The Biology and Pathophysiology of Complement Receptors*

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Abstract. Activation of the complement cascade leads to the generation of multiple breakdown products which bind on to specific cellular receptors and regulate their function. In this review, we describe the biochemical and physiological features of the 7 known complement receptors. Four of them (complement receptors 1, 2, and 3 and receptors for C3a) bind cleavage fragments of the third component of the complement and three have specificity for C1q, factor H and C5a. In patients with systemic lupus erythematosus, a unique human autoimmune disorder, the numbers of CR1 on the surface of the red blood cells are decreased; in this review we discuss the implications in the pathogenesis of SLE. A number of patients have now been reported whose cells lack CR3 from their surface; this deficiency is associated with a number of immune cell dysfunctions which are discussed in detail. Finally, we discuss aberrations in the expression of complement receptors in certain human leukemic cells.

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Introduction

Complement, consisting of 18 proteins in plasma and in extravascular fluids, is an important component of host defense against foreign substances. Activation of the complement system leads to the generation of numerous cleavage fragments which interact with specific receptors of the host cells and regulate their functions. These ligand-receptor interactions produce cellular responses that can enhance inflammatory reactions or modulate host defense reactions. Currently, seven receptors for complement have been identified, four of which (CR1, CR2, CR3, and C3a) have specificity for the various cleavage fragments of the third component of complement, and three react with C1q, factor H, or C5a (Table I). This review considers the chemistry and biological activities of these complement receptors and their expression in several human diseases.

The Structure and Function of Complement Receptors

2.1. C3 Receptors

2.1.1. The Ligand. C3 (mw of 185,000) is the most abundant complement protein in serum (1.2 μg/ml). It comprises of two polypeptide chains, α (120,000) and β (75,000) (Figure 1), linked by disulfide bonds and non-covalent forces. Approximately 2% of its total weight is carbohydrate made up of N-linked high-mannose-type oligosaccharides (1,2). Cleavage of C3 by the classical (C4b,2a) or alternative (C3b,Bb) pathway convertases at an Arg-Ser peptide bond between residues 77 and 78 of the α-chain produces the C3a and C3b fragments. C3a is a 9,000 mw polypeptide representing the N-terminus of the intact α-chain of C3, whereas C3b is composed of the α'- and β-chains. Following cleavage of C3 to C3a and C3b, C3b undergoes a rapid conformational change associated with exposure and activation of a thioester bond located in positions 987-991 of the α-chain of C3 (reviewed in References 3 an 4.q.v.). The activated thioester mediates the covalent binding of C3b to hydroxyl or amino groups of cell surfaces, complex polysaccharides, or immune aggregates by
DEGRADATION OF C3

![Diagram of C3 degradation](image)

Figure 1. Schematic representation of the physiologic degradation of the C3 molecule.

torming an ester or amide bond. Alternatively, the thioester bond can be hydrolyzed by water, after which it is unreactive. Unlike C3, the C3b fragment expresses multiple binding sites (reviewed in reference 5, q.v.) for other complement proteins including factors I (6), H (7-9), and B (10,11), properdin (12, 13), and C5 (14). Binding of factor B to C3b makes it susceptible to factor D cleavage, generating the C3a, Bb convertase, which is then stabilized by properdin. Binding of factor H to C3b accelerates the decay/dissociation of C3 convertase and modulates C3b, which then becomes susceptible to factor I degradation. Many of the activities ascribed to surface C3b are regulated by the proteolytic fragmentation of the C3b molecule by factor I in the presence of H or CR1 as cofactors (15-18). Following binding of H to C3b, Factor I cleaves the α-chain at an Arg-Ser peptide bond between amino acid positions 1298-1299, generating 62,500 mw N-terminal and 41,500 mw C-terminal fragments. A second cleavage of the 41,500 fragment between positions 1281 and 1282 generates 39,500 mw and 2,000 mw N-terminal fragments. The generated fragment, termed iC3b, has similar molecular weight to C3b since the units of the 62,500 and 39,500 mw β-chain are disulfide bonded. In the presence of CR1, and with slower rate in presence of factor H, factor I makes a third cleavage at an Arg-Asn peptide bond between position 932 and 933 of the α-chain, generating two dissociable molecules, C3dg and C3c (16, 17, 19, 20). Further degradation of C3dg by plasmin, elastase, or trypsin, results in C3d and C3g (16,20). Recently, kallikrein has been shown to cleave iC3b to C3c and C3dk, a fragment nine more amino acids toward the N-terminus of C3dg (21).

2.1.2. C3a Receptor. Despite the ability of C3a to induce several functions in various cell types, no definitive biochemical studies have been performed to prove which cells it binds to or the nature of its receptor. In fact, the existence of a C3a receptor is mostly based on biological responses elicited by purified C3a. The C3a receptor appears to react with both C3a and C4a but not C5a (received in Reference 22, q.v.). The ensuing responses include the secretion of lysosomal enzymes by neutrophils, release of histamine from mast cells (23, 24), neutrophils, eosinophils, and basophils (24), and release of thrombokine A from macrophages after stimulating the cyclo-oxygenase pathway of arachidonic acid metabolism (25). In addition, C3a has been found to inhibit certain lymphocyte functions including mitogenesis caused by pokeweed mitogen, concanavalin α, and phytohemagglutinin as well as polyclonal and specific antibody production (26). The C3a peptide also increases vascular permeability and induces contraction of smooth muscle (22).

2.1.3. C3b Receptor (CRI). Nelson discovered the C3b receptor (CRI) in 1953, and showed that antibody coated bacteria treated with complement had the ability to adhere to human erythrocytes (27). The immune adherence receptor of erythrocytes was later found to be specific for C3b, iC3b, or C4b (20, 29), and present on other cell types including monocytes, macrophages, and some T-lymphocytes, eosinophils, mast cells, and glomerular podocytes (30-32). Fearon first isolated the C3b receptor from human erythrocytes in 1979, and established it as a glycoprotein of mw 205,000-250,000 (33, 34). Four genetic forms of the human C3b receptor have been identified by molecular weight differences: 1) the more common allele, A, with a mw of 190,000 has a gene frequency of 0.83, the less common, B, whose mw is 220,000 has a frequency of 0.16, and the two rarer alleles, C and D, have mws of 160,000 and 250,000 with gene frequencies of 0.01 and 0.001, respectively (35, 36).

The number of C3b receptor on cells varies among the different cell types; erythrocytes have 500-600 receptors per cell, monocytes 30,000, lymphocytes 30,000-40,000, and neutrophils 5,000-38,000, depending on the purification conditions (34, 37, 38). Experiments with dimeric C3b revealed that the C3b receptor on erythrocytes, neutrophils, B-lymphocytes, and monocytes has an association constant for this ligand of 2.65 x 10^7 M^-1 (34, 37). The large number of functions involving the C3b receptor include a regulating complement activation by increasing the decay/dissociation of classical (39) and alternative pathway convertases (33), (b) acting as a cofactor for factor I cleavage of C3b and C4b (39,
### Table I. Types of complement receptors.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Specificity</th>
<th>Structure</th>
<th>Cell Type</th>
<th>Monoclonal Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1q</td>
<td>C1q, collagen like region with 70K chains</td>
<td>Granulocytes, Lymphocytes, Platelets, Fibroblasts, Mast cells, Granulocytes, Monocytes</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>C3b</td>
<td>C3b, C4b</td>
<td>—</td>
<td>B/T Lymphocytes, Neutrophils, Glomerular podocytes</td>
<td>C3RTo5, E11, 57H</td>
</tr>
<tr>
<td>CR1</td>
<td>C4b, C3b, C2b, C3c</td>
<td>4 allotypes 100K, 190K, 220K, 250k</td>
<td>Erythrocytes, Eosinophils, Monocytes, Macrophages</td>
<td>31D, 44D</td>
</tr>
<tr>
<td>CR2</td>
<td>C3b, C3dgC3d</td>
<td>145K</td>
<td>B-lymphocytes</td>
<td>anti-B2 HB-5, OKB7, anti-Mac1, anti-Mo1, anti-Leu 15</td>
</tr>
<tr>
<td>CR3</td>
<td>C3b</td>
<td>165K α-chain, 95K β-chain</td>
<td>Same as CR1 except erythrocytes</td>
<td>OKM1, OKM9, OKM10, MN41</td>
</tr>
<tr>
<td>C5aR</td>
<td>C5aC5ades-arg48K</td>
<td>Mast cells, Granulocytes, Monocytes, Macrophages, B-lymphocytes, Granulocytes, Monocytes</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>H₈</td>
<td>Factor H</td>
<td>100K α-chain, 50K β-chain</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

40), (c) processing of immune complexes, possibly by directing the traffic of immune complexes (41-43), and (d) mediating several biological responses (Table II reviewed in References 30 - 32, q.v.).

### 2.1.4. C3d Receptor (CR2). The C3d receptor expressed on B lymphocytes was identified in 1973 by three different groups simultaneously (44-46). It is now established that the intact C3d receptor is a single chain glycoprotein of mw 140,000 (47, 48). The C3d receptor, as recently shown (49-50), also serves as the receptor for Epstein-Barr virus (EBV). Additionally, the 72,000 mw fragment purified earlier (51) is now considered as the part of CR2 that binds C3d, but not EBV (32). Studies on the specificity of this receptor have shown that it bind iC3b, C3dg, and C3d fragments of C3. Recently, using C3d fragments and overlapping synthetic peptides covering amino acid residues 1209-1236 of the C3 sequence showed that the receptor binding site in C3d is located between residues 1227-1232 of the C3 sequence (52, 53).

### Table II. Cellular responses elicited by C3 fragments.

<table>
<thead>
<tr>
<th>Fragment</th>
<th>Cell Type</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3a</td>
<td>Monocytes</td>
<td>Stimulation of thromboxane A₂ and prostaglandin production</td>
</tr>
<tr>
<td></td>
<td>Mast Cells Basophils</td>
<td>Stimulation of histamine release</td>
</tr>
<tr>
<td></td>
<td>Eosinophils Neutrophils</td>
<td>Stimulation of lysosomal enzyme release</td>
</tr>
<tr>
<td></td>
<td>T-cells</td>
<td>Inhibition of both polyclonal and specific antibody responses</td>
</tr>
<tr>
<td></td>
<td>Macrophages</td>
<td>Stimulation of thromboxane B₂ release</td>
</tr>
<tr>
<td>C3b</td>
<td>Monocytes</td>
<td>Enhancement of pinocytosis Simulation of prostaglandin E release En-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Macrophages</td>
<td>Stimulation of prostaglandin E and thromboxane B₂ production and release</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Promotion of phagocytosis by elicited and activated macrophages</td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
<td>Release of neutrophil chemotactic factor and galactosidase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enhancement of phagocytosis, Release of histaminase Induction of respir-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3b/C3d</td>
<td>Lymphocytes</td>
<td>Enhancement of ADCC Inhibition of B-cell differentiation</td>
</tr>
<tr>
<td></td>
<td>Basophils</td>
<td>Release of macrophage chemotactic factor</td>
</tr>
<tr>
<td></td>
<td>mast cells</td>
<td>Enhancement of IgE induced histamine release</td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
<td>Enhancement of ATP induced histamine release</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Release of granule-associated enzymes</td>
</tr>
<tr>
<td></td>
<td>iC3b</td>
<td>Same as C3b and C3d Inhibition of blastogenesis triggered by PMN, MLR or</td>
</tr>
<tr>
<td></td>
<td>C3dg/C3d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enhancement of allogegenic CML responses</td>
</tr>
<tr>
<td>C3e/C3dK</td>
<td>Neutrophils</td>
<td>Stimulation of B-lymphocytes to enter from G1 phase to S</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stimulation of granule-associated enzyme release</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Release of leukocytes from bone marrow</td>
</tr>
</tbody>
</table>
Although the C3d receptor is predominantly expressed on B-lymphocytes, some reports have described its presence on K-cells (54, 55) and monocytes (56). In a recent study using the monoclonal antibody HB-5 it has been shown the human thymocytes but not peripheral T cells express the C3d receptor (Lambiris and Tsoukas submitted for publication). The C3d receptor is involved in the regulation of lymphocyte proliferative responses (Table II). In 1982, Lambiris et al (57) noted that F(ab’)2 anti-CR2 and soluble C3d fragments inhibited lymphocyte proliferation induced by the mixed lymphocyte reaction or tetanus toxoid. Later experiments showed that the C3dk fragment of C3 suppressed mitogen-induced B-lymphocyte growth and interleukin 2 synthesis in mixed lymphocyte culture (21, 58). Recently, in synchronized murine B-cells, crosslinked C3d replaced α-factor essential for the cells to progress from growth phase G1 to S. In contrast, soluble C3d inhibited the action of these factors (59).

2.1.5. iC3b receptor (CR3). The iC3b receptor, known as CR3, is a member of family whose three membrane proteins have identical 95,000 β-chains and distinct α-chains. The α-chain of CR3 is 165,000 in mw and the α chain of the two other molecules, LFA1 and P150-95, are 185,000 and 150,000 mw, respectively (60-62). The iC3b receptor is found on cell types such as monocytes, neutrophils, macrophages, eosinophils, and K-cells (30,32,63). The receptor is specific for the iC3b fragment of C3 (29, 63). The major biological role of CR3 is the promotion of either antibody dependent or independent effect or cell functions (Table II). For example, the binding of iC3b to CR3 on the surface of K-cells and polymorphonuclear leukocytes or monocytes enhances the antibody dependent cytotoxicity of erythrocytes (54, 55)) or tumor cells (64) and also enhances IgG dependent phagocytosis of microorganisms (65-67). CR3 mediated antibody independent phagocytosis by mononuclear cells is regulated by cellular differentiation and humoral components. Among the latter are lymphokine (68), fibronectin, and the amyloid P component (69).

2.2 C5d Receptor. C5 is an N-terminus C5 fragment of mw 11.40 released from C5 after cleavage of Arg 74-Leu 75 by the classical or alternative pathway C5 convertases [C4b, 2a3b and C3b(n)Bb] received in Reference 22, q.v.). Complete chemical analysis of human C5a has identified it as a 74 residue polypeptide of 8,400 mw carrying a complex type oligosaccharide moiety of 3,000 mw. In contrast to C3a and C4a, which lose their biological activity upon removal of C-terminal arginines by serum carboxypeptidase N, C5a retains a significant degree of its capacity to interact with the C5a receptor and stimulate responses. Receptors for C5a are present in mast cells, basophils, neutrophils, eosinophils, monocytes, and macrophages (24). Specificity studies with C5a derivatives and analogues indicate that C5a contains two binding sites for its receptor, one within the 69 N-terminal residues reactive with a recognition domain and a second

<p>| Table III. C5a Receptor functions. |</p>
<table>
<thead>
<tr>
<th>Ligand</th>
<th>Cell Type</th>
<th>Cellular Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5a/C5a des Arg</td>
<td>Monocytes</td>
<td>Chemotaxis</td>
</tr>
<tr>
<td></td>
<td>Macrophages</td>
<td>Induction of leukotriene synthesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enhancement of polyclonal and specific antibody responses</td>
</tr>
<tr>
<td>Mast cells</td>
<td></td>
<td>Stimulation of IL-1 release</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction of leukotriene synthesis</td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td>Induction of vasoactive amine release</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enhancement of C3b receptor expression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction of cell adherence and aggregation reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction of c-glucoroni- dase and myeloperoxidase release</td>
</tr>
</tbody>
</table>

<p>| Table IV. Factor H Receptor Functions |</p>
<table>
<thead>
<tr>
<th>Ligand</th>
<th>Cell Type</th>
<th>Cell responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymeric forms of Factor H</td>
<td>B-Lymphocytes</td>
<td>Increases Factor I secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td></td>
<td>Induces respiratory burst</td>
</tr>
<tr>
<td>Macrophages</td>
<td></td>
<td>Induces release of prostaglandin E and thromboxane</td>
</tr>
</tbody>
</table>

composed of the five C-terminal residues and reactive with an “activation” domain on C5 (70). Preliminary studies on the structure of C5a receptor of neutrophils using crosslinking reagents have shown that its molecular wight is approximately 48,000 (71). Several cellular functions have been attributed to the binding of C5a to its receptor (Table III). For instance, the binding of C5 to mast cells and basophils has long been known to induce release of their granules and histamine (24). In addition, recent results have shown that C5a induces the release of leukotrienes from mast cells and macrophages, thereby broadening the potential pathobiologic consequences of complement activation (72,73). The binding of C5a to neutrophils induces several cellular reactions including: chemotaxis, cell adherence, aggregation specific granule release, superoxide production, and enhanced expression of C3b receptors (38,74-76). Moreover, recent studies suggest that
C5a enhances both polyclonal and specific responses in vitro by stimulating release of interleukin-1 from macrophages 926,77), thus indicating an immunoregulatory role of the C5a receptor.

2.3. Factor H Receptor. Factor H is a 150,000 mw glycoprotein consisting of a single polypeptide chain and present in serum at a concentration of about 300 μg/ml. Two different forms of factor H have been recently isolated from serum, using hydrophobic affinity chromatography, and found to differ distinctly in their ability to aggregate (79). The very important regulatory role factor H plays in the alternative pathway, is binding to the C3b molecule and acting as antagonist for the interaction of factor B with C3b. This can lead either to the inhibition of the preformed enzyme (C3b,Bb) or its formation. In addition, factor H acts as a cofactor for the cleavage of C3b by factor I. Recently the binding sites on C3b for H and on H for C3b have been localized in C3d and a 38,000 N-terminal H fragment, respectively (8, 79, 80). Receptors for factor H have been found so far on B-lymphocytes, neutrophils, and monocytes (81-83). To date, the nature of ligands that bind to the H receptors is unclear, but they may be polymeric. The use of antibody specific for the idiotype of anti-H antibody and affinity chromatography on an H-agarose column showed that the lymphocytes' H receptor consists of two polypeptides of 100,000 and 50,000 mw (82). Among the cellular functions attributed to the binding of H to its receptor (Table IV) is the release of endogenous factor I from Lymphocytes by aggregated H or H bound to C3b (81). H also stimulates the respiratory burst in human monocytes (983) and release of prostaglandin E and thromboxane by macrophages (84). In a recent study, factor H was found to inhibit B cell differentiation in vitro without blocking their proliferation (85).

2.4. C1q Receptor. C1q is a protein with mw 410,000 and complexes with C1r and C1s to form a trimolecular complex known as C1 (reviewed in Reference 86, s.v.). Under the electron microscope, the C1q molecule appears as six globular heads linked through collagen-like stalks forming a stemmed structure. The globular heads of C1q bind to the Fc region of IgM and IgG and the collagen-like regions to C1r and C1s. Upon complement activation, C1q remains bound to the activators with the collagen-like regions exposed, which enables the molecule to interact with the cellular C1q receptors. C1q receptors have been found on a number of cells including B-lymphocytes, neutrophils, and fibroblasts and on a small proportion of T-cells, and null cells (87-89). Cellular responses attributed to the binding of C1q to its receptor include stimulation of neutrophil oxidative metabolism (90), aggregation of platelets and release of serotonin by them (91) as well as induction of cytotoxicity toward chicken erythrocytes (92) (Table V).

3. Pathophysiology of Complement Receptors

3.1. The C3b receptor in system Lupus Erythematosus (SLE) and Other Diseases. SLE is a prototype of human autoimmune disease, characterized by an abundance of circulating autoantibodies and immune complexes. The specificities of the autoantibodies are quite diverse, including but not restricted to DNA, nuclear proteins and cell surface antigenic structures. Both the autoantibodies and immune complexes have been variably associated with clinical features of the disease. Cellular mechanisms that lead to the uncontrolled production of autoantibodies, although extensively studied, remain unclear among the most prominent theories are failure of the suppressor cell circuit to block the production of immunoglobulin by B-cells, failure of cytotoxic cells to eliminate autoreactive B-cell clones, presence of viral infection that leads to clonal expansion of autoreactive B-cells, and finally, continuous, excessive stimulation of B-cells by exogenous stimuli (reviewed in Reference 93, q.v.).

Circulating immune complexes are believed to be cleared by the reticuloendothelial system after binding to Fc receptors or complement receptors on the surface membranes of cells belonging to this system. Clearance of C3b or anti-erythrocyte antibody coated autologous erythrocytes is deficient in patients with SLE and other autoimmune rheumatic diseases (94, 95). Comparing CR1 molecules on the surface membranes of the erythrocytes in normal humans and patients with SLE indicates that these patients have significantly fewer CR1. In a report describing of a fairly large sample of patients with SLE, erythrocytes from 667 failed to bind to aggregated γ-globulin in the presence of complement (96). This defective immune adherence did not correlate with disease activity, and in certain patients studied serially the defect persisted through various phases of the disease. Furthermore, some family members with no evidence of clinical disease similarly lacked immune adherence. Enumeration of the CR1 molecules on membrane surfaces of erythrocytes with a murine anti-CR1 monoclonal antibody showed that patients who had SLE exhibited 600 ± 307 CR1/E, whereas normal persons had 1410 ± 620 CR1/e (97). In addition, patients with rheumatoid arthritis had significantly decreased numbers of CR1/E (930 ± 417). In the group of patients with
SLE, the numbers of CR1/E correlated with the hemolytic
titers of C4 and the levels of immune complexes estimated by
the C1q binding assay. The contribution of disease activity to
the expression of CR1 on erythrocyte surface membranes is
unproven. Masking of the CR1 by either immune complexes
or C3 breakdown products which are abundant during disease
activity (3), could be partially responsible for the defective
immune adherence in these patients. The use of immune
adherence hemagglutination methods to measure CR1 in
patients with SLE and other connective tissue diseases (98),
as well as insulin dependent diabetes mellitus (99), has
disclosed a correlation between CR1 levels and various
complement factors. Support for the hypothesis that deficient
CR1 expression on the surface membranes of the SLE
erythrocytes is an epiphenomenon, comes from the report of
a single patient with SLE whose circulating autoantibody was
CR1 specific (100). High titers of the autoantibody at different
time points during the disease correlated with absence of CR1
on E. Although similar cases are rare, one can assume that
circulating anti-CR1 autoantibodies are responsible for the
decreased CR1/E in some patients with SLE. Ross et al (101)
reported that the erythrocytes from patients with rheumatoid
arthritis, cryoglobulinemia, Sjögren's syndrome, autoim-
une idiopathic anemia and paroxysmal nocturnal hemoglo-
bulinuria, as in SLE exhibit in addition to low numbers of
CR1/E, significant numbers of fixed to C3dg/E molecules. In
255 individuals (normal controls and patients), a significant
(r=0.498) was found between (CR1/E and cell
bound C3dg/e. Estimation of C3dg/E and CR1/E in indi-
vidual patients further confirmed the reverse association
between bound C3dg/E and CR1/E. In a recent study (102),
the low numbers of CR1/E, in patients with SLE, rheumatoid
arthritis, Sjögren's syndrome, and paracoccidiomycosis, esti-
imated by the use of 125I F(ab')2 anti-CR1 antibody, failed to
correlate with the levels of circulating immune complexes.
This finding is of particular importance, since highly sensitive
assays were used for the detection of circulating immune
complexes.

Evidence that the deficient CR1/E in SLE patients is not
an epiphenomenon but rather a genetically determined
feature, comes from studies of family members and the
patients among them for expression of the various CR1
alleles in cell surface membranes. Using radiolabeled anti-
CR1 antibody Wilson et al (103) enumerated the CR1/E in 38
patients with SLE and 47 family members. Patients had 2804 ±
241 and the family members had 3187 ± 196 CR1/E
compared to normal individuals, 5014 ± 155 CR1/E. The
numbers of the receptor sites in spouses of these patients did
not differ from those of other normal individuals. The
authors constructed a trimodel distribution pattern for the
numbers of CRE1/E: a high CR1/E phenotype (HH), an
intermediate phenotype (HL), and a low phenotype (LL).
Only 12% of the normal individuals had the LL hemotype
whereas 53% of the patients with SLE were LL. Pedigree
analysis demonstrated that the H or L numbers of CR1/E are
ingerited in an autosomal co-dominant manner. The genetic
nature of both murine and human SLE has been stressed
emphatically in the literature and has been reviewed else-
where (104). Clinical studies in twins, studies on the preva-
lence of certain HLA antigens, and studies of certain ceuliar
and humoral features have provided clear evidence of the
hereditary (multigenetic) nature of the disease (104, 105).

The decreased number of CR1/E in patients with SLE and
other diseases associated with complement activation
appearsingly has no single cause. As the data reviewed above
indicate, both genetic and disease activity-related factors play
important roles in the final expression of CR1 on the surfaces
of erythrocytes. Autoimmunity, in general, has been consid-
ered the outcome of both genetic and environmental fac-
tors. It seems that for our area of discussion, the expression
of CR1, the same general rule is applicable.

3.2. CR3 Deficiency in Man. In clinical immunology, a
newly recognized group of immunodeficiencies includes dis-
ease entities in which cell surface membrane molecules are
either numerically decreased or not expressed. Examples
include: (a) chronic granulomatous disease, (b) bare leuko-
cyte syndrome, (c) interleukin-1 receptor deficiency, and (d)
Mo1 glycoprotein (CR3) deficiency. We will present studies
performed on patients with CR3 deficiency. Recently, a
clinical immunodeficiency syndrome has been recognized
that is characterized by recurrent bacterial and fungal infec-
tions, progressive periodontitis, persistent leucocytosis, se-
everly depressed neutrophil adherence, chemotaxis, and pha-
gocytic function. These patients have in common the de-
ciciency of a certain neutrophil surface membrane glycopro-
tein (105, 106). A patient with the above clinical characteris-
tics was reported to be deficient in both subunits of CR3 on
the granulocytes (107). Monocytes and granulocytes were
defective in IgG- and C3-dependent phagocytosis. Natural
killer activity was normal. In normal leukocytes the expres-
sion of both LAF-1 and CR3 is regulated by the state of
activation of the cell. Upon mitogenic or alloantigenic stimu-
lation, LFA-1, which is expressed in small amounts by
peripheral T-lymphocytes, a marked increase can be de-
tected. In normal unstimulated granulocytes, a major portion
of CR3 is located intracellularly in a specific granule fraction.
Degrannulating stimuli such as the calcium ionophore A23187,
chemotactic peptide (ex-Met-Leu-Phe, or C5a), and PMA
induce a 3- to 10-fold increase of surface CR3 (108). Arnaout
et al (108) reported two patients with normal cytoplasmic T-
lymphocytes generated in mixed lymphocyte culture and
natural killer cell activity but deficient responses to phy-
tohemagglutinin. LFA-1 was undetectable in the patient's
resting T-lymphocytes either by immunoprecipitation or im-
munofluorescence, although their mitogen and alloantigen
stimulated cells expressed small but detectable amounts of
the LFA-1 heterodimer. Similarly, the expression of CR3 on
the patients monocytes was dependent on the state of cellular
activation. CR3 expression was decreased on resting grani-
lyocytes, but increased after stimulation with the ionophore A23187. Similar cellular abnormalities, i.e., normal T-cell associated functions but deficient granulocyte function, were reported by Miedema et al (109).

The mode of inheritance of the CR3 deficiency has not been established. In one family, both parents had reduced levels of CR3 (105). The mother of another patient had decreased CR3 (110). Elsewhere, both parents of a CR3/ LFA-1 deficient patient had decreased expression of both CR3 and LFA-1 glycoproteins (109).

3.3 Expression of Complement Receptors on Leukemic Cells. Complement receptors have been studied in patients with lymphocytic leukemias; the majority of the studies have utilized erythrocyte antibody-complement-cellular intermediates as indicator cells. The methodological drawbacks are similar to those which have arisen when these cellular intermediates have been used for the study of the expression of complement receptors on normal cells (111). The current availability of monoclonal antibodies directed against complement receptors will certainly shed light on the expression of these receptors on the leukemic cells. In this section, we will summarize the available information on the expression of complement receptors on leukemic cells by using cellular intermediates as indicator cells.

Chronic lymphocytic leukemia (CLL) is considered to be of B-cell origin although not restricted to mature B-lymphocytes, but including earlier phases of differentiation. B-cells from peripheral blood, spleen cells and lymph node cells from patients with CLL have been described with decreased C3b binding and increased C5a binding (112). Lymph node cells from patients with nodular lymphoplastic non-Hodgkin’s lymphomas also had increased binding of Fc×3d indicator cells using Fc×3b/Fc×3d indicator cells. Cosman and Jaffe (113) described three different lymphocytic subpopulations in normal human individuals depending on the expressions of CR1 and / or CR2. CR1', CR2+ cells predominated in tissues from patients with CLL, will differentiated and intermediated differentiated lymphocytic lymphomas. A clinical study has shown that B-cell lymphomas with more than 10% EAC forming cells, have a statistically significant longer survival than those that form less than 10% EAC rosettes (114).

In a number of studies, the existence of leukemic cells bearing both T- and B-lymphocyte markers has been stressed. Such leukemias have caused researchers to consider the cellular origin of these malignancies (possibly they originate from a «primitive» cell not yet committed to the T- or B-cell lineage) and the functional status of these «double» cells. A patient whose disease clinically resembled CLL, was reported to possess peripheral blood cells that formed sheep erythrocyte rosettes as well as complement receptor rosettes (115). Subsequently, more patients with CLL were described as carrying markers for both T-lymphocytes (positive staining with anti-T-cell antibodies) and B-lymphocytes (surface im-
munoglobulin and EAC rosettes) (116). This simultaneous presence of T- and B-cell markers has also been reported on cells from individuals with acute lymphoplastic leukemias (117-119). The physiological significance of these «double» cells remains speculative. Moreover, the clinical implications in patients with leukemias have not been analyzed. Usage of currently available monoclonal antibodies in documenting the differential expression of complement receptor and other markers on leukemic cells, will certainly improve our understanding of these leukemias, particularly with respect to their cellular biology.

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