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CD28 augments phosphoinositide turnover

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Keywords

B7, Ca_i mobilization, CD28, co-stimulation, lipid mediator, T-lymphocyte activation

Context

CD28-B7 interaction has been implicated in the development and progression of autoimmune diseases, although the mechanism of its action is unclear. Co-stimulation plays a critical role in sustaining the TCR-CD3 mediated signals initiated by cognate APC/naive T lymphocyte interactions. The authors examined the effect of CD28 co-stimulation on the prolonged activation of inositol lipid metabolism in T lymphocytes.

Significant findings

Ligation of the TCR-CD3 complex in T lymphocytes released inositol trisphosphate (IP_3) and its breakdown products IP_2 and IP_1 into the cytoplasm as a result of the hydrolysis of membrane phosphatidyl inositol 4,5-bisphosphate (PtdIns[4,5]-P_2). This was associated with the incorporation of free phosphoinositides into the lipid membrane in the form of PtdIns, PtdIns(4)-P, and PtdIns(4,5)-P_2. Activation of T lymphocytes with monocyte chemoattractant protein-1, a chemokine that only transiently activates phospholipase C (PLC), led to the release of IP_3 and its metabolites into the cytoplasm without resynthesis of membrane phosphoinositides; thus, breakdown and resynthesis of phosphoinositides was found to be specific to TCR signals. Addition of the CD28 signal to the TCR-CD3 signal led to dramatic augmentation of phosphoinositide incorporation in T-lymphocyte membranes, and prolongation of the intracellular Ca^{2+} (Ca_i) signal. Pharmacologic inhibition of Src protein tyrosine kinase (PTK) and PLC?1 obliterated the co-stimulatory effects on Ca_i levels.

Comments

This study suggests a novel mechanism to explain CD28-mediated co-stimulation. TCR and CD28 cooperate to re-synthesize a larger store of membrane PtdIns(4,5)-P_2, and this increase is correlated with a more sustained inositol phosphate release and Cai rise. Questions remain regarding the relationship between proximal signaling proteins and lipid mediators. For instance, although the effects of pharmacologic inhibition of Src PTK and PLC?1 on Ca_i after TCR and CD28 co-stimulation was shown, parallel experiments showing their effects on the synthesis of membrane phosphoinositides were not performed. Also, it is not clear why no significant changes in the products of PI3 kinase such as PtdIns(3,4,5)-P_3 were found. Nevertheless, this study emphasizes the need for further study of PI kinases and phosphatases as important regulators of signaling and disease propagation, and as possible targets for the treatment of autoimmune and inflammatory diseases. Recent evidence shows that many phophoinositides are compartmentalized to lipid rafts where signaling molecules are concentrated and organized. Local regulation of phosphoinositide turnover in the immunologic synapse may very likely play a significant role in T-cell activation.

Methods

Ion exchange chromatography, high performance liquid chromatography, TLC

Additional information

References

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