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

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

The role of TLR7 in spontaneous germinal center formation and the development of autoimmunity

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Spontaneous germinal center (Spt-GC) B cells and follicular helper T cells (Tfh) generate high affinity autoantibodies involved in the development of systemic lupus erythematosus (SLE). Toll like receptors (TLRs) play a pivotal role in SLE pathogenesis. While previous studies have focused on the B cell intrinsic role of TLR-MyD88 signaling on immune activation, autoantibody repertoire and systemic inflammation, a thorough investigation of the mechanisms by which TLRs control the formation of Spt-GCs remains unclear. Using non-autoimmune C57BL/6 (B6) mice deficient in MyD88, TLR2, 3, 4, 7 or 9, we identified B cell-intrinsic TLR7 signaling as a prerequisite to Spt-GC formation without the confounding effects of autoimmune susceptibility genes and the overexpression of TLRs. TLR7 deficiency also rendered autoimmune B6. Sle1b mice unable to form Spt-GCs, leading to markedly decreased autoantibodies. Conversely, B6.yaa and B6.Sle1b.yaa mice expressing an extra copy of TLR7 and B6.Sle1b mice treated with aTLR7 agonist had increased Spt-GCs and Tfh. Further, TLR7/ MyD88 deficiency led to compromised B cell proliferation and survival after B cell stimulation both in vitro and in vivo. In contrast, TLR9 inhibited Spt-GC development. Our findings demonstrate an absolute requirement of TLR7 and anegative regulatory function for TLR9 in Spt-GC formation under non-autoimmune and autoimmune conditions. Our data suggest that, under non-autoimmune conditions, Spt-GCs initiated by TLR7 produce protective antibodies. However, in the presence of autoimmune susceptibility genes TLR7 dependent Spt-GCs produce pathogenic autoantibodies. Thus, a single copy of TLR7 in B cells is the minimal requirement for breaking the GC-tolerance checkpoint.

Biography

Zia Rahman received his MD from Beijing University in 1993, PhD from National University of Singapore in 2002 and completed Postdoctoral studies at Thomas Jefferson University in Philadelphia in 2006. He is an Assistant Professor in the Department of Microbiology and Immunology at Penn State College of Medicine. His research focuses on understanding the mechanisms of loss of peripheral B cell tolerance in an autoimmune disease SLE (systemic lupus erythematosus).

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