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Glucocorticoid enhances gamma interferon effects on human monocyte antigen expression and ADCC

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SUMMARY

The expression of HLA-DR antigen by highly enriched human monocytes cultured in serum free medium was found to be markedly elevated by human recombinant gamma interferon (IFN-gamma). This effect was maximal after 48 h in culture with 300 u/ml IFN-gamma. Class I MHC antigen also increased with IFN-gamma treatment. By contrast, binding of a myeloid-specific monoclonal antibody, AML-2-23, was dramatically decreased by IFN-gamma. The augmentation of MHC antigens was not ablated by an immunosuppressive concentration (2×10^{-7} M) of the glucocorticoid dexamethasone (DEX). In fact, both the enhancement of Class I and Class II MHC antigen expression and the suppression of AML-2-23 antigen by IFN-gamma were often more profound in the presence of DEX. IFN-gamma treatment also resulted in elevated monocyte effector function, as measured by antibody dependent cellular cytotoxicity (ADCC). This functional activation was not inhibited by DEX. On the contrary, DEX slightly augmented IFN-gamma effects on ADCC. This contrasts with other reports that glucocorticoids inhibit monocyte responsiveness to lymphokines, and suggests that the interplay between lymphokines and the glucocorticoid hormones may be more complex than previously thought.

Keywords Monocyte HLA-DR gamma interferon glucocorticoids ADCC

INTRODUCTION

The participation of monocytes and macrophages in various reactions, including the presentation of antigen to lymphocytes (Yamashita & Shevach, 1977), non-specific killing of tumor cells (Normann & Weiner, 1983; Evans & Alexander, 1972), and killing of antibody or antibody and complement opsonized pathogens (Mantovani *et al.*, 1977; Johnston, 1978), involves recognition at the cell surface of critical molecules such as Ia antigens and receptors for complement and the Fc region of IgG. Recent studies have demonstrated that lymphokines, particularly gamma interferon, are potent stimulators of monocyte/macrophage function (Guyre, Morganelli and Miller, 1983; Stanwick, Campbell & Nahmias, 1982). Glucocorticoids, on the other hand, have suppressive effects on the immune system, resulting in a decrease in production of lymphokines, including interferons (Gillis, Crabtree & Smith, 1979; Guyre, Bodwell & Munck, 1981; Arya, Wong-Staal & Gallo, 1984). We have undertaken a study of the ability of gamma interferon (IFN-gamma) to modulate monocyte antibody mediated function and cell surface antigens, in particular HLA-DR, believed to be involved in cell surface interactions such as antigen presentation (Raff, Picker & Stobo 1980). In addition, we have explored the possibility that the suppressive effect of

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glucocorticoids might include an influence on effector cell function by examining the effects of an immunosuppressive concentration of dexamethasone (DEX) on monocyte surface antigen expression and antibody mediated killing. Furthermore, since another mechanism by which glucocorticoids mediate suppression might be by blocking the stimulatory effects of lymphokines on their target cells, as suggested by our previous studies (Shen, Guyre & Fanger, 1984), we have examined the effects of simultaneous exposure to IFN-gamma and dexamethasone on monocyte surface antigen expression and ADCC.

MATERIALS AND METHODS

Monocytes. Mononuclear cells enriched for monocytes were obtained by cytopheresis of peripheral blood from normal volunteers. This fraction, which usually contained 50% monocytes, was further purified by centrifugation over Ficoll-Hypaque. The mononuclear cell layer was washed five times in RPMI and resuspended in 10% autologous serum at 5×10^7 cells/ml in a 50 ml polypropylene tube. The tube was rotated for 90 min at 4°C, causing the monocytes to clump, and then placed upright in an ice bath for 30 min, allowing the clumped cells to settle as a pellet. Pelleted cells were washed three times in RPMI 1640. Alternatively, monocytes were enriched from the mononuclear fraction by centrifugation through Percoll (Wright & Silverstein, 1982). Monocytes prepared by either method were 80–90% pure as judged by morphology and expression of the monocyte-associated antigen AML-2-23 (Ball *et al.*, 1982), the rest being lymphocytes. Monocytes (2×10^6/ml) in Iscove's medium (Baker & Knoblock, 1982), supplemented with 2 mg/ml pyrogen-free bovine serum albumin (BSA) and 50 μg/ml gentamicin (Schering Corp., Kenilworth, NJ), were cultured in Teflon screw-top vessels (Savillex, Minitonka, MN), to which the cells did not adhere, at 37°C in a 5% CO_2 gassed incubator.

Interferons. Human gamma-interferon (generously provided by Dr C. Sevastopoulos, Genentech Inc.) was highly purified from bacterial cultures following cloning of the appropriate gene into *E. coli* (Gray *et al.*, 1982). The endotoxin content of the IFN was estimated using the Limulus lysate assay (Cape Cod Associates) which was sensitive to 13 pg/ml LPS and found to be $< 0{\cdot}001$ pg LPS per international reference unit (IRU) of interferon. Appropriate dilutions of IFN were made in Iscove's medium supplemented with BSA and gentamicin and added to the monocyte cultures.

Glucocorticoid effects on cultured monocytes. An ethanol stock solution of DEX was evaporated onto a polystyrene dish (Crabtree, Munck & Smith, 1979) and redissolved in RPMI-1640 to 2×10^{-5} M by incubation at 37°C for 30 min. Monocyte cultures were supplemented with DEX to a final concentration of 2×10^{-7} M.

Cytofluorograph analysis. Freshly prepared monocytes or monocytes cultured for various time periods with or without IFN and DEX were washed in PBS containing 0·5% BSA and 0·05% sodium azide (PBS-BSA-Az). Pelleted cells (1×10^6) at 4°C were mixed with 5 μl of purified human IgG1 at 16 mg/ml and then with monoclonal antibodies to a final volume of 100 μl. After 1 h incubation at 4°C the cells were washed once with PBS-BSA-Az and treated for 45 min at 4°C with 25 μl of a 1:20 dilution of fluorescein isothiocyanate (FITC) conjugated affinity purified F(ab′)2 goat anti-mouse immunoglobulin (Boehringer-Mannheim, Indianapolis, IN). They were then washed, the cell pellet disrupted, and the cells fixed with 200 μl ice-cold 2% paraformaldehyde in PBS accompanied by vigorous pipetting to prevent clumping. The Ortho (Westwood, MA) Cytofluorograf system 50H was used to quantify binding of monoclonal antibodies.

Monoclonal antibodies. An IgG2 monoclonal antibody (MoAb) to human Ia framework, OkIa1 (Reinherz *et al.*, 1979), was obtained from Ortho Diagnostic Reagents Ltd. An IgG2a antibody to a common specificity on all HLA bearing cells, anti-HLA-A,B,C (Ugolini *et al.*, 1981) was obtained from BRL, Inc., Gaithersburg, MD. AML-2-23 (Ball *et al.*, 1982), is an IgG2b MoAb prepared in our laboratories which is reactive with the majority of normal monocytes and a subpopulation of neutrophils.

Antibody dependent cellular cytotoxicity. Monocytes cultured in absence or presence of interferon and dexamethasone were assessed for their abilities to mediate antibody-dependent cellular cytotoxicity against chicken erythrocytes. Chicken erythrocytes labelled with ^{51}chromium

were mixed with a rabbit anti-chicken erythrocyte IgG fraction at 0·15 μg/ml and exposed to control or stimulated monocytes in round-bottom microtitre wells. After incubation at 37°C for 6 h, the supernatant fluid was collected and the radioactivity counted in a gamma counter. Maximal lysis was obtained by treating target cells with detergent. Results are expressed as mean ± standard deviation (s.d.) of triplicate wells. Cytotoxicity was calculated as follows:

$$\% \text{ cytotoxicity} = \text{ct/min (experimental)} - \text{ct/min (medium)}/\text{ct/min (max)} - \text{ct/min (medium)} \times 100$$

RESULTS

We have previously shown that recombinant IFN-gamma and not alpha or beta-IFN caused a dramatic increase in Fc receptor expression on monocytes and of monocyte-like U-937 cells (Guyre, Morganelli & Miller, 1983). The results in Table 1 show that monocytes also exhibited marked increases in HLA-DR expression after 18 h of culture with recombinant IFN-gamma. This was seen as an increase in density of antigen rather than in number of positive cells. In order to rule out uptake of anti-DR or FITC labelled antibody through Fc receptors which are expressed in very high density on IFN-gamma treated monocytes, the cells were stained in the presence of 2 mg/ml purified human IgG1 to block Fc receptors before staining. Monocytes cultured without IFN-gamma also exhibited a substantial increase in HLA-DR expression. A maximal difference between HLA-DR expression by IFN-gamma treated and control cells was observed after 2–3 days in culture (data not shown).

It has been reported that glucocorticoids ablate the production of various immunological mediators including interferons (Arya, Wong-Staal & Gallo 1984) and also moderate the response of the monocyte-like cell line U-937 to IFN-gamma (Shen, Guyre & Fanger, 1984). We therefore examined the ability of monocytes to respond to IFN-gamma in the presence of an immunosuppressive concentration of the glucocorticoid dexamethasone (DEX). Surprisingly, DEX significantly augmented the effects of IFN-gamma on HLA-DR expression (Fig. 1). The density of HLA-DR, as assessed by mean fluorescence intensity, on monocytes treated with IFN-gamma and DEX was even greater than those exposed to IFN-gamma alone. This was not due simply to an additive effect between IFN-gamma and DEX since in only one case did DEX alone elevate HLA-DR expression. A similar effect on expression of HLA-A,B,C was observed (Fig. 2). Culture with IFN-gamma produced an increase in HLA-A,B,C which was further enhanced by DEX.

Table 1. Staining of monocytes with OKIa (HLA-DR)

	Total MFI		MFI of + Cells		% +	
Donor	Con	IFN	Con	IFN	Con	IFN
A	153	340	294	352	50	57
B	407	634	348	487	81	89
C	214	426	418	559	46	74
D	328	497	174	490	84	85

HLA-DR expression by monocytes after culture with recombinant IFN-gamma (IFN). Monocytes were stained with MoAb OKIa, specific for HLA-DR, or P_3 a MoAb of irrelevant specificity secreted by the myeloma line P3X63Ag8 after 18 h culture with 300 IRU/ml recombinant IFN-gamma, or serum free medium (Con). Cells were fixed after staining, and immunofluorescence of 10,000 cells measured by cytofluorography. Results are corrected for non-specific P_3 staining. MFI refers to mean fluorescence intensity.

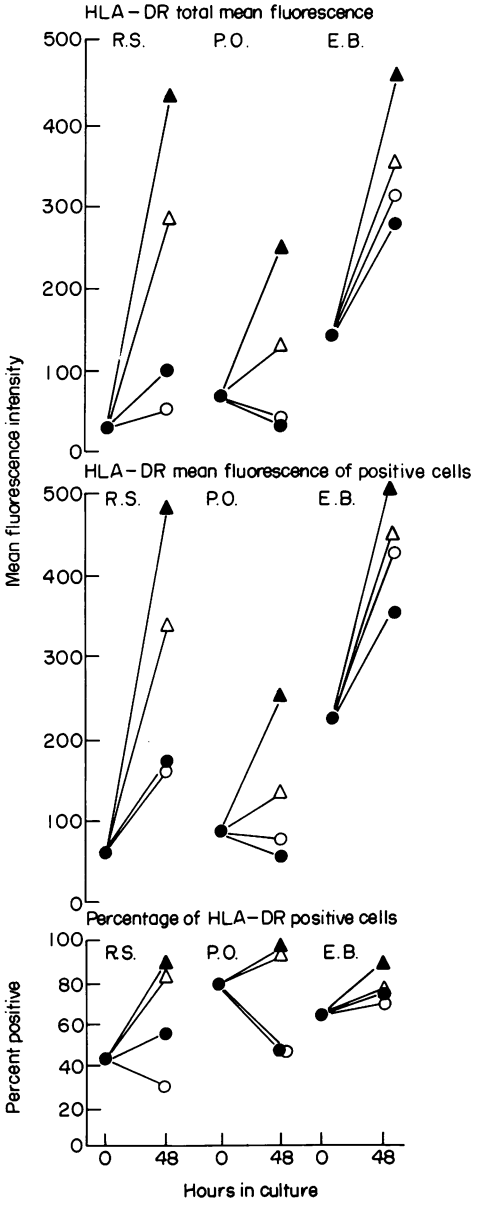

Fig. 1. Combined effect of recombinant IFN-gamma (300 IRU/ml) and dexamethasone (2×10^{-7} M) on HLA-DR expression of monocytes from three donors (R.S., P.O., E.B.). Monocytes were stained with a monoclonal antibody to HLA-DR before or after 48 h culture in serum free medium (●), or after culture with IFN-gamma (△), DEX (○), or IFN-gamma and DEX (▲). Cells were fixed, and immunofluorescence of 10,000 cells was measured by cytofluorography.

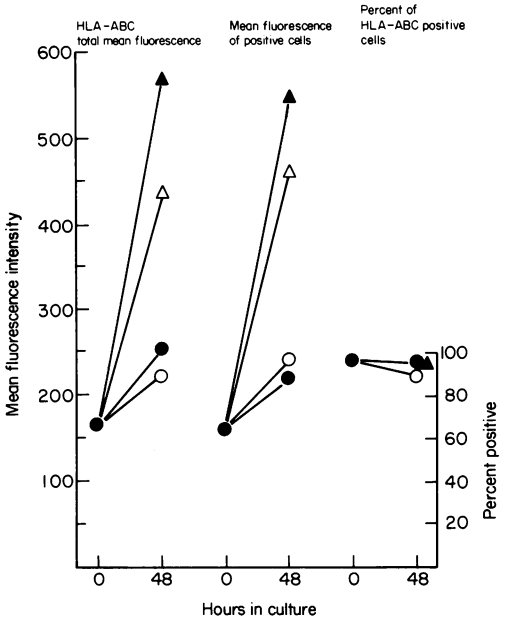

Fig. 2. Combined effect of IFN-gamma (300 IRU/ml) and DEX (2×10^{-7} M) on HLA-A,B,C expression of monocytes. In this representative experiment monocytes were stained with a monoclonal antibody to HLA-A,B and C, or an irrelevant antibody, before or after 48 h culture in serum free medium (●), or after culture with IFN-gamma (△), DEX (○), or IFN-gamma and DEX (▲). Immunofluorescence of 10,000 cells was measured by cytofluorography.

In contrast with the above two antigens, surface density (mean fluorescence intensity) of the myeloid-specific antigen recognized by monoclonal antibody AML-2-23 was strikingly reduced by culture with IFN-gamma (Fig. 3). Treatment with DEX also resulted in strong suppression of antigen expression. Thus the much larger decrease in antigen expression obtained by culture with IFN-gamma and DEX probably resulted from an additive effect of the two reagents. In addition, the number of cells positive for AML-2-23 was decreased by IFN-gamma and DEX, when used separately or combined, on cells from two out of three donors. Since the AML-2-23 antigen was decreased on IFN-gamma or IFN-gamma and DEX-treated cells, it appears that the increased expression of HLA-DR and HLA-A,B,C cannot be accounted for by a physical phenomenon such as an increase in surface area due to ruffling of the membrane, or greater numbers of pseudopodia.

In addition to surface marker expression, we examined the effects of IFN-gamma and DEX on monocyte function. Treatment for 18 h with IFN-gamma produced two-fold or greater increase in the ability of monocytes to lyse antibody-coated chicken erythrocytes (Fig. 4). DEX did not suppress the stimulation of ADCC by IFN-gamma (Fig. 4); rather, monocytes treated with both IFN-gamma and DEX were usually more cytotoxic than those which received IFN-gamma alone. Thus, a potentially immunosuppressive concentration of DEX could enhance the in-vitro action of IFN-gamma on both monocyte function and antigen expression.

DISCUSSION

These results demonstrate that IFN-gamma increases the density of HLA-DR and HLA-A,B,C on monocytes. This increase in histocompatability antigen is accompanied by a substantial decrease in expression of the myeloid-specific differentiation antigen defined by monoclonal antibody AML-2-

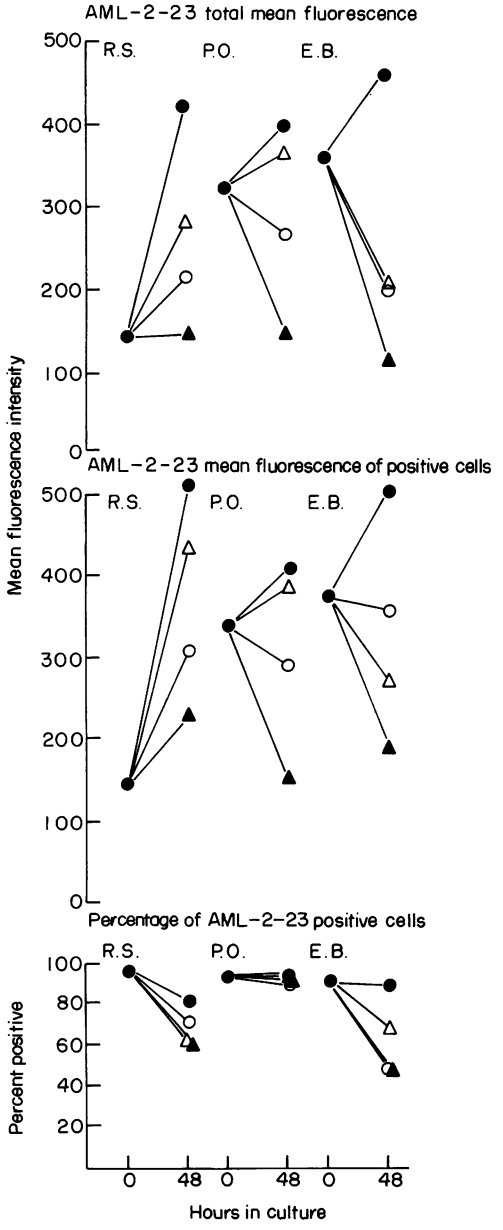

Fig. 3. Combined effect of IFN-gamma (300 IRU/ml) and DEX (2×10^{-7} M) on AML 2-23 staining of monocytes from three donors (R.S., P.O., E.B.). Monocytes were stained with monoclonal antibody AML-2-23 or an irrelevant antibody before or after 48 h culture in serum free medium (●), or after culture with IFN-gamma (△), DEX (○), or IFN-gamma and DEX (▲). Cells were fixed and immunofluorescence of 10,000 cells was measured by cytofluorography.

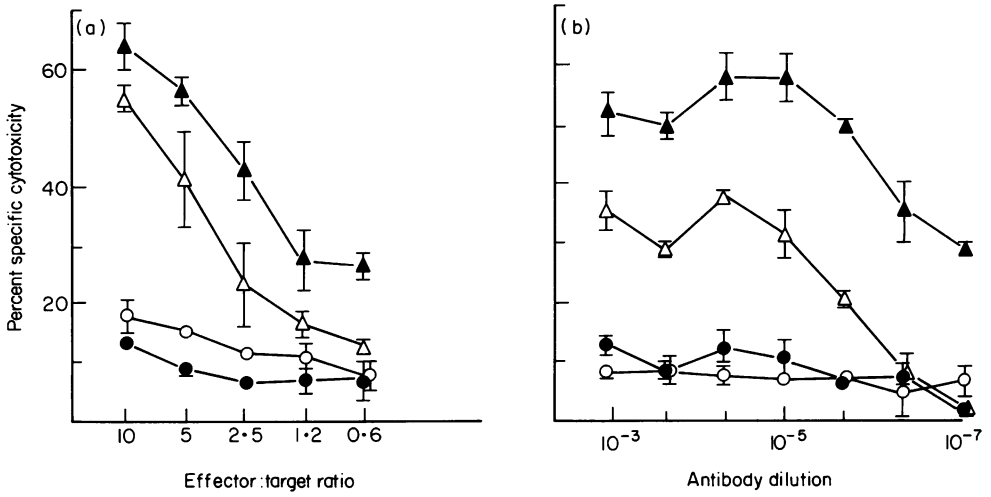

Fig. 4. ADCC of monocytes after culture with IFN-gamma and DEX. Monocytes were cultured for 18 h in serum free medium (●), 300 IRU/ml IFN-gamma (△), 2×10^{-7} M DEX (○), or IFN-gamma and DEX (▲), after which they were washed and assayed for ability to kill antibody-coated chicken erythrocytes with a 10^{-5} dilution of rabbit IgG antibody and (a) varying effector target ratio or (b) at a constant effector to target ratio (10:1) and varying concentrations of antibody (stock solution 16 mg/ml).

23. These antigen changes were accompanied by activation of the monocyte function of ADCC. Furthermore, the glucocorticoid dexamethasone did not inhibit the action of IFN-gamma on monocytes. The effect of DEX was actually additive or greater than additive with the effect of IFN-gamma in enhancing HLA-DR and diminishing AML-2-23 expression. A similar effect was observed on monocyte ADCC, in which DEX not only failed to inhibit, but even increased, the effect of IFN-gamma.

It has been known for some time that products of activated mouse T cells elevate Ia expression (Scher, Beller & Unanue, 1980) and antigen presenting abilities of mouse macrophages and monocytes (Beller & Ho 1982). Our studies are consistent with these observations and other studies (Basham & Merigan 1983) that suggest that cloned human IFN-gamma can enhance HLA-DR expression and ADCC of human peripheral blood monocytes. More important, we have ruled out, by culturing cells in a defined serum-free medium, the possible cooperation between serum factors and IFN-gamma. Thus, pure cloned IFN-gamma acts on monocytes, in the absence of other serum factors, to elevate expression of HLA-DR and Class I HLA antigens and ADCC.

Augmentation of these antigens may be immunologically relevant since it has been shown that mouse macrophages which have been induced to display increased amounts of Ia antigen are also more effective in antigen presentation (Beller & Ho 1982). Type I MHC antigens have also been shown to be necessary for recognition of viral antigens by T cells (Germain, Dorf & Benacerraf, 1975; Doherty, Blanden & Zinkernagel, 1976).

In striking contrast to Class I and II HLA antigens, the expression of a myeloid-specific antigen, defined by MoAb AML-2-23, was greatly reduced by IFN-gamma. Since this antigen appears to be a glycoprotein (Maliszewski *et al.*, 1985), the increases in HLA-DR and HLA-A,B,C antigens are not due to an overall IFN-gamma induced increase in cell surface glycoprotein. While the significance of this antigen is not known at present, it is possible that its modulation by IFN-gamma would also occur *in vivo*. Conceivably changes in display of this surface antigen might then be involved in altered function, for example, redirection of monocyte traffic during an immune response.

Production of soluble mediators such as the interferons (Arya, Wong-Staal & Gallo, 1984) and IL-2 (Gillis, Crabtree & Smith 1979) are suppressed *in vitro* by concentrations of DEX (10^{-7} M)

which also cause in-vivo immunosuppression (10^{-7} M) (Silberman, 1981; Cupps & Fauci, 1982). While glucocorticoids exert suppressive effects on many facets of the immune system, the results here indicate that monocyte HLA-DR and HLA-ABC are not affected by pharmacological concentrations of DEX and therefore that immunosuppression by glucocorticoids is probably not effected at the level of HLA-DR expression. These results contrast with other findings that hydrocortisone treatment of monocytes resulted in increased expression of HLA-DR antigens (Gerrard *et al.*, 1984). This diversity in observations might result from the use of different culture techniques or media. It is also likely that monocytes respond differently to the higher concentrations (10^{-5}–10^{-6} M) of glucocorticoids used in the previous study.

Glucocorticoids might also alter immune responsiveness by inhibiting the action of lymphokines on their target cells as have been shown to occur in mice. Mouse macrophages, which normally lose their Ia antigens in culture, were stimulated to re-express them under the influence of a T cell line supernatant, and this expression was strongly inhibited by hydrocortisone (Beller & Ho, 1982; Warren & Vogel, 1985). Our data show that the glucocorticoid dexamethasone potentiated the effects of cloned IFN-gamma on human monocytes. Antigens whose expression was increased by IFN-gamma (HLA-DR, HLA-A,B,C) were more strongly expressed when dexamethasone was added in conjunction with IFN-gamma. Also, in the case of the AML-2-23 antigen which was decreased by IFN-gamma, the addition of dexamethasone further decreased expression of this marker. This suggests that there are fundamental differences in the action of glucocorticoids on mononuclear phagocytes of mouse and man.

The inability of DEX to exert suppressive effects on monocytes is further emphasized by our studies on ADCC. Culture with DEX alone either had no effect, or even enhanced ADCC. Furthermore, the marked increase in monocyte antibody-mediated function following IFN-gamma treatment was unaffected or even augmented by DEX, in agreement with the studies of Warren & Vogel (1985) using mouse macrophages. Our study demonstrates that pharmacological concentrations of DEX do not interfere with the functional activation of human monocytes by IFN-gamma, and extends the findings of Girard *et al.* (1984) that augmentation of monocyte Fc receptor expression by IFN-gamma is enhanced in the presence of DEX. Examination of Fc receptor mediated function in this study has established that the DEX enhancement of the IFN-gamma effect is evident not only as cell surface changes, but also as an increase in overall cellular function. The ability of recombinant IFN-gamma to augment monocyte function in the presence of immunosuppressive glucocorticoid concentrations might be of therapeutic value in counteracting some of the effects of glucocorticoid therapy. Glucocorticoid production increases significantly during a normal immune response or following injection of lymphokine (Besedovsky, del Rey & Sorkin 1983) and this increased glucocorticoid is thought to act as a negative regulator of the immune response. Our results suggest that in addition to inhibiting further secretion of lymphokines (an effect which probably requires chronic exposure to high levels of glucocorticoid) acute elevation of glucocorticoids may actually increase cellular responsiveness to lymphokines which are already in circulation. Both acute enhancement and chronic suppresion of immune responses are consistent with the role glucocorticoids play in resistance to stress (Munck, Guyre & Holbrook, 1984).

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REFERENCES

ARYA, S.K., WONG-STAAL, F. & GALLO, R.C. (1984) Dexamethasone-mediated inhibition of human T cell growth factor and gamma interferon messenger RNA. *J. Immunol.* **133,** 273.

BAKER, P.E. & KNOBLOCK, F.F. (1982) Bovine costimulator. I. Production kinetics, partial purification and quantification in serum free Iscove's medium. *Vet. Immunol. Immunopathol.* **3,** 365.

BALL, E.D., GRAZIANO, R.F., SHEN, L. & FANGER, M.W. (1982) Monoclonal antibodies to novel myeloid antigens reveal human neutrophil heterogeneity. *Proc. natn. Acad. Sci. USA.* **79,** 5374.

BASHAM, T.Y. & MERIGAN, T.C. (1983) Recombinant interferon-gamma increases HLA-DR synthesis and expression. *J. Immunol.* **130,** 1492.

BELLER, D.I. & HO, K. (1982) Regulation of macro-

phage populations. V. Evaluation of the control of macrophage Ia expression *in vitro*. *J. Immunol.* **129,** 971.

BESEDOVSKY, H.O., DEL REY, A. & SORKIN, E. (1983) Neuroendocrine immunoregulation. In *Immunoregulation* (ed. by N. Febris, E. Guraci, John Hadden & N.A. Mitchison) p. 315. Plenum Publishing Corp., New York.

CRABTREE, G.R., MUNCK, A. & SMITH, K.A. (1979) Glucocorticoids inhibit expression of Fc receptors on the human granulocytic cell line HL-60. *Nature*, **279,** 338.

CUPPS, T.R. & FAUCI, A.S. (1982) Corticosteroid-mediated immunoregulation in man. *Immunol Rev.* **65,** 133.

DOHERTY, P.C., BLANDEN, R.V. & ZINKERNAGEL, R.M. (1976) Specificity of virus-immune effector T Cells for H-2K or H-2D compatible interactions: Implications for H-antigen diversity. *Transpl. Rev.* **29,** 89.

EVANS, R. & ALEXANDER, P. (1972) Role of macrophages in tumor immunty. II. Involvement of a macrophage cytophilic factor during syngeneic tumor growth inhibition. *Immunology*, **23,** 627.

GERMAIN, R.N., DORF, M.E. & BENACERRAF, B. (1975) Inhibition of T-lymphocyte mediated tumor specific lysis by alloantisera directed against the H-2 serological specificities of the tumor. *J. exp. Med.* **142,** 1023.

GERRARD, T.L., CUPPS, T.R., JURGENSEN, C.H. & FAUCI, A.S. (1984) Increased expression of HLA-DR antigens in hydrocortisone treated monocytes. *Cell. Immunol.* **84,** 311.

GILLIS, S., CRABTREE, G.R. & SMITH, K.A. (1979) Glucocorticoid-induced inhibition of T-cell growth factor production. I. The effect on mitogen-induced lymphocyte proliferation. *J. Immunol.* **123,** 1624.

GIRARD, M.T., GUYRE, P.M., NARAY FEJES-TOTH, A. & MUNCK, A. (1984) Glucocortoids enhance the immune-interferon-induced increase in human monocyte IgG Fc receptors. *Fed. Proc.* **43,** 1434 (abstr.).

GRAY, P.W., LEUNG, D.W., PENNICA, D., YELVERTON, E., NAJARIAN, R., SIMONSON, C.C., DERYNK, R., SHERWOOD, P.J., WALLACE, D.M., BERGER, S.L., LEVINSON, A.D. & GOEDDEL, D.V. (1982) Expression of human immune interferon cDNA in *E. coli* and monkey cells. *Nature*, **295,** 503.

GUYRE, P.M., BODWELL, J.E. & MUNCK, A. (1981) Glucocorticoid actions on the immune system: Inhibition of an Fc-receptor augmenting factor. *J. Steroid Biochem.* **15,** 35.

GUYRE, P.M., MORGANELLI, P.M. & MILLER, R. (1983) Augmentation of human blood monocyte Fc receptors by gamma interferon. *J. clin. Invest.* **72,** 393.

JOHNSTON, R.B. (1978) Oxygen metabolism and the microbicidal activity of macrophages. *Fed. Proc.* **37,** 2759.

MALISZEWSKI, C.R., BALL, E.D., GRAZIANO, R.F. & FANGER, M.W. (1985) Isolation and characterization of My23, a myeloid cell-derived antigen reactive with the monoclonal antibody AML-2-23. *J. Immunol.* **135,** 1929.

MANTOVANI, A., CAPRIOLI, V., GRITTI, P. & SPREAFICO, F. (1977) Human mature macrophages mediate antibody-dependent cellular cytotoxicity on tumor cells. *Transplantation.* **24,** 291.

MUNCK, A., GUYRE, P.M. & HOLBROOK, M.J. (1984) Physiological functions of glucocortoids in stress and their relationship to pharmacological actions. *Endocrine Reviews*, **5,** 25.

NORMANN, S.J. & WEINER, R. (1983) Cytotoxicity of human peripheral blood monocytes. *Cell. Immunol.* **81,** 413.

RAFF, H.V., PICKER, J.J. & STOBO, J.D. (1980) Macrophage heterogeneity in man. A subpopulation of HLA-DR bearing macrophages required for antigen-induced T cell activation also contains stimulators for autologous reactive T cells. *J. exp. Med.* **152,** 581.

REINHERZ, E.L., KUNG, P.C., PESANDO, J.M., RITZ, J., GOLDSTEIN, G. & SCHLOSSMAN, S.F. (1979) Ia determinants on human T cell subsets defined by monoclonal antibody. Activation stimuli required for expression. *J. exp. Med.* **150,** 1472.

SCHER, M.G., BELLER, D.I. & UNANUE, E.R. (1980) Demonstration of a soluble mediator that induces exudates rich in Ia positive macrophages. *J. exp. Med.* **152,** 1684.

SHEN, L., GUYRE, P.M. & FANGER, M.W. (1984) Direct stimulation of ADCC by cloned gamma interferon is not ablated by glucocorticoids: Studies using a human monocyte-like cell line (U937). *Molecular Immunol.* **21,** 167.

SILBERMAN, H. (1981) Dosage of corticosteroids in renal allograft rejection. *Am J. Surgery.* **142,** 413.

STANWICK, T.L., CAMPBELL, D.E. & NAHMIAS, A.J. (1982) Cytotoxic properties of human monocyte-macrophages for human fibroblasts infected with herpes simplex virus: interferon production and augmentation. *Cell. Immunol.* **70,** 132.

UGOLINI, V., NUNEZ, G., SMITH, R.G., STASNY, P. & CAPRA, J.D. (1981) Initial characterization of monoclonal antibodies against human monocytes. *Proc. natn. Acad. Sci. USA.* **77,** 6764.

WARREN, M.K. & VOGEL, S.N. (1985) Opposing effects of glucocorticoids on interferon-γ-induced murine macrophage Fc receptor and Ia antigen expression. *J. Immunol.* **134,** 2462.

WRIGHT, S.D. & SILVERSTEIN, S.C. (1982) Tumor-promoting phorbol esters stimulate C_3b and C_3b' receptor mediated phagocytosis in cultured human monocytes. *J. exp. Med.* **156,** 1149.

YAMASHITA, Y. & SHEVACH, E.M. (1977) The expression of Ia antigens on immunocompetent cells in the guinea pig. II. Ia antigens on macrophages. *J. Immunol.* **119,** 1584.