MECHANISMS AND CONSEQUENCES OF COMPLEMENT ACTIVATION DURING HEMODIALYSIS

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Activation of the complement system and secondary leukocyte activation mediate, both directly and indirectly, the acute and chronic effects resulting from immunological bioincompatibility of extracorporeal circuits. This manuscript briefly reviews the mechanisms and consequences of complement activation during hemodialysis. It focuses on recent studies from our laboratory suggesting a role for specific antibodies in the initiation of alternative pathway activation by cellulosic membranes, and indicating that circulating monocytes are stimulated to produce Interleukin-1 (IL-1) in vivo during bioincompatible hemodialysis.

COMPLEMENT ACTIVATION DURING HEMODIALYSIS

Complement activation invariably occurs during hemodialysis with first use cellulosic or Cuprophane hollow fiber dialyzers (Chenoweth et al., 1983a; Hakim et al., 1984). Activation may be quantitated by measuring the plasma concentration of the C3a/C3adesArg antigen in the venous line of the hemodialyzer. During dialysis with Cuprophane membranes, the plasma concentration of C3a antigen rapidly increases during the first 15 min of dialysis to reach 2000-8000 ng/ml, which represents approximately 3 to 10% cleavage of circulating C3. After 15-20 min, the C3a/C3adesArg antigen concentration decreases and returns to predialysis values at the end of the dialysis session. The decrease in C3a concentration partly reflects the catabolism of the molecule and its transmembrane passage (Smeby et al., 1986). It also reflects a progressive loss in the activating capacity of Cuprophane during the first half hour of dialysis, which is probably secondary to passivation of the membrane with serum proteins rather than to saturation of available C3b-binding sites by covalently bound C3b molecules. Used Cuprophane membranes are coated with C3 fragments which had first been suggested to be ester-linked C3b molecules (Chenoweth, 1984). Recent studies have characterized these fragments as mostly consisting of non-covalently bound C3c (Cheung et al., 1989). Passivation of membranes results in
(Cheung et al., 1989). Passivation of membranes results in decreased complement activation with reused membranes as compared with first-use membranes (Hakim and Lowrie, 1980; Chenoweth et al., 1983b). Complement activation with cellulosic membranes occurs through the alternative pathway as shown by an increase in the plasma concentration of the Ba fragment of Factor B and the lack of significant increase in the concentration of C4a. The rapid rate of C3 cleavage occurring, following the contact of blood with cellulosic membranes is directly related to the high density of sites on the membrane on which bound C3b is relatively protected from H and I and may efficiently interact with Factors B and D to form surface-bound amplification C3 convertase sites (Kazatchkine and Nydegger, 1982). Thus, in an in vitro model, we have shown that C3b bound to Sephadex, a structural analog of Cuprophane, is relatively resistant to inactivation by H and I in whole serum (Carreno et al., 1988a). In addition, the high density of OH-groups that are available for C3b binding on unpassivated membranes, increases the chances for a newly generated C3b molecule to bind in close vicinity of a surface-bound C3 convertase complex in order to form a C5-cleaving enzyme. Thus, the relative efficiency of C5 cleavage relative to that of C3 cleavage on Sephadex is much higher than in the case of other activators such as immune complexes (Bhakdi et al., 1988). This may explain why significant amounts of C5a may be generated upon complement activation in extracorporeal circuits although relatively small amounts of C3 are being cleaved.

The activating capacity of polysaccharides may be influenced by the length of the sugar chain to which C3b has covalently bound (Pangburn, 1987) and by chemical substitution of oligosaccharidic units of the polymer. Substitution of Sephadex with carboxymethyl groups or carboxymethyl sulfonates suppresses the alternative pathway activating capacity of the polysaccharide. The inability of substituted Sephadex to activate complement is due to the formation of stable ternary complexes between H, bound C3b and carboxymethyl groups on the substituted polymer (Carreno et al., 1989). A similar mechanism is likely to be operative in the case of cellulosic membranes on which hydroxyl groups have been modified by addition of a diethylaminoethyl group (Hemophan®).

In contrast to cellulosic membranes, polyacrylonitrile and polysulfone membranes induce no or very mild C3a generation. The membranes induce little or no C3 cleavage upon incubation with normal human serum in vitro and adsorb the small amounts of C3a that may have been generated. Rates of C3 cleavage are in any case insufficient to induce the cleavage of C5 and generation of C5a.

An early observation made in patients dialyzed with cellulosic membranes was that the amount of C3a generated could differ considerably between patients dialyzed with the same type of membrane under similar conditions (Hakim et al., 1984). High rates of C3 cleavage were suggested to be associated with an increased risk of occurrence of wheezing, chest tightness and dyspnea ("First-use" syndrome) within the first 30 minutes of dialysis. The serum of patients who