In the Beginning Was Sm

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Up to 1966, it was known that sera from patients with systemic lupus erythematosus (SLE)2 have Abs with specificities against DNA and nucleoprotein. Eng Tan and Henry Kunkel (1) observed, while performing experiments to detect precipitating Abs using the Ouchterlony agar diffusion method, that a significant number of SLE sera produced precipitin bands with soluble tissue extracts that could not be explained by their anti-DNA and antinucleoprotein Ab content. What I like about this paper the most is its novelty. An astute observation followed by the complete—according to the mid-1960s standards—characterization of the nature of the Ag. The Sm Ag was shown to be a protein that was localized in the nucleus. The absolute specificity of Sm precipitating Abs for SLE was declared at that point. The paper was presented in an amazingly clear and laconic manner.

The serum came from Stephanie Smith, who was diagnosed with SLE at the age of 15 in 1959 at the Rockefeller University Hospital, where she presented with arthritis, rash, pleuritis positive lupus erythematosus preparation, complement-fixing Abs with cell nuclei and cytoplasm, elevated sedimentation rate, γ-globulin, and anemia without renal disease. Stephanie succumbed to complications of her disease and treatment 7 years later at the age of 22. According to one of her physicians, Dr. Eng Tan, she was a very intelligent and talented young woman. She was a skillful painter, and one of her paintings is shown in the figure, courtesy of Dr. Tan (Fig. 1).

Today it has been established that anti-Sm Abs are present in approximately one-quarter of the sera of patients with SLE and never in sera from patients with other rheumatic diseases. Sm Abs bind B, D, and, sometimes E and rarely F and G polypeptides that comprise the Sm protein complex. Fine-speckled staining with nucleolar sparing at the initial screening immunofluorescent anti-nuclear Ab test suggests the presence of anti-Sm Abs. Enzyme-linked immunoassays and immunoblots nowadays combine the sensitivity of immunoprecipitation and the specificity of immunodiffusion. Linear epitopes within the Sm polypeptides do not share the same high specificity and low sensitivity. For example, Abs against SmD1 C terminus 83–119 peptide are present in 70% of SLE sera and 8% of sera from patients with other inflammatory disorders (2).

What is it that qualifies this paper as a “Pillar of Immunology?” At the time of this writing it has been cited 522 times in the medical literature. However, this is not the reason that the article was chosen to be featured in the “Pillars of Immunology” series of The Journal of Immunology. The identification of anti-Sm Abs in the sera of patients now forms part of the American College of Rheumatology criteria for the diagnosis of SLE. This fact solely speaks to the impact of the Tan and Kunkel paper. Immediately after the recognition of Sm Ag, another nuclear Ag was identified with Abs present in the sera of patients with SLE and mixed connective tissue disease. This was designated nuclear ribonucleoprotein (RNP) because both RNA and protein were required for antigenicity. Subsequently, many nonhistone Ags were recognized, including Ro, La, and Ku.

Years later Lerner and Steitz (3), with the help of these lupus autoantibodies, showed that the Sm and RNP Ags were RNP particles composed of small nuclear (sn)RNAs, known as uridylate-rich RNAs. These particles are known as snRNPs. The autoantibodies against Sm and RNP have been instrumental in elucidating the structure of the snRNPs as well as in deciphering their important function in splicing precursor mRNA. The importance of the anti-Sm Abs as tools in molecular biology cannot be overestimated. Dr. Tan, in one of his more recent reviews (4), points out that they were used to characterize the snRNP analogues in Saccharomyces cerevisiae and to fully understand the structure and function of the spliceosome.

The response to Sm Ag has been used extensively to establish that anti-Sm Abs are produced following antigenic stimulation and with the help of T cells. In sampling the published work, it was shown that the anti-Sm Abs in MRL/lpr mice exhibit restriction in J(H) and V(H) gene use (5) and that it is Ag driven and T cell dependent (6).

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2 Abbreviations used in this paper: SLE, systemic lupus erythematosus; RNP, ribonucleoprotein; sn, small nuclear.

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In conclusion, the Tan and Kunkel paper identified Sm, the first nonhistone Ag against which patients with SLE produce autoantibodies. The presence of these Abs entered the criteria physicians use to establish the diagnosis of SLE and helped molecular biologists define the structure and function of the spliceosome. The anti-Sm Ab-Sm Ag system was used extensively to demonstrate the requirements for the production of the Ab. The use of the Ab to elucidate the mechanisms that are involved in the splicing of precursor mRNA represents an example of the mutual give and take that has evolved between observations at the bedside and the bench.

Acknowledgments

I thank Dr. Tan for sharing information about Stephanie Smith and one of her paintings. The opinions expressed herein are those of the author and do not reflect those of the Department of Defense.

References