

Volume 12, issue 2, June 2001 | Compte-rendu

Presence of estrogen receptors in human myeloid monocytic cells (THP-1 cell line)

Abstract

Objective: To test THP-1 cells for the presence of estrogen receptors (ER) since studies have demonstrated in vivo and in vitro, the influence of estrogens on cells involved in immune response (i.e. macrophages), and since it has been demonstrated that human myeloid monocytic THP-1 cells acquire phenotypic and functional macrophage-like features after incubation with several cytokines or pharmacological agents. Design: Stimulation of THP-1 cells with phorbol myristate acetate (PMA) to prompt their differentiation into macrophage-like

cells and evaluation of the possible induction of ER. Methods: The expression of ER was analyzed by immunocytochemical assay, reverse transcriptase polymerase chain reaction (RT-PCR) and Western blot analysis. Results: After stimulation by PMA, the human myeloid monocytic THP-1 cells showed the presence of ER, together with markers of monocytic cell differentiation such as CD68, CD54 and HLA-DR. Conclusion: Estrogen effects may be exerted directly through ER on monocytes/macrophages. PMA-treated THP-1 cells may constitute a useful in vitro model to determine the effects of estrogens on macrophage-like cells and their implications in the inflammatory and immune processes.

Full text

INTRODUCTION

The differentiation of monocytic cells is accompanied by the expression of surface antigens, cytokine production, and the capacity to interact with specific ligands [1]. These activities can be modulated by interaction with different cytokines, as well as hormones [1].

THP-1 is a leukemic cell line derived from a patient with acute monocytic leukemia and, unlike other leukemic cell lines, has non-prominent chromosomal abnormalities [2, 3]. Previous studies have demonstrated that THP-1 cells acquire phenotypic and functional features of macrophages after incubation with several cytokines and/or hormones such as interferon-gamma (IFN-gamma) granulocyte-macrophage coloningy-stimulating factor (GM-CSF), or 1alpha, 25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), as well as pharmacological agents such as phorbol myristate acetate (PMA) [4-14]. In particular, the THP-1 cells, following exposure to PMA, become adherent and do not grow [13].

Several authors have reported the regulation of immune response by estrogens *in vivo* and *in vitro* [15-17]. Estrogen receptors (ER) have been identified in several cells of the immune system, including thymocytes [17], T lymphocytes $CD8^+$ [19], mononuclear cells [20] and synovial macrophages [21, 22]. Since estrogens can modulate IL-1beta and TNF-alpha mRNA expression in human monocytic THP-1 cells, we decided to investigate the induction of ER in these monocytic cells following their differentiation into macrophage-like cells [22, 23].

MATERIALS AND METHODS

Cell culture

THP-1 cells were cultured in RPMI-1640 supplemented with 10% fetal bovine serum (FBS) (containing < 0.5 EU/ml endotoxin), 2 mM L-glutamine, 100 mug/ml streptomycin, and 100 U/ml penicillin, in 5% CO_2, humidified atmosphere at 37° C. Cells used were in exponential growth. For differentiation of THP-1, PMA was added at a concentration of 50 ng/ml [23-25]. Briefly, cells were seeded into 6-well, flat-bottomed plates (5×10^5 cells/well) and incubated for 48 hours with 50 ng/ml of PMA (Sigma Chemical Co., St. Louis, MO, USA). At the end of incubation, the cells were harvested, centrifuged and used for the different experiments.

Immunocytochemical assay

THP-1 cells were cytocentrifuged on glass slides, fixed in cold acetone for 30 s, then incubated for 30 min at room temperature with a mouse monoclonal antibody (dilution 1:70) to the DNA-binding domain of ER (anti-ER mAb, BioReagents, Neshanic Station, NJ, MA1-310 clone 33).

The second and third steps were performed using the improved biotin-streptavidin-amplified detection system (BioGenex Laboratories, San Ramon, CA, USA). Briefly, we incubated the samples with the secondary antibody (biotinylated anti-mouse IgG; 1:20 dilution) for 30 min at room temperature and, after several washes (PBS), with the concentrated enzyme label (alkaline phosphatase) for 30 min, at room temperature. Control slides were treated in an identical manner, except that the first step was replaced by nonspecific mouse antibodies. The samples were dehydratated in ethanol (50, 70, 100%), fixed in xylol, mounted on Eukitt and then examined with a Leitz epifluorescence microscope (Figure 1).

Reverse transcriptase polymerase chain reaction (RT-PCR)

Total RNA was extracted from pellets containing 10^7 cultured cells (THP-1, MCF7) resuspended with 1 ml of Trizol Reagent (Life Technologies, Gaithersburg, MD, USA) and 200 mul chloroform. After the extraction, RNA was precipitated with absolute isopropanol 1:1 (or V/V), and washed with 500 mul of 75% ethanol, and

the RNA pellet was resuspended in 40 mul sterile double-distilled water containing 0.1% diethylpyrocarbonate (DEPC).

cDNA synthesis was performed in a 30 mul reaction volume containing 1 mug of total RNA, 200 U Moloney murine leukemia virus (M-MLV RT) reverse transcriptase (Promega, Madison, WI, USA), 150 ng random primers (Promega, Madison, WI, USA), 10 mM HCl pH 8.3, 3 mM $MgCl_2$, 10 mM DTT, 75 mM KCl, 30 U RNasin ribonuclease inhibitor (Promega, Madison, WI, USA), 500 muM of each of four deoxyribonucleotide triphosphates (dNTPs) (Promega, Madison, WI, USA). The mixture was incubated at 37° C for 70 min, followed by 5 min of denaturation.

To establish the presence of specific ER mRNA, we amplified a fragment of 225 bp, corresponding to the entire DNA binding domain of ER (amino acid 185-261) as previously described [1]. The sequence of the sense primer was 5'-GTG.CAG.TGT.GCA.ATG.ACT.ATG.C-3'; the reverse primer is 5'-CCT.CTT.CGG.TCT.TTT.CGT.ATC.C-3', respectively nucleotides 846-867 and nucleotides 1053-1074 of the ER mRNA sequence (GenBank accession number M12674). PCR amplification was carried out in a total volume of 50 mul, containing 5 mul of cDNA, 1.25 U TAQ polymerase (Promega, Madison, WI, USA), 1x TAQ buffer, 200 muM of each of four deoxynucleotide triphosphates (dNTPs), 1.5 mM $MgCl_2$, 100 ng for each primer. The reaction was performed on a Perkin Elmer (9600) thermal cycler (Perkin-Elmer Italia, Monza, Italy), for 4 min at 95° C; 35 cycles with an annealing time of 1 min at 59° C, 1 min at 72° C (elongation time), 30 s at 95° C (denaturation time) for 35 cycles; and a final step of 5 min at 72° C.

Ten mul aliquots of the amplified products were electrophoresed on 6%, polyacrylamide, non-denaturing gel, stained by ethidium bromide, and photographed under UV illumination. The products had the expected molecular weight (225 bp; Figure 2, lanes 3, 4 and 5) and the negative control, obtained by amplifying RNA without RT reaction (lane 2), showed no amplified products, ruling out any DNA contamination.

Western blot analysis

THP-1 pellets (15×10^4 cells) were washed three times in cold DPBS and lysed in buffer containing TRIS-HCl 20 mM, NaCl 150 mM, phenylmethyl sulfonylfluoride 1 mM, aprotinin 5 mg/ml, and Nonidet P-40 0.5% for 1 hour at 4° C. The lysates

were centrifuged for 10 min at 3,000 rpm. Samples were diluted with non-reducing sample buffer, and separated by electrophoresis on 10% SDS-PAGE gel. The proteins were transferred to Hybond-C-nitrocellulose membrane, it was blocked by PBS with 5% non-fat powdered milk at 4° C overnight.

For immunoblot analysis, the blot was incubated with monoclonal mouse anti-human ER (Novocastra Laboratories Ltd, Newcastle, UK, NCL-ER-6F11/2, clone 6F11) (1:1,000 in PBS/milk 1%) for 1 hour at room temperature on a shaker, washed extensively in PBS/Tween20 0.05% pH 7.4 (PBST) and then incubated in secondary HRP-labeled goat anti-mouse Ab (1:1,000 in PBS) for 1 hour at room temperature. After three washes in PBS, bound secondary Ab was detected by an enhanced chemiluminescence system (ECL).

Expression of surface antigens

In order to determine the potential effects of PMA on the expression of macrophage surface antigen CD54 (ICAM) (Cymbus Bioscience Ltd., Chandlers Ford, Hampshire, UK), CD68 (Dako SpA, Milan, Italy) and HLA-DR (Immunotech, Marseille, France), we analysed the PMA-stimulated THP-1 cells on a fluorescence-activated cell sorter (FACS) (Coulter®, Epics®) stained with FITC goat anti-mouse IgG as secondary antibody (Immunotech, Marseille, France).

RESULTS

Immunocytochemical findings

Cells exposed for 24 hours to 50 ng/ml PMA showed positive staining for ER, with more positive cells having a small size, a dense nucleus and a strong stain intensity, mostly located in the nucleus with some peri-nuclear cytoplasmic staining (Figure 1a). The proportion of ER positive cells ranged from 60 up to 75% in different cell cultures. Unstimulated, control cells were found to be ER negative (Figure 1b).

Reverse transcriptase polymerase chain reaction

The presence of mRNAs for ER was assessed using reverse transcription and PCR amplification of total RNA extracted from THP-1 cells. As illustrated in Figure 2, a single band of 225 bp was observed in control (unstimulated) THP-1 cells as

compared to ER-positive estrogen-responsive MCF7 breast tumor cells. This band corresponds to the expected length of a normal ER transcript, as determined by comparison with the phix-HaeIII marker fragments. Although it was not possible to use this RT-PCR method to estimate relative amounts of mRNA for ER, a comparison with normal ER mRNA amplification products was made also taking into account slight sample to sample variations. Therefore, we can not consider the RT-PCR performed in our study to be a semiquantitative assay. In fact an internal control was not used since the mRNA evaluation on agarose gel and the optical density (OD) values at 260 nm allowed us to ensure that equal amounts of mRNA were used for RT-PCR reaction from both unstimulated and stimulated PMA cells. As shown in Figure 2, control THP-1 cells expressed markedly lower amounts of ER mRNA with respect to MCF7 cells. Interestingly, treatment of cells with PMA resulted in a significant increase of this mRNA. No amplification product was detected in either blank or negative control, obtained by amplifying RNA without the RT reaction, thus ruling out any potential DNA contamination.

Western blot analysis

According to the results of Western blot analysis, the presence of ER on the PMA-stimulated THP-1 cells (50 ng/ml for 24 hours) (Figure 3). A band of molecular weight of 53 kd corresponding to the ER (PMA), was absent in unstimulated THP-1 cells (CNT).

Expression of surface antigens

The addition of 50 ng/ml PMA THP-1 cells for 24 hours resulted in a significant increase in the expression of individual macrophage surface antigens as compared to controls. PMA-stimulated cells stained positively for CD68, CD54 and HLA-DR markers (data not shown).

DISCUSSION

The results of this study show for the first time the expression of ER on PMA-stimulated human myeloid monocytic THP-1 cells, contrary to unstimulated THP-1 cells, which were ER negative. In particular, these cells, after stimulation by agents such as PMA were found to be positive for ER as demonstrated by

different detection assays, including immunocytochemical assay, RT-PCR and Western blot analysis.

Previous observations support the concept that estrogens may influence human monocyte-macrophage functions *in vitro* [26]. Moreover, Polan *et al.* reported that estrogen may modulate IL-1beta and TNF-alpha synthesis/release in cultured human peripheral monocytes [27, 28].

In addition, recent reports show that physiological concentrations of estrogens (10^{-9} M), stimulate the inducible expression of IL-1beta mRNA in PMA-treated THP-1 cells [23]. Similar PMA-induced effects were reported for TNF-alpha mRNA expression [24].

More recently, the same authors described the modulation of platelet-derived growth factor A (PDGF-A) gene expression by estrogens in the same cells [29]. Our findings support the concept that estrogens may induce these effects directly on differentiating THP-1 cells through interaction with their specific ER.

Besides, we found that these ER are expressed particularly in the late stages of THP-1 cell differentiation into macrophage-like cells, as demonstrated by the reported PMA-induced changes [23].

In fact, it should be emphasized that PMA-treated THP-1 cells, may be considered differentiated monocytic cells, acquiring functions of macrophages, as also supported by the appearance or increased expression of cell surface markers (CD68, CD54 and HLA-DR) specific for macrophages and/or differentiated monocytes with phagocytic functions [13].

These results may also account for the divergent effects of PMA on ER expression, seen in different normal or cancer cells [30]. PMA effects on ER expression may well be dependent on the cell type, other than being dose- and time-related [30].

CONCLUSION

In conclusion, estrogen effects on monocytes/macrophages seem to be directly due to ER. Our results suggest that the activated THP-1 cells may constitute a useful *in vitro* model with which to study the effects of estrogens on

monocyte/macrophages, and their implication in the inflammatory and immune processes [31].

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Figures

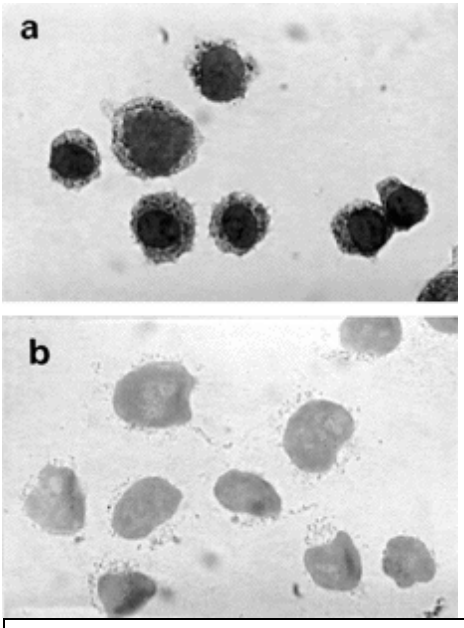


Figure 1

Immunocytochemical assay of ER in THP-1 cells.

(a) PMA-stimulated cells. **(b)** Unstimulated, control cells. THP-1 cells were exposed to a primary mouse anti-ER mAb and the specific binding revealed through a secondary step with biotinylated anti-mouse IgG, using alkaline phosphatase as the enzyme label (red staining).

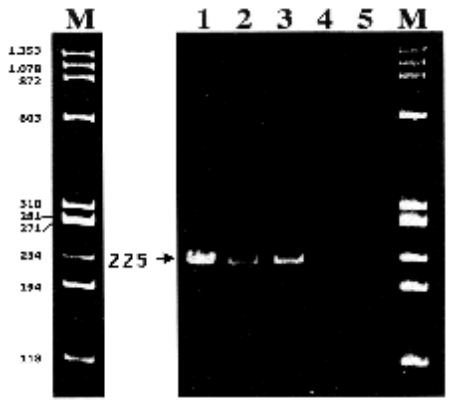


Figure 2

RT-PCR analysis of ER.

The figure shows the amplification products of an ethidium bromide-stained 6% polyacrylamide gel. Lane 1, MCF7 cells; lane 2, unstimulated (control) THP-1 cells; lane 3, PMA-stimulated THP-1 cells; lane 4, RNA-free sample (blank control); lane 5, RT-free sample (negative control). Marker lane, phi x-HaeIII digest fragments (length given in base pairs).

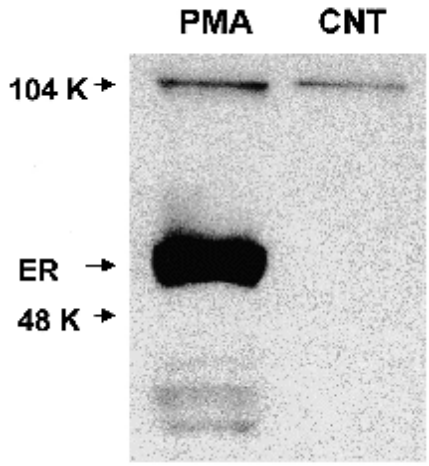


Figure 3

Western blot analysis of ER.

The figure shows a band of 53 kd, revealed by a primary mouse anti-human-ER mAb on PMA-stimulated THP-1 cells (PMA); unstimulated THP-1 cells (CNT, negative control).

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Presence of estrogen receptors in human myeloid monocytic cells (THP-1 cell line)

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