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Impaired cellular immune function in patients with end-stage renal failure

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Patients with chronic renal failure are at high-risk for infectious complications, similar to patients with other types of acquired immune defects or those on immunosuppressive therapy. Secondary immune failure in uraemia is multi-faceted and is influenced by uraemic intoxication *per se*, by altered renal metabolism of immunologically active proteins and by specific effects of renal replacement therapy. Large interindividual variability points to the importance of individual factors. A high incidence of infection is found in uraemic patients and infections remain the second most frequent cause of death.

One specific problem is hepatitis B. Vaccination against hepatitis B is routinely performed in dialysis patients. Although effective in only 60–70% of patients, it helped to eliminate the threat of hepatitis B from dialysis centres. The response to hepatitis B vaccine proved to be a valid clinical index for individual immune reactivity in dialysis patients.

Cellular dysfunction: a defect of the antigen-presenting cell

Low response rates after vaccination against hepatitis B lead to several studies on antigen-specific immune activation in renal failure patients. Obviously, there are also alterations of antigen-unspecific immune mechanisms, e.g. phagocyte function, but these will not be discussed here. The original observation of reduced responses to hepatitis B vaccination [1] was complemented by documentation of hyporesponsiveness to other vaccines such as tetanus or diphtheria. Non response to vaccination is closely associated with an impaired proliferation of T-cells *in vitro* and a reduced production of the autocrine T-cell growth promoting cytokine interleukin-(IL-)2 [2,3]. Activation of helper T-cells is needed for both cellular and antibody responses to T-cell-dependent antigens such as those tested in the vaccination trials. Only a few antigens lead to T-cell independent production of antibodies by B-lymphocytes, among them highly polymeric bacterial antigens, for instance Pneumococcal vaccine. Vaccination responses to Pneumococcus vaccine are normal in renal failure patients. These findings focused interest on T-cell activation as a crucial step to explain defective antigen specific immune responses in patients with renal failure.

Lymphocyte numbers as well as the CD4/CD8 relation are slightly diminished in dialysis patients, but these findings cannot explain reduced T-cell function. Although functional data suggested a defect of the T-lymphocytes, cell behaviour was entirely normal when activated *in vitro* in the presence of antigen-presenting cells from healthy people [3]. Antigen-presenting cells give at least two essential signals for

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T-cell activation. The antigen specific first signal is mediated by the presentation of antigen-derived peptides on HLA class II molecules. It is accompanied by a second signal defining the quality of the T-cell reaction to the antigen, which can vary between apoptosis, anergy or activation. One major feature of the uraemic immune defect is reduced co-stimulation by antigen presenting cells.

T-cell response: amplitude reduction and functional deviation

Impaired proliferation and production of IL-2 by T-cells are markers of a reduced quantity of T-cell activation. Their close relations to the individual vaccination response indicate that they are also relevant *in vivo*. However, recent data show that not only the quantity but also the quality of T-cell activation is influenced by chronic renal failure. There is a functional dichotomy of T helper cell differentiation that can be characterized by the production of typical cytokines the pattern of which is closely related to its functional differentiation [4]. T helper 1 cells (Th1) are characterized by the production of interferon-γ. They strongly promote the activation of effector cells and the cellular immune reaction. In contrast, T helper 2 cells (Th2) are characterized by the production of IL-4 and provide signals important for the humoral immune response. The Th2 cells induce antibody production against T-cell-dependent antigens such as hepatitis B virus. In dialysis patients one finds not only a global reduction of T helper cell activation, but also preponderance of the Th1 cytokine pattern (Sester U, Sester M, Hauk M *et al.* T-cell activation follows Th1 rather than Th2 pattern in haemodialysis patients, submitted for publication). This may serve as an additional explanation for the impaired humoral response to T-cell dependent vaccines in renal failure patients.

The Th2 bias may also be relevant for the clinical course of several autoimmune diseases with renal involvement. It is well known that disease activity greatly diminishes or even ceases in patients with systemic lupus erythematodes once they reach end-stage renal failure. In contrast, patients with Wegener's granulomatosis often continue to require immunosuppressive treatment on dialysis. Studies are now under way to examine whether the Th1 deviation in end-stage renal failure limits activity of the Th2-associated systemic lupus, but not of Wegener's disease which is characterized by Th1 cells activation.

Monocytes in uraemia: defect in co-stimulation and chronic inflammation

Reduced activation of T helper cells in renal failure patients is caused by alterations of the antigen-presenting cells (Figure 1). In-vitro studies of these antigen-presenting cells can readily be performed using monocytes from peripheral blood which are easily accessible. Blood differential counts show a moderate monocytosis. The expression of HLA class II molecules is not different from healthy controls. In contrast we found a significant reduction in the expression of CD86 (B7–2), one of the most important co-stimulatory molecules for the activation of T helper cells, on freshly isolated monocytes (Girndt M, Sester U, Kaul H *et al.* Analysis of the expression of B7-molecules on monocytes of patients with chronic renal failure, submitted for publication). This leads to a reduction in the relation between secondary (CD86) and primary (HLA class II) signal for T-cell activation.

Another characteristic feature of monocytes from renal failure patients is the production of high levels of proinflammatory cytokines such as IL-1β, IL-6 or tumour necrosis factor alpha (TNF-α) [5,6]. It has therefore been proposed that uraemia and haemodialysis are chronic inflammatory states. In the early days of dialysis such proinflammatory activation led to typical side effects, e.g. hypotension or fever. With the improvement of therapeutic techniques such clinically

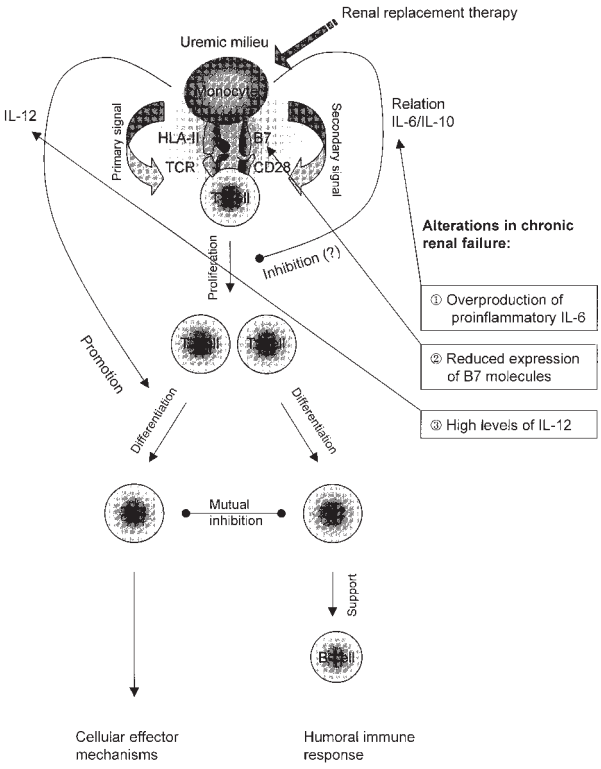

Fig. 1. T-cell activation and differentiation in response to monocyte antigen presentation and co-stimulatory signalling in chronic renal failure. Primary signalling from monocytes to T-cells together with B7 induced co-stimulation lead to T-cell activation and proliferation. Impaired signalling through the B7-CD28 pathway reduces the activation amplitude that is probably further influenced by the overproduction of proinflammatory cytokines like IL-6. Differentiation of T-cells for effector function is strongly influenced by IL-12, a cytokine that monocytes in renal failure patients produce at high levels. Thereby, the low-amplitude T-cell response is biased towards a Th1 differentiation. Thus antibody responses are even more impaired than cellular mechanisms in chronic renal failure.

manifest reactions became infrequent. Today, the interest focuses on potential long-term effects of inflammation, e.g. amyloidosis, progressive atherosclerosis and immune failure. The levels of IL-6 and its counter regulatory factor IL-10 are strongly correlated with the individual immune response [7] (Figure 1).

Inflammatory activation of monocytes is found in patients with compensated chronic renal failure who are not yet on dialysis. This indicates that uraemia *per se* and the altered metabolism of immunologically active proteins are important for its pathogenesis. Dialysis treatment further enhances the production of cytokines. Both cellular and cytokine alterations have been known for several years, but it has been only recently that the relation between these phenomena could be shown. Excessive production of IL-6 as a prototype of proinflammatory factors is associated with non response to hepatitis B vaccination and impaired T-cell activation [7]. Some patients are able to limit the uraemia-induced overproduction of IL-6 by upregulation of the counter regulatory factor IL-10. This first link between cytokines and cellular reaction was supported by the finding that monocytes from dialysis patients also produce increased amounts of the cytokine IL-12 (Sester U, Sester M, Hauk M *et al.* T-cell activation follows Th1 rather than Th2 pattern in haemodialysis patients, submitted for publication). This factor belongs to the family of proinflammatory cytokines such as IL-6, but it has additional effects on T-cell activation. It is one of the strongest determinants of T helper cell differentiation and drives T helper cell responses towards the Th1 cytokine pattern.

Renal replacement therapy: influences on immune function

On the background of uraemia-induced inflammatory activation of monocytes, dialysis therapy causes additional abnormalities. It activates complement and leads to further induction of cytokines such as IL-6 and TNF-α. Many studies use these factors to characterize the biocompatibility of dialyser membranes [8,9]. Although induction of cytokine production by blood membrane contact has been well documented, rather low levels of cytokines are found in cells harvested from the circulating blood of the patient during dialysis sessions. This observation is explained by the adhesion of activated monocytes to capillary endothelium [10]. Complement activation at the dialyser membrane activates monocytes. Subsequently they upregulate adhesion molecules and adhere to the endothelium. The number of circulating monocytes decreases dramatically during the first 20 min of a treatment session. Only cells with a low degree of activation and low production of IL-6 remain in circulation [11]. For a few hours the activated cells move from circulation into the capillary system. The potential consequences of this phenomenon are not yet known. One possibility could be promotion of atherosclerosis, because monocytes infiltrate early atherosclerotic lesions and are transformed into foam cells. It is tempting to speculate that inflammatory activation of these cells promotes progression of active atherosclerotic lesions.

Preliminary data indicate that the impairment of expression of the co-stimulatory molecule CD86 is modulated by the dose of dialysis. While the defect was detected in a group of chronic dialysis patients with a low dialysis dose according to current guidelines (mean Kt/V 0.82), it was absent in patients on high-dose treatment (mean Kt/V 1.16). The defect could also be shown in peritoneal dialysis patients in whom we did not observe the excessive production of proinflammatory cytokines.

Summary and perspective: a curable defect?

Immune alterations of chronic renal failure are the result of numerous influences by uraemia and its treatment.

(i) A defect in the co-stimulatory function of antigen-presenting cells is pathogenetically linked to the uraemic state. Its substrate is the CD86 molecule on monocytes.
(ii) Monocytes exhibit inflammatory activation and this is caused by uraemia *per se* and by renal replacement therapy.
(iii) The inflammatory changes involve IL-12 that shifts the globally reduced activation of T helper cells towards the Th1 function. This causes further deterioration of the antibody response to vaccination antigens.
(iv) The individual capacity to upregulate the counter regulatory molecule IL-10 determines, at least in part, the patient's immune competence.

Several strategies are currently under evaluation to influence the immune alterations therapeutically. High-dose haemodialysis therapy seems to improve those aspects that are directly related to uraemic intoxication. Improvement of dialyser biocompatibility has already been shown to influence proinflammatory activation. New membranes may provide active reduction of inflammatory factors, e.g. by coating of surfaces with anti-inflammatory agents such as vitamin E [12]. Supplementation of IL-10 in those patients who cannot up regulate this factor might be a promising approach to further normalize the immune defect.

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