Autoantibodies to Nonhistone Nuclear Antigens
Their Immunobiology and Clinical Relevance

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I. INTRODUCTION

In the absence of precise etiologic and pathogenetic information, the diagnosis of the rheumatic diseases is based on a combination of clinical, laboratory, and pathological features. Serologic findings have assumed increasing diagnostic importance since the discovery by Hargraves et al. (1948) of the LE cell, the forerunner of the antinuclear antibodies. Subsequent studies by Holman and Kunkel (1957) showed that the LE cell phenomenon was caused by a circulating autoantibody reacting with autologous nuclear material (DNA–histone). More recently, the widely used indirect immunofluorescent test has served as a sensitive screening test and has revealed the presence of circulating autoantibodies to nuclear antigens (ANA) in systemic rheumatic diseases such as systemic lupus erythematosus (SLE), progressive systemic sclerosis or scleroderma (PSS), mixed connective tissue disease (MCTD), Sjogren’s syndrome, and poly/dermatomyositis.

During the past 30 years a variety of immunologic techniques (e.g., immunoprecipitation, complement fixation, hemagglutination) have been used to identify antibodies to specific nuclear constituents. Testing of patient sera by the immunofluorescent method (fluorescent ANA), typically using sections of cryopreserved tissues as substrates, has revealed a wide spectrum of patterns. Certain fluorescent ANA patterns were shown to

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correlate with the presence of specific antinuclear antibodies defined by other immunologic tests (e.g., the rim fluorescent ANA pattern correlated with antibody to DNA). However, a complex array of speckled ANA patterns with variations in size and density of speckles is produced by sera containing antibodies to many different nonhistone nuclear antigens (Nakamura and Tan, 1977). The more recent use of tissue culture cell lines, which have larger nuclei and nucleoli than those in tissue sections, has improved the sensitivity and differentiation of patterns and has facilitated the detection of distinct new ANAs such as anticientromere (Tan et al., 1980) and anti-mitotic-spindle-apparatus (McCarty et al., 1981).

Of all the systemic rheumatic diseases, SLE is the one in which the greatest abundance of autoantibodies have been described. Initially it was not known which of these autoantibodies might have the most clinical significance. However, numerous published reports document the special relationship between antibody to native DNA and SLE and the role of DNA–anti-DNA complexes in SLE nephritis (Tan et al., 1966; Koffler et al., 1967; Bruneau and Benveniste, 1979). Antibodies to single-strand DNA lack the same specificity for SLE since they are found in numerous diseases (Koffler et al., 1971), but they may also be involved in pathological changes in lupus kidneys (Koffler et al., 1974). Antibodies to histones have also been detected in SLE, have a particularly strong relationship with drug-induced LE, and have also been detected in rheumatoid arthritis (Tan, 1982). These important autoantibodies are discussed in detail elsewhere in this book. The remainder of this chapter focuses on another group of autoantibodies reactive with various nonhistone antigens that have become of increasing biological and clinical interest during the past two decades.

The list of autoantibodies to nonhistone antigens is long and no doubt will increase steadily as ANAs presently under investigation prove to have biological and/or clinical significance. Shown in Fig. 1 are nuclear antigens (excluding DNA and histone) that have proven or potential clinical relevance and the rheumatic diseases with which their autoantibodies are associated. Some of these autoantibodies are restricted to certain diseases or subsets and therefore can serve as disease markers, whereas others occur in combination or are more widely distributed. High titers of antibody to nuclear ribonucleoprotein (RNP) in the absence of other ANAs constitute a serologic pattern that is especially related to MCTD. Antibodies to Sm and native DNA are markers for SLE. Other antibodies that appear useful as markers include anticientromere in the CREST subset of PSS, anti-Scl-70 in PSS, and antibodies to Ku, PM-1, and Jo-1, which are closely linked with polymyositis (PM) or PM–PSS overlap syndrome. Although antibodies to Me, Su, and MA are still in a preliminary phase of investigation and their true clinical significance remains uncertain, these systems are discussed since the work has been pursued in the authors' laboratory, and this permits inclusion of new information that has not been widely disseminated.

Other systems that are of considerable biological interest but whose clinical diagnostic and prognostic roles have not been fully elucidated [e.g., rheumatoid arthritis nuclear antigen (RANA), Alspaugh et al., 1976; proliferating cell nuclear antigen (PCNA), Miyachi et al., 1978; mitotic spindle apparatus (MSA), McCarty et al., 1981; and SL antigen, Harmon et al., 1981] are not discussed in this chapter. Particular emphasis is given to the elucidation of nuclear RNP and Sm antigens and to the new clinical, immunopathological, and molecular biological information that has been generated as a result of scientific investigation of these systems.