EVENT ABSTRACT

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The recruitment and activation of phosphatidylinositol 4-phosphate 5-kinases α critically regulate CD28-dependent signaling responses

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CD28 costimulatory receptor is a crucial determinant of the outcome of T lymphocyte activation. The engagement of CD28 by its natural ligands, B7.1/CD80 or B7.2/CD86, expressed on the surface of professional APC, lowers T cell receptor (TCR) activation threshold, thus leading to the enhancement of early signalling events necessary for efficient cytokine production, cell cycle progression, survival and regulation of T cells effector responses. CD28 is also able to act as a unique signalling receptor and to deliver TCR-independent autonomous signals, which account for its critical role in the regulation of pro-inflammatory cytokine/chemokine production and T cell survival. Most of the CD28-dependent signalling functions are initiated by the recruitment and activation of class IA phosphatidylinositol 3-kinase (PI3K), The intracytoplasmic domain of CD28 contains a N-terminal YMNM motif that following phosphorylation binds the p85 subunit of phosphatidylinositol 3-kinase (PI3K). Once activated, PI3K catalyzes the conversion of phosphatidylinositol 4,5-biphosphate (PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3) and generates the docking sites for key signalling proteins. PIP2 plays a critical role in the regulation of both cytoskeleton dynamics and second messenger generation. Indeed, PIP2 is the common source for two major distinct signalling cascades involving PI3K and PLCγ1 that often colocalize in the same signalling complexes competing for the common pool of substrate. Consequently, PIP2 levels decrease following receptor activation, thus suggesting that stimulation of PIP2 synthesis may be an essential regulatory step to sustain the activation of both PI3K and PLCγ1 following CD28 engagement. The main biosynthetic pathway of PIP2 involves phosphorylation of phosphatidylinositol 4-monophosphate (PI4P) at the D5 position of the inositol ring by PIP5K. Three PIP5K isoforms (α, β and γ) have been identified. Several data obtained in different cell systems evidenced differential subcellular localizations of each isoform. PIP5Kα, for instance, is localized at the plasma membrane, where it guarantees the local availability of PIP2.
Here we show that CD28 stimulation by both B7.1/CD80 or agonistic Abs induces the recruitment and activation of PIP5Kα in human primary CD4+ T lymphocytes. This event leads to the neo-synthesis of PIP2 that is consumed by CD28-activated PI3K. By either small interference RNA (siRNA)-driven cell silencing or overexpressing a kinase dead mutant, we evidenced that PIP5Kα activation is required for both CD28 autonomous signals regulating IL-8 gene expression as well as for CD28/TCR-induced Ca2+ mobilization, NF-AT nuclear translocation and IL-2 gene transcription. Our findings identify PIP5Kα as a critical mediator of CD28-dependent responses.

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