD). Furthermore, uremic plasma increases the production of osteoactivin by monocytes and macrophages, which additionally affects vascular calcification in these patients [13], pointing to the proatherogenic properties of the uremic environment. The unprovoked activation of monocytes is accompanied by decrease in their phagocytic capacity [11], which contributes to immune deficiency and increased frequency and severity of infections in patients with CKD [12].

3.1.3. Dendritic cells (DC)

Dendritic cells are admitted for professional APCs. They reside and protect the surfaces of the body, playing an important role in the innate immunity with subsequent activation of T-cell responses to provide cell-mediated immunity against microbial pathogens [14]. DCs act as sentinels for innate immunity system by regulating immune responses in T-, B-, and NK cells. So far, two types of dendritic cells have been identified: 1. Plasmocytoid (pDC) dendritic cells contain intracellular TLRs (TLR7 and TLR9) for the detection of viral and/or nucleic acids only; they produce large amounts of type I interferons, such as IFNα in response to viral infections. 2. Myeloid dendritic cells (mDC) have cellular surface TLRs, including TLR3 and TLR4, and produce IL-12 and type I interferons in response to agonists of those receptors [12]. In patients with CKD the number of DCs is known

to be significantly reduced. The decrease in pDC is more pronounced than that of mDC, but both types decrease additionally after hemodialysis sessions [15-18]. Despite the fact that most results from experimental studies and clinical data suggest that changes in DC associated with CKD are related to their number and function, the exact causes are not clear [10, 17, 19, 20]. Secondary hyperparathyroidism in these patients can also lead to DC dysfunction through the presence of parathyroid hormone receptors in most immune cells, including neutrophils, B- and T-lymphocytes, and chronically elevated levels of this hormone affect the function of these blood cells through lasting increase in their intracellular calcium levels [21].

3.2. Soluble mediators

3.2.1. Cytokines

The concentration of cytokines gradually increases in CKD, which is due to both their increased production in response to uremic toxins and their decreased renal clearance [22]. *In vitro* IL-6, tumor necrosis factor alpha (TNFα) and IL-18 induce leukocyte oxidative stress at concentrations in the range of or above those observed in extreme clinical conditions, such as sepsis [23, 24, 25].

Interleukin-10 (IL-10)

IL-10 (18 kD) is mainly produced by monocytes and lymphocytes. Its secretion always follows that of pro-inflammatory factors with a latency of several hours. In patients with renal insufficiency, the major production of IL-10 is by monocytes and macrophages. Typical stimuli leading to its production are endotoxins and activated complement fragments, agents that are known to mediate biocompatibility reactions during hemodialysis sessions. Thus, dialysis treatment may contribute to an increase in total IL-10 levels. Its production can also be induced by catecholamines or TNF-α [26], linking its production to a stress response and/or inflammation. Because IL-10 is cleared primarily by the kidneys, possibly by glomerular filtration and tubular metabolism, its plasma half-life is significantly increased by ESRD. In addition, uremic monocytes produce larger amounts of this cytokine than those of healthy individuals [27].

Interleukin-6 (IL-6)

Although a number of cytokines mediate the inflammatory response, IL-6 is particularly interesting because it has pro- and anti-inflammatory effects. The IL-6 system supports inflammatory processes through the activation and proliferation of lymphocytes, the differentiation of B cells, the accumulation of leukocytes and the production of acute phase proteins in the liver. IL-6 (22 to 27 kD) is produced by many immune cells, including monocytes, mesothelial cells, fibroblasts, adipocytes, and lymphocytes, usually in response to physiological stimuli such as TNF-α, IL-1β, bacterial endotoxins, and the like; exercise and oxidative stress. The reasons for the increased plasma levels of IL-6 and TNF-α in patients with CKD are: genetic factors, older age, various comorbidities, impaired renal function; hyperhydration or heart failure, persistent infections (catheter infections, peritonitis, Chlamydia pneumoniae), oxidative stress, obesity and dialysis-dependent factors (membrane biocompatibility, non-sterile dialysis solution) [27, 28]. K. Caglar (2002) showed that circulating levels of IL-6 increase after hemodialysis sessions, which causes a delayed inflammatory response [29]. K. Kalantar-Zadeh found (2004) that anorexia in hemodialysis patients was associated with higher levels of IL-6 [30].

Tumor-necrotizing factor-α (TNF-α)

The reasons for the increased plasma levels of IL-6 and TNF-α in patients with CKD are: genetic factors, old age, various comorbidities, impaired renal function; hyperhydration or heart failure, persistent infections (catheter infections, peritonitis, Chlamydia pneumoniae), oxidative stress, visceral obesity and dialysis-dependent factors (membrane biocompatibility, non-sterile dialysis solution) [27, 28]. Tumor necrotizing factor α (also known as cachexin) is a proinflammatory cytokine (17 kD) initially associated with tumor cell death. It is considered the "main regulator" of the cytokine cascade, providing rapid protection of the host against infection, but is "fatal" when in excess. Its main cellular origin is activated macrophages. Deterioration of renal function is perhaps the most important factor associated with a significant increase in the activity of this cytokine in patients with CKD [27].

3.2.2. C-reactive protein (CRP)

C-reactive protein was discovered in 1930 during a study of patients with streptococcal pneumonia. It is a plasma protein that reflects the acute phase

of inflammation and is one of its markers. It is a pattern recognition molecule that binds to specific molecules that are produced during cell death or are found on the surfaces of various bacterial pathogens. Serum CRP concentration does not change in CKD, but is a predictor of mortality in hemodialysis patients [31].

3.2.3. Complement system

Complement proteins provide an important protection against bacteria, fungi and viruses. This system facilitates the effective removal of damaged cells and immune complexes. Inactive complement proteins (cymogens) circulate in the plasma and are activated in 3 different ways: classical, alternative and lectin pathways. The biocompatibility of materials used for dialysis is an important clinical challenge. In hemodialysis (HD), the membrane provokes an inflammatory reaction, as it is where the blood has direct contact with a foreign surface. In peritoneal dialysis (PD), fluids characterized by high glucose levels, hyperosmolarity, and acid pH are considered biologically "unpleasant" and this causes damage to the peritoneal membrane. Improving biocompatibility in HD and PD is a critical factor in ensuring dialysis adequacy and long-term treatment. The consequences of complement activation in these patients are induction of inflammation, promotion of coagulation, and impaired host protection due to accelerated consumption of complement proteins [32].

4. Cellular receptors

Pattern recognition receptors (PRRs) are an essential part of the innate immune system. They can be derived from exogenous, pathogen-associated molecular model (PAMP) or endogenous, damage-associated molecular model (DAMP) ligands. Four separate PRR classes are currently identified:

- Toll-like receptors (TLRs);
- C-type lectin receptors (CLRs);
- Retinoic acid inducing gene (RIG) -I-like receptors (RLRs);
- Nucleotide binding oligomerization domains (NOD) - similar receptors (NLRs) [33].

These receptors are widely expressed, although expression levels vary between tissues. They are found not only in the classic cells of the innate immune system (i.e. monocytes, macrophages, dendritic cells), but also in endothelial cells, epithelial cells and fibroblasts. While CLRs and RLRs are mainly involved in the recognition of viruses and fungi, TLRs and NLRs play a crucial role in the recognition of endogenous ligands associated with various disease states such as atherosclerosis, hypertension and CKD [5].

TLRs belong to the family of receptors that recognize patterns of the innate immune system. They recognize various common pathogenic components, such as lipopolysaccharides (LPSs), peptidoglycans, RNA from viruses and bacterial oligodedoxynucleotides, and other stimuli [34-37]. Their tasks include activation of phagocytosis through complement activation and cytokines' production, such as IL-1β, IL-6 and TNF-α. TLRs are also involved in the maturation of dendritic cells, which are APCs.

It is now recognized that uremia results in impaired TLR expression and/or activity, which causes impaired APC function. In fact, TLR4 expression has been shown to be constitutively reduced in patients with predialysis ESRD, especially in those prone to infections. Decreased TLR4 expression is associated with decreased synthesis of TNF-α, IL-1β, IL-6 and IL-8 in response to LPS challenge. Similar results have been obtained in patients with HD, and it has been suggested that in addition to uremia, endotoxins contained in dialysis, through continuous stimulation, may ultimately lead to decreased TLR4 expression [5].

5. Conclusion

CKD should be considered as a condition of immune dysfunction, characterized by immunosuppression, contributing to the high prevalence of infections in these patients, as well as immune activation, also leading to inflammation, which may contribute to the progression of cardiovascular disease. Knowledge of the mechanisms of innate immune disorders should be the basis for the development of therapeutic strategies to improve the proinflammatory status in these patients.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest is declared by the authors.

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