Cell mediated immunity in uremia

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In renal insufficiency lymphopenia is common and is not improved by hemodialysis. The lymphopenia of uremic and of hemodialyzed patients affects both B and T cells, although B cells number appear to be consistently more depressed [1, 2]. In patients receiving chronic dialysis Revillard et al [3] found that T cells subsets bearing FCμ receptor to be particularly depressed.

In chronic hemodialyzed patients natural killer cells (NK), a lymphocyte subset are depressed [4]. Previous studies have shown that NK function does not improve with chronic hemodialysis and in fact it progressively worsens [4]. Recent studies performed in our laboratories strongly suggest that certain hemodialysis membranes may adversely affect NK function (see below).

Cell mediated responses to protein antigens are decreased in uremia [5, 6]. The blastogenic response of uremic lymphocytes to protein antigens and to plant lectins are often depressed. The response to particular antigens such as in the mixed lymphocyte culture (MLC) is depressed in a great majority of uremic patients [7, 8]. The depressed cellular immunity of uremia appears to be due to both cellular as well extracellular (uremic environment) factors [9].

In chronic renal insufficiency there is a decreased reactivity to common antigens such as mumps, trichophyton and candida [10]. The cutaneous anergy of patients with chronic renal failure very seldom improves with chronic hemodialysis and in some patients it in fact worsens [11]. Several studies have been unable to find a relationship between depressed delayed hypersensitivity and lymphopenia [12]. Since local coagulation appears necessary for a well developed delayed cutaneous reaction, determination of these reactions in heparinized patients on hemodialysis may yield false negative results [13]. The function of lymphocytes has been studied *in vitro* in both dialyzed and non dialyzed chronic renal insufficiency patients. The depressed *in vitro* response of lymphocytes studies has been attributed to the lymphocytes as well as to circulating factors present in uremic serum. Many of the factors present in uremic serum are non-dialyzable and that explains the reason why few of the *in vitro* abnormalities of uremic lymphocytes improve with hemodialysis [9]. Peritoneal dialysis has been reported to decrease some of the inhibitory effects of uremic serum [14]. Experimentally the spleen cells of uremic rats have decreased GVH reaction which appears to be due to the activity of suppressor monocytes [15]. Similarly it would appear that the decrease MLC response is in part due to suppressive monocytes [16]. However, other plasma factors also appear to play an important role. Recent studies performed by Raska et al [17-19] have indicated that the immunosuppressive factors present in uremic serum may belong to a group of lipoproteins which have immunoregulatory properties. Indeed, VLDL's present in uremic serum appear to have strong immunosuppressive properties which may explain the depressed MLC and GVH reactivity. Their exact nature as well as the mechanism of action of these lipoproteins is unclear but they appear to have a powerful immunoregulatory effect upon T cells [20]. However it is unlikely that these abnormalities in lipoproteins may explain all the immune disturbances present in uremia since other factors equally as important may also play a role. For instance zinc as well as vitamin B_6 deficiency have also been found to be important in the altered immune function of uremic patients [21, 22]. Recently the role played by «middle molecules» such as methyl guanidine and guanidinosuccinic acid in the immunosuppression of uremia is believed to be less important [23, 24].

Patients undergoing chronic hemodialysis have an increased incidence of hepatitis B infection [9]. In addition, those patients who become infected with the virus have a high tendency of becoming chronic carriers [9]. Immediately after transplantation chronically dialyzed patients have a high susceptibility to acquire severe CMV infections, particularly those patients who have been treated with ALG and Immuran [9]. Tuberculosis is not common in regularly dialyzed patients. However, in those instances in which patients have acquired this infection it appears to have been unusually severe and life threatening [25-27].

Patients with chronic renal failure receiving regular hemodialysis have been found to have an increased incidence of malignancies. Different from renal transplant patients who have an increase in lymphoreticular malignancies, hemodialysis patients have a 3 fold increase in non renal cancers and a 7 fold increments in renal carcinomas [28-30]. The latter appear

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to arise from cystic changes which frequently occur in end stage kidneys of regularly hemodialyzed patients [30]. The reason for the increased tendency to malignancies in this population is unclear. However a deficient immune surveillance appears to be important. NK cells and ADCC are felt to be an important part in the body's natural immune surveillance against tumors and certain type of infections. Uremic serum has been found to be partially inhibitory of both NK and ADCC activity. Bender et al. found that NK activity seldom improved with chronic hemodialysis and in some patients it became worse [4]. These findings prompted us to develop an *in vitro* model to more precisely define the effects of hemodialysis on human peripheral blood PBL NK activity.

We perfused fresh whole blood through dialyzers in order to study the effect of hemodialysis membranes upon lymphocyte function. In blood perfused through dialyzers we studied peripheral lymphocyte populations (PBL) and found that certain dialysis membranes negatively affected NK function. The effect of these membranes upon NK function appeared independent of activation of the complement system [5, 31] and also independent of the generation of inhibitory prostaglandins by monocytes. The effect of these membranes upon NK cell activity was reversible since the decrease of NK activity of PBL exposed to these membranes could be restored by exposing PBL to interferon [5, 31]. Of interest is that other dialysis membranes such as those made with polycarbonate did not have a negative effect upon NK cells. Cellulose acetate membranes had an intermediate effect between cuprophan and polycarbonate membranes [5, 31].

The effect of cuprophan upon NK cell was quantitative as well as qualitative. Perfusion of whole blood through dialyzers provided with this type of membranes resulted in a quantitative decrease in NK cells probably by adhesion of the cells to the membrane. In addition, those cells which were not removed had a decrease in many of their intrinsic functions such as decreased binding to NK target, decrease maximum velocity etc. Preliminary studies performed *in vivo* in patients receiving regular hemodialysis with either cuprophan or polycarbonate membranes have confirmed that progressive NK dysfunction is observed in patients dialyzed with cuprophan and that after switching the same patients to polycarbonate membranes NK cells activity improves [32].

Thus, specific interaction between hemodialysis membranes and lymphocytes may explain, at least in part, some of the immune abnormalities observed in uremia as well as the morbidity due to infections or neoplasms observed in uremic patients. It is possible that future dialysis membranes may be less active in inducing depression of cellular immunity and consequently the immune surveillance of these patients may be improved.

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