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The accumulated V_H replacement products contribute to the generation of auto/polyreactive antibodies in systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is characterized by over-production of autoantibodies. However, it is not clear how these autoantibodies are generated and selected in SLE patients. V_H replacement is originally considered as a receptor editing process during B cell development to change non-functional or autoreactive immunoglobulin heavy chain (IgH) genes. However, our preliminary analysis of published IgH gene sequences suggested that V_H replacement products are enriched in Ig genes derived from patients with viral infections or autoimmune diseases, including SLE. To gain insight into the potential role of V_H replacement in the generation of autoantibodies in SLE, we used a single cell PCR-based cloning technology to isolate and express immunoglobulin genes from B cells of SLE patients and healthy controls. We found that 56% of the antibodies derived from SLE plasmablasts react with self-antigens and also react with more than two different antigens (termed auto/polyreactive) whereas only 17% of the antibodies derived from healthy control plasmablasts are auto/polyreactive. Detailed sequence analysis revealed that V_H replacement products are significantly increased in IgH genes obtained from SLE patients and contribute to more than 20% of IgH genes in SLE patients compared to 6% in healthy controls. Importantly, the accumulated V_H replacement products in SLE patients have long CDR3 regions enriched with charged amino acids and 74% of them encode auto/polyreactive antibodies. Our results show that V_H replacement products are significantly enriched in IgH genes from SLE patients and V_H replacement products directly contribute to the generation of auto/polyreactive antibodies in SLE patients.

Biography

Yangsheng Yu is currently a senior research associate in the Department of Pathology and Microbiology at the University of Nebraska Medical Center. After he obtained his bachelor and doctorate degrees at Nankai University in China, he went to the United States and joined Dr. Kaihong Su's lab as a postdoctoral fellow in 2009. Since then, he has been investigating the potential contribution of V_H replacement to the generation of poly/auto reactive antibodies in systemic lupus erythematosus (SLE), as well as the pathogenic roles of tissue-reactive auto antibodies in SLE organ manifestations. His long term goal is to understand the molecular mechanisms for autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis.