OMICS Group Conferences
Accelerating Scientific Discovery
3rd World Congress on
Cell Science & Stem Cell Research
November 20- 22, 2013 DoubleTree by Hilton Baltimore-BWI Airport, USA

Actin-mediated negative regulation of B-cell receptor signaling

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Abstract

Negative regulation of receptor signaling is essential for controlling cell activation and differentiation. In B-lymphocytes, the down-regulation of B-cell antigen receptor (BCR) signaling is critical for suppressing the activation of self-reactive B cells; however, the mechanism underlying the signaling negative regulation remains elusive. Using genetic manipulated mouse models and total internal reflection fluorescence microscopy, we demonstrate that neuronal Wiskott–Aldrich syndrome protein (N-WASP), which is co-expressed with WASP in all immune cells, is a critical negative regulator of B-cell signaling. B-cell–specific N-WASP gene deletion causes enhanced and prolonged BCR signaling and elevated levels of autoantibodies in the mouse serum. The increased signaling in N-WASP knockout B cells is concurrent with increased accumulation of F-actin at the B-cell surface, enhanced B-cell spreading on antigen-presenting membrane, delayed B-cell contraction, inhibition in the merger of signaling active BCR microclusters into signaling inactive central clusters, and a blockage of BCR internalization. Upon BCR activation, WASP is activated first, followed by N-WASP in mouse and human primary B cells. The activation of N-WASP is suppressed by Bruton's tyrosine kinase-induced WASP activation, and is restored by the activation of SH2 domain-containing inositol 5-phosphatase that inhibits WASP activation. Our results reveal a new mechanism for the negative regulation of BCR signaling and broadly suggest an actin-mediated mechanism for signaling down-regulation.

Biography:

Wenxia Song completed her Ph.D. from Kansas State University and postdoctoral training from University of California, San Francisco, School of Medicine, and Northwestern University. She currently is an Associate Professor in University of Maryland. She has published more than 50 papers in peer-reviewed journals and served on several grant review panels and editor boards.