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Increased cell surface expression of histocompatibility class II IAd in c-FOS transfected clones of the P388D1 murine macrophage cell line.

Abstract

Numerous biological functions of the monocyte-macrophage lineage are affected by the presence of immunomodulators. Enhancement in transcription of c-fos has been shown in the murine P388D1 macrophage line treated by LPS, TPA, Ca++ ionophore or dibutyryl cAMP. In order to study the effects of an increased c-Fos protein level on macrophage functions, we previously have

established stable c-fos-overexpressing clones in the P388D1 cell line. Here we report that the expression of class II MHC antigens (I-Ad antigen) is increased in these clones, particularly after IFN-g treatment. No variation in the cell surface expression of IFN-g receptor was observed. The increase of I-Ad cell surface expression was well correlated with the level of I-Ad mRNA. No inducible NO synthase activity and no increase of TNF-a release were observed in c-fos transfected cells. A slight increase of the basal expression of the main class II MHC transcription factor CIITA which is further amplified by IFN-g treatment, was observed in the c-Fos overexpressing clones. This suggests that the increased I-Ad expression in clones could result from a transactivating action of the c-Fos protein on the CIITA factor.

Full text

INTRODUCTION

Class II MHC antigens are cell surface, heterodimeric proteins which present antigens to $CD4^+$ T lymphocytes and thus play a crucial role in the regulation of the immune response [1]. The expression of class II antigens is restricted to a few types of immune cells (dendritic cells, macrophages, activated T cells, B lymphocytes and thymic epithelium). The ability to present antigens is dependent on the number of class II molecules [2]. Thus, modulators of class II expression play an important role in regulating the immune response. Murine class II genes are located in the I (immune response) region of the MHC and consequently, are referred to as Ia (I region-associated) antigens [3]. Two types of Ia antigen have been defined in mice, I-A and I-E antigens, both encoded by distinct alpha-chain (A) and beta-chain (B) genes [4]. In murine macrophages, the basal expression of class II antigens is low and can be induced by IL-4, GM-CSF, CSF-1 and IFN-gamma [5-7]. Such increases can be inhibited by IFN-beta, glucocorticoids [8], PGE2 or agents which elevate intracellular cyclic AMP [9]. Thus the expression of class II MHC antigens is an important marker of functionally differentiated macrophages [10]. We assumed that some negative correlation might exist between the overexpression of c-Fos protein induced by dibutyryl cAMP and the down-regulation of Ia antigen expression achieved by agents which increase the intracellular cAMP level. To investigate the modulation of class II antigen expression in this murine macrophage cell line, we established stable transfected clones overexpressing the c-Fos proto-oncogene, using the murine c-fos gene under the control of the inducible

human metallothionein protein promoter. We previously reported the isolation of such clones. Of these, clones 4 and 44, exibiting respectively a 7- and 10-fold increase of the c-Fos protein, were selected and used in this study [11]. Here we report the basal and IFN-gamma-induced expression of Ia^d antigen at the cell surface of these clones without $CdCl_2$ induction. No increase of two other main parameters of macrophage activation, inducible NO synthase and TNF-alpha, was observed. The hypothesis that the class II antigen-up-regulation in clones could result from induction of the CIITA transactivator was investigated.

MATERIALS AND METHODS

Cells and cell culture

Monocyte-macrophage P388D1 cells and its derived, stable transfected clones 4 and 44 described previously [11], were grown as adherent cells in RPMI 1640 medium supplemented with 10% FCS, 100 units/ml penicillin, 50 mug/ml streptomycin (Biomerieux), 10 mM Hepes pH 7.4, 1 mM sodium pyruvate, 1% non-essential amino acids and 1% glutamine at 37° C in a humidified atmosphere with 5% CO_2. After seeding for 24 hours in the presence of Fos, cells were treated or not with recombinant IFN-gamma (200 UI/ml, Genzyme) in the absence of Fos.

Cell surface antigens staining

Cells (1×10^5) were centrifuged, then resuspended in 50 mul of PBS containing 5% rabbit serum for 30 min at room temperature to prevent nonspecific antibody association to the Fc receptors before the addition of specific antibodies. The FITC anti-mouse $I\text{-}A^d$ monoclonal antibody (Cedarlane) was used at a 1/50 final dilution for 30 min at room temperature, in the dark. The incubation was stopped by addition of 1.5 ml PBS + serum. Cells were centifuged for 5 min at 1,200 g and fixed by addition of 100 mul of 1% PFA (in PBS) to the cell pellet .

The FITC anti-mouse CD14 monoclonal antibody (Becton Dickinson) was used at a 1/30 final dilution under the same conditions as described above.

The alpha- and beta-chains of the IFN-gamma receptor were detected at the cell surface using the polyclonal antibodies (sc-700 and sc-972 respectively, Santa Cruz Biotechnology). As these antibodies recognize intracellular carboxy-terminus epitopes, cells were permeabilized by use of both the FACS lysing and

FACS permeabilizing solutions from Becton Dickinson (as indicated by the manufacturer) before addition of antibodies, at a 1/250 final dilution, for 30 min at room temperature. Then cells were washed with 1.5 ml of PBS + 2% FCS, centrifuged, resuspended in 50 mul of PBS + 2% FCS and incubated with the secondary antibody (anti-rabbit IgG-FITC antibody at a 1/100 final dilution, again for 30 min in the dark). Cells were washed and fixed as described above. Each antibody was used at a saturating concentration, which had been determined in preliminary experiments. Fluorescence background (determined either in the presence of the secondary antibody-FITC conjugate only, or in the presence of a non specific antiboby-FITC conjugate of the same isotype) was maintained at < 1%. Dead cells were excluded from analysis by gating. At least 15,000 cells were analyzed. Data acquisition and analysis were performed with FACScan flow cytometer and Cellquest software from Becton Dickinson.

Nitrite assay

5.10^4 cells (parental or clones) grown in 24-well plates were incubated with or without IFN-gamma for 16 or 24 hours. Nitrite content, as an indicator of NO release, was determined in the culture supernatant, by a procedure based on the Griess reaction, as a stable end product, according to Green [12].

*TNF-*alpha *determination*

2.10^5 cells (parental or clones) were grown in the same conditions as for nitrite assay. Supernatants with or without IFN-gamma were recovered after 8 or 24 hours. TNF-alpha determination was done by ELISA with the R&D Systems murine Duoset kit. Results are expressed in pg/ml by comparison with the standard curve.

Northern blot analysis

Total RNA was extracted from cells under the same conditions (with or without IFN-gamma) as previously described [11] and 10 mug were used to perform Northern blot. CIITA probe (450 bp) was obtained by RT-PCR using murine CIITA primers as described by Lennon *et al.* [13]. The I-A^d probe was obtained by EcoR1 digestion from a pUC plasmid harbouring a 900 bp sequence of I-A^d gene [14]. Murine beta-actin probe (286 bp) was obtained by PCR. Probes were radiolabeled using the Megaprime DNA labeling system from Amersham.

Densitometry of autoradiographs was performed using the Bio 1D software from Vilber Lourmat (France).

RESULTS

*Cell surface expression of I-A^d antigen in the macrophage cell line and derived clones 4 and 44: effect of IFN-*gamma *treatment*

The monocyte-macrophage P388D1 cell line and the c-fos stable transfected clones were first tested for the presence of the CD14 antigen, the specific macrophage cell surface marker [15]. The presence of the CD14 antigen was observed with identical fluorescence intensity in parental cells and clones (data not shown).

Flow cytometry analysis of I-A^d expression is shown in Figure 1A and the mean fluorescence values are indicated in Figure 1B. The basal expression of the I-A^d antigen for the parental cells is barely detectable (0.49). In the absence of IFN-gamma only a weak increase of I-A^d could be observed in clones 4 and 44 (2.22 and 4.89 respectively). After treatment with IFN-gamma for 40 hours, the expression was significantly increased in clones 4 and 44 (8.29 and 9.23 respectively) as compared to the increase seen in the parental cell line (1.83).

*Cell surface expression of IFN-*gamma *receptor in parental cells and clones*

To determine whether differences in the responsiveness to IFN-gamma could be due to a modulation of IFN-gamma receptor in the clones, we examined the cell surface IFN-gamma receptor expression. Signaling by IFN-gamma requires a ligand-binding component (alpha-chain) and an accessory factor (beta-chain). While the alpha-chain does not seem to be regulated by external stimuli [16], IFN-gamma appears to regulate expression of its own receptor beta-chain in some cell types [17]. Nevertheless, we chose to ascertain the expression of both chains of the IFN-gamma receptor since they both contribute to the high affinity receptor [16, 18]. FACS analysis of the cell surface expression showed no significant difference either in the percentage of cells expressing these chains (data not shown) or in the fluorescence intensity (Table 1).

*NO synthase expression and TNF-*alpha *release*

As for parental cells, no nitrite formation was detected in the supernatants of clones 4 and 44 either of IFN-gamma.

A weak production of TNF-alpha was observed in the presence or absence at 8 hours in the supernatant of P388D1 cells. At 24 hours, the TNF-alpha level was further increased in the presence of IFN-gamma (Table 2). Similar or lower values were observed with clones 4 and 44.

Northern blot analysis of I-A^d and CIITA mRNAs in the parental cells and clones

The increased I-A^d expression we observed in the clones, and its further increase after IFN-gamma treatment, could be due to an increased level of the transcription factor CIITA.The Northern blot was successively hybridized with the I-A^d, CIITA and beta-actin labeled probes (Figure 2A). Densitometric values for I-A^d and CIITA mRNAs were normalized according to beta-actin (Figure 2B). The constitutive expression of I-A^d mRNA is barely detectable in the parental cells but is clearly increased in clones, especially in clone 44 (0.45). IFN-gamma treatment leads to a 6- to 10-fold increase. The highest induced I-A^d mRNA expression is obtained with clone 44 (2.52), in which we observed also the highest I-A^d cell surface expression. In contrast with the I-A^d mRNA, the CIITA mRNA was easily detectable in untreated parental cells, but IFN-gamma treatment of cells (parental and clones) leads to a linear increase of both the CIITA and I-A^d mRNAs.

DISCUSSION

As a member of the AP1 complex, in association with c-Jun, the c-Fos protein has been shown to modulate the transcription of genes involved in cell proliferation and/or differentiation [19]. As far as the monocytic-macrophage lineage is concerned, a number of studies have focused on the role of c-Fos in their differentiation [20, 21]. We were interested in the immunoregulation of the class II MHC antigens expression in macrophage as an important marker of differentiation for this cell type [10]. Here we report that stable over-expression in clones of the macrophage P388D1 cell line leads to a weak cell surface expression of class II MHC antigens (I-A^d antigen), whereas its expression is barely detectable in the parental cells. Moreover, we have shown that this effect

is greatly increased by IFN-gamma treatment of clones whithout any modification of the cell surface expression of the IFN-gamma receptors.

As mentioned, no modulation of the macrophage specific CD14 antigen was observed in the clones as compared to parental cells.

IFN-gamma alone or in combination with TNF-alpha can be a potent inducer of L-arginine-dependent pathway. However, it has been shown that whereas this pathway is involved in murine activated macrophages, it is not induced by IFN-gamma (or LPS) in the P388 D1 cells [22]. The increased expression of the c-Fos transcription factor could have overshadowed this defect, but we were unable to detect nitrite formation even after stimulation by IFN-gamma. Moreover, if TNF-alpha is usually unable to initiate transcription of class II genes in macrophages, it was demonstrated either to enhance or to supress their IFN-gamma induction [23, 24]. In the present study, a lower level of TNF-alpha was observed in the c-fos clones as compared to the parental cells. Thus TNF-alpha does not appear to be involved in the positive regulation of I-A^d observed in the c-Fos overexpressing clones.

CONCLUSION

Analysis of cell lines derived from patients with the so-called bare lymphocyte syndrome has led to the identification of different factors involved in the transcriptional control of class II antigens, namely CIITA [25, 26]. This transcription factor was also demonstrated to be implicated in the induction of class II antigens by IFN-gamma [27]. So, we investigated if c-Fos could act by increasing the CIITA expression. Our results show that, in contrast to the almost undetectable I-A^d mRNA in the untreated parental cells, CIITA mRNA is easily detectable in these cells, and that c-Fos overexpresssion itself is able to effectively induce its increased level in clones treated with IFN-gamma. In the untreated clone 4, the I-A^d mRNA is slightly increased and the CIITA mRNA level is equivalent to that in the parental cells treated with IFN-gamma. Moreover, the more the c-Fos protein is expressed in both clones (7- and 10-fold respectively in clones 4 and 44), the more the I-A^d and CIITA mRNA levels are elevated after IFN-gamma treatment. This reinforces the hypothesis of c-Fos involvment in the I-A^d expression *via* transcriptional activation of the CIITA factor. Recently, the observation by Williams *et al.* [28] of a significant class II expression in CIITA-deficient mice indicates that the CIITA gene is not the unique "master" gene

controlling the MHC class II expression and that distinct regulatory pathway(s) can take place besides the CIITA mechanism. However, a more general amplification of differentiation parameters of macrophage activation such as CD14, NO synthase and TNF-alpha release, was not observed.

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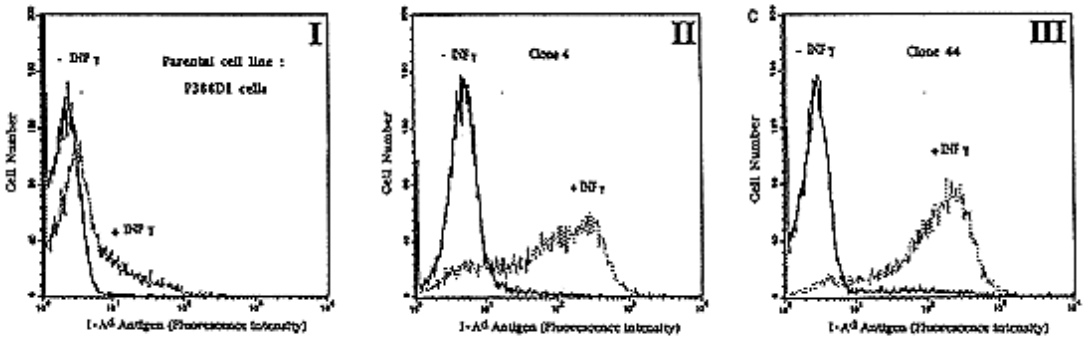
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Figures

A



B

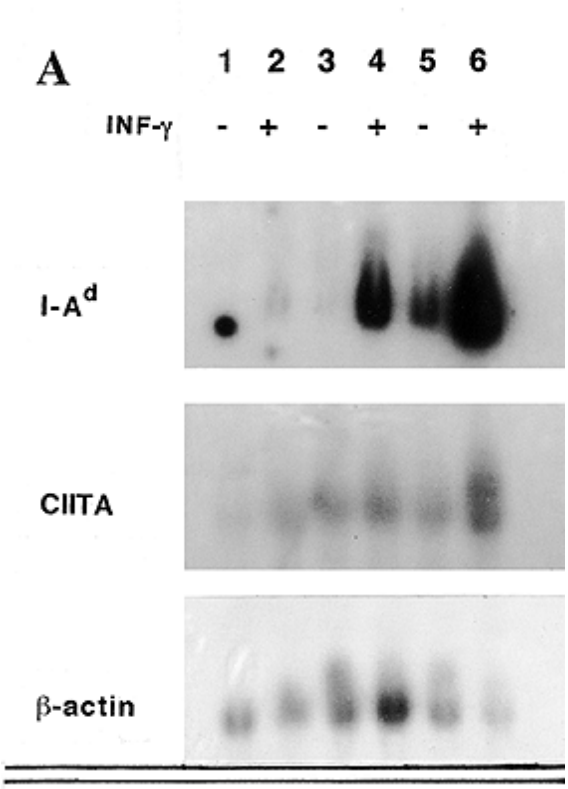
	I-Ad Expression	
	- INF-γ	+ INF-γ
Parental cells	0.49 ± 0.68	1.83 ± 0.54
Clone 4	2.22 ± 0.56 **	8.29 ± 2.36 **
Clone 44	4.89 ± 2.15 **	9.23 ± 5.05 *

Figure 1

Cell surface expression of the I-A^d antigen in the parental P388D1 cell line and its derived clones: effect of IFN-gamma **treatment.**

(A) Flow cytometric analysis of I-A^d staining after 30 hours with or without IFN-gamma. **(B)** Results are the

mean ± SD of four individual experiments. Statistical analysis of the difference between means in clones as compared with the parental cells was performed using Student's t test (* $p < 0.001$).



B

		I-A^d	CIITA
Parental cells	- INF-γ	0.02	0.08
	+ INF-γ	0.27	0.25
Clone 4	- INF-γ	0.07	0.26
	+ INF-γ	0.78	0.32
Clone 44	- INF-γ	0.45	0.15
	+ INF-γ	2.52	0.95

Figure 2

Northern blot analysis of I-A^d and CIITA mRNA expression in the macrophage P388D1 cell line and in its c-fos stable transfected derived clones. (A) Blot from the parental cell line and clones 4 and 44 mRNA, either untreated (wells 1, 3, 5) or IFN-gamma treated for

30 hours (wells 2, 4, 6). The membrane was successively hybridized (then stripped) with the following probes: I-A^d, CIITA and beta-actin. Data shown are representative of two independent experiments. **(B)** I-A^d and CIITA densitometric values normalized *versus* the corresponding beta-actin densitometric values.

Table 1
IFN-gamma receptor expression

Cell surface expression (mean fluorescence values) of a and beta-chains of the IFN-gamma receptor in the parental cell line and derived clones

Results are the mean ± SD of three individual experiments. No significant differences were observed between clones *versus* respective controls (parental cells).

	alpha-chain		beta-chain	
	– IFN-gamma	+ IFN-gamma	– IFN-gamma	+ IFN-gamma
Parental cells	5.91 ± 2.46	6.40 ± 2.21	6.85 ± 0.86	7.25 ± 2.52
Clone 4	6.79 ± 2.77	6.02 ± 2.02	5.36 ± 2.24	4.85 ± 1.99
Clone 44	4.37 ± 1.57	6.44 ± 1.69	4.08 ± 1.88	5.49 ± 2.35

Table 2
TNF-alpha release

TNF-alpha release determination by ELISA in the supernatant of clones and parental cells, after 8 or 24 hours with or without IFN-gamma

Results are the means ± SD of 2 independent experiments. Significant differences between clones *versus* respective controls

	8 hours		24 hours	
	– IFN-gamma	+ IFN-gamma	– IFN-gamma	+ IFN-gamma
Parental cells	137 ± 19	235 ± 5	199 ± 62	668 ± 190
Clone 4	39 ± 22**	53 ± 19**	77 ± 36	102 ± 39*
Clone 44	65 ± 29*	76 ± 46**	69 ± 39	88 ± 29*

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human, IFN-g, IFN-g receptor, signal transduction, cellular proliferation, apoptosis.

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interleukin-6, embryo, blastocyst, endometrium, heart, gp130.

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transforming growth factor-beta1, HIV-RNA, AIDS-dementia complex, interferon-alpha.

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HCV-RNA, interleukin-10, H9 T cells, CD81, capsid mutation, protein kinase C.

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intestinal mucosa, Crohn's disease, interleukin-18, caspase-1/ICE, immunohistochemistry, reverse transcription polymerase chain reaction.

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TNF, cytokine, LPS.

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rodent, inflammation, nitric oxide, cytokines, in vivo animal models.

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apoptosis, caspases, Hsp27, Hsp70, T lymphocytes.

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MHC class II antigens, murine macrophages, c-Fos.

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transforming growth factor-b1, interleukin-10, U. 937 cells.

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MRC5, fibroblasts, TNF receptor, RT-PCR, binding, flow cytometry.

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cytokines, lipid mediators, macrophages, rat.

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IL-10, recombinant, rat, cytokines.

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