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(REVIEW ARTICLE)

The interactive association between Immune system and Kidney function

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Abstract

The Immune System (IS) and Kidney function are closely and interactively connected. IS dysfunction happening in autoimmune diseases, infections, malignancies, etc. is implicated in the pathogenesis of kidney involvement, leading to a great spectrum of glomerular and interstitial injury through several immunological pathways, such as immune complex deposition, activation of complement and signaling pathways.

Complications of chronic kidney disease (CKD), including accumulation of uremic toxins, O2 free radicals, advanced glycation end products, increased expression of Toll Like Receptors on monocytes, cytokine overproduction, result in a situation characterized by chronic inflammation combined with premature ageing, and usually designated as "inflamm-aging", followed by detrimental clinical consequences in CKD patients, such as increased cardiovascular risk, susceptibility to infections and malignancies.

Kidney transplant can potentially restore the immune profile of patients, albeit immunosuppression treatment may be followed by further complications. The presence of certain T cell subsets at time of renal transplantation may affect response to immunosuppression and acute or chronic rejection, suggesting that patients' immune profile at time of transplantation may have substantial impact in short and long term graft function.

Keywords: Kidney function; Immune system; Clinical complications; Lymphocytes

1. Introduction

The Immune System (IS) and Kidney function are closely and interactively connected [1]. Deregulation of the IS, as it occurs in chronic infections, chronic inflammation, systemic autoimmune diseases or malignancies, may affect kidneys through several pathways, including immune complex deposition, signaling transduction pathways or complement activation, leading to stimulation of native kidney cells and infiltration of renal tissue by circulating inflammatory cells, a process which results to an excessive variety of glomerular and interstitial disorders [2-5]. Systemic Lupus Erythematosus, Vasculitis, hepatitis B and C, solid organ malignancies, hematological diseases, are only a small example of primary causes affecting kidneys through several immunological pathways, such as immune complex deposition, activation of complement and signaling pathways etc. Clinical complications of chronic activation include a great spectrum of glomerular and interstitial injuries.

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2. Chronic Kidney Disease

When renal function declines and chronic kidney disease (CKD) is established, consequences lead to a chronic inflammatory condition, yet seems to affect immune integrity in a way similar to ageing process; leading to a shift of lymphocytes towards senescent and exhausted phenotypes. For these reasons CKD has been characterised as an "inflamm-aging" condition, [6, 7]. Clinical consequences, including increased cardiovascular risk, susceptibility to infections and reduced response to immunization, are critical and described on table 1[8, 9].

CKD affects both innate and adaptive immunity, although the main detrimental consequences include function of the adaptive immune system cells. Innate immunity is based on cells such as neutrophils, macrophages, eosinophils, mast cells, dendritic cells, Natural Killer (NK) cells, B1 cells and soluble factors, such as complement proteins. Its function is stable and determined by specific surface receptors, such as toll like receptors (TLRs), nucleotide-binding oligomerization domain (NOD) like receptors, retinoic acid-inducible gene-I (RIG-I) -like receptors, C-type lectin and scavenger receptors, which recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs)[1].

Adaptive immunity is antigen specific, develops slowly, and mainly governed by lymphocytes, T and B lymphocytes. Precise receptors on the surface of these cells determine lymphocyte subpopulations, with different phenotype and divergent activities, including antigen recognition and proliferation. Effects of CKD are mainly directed to adaptive immunity, and the main characteristic is that they result to a reduction of naïve populations [1,6,7,10]. Moreover, complications of chronic kidney disease (CKD), including accumulation of uremic toxins, O2 free radicals, advanced glycation end products, increased expression of Toll Like Receptors on monocytes, cytokine overproduction are evident even at CKD pre-dialysis stages, accompanied by the biocompatibility reactions post-dialysis, and result in a situation characterized by chronic inflammation combined with premature ageing, and usually designated as "inflamm-aging", followed by detrimental clinical consequences in CKD patients, such as increased cardiovascular risk, susceptibility to infections and malignancies. Clinical consequences, including increased cardiovascular risk, susceptibility to infections and reduced response to immunization, are critical [6,7,9].

As the adaptive immunity is predominantly affected in CKD, resulting in lymphocyte phenotypic changes. B lymphocytes are reduced in peritoneal dialysis patients, while CD14++CD16+ monocytes and Natural Killer cells (NKs) are increased and closely associated with the presence of CVD. Even more importantly these type cells are associated by the adequacy of dialysis and fluid balance [11].

Three types of T cells are known to have central roles in the immune disturbances in CKD patients, CD4CD28null, CD8CD28null and Treg cells (Table 2).

The first two subtypes are CD4 and CD8 cells which lack the CD28 receptor. CD28 is a T lymphocyte membrane receptor that binds to B7 family receptors, CD80 (B7.1) and CD86 (B7.2). CD4CD28null and CD8CD28null cells may exacerbate atherosclerosis, as they accumulate in atherosclerotic plaques, and through INF-γ and MMPs production and direct damage to endothelial cells may destabilize them causing rapture of the plaques (Table 3) [1,6,7].

Regulatory T (Treg) cells are characterized as the fire-men of the immune system. They down regulate immune responses, maintain peripheral tolerance, and prevent exacerbation of autoimmune diseases. Regulatory T lymphocyte function are described on Table 4 [1, 10].

Apparently, the interaction between IS and kidneys is multifaceted and extremely important in many aspects [1,12,13].

The gut microbiome seems to play a tremendously important role in the pathogenesis of immune system dysfunction in both ageing and chronic kidney disease [13]. From the first day of life, microbiota evolves normally, through all life years, to elderly, guided by genetic, epigenetic and environmental parameters, but also, by nutrition, personal habits, etc. Some of the most frequent primary glomerular diseases, such as IgA nephropathy, in young adults, and membranous nephropathy, in elderly population, have been associated by changes in microbiota [13].

CKD patients show an increased incidence of frailty, muscle wasting, and osteoporosis. Premature thymic involution is the main reason for reduction of naïve and increase incidence of senescent T cell subtypes, such as highly differentiated memmory Tlymphocytes [14]. Potential therapeutic interventions to prevent or even reverse ESRD-related premature immune-senesence have been proposed and focused on increased physical activity and dietary interventions [14, 15]. Kidney transplantation, although essentially restores renal function, it cannot reverse thymus involution and its effect on recovering adaptive immunity is still under investigation.

Increased risk of infection in ESRD has become more profound the last two years, during the COVID-19 pandemic. Co-morbid conditions, such as CKD and organ transplantation, are associated with the highest mortality risk from COVID-19 infection. The contracted TcR repertoire in naïve T lymphocytes and reduced numbers of plasmocytoid dendritic cells, in CKD patients, may have a profound negative effect on control of viral infections. Moreover, CKD and elderly patients are characterized by increased proportion of CD4+CD28null cells, advanced differentiated cells, highly activated and poorly controlled, responding with a cytokine storm, responsible for lung parenchyma damage [6,7,16].

3. Kidney Transplantation

KT is undoubtably the treatment of choice for CKD, although this usually comes after protracted periods undergoing on dialysis. Following kidney transplantation (KT), renal function is reinstated. Kidney transplant can potentially restore the immune profile of patients, albeit immunosuppression treatment may be followed by further complications. The presence of certain T cell subsets at time of renal transplantation may affect response to immunosuppression and acute or chronic rejection, suggesting that patients' immune profile at time of transplantation may have substantial impact in short and long term graft function [9, 17].

Regulatory T cells may have advantageous effect on kidney transplantation which are described on table 5.

4. Conclusion

The close association between IS and kidney function is important in many aspects, in the pathogenesis of glomerular and interstitial disorders, in the complications following chronic renal failure, leading to increased morbidity and mortality, and finally in the consequences of kidney transplantation.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contribution

MS: conceptualization, writing the original draft. MF: conceptualization, writing—review, and editing. MI: conceptualization, writing—review, and editing. IT: conceptualization, writing—review, and editing. All authors approved the submitted version

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