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KIDNEY DISEASES (G CIANCIO, SECTION EDITOR)

Chronic Kidney Disease and Premature Ageing of the Adaptive Immune Response

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Abstract Los of renal function is associated with uremia-associated immune deficiency, which contributes significantly to the mortality and morbidity of end-stage renal disease (ESRD) patients. In this review, the effect of ESRD on the adaptive cellular immune system is discussed. Progressive loss of renal function causes a preferential loss of number and function of lymphoid cells. More in depth analysis of these changes reveals a loss of thymic function, attrition of telomeres, and expanded memory T cell population, which is compatible with the concept of premature immunological ageing. Latency for cytomegalovirus is associated with more profound changes and the expansion of a unique pro-inflammatory, cytotoxic subset of CD4-positive CD28null T cells. Epigenetically, modifications in hematopoietic stem cells may underlie uremia-associated immunological ageing, which is not reversed by kidney transplantation. Possible therapeutic options to reverse or halt uremia-associated immunological ageing are discussed.

Keywords Uremia · Inflammation · Oxidative stress · End-stage renal disease · Ageing · Immune system

Introduction

Patients with end-stage renal disease (ESRD) have a decreased function of their immune system, which is known as uremia-associated immune deficiency. The consequences of this acquired immune deficiency on morbidity and mortality are substantial as ESRD patients are at increased risk for infection which is the second leading cause of mortality in dialysis patients. In addition, they may respond poorly to vaccinations, for example, against hepatitis B and have an increased risk for virus-associated cancers [1, 2].

The immune system can be divided into an adaptive and innate part. The innate immune system typically uses general mechanisms of cellular and humoral defense mechanisms against invading organisms such as bacteria and viruses. Phagocytes like neutrophils and macrophages are key players of the innate immune system. The adaptive immune system is characterized by its ability to respond specifically to these infectious threats and builds up a memory response thereafter. Lymphocytes like T and B cells belong to this system and antigen-specific memory lymphocytes can be identified. Although both parts of the immune system may operate independently, collaboration between both systems yields maximum effectivity. For instance, naïve T cells (antigen-inexperienced cells) need antigen-presenting cells (macrophages and dendritic cells belonging to the innate immune system) to respond to their cognate antigen. In addition, the tissue cells themselves may interact with the immune system by expression of molecular pattern recognition receptors. This class of receptors responds to damage or invading pathogens and allow for activation of a variety of both immune and non-immune cells. This is relevant to the uremia-associated pro-inflammatory response as the products of increased oxidative stress such as advanced glycation end-products (AGE) or oxidized low-density lipoprotein may activate cells via these families of receptors [3].

The negative effect of ESRD has been shown on all parts of the immune system, and in general, a combination of activation of cells and decreased immune function is observed.

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In particular, the effects on the T cell system have been studied as they are key players in the response to vaccines and virus-infected cells. In addition, after kidney transplantation, the T cell function of the recipient is highly relevant for acute and chronic rejection of the allograft.

Importantly, T cells may also be involved in atherosclerotic vascular events that are highly frequent in ESRD patients [4]. Recently, premature immunological ageing has been identified as a novel explanation for the ESRD-related impaired T cell system [5••]. In addition, cytomegalovirus (CMV) infection is involved in the ageing of the immune system [6, 7]. This review discusses these new findings and the clinical implications.

The Adaptive Immune System

Cells belonging to the adaptive immune system are B lymphocytes (B cells) and T lymphocytes (T cells). Both of these cell types are equipped to deal with an infectious threat in a specific way such that thereafter, a long-lasting memory function persists. T cells carry T cell receptors which are unique for a given T cell clone. The thymus generates a great diversity of T cell receptors by somatic mutation and thereby guaranties a highly diverse repertoire for antigen recognition. The T cells leaving the thymus into the circulation are called naïve T cells or antigen-inexperienced T cells. These cells may carry a circular DNA in their cytosol which is a remnant of the TcR formation and called a T cell receptor excision circle (TREC). The TRECs are not replicated during cell division and therefore rapidly dilute out in daughter cells during cell proliferation. Therefore, assessment of TREC content is a method to estimate the production of naïve T cells by the thymus. After antigen-specific stimulation of via the TcR, the T cell switches to a memory T cell phenotype and there is a gain of specific functions such as rapid cytokine production. The type of stimulation and cytokine environment determines what kind of differentiation pathway is taken and whether a T helper type 1, 2, 17 or regulatory T cells will develop. To obtain an optimal antigenic stimulation of lymphocytes, signaling via the antigen receptor in combination with co-stimulatory molecules and pro-inflammatory "danger" signals is required.

B lymphocytes have the membrane-bound immunoglobuline as their B cell receptor. Similar to the TcR, the diversity of the immunoglobulines is substantial. After antigenic stimulation, the naïve B cell develops to a memory B cell and further differentiates to a plasma cell secreting large amounts of a specific immunoglobuline. These plasma cells migrate to the bone marrow where they constitute a long-lived population of cells providing humoral immunity. Optimal differentiation of B cells to plasma cells is provided by helper T cells (CD4-positive T cells).

Dendritic cells Dendritic cells are so-called professional antigen-presenting cells as they are dedicated to show antigen on their MHC molecules and activate the responding T cells via the MHC-TcR interaction and various co-stimulatory molecules. Dendritic cells (DCs) belong to the innate immune system but are essential for the presentation of antigen to the adaptive immune system. As such, their presence and function are essential for antigen-specific T cell responses and indirect the B cell response. Different sources of dendritic cells exist, skin-derived Langerhans cells, monocyte differentiating to DC and circulating DC within the circulation [8]. The latter population is divided in myeloid DC (mDC) and plasmacytoid DC (pDC).

Effects of Renal Failure Function on the Adaptive Immune Response

T Cells Increasing lymphopenia is observed in relation with loss of renal function. This is caused by a remarkable loss of naïve T cells [5••, 9, 10]. The naïve cells have an increased expression of interleukin-2 receptors (CD25) and express a pro-apoptotic profile which makes them prone for activation-induced cell death. T cell proliferation after polyclonal stimulation is poor if performed in uremic serum [5••]. The increase in virus-associated cancers, tuberculosis, and decreased vaccination response to T cell-dependent antigens in ESRD patients suggest a major clinical role for the impairment of T cells [11]. The function of regulatory T cells also have been shown to be diminished [12•].

B Cells Similar to T cells, a decrease in naïve B cells in the total circulating B cell population is found in ESRD patients. In addition, B cells are also prone for apoptosis [13]. The differentiation from B cells into immunoglobulin-secreting plasma cells has not been studied in ESRD patients.

Dendritic Cells ESRD influences both the total numbers and function of DC although to a different extent [1]. The density of DC in the skin may be decreased, thereby reducing the capacity to present antigen in the skin (e.g., vaccination antigens) to T cells in the draining lymphnode. In predialysis ESRD patients, the pDCs are decreased in relation to the loss of GFR, while the mDCs remain relatively unaffected [1, 14–17].

Given these findings, it is evident that progressive loss of renal function negatively affects all cellular parts of the adaptive immune response and this may well explain the clinical observations on impaired immune responses.

Oxidative Stress, Inflammation, and Premature Immunological Ageing in ESRD Patients

One of the hallmarks of ERSD patients is their pro-inflammatory condition, which is reflected in an increased C-reactive protein and increased levels of pro-inflammatory cytokines and their soluble receptors [18]. Several pathways contribute to the pro-inflammatory state of which increased oxidative stress because of retention of uremic solutes is a widely accepted concept [19]. Markers of oxidative stress are elevated and correspond to increased levels of pro-inflammatory cytokines. A vicious loop is present as for instance advanced glycated proteins may activate the immune system and pro-inflammatory cytokines may generate oxidative stress. Oxidated LDL may also directly activate T cells and induce apoptosis [3].

Another, more recently described pathway is the effect of parodontitis on the pro-inflammatory conditions of ESRD patients. Poor oral hygiene and increased susceptibility for paradontitis as a consequence of the ESRD-related impaired immunity are contributing to an increased frequency of this condition in these patient complications [20]. Recently, it has been shown that a "leaky" gut in uremia may contribute significantly to the low-grade systemic inflammation [21•].

The chronic activation of the immune system is leading to the combination of activated immune cells with impaired function. The latter may be a consequence of counter regulation as has been shown for instance for the response to TNFalfa, which is decreased in circulating T cells of ESRD patients [22].

Premature Ageing of the Adaptive Immune System

Physiological ageing of the immune system may be accompanied by low-grade inflammation and specific changes in the composition and function of the adaptive immune system. Specific age-related alterations in immunological functions are shown in Table 1 in which the similarities between physiological ageing and premature ageing are given.

The typical combination of ageing and inflammation has been coined "inflamm-ageing" [23•]. The classical feature of healthy ageing is the progressive loss of newly formed naïve T cells (recent thymic emigrants) by the thymus as this undergoes involution. Due to the very long half-life of circulating T cells and some remnant output of naïve T cells, the TREC content can still be measured in the circulating T cell population [24••, 25]. Another measure to estimate the number of RTE is the assessment of the CD31 expression on naïve T cells [26]. Both assays usually show similar results and with increasing age, an almost linear decline in RTE is observed. The conversion to memory T cells after antigenic stimulation of naïve T cells may lead to repetitive rounds of T cell proliferation. At this stage in their development, they have a decrease in telomere length of their DNA strands and may become progressively differentiated and even senescent [9]. Senescent T cells are characterized by lack of a proliferative response and expression of cell surface markers facilitating apoptosis.

The decrease in telomere length of circulating T cells is, similar to the decline in RTE, almost linearly associated with increase in age [5••].

The assessment of the biological age of the T cell system can therefore be performed by measuring RTE, telomere length, and differentiation status of the memory T cells. In unselected ESRD patients, a major difference was observed between the biological age of the T cell system and the calendar age, with an average difference of 15–30 years (depending on the assay performed). Further dissection into subgroups of ESRD patients did show that uremia was the major determinant and little differences were found between dialysis and pre-dialysis patients or the type of renal replacement therapy [9, 27]. However, a previous infection with cytomegalovirus aggravated some aspects of immunological ageing (see below). A caveat in the interpretation of the results is the impossibility to distinguish between loss of thymic function (decrease in generation of naïve T cells) and loss of naïve T cells by decreased homeostasis. Therefore, increased turnover of T cells with loss of naïve T cells may be a result of activation/proliferation-induced apoptosis in ESRD patients. The net result is an immunological age of the T cell system, which is some decades older than the corresponding calendar age in healthy individuals.

Cytomegalovirus Infection and Immunological Ageing

There is an ongoing and increasing interest in the role of cytomegalovirus (CMV) infection in inflamm-ageing. CMV belongs to the herpes virus family, and after infection (usually early in life) and subsequent seroconversion, CMV becomes latent and resides in hematopoietic cells and endothelial cells. CMV infection is associated with some major changes in the circulating T cells, and it is estimated that on average, 10 % of the total circulating pool of T cells becomes CMV antigen specific (normally, <0.1 % of T cells are antigen specific for a given pathogen). One of the most striking features of CMV infection is the induction of T cells lacking the pivotal costimulatory CD28 molecule on their cell surface (CD28null cells). The loss of the CD28 molecule is considered a feature of highly differentiated T cells. Moreover, only CMV-infected individuals may have a sizeable population of CD4 T cells lacking CD28 (CD4posCD28null T cells). These CD4posCD28null T cells are highly pro-inflammatory, contain cytotoxic granulae, and are almost unique in the expression of the fractalkine receptor [28]. The fractalkine receptor

Table 1 Changes in the adaptive immune system observed in uremia-associated immunodeficiency and physiological ageing

Cell type	Normal function	Circulating cell numbers	Phenotype and function	Clinical relevance
Dendritic cells	Antigen presentation IFN-alpha production	DC precursors mDC/pDC balance change	Decreased costimulation ↓ Decreased antigen presentation	Decreased T cell dependent immune responses (e.g., impaired hepatitis B vaccination)
Gamma-delta T cells	Recognition of: tumor cells bacteria aminobisphosphonates	Unknown	Unknown	Unknown
Effector T cells	Support for antigen presentation (helper CD4 T cells) Cytotoxicity against virus-infected and tumor cells (cytotoxic CD8 T cells)	Naïve T cells ↓	Function decreased	Decreased vaccination response
		Memory T cels ↑	Differentiation status increased	Increased risk for severe infections
			Telomere length shortened	Cardiovascular risk factor
			CD4posCD28null T cells expanded	Pro-inflammatory milieu
Regulatory T cells	Suppression of T cell-mediated immune responses	↓	Decreased suppression	Unknown
B cells	Producing specific antibodies antigen presentation	Naïve B cells ↓	Decreased function blunted vaccination response	Decreased serological responses

mDC myeloid dendritic cell, *pDC* plasmacytoid dendritic cell

enables cells to respond to the chemokine fractalkine which is released by endothelial cells. Endothelial cells and myofibroblast are targets for the cytotoxicity of these cells. By this mechanism, the CD4posCD28null T cells have the potential to destabilize atherosclerotic plaques [28, 29]. In ESRD patients, the effect of CMV infection on the composition of the circulating T cell pool is even more pronounced and numbers of CD4posCD28null T cells may expand extraordinarily [29, 30] (Fig. 1).

However, as in healthy individuals, the CD4CD28null T cells appear to be a non-traditional risk factor for cardiovascular disease [28]. Recently, it was shown that a primo CMV infection after kidney transplantation resulted in an increased incidence of cardiovascular events [31••].

CMV infection in healthy individuals and ESRD patients not only increases T cell differentiation of both CD4 and CD8 T cells but also decreases the T cell telomere length and introduces a pro-inflammatory milieu [7, 32, 33]. After primo infection, there is a decrease in thymic output (unpublished observations) which is consistent with the observed decrease of naive T cells in the CD4 T cell compartment in CMV seropositive ESRD [6]. Therefore, CMV infection has a major impact on the composition and function of the circulating T cell system, effects which are in part similar to or mimic immunological ageing.

Immunological Ageing, Epigenetics, and Reversibility

Physiological ageing has a differential effect on lymphoid and myeloid cell populations; while lymphoid cell populations are decreased, the myeloid cell populations, e.g., granulocytes and monocytes, remain fairly intact. The immune system of patients with renal failure shows a similar change, with an almost unaffected myeloid cell population while numbers of lymphoid cells are severely decreased. Data from a mouse model suggested that ageing is associated with a skewing at the level of hematopoietic stem cells (HSCs) towards myeloid-generating subsets because of a shorter life span of the lymphoid-generating HSC subset. This hypothesis explains the age-associated loss of naïve T cells, B cells, and plasmacytoid DC in the ageing healthy individual and ESRD patients [23•]. This age-related skewing of HSC subsets may be caused by epigenetic changes. Epigenetics is a process of DNA and histone modification by, e.g., acetylation and methylation which alters the accessibility of the genes for transcription and therefore offers an extra layer of transcriptional control. Epigenetic modification of the DNA is a very important cellular control mechanism and influenced by many environmental factors and, e.g., inflammation. Also, uremia is associated with major epigenetic changes although it is not known whether uremia and/or the associated inflammation is the underlying mechanism [34]. The KLOTHO gene is important for the calcium-phosphate homeostasis and KLOTHO knock-out mice have a typical premature aged phenotype. The altered KLOTHO gene expression in ESRD patients is an example of uremia-induced epigenetic changes as this is repressed by methylation of the promoter region initiated by the elevated oxidative stress [19]. Within this concept, the epigenetic changes which normally arise late in life are now accelerated by chronic inflammation/increased oxidative stress.

The therapeutic options to reverse premature immunological ageing are limited. Starting renal replacement therapy does not seem to reverse the immunological ageing [27], which may be partly due to the fact that no significant reduction in the pro-inflammatory status and oxidative stress is

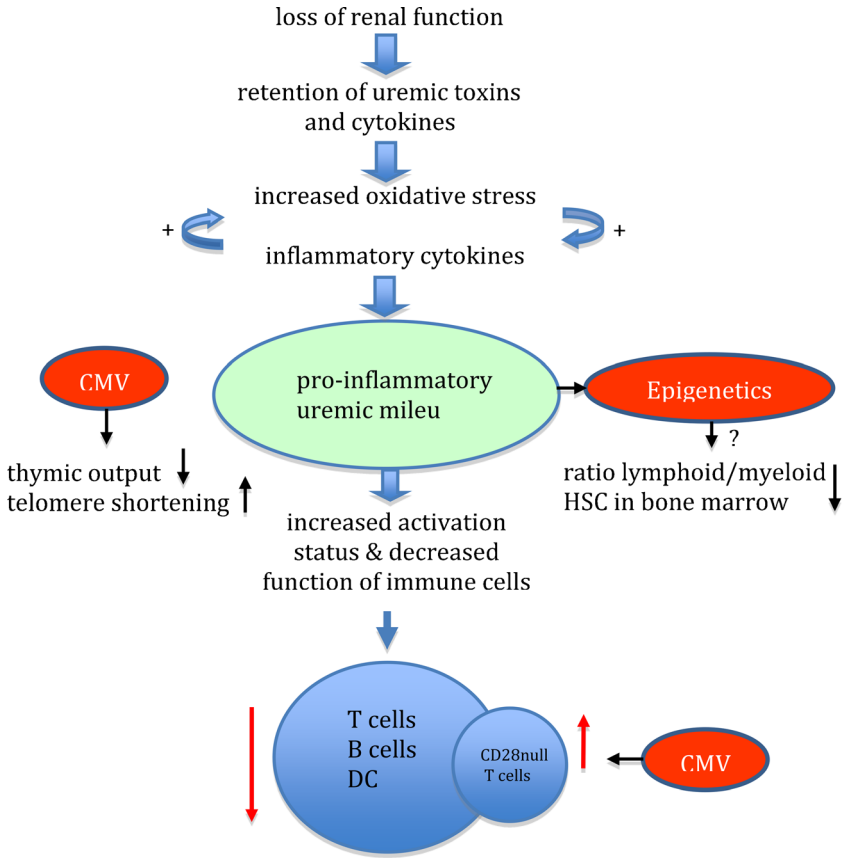

Fig. 1 Uremia-associated impaired adaptive immunity. Uremia has a substantial effect on cells important for the adaptive immunity like B cells, effector or regulatory T cells, and dendritic cells (*DCs*) which are all diminished in number and function. This may be caused by the combination of a pro-inflammatory milieu with increased oxidative stress. Activated effector T cells and diminished regulatory T cell function may foster systemic inflammation. Circulating pro-inflammatory T cells are expanded (CD28null T cells). Cytomegalovirus (CMV) infection affects thymic output, T cell differentiation with loss of telomere length, and expansion of CD4CD28null T cells, enhancing premature immunological ageing. Oxidative stress and inflammation cause epigenetic changes which may be involved in skewing of the hematopoietic stem cells (*HSCs*) in favor of myeloid biased HSC

achieved by dialysis. After kidney transplantation with an adequate allograft function, there is a rapid decrease in pro-inflammatory parameters [12•, 29, 35]. However, we could not observe any major changes in lymphopenia, T cell subsets, thymic output, and telomere length of T cells in the year following transplantation [36•]. These findings were similar for subgroups like young patients and independent of the glomerular filtration rate achieved by the allograft kidney. Therefore, after transplantation, the ESRD-induced immunological risk factors for infection and cardiovascular disease remain unchanged. This indicates that uremia leaves a stable imprint on the lymphoid system which cannot be reversed by altering the uremic condition. Again, stable epigenetic changes may be the pathophysiological explanation for this observation. One of the consequences is that the expanded cytotoxic CD4posCD28null population remains a cardiovascular risk factor after transplantation [37]. On the other side, the ESRD patients with a more "aged" T cell system have a lower risk for acute rejection [23•, 38].

Other potential therapeutic option to reverse the prematurely aged immune system are interventions with interleukin-7 (IL-7) and bardoxolone methyl. Interleukin (IL)-7 is a pivotal cytokine for T cell homeostasis and IL-7 administration in humans expanded both naïve and memory T cells [39]. Whether IL-7 is able to reverse the premature immunological ageing of ESRD patients is not known.

The transcription factor Nrf2 is a key player in the inflammatory response as it controls a large number of pro-inflammatory genes [40]. Therefore, suppression of Nrf2 by, e.g., bardoxolone methyl may ameliorate oxidative stress and inflammation in ESRD patients and favorably attenuate the effects on the immune system.

Conclusion

Progressive loss of renal function is associated with a profound effect on the lymphoid cell lineage causing reduced numbers of naïve T and B cells, increased T cell differentiation, and loss of telomere length. These changes resemble immunological ageing and are associated with a reduced adaptive immunity, commonly found in ESRD patients. Epigenetic changes induced by chronic inflammation and increased oxidative stress may be the underlying mechanism and appears irreversible by renal replacement therapy, including kidney transplantation.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Michiel G. H. Betjes and Dr. Nicolle H. R. Litjens each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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