The Human C3b Receptor*

Douglas T. Fearon

Department of Medicine, Harvard Medical School, and Department of Rheumatology and Immunology, Brigham and Women's Hospital, Boston MA 02115, USA

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Introduction

Many of the biologic effects of the complement system are mediated by cellular receptors that specifically bind certain cleavage peptides and larger fragments of complement proteins that are generated during activation of the system. As is discussed elsewhere in this volume and in a recent review [15], there may be as many as eight different complement receptors on the various cell types that participate in immune and inflammatory reactions. A comprehensive understanding of the mechanisms by which the binding of ligands to these receptors evokes cellular responses requires that the membrane proteins serving as receptors be identified, isolated, and characterized. Recent studies of the first complement receptor to be purified, the human C3b receptor, which is also termed CR1, is the subject of this review.

Structure of the Human C3b Receptor

The human C3b receptor was purified initially during investigations of an erythrocyte membrane protein that had inhibitory activity in the alternative complement pathway [11]. A glycoprotein was purified 1500-fold from proteins that were solubilized with NP-40 from erythrocyte membranes. When analyzed by polyacrylamide gel electrophoresis with sodium dodecyl sulfate (SDS-PAGE), the

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Offprint requests to: D.T. Fearon, 607 Seeley G. Mudd Building, 250 Longwood Avenue, Boston, MA 02115, USA
glycoprotein had an Mr of 205,000 in the presence of NP-40, and an Mr of 250,000 in the absence of this nonionic detergent. Picomolar concentrations of the purified, solubilized protein displaced Bb from the amplification C3 convertase, C3b, Bb, and nanomolar concentrations served as a cofactor for the cleavage of soluble C3b to iC3b by factor I. These functions of glycoprotein and its adsorption to Sepharose-C3 indicated that it had an affinity for C3b and prompted an investigation of its possible C3b receptor function. Its identity as the C3b receptor not only of erythrocytes but also of peripheral blood leukocytes was established by the finding that monospecific rabbit antibody raised to the purified erythrocyte membrane protein inhibited receptor function of erythrocytes, neutrophils, monocytes, and B lymphocytes. In addition, the membrane protein that was immunoprecipitated from each of these cell types was identical on SDS-PAGE analysis to the purified erythrocyte protein [12]. Thus, the C3b receptor of all peripheral blood cells having this function was shown to be identical to the glycoprotein that had been purified from erythrocytes. Other studies employing polyclonal [10] and monoclonal antibodies [18, 25] have supported these findings with one possible exception. A single report has described three monoclonal antibodies that apparently inhibited C3b receptor function of lymphocytes, erythrocytes, and glomerular podocytes, but not that of monocytes and neutrophils [9]. The cellular antigens recognized by these monoclonal antibodies was not evaluated.

Although these initial studies found the C3b receptor to be homogeneous by SDS-PAGE, a genetically regulated structural polymorphism of the C3b receptor has recently been found [10a, 57]. Analysis by SDS-PAGE of specific immunoprecipitates from K125i-surface labeled erythrocytes, neutrophils, and mononuclear leukocytes from individual donors revealed one of three patterns of the C3b receptor: a single band of receptor displaying relatively fast mobility (Mr = 250,000) that was designated as the "F" form; a single band having slightly slower electrophoretic mobility (Mr = 260,000) and designated "S"; and the presence of two bands corresponding to the F and S forms. All peripheral blood cell types of respective donors displayed the same pattern of receptor, and repeat analyses of cells obtained over a period of 12 months indicated that an individual's particular pattern did not change. Thus, the occurrence of the F and S forms of the C3b receptor among normal individuals represented a stable characteristic, and persons were categorized as being homozygous for the F and S forms, having the FF and SS phenotypes, respectively, or as heterozygotes, FS. Seventy-six of 116 unrelated individuals were FF (65.5%), 37 were FS (31.9%), and only three persons had the SS phenotype (2.6%), a distribution that did not differ from that predicted by the Hardy-Weinberg equilibrium assuming two autosomal codominant alleles regulating the expression of the F and S forms of the receptor. Analysis of the occurrence of these phenotypes in 76 individuals comprising 15 families also indicated an autosomal codominant mode of inheritance. Previous reports of only the F form of the C3b receptor on SDS-PAGE are accounted for by the low frequency of the S product.

This structural polymorphism of the C3b receptor differs from that of most complement proteins because the receptor allotypes can be distinguished by SDS-PAGE, whereas the allotypes of human C4, C2, C3, C6, C8, and factor B are resolved only by procedures that separate proteins according to net charge [45]. An