Monocyte-Associated Tissue Factor Is Suppressed by Phorbol Myristate Acetate

By John P. Brozna and Steven D. Carson

The monocyte is the only normal circulating cell type capable of initiating blood coagulation through the expression of tissue factor. Recently isolated peripheral blood monocytes that contain no demonstrable tissue factor activity can be induced to express tissue factor activity by a number of stimulatory agents. Monocyte-associated tissue factor activity transiently increases in response to adherence to tissue culture plates and, consistent with other reports, markedly increases after the isolated monocytes are treated with endotoxin. Phorbol myristate acetate (PMA) induced an increase in tissue factor activity at low doses (10^{-11} to 10^{-8} mol/L). Conversely, concentrations of PMA that stimulate release of oxygen metabolites or that cause the cytosol-to-membrane translocation of protein kinase C (PKC) (10^{-8} to 10^{-7} mol/L) resulted in a rapid decrease in both adherence-induced and endotoxin-induced monocyte tissue factor activity. The effects of PMA on monocytes were time- and dose-dependent with respect to PKC translocation, release of oxygen metabolites, and changes in tissue factor activity. Immunofluorescent staining of monocytes with monoclonal antibody (MoAb) HTF1-7BB, directed against human tissue factor, revealed that tissue factor antigen was induced concurrently with tissue factor activity by adherence and endotoxin and that tissue factor antigen decreased after PMA stimulation.

**Materials and Methods**

**Reagents.** PMA (LC Services, Woburn, MA) was prepared as concentrated stock solutions in dimethyl sulfoxide (DMSO) and stored at -20°C. In all experiments, the concentration of DMSO in cell medium was <0.001% and was determined to have no effect on cell viability, production of O_2^{-}, or tissue factor by monocytes. Horse cytochrome c (Type III and catalase were obtained from Sigma Chemical, St Louis and superoxide dismutase (SOD) was obtained from Diagnostic Data, Inc, Mountain View, CA. Lipopolysaccharide (LPS) purified from Salmonella abortus equus was obtained from Difco Laboratories, Detroit. In some experiments highly purified LPS from Escherichia coli K235 was used (a gift from Dr. M.J. Pabst, University of Tennessee Medical Center, Memphis). All cell culture reagents were determined to be free of endotoxin by the limulus amebocyte lysate assay (Sigma Chemical), which can detect the reagent LPS at 10 pg/mL. In addition, culture medium was routinely screened for LPS contamination by culturing monocytes in Teflon bags (Chemical Fabrics, West Palm Beach, FL) and monitoring for monocyte activation as determined by increased O_2^{-} release. Monocytes not exposed to LPS (1 to 10 pg/mL) released <75 to 100 nmol O_2^{-}/60 min/mg protein. Bovine factor VII was provided by Dr. Yale Nemerson and Arabinda Guba (Mt Sinai School of Medicine, New York). Other coagulation reagents were prepared as described previously.

**Monocyte Isolation.** Peripheral blood monocytes were obtained from healthy donors by venipuncture using 0.38% citrate as anticoagulant. Mononuclear cells were separated by a plasma-percoll procedure using a two-step discontinuous gradient. The two-step protocol causes less artifactual activation of monocytes than the standard Ficoll-Hypaque procedure as determined by production of O_2^{-}.

Plasma-percoll separated mononuclear cells consisted of approximately 64% lymphocytes, 33% monocytes, and 3% neutrophils. The monocytes were further purified by adherence to plastic tissue culture plates (Costar, Cambridge, MA) for one hour followed by washing twice with a modified Earl's salt solution (described below). This procedure resulted in cell cultures consisting of approximately 86% monocytes, 10% lymphocytes, and 4% neutrophils as determined by differential counting of stained tissue culture plates. Platelets were present at a ratio of 4 to 1 with monocytes. In some experiments platelets were removed by additional plasma-percoll gradient purification. The presence of platelets in cell cultures with monocytes resulted in an absolute increase in tissue factor activity,
but had no effect on qualitative results. Neutrophils were absent after culturing overnight.

**Cell culture procedure.** Plasma-percoll separated mononuclear cells were plated in either 16 mm multi-well tissue culture plates (Costar) at 1 x 10^6 cells/well or in 96-well microtiter plates at 2 x 10^5 cells/well in an endotoxin-free modified Earl's salt solution, consisting of 0.9 mmol/L NaCl, 14.9 mmol/L NaHCO_3, 115 mmol/L NaCl, 5.3 mmol/L KCl, 1.36 mmol/L CaCl_2, 0.8 mmol/L MgSO_4, and 0.1% glucose adjusted with CO_2 to pH 7.3. The buffered salt solution was made with endotoxin-free, glass-distilled water. A simple serum-free salt solution was used as culture medium to minimize exposure of the cells to endotoxin and other bacterial products that are present in commercial media, since serum and endotoxin promote monocyte differentiation into activated macrophages. One hour after plating, non-adherent cells were washed off the culture plates two times with buffer and then incubated at 37°C in an atmosphere containing 5% CO_2. Monocytes remained viable for at least four days in culture with this simple salt solution and remained functional as determined by trypan blue exclusion and O_2 production.

In some experiments, mixed mononuclear cells were cultured in Teflon bags (Chemical Fabrics Corp) as described previously. Concentration of monocytes in the mixed mononuclear cell suspensions was determined by differential cell counts and by determination of protein content of mixed mononuclear cells adherent to tissue culture plates.

Endotoxin-free minimum essential medium (MEM) (MA Bioproducts, Walkersville, MD) culture medium with or without 10% heat inactivated endotoxin-free fetal calf serum (FCS) was compared with the simple salt solution. There was no enhancement of viability when monocytes were cultured in MEM or MEM supplemented with serum compared with the simple salt solution.

**Measurement of superoxide anion production.** The production of superoxide anion (O_2^-) was measured by the SOD-inhibitable reduction of cytochrome c. After varying time periods in culture, monocytes were washed, and cytochrome c in one milliliter of endotoxin free Kreb's Ringer phosphate dextrose (KRPD) buffered salt solution was added to each culture well. Adherent monocytes were stimulated with PMA (0.01 to 10 nmol/L) for 60 minutes, and the amount of reduced cytochrome c was determined by measuring the absorbance at 550 nm and using the extinction coefficient 21 mmol/L-1. Results are expressed as nanomoles of O_2^- released per 60 minutes per milligram of protein.

**Measurement of monocyte-associated tissue factor activity.** Adherent mononuclear cells were incubated for various time periods, washed with Tris-buffered saline (0.05 M/L Tris, 0.1 mol/L NaCl, and 0.02% NaN_3, pH 7.6) and frozen without buffer at -70°C still adherent to the tissue culture plates for 24 to 72 hours. There was no noticeable change in total tissue factor activity during storage. Immediately before assay, 600 μL of Tris-buffered saline was added to each culture well and allowed to sit for 15 minutes at room temperature. Fluorescein labeled antibody directed against mouse IgG was then incubated with each monolayer for 15 minutes at room temperature. Controls included monocyte monolayers known to have no tissue factor activity and monocyte monolayers incubated with a mouse IgG MoAb directed against rabbit IgG.

**RESULTS**

**Monocyte-associated tissue factor activity with time in culture.** Monocytes cultured in 16-mm tissue culture plates for two days in endotoxin-free media without serum expressed a transient increase in tissue factor activity. In four different experiments the maximum tissue factor activity occurred after eight to 12 hours in culture (mean ± SD peak activity 645 ± 221 [A_405 (× 10^-8)/min]/μg protein) and tissue factor activity expressed as A_405/min/μg of monocyte protein. Protein concentration of cell extracts did not vary by more than 25%. In the chromogenic assay, PMA over the concentration range of 10^{-5} to 10^{-1} mol/L did not inhibit the activity of purified tissue factor. However, 10^{-2} mol/L PMA was associated with a 10% to 20% apparent increase in activity of purified tissue factor measured by the continuous chromogenic assay compared with activity measured in the absence of PMA. Factor X activation was not demonstrable in the absence of factor VIIa.

In those experiments where monocytes were incubated in 96-well microtiter plates, adherent monocytes were gently washed twice with Tris-buffered saline, freeze-thawed three times, and sonicated in 60 μL of Tris-buffered saline. Tissue factor activity was then measured in individual microtiter wells. In some experiments, procoagulant activity was also determined using a two-stage clot assay.

**Immunofluorescent staining of monocyte tissue factor antigen.** In order to induce a maximum amount of monocyte tissue factor activity, mononuclear cells were cultured in the simple salt solution described above supplemented with 10% FCS and 10 ng/mL LPS for 12 to 15 hours. After washing with the simple salt solution, cultures were stimulated with 10^{-2} mol/L PMA for one hour. Culture plates were then washed three times with Tris-buffered saline and air dried before storing at -70°C.

After blocking with FCS, monoclonal antibody (MoAb) IgGl, HTF1-788 directed against human tissue factor was incubated with air dried monocyte monolayers for 15 minutes at room temperature. Fluorescein labeled antibody directed against mouse IgG was then incubated with each monolayer for 15 minutes at room temperature. Controls included monocyte monolayers known to have no tissue factor activity and monocyte monolayers incubated with a mouse IgG MoAb directed against rabbit IgG.

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**Fig 1. Effect of adherence and PMA on monocyte-associated tissue factor activity.** At different time intervals tissue factor activity was measured in monocytes cultured for up to 48 hours in serum- and endotoxin-free buffered salt solution (a). Nine hours after allowing monocytes to adhere to plastic, 1.8 × 10^{-7} mol/L PMA was added to the culture media, and tissue factor activity was measured at 30 minutes, 60 minutes, and 120 minutes after PMA treatment (O). Data represent mean ± SD tissue factor activity of triplicate monocyte cultures.
tended to return to the baseline of tissue factor activity (mean ± SD, 11.9 ± 7.4 [A_{405} (× 10^{-6})/min]/μg protein), which was determined with freshly isolated peripheral blood monocytes 48 hours after culturing. One representative experiment is shown in Fig 1, solid symbols.

In the same four experiments, monocytes incubated with 8 × 10^{-7} mol/L PMA for two to 42 hours did not show a significant increase in tissue factor activity (mean ± SD peak activity 47 ± 3 [A_{405} (× 10^{-4})/min]/μg protein), in contrast to a report by Lyberg et al. In ten different experiments 10^{-9} to 10^{-4} mol/L PMA routinely stimulated release of superoxide anion (O_2^- released ranged from 50-600 nmol/L/60 min/mg protein), but monocyte-associated tissue factor activity never increased in response to PMA over the period two to 24 hours after stimulation. In all experiments 10^{-8} to 10^{-4} mol/L PMA prevented the increase in monocyte-associated tissue factor during culturing for two to 24 hours.

Because of the discrepancy with previous reports the ability of 10^{-7} mol/L PMA to induce an increase in monocyte-associated tissue factor activity was also investigated under different culture conditions. In some experiments, adherent monocytes were incubated in MEM containing 10% heat-inactivated endotoxin-free FCS with or without additional platelets and/or non-adherent lymphocytes present. Under none of these culture conditions did 10^{-7} mol/L PMA cause an increase in tissue factor activity, and in all experiments 10^{-7} mol/L PMA prevented the increase in tissue factor activity associated with monocyte adherence to tissue culture plates.

Mixed mononuclear cells cultured in serum-free endotoxin-free media in teflon bags that prevent adherence show a small increase in tissue factor activity, but of a lower magnitude than that observed with adherent cells. At 0, 3, 9, 17, 24, and 41 hours after culturing tissue factor activity was 5 ± 0.2, 12 ± 2, 108 ± 23, 89 ± 16, 20 ± 2, and 14 ± 6 (A_{405} [× 10^{-4}] /min)/μg monocyte protein (mean ± SD), respectively. The small increase in tissue factor activity nine and 17 hours after culturing may have been caused by the isolation procedure, weak adherence to teflon, or to undetectable amounts of endotoxin in the culture media.

These data taken together indicate that adherence of monocytes to tissue culture plates causes a time dependent increase in monocyte-associated tissue factor activity that returns to the baseline activity of freshly isolated peripheral blood monocytes, and that 10^{-7} mol/L PMA prevents the increase in monocyte-associated tissue factor activity associated with adherence to tissue culture plates.

**PMA induces both a decrease and increase of tissue factor activity in cultured monocytes.** In addition to blocking the increase in monocyte-associated tissue factor activity associated with adherence, it was found that 10^{-7} mol/L PMA added to adherent-monocytes near the peak in tissue factor activity nine hours after culturing caused a rapid decrease in tissue factor activity (Fig 1, open symbols). Nine hours after culturing, PMA caused monocyte-associated tissue factor activity to decrease from 892 ± 84 to 90 ± 21 (A_{405} [× 10^{-4}] /min)/μg protein within 60 minutes of stimulation. Superoxide anion was produced in response to the PMA treatment which induced loss of tissue factor activity. At 30 minutes and 60 minutes after PMA stimulation, 247 nmol/L O_2^-/mg protein and 368 nmol/L O_2^-/mg protein was produced, respectively, while tissue factor activity decreased over 80% within the same time period (Fig 1). DMSO had no effect on tissue factor activity associated with monocytes in culture or the production of O_2^- by monocytes. Monocyte viability was determined by trypan blue exclusion two hours after PMA stimulation was >98%. Protein extraction from PMA and non-PMA stimulated monocyte cultures were similar in all experiments.

In four additional experiments, 10^{-7} mol/L PMA caused a 60% to 90% decrease in endotoxin-induced monocyte-associated tissue factor activity (10 ng/mL) 60 minutes after PMA treatment (Table 1). SOD, catalase, and the protease inhibitors soy bean trypsin inhibitor and leupeptin did not block the decrease in monocyte-associated tissue factor activity following PMA treatment. In these experiments the release of superoxide and the inhibition of cytochrome c reduction by SOD was measured either in cultures that were eventually assayed for tissue factor activity or in separate paired monocyte cultures. SOD completely blocked cytochrome c reduction following PMA stimulation but had no effect on tissue factor suppression by PMA.

Low concentrations of PMA (5 × 10^{-11} to 4 × 10^{-10} mol/L) were found to induce an increase in monocyte-associated tissue factor activity eight hours after stimulation relative to controls (Fig 2 panel B), which is similar to a previous report by Janco et al. In addition, it was found that low doses of PMA (10^{-12} to 10^{-9} mol/L) did not cause PKC to translocate from the cytosol to the membrane particulate fraction of monocytes. Higher doses of PMA (5 × 10^{-7} to 5 × 10^{-4} mol/L), which induce a rapid decrease in tissue factor activity, also caused PKC activity to rapidly appear in the particulate fraction (Fig 2 panel A). In these experiments a maximum release of superoxide anion (273 ± 46 nmol/L/60 min/mg protein) occurred with 5 × 10^{-8} mol/L PMA.

**PMA-induced loss of tissue factor activity in cultured monocytes is both dose- and time-dependent.** In three different experiments, the PMA-induced decrease in mono-

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**Table 1. Effects of PMA on Monocyte-Tissue Factor Activity**

<table>
<thead>
<tr>
<th>Monocyte Treatment</th>
<th>A_{405}/min (× 10^{-4})/μg protein</th>
<th>% Inhibition</th>
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<tbody>
<tr>
<td>No LPS</td>
<td>250 ± 106 (3)</td>
<td>77 ± 32 (3) 69</td>
</tr>
<tr>
<td>No LPS + SOD</td>
<td>322 ± 44 (2)</td>
<td>102 ± 17 (2) 67</td>
</tr>
<tr>
<td>LPS</td>
<td>1333 ± 409 (4)</td>
<td>229 ± 131 (4) 83</td>
</tr>
<tr>
<td>LPS + SOD + Catalase</td>
<td>1180 ± 190 (2)</td>
<td>373 ± 81 (2) 69</td>
</tr>
<tr>
<td>LPS + SBTI + Leupeptin</td>
<td>1011 ± 224 (2)</td>
<td>253 ± 97 (2) 78</td>
</tr>
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</table>

Monocyte-associated tissue factor activity was determined in adherent monocytes cultured for eight to 15 hours in the presence or absence of 10 ng/mL endotoxin (LPS). Monocyte cultures were then stimulated with PMA in the presence of 25 μg/mL SOD and 100 μg/mL catalase, or 200 μg/mL soybean trypsin inhibitor (SBTI) and 50 μg/mL leupeptin. Data represent the mean ± SD tissue factor activity. Numbers in parentheses indicate the number of different experiments for each experimental condition. Standard deviations (SD) were calculated by combining replicates (three to five) from each different experiment.
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Fig 2. Comparison of the effect of PMA concentration on the subcellular distribution of PKC activity and the stimulation of tissue factor activity in human monocytes. Panel A. PKC activity from cytosolic (○) or particulate (■) fractions from control or PMA-treated monocytes was determined. Data represent mean ± SD of replicates from duplicate culture wells from one experiment representative of three performed. Panel B. Tissue factor activity was determined in monocytes cultured in microtiter plates for nine hours with different concentrations of PMA (△) or DMSO (●). Data represent the mean ± SD tissue factor activity of five different replicates for PMA and three different replicates for DMSO from one experiment representative of three performed.

Cyto-associated tissue factor activity was found to be dose-dependent. Figure 3 shows data from one representative experiment demonstrating that (10⁻⁷ to 10⁻⁵ mol/L) PMA stimulation of monocytes caused a rapid decrease in tissue factor activity that is dependent upon both the concentration of PMA and time after treatment. As early as 15 minutes after addition of 10⁻⁷ mol/L PMA, a significant decrease in tissue factor activity can be detected, whereas 10⁻⁴ mol/L PMA required approximately 30 minutes to cause a significant decrease in tissue factor activity. During the one hour time period examined, 10⁻⁵ mol/L PMA did not cause a significant decrease in tissue factor activity (P > .05, t-test).

Superoxide anion production was measured in the same cells in which tissue factor activity was measured. Figure 4 shows that increasing amounts of superoxide anion were produced in response to increasing amounts of PMA (10⁻⁷ to 10⁻⁵ mol/L) at each time point after PMA stimulation as expected. Higher concentrations of PMA did not cause an increase in O₂⁻ production or more rapid decrease in tissue factor activity.

Immunofluorescence detection of monocyte tissue factor antigen. In three different experiments, MoAb HTF1-7B8 directed against human tissue factor was used to identify tissue factor before and after treatment of monocytes with PMA and LPS. Figure 5 shows that monocytes cultured for one hour with 10 ng/mL LPS (Fig 5B) had less tissue factor antigen than monocytes cultured for 15 hours with LPS (Fig 5C). Furthermore, stimulation with 10⁻⁷ mol/L PMA for 60 minutes appears to cause a decrease in tissue factor antigen as determined by intensity of immunofluorescent staining (Fig 5D). In two parallel plates with identical monocytes, tissue factor activity was determined to be 1586 ± 589 (Å450 [× 10⁻⁴]/min)/μg protein for LPS-stimulated monocytes

Fig 3. Dose response of PMA-stimulated decrease of monocyte-associated tissue factor activity. Monocytes were cultured for 12 hours before the addition of 0.001% DMSO (○), 1.6 × 10⁻⁹ mol/L (△), 1.6 × 10⁻⁸ mol/L (●), and 1.6 × 10⁻⁷ mol/L (■) PMA. Tissue factor activity was measured 15, 30, and 60 minutes after PMA stimulation. Data represent mean ± SD tissue factor activity of triplicate monocyte cultures. Monocyte-associated tissue factor activity in 1.6 × 10⁻⁸ mol/L PMA-stimulated cultures is not significantly different from cultures with no PMA (t-test).

Fig 4. Dose response of PMA stimulated superoxide anion release. Monocytes were cultured for 12 hours before the addition of 1.6 × 10⁻⁹ mol/L (△), 1.6 × 10⁻⁸ mol/L (●), and 1.6 × 10⁻⁷ mol/L (■) PMA. Superoxide anion release was measured at 15, 30, and 60 minutes after PMA stimulation in the identical monocyte cultures that tissue factor activity was measured in for Fig 3. Data represent mean ± SD of triplicate monocyte cultures.
and 528 ± 18 (A_{405} \times 10^{-6})/\mu g protein for PMA-treated, LPS-stimulated monocytes, which represent a 67% decrease in tissue factor activity at the time point when the monocytes were stained. These data suggest that a decrease in tissue factor antigen is associated with PMA-induced decrease in monocyte tissue factor activity. The quantitative relationship of these independent measurements remains to be established.

**DISCUSSION**

This report demonstrates that PMA at doses that stimulate the respiratory burst or induce the movement of PKC from the cytosol to the particulate fraction in human monocytes causes a rapid decrease in monocyte-associated tissue factor activity. The effect is both dose- and time-dependent. Furthermore, 10^{-7} mol/L PMA was found to suppress the increase in tissue factor activity associated with monocyte adherence to plastic for at least 48 hours after culturing.

Doses of PMA that do not stimulate the release of \(O_2^-\) or PKC translocation (5 × 10^{-9} to 10^{-8} mol/L) were found to increase monocyte-associated tissue factor activity. This result is different from a previous report by Lyberg et al indicating that 10^{-8} to 10^{-7} mol/L PMA causes an increase in adherent monocyte-associated tissue factor activity, but similar to a report by Janco et al showing low doses of PMA (6.5 × 10^{-10} mol/L) stimulate an increase in monocyte-associated tissue factor activity. In the report of Lyberg et al, which demonstrates that 10^{-8} to 10^{-4} mol/L PMA causes an increase in tissue factor activity, PMA was solubilized with acetone instead of DMSO, and cells were incubated in medium with 20% FCS, whereas in the report of Janco et al, which support our data that PMA was solubilized with DMSO and cells were incubated in serum-free media (similar to the investigators’ experimental technique). The effective concentration of PMA dissolved in acetone and used to stimulate cells in media with 20% FCS could be decreased compared with PMA dissolved in DMSO, since DMSO is a better solvent for most hydrophobic agents and serum components could, in theory, bind to lipophilic compounds such as PMA. Regardless of the reason for the discrepancy, the investigators’ dose response curves for PMA induced \(O_2^-\) release, PKC movement from the cytosol to particulate fraction and tissue factor generation in monocytes is similar to previous reports.

PMA (10^{-9} to 10^{-4} mol/L) has been shown to increase tissue factor activity in the neoplastic myelomonocytic cell
lines HL-60 and U937 which have only a marginal capacity to generate H2O2 and O2− and have a scant number of Fc and C3b membrane receptors. It is not clear how the increase in tissue factor activity associated with myelomonocytic cell lines in response to relatively high PMA concentrations is related to peripheral blood monocyte responses to PMA since a primary response of the HL-60 and U937 cell lines to PMA is differentiation. It has been shown that the cytotoxic drugs actinomycin D, cytosine arabinoside, and cycloheximide inhibit tissue factor generation in monocytes and endothelial cells but enhance tissue factor activity in HL-60 cells. Some of these drugs have been reported to induce differentiation of HL-60 cells. Tissue factor expression induced in neoplastic cell lines by PMA may represent an early change associated with monocytic differentiation.

There are many biochemical events that are set into operation by treatment of monocytes with PMA. As a result of O2− and OH− production, endogenous membrane lipids can be oxidized, which in principle might alter tissue factor activity. While this remains a possible explanation for the decrease in tissue factor activity, SOD and catalase at levels capable of preventing the reduction of cytochrome c in the media, did not prevent the loss of tissue factor activity.

Phorbol esters are analogs of diacyl glycerols which can cause perturbations in the structure of phospholipid bilayers. Perturbation of membrane lipids by PMA might also alter tissue factor activity. However, when added to purified tissue factor in phosphatidylserine-phosphatidylcholine vesicles, PMA did not suppress tissue factor activity. It remains plausible that such perturbations of the monocyte lipids may have enhanced the activity of cell associated phospholipases which can inactivate tissue factor.

Since PMA can cause an increase in turnover of membrane proteins, PMA might cause a decrease in tissue factor activity by increasing turnover or cause tissue factor to be shed from the cell membrane. In studies conducted by the investigators, indirect immunofluorescence using a MoAb directed against human tissue factor suggests that there is a decrease in the amount of tissue factor antigen associated with monocytes stimulated with PMA compared with monocytes not treated with PMA. Experiments are currently underway to quantitate the amount of tissue factor antigen shed from the cell membrane and the amount of antigen associated with extracts of monocytes stimulated with PMA.

PKC is the major receptor for PMA which can substitute for diacylglycerol in activating PKC. The investigators showed that concentrations of PMA that cause a decrease in monocyte-associated tissue factor activity closely concurred with concentrations of PMA that cause PKC to translocate from the cytosol to the particulate fraction of monocytes. The causal relationship of activation of PKC and suppression of tissue factor activity by PMA remains to be established.

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