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EFFECT OF UREMIA ON STRUCTURE AND FUNCTION OF IMMUNE SYSTEM

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Abstract

End stage renal disease (ESRD) is simultaneously associated with immune activation, marked by systemic inflammation, and immune deficiency. Systemic inflammation contributes to atherosclerosis, cardiovascular disease, cachexia and anemia, while immune deficiency leads to impaired response to vaccination, and increased incidence and severity of microbial infections. ESRD-associated inflammation and immune deficiency are associated with: a) General expansion of monocytes and elevations of their basal integrin, Toll-like receptor (TLR)-2, and TLR-4 expression, cytokine production, and reactive oxygen species (ROS) generation and reduced phagocytic capacity, b) Depletion and impaired inhibitory activity of regulatory T cells (Treg), c) Spontaneous activation, degranulation, increased basal ROS production, decreased phagocytic capacity and increased apoptosis of the circulating polymorphonuclear leukocytes (PMNs), d) Upregulation of ROS production machinery and chemokine expression in the cellular constituents of various tissues, highlighting participation of non-immune cells in the prevailing inflammatory state. e) Depletion of the antigen-presenting dendritic cells (DC), f) Reduced CD4/CD8 T cell ratio and depletion of naïve and central memory T cells, g) Diffuse B cell lymphopenia leading to impaired humoral immunity, and h) Increased pro-inflammatory activity of LDL and reduced anti-inflammatory capacity of HDL. Thus, ESRD-associated inflammation is due to activation of innate immune system, orchestrated by monocytes, macrophages, granulocytes and cellular constituents of other organs/tissues. This is coupled with immune deficiency which is caused by depletion of dendritic cell, naïve and central memory T cells and B cells and impaired phagocytic function of PMNs and monocytes.

Keywords

Chronic kidney disease; inflammation; infection; oxidative stress; vaccination; dialysis

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Background

The immune system comprises a complex set of interactions between soluble factors and cells designed to protect the host against various diseases. The key functions of immune system include detecting and destroying invading microbes and cancer cells, and identifying, removing and helping to repair tissues damaged by traumatic, infectious, ischemic, toxic, autoimmune or other types of injury. Inflammation is the critical step in immune response to infections and tissue damage. Immune defense against microbial infections is accomplished by innate and adaptive immune systems. The innate immune system comprises cells and processes that culminate in a prompt and non-specific response to infection and tissue injury. The innate immune system includes circulating monocytes and their tissue counterparts, macrophages, neutrophils (PMN), dendritic cells, natural killer cells, mast cells, eosinophils, basophils, and to some extent nearly all other cells in the body.

The adaptive immune response enables the host to recognize and remember specific pathogens and mount stronger attacks upon reencounter with the same pathogen. Adaptive immune cells include T lymphocytes and B lymphocytes. T cells and B cells express cell-specific receptors (TCR and BCR) with which they recognize their cognate antigens. Primed B cells express a unique B cell receptor (BCR) which is made of an immobilized antibody molecule. The BCR on the primed B cell recognizes and binds only to one particular antigen. While T cells recognize their cognate antigen in a processed form as a peptide in the context of a major histocompatibility complex (MHC) molecule. When T cells are presented with the peptide antigens by MHC molecules expressed on the antigen presenting cells, they rapidly proliferate and secrete cytokines to direct the immune response in the relevant direction. B cells recognize antigens in their native forms. Once a B cell encounters its cognate antigen and receives additional signals from a helper T cell (predominately Th2 type), it further differentiates into short-lived antibody-producing plasma cells and long-lived memory B cells.

ESRD is simultaneously associated with immune activation which is marked by systemic inflammation and immune deficiency (1,2). Systemic inflammation contributes to atherosclerosis, cardiovascular disease, cachexia and anemia, while immune deficiency leads to impaired response to vaccination, and increased incidence, severity and poor outcome of microbial infections. Together these abnormalities account for the large proportion of morbidity and mortality in patients with advanced CKD.

CKD-associated immune deficiency

While bacterial infections have diminished as a cause of death in the general population, they remain the second most common cause of death in patients ESRD (2–4). This is largely due to the impaired immune response in uremia (2,5,6) which is caused by: a) decreased granulocyte and monocyte/macrophage phagocytic function (5,7,8), b) defective antigen presenting capacity of antigen presenting cells (5,9,10), c) depletion of the antigen presenting dendritic cells (11), d) reduced numbers and antibody producing capacity of B lymphocyte (5,12–14), e) increased T cell turnover and apoptosis leading to depletion of naïve and central memory CD 4+ and CD8+ T lymphocyte (15–17) and f) impaired cell-mediated immunity (5,15,16). The exact mechanisms responsible for these derangements are not fully understood. Numerous factors appear to contribute to these abnormalities, the coverage of which is beyond the scope of the present review.

CKD-associated inflammation

CKD is invariably associated with systemic inflammation and oxidative stress which are the main mediators of atherosclerosis and cardiovascular disease as well as cachexia, anemia,

among other morbidities (1,18). ESRD-associated inflammation is due to the activation of innate immune system, orchestrated by monocytes, macrophages, granulocytes and cellular constituents of other organs/tissues. It is associated with: a) general expansion of monocytes and elevations of their basal integrin, Toll-like receptor (TLR)-2, and TLR-4 expression, cytokine production, and reactive oxygen species (ROS) generation (19,20), b) depletion and impaired inhibitory activity of regulatory T cells (Treg) (21,22), c) Polymorphonuclear leukocytes (PMN) activation, degranulation and basal ROS production (19), d) Upregulation of ROS production machinery and chemokine expression in the cellular constituents of various tissues, highlighting participation of non-immune cells in the prevailing inflammatory state (23), e) Increased pro-inflammatory activity of LDL and reduced anti-inflammatory capacity of HDL (24,25), and f) Paralysis of the endogenous antioxidant, anti-inflammatory and cytoprotective defense systems (26).

This review is intended to provide an overview of the functional and structural changes in immune cell populations that collectively contribute to the pathogenesis of inflammation and impaired host response to microbial infections in ESRD.

Effects of CKD on Components of Innate Immunity

As noted above, CKD-associated inflammation and immune deficiency are, in part, due to activation and dysfunction of the innate immune system which largely consists of monocytes and their tissue counterparts, macrophages, neutrophils (PMN), dendritic cells, natural killer cells, mast cells, eosinophils and basophils. In addition nearly all other cells in the body such as endothelial cells, vascular smooth muscle cells, adipocytes, neuronal cells, renal cells, epithelial and many other cells participate in the systemic oxidative and inflammatory responses. The innate immune cells and some non-immune cells express molecules that recognize pathogen-associated molecular patterns and modified endogenous molecules. These include signaling receptors such as CD14 and Toll-like receptor (TLR) family, endocytic receptors such as SRA-1, CD36 and LOX-1 and secreted molecules such as mannose-binding lectins family.

Monocytes and macrophages and their abnormalities in ESRD

Monocytes are produced by the bone marrow, stored in spleen, and distributed in all body tissues as macrophages. Monocytes/macrophages play a key role in host defense against microbial infections, tissue healing process, and in the pathogenesis of inflammation and atherosclerosis. They engulf microbes, infected cells & tissue debris directly or via intermediary proteins such as antibodies or complement components. This phenomenon represents a critical step in defense against microbial infections and healing of the injured tissues. On the other hand uptake of oxidized LDL and oxidized phospholipids via scavenger receptors by macrophages in the artery wall and glomerular mesangium constitutes the primary steps in the development and progression of atherosclerosis and glomerulosclerosis. Finally via production of cytokines and ROS, release of growth factors, metalloproteinases and tissue factor, macrophages participate in healing of the damaged tissues, development of local and systemic inflammation and oxidative stress, and rupture of atheromatous plaque. Monocytes are classified based on expressions of CD14 (pattern-recognition receptor) and CD16 (Fc gamma III receptor) into 4 major subsets: CD14⁺⁺/CD16⁻; CD14⁺⁺/CD16⁺; CD14⁺/CD16⁻ and CD14⁺/CD16⁺. The CD14⁺CD16⁺ monocytes have high capacity to produce inflammatory cytokines (TNF-alpha, IL-6, and IFN-α) and promote inflammation.

Patients with ESRD exhibit a general expansion of circulating monocytes particularly of CD14⁺CD16⁺ subset (20). This is associated with elevated basal expressions of Toll-like receptors TLR-2 and TLR-4, up-regulation of cell surface expression of integrins, and

increased basal production of cytokines and ROS (19,20). These abnormalities point to spontaneous activation of monocytes and their contribution to the prevailing oxidative stress and systemic inflammation in ESRD. In addition the uremic plasma induces production of osteoactivin by monocytes and macrophages which can contribute to the prevailing vascular calcification in the ESRD population (27). Likewise uremic plasma stimulates adhesion and infiltration of normal monocytes in cultured human endothelial monolayer used to simulate arterial wall in vitro (28) pointing to the pro-atherogenic properties of uremic milieu. Spontaneous activation of monocytes is accompanied by decreased monocyte phagocytic capacity (5,7,8) which contributes to immune deficiency and increased incidence and severity of infections in ESRD population.

Ploymorphonuclear leukocytes (PMN) and their abnormalities in ESRD

PMN are short-lived (5 days) professional phagocytes which avidly engulf antibody-coated and complement-coated microbes, damaged cells & cellular debris. They have many intracellular granules which contain bacteriocidal proteins such as cationic proteins and defensins, proteolytic enzymes and cathepsin G (to degrade bacterial proteins), lysozyme (to lyse bacterial cell walls), NAD(P)H oxidase-II (to generate ROS), myeloperoxidase (to produce HOCl), and lactoferrin (to inhibit bacterial replication via iron deprivation). PMNs are the first line of defense against invading microbes and important players in inflammation.

Patients with ESRD exhibit basal upregulation of TLR-4, TLR-2 and integrin expressions, increased ROS production and marked degranulation reflecting their spontaneous activation (19,20). These abnormalities contribute to the prevailing systemic oxidative stress, inflammation and tissue damage in this population. This is accompanied by decreased phagocytic capacity and increased apoptosis of PMNs (7,8). These abnormalities are transiently intensified by hemodialysis (19,20), most likely as a result of exposure to dialyzer membrane, cytoskeletal stresses from the roller pump, and influx of impurities from the dialysate compartment.

Dendritic cells (DCs) and their abnormalities in ESRD

DCs are the major antigen presenting cells that play a key role in initiation and maintenance of both innate and adaptive immunity. These cells continuously survey antigenic milieu of the body and act as the sensors of microbial invasion and tissue damage. Activation of DCs by pathogens triggers secretion of cytokines and upregulation of co-stimulatory molecules which are essential for priming the naïve T cells to the captured antigens. DCs act as the sentinels for adaptive immunity by regulating immune responses in T cell, B cell and natural killer cells and thereby play a critical part in tumor surveillance, defense against microbial pathogens and tolerance to self antigens. Two types of DCs have thus far been identified:

- a. plasmacytoid dendritic cells (pDC) which contain intracellular TLRs (TLR7 and TLR9) with which they can sense viral or self nucleic acids; they produce large amounts of type I interferons such as IFN α in response to viral infections.
- b. Myeloid dendritic cell (mDC) which possess cell surface TLRs including TLR3 and TLR4 and produce IL-12 and type I interferons in response to TLR3 and TLR4 agonists.

ESRD results in dendritic cell depletion and dysfunction (11,29,30) which is primarily due to the reduction of pDC subset (11). DC depletion in ESRD is transiently exacerbated by hemodialysis procedure (11) and reversed by renal transplantation (30). Given the critical role of DCs in regulation of innate and adaptive immunity, DC depletion must contribute to impaired defense against microbial infections and poor response to vaccination in the ESRD population. Interestingly basal and LPS-stimulated TNF production by DCs is increased in

ESRD, suggesting their potential role in the pathogenesis of uremia-associated inflammation (11).

Non-immune cells

Studies in experimental animals with CKD have shown upregulation of ROS production machinery and chemokine/chemokine expression in the cellular constituents of various tissues highlighting their participation in the prevailing oxidative and inflammatory states (23).

Components of the Adaptive Immunity and Their Abnormalities in ESRD

In addition to profoundly affecting the structure and function of the innate immune system, CKD adversely impacts the agents of adaptive immunity namely T and B lymphocytes.

T lymphocytes (T cells) and their abnormalities in ESRD

T cells represent a major component of adaptive immune system and play a central part in cell-mediated immunity. They are distinguished from other lymphocytes by their unique surface receptor known as T cell receptor (TCR). Exposure of naive T cells to antigen leads to clonal expansion and differentiation and generation of the memory T cells and effector T cells. Effector T cells perform their effector function via secretion of cytokines and destruction of target cells. At the conclusion of a specific immune reaction, the population of the related effector T cells contracts. However a small number of the memory T cells remain indefinitely enabling the host to mount a robust immune response upon re-exposure to the same pathogen. T cells are derived from bone marrow stem cells which populate the thymus as thymocytes and subsequently differentiate into several functionally distinct subtypes; several, but not all, of which are briefly described below:

Helper T cells (CD4+ T cells)—These cells express CD4 protein on their surface. They play a key role in various immunologic processes such as activation of cytotoxic T cells and macrophages, maturation of B cells into plasma cells and memory B cells, antibody production by B cells, recruitment of PMNs, eosinophils and basophils to the loci of infection/inflammation, amplification of microbicidal activity of macrophages as well as development of tolerance or suppression of inflammatory response among others. When presented with the peptide fragments of the processed antigens on the MHC class II molecules expressed by the antigen presenting cells, CD4+ T cells rapidly proliferate and secrete cytokines to direct the immune response in relevant direction. The helper T cells can differentiate into a number of distinct subtypes, including T_H1 , T_H2 , T_H3 , T_H17 , or T_{FH} . Each of these subtypes secretes a different panel of cytokines which drive the immune response in specific direction. The CD4+ cell differentiation into the given subtypes is driven by the signaling patterns from the antigen presenting cells.

Cytotoxic T lymphocytes (CD8+ T cells)—These cells express CD8 protein on their surface. CD8+ T cells can destroy virally infected cells and tumor cells and participate in transplant rejection. These cells recognize antigens associated with MHC class I which is expressed by nearly all cell in the body. The regulatory T cells inactivate and transform the CD8+ cells into an anergic state by secreting IL-10, adenosine and other molecules, a process that is critical in preventing autoimmune diseases.

Memory T cells—Following acute infection a small fraction of the primed CD4+ or CD8+ cells persist indefinitely as central memory T cells and effector memory T cells which typically express CD45RO. Upon re-exposure to their cognate antigen these cells undergo rapid proliferation to form large numbers of effector T cells. Accordingly the memory T

cells play a central part in adaptive immunity by providing the immune system with “memory” against past infections.

Regulatory T cells (T_{reg} cells)—T_{reg} cells are derived from two distinct origins: a) adapted regulatory T cells (also known as Tr1 cells or Th3 cells) which originate from alternative differentiation of naïve T cells, and b) Natural regulatory T cells (also known as CD4⁺ CD25⁺ FoxP3⁺ T_{reg} cells) which mature in thymus as distinct lineage and comprise 5–10% of the circulating CD4⁺ T cells. T_{reg} cells which were previously known as suppressor T cells play a central role in maintaining immunological self tolerance, limiting the inflammatory response to foreign antigens, ceasing T cell-mediated immunity upon completion of the immune reaction, and suppressing auto-reactive T cells that escape negative selection in the thymus. Via cytokine-mediated or contact-dependent mechanisms, activated nTregs suppress proliferation and blunt the effector functions of B cells, monocytes, and other T cells. Through their actions Tregs protect the host by preventing the inflammatory response from becoming perpetual or disproportionately exuberant.

Natural killer T cells (NKT cells)—NKT cells are large granular lymphocytes that recognize glycolipid antigens presented by CD1d. They are distinct from the conventional T cells which recognize peptide antigens presented by MHC molecules. Upon activation, the NKT cells can kill the cell by releasing cytolytic molecules such as perforin which creates holes in the targeted cell membrane and proteases known as granzymes which digest cellular proteins. For instance the NKT cells can recognize and eliminate virally-infected cells and tumor cells. Alternatively the NKT cells can serve as helper agent by secreting cytokines.

CKD-associated T cell abnormalities

Patients with advanced CKD and ESRD exhibit reduced CD4/CD8 ratio, increased Th1/Th2 ratio and depletion of naïve and central memory CD4⁺ and CD8⁺ T cells (6,15,16,17). This is associated with increased apoptosis of naïve and central memory CD4⁺ and CD8⁺ T cells. The magnitude of the naïve and central memory CD4⁺ and CD8⁺ T cell depletion is directly related to severity of azotemia, oxidative stress, secondary hyperparathyroidism and iron overload and inflammation (17). Given the critical role of naïve and central memory T-cells in orchestrating the immune response to the *de novo* exposure and re-exposure to pathogens, their depletion must be, in part, responsible for increased incidence and poor outcome of various infections in ESRD population.

In recent studies Meier et al (21) and Hendrikx et al (22) demonstrated increased apoptosis and marked reduction of the nTreg cells (CD4⁺/CD25⁺) in as-yet dialysis-independent CKD patients and ESRD patients maintained on peritoneal or hemodialysis. The observed depletion of the nTreg cells was accompanied by their impaired ability to inhibit PHA-induced CD4⁺ cell proliferation reflecting the reduction in their anti-inflammatory capacity. The magnitude of nTreg cell depletion and dysfunction was greatest in hemodialysis-treated patients followed by peritoneal dialysis-treated and as-yet dialysis-independent CKD patients. Incubation of isolated nTreg cells from normal subjects with the uremic serum *ex vivo* lowered the number and reduced the suppressive capacity of these cells, pointing to the deleterious effect of uremic milieu on these cells. This effect could be reproduced by addition of oxidized LDL which is consistently elevated in CKD patients. This observation illustrates the interconnection between oxidative stress and lipid disorders and immunological abnormalities and the associated atherogenic diathesis in CKD. Given the critical role of Treg cells in mitigating inflammation, nTreg cell deficiency and dysfunction in CKD/ESRD population must contribute to the prevailing systemic inflammation and its cardiovascular and numerous other complications.

B Lymphocytes and Their Abnormalities in ESRD

B lymphocytes are generated from hematopoietic stem cells in the bone marrow throughout life. They contribute to the immune system by producing antigen-specific antibodies. The pleiotropic cytokine, IL-7 plays a major part in B-lymphopoiesis by promoting maturation of pre-B cells to B cells in the bone marrow (31). After differentiation and selection in the bone marrow, newly emerging B lymphocytes (termed transitional B cells; CD19+ CD10+) migrate to the spleen. Further differentiation of transitional B cells into mature long-lived lymphocytes is driven by B Cell Activating Factor of tumor necrosis family (BAFF) (32). B cells failing any maturation steps undergo clonal deletion (by apoptosis) and those recognizing self-antigen during maturation become suppressed (anergy or negative selection). In the blood and lymphatic system B cells conduct immune surveillance via their B cell receptor (BCR) which consists of a membrane-bound immunoglobulin molecule capable of binding a specific antigen. In adults, innate B1 cells (CD5+ B cells) account for 25–27% of peripheral blood B lymphocytes. Innate B1 cells produce mainly IgM antibodies that have high cross-reactivity but low-affinity (33). These antibodies constitute a readily-available pool of immunoglobulin for use against a variety of infections before the specific high-affinity antibodies are produced. In contrast, the conventional B cells (CD5– B cells, also known as B2 cells) produce more diverse and high-affinity antibodies. They account for 75–80% of peripheral blood B lymphocytes.

When the naive mature B lymphocytes recognize an antigen with their receptors and receive an additional signal from the T helper cells, they undergo proliferation and differentiation into long-lived memory B cells (CD27+) and short-lived plasma cells. Most activated B cells differentiate into plasma cells that secrete antibodies against the specific epitope of the inciting antigen. A small minority of these cells survives as *memory cells* that recognize the given antigen. However, with each re-exposure, the number of surviving memory cells rises and specificity of immune response improves. Memory cells which can survive decades actively circulate from blood to lymph nodes and populate mucosal tissues. Upon subsequent encounter with the antigen, memory B cells rapidly produce Ig isotypes with high affinity for the given antigen. In adult humans memory B cells constitute approximately 40% of all circulating B cells. Peripheral blood B cells are comprised of distinct phenotypical and functional subpopulations including innate B1 cells (CD19+, CD5+), conventional B2 cells (CD19+, CD5–), newly formed transitional B cells (CD19+, CD10+, CD27–), Naïve B cells (CD19+, CD27–) and Memory B cells (CD19+, CD27+).

CKD-associated B cell abnormalities

Several studies have demonstrated significant B lymphopenia in adults and children with ESRD (14,34–39). In addition, diminished population of CD5+ innate B cells and CD27+ memory B cells has been demonstrated in children with chronic renal failure (34). In a recent study, Pahl et al (14) demonstrated depletion of several other B cell subtypes in adult patients with ESRD. The observed B cell lymphopenia was accompanied by elevated levels of IL-7 or BAFF which are the key B cell differentiation and survival factors. Moreover the number of transitional B cells was not significantly reduced in the ESRD patients. These observations suggest that decreased output of B cells from bone marrow may not be the main cause of the B cell lymphopenia in ESRD patients. This view is supported by the finding that plasma levels of IL-7, a cytokine that facilitates conversion of pre-B cells to B cells was increased in ESRD patients. Two alternative mechanisms can account for B lymphopenia in ESRD. First, the uremic milieu may increase susceptibility of B cells to apoptosis in ESRD patients. This supposition is supported by the study of Fernández-Fresnedo et al who reported increased apoptosis of B cells in their CKD patients (39). The second possibility is that the uremic environment may interfere with the maturation of transitional B cells to mature B cells by promoting resistance to BAAF-mediated

differentiation and survival signals. This supposition was supported by marked down-regulation of BAAF receptor in ESRD patients reported by Pahl et al (14). Thus B cell deficiency and dysfunction in advanced CKD can be simultaneously mediated by increased B cell apoptosis and impaired Transitional B cell differentiation and maturation.

In contrast to the observed reduction of BAFF-R expression in transitional B cells, BAFF receptor expression was unchanged in circulating mature B cells (CD19+ CD10– cells) in ESRD patients. Since BAFF receptor expression and activity contributes to the survival of mature B lymphocytes (40), the observed elevation of the circulating BAFF levels and the normality of BAFF-R expression in mature B cells preclude the deficiency of either as the primary cause of the observed reduction of mature circulating B cells (CD19+ CD10–) in ESRD.

It is of note that the studies of the effect of CKD/ESRD on B cell populations in humans have been restricted to the examination of cells found in the blood samples. This is necessarily inadequate for the full understanding of the impact of the disease due to lack of relevant studies of the bone marrow and lymphoid tissues which are critical sites in the maturation and functional development of these cells. Further studies are needed to explore the effects of uremia on B cell precursors in the bone marrow and downstream signal transduction pathways involved in B cell growth, differentiation and survival. Regardless of the cause, uremia-induced naïve and memory B cell lymphopenia is, in part, responsible for the defective humoral response to infections, vaccination and recall antigens and increased incidence of infection in ESRD patients.

Conclusions

The ESRD-associated inflammation is due to activation of innate immune system, orchestrated by monocytes, macrophages, granulocytes and cellular constituents of nearly all organs/tissues in the body. The ESRD-associated inflammation is coupled with immune deficiency which is caused by depletion of the antigen-presenting dendritic cells, naïve and central memory T cells and B cells and impaired phagocytic ability of monocytes and PMNs (Figure 1).

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Figure 1.
Schematic summary of the impact of advanced CKD on agents of innate and adaptive immunity and their adverse consequences