Regulatory functions of transmembrane tyrosine phosphatases in TCR signal transduction

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CD45, a transmembrane tyrosine phosphatase constitutively expressed on all nucleated hematopoietic cells, is required for antigen receptor-mediated signaling in T and B lymphocytes. The required function of CD45 involves its positive regulation of *src* kinases. CD45 function can be regulated by homo-dimerization. In previous studies using a chimeric EGFR/CD45 receptor, we found that dimerization of the CD45 cytoplasmic domain negatively regulates its function. Based on the crystal structure of a related transmembrane tyrosine phosphatase, PTPase a, we developed a model to explain the observed inhibitory effect of dimerization on CD45 function. This model proposes that a putative wedge-like structure, formed from sequences in the juxtamembrane domain of CD45, mediates dimerization-induced inhibition of catalytic function. This model was supported by experiments with mutations introduced into the EGFR/CD45 chimera expressed in cell lines. Moreover, inactivation of the wedge by introducing a single amino acid mutation into the CD45 gene of mice resulted in a lymphoproliferative and autoimmune syndrome. These data strongly support a model in which CD45 function is negatively regulated by dimerization of its cytoplasmic domain. Such regulation appears to play an important physiologic role. But, what regulates CD45 homo-dimerization? We recently obtained evidence that the distinct isoforms of CD45, which result from alternative splicing of exons 4-6, homo-dimerize to a different extent. Thus, differential expression of CD45 isoforms can play a role in titrating available CD45 tyrosine phosphatase activity in lymphocyte function.

CD148 appears to play a distinct role in regulating T cell function. Whereas CD148 is constitutively expressed on some cells, including B cells, it is inducibly expressed on activated T cells. Unlike CD45 and most transmembrane tyrosine phosphatases, CD148 has only a single tyrosine phosphatase domain. The inducible expression of CD148 inhibits TCR signal transduction. Biochemical analyses suggest that the adaptor LAT and phospholipase C g1 are targets of CD148 regulation.

Thus, the transmembrane tyrosine phosphatases CD45 and CD148 play distinct functions in regulating TCR signaling. Moreover, their functional activities are controlled through different mechanisms.

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