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The Fc receptor, FcRI, and other activation molecules on human mononuclear phagocytes after treatment with interferon-gamma

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SUMMARY

Human monocytes and the myeloid cell lines U937 and HL60 have been tested with monoclonal antibodies (MoAbs) reactive with 22 different cell surface molecules before and after treatment with interferon-gamma (IFN-γ). An increase in the expression of the high affinity Fc receptor, FcRI, and the receptor for interleukin 2, IL-2R, were the most consistent alterations which were observed. In addition, expression of the gp55 molecule recognized by CD14 MoAbs was decreased on monocytes. Of the MHC Class II molecules, there was little expression by the myeloid cell lines and no enhancement after IFN-γ treatment. In contrast monocytes expressed all three MHC Class II subloci with DR $\gg$ DQ and DP. However there was much variation in IFN-γ-mediated increase in expression of the individual subregions. In monocytes, the alteration in expression of FcRI, IL-2R, gp55 and MHC Class II molecules took place in a co-ordinate fashion and reached a plateau only after 48 h. In U937 cells, activation proceeded more rapidly and was at maximum levels between 12–16 h. This increase in FcRI appears to be a hallmark of IFN-γ activation for mononuclear phagocytes (Mph) as the other alterations are either not found on all types of Mph (gp55, MHC Class II) or are induced by other cytokines on Mph and on other cells (IL-2R, MHC Class II). Conversely, other cytokines do not induce FcRI on Mph. These results also suggest that the cell membrane phenotypic changes induced in Mph by IFN-γ may not be extensive and that FcRI must play a specific role in the IFN-γ-activated Mph.

Keywords mononuclear phagocytes IFN-γ FcRI

INTRODUCTION

The mononuclear phagocyte (Mph), ubiquitous within the body, will come into contact with many molecules which are capable of affecting its function. One of the most potent is IFN-γ, a lymphokine which is produced by activated T cells (Chang *et al.*, 1982). IFN-γ causes the respiratory burst pathway to be activated, it is a priming or potentiating signal for direct tumour cell killing and it causes Mph to be more active in antibody-dependent tumour cell killing (ADCC) and to become more phagocytic (reviewed in Trinchieri & Perussia, 1985; Hogg, 1986). The increased ability of activated Mph to kill intracellular pathogens may be associated with several of these functions. These alterations in activity are the result of molecular changes which are not completely understood. However modifications in cell membrane molecules ought to affect those activities which require cell contact. In this study we have looked for changes in the human Mph phenotype mediated by IFN-γ using monoclonal antibodies to 22 molecules found on Mph. The conclusion is that an increase in expression of FcRI is a hallmark of Mph activation by IFN-γ.

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MATERIALS AND METHODS

Cells and cell lines

Monocytes were purified and characterized as described previously (Hogg *et al.*, 1984) and were incubated as non-adherent clusters on bacteriological petri dishes (Sterilin) in RPMI-1640 containing 5% fetal calf serum (FCS). Fractionated monocytes were always analysed with a CD3 MoAb, UCHT1, to monitor contamination by T cells. Preparations which contained detectable T cell levels were not used. The histiocytic cell line, U937, and the promyelocytic cell line, HL60, were maintained as described (Hogg *et al.*, 1984).

Interferons

Human recombinant interferon-gamma (rIFN-γ) named Immuneron, at $1{\cdot}3 \times 10^6$ units/ml, was a gift from Biogen, Boston and Geneva. Human interferon-alpha (IFN-α), named Wellferon, at 11×10^6 units/ml (Wellcome), was a gift from Dr Ian Kerr (I.C.R.F.).

Table 1. Monoclonal antibodies used in this study

Monoclonal antibody	Isotype	CD group	Specificity	Reference
Myeloid				
SJ1D1	IgG1	CD13	gp150	LDAIII†
MEM-15, UCHM1*	IgG1, IgG2a	CD14	gp55	LDAIII, Hogg *et al.*, 1984
29	IgM	CD15	X hapten	Bernstein & Self, 1986
CLB Fc-Grant	IgG2a	CD16	FcRIII, p50–60	LDAIII
T5A7	IgM	CDw17	lactoceramide	LDAIII
TM3	IgG1	CD31	gp130–140	LDAIII
CIKM5	IgG1	CDw32	FcRII, p40	LDAIII
L4F3	IgM	CD33	gp67	LDAIII
My10	IgG1	CD34	gp115	LDAIII
E11	IgG1	CD35	CR1, p220	Hogg *et al.*, 1984
5F1	IgM	CD36	gp85	LDAIII
10.1*	IgG1	–	FcRI, p72	Dougherty *et al.*, 1987
52U	IgG1	–	p55	unpublished
LFA-1 Family				
MHM24	IgG1	CD11a	LFA-1 α chain	LDAIII
44	IgG1	CD11b	CR3 α chain	Malhotra *et al.*, 1987
3.9	IgG1	CD11c	p150,95 α chain	Hogg *et al.*, 1985
MHM23	IgG1	CD18	β chain	LDAIII
MHC Class II				
52,35	IgG3, IgG3		DR/DQ	Allen & Hogg, 1987
DA6 164	IgG1		DR β chain	van Heyningen, 1982
SDR4.1	IgG2b		DQw1	Bodmer *et al.*, 1984
Leu10	IgG1		DQw2	Chen *et al.*, 1984
2HB6	IgG1		DQw3	Shannon *et al.*, 1984
TU22	IgG?		DQ monomorphic	Powelec *et al.*, 1982
B7/21	IgG2a		DP	Watson *et al.*, 1983
Other				
anti-Tac	IgG2a	CD25	IL-2R	Uchiyama *et al.*, 1981
UCHT1, OKT3	IgG1, IgG2a	CD3	T3	LDAIII

* $(Fab')_2$ fragments used in some experiments.

† LDAIII refers to the Third International Workshop on Human Leukocyte Differentiation Antigens, Oxford, 1986.

Incubation of cells with interferon-gamma

Purified monocytes or the cell lines U937 and HL60 were incubated at an initial cell concentration of 5×10^5/ml in RPMI-1640 plus 5% FCS. Routinely, U937 and HL60 were incubated with 100 units/ml of IFN-γ and monocytes with 500 units/ml for a 24 h period unless noted.

Monoclonal antibodies

The MoAbs used in this study are listed in Table 1. Antibodies selected from the panel supplied by the Third International Workshop on Human Leukocyte Differentiation Antigens (Oxford) are indicated as LDA III (Hogg & Horton, 1987).

Immunofluorescence assay and FACS analysis

Cells in suspension (10 μl of 4×10^7 cells/ml) were incubated on ice for 30 min with 30 μl of hybridoma tissue culture supernatant or ascitic fluid (diluted 1:200) followed, after appropriate washing, by 25 μl of fluorescein isothiocyanante-conjugated (FITC) goat anti-mouse IgG (Cappel Laboratories, Downington, Pa., 1:100). All solutions contained 1% human serum to prevent 'non-specific' Fc receptor binding. MoAbs W6/32 specific for HLA-A,B,C and 2D1, specific for leucocyte common antigen (CD45), were used as positive controls. Negative controls consisted of either normal medium as the first layer or the following murine Ig subclass controls: 52U, IgG1 MoAb reacting with monocyte intracellular protein (unpublished), anti-CD3 MoAbs UCHT1 (IgG1) and OKT3 (IgG2a), AUA1, an anti-epithelial MoAb (IgG1), plus 4U, a null MoAb (IgG2a). The negative reaction of the IgM MoAb 29 provided an internal control for this Ig subclass.

The percentage of MoAb-positive cells was determined using a modified FACSII (ICRF). In addition, a relative measure of antigen expression was obtained by determining the ratio of the median level of fluorescence intensity for each antibody-positive population. Results are presented as the $\log_{10}$ ratio of antigen expression of IFN-γ-treated to untreated cells which were incubated for the same length of time.

RESULTS

Effect of IFN-γ on the cell surface phenotype of myeloid cell lines and monocytes

Nineteen MoAbs specific for myeloid molecules and 8 MoAbs reactive with MHC Class II molecules (see Table 1) were tested

Table 2. Levels of expression of myeloid molecules before (−) and after (+) treatment with IFN-γ

	U937		Monocytes	
Monoclonal antibody	−IFN-γ	+IFN-γ	−IFN-γ	+IFN-γ
Mononuclear Phagocytes				
CD13	91 (6·6)	94 (7·7)	97 (239)	97 (228)
CD14	–	–	94 (168·7)	84 (102·4)
CD15	19 (1·1)	22 (1·2)	–	–
CD16	–	–	50 (3·5)	43 (3·9)
CDw17	–	–	15 (1·9)	18 (2·5)
CD31	97 (8·2)	95 (6·5)	97 (18·4)	91 (18·4)
CDw32	88 (4·6)	80 (4·0)	96 (13·6)	90 (17·2)
CD33	–	–	–	–
CD34	–	–	–	–
CD35	–	–	84 (8·2)	79 (10·2)
CD36	–	–	26 (2·3)	17 (2·4)
MoAb 10.1	62 (2·3)	95 (7·4)	79 (5·3)	76 (12·4)
LFA-1 Family				
CD11a	85 (4·1)	84 (4·0)	99 (56·9)	97 (70·8)
CD11b	15 (1·2)	19 (1·2)	93 (73·9)	87 (70·8)
CD11c	18 (1·3)	16 (1·2)	96 (31·0)	87 (43·8)
MHC Class II				
HLA-D/DR	–	–	97 (80)	97 (225)
HLA-D/DQ	–	–	24 (3)	52 (8)
HLA-D/DP	–	–	54 (6)	72 (20)
Other				
anti-Tac (CD25)	60 (2·28)	99 (15·6)	66 (2·5)	90 (4·68)

Results are expressed as percentage positive cells (antigen expression).

on the myeloid cell lines U937 and HL60 after 18 h incubation with or without 100 units/ml of IFN-γ. A selection of the results for the U937 cell line is shown in Figure 1a ($n=4$–11) and Table 2 shows a typical experiment using U937 cells in which the percentage positive values and relative levels of antigen expression are illustrated for each category of myeloid molecule. The most significant alterations were the increase in the membrane expression of both FcRI, the high affinity receptor for the Fc region of IgG and in the receptor for interleukin 2, IL-2R.

Purified human monocytes were tested with the same MoAbs before and after treatment with IFN-γ used at 500 units/ml ($n=4$–17) (Fig. 1b and Table 2). Amongst the exclusively myeloid molecules, the highest increase in levels of expression were again observed for FcRI (4·5-fold) although there was great variation in the ratio of increased FcRI ranging between 1·7 and 11. Expression of the IL-2R increased in similar degree to FcRI (3·9-fold, $n=4$). Only one class of myeloid molecule decreased after IFN-γ treatment of monocytes. This was the 55 kD protein detected with CD14 MoAbs (Fig. 1b).

In contrast to U937, monocytes expressed all three subclasses of MHC Class II molecules and when results were averaged, an equivalent increase was seen in expression of all three after IFN-γ treatment. This was in spite of the fact that HLA-D/DR is much more highly expressed both before and after activation than HLA-D/DQ/DP (Table 2). However, when the monocyte samples were examined individually, the conclusions became less straightforward. Of the 14 samples which could be directly compared, DQ was most activated in four cases, DR in three and DP in two; in two cases DR and DQ were equivalent and in three cases DR and DP were equivalent (Fig. 2).

Dosage effects of IFN-γ and IFN-α on U937 and monocytes

We tested the ability of various amounts of IFN-γ to induce FcRI, IL-2R, MHC Class II and other myeloid molecules on the U937 cell line and monocytes. IFN-γ at 100–1 000 units/ml, induced a maximal 10–15-fold increase in expression of FcRI and IL-2R on U937 cells after 24 h ($n=3$) (Fig. 3a). Some activation was observed using IFN-γ at 1 unit/ml. In contrast, IFN-α produced little alteration in FcRI or IL-2R even when used at 1 000 units/ml and none of the other myeloid molecules investigated showed any change.

We then tested the effect on monocytes of IFN-γ and IFN-α treatment at levels of 50, 500 and 5 000 units/ml after a 48 h incubation time. IFN-γ caused increases in FcRI, IL-2R and MHC Class II molecules. In the example shown in Fig. 3b, variable alteration of these molecules was achieved after incubation with 50–5 000 IFN-γ units/ml. In some samples, 5–25 units/ml was sufficient to produce small but significant increases in molecule expression. On the other hand, between 500 and 5 000 units/ml usually achieved maximal stimulation. As the

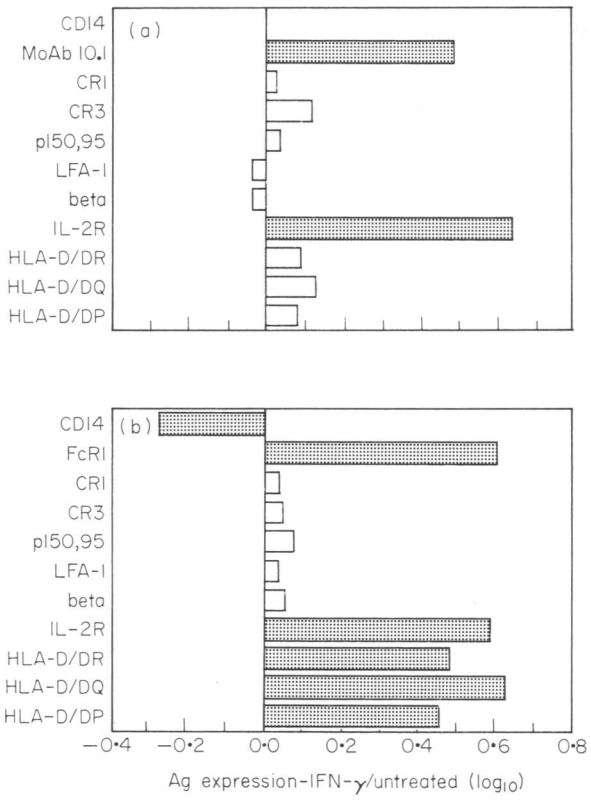

Fig. 1. Effect of rIFN-γ treatment on cell membrane expression of selected myeloid molecules on the U937 cell line (a) and monocytes (b). Changes in antigen levels are expressed as the ratio of IFN-γ-treated compared to untreated cells (log $_{10}$). CD14 molecules were not detected on U937 cells.

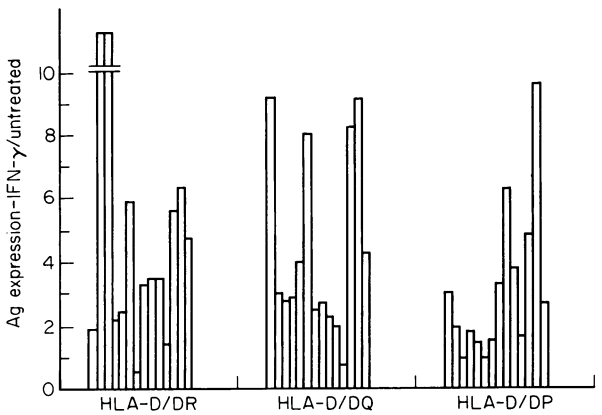

Fig. 2. Effect of rIFN-γ treatment on expression of MHC class II subregion molecules on 14 individual samples (Nos. 1–14, left to right) of monocytes. Changes in antigen levels are expressed as a ratio of IFN-γ-treated compared to untreated cells. The HLA-D/DR ratio for sample 2 was 77 and for sample 3 was 26.

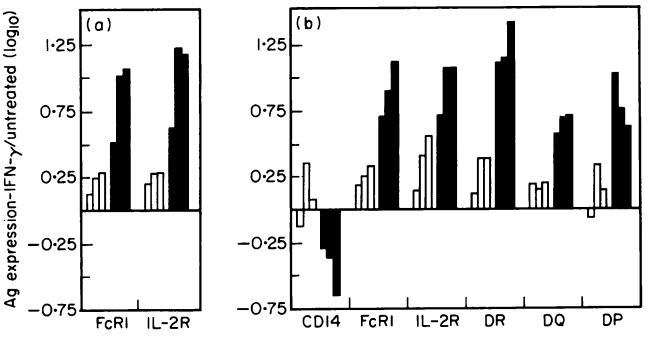

Fig. 3. Representative histograms showing the effect of various amounts of IFN-γ and IFN-α on the cell membrane expression of selected IFN-γ-inducible molecules on the U937 cell line (a) and monocytes b). Changes in antigen levels are expressed as the ratio of IFN-γ-treated compared to untreated cells (log $_{10}$). All open columns represent IFN-α (from left to right: (a) 10, 100 and 1000 units/ml (b) 50, 500 and 5000 units/ml). All shaded columns represent IFN-γ (from left to right: (a) 10, 100 and 1000 units/ml (b) 50, 500 and 5000 units/ml).

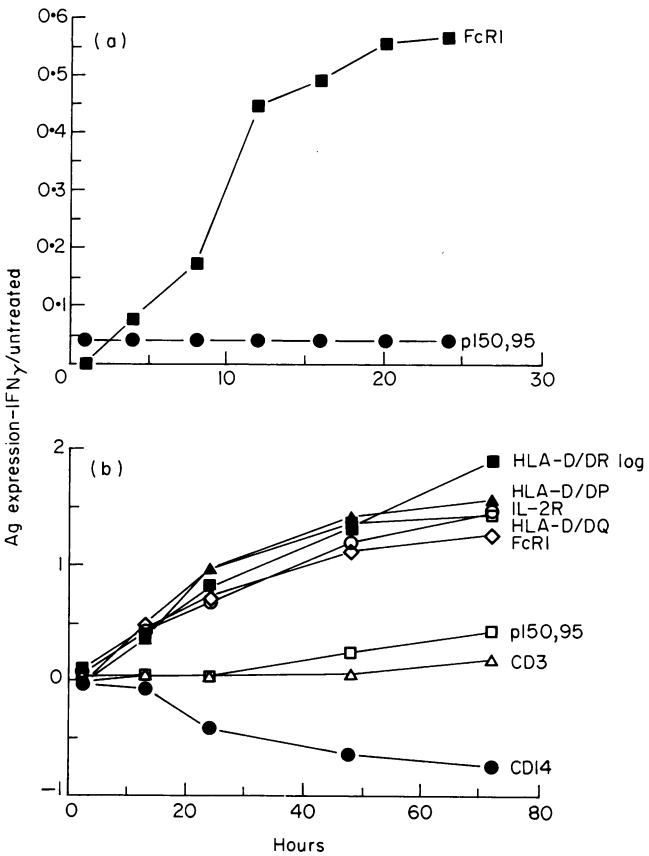

Fig. 4. Time course of FcRI and other molecules after IFN-γ treatment on U937 cells (a) and monocytes (b). Changes in antigen levels are expressed as the ratio of IFN-γ-treated compared to untreated cells (log $_{10}$).

molecules in general showed co-ordinate increases over the selected range of IFN-γ, the variation in sensitivity appeared to be caused either by some other property of the cells or by exposure *in vivo* to conditions which affected their subsequent responsiveness to IFN-γ. IFN-α failed to alter the expression of monocyte cell surface molecules (< 2-fold) with the exception of an increase in IL-2R. In the experiment illustrated in Fig. 3b, IL-2R was increased 3- and 4-fold by 500 and 5 000 units of IFN-α/ml, respectively.

Time course of the increase in expression of FcRI and other molecules on U937 Cells and monocytes

To discover how rapidly IFN-γ caused its activating effect, the U937 cell line was incubated with 100 units/ml of IFN-γ for times between 1 h and 3 days. Figure 4a shows that a small increase in FcRI was detectable at 4 h after IFN-γ treatment but that the maximum increase was not seen until 12–16 h after IFN-γ treatment ($n=3$). This level of expression was maintained for the 2–3 days of the experiment (data not shown).

Monocytes, treated with 500 units IFN-γ/ml showed a gradual and co-ordinate increase in FcRI, IL-2R and MHC Class II molecules and a decrease in the gp55 molecule over a 48 h period (Fig. 4b; $n=3$). Detectable increases in these molecules occurred between 8–13 h.

DISCUSSION

In this study we have investigated the early phenotypic alterations of human monocytes and the myeloid cell lines U937 and HL60 after exposure to rIFN-γ. MoAbs to 16 classes of myeloid molecules plus three subregions of MHC Class II molecules were used. As IFN-γ induces major changes in Mph cell function, it was expected that many changes would be seen. However the most universal alteration was in the increased expression of FcRI, the receptor which binds the Fc domain of immunoglobulin G with high affinity. This increase which has been reported by others (Guyre, Morganelli & Miller, 1983; Perussia *et al.*, 1983) was evident in U937 and HL60 cells treated with as little as 1 unit of IFN-γ/ml. Monocytes required between 50–500 units/ml for moderate stimulation and 500–5000 units for maximal stimulation. As increases in membrane expression of FcRI and the other molecules were evident within hours of IFN-γ exposure, these changes are most likely due to the direct effect of IFN-γ and it follows that such events must be important in the functional alterations induced by IFN-γ.

The role of FcRI remains obscure. Although until recently considered to be an exclusively Mph molecule, it is now certain that it can be expressed by IFN-γ-activated neutrophils (Perussia *et al.*, 1987; Shen, Guyre & Fanger, 1987; Buckle *et al.*, submitted). As it binds IgG with an affinity of 5×10^{-8} M, it ought to be continually occupied with serum IgG. However, the level of FcRI on circulating monocytes is highly variable with $60{\cdot}8\pm22{\cdot}1\%$ of monocytes expressing detectable levels of FcRI. As IFN-γ is a product of activated CD4-positive T cells (Chang *et al.*, 1982), FcRI may be induced on monocytes at the site of tissue inflammation and would therefore only be exposed to locally produced immunoglobulin and antibodies. Such activated Mph are capable of ADCC where FcRI is thought to play a role (Herlyn & Koprowski, 1982).

Expression of the other two FcR for IgG, named FcRII and FcRIII and recognized by the CDw32 and CD16 MoAbs, was not altered by IFN-γ. Both these receptors are involved in clearance of immune complexes, a function which could have more importance in the later stages of an immune response. Similarly, IFN-γ caused no change in any of the receptors for complement, namely CR1, CR3 and p150,95 (Malhotra, Hogg & Sim, 1986) detected by CD35, CD11b and CD11c MoAbs, these molecules being poorly expressed by U937 cells but well expressed by monocytes. This finding was somewhat surprising as Mph are known to have increased phagocytic capacity after IFN-γ treatment (Trinchieri & Perussia, 1985). However, changing membrane expression of a particular receptor may be only one way to alter the effective functioning of such a molecule. IFN-γ has been shown to depress the ability of CR1 and CR3 to bind ligand although membrane levels of these molecules are maintained (Wright *et al.*, 1986). The lack of modulation of CR1 and p150,95 agrees with similar findings by others (Esparza, Fox & Schreiber, 1986; Miller, Schwarting & Springer, 1986; Wright *et al.*, 1986). A time-dependent loss of CR1 has been observed but as this occurs 3–6 days after IFN-γ exposure, it may be a secondary effect (Esparza, Fox & Schreiber, 1986). CR3 and p150,95 belong to the LFA family of adhesive molecules. The third family member is LFA-1, a molecule which plays a key role in adhesive interactions occurring in immune responses. In this study we did not detect any alteration in the expression of LFA-1. Although others have observed a two-fold increase in LFA-1 after 3 days (Miller, Schwarting & Springer, 1986), it is unlikely that such a change is a direct effect of IFN-γ.

A second molecule which was consistently elevated in expression on both IFN-γ-treated U937 cells and on monocytes was the receptor for IL-2, now recognized to be widely distributed on cells of haematopoietic origin after activation by various cytokines including IL-1 and TNF (Shirakawa *et al.*, 1986; Holter *et al.*, 1987; Plaetinck *et al.*, 1987; Rambaldi *et al.*, 1987). In this study IFN-α was also able to induce IL-2R on monocytes at levels between 500–5000 units/ml. Although IL-2R has a key role in the regulation of proliferation in T cells and B cells, this is probably not its function on monocytes. One study has suggested that IL-2 is able to induce monocytes to become cytotoxic effector cells (Malkovsky *et al.*, 1987).

Another alteration in expression of myeloid-specific molecules was the down-regulation of the gp55 molecule recognized by CD14 antibodies, as recently reported (Firestein & Zvaifler, 1987). This change was not universal in cells of the Mph lineage as this protein is expressed by monocytes but not found on the less mature cells represented by U937 and HL60. Such a finding is in agreement with the observation that gp55 is detected on 30–40% of cells of AM/ML (M4) samples but not on the less mature AML (M1, M2) or APL (M3) leukaemias (Hogg & Horton, 1987).

The up-regulation of MHC Class II molecules on numerous cell types after IFN-γ exposure is a well-recognized phenomenon (Basham *et al.*, 1984; Virelizier *et al.*, 1984; Gonwa, Frost & Karr, 1986; Amatruda *et al.*, 1987). In this study the myeloid cell lines U937 and HL60 were found, in general, to lack expression of all three subtypes of MHC Class II molecules both before and after IFN-γ exposure. On the other hand, monocytes express the products of all three MHC Class II subregions, although HLA-D/DR is more highly expressed than the other two. However the observations suggest that the regulation of these molecules is not entirely co-ordinate and that individually specific factors, presently unknown, can affect the final levels of the HLA-D molecules. These considerations apply also to the other IFN-γ-induced molecules as the absolute amounts of alteration of all the molecules affected by IFN-γ did not correlate from person to person nor appear to depend on the primary levels of expression. These observations suggested influence by other unknown factors on the inducibility of FcRI, IL-2R, gp55 and MHC Class II molecules.

Although IFN-γ has a key role in Mph activation, it is now certain that other lymphokines are able to affect Mph functions.

It is a reasonable hypothesis that monocytes have a functional plasticity and respond to microenvironmental signals in accordance with the situation in which they find themselves. It remains to be tested whether other modulators also up-regulate expression of the same set of molecules, in particular FcRI. We have compared IFN-γ to IFN-α but preliminary data suggest that other cytokines such as the colony-stimulating factors do not alter FcRI levels (Buckle, A-M. *et al.*, submitted). Moreover, neither TNF nor IL-1β stimulate increases in FcRI levels of expression on Mph (Arend, Ammons & Kotzin, 1987; Trinchieri *et al.*, 1986; Buckle, preliminary observations). Thus, the rapid increase in FcRI appears to be a hallmark of IFN-γ-induced Mph activation.

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