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Pathogenic Effects of IgG and IgM Apoptotic Cell-Reactive Monoclonal Auto-Antibodies on Innate and Adaptive Immunity in Lupus

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Abstract : Apoptotic debris is believed to be the antigenic trigger in lupus. Whether such debris and autoantibodies induced in lupus-prone mice which specifically recognize its constituents can mediate differential effects on innate and humoral responses in such mice was assessed. The influence of apoptotic blebs and apoptotic cell-reactive monoclonal antibodies on phenotypic markers expressed on bone marrow-derived dendritic cells (BMDCs) and secreted cytokines were evaluated. Sera from lupus-prone and healthy mice immunized with the antibodies were analyzed for anti-self reactivity. Apoptotic blebs, as well as somatically-mutated IgG and non-mutated IgM apoptotic-cell reactive monoclonal antibodies, induced the preferential maturation of BMDCs derived from lupus-prone mice relative to BMDCs derived from healthy mice; antibody specificity and cell genotype both influenced the secretion of inflammatory cytokines. Immunization of lupus-prone mice with IgM and IgG antibodies led to hypergammaglobulinemia; elicited antibodies were self-reactive, and exhibited enhanced recognition of lupus-associated autoantigens (dsDNA, Ro60, RNP68, and Sm) in comparison with adjuvant-induced sera. While 'natural' IgM antibodies are believed to contribute to immune homeostasis, this study reveals that apoptotic cell-reactive IgM antibodies can promote inflammation and drive anti-self responses in lupus. Only in lupus-prone mice did immunization with IgG auto-antibodies enhance the kinetics of humoral anti-self responses, resulting in advanced-onset glomerulosclerosis. This study reveals that preferential innate and humoral recognition of the products of cell death in an autoimmune milieu influences the indices associated with lupus pathology.

Keywords : antigen spreading, apoptotic cell-reactive pathogenic IgG, and IgM autoantibodies, glomerulosclerosis, lupus
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