Special Lecture 1

Stephanie Smith and the Past, Present, and Future of Clinical Immunology

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Perhaps nothing better illustrates the remarkable progress of clinical immunology than the history of the Sm/RNP antigen-autoantibody system. In 1966, serum from Stephanie Smith, a young woman with SLE, revealed autoantibodies against a nuclear antigen termed “Sm”. The antigen is a complex of 11 proteins plus U1 small RNA involved in RNA splicing. Interestingly, most lupus autoantigens are RNA or DNA–protein complexes, a fact that took on added significance with the discovery that TLR7 recognizes U1RNA. Indeed, lupus autoantigens may be targeted because they carry “endogenous adjuvants”, such as U1RNA, which engage TLRs. We have studied lupus in mice treated with pristane, which is characterized by anti-Sm/RNP autoantibodies and nephritis. Both are abolished in mice lacking TLR7 or intermediates in the TLR7 signaling pathway, such as IRF5, which promote interferon α (IFN α) production. Consistent with pristane-lupus, SLE is associated with genetic polymorphisms of IRF5 and overproduction of IFN α . Besides stimulating IFN α via IRF5, TLR7 signaling activates NF κ B leading to proinflammatory cytokine production. This pathway is involved in the pathogenesis of hematological manifestations of lupus. Thus, the Sm antigen has moved from a serological phenomenon into the realm of molecular and immunobiology, and back again to the patient. In 2012, the Sm/RNP system is at the cusp of exciting new developments in clinical immunology that may unravel the mysteries of autoimmune disease.