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Meeting abstract

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B cell antigen receptor-induced plasma membrane recruitment of the SH2 domain-containing inositol phosphatase is mediated by the protein tyrosine kinases Lyn and Syk

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Signals transduced by the B cell antigen receptor (BCR) are essential for B cell development and activation. Precise regulation of BCR signals is required to provide antigen-specific humoral immunity on one hand and tolerance of self proteins on the other hand. The SH2 domain-containing inositol 5' phosphatase (SHIP) is an important component for limiting antigen-induced signals in B cells. SHIP hydrolyzes the 5' phosphate of phosphatidyl-3,4,5-trisphosphate (PIP3) at the inner leaflet of the plasma membrane thereby disrupting binding motifs for the plextrine homology domains and attenuating the activities of Bruton's tyrosine kinase and phospholipase C-γ (PLC-γ2), respectively. Initially SHIP activation was believed to depend on inhibitory coreceptors like the Fc-γRIIB. However, studies using *ship-/-* DT40 cells or mice revealed that SHIP is activated downstream of BCR engagement in absence of Fcγ-RIIb also. The mechanism of BCR-induced SHIP activation and its relocalization towards the substrate PIP3, however, remains obscure to date. Here we report a real time imaging approach to analyze the molecular mechanism of BCR-induced SHIP relocalization. Interestingly, neither Fcg-RIIb nor the SHIP SH2 domain contributed to this process. Using genetic variants of DT40 B cells we could show that SHIP plasma membrane recruitment occurs upstream of PLC-γ2 activation. Our studies revealed that two apparently independent mechanisms are involved. First the Lyn-dependent assembly of a trimolecular complex comprising SHIP, the SH2 domain-containg adapter protein (Shc) and the growth factor receptor-bound protein 2 (Grb2) supports the SHIP relocalization. Second, the protein tyrosine kinase Syk is required for efficient SHIP plasma membrane recruitment.