Tyrosine 192 of P56Lck regulates T-cell activation independently of Lck/CD45 interactions

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Abstract

The tyrosine kinase p56 Lck is critical for T-cell development and activation. Lck initiates signaling events downstream of the T-cell receptor (TCR) by phosphorylating ITAM motifs located within CD3 chains, which in turn recruits the kinase Zap-70 to the activated TCR/CD3 complex. But while the regulation of its enzymatic activity is mostly attributed to two tyrosine residues, Y394 and Y505, Lck has an additional highly conserved tyrosine, Y192, whose function in the regulation of Lck activity is not fully understood. A recent study examined the role of this residue in primary T cells and T cell lines. Using knock-in mice expressing a phosphomimetic mutant of Lck (LckY192E), researchers found that Lck Y192E bound poorly to CD45 and showed hyperphosphorylation at Y505, similar to previous data in Jurkat cell lines. However, in vitro, Lck Y192E had normal enzymatic activity in both human and mouse T cells, suggesting that this residue acts independently of the interaction with CD45. The phosphomimetic protein was also recruited less to CD3 after TCR stimulation, and T-cell activation was diminished. These results suggest that phosphorylation of Y192 regulates Lck functions in two ways – by preventing Lck/CD45 interaction and modulating the recruitment of Lck to the TCR, providing insight into potential new avenues to regulate the T-cell response in autoimmune disease and cancer.