Complement Activation and Complement Receptors in Systemic Lupus Erythematosus

John P. Atkinson

Howard Hughes Medical Institute Laboratories and Department of Medicine, Division of Rheumatology, Washington University School of Medicine, St. Louis, MO 63110, USA

I. Introduction

The activation of complement in systemic lupus erythematosus (SLE) was first documented in the early 1950's [52]. Since that time many excellent studies of the biology of complement in SLE have been reported and the general subject has been recently reviewed [3, 13, 49]. In fact, more has been written about the workings of this potent effector pathway in SLE than for any other disease.

SLE is characterized serologically by excessive quantities of autoantibodies and immune complexes, and IgG and IgM-bearing immune complexes activate the classical complement pathway. Complement fragments are found on cells and in areas of tissue destruction. Damage to vital tissues in SLE is in part mediated by this effector arm of the humoral immune system. The major observation has been that the characteristic reduction in serum levels of the classical complement pathway components and whole complement activity (THC or CH50) is secondary to increased utilization [3, 13, 23, 33, 49]. An unexplained observation is that up to 20% of SLE patients also have reduced synthetic rates [1, 43, 50]. Upon reviewing this extensive literature relating to complement and SLE, several clinical points can be made. The measurement of complement components can be helpful adjunct in the initial diagnosis of SLE and is a means of evaluating the results of therapy. For example, if with therapy the complement levels return to normal, the prognosis is better than for patients whose values remain low. These and other data indicate that the more clinically active the disease process, the greater the magnitude of complement activation. These points are well known to students of this illness and will not be further addressed here.
Instead, in this chapter I will focus on two newer aspects of the relationship between SLE and complement. This recent literature is potentially of greater interest because it provides insights not only into the pathophysiology of SLE but also into the etiology of this fascinating illness. The two topics to be discussed are the association of complement deficiency states and SLE, and the role of complement receptors and regulatory proteins in SLE. The most important function of the complement system is the elimination (to be used interchangeably with clearance or removal) of antigens identified by the humoral immune system as foreign. The underlying hypothesis to be addressed is that defects of complement activation or of complement receptors will decrease the efficiency of the clearance process and lead to prolonged survival and inappropriate deposition of immune complexes containing foreign or auto antigens.

II. Complement Deficiency States and SLE

A. Inherited Deficiencies of C1, C4, or C2

A majority of individuals with C1, C4, or C2 deficiency come to medical attention because of SLE or a lupus-like-illness (LLI). Two comprehensive reviews of this association were recently published [40, 44]. The LLI designation arose because many of these patients were antinuclear antibody (ANA) negative or had a low titer with mouse liver or kidney as the substrate. Employing human epithelial tissue as substrates or more sensitive ELISA assays, a majority of these patients have now been shown to be positive for antibodies to the Ro antigen [36]. However, in most other respects SLE as a clinical entity in these complement deficient patients resembles SLE in complement-sufficient hosts.

Over 100 individuals with a deficiency of one of these (C1, C4, or C2) early acting components of the classical complement pathways have been reported (Table 1). The deficiency in each case is inherited as an autosomal recessive disorder. C1 is composed of three subunits, q, r, and s, and a deficiency of any one of these subcomponents leads to an inactive C1 molecule and is associated with SLE. C2 deficiency is the most common with over 70 individuals reported. About 50% of these homozygous C2 deficient individuals have had SLE and another 25% glomerulonephritis or another type of an immune complex-mediated illness. A deficiency of C3 is associated with severe, recurrent, life-threatening infections and a deficiency of C5, C6, C7, C8, or C9 is associated with recurrent Neisseria infections. The latter group is not predisposed to SLE. The former group is small in number (14 total) and have been so ill with infections that it has not been possible to accurately evaluate a predisposition to SLE, although manifestations compatible with SLE have been present in over half.

The important question of course is how does a deficiency of one of the early acting components of the classical complement pathway predispose an individual to SLE. Two theories have been put forward. One is that, because the genes that code for C4 and C2 are located within the major histocompatibility complex (Fig. 1), the deficient gene is linked to an immune response gene or a transplantation gene. It is this "linked" gene which is responsible for the disease predisposition.