Arch. Immunol. Ther. Exp. (2012) 60:453–459
DOI 10.1007/s00005-012-0191-0

REVIEW

# Aberrant Function and Differentiation of Monocytes in End Stage Renal Disease

**Krzysztof Laudański · Zbigniew Nowak**

Received: 19 April 2012 / Accepted: 23 July 2012 / Published online: 19 October 2012


**Abstract** Patients with end stage renal disease (ESRD) suffer from many disturbances of the immune system. These immunopathologies are related to the higher failure of vaccination, and increased prevalence of infections and neoplasms. In the presented article, we review the current data regarding the role of monocytes in immune dysfunctions which are observed in terminal renal failure. As monocytes play a pivotal role in regulating the function of the immune system, their dysfunction can have a profound effect on the immune system and may lead to accelerated arteriosclerosis and deteriorating overall health conditions. More specifically, we suggest that peripheral blood monocytes in patients with ESRD are chronically activated, and their functional and phenotypical features resemble those of inflammatory macrophages. This state of chronic inflammation is unfavorable for dendritic cells and consequently, the prevalence of dendritic cells is reduced. As these effects are consistent across different modes of dialysis, they are probably mediated by the uremia itself.

**Keywords** End stage renal disease · Monocyte · Dendritic cells · Inflammation

K. Laudański (✉)
Department of Anesthesiology and Critical Care,
University of Pennsylvania, Dullas 6, 3400 Spruce Street,
Philadelphia, PA 19104, USA
e-mail: klaudanski@gmail.com

Z. Nowak
Nephrology Department with Dialysis Unit,
Military Institute of Medicine, Warsaw, Poland

## Immune System Pathologies in Patients with End Stage Renal Disease

The prevalence of end stage renal disease (ESRD) continues to increase worldwide. These patients suffer from various aberrations of the immune system with several significant clinical implications (Abbott et al. 2001; Abbott and Agodoa 2002; Kamalakannan et al. 2007; Ozdemir et al. 2001; Perunicic-Pekovic et al. 2008; Pesanti 2001; Sezer et al. 2000; Stewart-Phillips et al. 1990; Vamvakas et al. 1998). Compared to age-matched peers, these patients are more susceptible to sepsis, tuberculosis, endocarditis, opportunistic or fungal infections (Abbott and Agodoa 2001, 2002; Kamalakannan et al. 2007; Ozdemir et al. 1998). Moreover, the induction of acquired immunity after vaccination is significantly less common (Pesanti 2001; Sezer et al. 2000). There is increased prevalence of various neoplasms (Maisonneuve et al. 1999; Vamvakas et al. 1998). Atherosclerosis process is significantly accelerated in ESRD patients which can be at least partially attributed to increase in the frequency of inflammatory cells (Berg et al. 2012; Nockher and Scherberich 1998; Saionji and Ohsaka 2001). All of these findings suggest that the performance of the immune system in ESRD is aberrant and has several characteristics typical for immunosuppression. On the other hand, some features of the immune system are suggestive of over-activation. Presence of auto-antibodies, increased activity of complement, or elevated serum level of the acute-phase protein are some of the examples of the increased activation of the immune system in patients with ESRD (Marchant et al. 1996; O'Byrne et al. 2001; Sezer et al. 1998). Some authors even suggested increased prevalence of the autoimmune disease in ESRD, but definitive epidemiological evidence is lacking (Sezer et al. 1998). In summary, in the patients with ESRD the immune

system exhibits the features typical for both over-activation and immunosuppression, resulting in its overall aberrant function.

Here, we focus our attention on a relatively narrow but pivotal aspect of the immune system aberrancy in the patients with ESRD. We hypothesize that monocyte (MO)-related pathologies underlie several symptoms and clinical phenomenons seen in these patients. MO play a critical role in phagocytosis, emergence of the dendritic cells (DCs) and macrophages (Mac) under physiological and stressful conditions, as well as regulate the function of the T and B cells. Aberrant activation of the monocytes is related to the development of atherosclerosis, increased susceptibility to infections and neoplasms as well as failure to induce immunity after vaccination (Berg et al. 2012; De et al. 2003; Jeneway 2004; Stewart-Phillips et al. 1990). All of the above suggest that MO play significant role in pathology of immune system aberration in ESRD. This process is frequently characterized as smoldering inflammation. It is believed that it is responsible for accelerated atherosclerosis among other pathologies (Papagianni et al. 2003; Perunicic-Pekovic et al. 2008). Also low level of inflammation can explain frequent pruritus in patients with ESRD since it is speculated that pruritus is low-grade pain triggered by inflammation (Kimmel et al. 2006; Mettang et al. 2002). The degree of complaint of pruritus strongly correlated with serum IL-6 levels (Kimmel et al. 2006).

## Differentiation Plasticity of the Peripheral Blood Monocytes

Peripheral blood MO are sentinel cells under physiological condition (Jeneway 2004). Upon activation they are able to produce a large number of cytokines. While most monocytes undergo activation and apoptosis, some undergo differentiation into terminally differentiated cells (Tacke and Randolph 2006). MO are unique cells in their ability to differentiate into several effector cells including Mac, activated monocytes, or DCs. MO-derived offspring cells differ from each other in respect to their function or involvement in etiology of certain clinically prevalent pathologies (Gordon and Taylor 2005; Palucka and Banchereau 2006; Tacke and Randolph 2006; Ziegler-Heitbrock 2000). Mac are most commonly recognized for their phagocytic properties. They play a pivotal role in the removal of damaged tissue and pathogens as well as tissue repair (Gordon and Taylor 2005; Palucka and Banchereau 2006; Tacke and Randolph 2006; Ziegler-Heitbrock 2000). Lack of Mac is related to the impaired healing as well as the storage diseases (Pastores 1997; Stefater et al. 2011). On the other hand, they also play a role in the progression of atherosclerosis (Berg et al. 2012; Gordon and Taylor 2005). Both activated monocytes and Mac seem to play an important role in the etiology of septic shock (Abbott and Agodoa 2001; Gordon and Taylor 2005; Joffre et al. 2009; Kimmel et al. 1998). Alternatively, MO can differentiate into DCs (Tacke and Randolph 2006). DCs exhibit superb ability to detect, process and present antigens to the effector cells (Palucka and Banchereau 2006; Tacke and Randolph 2006). Activation of DC is critical for selection of optimal clones of T and B cells with subsequent elimination of pathogens (Auffray et al. 2009; Geissmann et al. 2008; Gordon and Taylor 2005; Joffre et al. 2009; Palucka and Banchereau 2006; Tacke and Randolph 2006). MO can perform these functions as well but with much less efficiency. Some estimate that single DC can stimulate up to $10^4$ of T cells while MO can only stimulate $10^2$. These unique features of DC are related to the expression of several stimulatory receptors and the secretion of cytokines critical for optimal stimulation of T and B cells (Auffray et al. 2009; Geissmann et al. 2008; Gordon and Taylor 2005).

The emergence of offspring cells from peripheral blood MO depends on the delicate balance of the local cytokine environment (Auffray et al. 2009; Geissmann et al. 2008; Gordon and Taylor 2005; Palucka and Banchereau 2006; Tacke and Randolph 2006). Interleukin (IL-6), IL-10, macrophage colony-stimulating factor (M-CSF), tumor necrosis factor (TNF-$\alpha$), interferon $\gamma$, lipopolysaccharide (LPS) and vitamin $D_3$ support the emergence of Mac while IL-4, IL-3, IL-13, and granulocyte macrophage colony-stimulating factor (GM-CSF) are critical for the differentiation of MO into DC (Auffray et al. 2009; Geissmann et al. 2008; Gordon and Taylor 2005; Palucka and Banchereau 2006; Tacke and Randolph 2006; Wu et al. 2001). IL-4 and GM-CSF can differentiate MO into DC in vitro resembling those in lymph nodes or after severe inflammation (Auffray et al. 2009; Geissmann et al. 2008). Conversely, IL-3 or TGF-$\beta$ IS more supportive for population of Langerhans-like cells (Auffray et al. 2009; Geissmann et al. 2008; Palucka and Banchereau 2006). Not only is the composition of the local cytokine environment critical, but also its timing. For example IL-6 is supportive in the maturation of DCs late in their differentiation process while if they are introduced early it results in Mac from precursory MO (Auffray et al. 2009; Geissmann et al. 2008; Gordon and Taylor 2005; Tacke and Randolph 2006). Macrophages are usually divided into tissue and inflammatory Mac (Gordon and Taylor 2005). The latter ones are the most common offspring of peripheral blood MO (Gordon and Taylor 2005; Tacke and Randolph 2006).

MO exhibit several properties typical for DC or Mac. They can stimulate T and B cells but not as effectively as DC (Auffray et al. 2009; Geissmann et al. 2008; Gordon and Taylor 2005; Tacke and Randolph 2006; Ziegler-Heitbrock 2000). They also have some phagocytic properties, but Mac

can do this process much more effectively. Differentiation spectrum of Mac ← MO → DC should be understood as continuum in both differentiation and functional sense. Cells evolving through this spectrum exhibit different level of professionalism and may complement each other's functions. Also, a deficit in one population can be compensated for by the expansion or increased activation of the alternative population to some extent.

## Function of Peripheral Blood Monocytes in Dialyzed Patients

In general, the absolute number of the MO in peripheral blood is usually increased in dialyzed patients. This is probably a non-specific answer to the stress secondary to the uremia and renal replacement therapy as being signified by increase in $CD14^{+}CD16^{+}$ positive cells (Nockher and Scherberich 1998; Saionji and Ohsaka 2001).

Peripheral blood MO obtained from patients with ESRD are characterized by the chronic low-grade activation even if an offending pathogen cannot be identified. This increased baseline activation is characterized by increased production of IL-1$\beta$, TNF-$\alpha$, neopterin and increased expression of MHC type II receptors. (Girndt et al. 1998; Morita et al. 1997; Nockher and Scherberich 1998; O'Byrne et al. 2001; Papayianni et al. 2002). Also, expression of surface adhesion molecules (ICAM-1, CD11b/CD18, CD11c/CD18) is elevated (O'Byrne et al. 2001; Papayianni et al. 2002). Both chronic activation and elevated expression of adhesion molecules are frequently linked to accelerated atherosclerosis (Gordon and Taylor 2005). Moreover, expression of CD16, a critical receptor for scavenging large immunocomplexes from blood, is elevated in ESRD (Cavaillon et al. 1992; Kawanaka et al. 2002; Nockher and Scherberich 1998; O'Byrne et al. 2001; Papayianni et al. 2002; Saionji and Ohsaka 2001). However, despite having increased surface levels of several adhesion molecules and receptors for immunoglobulin complexes, the phagocytic ability of the peripheral blood MO obtained from patients with ESRD is impaired versus MO obtained from healthy peers (Hubel et al. 1991; Lewis and Van Epps 1987; Ooi and Ooi 1983). Production of pro-inflammatory cytokines is not uniformly elevated in ESRD since secretion of pro-inflammatory IL-6 by ESRD patients cannot be easily depicted after reviewing different studies (Cavaillon et al. 1992; Malaponte et al. 2002; Paczek et al. 1991; Takahashi et al. 2000). Secretion of IL-6 by ESRD patient is significantly impaired in some studies (Cavaillon et al. 1992; Malaponte et al. 2002; Paczek et al. 1991; Takahashi et al. 2000). Others reported that elevated level of IL-6 in ESRD has significant impact on several clinical variables (Bossola et al. 2010; Kimmel et al. 2006; Meuwese et al. 2011). At present, it seems to be impossible to characterize the role of IL-6 in ESRD patients in a definitive way. Additionally, the serum level of the IL-10 is elevated in patients with ESRD (Girndt et al. 2001c; Morita et al. 1997). This cytokine is produced primarily by MO (Allavena et al. 1998; Auffray et al. 2009; Geissmann et al. 2008; Gordon and Taylor 2005) and also by B cells and Th2. Interestingly, IL-10 is one of the most potent anti-inflammatory cytokines as it provides a negative feedback loop to the activity of the immune system (Allavena et al. 1998). However, concomitant elevated levels of pro-inflammatory cytokines suggest a diminished response to immunoinhibitory production of IL-10 (Girndt et al. 2001c).

Since cytokines play an important role in the regulation of the function of monocytes and their offspring, it is not surprising that several of their functions are significantly impaired. Elevated surface expression of CD16 and several adhesion molecules suggest enhanced ability of MO/Mac to perform phagocytotic function (O'Byrne et al. 2001; Papayianni et al. 2002). However, it has been demonstrated that phagocytosis is impaired in ESRD patients (Hubel et al. 1991; Lewis and Van Epps 1987; Ooi and Ooi 1983; Schauer et al. 1991). Moreover, the response to common pathogen danger signal like LPS is impaired (Cavaillon et al. 1992; Descamps-Latscha et al. 1995; Girndt et al. 1998; Le Meur et al. 1999; Malaponte et al. 2002). This diminished ability to respond to LPS is inversely related to the duration of the dialysis (Malaponte et al. 2002). This suggests that ESRD patients develop a tolerance to LPS. The possible mechanism is the diminished expression of a critical receptor for common pathogens patterns like CD14 and Toll-like receptors (Calvano et al. 2003). However, the emergent phenomenon of LPS tolerance is not as straightforward. Subsequent challenge of MO from ESRD patients results in diminished production of TNF-$\alpha$, but enhanced secretion of IL-8 and IL-13 (Kimmel et al. 1998). This may suggest that aberrant response to LPS in ESRD is not a related to diminished expression of sensing receptor but change in mechanisms transducing stimulation from receptor (Calvano et al. 2003).

One can speculate that aberrant production of the cytokine results in faulty stimulation of the B cells. Optimal stimulation is critical in inducing production of immunoglobulins by B cells. This is a critical step in forming immune memory and providing adequate response to vaccination. However, it is difficult to assess which of the cytokine is responsible for this defect since cytokines are differently affected and uniformly reported across studies (Pesanti 2001; Sezer et al. 2000).

Peripheral blood MO in ESRD exhibit an interesting mix of features. Some of their function seems to be enhanced while some others are impaired. On one side, elevated production of TNF-$\alpha$, IL-1$\beta$, or IL-8, IL-6 under

resting condition suggests state of chronic activation of MO. On the other hand, several functional characteristics seem to be aberrant. Among many examples the response to LPS is abnormal. Impaired ability to perform their function and ability to precisely adjust their response may be a contributing factor to several pathologies seen in ESRD such as accelerated atherosclerosis (Papagianni et al. 2003; Perunicic-Pekovic et al. 2008). This resembles the profile of activated inflammatory monocytes and Mac as seen in some other medical conditions (Gordon and Taylor 2005; Joffre et al. 2009; Kurz et al. 1986).

## DCs in Dialysis Patients

DCs are important part of the acquired immunity (Palucka and Banchereau 2006; Auffray et al. 2009; Geissmann et al. 2008). They exhibit several regulatory properties and are able to limit collateral damage from inflammation. They also play a critical role in response to vaccines. DC can emerge from several specific precursory cells or MO. However, serum profiles of cytokines and chronic activation of the MO are not conducive to the emergence of DCs (Morita et al. 1997; Nockher and Scherberich 1998; Ventura et al. 1998; Weber et al. 1998). Instead, such cytokine environment supports development of Mac-like cells or inflammatory MO. As a matter of fact circulatory MO in patient with ESRD have several features suggesting their commitment to the Mac-like cells. Increased expression of CD16 or CD11b and diminished expression of co-stimulatory CD86 are stigmas of Mac-like characteristics (Girndt et al. 2001a; Kawanaka et al. 2002; Nockher and Scherberich 1998; Saionji and Ohsaka 2001) This predetermination of MO towards Mac can be partially related to the elevated serum level of M-CSF, G-CSF and MCP-1 (Brauner et al. 1998; Papayianni et al. 2002; Ventura et al. 1998). Additionally, elevated level of IL-10 in ESRD patients further retards an emergence of DCs and adequate activation of circulating MO (Allavena et al. 1998; Morita et al. 1997). These cytokines are potent stimuli for Mac commitment (Allavena et al. 1998; Gordon and Taylor 2005; Tacke and Randolph 2006). Their influence can be potentially counter-balanced by IL-4 or IL-13, two cytokines supportive emergence of the DC from precursory MO (Auffray et al. 2009; Geissmann et al. 2008; Ziegler-Heitbrock 2000). Both cytokines are produced by Th2 cells. Interestingly, the percentage of these T cells is elevated in patients with uremia (Libetta et al. 2001). Despite elevated levels of Th2 cell, Mac-like characteristics are predominant among circulatory MO suggesting that their influence on the differentiation fate of circulating MO is diminished (Girndt et al. 2001a; Kawanaka et al. 2002; Nockher and Scherberich 1998; Saionji and Ohsaka 2001). As a matter of fact ability of MO to differentiate into DC has been reported as seriously impaired in several studies even with optimal cytokine stimulation (Choi et al. 2011; Lim et al. 2007; Puig-Kroger et al. 2007).

There are few studies directly assessing the prevalence of DC in ESRD patients. Betjes et al. (1993a, b) analyzed the frequency of DC in the lymph nodes but failed to generate a definitive conclusion. Other investigators measured the frequency of the Langerhans cells in the skin of ESRD patient (Alscher et al. 2002; Mettang et al. 1993). Frequency of these cells was lower after initiation of dialysis. However, since Langerhans cells emerge from specific precursors, it is difficult to extrapolate this result into MO-derived DC populations (Auffray et al. 2009; Geissmann et al. 2008; Palucka and Banchereau 2006). It is also unclear whether functional properties of the differentiated DC in ESRD are fully matured and are reflected in their ability to optimally stimulate effector T and B cells. It should also be noted that T cells have some features of anergy in ESRD, but it is unclear whether this defect is independent of DC/MO aberrations (Girndt et al. 2001b; Kurz et al. 1986).

## Etiology of Aberrant MO Function and Differentiation

It is believed that chronic inflammatory state in ESRD is at least partially responsible for the aberrant function and differentiation of peripheral blood MO in ESRD. The etiology of these changes is sometimes attributed to the hemodialysis treatment itself. Hemodialysis membrane and fluid are most often cited (Alscher et al. 2002; Mettang et al. 1993, 2002; Paczek et al. 1991; Schauer et al. 1991). Some observations confirmed the ability of different membranes to activate MO while buffers seemed to have minimal impact (Alscher et al. 2000). Some authors suggest that during dialysis, activation of MO is due to the presence of residual LPS but data failed to confirm this (Weber et al. 1998). The critical involvement of dialysis membranes in chronic activation of peripheral blood MO is questioned by some authors while others showed convincing evidence (Memoli et al. 2000; Ventura et al. 1998). Interestingly, peritoneal dialysis induces similar aberrations of the immune system despite not utilizing artificial membranes. In these subjects, the waste products are exchanged with the patient's own peritoneum. Activation related to this process should be minimal, but activation of the immune system is still detected (Alscher et al. 2002; Mettang et al. 2002; Puig-Kroger et al. 2007). Implementing special dialysis fluid may alleviate the immuno system aberration but does not remove them completely (Alscher et al. 2000). This suggests that uremia itself can result in chronic activation of monocytes or Mac-like

characteristics (Chatenoud et al. 1994; Descamps-Latscha et al. 1994; Girndt et al. 2001a; Pesanti 2001). Alternatively, loss of the kidney function can be blamed for chronic activation of the immune system. Mesangial cells in the Bowman apparatus have an important role in the removal of the immune complexes from blood (Jeneway 2004). Circulating excessive immune complexes seen in ESRD stimulate peripheral MO and induce their Mac development with concomitant increase in CD16 expression (Rus et al. 1983). This molecule is critical in scavenging complexes but it is seen in Mac-like cells (Jeneway 2004). Another mechanism of MO pathology in terminal renal disease is increased activation of the platelets seen in ESRD (Gawaz et al. 1994). Platelets contain several cytokines critical for MO differentiation and their activation can support the differentiation of MO into Mac. No study has directly addressed this question to date.

## Conclusion

Here, we have reviewed data to suggest profound aberrancy in the function of peripheral blood monocytes in ESRD. These aberrations may be related to impaired mechanisms of acquired immunity related to the deficit of DCs and pathological chronic activation of the MO. It would be interesting to conduct studies directly linking described MO aberrant characteristics to clinical outcome since there is some potential for therapeutic intervention.

## References


Abbott KC, Agodoa LY (2001) Etiology of bacterial septicemia in chronic dialysis patients in the United States. Clin Nephrol 56:124–131

Abbott KC, Agodoa LY (2002) Hospitalizations for bacterial endocarditis after initiation of chronic dialysis in the United States. Nephron 91:203–209

Abbott KC, Hypolite I, Tveit DJ et al (2001) Hospitalizations for fungal infections after initiation of chronic dialysis in the United States. Nephron 89:426–432

Allavena P, Piemonti L, Longoni D et al (1998) IL-10 prevents the differentiation of monocytes to dendritic cells but promotes their maturation to macrophages. Eur J Immunol 28:359–369

Alscher DM, Pauli-Magnus C, Kirchgessner J (2000) A new lactate-based, plasticizer-free, neutral peritoneal dialysis fluid provided in a two-compartment system: effect on peripheral leukocyte function. Nephron 86:62–69

Alscher DM, Bruckner A, Fritz P et al (2002) Metallothionein and dendritic cells in skin of end-stage renal disease patients not on dialysis, or on hemodialysis or peritoneal dialysis. Perit Dial Int 22:449–453

Auffray C, Sieweke MH, Geissmann F (2009) Blood monocytes: development, heterogeneity, and relationship with dendritic cells. Annu Rev Immunol 27:669–692

Berg KE, Ljungcrantz I, Andersson L et al (2012) Elevated CD14++CD16− monocytes predict cardiovascular events. Circ Cardiovasc Genet 5:122–131

Betjes MG, Tuk CW, Struijk DG et al (1993a) Antigen-presenting capacity of macrophages and dendritic cells in the peritoneal cavity of patients treated with peritoneal dialysis. Clin Exp Immunol 94:377–384

Betjes MG, Tuk CW, Struijk DG et al (1993b) Immuno-effector characteristics of peritoneal cells during CAPD treatment: a longitudinal study. Kidney Int 43:641–648

Bossola M, Luciani G, Giungi S et al (2010) Anorexia, fatigue and plasma interleukin-6 levels in chronic hemodialysis patients. Ren Fail 32:1049–1054

Brauner A, Hylander B, Lu Y (1998) Granulocyte stimulating factor in patients on peritoneal dialysis and LPS stimulated peripheral blood mononuclear cells. Inflammation 22:393–401

Calvano JE, Agnese DM, Um JY et al (2003) Modulation of the lipopolysaccharide receptor complex (CD14, TLR4, MD-2) and toll-like receptor 2 in systemic inflammatory response syndrome-positive patients with and without infection: relationship to tolerance. Shock 20:415–419

Cavaillon JM, Poignet JL, Fitting C et al (1992) Serum interleukin-6 in long-term hemodialyzed patients. Nephron 60:307–313

Chatenoud L, Jungers P, Descamps-Latscha B (1994) Immunological considerations of the uremic and dialyzed patient. Kidney Int Suppl 44:S92–S96

Choi HM, Woo YS, Kim MG et al (2011) Altered monocyte-derived dendritic cell function in patients on hemodialysis: a culprit for underlying impaired immune responses. Clin Exp Nephrol 15:546–553

De A, Laudanski K, Miller-Graziano CL (2003) Failure of monocytes of trauma patients to convert to immature dendritic cells is related to preferential macrophage-colony-stimulating factor-driven macrophage differentiation. J Immunol 170:6355–6362

Descamps-Latscha B, Herbelin A, Nguyen AT et al (1994) Immune system dysregulation in uremia. Semin Nephrol 14:253–260

Descamps-Latscha B, Herbelin A, Nguyen AT et al (1995) Balance between IL-1 beta, TNF-alpha, and their specific inhibitors in chronic renal failure and maintenance dialysis. Relationships with activation markers of T cells, B cells, and monocytes. J Immunol 154:882–892

Gawaz MP, Mujais SK, Schmidt B et al (1994) Platelet-leukocyte aggregation during hemodialysis. Kidney Int 46:489–495

Geissmann F, Auffray C, Palframan R et al (2008) Blood monocytes: distinct subsets, how they relate to dendritic cells, and their possible roles in the regulation of T-cell responses. Immunol Cell Biol 86:398–408

Girndt M, Sester U, Kaul H et al (1998) Production of proinflammatory and regulatory monokines in hemodialysis patients shown at a single-cell level. J Am Soc Nephrol 9:1689–1696

Girndt M, Sester M, Sester U et al (2001a) Defective expression of B7-2 (CD86) on monocytes of dialysis patients correlates to the uremia-associated immune defect. Kidney Int 59:1382–1389

Girndt M, Sester M, Sester U et al (2001b) Molecular aspects of T- and B-cell function in uremia. Kidney Int Suppl 78:S206–S211

Girndt M, Sester U, Sester M et al (2001c) The interleukin-10 promoter genotype determines clinical immune function in hemodialysis patients. Kidney Int 60:2385–2391

Gordon S, Taylor PR (2005) Monocyte and macrophage heterogeneity. Nat Rev Immunol 5:953–964

Hubel E, Kiefer T, Weber J et al (1991) In vivo effect of 1,25-dihydroxyvitamin D3 on phagocyte function in hemodialysis patients. Kidney Int 40:927–933

Jeneway C (2004) Immunobiology. Garland Science, New York

Joffre O, Nolte MA, Sporri R et al (2009) Inflammatory signals in dendritic cell activation and the induction of adaptive immunity. Immunol Rev 227:234–247

Kamalakannan D, Pai RM, Johnson LB et al (2007) Epidemiology and clinical outcomes of infective endocarditis in hemodialysis patients. Ann Thorac Surg 83:2081–2086

Kawanaka N, Nagake Y, Yamamura M et al (2002) Expression of Fc gamma receptor III (CD16) on monocytes during hemodialysis in patients with chronic renal failure. Nephron 90:64–71

Kimmel PL, Phillips TM, Simmens SJ et al (1998) Immunologic function and survival in hemodialysis patients. Kidney Int 54:236–244

Kimmel M, Alschner DM, Dunst R et al (2006) The role of microinflammation in the pathogenesis of uraemic pruritis in haemodialysis patients. Nephrol Dial Transplant 21:749–755

Kurz P, Kohler H, Meuer S et al (1986) Impaired cellular immune responses in chronic renal failure: evidence for a T cell defect. Kidney Int 29:1209–1214

Le Meur Y, Lorgeot V, Aldigier JC et al (1999) Whole blood production of monocytic cytokines (IL-1beta, IL-6, TNF-alpha, sIL-6R, IL-1Ra) in haemodialysed patients. Nephrol Dial Transplant 14:2420–2426

Lewis SL, Van Epps DE (1987) Neutrophil and monocyte alterations in chronic dialysis patients. Am J Kidney Dis 9:381–395

Libetta C, Rampino T, Dal Canton A (2001) Polarization of T-helper lymphocytes toward the Th2 phenotype in uremic patients. Am J Kidney Dis 38:286–295

Lim WH, Kireta S, Russ GR et al (2007) Uremia impairs blood dendritic cell function in hemodialysis patients. Kidney Int 71:1122–1131

Maisonneuve P, Agodoa L, Gellert R et al (1999) Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 354:93–99

Malaponte G, Bevelacqua V, Fatuzzo P et al (2002) IL-1beta, TNF-alpha and IL-6 release from monocytes in haemodialysis patients in relation to dialytic age. Nephrol Dial Transplant 17:1964–1970

Marchant A, Tielemans C, Husson C et al (1996) Cuprophane haemodialysis induces upregulation of LPS receptor (CD14) on monocytes: role of complement activation. Nephrol Dial Transplant 11:657–662

Memoli B, Postiglione L, Cianciaruso B et al (2000) Role of different dialysis membranes in the release of interleukin-6-soluble receptor in uremic patients. Kidney Int 58:417–424

Mettang T, Fritz P, Weber J et al (1993) Epidermal langerhans cells in uremic patients on hemodialysis or continuous ambulatory peritoneal dialysis. Nephron 65:278–283

Mettang T, Pauli-Magnus C, Alsher DM (2002) Uraemic pruritus–new perspectives and insights from recent trials. Nephrol Dial Transplant 17:1558–1563

Meuwese CL, Sneadal S, Halbesma N et al (2011) Trimestral variations of C-reactive protein, interleukin-6 and tumour necrosis factor-alpha are similarly associated with survival in haemodialysis patients. Nephrol Dial Transplant 26:1313–1318

Morita Y, Yamamura M, Kashihara N et al (1997) Increased production of interleukin-10 and inflammatory cytokines in blood monocytes of hemodialysis patients. Res Commun Mol Pathol Pharmacol 98:19–33

Nockher WA, Scherberich JE (1998) Expanded CD14+CD16+ monocyte subpopulation in patients with acute and chronic infections undergoing hemodialysis. Infect Immun 66:2782–2790

O'Byrne D, Devaraj S, Islam KN et al (2001) Low-density lipoprotein (LDL)-induced monocyte-endothelial cell adhesion, soluble cell adhesion molecules, and autoantibodies to oxidized-LDL in chronic renal failure patients on dialysis therapy. Metabolism 50:207–215

Ooi YM, Ooi BS (1983) Identification of a monocyte phagocytic defect in a subpopulation of patients with nephritis. Kidney Int 23:851–854

Ozdemir FN, Guz G, Kayatas M et al (1998) Tuberculosis remains an important factor in the morbidity and mortality of hemodialysis patients. Transplant Proc 30:846–847

Ozdemir FN, Guz G, Sezer S et al (2001) Atherosclerosis risk is higher in continuous ambulatory peritoneal dialysis patients than in hemodialysis patients. Artif Organs 25:448–452

Paczek L, Schaefer RM, Heidland A (1991) Dialysis membranes decrease immunoglobulin and interleukin-6 production by peripheral blood mononuclear cells in vitro. Nephrol Dial Transplant 6(Suppl 3):41–44

Palucka AK, Banchereau J (2006) Langerhans cells: daughters of monocytes. Nat Immunol 7:223–224

Papagianni A, Kalovoulos M, Kirmizis D et al (2003) Carotid atherosclerosis is associated with inflammation and endothelial cell adhesion molecules in chronic haemodialysis patients. Nephrol Dial Transplant 18:113–119

Papayianni A, Alexopoulos E, Giamalis P et al (2002) Circulating levels of ICAM-1, VCAM-1, and MCP-1 are increased in haemodialysis patients: association with inflammation, dyslipidaemia, and vascular events. Nephrol Dial Transplant 17:435–441

Pastores GM (1997) Gaucher's disease. Pathological features. Baillieres Clin Haematol 10:739–749

Perunicic-Pekovic G, Pljesa S, Rasic-Milutinovic Z et al (2008) Inflammatory cytokines and malnutrition as related to risk for cardiovascular disease in hemodialysis patients. Can J Physiol Pharmacol 86:205–209

Pesanti EL (2001) Immunologic defects and vaccination in patients with chronic renal failure. Infect Dis Clin North Am 15:813–832

Puig-Kroger A, Pello OM, Selgas R et al (2007) Peritoneal dialysis solutions inhibit the differentiation and maturation of human monocyte-derived dendritic cells: effect of lactate and glucose-degradation products. J Leukoc Biol 73:482–492

Rus HG, Cristea A, Gherman M et al (1983) Immunologic alterations associated with chronic hemodialysis. Med Interne 21:289–295

Saionji K, Ohsaka A (2001) Expansion of CD4+CD16+ blood monocytes in patients with chronic renal failure undergoing dialysis: possible involvement of macrophage colony-stimulating factor. Acta Haematol 105:21–26

Schauer S, Stein G, Suss J et al (1991) Phagocytosis activity of polymorphonuclear cells of normal persons and dialysis patients is influenced by different dialysis membranes. Nephrol Dial Transplant 6(Suppl 3):35–40

Sezer S, Ozdemir FN, Turan M et al (1998) Comparison of panel reactive antibody levels with clinical and laboratory parameters in end-stage renal disease patients. Transplant Proc 30:844–845

Sezer S, Ozdemir FN, Guz G et al (2000) Factors influencing response to hepatitis B virus vaccination in hemodialysis patients. Transplant Proc 32:607–608

Stefater JA 3rd, Ren S, Lang RA et al (2011) Metchnikoff's policemen: macrophages in development, homeostasis and regeneration. Trends Mol Med 17:743–752

Stewart-Phillips JL, Gagnon RF, Stranix B (1990) Macrophage secretory activity and atherosclerosis during chronic renal failure. Adv Perit Dial 6:224–229

Tacke F, Randolph GJ (2006) Migratory fate and differentiation of blood monocyte subsets. Immunobiology 211:609–618

Takahashi T, Kubota M, Nakamura T et al (2000) Interleukin-6 gene expression in peripheral blood mononuclear cells from patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis. Ren Fail 22:345–354

Vamvakas S, Bahner U, Heidland A (1998) Cancer in end-stage renal disease: potential factors involved -editorial. Am J Nephrol 18:89–95

Ventura MT, Di Corato R, Giuliano G et al (1998) Evaluation of monocyte chemotactic responsiveness in uraemic patients undergoing haemodialysis with different dialytic membranes. Cytobios 96:171–178

Weber C, Stummvoll HK, Passon S et al (1998) Monocyte activation and humoral immune response to endotoxins in patients receiving on-line hemodiafiltration therapy. Int J Artif Organs 21:335–340

Wu L, Vandenabeele S, Georgopoulos K (2001) Derivation of dendritic cells from myeloid and lymphoid precursors. Int Rev Immunol 20:117–135

Ziegler-Heitbrock HW (2000) Definition of human blood monocytes. J Leukoc Biol 67:603–606