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Dynamic interaction between lymphoid tyrosine phosphatase and C-terminal Src kinase controls T cell activation

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Lymphoid tyrosine phosphatase (LYP) and C-terminal Src kinase (CSK) are negative regulators of signaling mediated through the T cell antigen receptor (TCR) and are thought to act in a cooperative manner when forming a complex. Here, we show that dissociation of the LYP/CSK complex is necessary for recruitment of LYP to lipid rafts, where it down-modulates TCR-mediated signaling. Our findings may also explain the reduced TCR signaling associated with a single nucleotide polymorphism, which confers increased risk for autoimmunity and results in the expression of a LYP allele that can no longer bind CSK. Development of a potent and selective chemical probe of LYP allowed us to confirm that the observed down-modulation of TCR-induced signaling was due to the LYP catalytic activity. Our compound also represents a starting point for the development of a LYP-based treatment of autoimmunity.