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Vitamin D controls T cell antigen receptor signaling and activation of human T cells

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Phospholipase C (PLC) isozymes are key signaling proteins downstream of many extracellular stimuli. Here we show that naive human T cells had very low expression of PLC-γ1 and that this correlated with low T cell antigen receptor (TCR) responsiveness in naive T cells. However, TCR triggering led to an upregulation of ~75-fold in PLC-γ1 expression, which correlated with greater TCR responsiveness. Induction of PLC-γ1 was dependent on vitamin D and expression of the vitamin D receptor (VDR). Naive T cells did not express VDR, but VDR expression was induced by TCR signaling via the alternative mitogen-activated protein kinase p38 pathway. Thus, initial TCR signaling via p38 leads to successive induction of VDR and PLC-γ1, which are required for subsequent classical TCR signaling and T cell activation.

Recognition of antigens by T lymphocytes and B lymphocytes occurs via two distinct sets of receptors: the T cell antigen receptor (TCR) and the B cell antigen receptor. Antigen-primed B cells increase their antigen responsiveness in part by affinity maturation mediated by somatic hypermutation of the B cell antigen receptor genes and selection of B cell clones of higher affinity[1]. Unlike the B cell antigen receptor, the TCR cannot undergo affinity maturation. Nevertheless, antigen-primed T cells substantially increase their antigen responsiveness compared with antigen-inexperienced (naive) T cells by a process called 'functional avidity maturation'[2,3]. Phenotypic and functional studies of naive and antigen-primed human T cells have found that antigen-primed T cells show much greater proliferation and cytokine production than do naive T cells after TCR stimulation[4–7]. Subsequent studies have confirmed functional avidity maturation in wild-type and TCR-transgenic mice[8–12]. Impaired calcium mobilization in naive T cells relative to that of primed T cells after TCR triggering has been described, which suggests that the coupling of the TCR to its signaling pathway is more efficient in antigen-primed T cells than in naive T cells[13,14]. In support of that idea, the 50-fold increase in T cell responsiveness to antigen found during the early stages of viral infection in mice correlates with an increase in expression of the tyrosine kinase Lck[3].

The present model for TCR signaling[15,16] postulates that after TCR ligation, Lck is activated, which results in phosphorylation of the CD3 coreceptor complex and ζ-chains of the TCR and activation of the ζ-chain-associated protein Zap70. Activated Zap70 phosphorylates the membrane adaptor Lat, which subsequently recruits several Src homology–containing proteins, including phospholipase C-γ1 (PLC-γ1). Activation of PLC-γ1 results in the hydrolysis of phosphatidylinositol-4,5-bisphosphate to inositol-3,4,5-triphosphate and diacylglycerol. Inositol-3,4,5-triphosphate regulates intracellular calcium mobilization, and diacylglycerol regulates the activation of protein kinase C and RasGRP, an activator of the GTPase Ras. By contributing to Ras activation, PLC-γ1 indirectly controls the mitogen-activated protein kinase (MAPK) cascades and the ensuing production of transcription factors, which leads to gene expression and cell-cycle entry. Thus, in the classical TCR signaling pathway, PLC-γ1 is a central, indispensable molecule.

An alternative TCR signaling pathway leading to activation of the MAPK p38 has been described[17,18]. In this pathway, after Zap70 is activated, it directly phosphorylates and activates p38. This makes the alternative TCR signaling pathway independent of Lat and thus of PLC-γ1 and the classical Ras-MAPK cascades[17,19,20].

Here we show that naive human T cells had very low expression of PLC-γ1. TCR signaling via the classical PLC-γ1-dependent pathway was consequently greatly impaired in these cells. However, TCR signaling via the alternative p38 pathway was intact in naive T cells, and it induced expression of the vitamin D receptor (VDR). Together with vitamin D, VDR subsequently activated the gene encoding PLC-γ1, which resulted in upregulation of PLC-γ1 protein expression by ~75-fold. This much higher PLC-γ1 expression allowed TCR signaling via the classical PLC-γ1-dependent pathway and explains the higher sensitivity of primed T cells to antigen stimulation.

RESULTS

Lower sensitivity of naive T cells to TCR triggering

To analyze antigen sensitivity in human T cells during their differentiation from naive to primed T cells, we purified naive T cells from freshly drawn human peripheral blood and propagated them with beads coated with antibody to CD3 (anti-CD3) and anti-CD28. We allowed the resulting primed T cells to 'rest' for at least 24 h before

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