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γ-Interferon induces expression of the HLA-D antigens on normal and leukemic human myeloid cells

(major histocompatibility complex class II antigens)

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ABSTRACT **γ-Interferon (IFN-γ) is a lymphokine produced by T lymphocytes. We find that recombinant human IFN-γ induces expression of HLA-D antigens on human promyelocytic leukemia cells (HL-60) and enhances expression of HLA-D antigens on normal human monocytes and macrophages. Induction of both HLA-D antigen expression and HLA-D mRNA accumulation occurs within 1 day of exposure of HL-60 to IFN-γ and is maximal by day 5. Maximal antigen expression occurs in the presence of 100–500 units of IFN-γ per ml. IFN-γ induces expression of DR but not DC antigens on HL-60, as confirmed by using four different murine monoclonal antibodies or one rabbit heterologous antibody. RNA blot data show that IFN-γ-exposed HL-60 cells contain mRNA for DRα and DRβ polypeptides but not for DCα and DCβ polypeptides, which also suggests that *HLA-DR* and *HLA-DC* gene regions can be independently regulated. IFN-γ induces 20% of HL-60 cells to differentiate to macrophage-like cells. However, IFN-γ dose–response studies using both HL-60 cells and a nondifferentiation variant of HL-60 cells (HL-60 blast) clearly show that induction of transcription and expression of *HLA-D* gene products by IFN-γ can be uncoupled from expression of other monocyte–macrophage characteristics. Further studies show that IFN-γ enhances expression of HLA-D antigens on normal human monocytes and macrophages. Expression of the HLA-D antigens is necessary for the interaction of macrophages and T lymphocytes; IFN-γ may play a fundamental role in this interaction.**

Human HLA-D antigens are class II major histocompatibility (MHC) locus products composed of two transmembrane polypeptides: the nonpolymorphic α-chain of ≈34,000 daltons and the polymorphic β-chain of ≈29,000 daltons (1, 2). Human MHC class II antigens are encoded in the *HLA-D* gene region, which is composed of at least three loci—*DR*, *DC*, and *SB*—and each locus codes for a different family of HLA-D antigens.

Human HLA-D antigens represent differentiation markers on hematopoietic cells (3, 4). The antigens are expressed on granulocyte and eosinophil colony-forming cells and normal and leukemic myeloblasts but are absent on normal or leukemic promyelocytes and more mature granulocytes and eosinophils. In contrast, the antigens are found on many human macrophages, which are the mature progeny of the granulocyte–macrophage colony-forming cells. We report that γ-interferon (IFN-γ) induces expression of the HLA-DR but not HLA-DC antigens on cells from a human promyelocytic line (HL-60), and HLA-D expression can be uncoupled from other monocyte–macrophage characteristics.

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MATERIALS AND METHODS

RNA Blots and Cytoplasmic Dot Blots. The mRNA isolation, RNA blot, and cytoplasmic dot blot analysis were carried out as described (5–7). The cDNA clones were generously provided and previously described by the following: HLA-DRα, B. Mach and colleagues (pHLA-DRα) (8) and D. Larhammar and colleagues (pII-α-1) (9); HLA-DRβ, B. Mach and co-workers (pHLA-DR) (10); HLA-DCα, C. Auffray and co-workers (pDCH1) (11); and HLA-DCβ, D. Larhammar and associates (pIIB-1) (12).

HLA-D Antibodies, Other Reagents, and Culture Conditions. Reactivities of the various HLA-D murine monoclonal and rabbit heterologous antibodies used in this study have been described: heterologous rabbit anti-human HLA-D (1); murine monoclonal antibodies known as H4 (13), anti-HLA-D (New England Nuclear), L243 [reacts with HLA-DR; kindly provided by T. Meeker and R. Levy (14)], and Leu 10 (reacts with HLA-DC; Becton Dickinson).

Recombinant IFN-γ (1.2×10^6 units per mg of protein), IFN-αA (9.0×10^6 units per mg of protein), IFN-α_2 (5.0×10^7 units per mg of protein), and IFN-β (9.2×10^7 units per mg of protein) were generously provided by Genentech (South San Francisco, CA), Hoffman–La Roche, Schering–Plough (Kenilworth, NJ), and CETUS (Oakland, CA), respectively. The 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] was kindly given by Hoffman–La Roche; 12-tetradecanoylphorbol 13-acetate (TPA) was purchased from Consolidated Midland (Milwaukee, WI), and dimethyl sulfoxide was purchased from Sigma.

The ME cell line is an HLA-D antigen positive T-lymphocyte cell line infected with human T-cell leukemia virus (HTLV) (15). The HL-60 promyelocytes and HL-60 blast cells were kindly provided by S. Collins and R. Gallo, and by P. Major, respectively (16, 17). The peritoneal and pleural cells were obtained from patients undergoing peritoneal dialysis and diagnostic removal of fluid from their pleural space, respectively. Pulmonary alveolar, peripheral blood, and marrow cells were obtained from normal volunteers. Written informed permission was obtained from each of the individuals from whom cells were obtained. Mononuclear cells were isolated by buoyant density centrifugation. Cells were placed in plastic flasks containing α medium (Flow Laboratories)/10% fetal calf serum, and nonadherent cells were removed from the flasks after 4 and 24 hr of culture. Over 95% of the adherent cells contained strong α-naphthyl acetate esterase activity, an enzyme present in monocytes and macro-

Abbreviations: IFN-γ, γ-interferon; MHC, major histocompatibility complex; HTLV, human T-cell leukemia virus; TPA, 12-tetradecanoylphorbol 13-acetate; $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D_3.

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phages but not in lymphocytes or granulocytes. Induction of differentiation experiments was done as described (18).

Immunofluorescence, Immunoprecipitation, and ^{125}I Immunoassay. Immunofluorescence experiments were done using either a Zeiss epi-illuminated fluorescence microscope or an EPICS V Cell Sorter (Coulter) coupled with an Innova 90 Laser.

For immunoprecipitation, cells (1×10^7) were labeled with ^{125}I by the iodogen method (19) and immunoprecipitated using either a heterologous rabbit antibody against human HLA-D (1) or a murine monoclonal HLA-D antibody (H4) (13) and *Staphylococcus* protein A. Immune complexes were boiled for 3–10 min in $NaDodSO_4$ sample buffer containing 10 mM dithiothreitol/5% 2-mercaptoethanol, subjected to $NaDodSO_4$/12% PAGE, and autoradiographed (20).

RESULTS

IFN-γ induced expression of HLA-D antigens on leukemic HL-60 promyelocytes (Fig. 1). Nearly 100% of the HL-60 cells weakly expressed the HLA-D antigens after 1 day of exposure to IFN-γ (1000 units/ml). Fluorescence intensity of antigen expression increased markedly up to 5 days of incubation with IFN-γ and then decreased on days 6 and 7. Background fluorescence on HL-60 obtained with fluorescent goat $F(ab')_2$ anti-mouse Ig was unaffected by IFN-γ exposure of the cells for days 1–7. Parallel results were obtained when indirect immunofluorescence was monitored by microscopy (data not shown). IFN-γ did not merely induce expression of Fc antibody receptors, because the cells did not bind Leu 5 as monitored by microscopy and by the cell sorter (data not shown). (The murine monoclonal Leu 5 recognizes the sheep rosette receptor, which HL-60 does not express.)

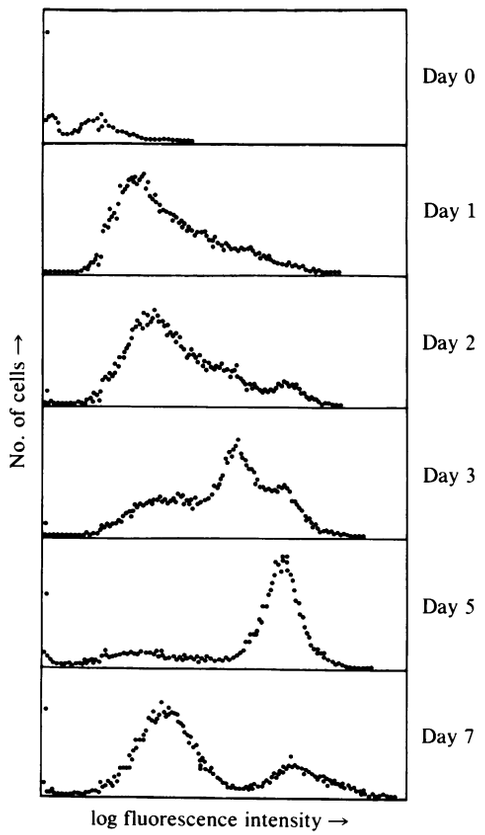

FIG. 1. Effect of IFN-γ on the expression of HLA-D antigens. HL-60 cells were cultured without (day 0) or with IFN-γ (1000 units/ml) for different days, stained with monoclonal anti-HLA-D (H4) antiserum and fluorescein-conjugated goat antimouse $F(ab')_2$ immunoglobulin, and analyzed with an EPICS V cell sorter.

Table 1. IFN-γ induction of HLA-D antigens on promyelocytic leukemia cells (dose response)

Cell type	IFN-γ, units/ml	% HLA-D positive cells (microscopy)	Mean fluorescence (EPICS V)
HL-60 promyelocytes	0	1	28
	1	12 ± 1	50
	10	22 ± 3	55
	100	63 ± 5	85
	500	87 ± 5	170
	1000	86 ± 4	180
HTLV-infected T lymphocytes (ME)	0	>95	830
B lymphocytes (P_3HR-1)	0	>95	80
T lymphocytes (HSB-2)	0	<1	27

Human leukemia cells were cultured for 3 days in different concentrations of IFN-γ and examined for HLA-D antigen expression by using the murine monoclonal antibody H4 (18). Microscopy data represent mean ± SD of three experiments. The number of HLA-D positive cells as analyzed by EPICS V (data not shown) agreed within 10% of the number of HLA-D positive cells as determined by microscopy. Mean fluorescence intensity is in arbitrary units.

Dose–response experiments showed that concentrations of IFN-γ as low as 10 units/ml induced expression of the HLA-D antigens on ≈20% of HL-60 cells within 3 days (Table 1). IFN-γ concentrations of 100–500 units/ml induced both peak intensity of HLA-D expression per cell and peak proportion of antigen positive cells with 60%–85% of the cells expressing the antigens.

We investigated the ability of a variety of different HLA-D antibodies to bind to IFN-γ-induced HL-60 cells. Rabbit heterologous antibodies against human HLA-D (1) and murine monoclonal antibodies H4 (13), anti-HLA-D (New England Nuclear), and L243 [reactive only with HLA-DR (19)] bound to nearly an equal number (>85%) of HL-60 cells exposed to IFN-γ (500 units/ml for 5 days) as monitored by indirect fluorescence microscopy (data not shown). In contrast, the murine monoclonal antibody anti-Leu 10 did not bind to IFN-γ-induced HL-60. (Anti-Leu 10 probably binds to HLA-DC but not to HLA-DR antigenic determinants.) Our findings show that products of the *HLA-DR* and *HLA-DC* gene regions can be independently regulated. As expected, none of the antibodies bound to HL-60 cells or T lymphocytes, but did bind to HTLV-infected T lymphocytes (>90%) and B lymphocytes (>80%) (Table 1).

The molecules recognized by immunofluorescence as HLA-D antigens on the surface of the leukemic cells were analyzed by $NaDodSO_4$/PAGE, after the cell-surface proteins were labeled with ^{125}I and immunoprecipitated with HLA-D antiserum (Fig. 2). The human HTLV-infected T lymphocytes (ME) contained the 34,000- and 29,000-dalton α and β polypeptide chains of the HLA-D antigens and a 63,000-dalton protein, which represents unseparated α and β polypeptide chains. The HL-60 cultured with IFN-γ (500 units/ml for 4 days) contained a 63,000-dalton protein, which probably represents the undissociated HLA-Dα and HLA-Dβ polypeptide complex. The experiments were repeated four times using either heterologous rabbit anti-human HLA-D antiserum or H4 murine monoclonal antibody to immunoprecipitate the protein complex, and the results were identical. The immunoprecipitated bands were fuzzy, consistent with the HLA-D antigens being glycoproteins. Attempts were made to dissociate the 63,000-dalton complex by adding 10 mM dithiothreitol and 5% 2-mercaptoethanol to the immunoprecipitated complex and boiling the material for 10 min before $NaDodSO_4$/PAGE, but these strong reducing and denaturing conditions did not alter the 63,000-dalton band. Neither the HL-60 cells nor the T lymphocytes (HSB-

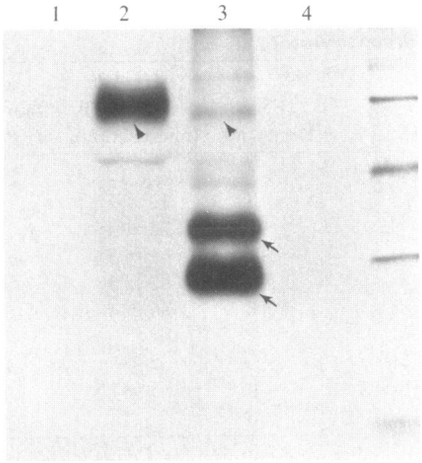

FIG. 2. $NaDodSO_4$/polyacrylamide gel analysis of material immunoprecipitated by monoclonal HLA-D antibody (H4). Immunoprecipitates from HL-60 promyelocytes (lane 1), HL-60 exposed to IFN-γ (500 units/ml for 5 days) (lane 2), HTLV-infected T lymphocytes (ME; lane 3), T lymphocytes (HSB-2; lane 4). Arrows represent α (34,000 daltons) and β (29,000 daltons) polypeptide chains; arrowheads represent the 63,000-dalton material (probably represents undissociated α and β polypeptides). Molecular weight standards are 14.3, 30, 46, 69, 93, and 200 kilodaltons.

2) expressed immunoprecipitable HLA-D antigens. Likewise, no immunoprecipitable band occurred when the lysate of IFN-γ-induced HL-60 cells was exposed to Leu 5 monoclonal antibody instead of HLA-D antibody, suggesting that the 63,000-dalton radioactive band does not represent Fc receptors (data not shown).

Accumulation of mRNA for HLA-DR Polypeptides Induced by IFN-γ. The HL-60 cells cultured with IFN-γ transcribed appropriately sized mRNA sequences that hybridized with the cDNA clones for the HLA-DRα (Fig. 3*a*, lane 4) and HLA-DRβ (Fig. 3*b*, lane 1) polypeptides, but not with cDNA clones for the HLA-DCα (Fig. 3*c*, lane 2) or HLA-DCβ (Fig. 3*d*, lane 2) polypeptides. Hybridization patterns identical to those in Fig. 3*a* were observed when the same mRNAs were hybridized with a different DRα cDNA clone [p11-α-1 (ref. 9; data not shown)]. The HL-60 cells not exposed to IFN-γ did not contain detectable mRNA for the HLA-D chains (Fig. 3). Taken together, these findings strengthen the conclusion that IFN-γ induces only HLA-DRα and HLA-DRβ transcripts and polypeptides in HL-60 cells.

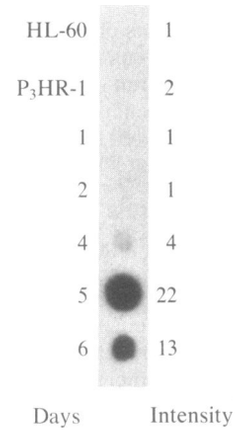

FIG. 4. Analysis of HLA-DR RNA by cytoplasmic dot hybridization from cultured cells. The HL-60 cells were cultured for 1–6 days with 1000 units of IFN-γ per ml; cytoplasmic RNA was placed on nitrocellulose and hybridized with ^{32}P-labeled pHLA-DRα (8). The P_3HR-1 (B lymphocyte) represents a weakly positive control. Intensities were determined by densitometer and results are expressed in arbitrary units. Experiments were done four times with comparable results.

The HTLV-infected T-lymphocyte line (ME) accumulated mRNA for the α and β polypeptides of both *HLA-DR* and *HLA-DC* loci. The cells contained larger quantities of DRα and DRβ mRNA sequences as compared to either B lymphocytes (P_3HR-1) or IFN-γ-induced HL-60 cells, which is consistent with the greater expression of HLA-D antigens on ME as compared to P_3HR-1 or IFN-γ-induced HL-60 (Table 1). The HTLV-infected thymocytes contained both the expected 1000-nucleotide mRNA sequence of HLA-DCα and, in addition, a 1400- and an 850-nucleotide sequence that also hybridized to the [^{32}P]cDNA DC (Fig. 3*c*). The function of the 1400- and 850-nucleotide mRNA sequences is not clear. In addition, ME contained mRNA of 1550 nucleotides, as well as the expected 1100 nucleotides, both of which hybridized to the HLA-DCβ cDNA clone (Fig. 3*d*). The longer than expected hybridizing transcripts (1550 nucleotides) were noted previously (21) and their function remains unclear. The same filters used to examine DC mRNA were washed to remove radioactivity and were rehybridized with the DRα and DRβ probes. Results were identical to those in Fig. 3 *a* and *b*.

We analyzed the time course of HLA-DRα mRNA accu-

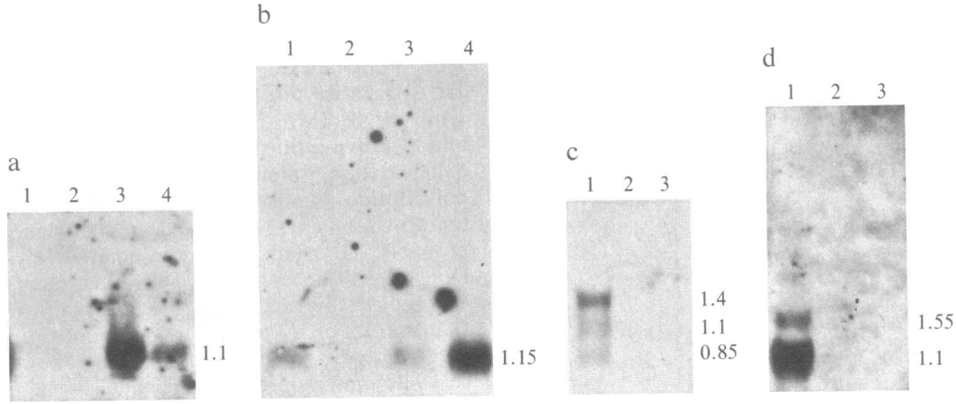

FIG. 3. Induction of HLA-D mRNA in HL-60 exposed to IFN-γ. Poly(A)$^+$ RNA (5 μg) was denatured and electrophoresed in a 1.0% agarose gel containing formaldehyde (6, 7) and transferred to either nitrocellulose or a nylon-based filter. The filters were hybridized with ^{32}P-labeled HLA-D cDNA clones. (*a*) HLA-DRα (8); (*b*) HLA-DRβ (9); (*c*) HLA-DCα (10); (*d*) HLA-DCβ (12). Total poly(A)$^+$ RNA samples were from the following sources: (*a*) HL-60 exposed to IFN-γ (lane 1), HL-60 (lane 2), P_3HR-1 (B lymphocyte) (lane 3), ME (HTLV-infected T lymphocyte) (lane 4); (*b*) HL-60 granulocytes (induced with dimethyl sulfoxide) (lane 1), HL-60 (lane 2), ME (lane 3), HL-60 exposed to IFN-γ (lane 4); (*c* and *d*) ME (lane 1), HL-60 exposed to IFN-γ (lane 2), HL-60 (lane 3). Molecular weights are in kilobases.

Table 2. Effect of IFN-γ and other agents on HL-60 blast and HL-60 promyelocyte leukemia cells

Cell line	IFN-γ, units/ml	Other agents	% HLA-D positive cells (microscopy)	Monocyte–macrophage morphology, % cells	NAE positive, % cells	Reduction NBT, % cells
HL-60 promyelocytes	0		<1	<3	<3	<3
	100		63 ± 4	<3	<3	<3
	1000		87 ± 4	17 ± 2	14 ± 2	21 ± 3
	0	TPA (50 nM)	<1	89 ± 4	85 ± 4	9 ± 1
	0	$1,25(OH)_2D_3$ (0.5 μM)	53 ± 5	63 ± 5	82 ± 5	86 ± 4
	0	IFN-αA, IFN-α_2, or IFN-β (10–10,000 units/ml)	<1	<5	<5	<5
HL-60 blasts	0		<1	0	0	0
	1000		85 ± 3	0	0	0
	0	Other agents*	<1	0	0	0

Cells were placed in culture on day 0; IFN-γ or other agents were added on day 1; cells were analyzed for HLA-D antigen expression and for macrophage differentiation on day 7. Data represent the mean ± SD of three experiments and at least 200 cells were counted for each test. NAE, α-naphthyl acetate esterase; NBT, nitroblue tetrazolium.
*TPA (5×10^{-8} M); $1,25(OH)_2D_3$ (5×10^{-7} M); IFN-αA, IFN-α_2, IFN-β (10–10,000 units/ml).

mulation in HL-60 cells cultured with IFN-γ (1000 units/ml) (Fig. 4). The mRNA accumulation for HLA-DRα in IFN-γ-exposed HL-60 cells paralleled the HLA-DRα antigenic expression on the cells. Peak HLA-DRα mRNA accumulation occurred on day 5 of IFN-γ exposure. Cells at days 6 and 7 of IFN-γ exposure decreased their HLA-DRα mRNA content. HL-60 cells not cultured with IFN-γ had little or no detectable DRα mRNA.

Uncoupling of HLA-D Antigen Expression and Macrophage Differentiation. High concentrations (1000 units/ml) of IFN-γ induced ≈20% of HL-60 cells to develop the morphology, cytochemistry, and function of macrophages (Table 2). However, IFN-γ could induce expression of HLA-D antigens on HL-60 without inducing macrophage characteristics of the cells. One thousand units of IFN-γ per ml induced 20% of the cells to differentiate toward macrophages but induced 90% of the cells to express the HLA-D antigens. Likewise, 100 units of IFN-γ per ml induced 60% of HL-60 cells to express the antigens but none of the cells acquired any other macrophage-like characteristics. Also, a variant subline of HL-60, known as HL-60 blast, developed expression of the HLA-D antigens after culture with IFN-γ (Table 2). In contrast, none of the HL-60 blast cells developed monocyte–macrophage characteristics after culture with IFN-γ (Table 2).

As previously shown (18, 22), HL-60 cells differentiated to monocytes and macrophages after exposure either to the potent phorbol diester, TPA (50 nM), or to the active metabolite of vitamin D [$1,25(OH)_2D_3$; 0.5 μM] (Table 2). The $1,25(OH)_2D_3$ induced ≈50% of the cells to express the HLA-D antigens, but 0.5 nM TPA did not induce HLA-D antigen expression (Table 2). Interferons enhance cellular expression of MHC class I antigens; we found that IFN-αA, IFN-α_2, and IFN-β did not induce expression of HLA-D antigens on HL-60. The HL-60 differentiated to granulocytes (>80%) in the presence of dimethyl sulfoxide (1.25%) and, as expected, these cells did not express the HLA-D antigens (data not shown).

Enhanced Expression of HLA-D Antigens on Normal Human Monocytes and Macrophages by IFN-γ. Prior studies showed that murine macrophages expressed the MHC class II antigens, but the cells often lost their antigen expression when placed in liquid culture for several days (23, 24). Conditioned medium from activated T lymphocytes reinduced expression of MHC class II antigens on the cultured macrophages (23, 25). The material in the T-lymphocyte-conditioned medium that stimulated HLA-D expression was probably IFN-γ (24). Recently, Basham and Merigan showed that IFN-γ enhanced expression of the HLA-D antigens on cultured normal human peripheral blood monocytes (26). We confirm and extend this finding. IFN-γ enhanced the HLA-D antigen expression on normal human monocytes–macrophages from each of the tissue sources examined including blood, bone marrow, alveoli, and pleural space (Table 3). The mean percent increase of HLA-D positive cells after IFN-γ exposure as determined by indirect fluorescence mi-

Table 3. Effect of IFN-γ on the expression of HLA-D antigens on human monocytes and macrophages

Tissue	IFN-γ (1000 units/ml)	% HLA-D positive (microscopy)	% increase*	^{125}I immunoassay, cpm	% increase*
Peripheral blood	+	63 ± 5	50	3300 ± 300	43
	−	42 ± 3		2300 ± 200	
Bone marrow	+	66 ± 6	47	3400 ± 400	62
	−	45 ± 3		2100 ± 300	
Pulmonary alveolar	+	83 ± 4	26	3700 ± 300	48
	−	65 ± 5		2500 ± 300	
Pleural	+	62 ± 6	34	3300 ± 500	43
	−	41 ± 5		2300 ± 200	
HL-60 (promyelocytes)	+	>86		1200 ± 200	240
	−	<3		360 ± 60	
ME (HTLV-infected T lymphocytes)	−	>95		2200	
HSB-2 (T lymphocytes)	−	<3		350	

Adherent monocytes and macrophages were harvested from culture after 5 days of incubation with IFN-γ at 1000 units/ml. Cells were examined for both α-napthyl acetate esterase positivity (≥95%) and expression of HLA-D antigens as determined by indirect fluorescence microscopy and by binding of ^{125}I-labeled protein A to the cells exposed to HLA-D antibody H4 (13). Results represent the mean of at least triplicate samples.
*Percent increase = (experimental minus control)/(control) × 100.

croscopy varied between 26% (alveolar pulmonary macrophages) and 50% (peripheral blood monocytes). The mean quantitative increase of HLA-D antigens expressed on the IFN-γ-exposed cell population as determined by ^{125}I-labeled protein A immunoassay varied from 43% (peripheral blood monocytes and pleural macrophages) to 62% (bone marrow macrophages).

DISCUSSION

The studies show that IFN-γ can induce expression of the HLA-DR antigens on HL-60 promyelocytes in a time- and dose-dependent fashion. In contrast, IFN-αA, IFN-α_2, and IFN-β were not able to induce HLA-D expression on HL-60 cells. IFN-γ probably modulates HLA-D expression at the transcriptional level. The IFN-γ-exposed HL-60 cells synthesized mRNA for HLA-DRα and HLA-DRβ chains, but untreated cells contained no detectable transcripts for *HLA-D* gene products. Cytoplasmic dot hybridization showed that the concentration of mRNA for HLA-DRα in IFN-γ-exposed HL-60 cells paralleled the HLA-D antigen concentration on the same cells. IFN-γ did not induce detectable HLA-DCα and HLA-DCβ mRNA in HL-60 cells. Likewise, DR, but not DC, antigens are expressed on IFN-γ-exposed HL-60 cells. Taken together, our results suggest that gene products of the *HLA-DR* and *HLA-DC* gene region can be independently regulated.

We identified a major 63,000-dalton band of radioactivity when IFN-γ-induced HL-60 cell surfaces were labeled, immunoprecipitated with HLA-D antibody, and examined after $NaDodSO_4$/PAGE. The 63,000-dalton band probably represents the unseparated 34,000- and 29,000-dalton α and β polypeptide chains. We were not able to dissociate the HLA-Dα and HLA-Dβ chains on IFN-γ-induced HL-60 cells even after fairly vigorous techniques. The 63,000-dalton band was not seen, however, in immunoprecipitates of HL-60 cells not exposed to IFN-γ. Also, only antibodies specific for HLA-D antigens were able to immunoprecipitate the 63,000-dalton protein, suggesting that the 63,000-dalton protein did not represent Fc receptors. Nevertheless, we lack unequivocal proof that the 63,000-dalton protein is the unseparated HLA-Dα and HLA-Dβ chains; further studies will be necessary.

The expression of HLA-D antigens on myeloid cells is frequently associated with a specific stage of differentiation. We found that after IFN-γ exposure, a greater percentage of HL-60 cells expressed the HLA-D antigens than developed other characteristics of monocytes–macrophages. Likewise, IFN-γ-exposed HL-60 blast cells expressed HLA-D antigens but none of the cells developed any other monocyte–macrophage characteristics. Our experiments also showed that TPA and $1,25(OH)_2D_3$ induced HL-60 to develop characteristics of monocytes–macrophages (Table 2), but only $1,25(OH)_2D_3$ induced expression of HLA-D antigens on HL-60 cells. Taken together, these findings suggest that the normal developmental program of monocyte–macrophage differentiation can be uncoupled, and expression of the DR antigens on myeloid cells is probably under separate genetic control.

We showed that IFN-γ enhanced expression of the HLA-D antigens on cultured human pleural, alveolar, peripheral blood, and bone marrow monocytes and macrophages. The physiological importance of HLA-D modulation by IFN-γ on myeloid cells is not clear. We hypothesize that IFN-γ may be a component of a coordinated pleiotropic immune response. T lymphocytes with helper/inducer activity recognize foreign antigens only when the antigens are presented by macrophages that express the same MHC class II glycoproteins as the T lymphocytes. Antigen-stimulated macrophages can synthesize interleukin 1, which may stimulate helper/inducer T lymphocytes. Stimulated T lymphocytes can express HLA-D antigens and can produce IFN-γ. The IFN-γ can activate macrophages and enhance their expression of HLA-D. Enhanced HLA-D expression on both macrophages and T lymphocytes might facilitate macrophage–T-lymphocyte interactions.

Note Added in Proof. After this manuscript was submitted, another report showed that IFN-γ induces cell-surface expression of HLA-D antigens on HL-60 (27).

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