

Beta 1 integrin cross-linking inhibits CD16-induced phospholipase D and secretory phospholipase A2 activity and granule exocytosis in human NK cells: role of phospholipase D in CD16-triggered degranulation

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Abstract

Recent data indicate that integrin-generated signals can modulate different receptor-stimulated cell functions in both a positive (costimulation) and a negative (inhibition) fashion. Here we investigated the ability of beta 1 integrins, namely alpha 4 beta 1 and alpha 5 beta 1 fibronectin receptors, to modulate CD16-triggered phospholipase activation in human NK cells. beta 1 integrin simultaneous cross-linking selectively inhibited CD16-induced phospholipase D (PLD) activation, without affecting either phosphatidylinositol-phospholipase C or cytosolic phospholipase A2 (PLA2) enzymatic activity. CD16-induced secretory PLA2 (sPLA2) protein release as well as its enzymatic activity in both cell-associated and soluble forms were also found to be inhibited upon beta 1 integrin coengagement. The similar effects exerted by specific PLD pharmacological inhibitors (2,3-diphosphoglycerate, ethanol) suggest that in our experimental system, sPLA2 secretion and activation are under the control of a PLD-dependent pathway. By using pharmacological inhibitors (2,3-diphosphoglycerate, wortmannin, ethanol) we also demonstrated that PLD activation is an important step in the CD16-triggered signaling cascade that leads to NK cytotoxic granule exocytosis. Consistent with these findings, fibronectin receptor engagement, by either mAbs or natural ligands, resulted in a selective inhibition of CD16-triggered, but not of PMA/ionomycin-induced, degranulation that was reversed by the exogenous addition of purified PLD from *Streptomyces chromofuscus*.