An early event of $\beta_2$ integrin activation is the increased diffusion rate of this molecule on the cell surface, thereby providing integrin molecules with a better chance to meet the ligands. The activation of protein kinase C (PKC) stimulates integrin diffusion by releasing the cytoskeletal constraint on integrin molecules. We report here that macrophage-enriched myristoylated alanine-rich C kinase substrate (MacMARCKS), a membrane-associated PKC substrate involved in integrin activation, is required for this PKC-stimulated diffusion of integrin molecules. Using the single-particle tracking technique, we observed that the activation of PKC stimulated an 11-fold increase in the diffusion rate of $\beta_2$ integrins in wild type J774 macrophage cells but not in those expressing mutant MacMARCKS. Further evidence is provided from a MacMARCKS-deficient cell line in which phorbol esters failed to stimulate the diffusion of integrin. Transfection of wild type MacMARCKS into these cells restored the rapid diffusion rate of the $\beta_2$ integrins. The phosphorylation of MacMARCKS is important because transfection of a non-phosphorylatable MacMARCKS mutant or the addition of staurosporine eliminates the rapid diffusion rate of integrin. Furthermore, adding cytochalasin D bypasses the MacMARCKS deficiency and stimulates $\beta_2$ integrin diffusion, suggesting that MacMARCKS's involvement in integrin activation is prior or at the site of cytoskeleton. Therefore, we conclude that MacMARCKS is required for releasing the cytoskeletal constraint on integrin molecules during PKC-mediated integrin activation.
phage cell spreading, likely the result of its effect on the tyrosine phosphorylation of the focal adhesion protein paxillin and on the activation of β2 integrin (25). Recently, the involvement of MacMARCKS in β2 integrin activation was also demonstrated in cells deficient in both MARCKS and MacMARCKS expression (27). The question is how MacMARCKS is required for integrin activation.

The recent application of the single-particle tracking technique provides a new insight into lateral movement of the integrin molecule (18, 28). This technique, developed in the late 1980s, visualizes the receptor or motor movement by conjugating it with small particles (40–200 nm) (18, 28–32) and observing particle movement in living cells with video-enhanced contrast microscopy. The technique allows us to study the behavior of a small group of molecules at the nanometer spatial precision with 30-ms time resolution (33, 34). The recorded particle track (Fig. 1) can then be analyzed for its randomness or restrictions, and a diffusion coefficient can also be obtained. In many cases, cytoskeletal constraints on receptors have been observed (35–38). In terms of β2 integrin, Kucik et al. (18) showed that an important step in the PKC-stimulated integrin activation is the relaxation of cytoskeletal constraints on β2 integrin molecules. This observation provided a basis for the hypothesis that certain proteins may be required for transducing the PKC signal to the cytoskeleton.

Here we report that MacMARCKS is required for releasing cytoskeletal constraints on integrin, a process initiated by PKC activation. Either mutation or lack of MacMARCKS blocks the PKC-stimulated increase of integrin mobility. Such a block can be bypassed by adding cytoskeleton depolymerizing reagent, suggesting that MacMARCKS indeed regulates the cytoskeleton-integrin link.

**EXPERIMENTAL PROCEDURES**

**Materials—**J774 cell and Wehi 274.1 cells were purchased from ATCC. Hybridoma HB 226, which produces hamster anti-mouse β2 integrin antibody (2E6) (39), was purchased from ATCC and was grown in serum-free medium from Life Technologies, Inc. After removing the hybridoma, we collected the antibody-containing supernatant and concentrated it for later use. Monoclonal anti-MHC II (M1/42) antibody was kindly provided by Dr. R. Steinman (Rockefeller University, New York, NY). The carboxylated fluorescent latex beads were purchased from Molecular Probe (catalog no. F-8811; 200 nm in size). Dulbecco’s modified Eagle’s medium and other cell culture media were purchased from Life Technologies, Inc. Phorbol 12-myristate 13-acetate (PMA), 1,2-dioctanoyl-sn-glycerol (DOG), cytochalasin D, nocodazole, neuraminidase X, and other routine chemicals were purchased from Sigma. Macrophage chemotactrant protein-1 (MCP-1) was purchased from R&D Systems (Minneapolis, MN).

**Cell Preparation—**J774 cells, Wehi 274.1 cells, or mutated cells were cultured in Dulbecco’s modified Eagle’s medium with 10% fetal bovine serum. Before the experiment, 5 × 10⁶ cells were washed with phosphate-buffered saline (PBS) once and then treated with neuraminidase X (1 milliunit in 3 ml of buffer containing 0.13 M NaCl, 0.05 M NaAc, pH 6.5) for 30 min. Then, 0.5 ml of the cell suspension was added to 2.5 ml of Hanks’ solution and plated on an acid-washed coverslip coated with poly-l-lysine (18, 40).

**Conjugation of Antibodies to the Fluorescent Latex Beads—**Antibody against β2 integrin (2E6) either in the form of whole antibody or Fab₂ fragments at a concentration of 10 mg/ml was conjugated to the carboxylated beads as described by the manufacturer’s instructions (Molecular Probes). Since no difference between Fab2-conjugated and whole antibody-conjugated beads was observed in our single-particle tracking (data not shown), the whole antibody-coated beads were used in most cases. In a glass tube, 100 μl of antibody or BSA were added to the reaction mixture containing 50 μl of MES (200 mM), 50 μl of H₂O, and 200 μl of carboxylated latex beads and left at room temperature for 15 min. Then 2 ml of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide were added to the tube, which was vortexed for 2 h at room temperature. At the end of 2 h, 450 μl of glycine (1 mM; pH 6.25) was added, and the tube was vortexed for an additional 30 min to terminate the reaction. The excess proteins were removed by dialyzing the reaction mixture in a dialyzing bag (MW cut-off 300,000) against 1 liter of 50 mM MES (pH 6.0) overnight. The buffer was then changed to PBS by dialyzing the beads against 1 liter of PBS for another 4 h. The beads were stored at 4 °C in 1.5 ml of PBS containing 1% BSA and 0.02% azide.

Since the microbeads used here have autofluorescence, at the end of the experiments, the beads were illuminated for their fluorescence so that they would not be confused with the subcellular organelles (Fig. 1A).

**Video Microscopy—**Cells were plated on poly-l-lysine-coated coverslips in a steel chamber and placed on a water-jacketed heating stage on an inverted microscope with minimum light to prevent “burning” the cells. On poly-l-lysine coated surfaces in the serum-free medium, all types of cells used in these report adhered and spread equally well (Fig. 1B), regardless the status of MacMARCKS protein in these cells. After the cells spread and clearly showed their lamellipodia, the anti-β2 integrin antibody (2E6)-conjugated beads were added at a concentration of 4–5 beads/cell. PMA (100 nM), DOG (20 μM), MCP-1 (40 ng/ml), or cytochalasin D (0.3 μg/ml) was added at the same time as the beads. Recording was started as soon as the 2E6-conjugated beads fell onto and bound to the cells and continued for 30 s. Although the larger latex beads could be phagocytosed by macrophages, the beads used here were not phagocytosed during the observation time judged by vertical imaging on confocal microscope. This is either because the beads are too small to cause phagocytic receptor aggregation or because the 30-s observation time is too short for macrophages to phagocytose them. Beads coated with BSA or antibody against MHC II were used as controls. Bead motion was observed using video-enhanced differential interference contrast microscopy. A CCD camera system (Optronic DE750) with digital contrast enhancement and a Pentium II 400-MHz computer with 384 MB of RAM recorded the beads’ motion directly into RAM at 30 frames/second. For each track, a 36-projection movie was recorded using PIXI software (Epix Inc., Buffalo Grove, IL) and transferred later to the hard drive. Location of the beads was determined manually in each video frame for 15 s, i.e. 450 frames. As examples, tracks of 2E6-coated beads were shown for each type of cells used in this report in the presence and absence of PMA (Fig. 1B).

**Data Analysis—**For each track of a bead, the mean square displacement (MSD) for each time interval was calculated from the x-y coordinates of the particles according to Equations 1–3 (for review see, Ref. 34) by programming a macro in SigmaPlot software.¹

\[ \mu_x(nΔT) = \sum_{i=0}^{N} (x_{i+1} - x_i)^2(N + 1) \]  

\[ \mu_y(nΔT) = \sum_{i=0}^{N} (y_{i+1} - y_i)^2(N + 1) \]  

\[ MSD_{total} = \mu_x(nΔT) + \mu_y(nΔT) \]  

The obtained MSD is the sum of the random and directed motion.

\[ MSD_{total} = MSD_{random} + MSD_{directed} \]  

because

\[ MSD_{random} = 4Dt \]  

\[ MSD_{directed} = (vt)^2. \]  

Thus, we obtain Equation 7.

\[ MSD_{total} = 4Dt + (vt)^2 \]  

By fitting the MSD calculated from the experimental data to the quadratic equation (Equation 7) using the SigmaPlot software, the diffusion coefficient D can be extracted.

**Protein Phosphorylation—**Protein phosphorylation in vector- or MacMARCKS-transfected cells was determined by prelabeling cells with ³²P-labeled inorganic phosphate (200 μCi) for 1 h in phosphate-free Dulbecco’s modified Eagle’s medium containing 10% diazylated fetal bovine serum. After adding PMA (100 ng/ml), the cells were lysed in the lysis buffer (20), and MacMARCKS protein was immunoprecipitated with polyclonal anti-MacMARCKS antibody (41). The immunoprecipi-

¹The computer program created in our laboratory for use in SigmaPlot software is available to anyone upon request.
**Fig. 1.** A, autofluorescence of the latex beads distinguishes them from the intracellular organelles. B, left panel, all types of cells used in the experiments spread equally well on the poly-L-lysine-coated coverslips, with 2E6-coated fluorescent beads on their surfaces; right panel, sample tracks of 2E6-coated beads on each type of cells treated with (+PMA) or without (−PMA) of PMA. In this case, the position of particles during 15 s of motion (450 frames at 30 frames/s) was extracted and a line connecting these points was drawn.

**RESULTS**

MacMARCKS Mutation Inhibits the PMA-stimulated Increase in the Random Diffusion of β2 Integrin in J774 Macrophage Cells—To determine whether MacMARCKS mediates PKC’s effect on the cytoskeletal constraint on integrin, we first examined the effect of the MacMARCKS mutation on the diffusion rate of the β2 integrin in J774 macrophage cells. J774 macrophage cells express endogenous wild type MacMARCKS, and their β2 integrin molecules can be activated by adding PMA, which activates PKC (25). We previously showed that expression of the effector domain deletion mutant of MacMARCKS in these cells blocks PMA-stimulated β2 integrin activation (25). Therefore, we tested whether this mutant affects the increased mobility of integrin in the initial steps of integrin activation.

We first measured the diffusion of β2 integrin of the wild type J774 cells before and after PMA treatment and compared it with that obtained from a B cell line by Kucik et al. (18). In agreement with their report, we, too, observed an approximately 11-fold increase in the diffusion rate of β2 integrin molecules after adding PMA to the wild type J774 cells that were transfected with empty vector as control (Fig. 2). For comparison, we examined the diffusion rate of β2 integrin molecules in J774 cells expressing the effector domain deletion mutant of MacMARCKS, the expression of which blocks activation of β2 integrin in these cells (25). Differing from the control J774 cells, no PMA-stimulated increase of integrin diffusion was seen in these mutant J774 cells (Fig. 2). Although the diffusion rate appeared slightly higher in unstimulated MacMARCKS mutant cells than that of unstimulated wild type cells, statistical analysis showed that this difference is not significant. In addition to PMA, DOG, another PKC activator, was also tested and a similar effect on integrin mobility was observed. Same as in the case of PMA, MacMARCKS mutation also blocked the increase in the mobility of β2 integrin stimulated by DOG (Fig. 2). These data coincide with the inhibitory effect of this mutant on the activation of β2 integrin (25), suggesting that MacMARCKS is likely involved in the initial step of β2 integrin activation, i.e. the release of integrin molecules from cytoskeletal constraint. This MacMARCKS effect appears not to be universally applied to all receptors. MHC II, another membrane protein with αβ dimeric structure, showed very little change in its mobility in response to PMA treatment. MacMARCKS mutation did not alter its mobility neither (Fig. 2). As negative control, the movement of BSA-coated beads was also recorded. Similar to previous reports, we too showed that the BSA beads were basically immobile and its diffusion coefficient is far smaller (≈10⁻¹²) than that of β2 integrin and MHC II.

In addition to the pharmaceutical reagents, we also tested MCP-1, a physiological stimulus that can activate PKC and β2 integrin. Our data showed that MCP-1 was also capable of inducing the increase in the mobility of β2 integrin molecules and MacMARCKS mutation again blocked the increase (Fig. 2).

Expression of Exogenous Wild Type MacMARCKS Restores β2 Integrin Mobility in MacMARCKS-deficient Macrophage Cell Line—To further test the above conclusion, we chose a cell line, Wehi 274.1.7, that has undetectable amounts of MacMARCKS protein and whose β2 integrin cannot be activated by adding PMA (27). Our previous report showed that, when wild type MacMARCKS is expressed in these cells, the PMA-induced, β2 integrin-mediated adhesion to ICAM-1-coated surface is restored in these cells (27). Thus, this cell line is a very useful model for studying β2 integrin diffusion by using the single-particle tracking technique. We observed that, although the diffusion rate of the β2 integrins in the vector-transfected control Wehi cells is similar to that of resting J774 cells, the diffusion rate of the β2 integrins does not increase in response to PMA as in the J774 cells (Fig. 3). The data correspond to the
inability of $\beta_2$ integrin to bind ICAM-1 (27). The data further support the observation made by Kucik et al. that the increased diffusion of $\beta_2$ integrin is closely correlated with $\beta_2$ integrin-mediated adhesion (18). After wild type MacMARCKS is expressed in these cells, the diffusion rate of $\beta_2$ integrin molecules increases approximately 11-fold to a level similar to that in PMA-treated J774 cells, even without adding PMA.

We suspected that this spontaneous increase in diffusion rate without PMA may be due to the uncontrolled phosphorylation of the transfected MacMARCKS in Wehi cells as compared with the endogenous MacMARCKS in J774 cells. Therefore, we examined the basal phosphorylation level of MacMARCKS in Wehi cells. Although the phosphorylated MacMARCKS in untreated J774 cells was only 30% of that in the PMA-treated J774 cells, this ratio reached to 80% in Wehi cells (Fig. 4). To be sure that MacMARCKS is phosphorylated at its PKC sites, we also performed two-dimensional phosphopeptide mapping and found that only the previously identified PKC sites was heavily phosphorylated (Fig. 4) (20). These data showed that a higher percentage of the transfected MacMARCKS in Wehi cells was phosphorylated when compared with endogenous MacMARCKS in J774 cells. We thus speculate that this higher phosphorylation may be due to loose control of MacMARCKS phosphorylation in Wehi cells because MacMARCKS is exogenous transfected protein.

MacMARCKS Phosphorylation Is Required for Integrin Mobility

FIG. 2. PMA, DOG, and MCP-1 stimulate the diffusion rate of $\beta_2$ integrin, and MacMARCKS mutation blocks such an increase. A, a plot of MSD versus time of a 2E6-coated bead on vector-transfected control J774 cells (VEC) and J774 cells expressing the effector domain deletion mutant of MacMARCKS (ED) in the presence of PMA. The calculation was described under "Experimental Procedures." B, bar graph shows the mean and standard deviation of the diffusion coefficient ($D$) in both types of J774 cells and without or with the addition of PMA, DOG, and MCP-1. J774 minus PMA, $D = 0.74 \pm 0.19 \times 10^{-10}$; J774 plus PMA, $D = 8.10 \pm 1.52 \times 10^{-10}$; J774 plus DOG = 7.99 $\pm$ 1.43 $\times$ 10$^{-10}$; J774 plus MCP-1 = 6.54 $\pm$ 2.05 $\times$ 10$^{-10}$; ED minus PMA, $1.92 \pm 0.38 \times 10^{-10}$; ED plus PMA: $1.50 \pm 0.15 \times 10^{-10}$; ED plus DOG: $0.29 \pm 0.19 \times 10^{-10}$; ED plus MCP-1: $0.46 \pm 0.24 \times 10^{-10}$. C, in addition, the diffusion coefficient of MHC II in both wild type and mutant cells stimulated with PMA are also shown: J774 minus PMA = 10.87 $\pm$ 2.15 $\times$ 10$^{-10}$; J774 with PMA = 11.21 $\pm$ 2.23 $\times$ 10$^{-10}$. The BSA-coated beads was included as negative control, and they were basically not moving diffusion coefficient at the range of 10$^{-12}$ (data not shown).

FIG. 3. Expression of MacMARCKS in Wehi 274.1.7 cells restored the rapid diffusion rate of $\beta_2$ integrin. Deficient in MacMARCKS expression, $\beta_2$ integrin in Wehi 274.1.7 cells showed a minimum diffusion rate ($D = 0.46 \pm 0.11 \times 10^{-10}$) even with PMA stimulation ($D = 0.68 \pm 0.13 \times 10^{-10}$). Introducing wild type MacMARCKS into these cells caused $\beta_2$ integrin to move at a higher rate ($D = 5.09 \pm 1.25 \times 10^{-10}$) in the absence of PMA treatment, a rate similar to that in the presence of PMA ($D = 6.76 \pm 1.78 \times 10^{-10}$). Such a rapid diffusion rate can be abolished by adding 100 nM staurosporine ($D = 0.37 \pm 0.10 \times 10^{-10}$). The $\beta_2$ integrin in cells expressing the SA mutant of MacMARCKS also showed a low diffusion rate both without ($D = 1.60 \pm 0.35 \times 10^{-10}$) or with ($D = 1.99 \pm 0.40 \times 10^{-10}$) PMA.
PKC and Integrin Mobility

MacMARCKS phosphorylation in Wehi 274.1.7 cells and in J774 cells without and with PMA. Top, the ratio of phosphorylated MacMARCKS in cells without and with PMA stimulation. Middle, the autoradiographs of the phosphorylated proteins on SDS gels (see "Experimental Procedures"). Wehi cells show much higher phosphorylation of MacMARCKS before PMA treatment. Bottom, the two-dimensional phosphopeptide maps of each of the phosphorylated band, indicating only the PKC sites were phosphorylated (for detailed reference of the sites, see Ref. 20).

MacMARCKS is able to stimulate the integrin mobility without PMA stimulation in Wehi cells, it is insufficient to fully activate the cell to adhere to ICAM-1-coated surface until PMA is added (27). This is likely due to that the increased mobility is only a first step in cell adhesion. A successful adhesion would require the involvement of many more proteins, and some of those may also be regulated by the addition of PMA. Therefore, this observation indicates that MacMARCKS is an essential but not sufficient condition. The phosphorylation of other components stimulated by PMA may also be required to fully activate integrin.

Cytoskeleton Depolymerizing Reagents Overcome MacMARCKS Defects—The above data suggest that MacMARCKS is involved in releasing the cytoskeletal constraint on integrin molecules. Either mutation or lack of MacMARCKS in these cells prevents releasing integrin from its cytoskeletal constraint. If this is true, then artificially breaking the cytoskeletal link between integrin and cytoskeleton should overcome the defect of MacMARCKS. Kucik et al. have shown that small concentrations of cytochalasin D, an actin-depolymerizing agent, can bypass the PKC requirement and directly break the cytoskeleton to promote integrin diffusion. Following this approach, we observed that, after adding 0.3 μg/ml cytochalasin D, both mutant J774 cells and the MacMARCKS-deficient Wehi cells presented highly motile integrin molecules (Fig. 5). The data show that defects caused by MacMARCKS deficiency indeed lie prior or on the cytoskeletal constraint on the integrin molecules.

DISCUSSION

Ample evidence has suggested a model in which cytoskeleton restricts the mobility of receptors, including β₂ integrin, on the cell surface (18, 35–38). Evidence suggests that PKC activation releases the cytoskeletal constraint on β₂ integrin, and that getting free from cytoskeletal constraint and diffusing rapidly on the membrane surface is a key step in β₂ integrin activation (18). Integrin has a better chance, then, of meeting and binding the multivalent ligand and then undergoing conformational changes to a high affinity state. Bound integrins become relatively stationary, and more integrin molecules join to form a large cluster. Under the cluster, a new and stronger cytoskeletal link forms and new signals are transduced (19). In accord with this model, we have shown that the β₂ integrin in J774 cells, similar to that in the B cells (18), response to PMA stimulation by increasing its lateral diffusion rate. We further
found that MacMARCKS protein is required for this PMA-stimulated increase of integrin diffusion. Either mutation or lack of MacMARCKS blocks the PMA-stimulated increased diffusion. Such a loss of a rapid diffusion rate likely results from the inability of the cell to release the cytoskeletal constraint on $\beta_2$ integrin molecules, because after cytoskeleton is artificially depolymerized, the cells can bypass the MacMARCKS deficiency. This observation indicates that the final target of MacMARCKS is likely to be the cytoskeleton, either directly or indirectly. What is also important is that MacMARCKS phosphorylation is required, because staurosporine and actin so that it may modulate the general fluidity of the membrane. However, in such cases, MacMARCKS would have an effect on all membrane-bound receptors. An explanation is needed for its selective effects on $\beta_2$ integrin but not on MHC II molecules. Alternatively, the membrane-associated MacMARCKS may serve as an anchor for other MacMARCKS binding proteins that may be linked to integrin. The key to this alternative hypothesis is to find the links between MacMARCKS and integrins. If this is the case, then other MacMARCKS like proteins such as MARCKS and GAP-43 (44) would likely be specific for other surface receptors. In addition, whether tyrosine kinases, for example focal adhesion kinase (45), are involved in this cytoskeletal constraint should also be examined.

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Macrophage-enriched Myristoylated Alanine-rich C Kinase Substrate and Its Phosphorylation Is Required for the Phorbol Ester-stimulated Diffusion of \( \beta_2 \) Integrin Molecules

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