Kaihong Su, J Clin Cell Immunol 2014, 5:5
http://dx.doi.org/10.4172/2155-9899.S1.017

OMICS Group Conferences
Accelerating Scientific Discovery

3rd International Conference and Exhibition on
Clinical & Cellular Immunology
September 29-October 01, 2014 DoubleTree by Hilton Baltimore-BWI Airport, USA

Circulating plasma blasts from patients with rheumatoid arthritis preferentially produce anti-citrullinated protein antibodies

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Anti-citrullinated protein antibodies (ACPAs) are highly specific serological markers for rheumatoid arthritis (RA) and are also believed to contribute to RA pathogenesis. However, the cellular and molecular basis of ACPA production is not fully understood. Using a single cell PCR-based antibody cloning technology, we analyzed if circulating plasmablasts (CD19dimCD27highCD20-) in RA patients produce ACPAs. Among the 195 antibodies generated from 6ACPA+RA patients, 18.5% (ranging 6.5-27.6%) specifically recognize citrullinated antigens, but not their native forms. However, none of the antibodies generated from ACPA-RA patient or healthy donors reacted with citrullinated antigens. Detailed sequence analyses showed that the IgH and IgL genes encoding these ACPAs are highly mutated. Reversion of the mutated IgH and IgL genes to their corresponding germline genes completely eliminated their ACPA reactivity, suggesting that the generation of circulating ACPAs is an antigen driven process. To identify the antigen sources for ACPAs, we found that about half of the ACPAs react with outer membrane proteins from Porphyromona gingivalis (P. ging) and/or citrullinated P. gingenolase. Some ACPAs also react with auto-antigens released in the human neutrophil extracellular traps. These results suggest that circulating plasmablasts in RA patients are a source of ACPA production and the generation of ACPAs is driven by both exogenous bacterial antigens and citrullinated self-antigens. Our data thus identify circulating plasmablasts as potential therapeutic targets and provide a mechanism for previous findings that plasmablasts in the blood predict non-response to anti-CD20 therapy in RA patients.

Biography

Kaihong Su obtained her Doctorate degree and Post-doctoral training from the University of Alabama at Birmingham (UAB). After being a faculty member at UAB for 5 years, she joined the University of Nebraska Medical Center in 2008 to continue her research. The long-term goal of her lab is to understand the molecular mechanisms for autoimmune diseases, including SLE and RA. She has published 26 papers in reputed journals and served as ad-hoc Reviewer for a number of scientific journals.

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