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SIGNAL TRANSDUCTION MEDIATED BY LFA-1 MOLECULES: EFFECT OF LFA-1 CROSSLINKING ON CALCIUM INFLUX, PKC TRANSLOCATION, AND CYTOLYTIC ACTIVITY.

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ABSTRACT

Lymphocyte function-associated antigen (LFA)-1 is an important adhesion molecule involved in early cell to cell conjugate formation. Although several investigators have provided evidence suggesting a possible implication of LFA-1 in signal transduction, very little is known about the early biochemical events that follow the binding of LFA-1 to its ligands.

In this study, we investigated whether crosslinking of surface LFA-1 by specific monoclonal antibodies (mAbs) would lead to calcium influx and to protein kinase C (PKC) translocation from the cytoplasm to the plasma membrane. We stimulated a natural killer (NK)-like cell line, YT-INDY, with two locally generated (1B11 and 4F9) and two commercially obtained (anti-CD11a and anti-CD18) anti-LFA-1 mAbs before transferring the cells to a $^{45}Ca^{2+}$-containing medium. We demonstrated that all four mAbs induced calcium influx, but to different degrees. We also demonstrated that in the absence of crosslinking, the binding of LFA-1 by specific mAbs did not lead to a significant calcium uptake. Furthermore, we showed that most of the calcium influx occured within the first 15 min following stimulation.

Next, we investigated the activation of PKC by analyzing the phosphorylation pattern of histone IIIs in cell lysates from untreated YT-INDY and from YT-INDY treated with the four anti-LFA-1 mAbs. We demonstrated that treatment of YT-INDY with each mAb led to PKC translocation. In addition, 1B11 and 4F9 led to the phosphorylation of other cellular proteins suggesting the recruitment of different PKC subfamilies.

Our data indicate that crosslinking of LFA-1 by specific mAbs causes calcium uptake and PKC translocation and that the magnitude of the response varies according to which epitope has been engaged.

TABLE OF CONTENTS